



Clinical trial results:

A randomized, placebo-controlled, multiple dose, double blind, phase IIb, dose guiding trial to explore safety and tolerability of four weeks treatment with sulthiame in patients with moderate to severe obstructive sleep apnea

Summary

EudraCT number	2017-004767-13
Trial protocol	SE
Global end of trial date	19 December 2019

Results information

Result version number	v1 (current)
This version publication date	16 December 2020
First version publication date	16 December 2020

Trial information

Trial identification

Sponsor protocol code	STM-026/K
-----------------------	-----------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Desitin Arzneimittel GmbH
Sponsor organisation address	Weg beim Jäger 214, Hamburg, Germany, 22335
Public contact	Clinical Trial Manager, Desitin Arzneimittel GmbH, info@desitin.de
Scientific contact	Clinical Trial Manager, Desitin Arzneimittel GmbH, info@desitin.de

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	03 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to explore the safety and tolerability of 4 weeks of treatment with different doses of sulthiame (STM) in patients with obstructive sleep apnea (OSA).

Protection of trial subjects:

The final clinical study protocol and the final version of the patient information and consent form, were reviewed and approved by an Independent Ethics Committee (IEC) prior to inclusion of patients. The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association. All patients received written and verbal information regarding the study. The given information emphasized that participation in the study was voluntary and that the patients could withdraw from the study at any time and for any reason. All patients were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study. Before any study-related procedures, the informed consent form was signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2018
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	Sweden: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	40
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

81 patients were screened. Eligible patients were 18-75 years old, previously treated with CPAP that was stopped because of non-acceptance or non-tolerability with BMI of ≥ 20 kg/m²- ≤ 35 kg/m², AHI ≥ 15 , ESS score ≥ 6 and able to provide informed consent. Patients with OSA treatment within 4 weeks of baseline or central sleep apnea were excluded.

Period 1

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

Arms

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

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

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily.

Arm title	200 mg STM
------------------	------------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ospolot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg and 200 mg. Administered once daily.

Arm title	400 mg STM
------------------	------------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ospolot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg and 200 mg. Administered once daily.

Number of subjects in period 1	Placebo	200 mg STM	400 mg STM
Started	22	12	34
Completed	22	12	25
Not completed	0	0	9
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	-	-	6
Non-compliance	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	200 mg STM
Reporting group description: -	
Reporting group title	400 mg STM
Reporting group description: -	

Reporting group values	Placebo	200 mg STM	400 mg STM
Number of subjects	22	12	34
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	60.9 ± 10.5	60.3 ± 11.4	60.6 ± 9.4
Gender categorical Units: Subjects			
Female	5	5	11
Male	17	7	23

Reporting group values	Total		
Number of subjects	68		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	21		
Male	47		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	200 mg STM
Reporting group description: -	
Reporting group title	400 mg STM
Reporting group description: -	

Primary: Systolic blood pressure

End point title	Systolic blood pressure ^[1]
End point description:	

End point type	Primary
End point timeframe:	
At baseline (Visit 2) and 4 weeks (Visit 6).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	132.8 (± 11.8)	135.4 (± 14.0)	132.1 (± 12.5)	
4 weeks (Visit 6)	130.5 (± 11.4)	132.5 (± 11.6)	133.4 (± 13.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Diastolic blood pressure

End point title	Diastolic blood pressure ^[2]
End point description:	

End point type	Primary
End point timeframe:	
At baseline (Visit 2) and 4 weeks (Visit 6).	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	79.6 (± 6.0)	84.3 (± 8.3)	79.3 (± 9.0)	
4 weeks (Visit 6)	79.5 (± 6.3)	82.4 (± 10.6)	79.9 (± 8.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Mean arterial blood pressure

End point title	Mean arterial blood pressure ^[3]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	97.4 (± 6.6)	101.4 (± 9.4)	97.1 (± 9.5)	
4 weeks (Visit 6)	96.4 (± 6.8)	99.3 (± 10.1)	97.6 (± 9.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Respiratory rate

End point title	Respiratory rate ^[4]
-----------------	---------------------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: breaths/min				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	14.1 (± 2.7)	13.3 (± 1.5)	14.2 (± 2.6)	
4 weeks (Visit 6)	13.9 (± 2.5)	13.1 (± 1.2)	14.5 (± 2.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Pulse

End point title	Pulse ^[5]
-----------------	----------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: beats/min				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	69.2 (± 10.6)	70.6 (± 13.4)	72.1 (± 8.5)	
4 weeks (Visit 6)	69.6 (± 11.7)	68.8 (± 12.3)	71.8 (± 8.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Body weight

End point title	Body weight ^[6]
-----------------	----------------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: kg				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	89.2 (± 11.7)	81.8 (± 11.1)	82.1 (± 14.6)	
4 weeks (Visit 6)	88.2 (± 11.5)	80.8 (± 10.5)	82.4 (± 14.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Body mass index (BMI)

End point title Body mass index (BMI)^[7]

End point description:

End point type Primary

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: kg/m ²				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	28.9 (± 3.0)	27.7 (± 3.1)	26.7 (± 3.1)	
4 weeks (Visit 6)	28.6 (± 3.0)	27.3 (± 2.9)	26.2 (± 3.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Waist-hip ratio

End point title Waist-hip ratio^[8]

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: unitless				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	1.0 (± 0.1)	1.0 (± 0.1)	0.9 (± 0.1)	
4 weeks (Visit 6)	1.0 (± 0.1)	0.9 (± 0.1)	0.9 (± 0.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Electrocardiogram (ECG)

End point title	Electrocardiogram (ECG) ^[9]
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	25	
Units: patients				
Baseline (Visit 2) - Normal	16	10	18	
Baseline (Visit 2) - Abnormal NCS	5	1	7	
Baseline (Visit 2) - Abnormal CS	1	1	0	
4 weeks (Visit 6) - Normal	18	11	16	
4 weeks (Visit 6) - Abnormal NCS	2	0	9	
4 weeks (Visit 6) - Abnormal CS	2	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Clinical chemistry

End point title Clinical chemistry^[10]

End point description:

End point type Primary

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: unit(s)				
arithmetic mean (standard deviation)				
Albumin (g/L) - Baseline (Visit 2)	42.9 (± 2.7)	40.9 (± 2.5)	42.6 (± 2.9)	
Albumin (g/L) - 4 weeks (Visit 6)	42.9 (± 3.5)	39.8 (± 3.1)	43.7 (± 3.1)	
Alkaline phosphatase (ukat/L) - Baseline (Visit 2)	1.2 (± 0.3)	1.3 (± 0.4)	1.2 (± 0.3)	
Alkaline phosphatase (ukat/L) - 4 weeks (Visit 6)	1.1 (± 0.2)	1.2 (± 0.3)	1.2 (± 0.4)	
Alanine aminotransf. (ukat/L) - Baseline (Visit 2)	0.6 (± 0.3)	0.7 (± 0.3)	0.5 (± 0.2)	
Alanine aminotransf. (ukat/L) - 4 weeks (Visit 6)	0.5 (± 0.3)	0.6 (± 0.4)	0.4 (± 0.2)	
Aspartate aminotransf.(ukat/L)- Baseline (Visit 2)	0.4 (± 0.1)	0.6 (± 0.1)	0.4 (± 0.1)	
Aspartate aminotransf.(ukat/L) - 4 weeks (Visit 6)	0.4 (± 0.2)	0.4 (± 0.2)	0.3 (± 0.1)	
Bilirubin (umol/L) - Baseline (Visit 2)	11.0 (± 4.1)	10.9 (± 5.9)	10.4 (± 5.7)	
Bilirubin (umol/L) - 4 weeks (Visit 6)	11.1 (± 5.5)	10.9 (± 5.7)	10.8 (± 4.9)	
Calcium (mmol/L) - Baseline (Visit 2)	2.4 (± 0.1)	2.4 (± 0.1)	2.4 (± 0.1)	
Calcium (mmol/L) - 4 weeks (Visit 6)	2.4 (± 0.1)	2.3 (± 0.1)	2.4 (± 0.1)	
Chloride (mmol/L) - Baseline (Visit 2)	103.0 (± 2.0)	102.7 (± 2.2)	102.8 (± 2.3)	
Chloride (mmol/L) - 4 weeks (Visit 6)	102.8 (± 2.2)	104.4 (± 2.4)	106.3 (± 1.9)	
Creatinine (umol/L) - Baseline (Visit 2)	80.0 (± 11.2)	90.1 (± 25.3)	80.8 (± 14.5)	
Creatinine (umol/L) - 4 weeks (Visit 6)	83.6 (± 11.0)	91.7 (± 27.4)	92.7 (± 14.1)	
Potassium (mmol/L) - Baseline (Visit 2)	4.3 (± 0.1)	4.3 (± 0.3)	4.3 (± 0.2)	
Potassium (mmol/L) - 4 weeks (Visit 6)	4.3 (± 0.3)	4.0 (± 0.3)	4.2 (± 0.3)	
Phosphate (mmol/L) - Baseline (Visit 2)	1.1 (± 0.2)	1.0 (± 0.1)	1.1 (± 0.1)	
Phosphate (mmol/L) - 4 weeks (Visit 6)	1.0 (± 0.2)	1.0 (± 0.2)	1.0 (± 0.1)	
Sodium (mmol/L) - Baseline (Visit 2)	141.2 (± 1.6)	141.3 (± 1.2)	141.4 (± 1.7)	
Sodium (mmol/L) - 4 weeks (Visit 6)	141.5 (± 1.6)	141.7 (± 1.6)	142.0 (± 1.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Hematology

End point title Hematology^[11]

End point description:

End point type Primary

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: unit(s)				
arithmetic mean (standard deviation)				
Basophils (10 ⁹ /L) - Baseline (Visit 2)	0.1 (± 0.0)	0.1 (± 0.1)	0.0 (± 0.1)	
Basophils (10 ⁹ /L) - 4 weeks (Visit 6)	0.1 (± 0.1)	0.0 (± 0.0)	0.0 (± 0.1)	
Eosinophils (10 ⁹ /L) - Baseline (Visit 2)	0.2 (± 0.1)	0.3 (± 0.1)	0.2 (± 0.1)	
Eosinophils (10 ⁹ /L) - 4 weeks (Visit 6)	0.2 (± 0.1)	0.2 (± 0.1)	0.2 (± 0.1)	
Hematocrit (L/L) - Baseline (Visit 2)	0.5 (± 0.0)	0.5 (± 0.0)	0.5 (± 0.0)	
Hematocrit (L/L) - 4 weeks (Visit 6)	0.5 (± 0.0)	0.5 (± 0.0)	0.5 (± 0.0)	
Hemoglobin (g/L) - Baseline (Visit 2)	148.7 (± 10.6)	156.9 (± 16.0)	148.6 (± 11.3)	
Hemoglobin (g/L) - 4 weeks (Visit 6)	147.9 (± 10.7)	145.5 (± 15.4)	147.8 (± 13.6)	
Lymphocytes (10 ⁹ /L) - Baseline (Visit 2)	1.9 (± 0.5)	2.1 (± 0.8)	1.9 (± 0.6)	
Lymphocytes (10 ⁹ /L) - 4 weeks (Visit 6)	2.0 (± 0.6)	1.9 (± 0.4)	1.8 (± 0.6)	
MCH (pg) - Baseline (Visit 2)	30.1 (± 1.2)	30.7 (± 1.0)	30.4 (± 1.4)	
MCH (pg) - 4 weeks (Visit 6)	30.3 (± 1.3)	30.0 (± 1.0)	30.8 (± 1.3)	
MCHC (g/L) - Baseline (Visit 2)	325.5 (± 8.2)	326.9 (± 11.4)	323.7 (± 8.9)	
MCHC (g/L) - 4 weeks (Visit 6)	325.8 (± 7.4)	316.9 (± 9.1)	319.8 (± 7.1)	
MCV (fL) - Baseline (Visit 2)	92.8 (± 2.8)	94.0 (± 3.0)	94.0 (± 4.4)	
MCV (fL) - 4 weeks (Visit 6)	93.2 (± 3.9)	94.8 (± 3.1)	96.4 (± 4.3)	
Monocytes (10 ⁹) - Baseline (Visit 2)	0.4 (± 0.2)	0.5 (± 0.2)	0.4 (± 0.1)	
Monocytes (10 ⁹) - 4 weeks (Visit 6)	0.4 (± 0.1)	0.4 (± 0.1)	0.4 (± 0.1)	
Neutrophils (10 ⁹ /L) - Baseline (Visit 2)	3.1 (± 0.9)	3.1 (± 0.8)	3.0 (± 0.9)	
Neutrophils (10 ⁹ /L) - 4 weeks (Visit 6)	3.4 (± 1.3)	3.2 (± 0.8)	3.5 (± 2.3)	
Platelet count (10 ⁹ /L) - Baseline (Visit 2)	235.0 (± 44.3)	228.8 (± 43.1)	252.7 (± 67.5)	
Platelet count (10 ⁹ /L) - 4 weeks (Visit 6)	241.9 (± 39.3)	230.0 (± 45.8)	260.0 (± 69.7)	
Erythrocytes (10 ¹² /L) - Baseline (Visit 2)	4.9 (± 0.3)	5.1 (± 0.5)	4.9 (± 0.4)	
Erythrocytes (10 ¹² /L) - 4 weeks (Visit 6)	4.9 (± 0.4)	4.9 (± 0.5)	4.8 (± 0.5)	
White blood cells (10 ⁹ /L) - Baseline (Visit 2)	5.6 (± 0.9)	6.0 (± 1.4)	5.5 (± 1.1)	

White blood cells (10 ⁹ /L) - 4 weeks (Visit 6)	6.0 (± 1.7)	5.8 (± 1.1)	5.8 (± 2.2)	
--	-------------	-------------	-------------	--

Statistical analyses

No statistical analyses for this end point

Primary: Lipid panel

End point title	Lipid panel ^[12]
-----------------	-----------------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: unit(s)				
arithmetic mean (standard deviation)				
Total cholesterol (mmol/mol) - Baseline (Visit 2)	5.6 (± 0.9)	5.4 (± 0.9)	5.5 (± 1.0)	
Total cholesterol (mmol/mol) - 4 weeks (Visit 6)	5.4 (± 1.1)	4.8 (± 0.7)	5.1 (± 0.9)	
HDL cholesterol (mmol/mol) - Baseline (Visit 2)	1.5 (± 0.4)	1.4 (± 0.4)	1.5 (± 0.4)	
HDL cholesterol (mmol/mol) - 4 weeks (Visit 6)	1.5 (± 0.3)	1.3 (± 0.4)	1.4 (± 0.4)	
LDL cholesterol (mmol/mol) - Baseline (Visit 2)	3.8 (± 0.9)	3.6 (± 0.9)	3.8 (± 0.8)	
LDL cholesterol (mmol/mol) - 4 weeks (Visit 6)	3.7 (± 1.2)	3.2 (± 0.8)	3.5 (± 0.7)	
Triglycerides (mmol/mol) - Baseline (Visit 2)	1.4 (± 0.4)	1.5 (± 0.5)	1.3 (± 0.5)	
Triglycerides (mmol/mol) - 4 weeks (Visit 6)	1.3 (± 0.5)	1.3 (± 0.5)	1.1 (± 0.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Glycemic variables

End point title	Glycemic variables ^[13]
-----------------	------------------------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: unit(s)				
arithmetic mean (standard deviation)				
P-glucose (mmol) - Baseline (Visit 2)	6.2 (± 0.9)	5.8 (± 1.0)	5.8 (± 1.1)	
P-glucose (mmol) - 4 weeks (Visit 6)	5.9 (± 0.8)	5.7 (± 1.1)	5.6 (± 0.9)	
HbA1c (mmol/mol) - Baseline (Visit 2)	36.0 (± 3.4)	36.3 (± 3.6)	35.9 (± 4.5)	
HbA1c (mmol/mol) - 4 weeks (Visit 6)	36.0 (± 4.7)	35.6 (± 3.8)	35.4 (± 4.7)	
Insulin (mIE/L) - Baseline (Visit 2)	16.1 (± 18.2)	16.4 (± 16.4)	12.0 (± 6.7)	
Insulin (mIE/L) - 4 weeks (Visit 6)	14.3 (± 10.0)	20.6 (± 25.5)	11.3 (± 8.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Venous blood gas

End point title	Venous blood gas ^[14]
-----------------	----------------------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary goal of this study was exploratory safety and tolerability, and therefore only exploratory statistics were applied.

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: unit(s)				
arithmetic mean (standard deviation)				
Base excess (mmol/L) - Baseline (Visit 2)	1.4 (± 1.5)	0.9 (± 3.1)	2.2 (± 1.7)	
Base excess (mmol/L) - 4 weeks (Visit 6)	1.4 (± 1.5)	-1.1 (± 1.7)	-1.3 (± 1.4)	
Bicarbonate (mmol/L) - Baseline (Visit 2)	26.0 (± 1.9)	25.4 (± 3.4)	26.9 (± 1.8)	

Bicarbonate (mmol/L) - 4 weeks (Visit 6)	26.0 (± 1.8)	23.5 (± 1.9)	23.6 (± 1.6)	
pH (unitless) - Baseline (Visit 2)	7.4 (± 0.0)	7.4 (± 0.0)	7.4 (± 0.0)	
pH (unitless) - 4 weeks (Visit 6)	7.4 (± 0.0)	7.4 (± 0.0)	7.4 (± 0.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apnea hypopnea index (AHI)

End point title	Apnea hypopnea index (AHI)
-----------------	----------------------------

End point description:

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

End point timeframe:

At baseline (Visit 2) and 4 weeks (Visit 6).

End point values	Placebo	200 mg STM	400 mg STM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	12	34	
Units: events/hour				
arithmetic mean (standard deviation)				
Baseline (Visit 2)	53.92 (± 21.11)	61.15 (± 24.21)	55.25 (± 22.26)	
4 weeks (Visit 6)	50.90 (± 24.21)	40.71 (± 24.06)	33.11 (± 16.44)	

Statistical analyses

Statistical analysis title	Estimated difference between 200mg STM and placebo
----------------------------	--

Statistical analysis description:

Change from baseline in apnea/hypopnea index analysed by ANCOVA for difference between 200 mg STM and placebo.

Comparison groups	Placebo v 200 mg STM
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.3
upper limit	-7.7

Notes:

[15] - Analysis performed on all randomized patients with post-baseline assessment, including 12 patients in the 200mg STM group and 22 patients in the placebo group.

Statistical analysis title	Estimated difference between 400mg STM and placebo
-----------------------------------	--

Statistical analysis description:

Change from baseline in apnea/hypopnea index analysed by ANCOVA for difference between 400 mg STM and placebo.

Comparison groups	400 mg STM v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-18.9

Confidence interval

level	95 %
sides	2-sided
lower limit	-25.6
upper limit	-12.1

Notes:

[16] - Analysis performed on all randomized patients with post-baseline assessment, including 25 patients in the 400mg STM group and 22 patients in the placebo group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment.

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

Dictionary used

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

Dictionary version	20.0
--------------------	------

Reporting groups

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

Reporting group description: -

Reporting group title	200 mg STM
-----------------------	------------

Reporting group description: -

Reporting group title	400 mg STM
-----------------------	------------

Reporting group description: -

Serious adverse events	Placebo	200 mg STM	400 mg STM
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 12 (0.00%)	1 / 34 (2.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	200 mg STM	400 mg STM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 22 (59.09%)	11 / 12 (91.67%)	30 / 34 (88.24%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Muscle rupture			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 12 (8.33%) 1	0 / 34 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 12 (8.33%) 1	1 / 34 (2.94%) 1
Nervous system disorders Balance disorder subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 12 (8.33%) 1	0 / 34 (0.00%) 0
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 12 (8.33%) 1	0 / 34 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 12 (8.33%) 1	2 / 34 (5.88%) 2
Dysgeusia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 12 (8.33%) 1	1 / 34 (2.94%) 1
Headache subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	3 / 12 (25.00%) 3	11 / 34 (32.35%) 14
Migraine subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 6	8 / 12 (66.67%) 10	27 / 34 (79.41%) 32
Poor quality sleep			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
General disorders and administration site conditions			
Chest discomfort subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	2 / 12 (16.67%) 2	5 / 34 (14.71%) 5
Pyrexia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 12 (8.33%) 1	1 / 34 (2.94%) 1
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 12 (0.00%) 0	2 / 34 (5.88%) 2
Nausea subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 12 (0.00%) 0	4 / 34 (11.76%) 4
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 12 (0.00%) 0	3 / 34 (8.82%) 3
Respiratory, thoracic and mediastinal disorders			
Asthma subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0

Cough subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	4 / 34 (11.76%) 4
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 12 (0.00%) 0	3 / 34 (8.82%) 3
Dyspnoea subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 12 (0.00%) 0	7 / 34 (20.59%) 7
Epistaxis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 4	0 / 12 (0.00%) 0	1 / 34 (2.94%) 1
Back pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Muscle rigidity subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 12 (0.00%) 0	0 / 34 (0.00%) 0
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	1 / 12 (8.33%) 1	3 / 34 (8.82%) 3

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	1	2

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