



## Clinical trial results:

### Efficacy, Safety and Tolerability of 3 doses of Sulthiame in Patients with Obstructive Sleep Apnea. A Randomized, Double-Blind, Placebo Controlled, Dose-Ranging Study

#### Summary

EudraCT number	2021-002926-26
Trial protocol	BE ES CZ FR DE
Global end of trial date	08 August 2023

#### Results information

Result version number	v1 (current)
This version publication date	21 September 2024
First version publication date	21 September 2024

#### Trial information

##### Trial identification

Sponsor protocol code	STM-042/K
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05236842
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	Dr. Corinna Hansen, Desitin Arzneimittel GmbH, +49 4059101-234, hansen@desitin.de
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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	08 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of three different doses of Sulthiame (STM) compared to placebo on sleep apnea activity in adult subjects with moderate to severe OSA after at least 12 weeks of treatment at target dose.

Protection of trial subjects:

This study was conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, in compliance with ICH GCP guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2021
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	Spain: 65
Country: Number of subjects enrolled	Belgium: 64
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 155
Worldwide total number of subjects	298
EEA total number of subjects	298

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)	224
From 65 to 84 years	74
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 28 sites in Belgium, Czech Republic, France, Germany, and Spain.

### Pre-assignment

Screening details:

A total of 535 subjects were enrolled, of which 237 subjects were screening failures, and 298 subjects were randomized and treated with study drug.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Subjects received STM matched placebo, tablets, orally, once daily within 1 hour prior to bedtime for 15 weeks.

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

Dosage and administration details:

Placebo was administered orally as tablets once daily within 1 hour prior to bedtime until Week 15.

<b>Arm title</b>	STM 100 mg
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Arm description:

Subjects received STM 50 milligrams (mg) (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Weeks 2 and 3 and continued taking 100 mg as a target dose until Week 15.

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

Dosage and administration details:

STM was administered orally as tablets once daily within 1 hour prior to bedtime until Week 15.

<b>Arm title</b>	STM 200 mg
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Arm description:

Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking 200 mg as a target dose until Week 15.

Arm type	Experimental
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Investigational medicinal product name	STM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
STM was administered orally as tablets once daily within 1 hour prior to bedtime until Week 15.	
<b>Arm title</b>	STM 300 mg

Arm description:

Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking STM 300 mg as a target dose until Week 15.

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

Dosage and administration details:

STM was administered orally as tablets once daily within 1 hour prior to bedtime until Week 15.

<b>Number of subjects in period 1</b>	Placebo	STM 100 mg	STM 200 mg
Started	75	74	74
Completed	71	70	64
Not completed	4	4	10
Consent withdrawn by subject	3	2	1
Adverse event, non-fatal	-	1	6
Other	1	1	2
Lost to follow-up	-	-	1

<b>Number of subjects in period 1</b>	STM 300 mg
Started	75
Completed	67
Not completed	8
Consent withdrawn by subject	2
Adverse event, non-fatal	4
Other	1
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received STM matched placebo, tablets, orally, once daily within 1 hour prior to bedtime for 15 weeks.	
Reporting group title	STM 100 mg
Reporting group description:	
Subjects received STM 50 milligrams (mg) (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Weeks 2 and 3 and continued taking 100 mg as a target dose until Week 15.	
Reporting group title	STM 200 mg
Reporting group description:	
Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking 200 mg as a target dose until Week 15.	
Reporting group title	STM 300 mg
Reporting group description:	
Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking STM 300 mg as a target dose until Week 15.	

Reporting group values	Placebo	STM 100 mg	STM 200 mg
Number of subjects	75	74	74
Age categorical			
Units: Subjects			
Adults (18-64 years)	63	53	56
From 65-84 years	12	21	18
Age continuous			
Units: years			
arithmetic mean	56.0	56.9	54.8
standard deviation	± 8.8	± 11.3	± 11.6
Gender categorical			
Units: Subjects			
Female	23	18	19
Male	52	56	55
Race			
Units: Subjects			
White	14	15	20
Missing	60	59	53
Other	1	0	1
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	71	67	61
Hispanic or Latino	2	3	7
Missing	2	4	6

Reporting group values	STM 300 mg	Total	
Number of subjects	75	298	

Age categorical			
Units: Subjects			
Adults (18-64 years)	52	224	
From 65-84 years	23	74	
Age continuous			
Units: years			
arithmetic mean	56.5		
standard deviation	± 10.4	-	
Gender categorical			
Units: Subjects			
Female	18	78	
Male	57	220	
Race			
Units: Subjects			
White	16	65	
Missing	59	231	
Other	0	2	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	72	271	
Hispanic or Latino	3	15	
Missing	0	12	

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received STM matched placebo, tablets, orally, once daily within 1 hour prior to bedtime for 15 weeks.	
Reporting group title	STM 100 mg
Reporting group description: Subjects received STM 50 milligrams (mg) (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Weeks 2 and 3 and continued taking 100 mg as a target dose until Week 15.	
Reporting group title	STM 200 mg
Reporting group description: Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking 200 mg as a target dose until Week 15.	
Reporting group title	STM 300 mg
Reporting group description: Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking STM 300 mg as a target dose until Week 15.	

### Primary: Relative Change From Baseline in Percentage of Score of Apnea-Hypopnea Index (AHI) at Week 15 as Measured by Polysomnography (PSG)

End point title	Relative Change From Baseline in Percentage of Score of Apnea-Hypopnea Index (AHI) at Week 15 as Measured by Polysomnography (PSG)
End point description: AHI was the number of apneas or hypopneas per hour of sleep. AHI severity was classified as follows: none/minimal: less than (<) 5.0, mild: 5.0 to <15.0, moderate: 15.0 to <31.0, severe: greater than or equal to (>=) 31.0. AHI scores are events (apneas or hypopneas) per hour. PSG is a assessment of sleep. The PSG measures the physiological process of sleep by monitoring body functions including brain waves, eye movements, muscle activity or skeletal muscle activation, heart rhythm, blood oxygen saturation, and breathing functions. Scoring of the AHI was conducted in accordance with the American Academy of Sleep Medicine (AASM) version 2.6 with a definition of AHI of 3% including arousals. Relative change was calculated as 100*absolute change/baseline value. The FAS consisted of all randomized subjects.	
End point type	Primary
End point timeframe: Baseline and at Week 15	

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of score				
least squares mean (standard error)				
Primary estimand	3.1 (± 5.3)	-13.2 (± 5.5)	-27.1 (± 5.9)	-31.4 (± 5.4)
Secondary estimand	5.0 (± 6.0)	-12.8 (± 5.7)	-29.8 (± 6.0)	-34.9 (± 5.8)



## Statistical analyses

<b>Statistical analysis title</b>	Primary estimand: STM 100 mg versus Placebo
Statistical analysis description:	
Least square means (LSM) differences, standard error (SE), and 95% confidence intervals (CIs) as well as the p-values were obtained from an analysis of covariance (ANCOVA) with relative change from baseline in AHI as dependent variable, randomized treatment group (STM group versus placebo, reference placebo) as independent variable, and the baseline AHI score as covariate, where baseline AHI was defined as the mean of the 2 baseline PSG assessments.	
Comparison groups	Placebo v STM 100 mg
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.0319
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-16.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.3
upper limit	-1.4
Variability estimate	Standard error of the mean
Dispersion value	7.6

Notes:

[1] - Primary estimand followed a treatment policy approach for intercurrent events (ICEs) related to the discontinuation of study drug (where prohibited medication was not received), treatment non-compliance, emergency unblinding, and a hypothetical strategy for death and ICEs related to the receipt of prohibited medication. For primary estimand, any monotone missing data or data considered missing due to hypothetical handling of an ICE were imputed based on the set of all subjects in placebo arm.

<b>Statistical analysis title</b>	Primary estimand: STM 200 mg versus Placebo
Statistical analysis description:	
LSM differences, SE, and 95% CIs as well as the p-values were obtained from an ANCOVA with relative change from baseline in AHI as dependent variable, randomized treatment group (STM group versus placebo, reference placebo) as independent variable, and the baseline AHI score as covariate, where baseline AHI was defined as the mean of the 2 baseline PSG assessments.	
Comparison groups	STM 200 mg v Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-30.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.4
upper limit	-15.1
Variability estimate	Standard error of the mean
Dispersion value	7.7

Notes:

[2] - Primary estimand followed a treatment policy approach for intercurrent events (ICEs) related to the discontinuation of study drug (where prohibited medication was not received), treatment non-compliance, emergency unblinding, and a hypothetical strategy for death and ICEs related to the receipt of prohibited medication. For primary estimand, any monotone missing data or data considered missing due to hypothetical handling of an ICE were imputed based on the set of all subjects in placebo arm.

<b>Statistical analysis title</b>	Primary estimand: STM 300 mg versus Placebo
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Statistical analysis description:

LSM differences, SE, and 95% CIs as well as the p-values were obtained from an ANCOVA with relative change from baseline in AHI as dependent variable, randomized treatment group (STM group versus placebo, reference placebo) as independent variable, and the baseline AHI score as covariate, where baseline AHI was defined as the mean of the 2 baseline PSG assessments.

Comparison groups	Placebo v STM 300 mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-34.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.1
upper limit	-20
Variability estimate	Standard error of the mean
Dispersion value	7.4

Notes:

[3] - Primary estimand followed a treatment policy approach for intercurrent events (ICEs) related to the discontinuation of study drug (where prohibited medication was not received), treatment non-compliance, emergency unblinding, and a hypothetical strategy for death and ICEs related to the receipt of prohibited medication. For primary estimand, any monotone missing data or data considered missing due to hypothetical handling of an ICE were imputed based on the set of all subjects in placebo arm.

<b>Statistical analysis title</b>	Secondary estimand: STM 100 mg versus Placebo
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Statistical analysis description:

Least square means (LSM) differences, standard error (SE), and 95% confidence intervals (CIs) as well as the p-values were obtained from an analysis of covariance (ANCOVA) with relative change from baseline in AHI as dependent variable, randomized treatment group (STM group versus placebo, reference placebo) as independent variable, and the baseline AHI score as covariate, where baseline AHI was defined as the mean of the 2 baseline PSG assessments.

Comparison groups	Placebo v STM 100 mg
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Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	= 0.0317
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.1
upper limit	-1.6
Variability estimate	Standard error of the mean
Dispersion value	8.3

Notes:

[4] - The secondary estimand applied a hypothetical strategy approach for all ICEs. Missing data were multiple imputed. For the secondary estimand, any monotone missing data or data considered missing due to an ICE were imputed based on the set of all subjects data from the randomized treatment group.

<b>Statistical analysis title</b>	Secondary estimand: STM 200 mg versus Placebo
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Statistical analysis description:

LSM differences, SE, and 95% CIs as well as the p-values were obtained from an ANCOVA with relative change from baseline in AHI as dependent variable, randomized treatment group (STM group versus placebo, reference placebo) as independent variable, and the baseline AHI score as covariate, where baseline AHI was defined as the mean of the 2 baseline PSG assessments.

Comparison groups	STM 200 mg v Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-34.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.8
upper limit	-17.8
Variability estimate	Standard error of the mean
Dispersion value	8.7

Notes:

[5] - The secondary estimand applied a hypothetical strategy approach for all ICEs. Missing data were multiple imputed. For the secondary estimand, any monotone missing data or data considered missing due to an ICE were imputed based on the set of all subjects data from the randomized treatment group.

<b>Statistical analysis title</b>	Secondary estimand: STM 300 mg versus Placebo
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Statistical analysis description:

LSM differences, SE, and 95% CIs as well as the p-values were obtained from an ANCOVA with relative change from baseline in AHI as dependent variable, randomized treatment group (STM group versus placebo, reference placebo) as independent variable, and the baseline AHI score as covariate, where baseline AHI was defined as the mean of the 2 baseline PSG assessments.

Comparison groups	Placebo v STM 300 mg
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Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-39.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56
upper limit	-23.9
Variability estimate	Standard error of the mean
Dispersion value	8.2

Notes:

[6] - The secondary estimand applied a hypothetical strategy approach for all ICEs. Missing data were multiple imputed. For the secondary estimand, any monotone missing data or data considered missing due to an ICE were imputed based on the set of all subjects data from the randomized treatment group.

### Secondary: Relative Change From Baseline in Percentage of Score of AHI at Week 4 as Measured by PSG

End point title	Relative Change From Baseline in Percentage of Score of AHI at Week 4 as Measured by PSG
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End point description:

AHI was the number of apneas or hypopneas per hour of sleep. AHI severity was classified as follows: none/minimal: <5.0, mild: 5.0 to <15.0, moderate: 15.0 to <31.0, severe: ≥31.0. AHI scores are events (apneas or hypopneas) per hour. PSG is a assessment of sleep. The PSG measures the physiological process of sleep by monitoring body functions including brain waves, eye movements, muscle activity or skeletal muscle activation, heart rhythm, blood oxygen saturation, and breathing functions. Scoring of the AHI was conducted in accordance with the American Academy of Sleep Medicine (AASM) version 2.6 with a definition of AHI of 3% including arousals. Relative change was calculated as 100\*absolute change/baseline value. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Week 4

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of score				
least squares mean (standard error)	4.1 (± 5.0)	-9.0 (± 5.3)	-36.1 (± 5.3)	-43.3 (± 4.9)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Change From Baseline in AHI at Weeks 4 and 15 as Measured by PSG

End point title	Absolute Change From Baseline in AHI at Weeks 4 and 15 as Measured by PSG
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End point description:

AHI was the number of apneas or hypopneas per hour of sleep. AHI severity was classified as follows: none/minimal: <5.0, mild: 5.0 to <15.0, moderate: 15.0 to <31.0, severe: ≥31.0. PSG is a assessment of sleep. The PSG measures the physiological process of sleep by monitoring body functions including brain waves, eye movements, muscle activity or skeletal muscle activation, heart rhythm, blood oxygen saturation, and breathing functions. Scoring of the AHI was conducted in accordance with the American Academy of Sleep Medicine (AASM) version 2.6 with a definition of AHI of 3% including arousals. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: event/hour				
least squares mean (standard error)				
Change at Week 4	1.3549 (± 1.3599)	-2.9822 (± 1.4159)	-10.5746 (± 1.3932)	-12.5846 (± 1.3334)
Change at Week 15	1.0526 (± 1.5157)	-3.7406 (± 1.5607)	-8.1983 (± 1.6038)	-9.3395 (± 1.5491)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Achieving ≥ 50% Reduction From Baseline in AHI and Achieving AHI < 15 at Weeks 4 and 15

End point title	Percentage of Subjects Achieving ≥ 50% Reduction From Baseline in AHI and Achieving AHI < 15 at Weeks 4 and 15
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End point description:

AHI was the number of apneas or hypopneas per hour of sleep. AHI severity was classified as follows: none/minimal: <5.0, mild: 5.0 to <15.0, moderate: 15.0 to <31.0, severe: ≥31.0. Scoring of the AHI was conducted in accordance with the American Academy of Sleep Medicine (AASM) version 2.6 with a definition of AHI of 3% including arousals. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of subjects				
number (not applicable)				
≥ 50% reduction from Baseline in AHI at Week 4	12.0	16.2	36.5	50.7

>= 50% reduction from Baseline in AHI at Week 15	9.3	23.0	32.4	33.3
AHI <15 at Week 4	17.3	23.0	47.3	54.7
AHI <15 at Week 15	18.7	29.7	39.2	46.7

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects who Transitioned to a Lower AHI Severity Class From Baseline at Week 4 and 15

End point title	Percentage of Subjects who Transitioned to a Lower AHI Severity Class From Baseline at Week 4 and 15
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End point description:

AHI was the number of apneas or hypopneas per hour of sleep. AHI severity was classified as follows: none/minimal: <5.0, mild: 5.0 to <15.0, moderate: 15.0 to <31.0, severe: >=31.0. A transition in a lower AHI severity class was defined as None/Minimal (AHI <5.0), Mild (AHI 5.0 to <15.0) or Moderate (AHI 15.0 to <31.0) (for Severe AHI at Baseline) at Weeks 4 or 15, respectively. Scoring of the AHI was conducted in accordance with the American Academy of Sleep Medicine (AASM) version 2.6 with a definition of AHI of 3% including arousals. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline to Week 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of subjects				
number (not applicable)				
Week 4	26.7	37.8	67.6	76.0
Week 15	34.7	36.5	56.8	61.3

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Oxygen Desaturation Index (ODI) 3 Percentage (%) and 4% at Weeks 4 and 15

End point title	Change From Baseline in Oxygen Desaturation Index (ODI) 3 Percentage (%) and 4% at Weeks 4 and 15
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End point description:

ODI 3% was the number of times per hour where the oxygen saturation falls by at least 3% from baseline and ODI 4% was the number of times per hour during time in bed where the oxygen saturation falls by at least 4% from baseline. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: events per hour				
least squares mean (standard error)				
Change in ODI 3% at Week 4	1.2446 (± 1.0278)	-1.6424 (± 1.0487)	-7.9822 (± 1.0507)	-8.7869 (± 1.0009)
Change in ODI 3% at Week 15	0.2052 (± 1.1232)	-1.9362 (± 1.1405)	-5.3416 (± 1.1951)	-6.2627 (± 1.1372)
Change in ODI 4% at Week 4	1.3730 (± 0.8322)	-0.7597 (± 0.8486)	-5.3371 (± 0.8505)	-5.5038 (± 0.8103)
Change in ODI 4% at Week 15	0.5858 (± 0.9316)	-0.7579 (± 0.9458)	-2.9943 (± 0.9906)	-3.5966 (± 0.9427)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Overnight Oxygen Saturation (SaO2) at Weeks 4 and 15

End point title	Change From Baseline in Mean Overnight Oxygen Saturation (SaO2) at Weeks 4 and 15
End point description: Change from baseline mean SaO2 during time in bed was reported. The FAS consisted of all randomized subjects.	
End point type	Secondary
End point timeframe: Baseline and at Weeks 4 and 15	

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of oxygen saturation				
least squares mean (standard error)				
Change in Mean Overnight SaO2 at Week 4	0.0967 (± 0.2040)	0.5069 (± 0.2086)	1.1477 (± 0.2087)	1.1106 (± 0.1983)
Change in Mean Overnight SaO2 at Week 15	0.0737 (± 0.1282)	0.3520 (± 0.1303)	1.0190 (± 0.1382)	0.9467 (± 0.1312)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Minimum Overnight SaO2 at Week 4 and 15

End point title	Change From Baseline in Minimum Overnight SaO2 at Week 4 and 15
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End point description:

Change from baseline minimum SaO2 during time in bed was reported. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of oxygen saturation				
least squares mean (standard error)				
Change in Minimum Overnight SaO2 at Week 4	0.7067 (± 0.5759)	-0.6282 (± 0.5877)	0.2362 (± 0.5886)	0.2613 (± 0.5595)
Change in Minimum Overnight SaO2 at Week 15	1.5396 (± 0.5569)	-0.3602 (± 0.5650)	0.3908 (± 0.5972)	-0.1846 (± 0.5671)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Percentage of Total Sleep Time (TST) With SaO2 <90% on PSG Night at Week 4 and 15

End point title	Change From Baseline in Percentage of Total Sleep Time (TST) With SaO2 <90% on PSG Night at Week 4 and 15
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End point description:

TST was defined as the total time asleep using PSG. PSG is a assessment of sleep. The PSG measures the physiological process of sleep by monitoring body functions including brain waves, eye movements, muscle activity or skeletal muscle activation, heart rhythm, blood oxygen saturation, and breathing functions. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of TST				
median (inter-quartile range (Q1-Q3))				



Change in SaO2<90% at Week 4 (n=72,69,68,72)	-0.200 (-2.310 to 1.440)	-0.260 (-2.620 to 0.640)	-0.970 (-2.535 to -0.065)	-0.510 (-3.845 to 0.000)
Change in SaO2<90% at Week 15 (n=68,67,59,61)	-0.295 (-2.580 to 1.110)	-0.420 (-3.100 to 0.280)	-0.480 (-3.090 to 0.040)	-0.300 (-3.130 to 0.470)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Percentage of Stage Non-rapid Eye Movement (NREM) 1 (N1), NREM Stage 2 (N2), and NREM Stage 3 (N3) Sleeps, Rapid Eye Movement (REM) Sleep Time at Week 4 and 15

End point title	Change From Baseline in Percentage of Stage Non-rapid Eye Movement (NREM) 1 (N1), NREM Stage 2 (N2), and NREM Stage 3 (N3) Sleeps, Rapid Eye Movement (REM) Sleep Time at Week 4 and 15
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End point description:

The change from baseline in percentage of sleep time of NREM sleep stages N1 (light sleep), N2 (also fairly light, with sudden increases in brain wave frequency known as sleep spindles), N3 (slow wave or deep sleep) and REM sleep was reported. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of sleep time				
least squares mean (standard error)				
Change in Percentage of N1 Sleep at Week 4	0.2126 (± 0.6174)	-0.1827 (± 0.6337)	-0.1886 (± 0.6333)	-2.0885 (± 0.6014)
Change in Percentage of N1 Sleep at Week 15	0.4373 (± 0.6748)	0.3042 (± 0.6878)	-0.5791 (± 0.7231)	-1.2720 (± 0.6864)
Change in Percentage of N2 Sleep at Week 4	2.4328 (± 0.8665)	4.3508 (± 0.8885)	5.1058 (± 0.8860)	6.7771 (± 0.8430)
Change in Percentage of N2 Sleep at Week 15	3.0319 (± 0.9403)	1.0809 (± 0.9577)	5.8111 (± 1.0067)	5.3470 (± 0.9572)
Change in Percentage of N3 Sleep at Week 4	-1.2726 (± 0.7378)	-2.2645 (± 0.7564)	-1.1551 (± 0.7550)	-0.5577 (± 0.7195)
Change in Percentage of N3 Sleep at Week 15	-2.2449 (± 0.7980)	-0.5508 (± 0.8134)	-2.5343 (± 0.8522)	-0.3423 (± 0.8118)
Change in Percentage of REM Sleep at Week 4	-1.2591 (± 0.6097)	-1.9773 (± 0.6271)	-3.6887 (± 0.6232)	-4.1920 (± 0.5912)
Change in Percentage of REM Sleep at Week 15	-1.0971 (± 0.6424)	-0.9321 (± 0.6556)	-2.6377 (± 0.6898)	-3.7777 (± 0.6544)

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Change From Baseline in Other Sleep Quality Parameter: Total Arousal Index During TST Based on PSG at Weeks 4 and 15**

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End point title	Change From Baseline in Other Sleep Quality Parameter: Total Arousal Index During TST Based on PSG at Weeks 4 and 15
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End point description:

The arousal index indicates the number of arousals from sleep per hour which last at least 3 seconds. TST was defined as the total time asleep using PSG. PSG is a assessment of sleep. The PSG measures the physiological process of sleep by monitoring body functions including brain waves, eye movements, muscle activity or skeletal muscle activation, heart rhythm, blood oxygen saturation, and breathing functions. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

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End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: events per hour				
least squares mean (standard error)				
Change at Week 4	1.1559 (± 0.9549)	-1.2494 (± 0.9773)	-4.5463 (± 0.9769)	-5.9754 (± 0.9288)
Change at Week 15	0.8981 (± 1.0447)	-2.2124 (± 1.0626)	-4.8210 (± 1.1191)	-5.8134 (± 1.0629)

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change From Baseline in Other Sleep Quality Parameter: Sleep efficiency Based on PSG at Weeks 4 and 15**

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End point title	Change From Baseline in Other Sleep Quality Parameter: Sleep efficiency Based on PSG at Weeks 4 and 15
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End point description:

Sleep efficiency refers to the percentage of time a subject sleeps, in relation to the amount of time the subject spends in bed. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

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End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of time in bed sleeping				
least squares mean (standard error)				
Change at Week 4	-1.6357 ( $\pm$ 1.1796)	0.3630 ( $\pm$ 1.2034)	-0.0241 ( $\pm$ 1.2046)	-1.1997 ( $\pm$ 1.1457)
Change at Week 15	-2.0994 ( $\pm$ 1.1010)	0.6276 ( $\pm$ 1.1177)	2.3200 ( $\pm$ 1.1750)	-0.0647 ( $\pm$ 1.1169)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Other Sleep Quality Parameter: Total Sleep Time (TST) Based on PSG at Weeks 4 and 15

End point title	Change From Baseline in Other Sleep Quality Parameter: Total Sleep Time (TST) Based on PSG at Weeks 4 and 15
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End point description:

TST was defined as the total time asleep (in minutes) using PSG. PSG is a assessment of sleep. The PSG measures the physiological process of sleep by monitoring body functions including brain waves, eye movements, muscle activity or skeletal muscle activation, heart rhythm, blood oxygen saturation, and breathing functions. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: minutes				
least squares mean (standard error)				
Change at Week 4	-6.8285 ( $\pm$ 5.6058)	2.5871 ( $\pm$ 5.7197)	-3.0824 ( $\pm$ 5.7250)	-6.0265 ( $\pm$ 5.4433)
Change at Week 15	-9.4841 ( $\pm$ 5.3791)	2.8998 ( $\pm$ 5.4617)	12.4267 ( $\pm$ 5.7446)	-0.6546 ( $\pm$ 5.4597)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Score of Patient Global Impression Scale Rating Severity (PGI-S) Score at Weeks 4, 8 and 15

End point title	Change From Baseline in Mean Score of Patient Global Impression Scale Rating Severity (PGI-S) Score at Weeks 4, 8 and 15
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End point description:

PGI-S was self-administered questionnaire employed a 4-point scale ranging from 1 to 4, where 1=normal, 2=mild, 3=moderate, 4=severe. The higher score indicates severe outcomes. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4, 8 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: score on a scale				
least squares mean (standard error)				
Change at Week 4	-0.1941 (± 0.0861)	-0.1040 (± 0.0861)	-0.3288 (± 0.0881)	-0.1445 (± 0.0831)
Change at Week 8	-0.3336 (± 0.0906)	-0.2439 (± 0.0906)	-0.3620 (± 0.0929)	-0.1991 (± 0.0885)
Change at Week 15	-0.3731 (± 0.0954)	-0.1210 (± 0.0954)	-0.5385 (± 0.0997)	-0.1159 (± 0.0943)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Score of Clinical Global Impression Scale Rating Severity (CGI-S) Score at Weeks 4, 8 and 15

End point title	Change From Baseline in Mean Score of Clinical Global Impression Scale Rating Severity (CGI-S) Score at Weeks 4, 8 and 15
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End point description:

CGI-S questionnaire was completed by the investigator, employed a 7-point scale to assess the severity of the subject's condition, ranging from 1 to 7, where 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill. The higher score indicates severe outcomes. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4, 8 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: score on a scale				
least squares mean (standard error)				
Change at Week 4	-0.2319 (± 0.0813)	-0.1376 (± 0.0819)	-0.3096 (± 0.0826)	-0.1924 (± 0.0794)
Change at Week 8	-0.3838 (± 0.0969)	-0.2842 (± 0.0977)	-0.3617 (± 0.0993)	-0.3994 (± 0.0958)

Change at Week 15	-0.4786 ( $\pm$ 0.1021)	-0.2242 ( $\pm$ 0.1029)	-0.4837 ( $\pm$ 0.1071)	-0.3427 ( $\pm$ 0.1019)
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## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Reported as Improved (Scores 1 to 2) on Patient Global Impression Scale Rating Improvement (PGI-I) at Weeks 4, 8 and 15

End point title	Percentage of Subjects Reported as Improved (Scores 1 to 2) on Patient Global Impression Scale Rating Improvement (PGI-I) at Weeks 4, 8 and 15
End point description: The PGI-I was a self-administered questionnaire, and improvement was rated using the PGI-I. PGI-I employed a 7-point scale, where the scale ranged from 1 to 7, where 1= very much better, 2= much better, 3= a little better, 4= no change, 5= a little worse, 6= much worse, 7= very much worse. The higher score indicates severe outcomes. The FAS consisted of all randomized subjects.	
End point type	Secondary
End point timeframe: At Weeks 4, 8 and 15	

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of subjects				
number (not applicable)				
Improved (Scores 1 or 2) at Week 4	10.7	9.5	14.9	13.3
Improved (Scores 1 or 2) at Week 8	12.0	13.5	16.2	17.3
Improved (Scores 1 or 2) at Week 15	20.0	17.6	23.0	18.7

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Reported as Improved (Scores 1 to 2) on Clinical Global Impression Scale Rating Improvement (CGI-I) at Weeks 4, 8 and 15

End point title	Percentage of Subjects Reported as Improved (Scores 1 to 2) on Clinical Global Impression Scale Rating Improvement (CGI-I) at Weeks 4, 8 and 15
End point description: The CGI-I was a investigator administered questionnaire, and improvement was rated using the CGI-I scale. CGI-I employed a 7-point scale, where the scale ranged from 1 to 7, where 1= very much improved, 2=much improved, 3=minimally improved, 4= no change, 5=minimally worse, 6= much worse, 7= very much worse due to treatment. The higher score indicates severe outcomes. The FAS consisted of all randomized subjects.	
End point type	Secondary

End point timeframe:

At Weeks 4, 8 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: percentage of subjects				
number (not applicable)				
Improved (Scores 1 or 2) at Week 4	5.3	6.8	9.5	17.3
Improved (Scores 1 or 2) at Week 8	10.7	10.8	20.3	16.0
Improved (Scores 1 or 2) at Week 15	17.3	12.2	21.6	20.0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Total Score of Epworth Sleepiness Scale (ESS) at Weeks 4, 8 and 15

End point title	Change From Baseline in Mean Total Score of Epworth Sleepiness Scale (ESS) at Weeks 4, 8 and 15
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End point description:

The ESS was a self-administered questionnaire that employed a total score ranging from 0 to 24, where higher score indicated severe excessive daytime sleepiness. ESS values greater than or equal to ( $\geq$ ) 11 indicate excessive daytime sleepiness and are considered pathological. The FAS consisted of all randomized subjects. Here, "overall number of participants analyzed" signifies participants who were evaluable for this outcome measure and "number analyzed" signifies those participants who were evaluable for the specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4, 8 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: score on a scale				
least squares mean (standard error)				
ESS-Total Score, Change at Week 4 (n=75,74,74,75)	-0.8120 ( $\pm$ 0.3640)	-1.2412 ( $\pm$ 0.3666)	-1.4683 ( $\pm$ 0.3693)	-0.6610 ( $\pm$ 0.3538)
ESS-Total Score, Change at Week 8 (n=75,74,74,75)	-1.1895 ( $\pm$ 0.3706)	-1.4341 ( $\pm$ 0.3741)	-1.8111 ( $\pm$ 0.3809)	-1.4415 ( $\pm$ 0.3647)
ESS-Total Score, Change at Week 15 (n=75,74,74,75)	-1.214 ( $\pm$ 0.3966)	-1.7521 ( $\pm$ 0.4004)	-1.6230 ( $\pm$ 0.4136)	-1.2856 ( $\pm$ 0.3939)
15-<31(Stratum I),Change at Week 4(n= 44,44,44,44)	-1.1799 ( $\pm$ 0.4391)	-0.9841 ( $\pm$ 0.4445)	-2.1284 ( $\pm$ 0.4561)	-0.7926 ( $\pm$ 0.4287)
15-<31(Stratum I), Change at Week8(n=44,44,44,44)	-1.2191 ( $\pm$ 0.4898)	-1.8400 ( $\pm$ 0.4927)	-2.2115 ( $\pm$ 0.5094)	-1.3065 ( $\pm$ 0.4793)

15-<31(Stratum I), Change at Week15(n=44,44,44,44)	-1.5054 (± 0.5500)	-2.2815 (± 0.5570)	-1.8277 (± 0.5853)	-0.9905 (± 0.5495)
31-50(Stratum II), Change at Week4(n=31,30,30,31)	-0.2302 (± 0.6212)	-1.6556 (± 0.6213)	-0.5701 (± 0.6098)	-0.4854 (± 0.5988)
31-50(Stratum II), Change at Week8(n=31,30,30,31)	-1.0873 (± 0.5687)	-0.9112 (± 0.5777)	-1.2599 (± 0.5745)	-1.6706 (± 0.5637)
31-50(Stratum II), Change at Week15(n=31,30,30,31)	-0.7247 (± 0.5538)	-1.0591 (± 0.5565)	-1.3322 (± 0.5604)	-1.7377 (± 0.5431)
ESS ≤ 10, Change at Week 4 (n=44,43,44,47)	-0.6582 (± 0.4088)	-0.1853 (± 0.4136)	-0.1275 (± 0.4241)	-0.3671 (± 0.3908)
ESS ≤ 10, Change at Week 8 (n=44,43,44,47)	-0.6621 (± 0.4353)	-0.3331 (± 0.4450)	-0.1869 (± 0.4568)	-0.3367 (± 0.4233)
ESS ≤ 10, Change at Week 15 (n=44,43,44,47)	-1.0227 (± 0.4512)	-0.8469 (± 0.4580)	-0.1370 (± 0.4865)	-0.3603 (± 0.4418)
ESS ≥ 11, Change at Week 4 (n=31,31,30,28)	-0.9511 (± 0.6599)	-2.9512 (± 0.6628)	-3.2734 (± 0.6530)	-1.0750 (± 0.6610)
ESS ≥ 11, Change at Week 8 (n=31,31,30,28)	-1.9191 (± 0.6396)	-3.2104 (± 0.6357)	-4.0302 (± 0.6418)	-3.1928 (± 0.6433)
ESS ≥ 11, Change at Week 15 (n=31,31,30,28)	-1.4326 (± 0.7046)	-3.2474 (± 0.7074)	-3.6138 (± 0.7071)	-2.7237 (± 0.7171)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Total Score of Sleep Apnea Quality of Life Index (SAQLI) at Weeks 4, 8 and 15

End point title	Change From Baseline in Mean Total Score of Sleep Apnea Quality of Life Index (SAQLI) at Weeks 4, 8 and 15
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End point description:

The SAQLI was a 35-item interview-administered scale that evaluated quality of life associated with sleep apnea in adults. It included four domains (A to D): daily functioning, social interactions, emotional functioning, and symptoms. Items were scored on a 7-point scale ranging from 1 to 7, where 1= all the time to 7= not at all, being the most extreme responses. Item and domain scores were averaged to yield a composite total score between 1 and 7. Higher scores represented better quality of life. For each domain (A to D), the mean score was derived. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4, 8 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4	0.205 (± 0.7720)	0.233 (± 0.6169)	0.162 (± 0.6025)	0.242 (± 0.6697)
Change at Week 8	0.144 (± 0.8624)	0.200 (± 0.6777)	0.162 (± 0.6639)	0.066 (± 0.5729)
Change at Week 15	0.230 (± 0.8094)	0.292 (± 0.6751)	0.189 (± 0.7042)	0.177 (± 0.6394)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Mean Global Score and Mean Domains of Pittsburgh Sleep Quality Index (PSQI) at Weeks 4, 8 and 15

End point title	Change From Baseline in Mean Global Score and Mean Domains of Pittsburgh Sleep Quality Index (PSQI) at Weeks 4, 8 and 15
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End point description:

The PSQI was a self-administered questionnaire that assessed sleep quality. It generated seven sub scores of domains/component: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The seven component scores were derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores were summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality. The FAS consisted of all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 4, 8 and 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: score on a scale				
least squares mean (standard error)				
Global Score at Week 4	-1.0762 (± 0.2891)	-0.9754 (± 0.2916)	-1.2147 (± 0.2955)	-1.2060 (± 0.2812)
Global Score at Week 8	-0.9515 (± 0.3034)	-1.1204 (± 0.3076)	-0.9417 (± 0.3122)	-1.5333 (± 0.2981)
Global Score at Week 15	-1.3142 (± 0.3078)	-1.1400 (± 0.3108)	-1.5175 (± 0.3241)	-1.7706 (± 0.3060)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Treatment Satisfaction as Assessed by End of Study Interview

End point title	Number of Subjects With Treatment Satisfaction as Assessed by End of Study Interview
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End point description:

Subjects satisfaction with the treatment was assessed using an end of study questionnaire developed for this study. Subjects were asked for their satisfaction with treatment and how likely they would continue treatment. Answers ranged from 1 "extremely satisfied/extremely likely" to 7 "extremely dissatisfied/extremely unlikely." Question asked were: Question 1: Overall, how satisfied or dissatisfied



are you with the ability of the medication to treat your obstructive sleep apnea?; Question 2: How likely would you be to continue to take the medication?; Question 3: If you have selected one of answers 4-7 ('Not very likely' to 'Extremely unlikely'), what is the primary reason you chose that you are not very likely or unlikely to take the medication?. The FAS consisted of all randomized subjects.

End point type	Secondary
End point timeframe:	
At Week 17	

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects				
Question 1: Extremely satisfied	7	4	6	1
Question 1: Very satisfied	10	7	10	13
Question 1: Satisfied	15	10	18	18
Question 1: Ambivalent	22	30	20	23
Question 1: Dissatisfied	8	7	3	6
Question 1: Very dissatisfied	2	4	1	1
Question 1: Extremely dissatisfied	2	3	1	5
Question 2: Extremely Likely	8	4	8	5
Question 2: Very Likely	16	10	14	13
Question 2: Likely	13	17	13	14
Question 2: Not very likely	17	17	14	18
Question 2: Unlikely	4	4	6	7
Question 2: Very unlikely	3	7	1	1
Question 2: Extremely unlikely	6	6	2	9
Question 3: Side Effects	3	10	3	16
Question 3: Medication ineffective	23	22	13	16
Question 3: More effective treatment elsewhere	0	1	1	1
Question 3: Inconvenient	1	0	2	1
Question 3: Other	3	1	4	2
Question 3: Not applicable/no answer	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Systolic Blood pressure (SBP) and Diastolic Blood Pressure (DBP) at Weeks 2, 4, 8, 15 and 17

End point title	Change From Baseline in Systolic Blood pressure (SBP) and Diastolic Blood Pressure (DBP) at Weeks 2, 4, 8, 15 and 17
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End point description:

Blood pressure was measured after the subject had been sitting in a quiet room for 5 minutes of rest. The change from baseline in blood pressure at Week 2, 4, 8, 15, and 17 was reported. The FAS consisted of all randomized subjects. Here, "n" refers to number of subjects evaluable at specified time points.

End point type	Secondary
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End point timeframe:

Baseline and at Weeks 2, 4, 8, 15 and 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)				
DBP at Week 2 (n=72,70,68,73)	-0.63 (± 8.541)	-2.59 (± 6.120)	-1.57 (± 7.527)	-3.55 (± 7.618)
DBP at Week 4 (n=69,68,67,73)	-0.39 (± 4.935)	-1.27 (± 6.221)	-1.88 (± 6.052)	-1.62 (± 5.466)
DBP at Week 8 (n=68,66,64,69)	-1.44 (± 8.454)	-0.68 (± 6.372)	-1.64 (± 6.836)	-2.36 (± 6.501)
DBP at Week 15 (n=66,64,58,65)	-1.07 (± 6.215)	-1.12 (± 6.858)	-2.06 (± 5.643)	-2.49 (± 5.411)
DBP at Week 17 (n=67,60,57,61)	-2.61 (± 9.468)	-2.54 (± 8.112)	-0.35 (± 6.541)	-2.26 (± 6.771)
SBP at Week 2 (n=72,70,68,73)	-0.72 (± 10.721)	-2.57 (± 10.633)	-0.86 (± 8.759)	-4.87 (± 9.891)
SBP at Week 4 (n=69,68,67,73)	-0.45 (± 7.155)	-3.09 (± 9.259)	-1.24 (± 7.881)	-2.57 (± 8.973)
SBP at Week 8 (n=68,66,64,69)	-2.09 (± 10.528)	-0.95 (± 8.858)	-2.35 (± 10.169)	-4.50 (± 10.716)
SBP at Week 15 (n=66,64,58,65)	-1.08 (± 7.933)	-0.12 (± 8.118)	-3.14 (± 9.039)	-2.62 (± 9.440)
SBP at Week 17 (n=67,60,57,61)	-2.07 (± 13.816)	-1.92 (± 11.764)	0.18 (± 9.023)	0.01 (± 11.756)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Body Weight at Week 15

End point title	Change From Baseline in Body Weight at Week 15
End point description: The change from baseline in body weight at Week 15 was reported. The FAS consisted of all randomized subjects.	
End point type	Secondary
End point timeframe: Baseline and at Week 15	

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: kilogram (kg)				
arithmetic mean (standard deviation)	0.29 (± 2.276)	0.29 (± 2.367)	-1.12 (± 2.456)	-0.90 (± 2.268)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Circumference of Waist and Hip at Week 15

End point title	Change From Baseline in Circumference of Waist and Hip at Week 15
End point description:	The change from baseline in circumference of waist and hip at Week 15 was reported. The FAS consisted of all randomized subjects.
End point type	Secondary
End point timeframe:	Baseline and at Week 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: centimetre (cm)				
arithmetic mean (standard deviation)				
Change in Circumference of Waist at Week 15	0.18 (± 5.074)	0.12 (± 5.084)	0.08 (± 4.272)	-0.78 (± 4.301)
Change in Circumference of Hip at Week 15	0.37 (± 4.267)	-0.81 (± 4.092)	-1.26 (± 8.932)	0.16 (± 7.152)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Metabolic Parameters: Cholesterol, Low-density Lipoprotein (LDL) Cholesterol, High-density Lipoprotein (HDL) Cholesterol, and Triglycerides at Week 15

End point title	Change From Baseline in Metabolic Parameters: Cholesterol, Low-density Lipoprotein (LDL) Cholesterol, High-density Lipoprotein (HDL) Cholesterol, and Triglycerides at Week 15
End point description:	The change from baseline in metabolic parameters, including cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, at Week 15 was reported. The FAS consisted of all randomized subjects. Here, "n" refers to number of subjects evaluable at specified time points.
End point type	Secondary

End point timeframe:  
Baseline and at Week 15

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)				
Cholesterol at Week 15 (n=75,74,74,75)	0.06 (± 0.714)	-0.11 (± 0.567)	-0.19 (± 0.637)	-0.19 (± 0.686)
LDL Cholesterol at Week 15 (n=75,73,74,75)	0.00 (± 0.606)	-0.14 (± 0.422)	-0.17 (± 0.501)	-0.15 (± 0.532)
HDL Cholesterol at Week 15 (n=75,74,74,75)	0.02 (± 0.186)	0.02 (± 0.168)	0.01 (± 0.119)	0.00 (± 0.132)
Triglycerides at Week 15 (n=75,74,74,75)	0.10 (± 0.707)	0.15 (± 1.051)	-0.07 (± 0.488)	-0.01 (± 0.449)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs
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End point description:

A TEAEs was defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsened in either intensity or frequency following exposure to the investigational product or medicinal product. An SAE was any untoward medical occurrence or effect that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability / incapacity, was a congenital anomaly / birth defect or was medically important due to other reasons than the above mentioned criteria. Safety analysis set (SAF) included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From the first dose of study drug up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects				
TEAEs	46	54	62	68
Serious TEAEs	2	2	3	1

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With TEAEs Regarding Clinically Significant Changes in Laboratory Parameters

End point title	Number of Subjects With TEAEs Regarding Clinically Significant Changes in Laboratory Parameters
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End point description:

Clinical laboratory parameters included evaluations of hematology, serum chemistry, coagulation, urinalysis, glycated haemoglobin (HbA1c), blood glucose and lipid panel. Any clinically significant change in laboratory parameters was based on the investigator judgment. SAF included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From the first dose of study drug up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects				
Leukopenia	0	0	0	1
Anaemia	1	1	0	0
Neutropenia	0	1	0	0
Hypothyroidism	0	0	0	1
Gamma-glutamyltransferase increased	0	1	0	1
Mean cell volume increased	0	0	0	1
Activated partial thromboplastin time prolonged	0	2	0	0
Alanine aminotransferase increased	0	1	0	0
Aspartate aminotransferase increased	0	1	0	0
Blood alkaline phosphatase increased	0	1	0	0
Blood bilirubin increased	1	1	1	0
Blood thyroid stimulating hormone increased	0	2	0	0
Hepatic enzyme increased	0	1	0	0
Liver function test increased	1	0	0	0
Pancreatic enzymes increased	1	0	0	0
Urine leukocyte esterase	0	0	1	0
Hyperglycaemia	0	1	0	1
Type 2 diabetes mellitus	0	0	0	1
Hypercholesterolaemia	0	0	1	0
Hyperlactacidaemia	0	0	1	0
Hypertriglyceridaemia	0	2	0	0

Iron deficiency	0	1	0	0
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Clinically Significant Changes in Vital Signs

End point title	Number of Subjects With Clinically Significant Changes in Vital Signs
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End point description:

Vital signs included evaluations of systolic and diastolic blood pressure, body temperature, respiratory rate, and pulse. Any clinically significant change in vital signs was based on the investigator judgment. SAF included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From the first dose of study drug up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Clinically Significant Abnormal Body Weight and Body Mass Index (BMI)

End point title	Number of Subjects With Clinically Significant Abnormal Body Weight and Body Mass Index (BMI)
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End point description:

Any clinically significant abnormal change in body weight and BMI was based on the investigator judgment. SAF included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From the first dose of study drug up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects	0	0	0	1

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Clinically Significant Abnormal 12-lead Electrocardiogram (ECG)

End point title	Number of Subjects With Clinically Significant Abnormal 12-lead Electrocardiogram (ECG)
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End point description:

12-lead ECG were evaluated. Any clinically significant abnormal change in 12-lead ECG was based on the investigator judgment. SAF included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From the first dose of study drug up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects	1	1	0	1

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Clinically Significant Abnormal Physical Examination

End point title	Number of Subjects With Clinically Significant Abnormal Physical Examination
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End point description:

Physical examination included assessments of the head, eyes, ears, nose and throat, cardiovascular, respiratory, abdomen, skin, cervical and axillary lymph nodes, and neurological and musculoskeletal systems. Any clinically significant abnormal change in physical examination was based on the investigator judgment. SAF included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From the first dose of study drug up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects	2	0	1	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Any Suicidal Ideation (SI) and Suicidal Behavior as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Subjects With Any Suicidal Ideation (SI) and Suicidal Behavior as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)
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End point description:

The C-SSRS is described as a scale developed at Columbia University that has 2-6 questions each in categories of suicidal ideation (SI), Intensity of Ideation, suicidal behavior, and actual attempts. Four constructs were measured. Severity of Suicidal ideation is rated on a 5-point ordinal scale. Intensity of ideation is comprised of 5 items (frequency, duration, controllability, deterrents, and reason for ideation), each rated on a 5-point ordinal scale. Suicidal behavior is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. Lethality, assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is 0, potential lethality of attempts is rated on a 3-point ordinal scale. The higher the C-SSRS score, the higher the suicide risk (i.e. worse outcome). SAF included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline up to Week 17

End point values	Placebo	STM 100 mg	STM 200 mg	STM 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: subjects				
Any SI	0	1	1	2
Any Suicidal Behavior	0	0	0	0

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to Week 17

Adverse event reporting additional description:

SAF included all randomized subjects who received at least 1 dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received STM matched placebo, tablets, orally, once daily within 1 hour prior to bedtime for 15 weeks.

Reporting group title	STM 100 mg
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Reporting group description:

Subjects received STM 50 milligrams (mg) (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Weeks 2 and 3 and continued taking 100 mg as a target dose until Week 15.

Reporting group title	STM 200 mg
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Reporting group description:

Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking 200 mg as a target dose until Week 15.

Reporting group title	STM 300 mg
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Reporting group description:

Subjects received STM 50 mg (as initial dose level), tablets, orally, once daily within 1 hour prior to bedtime in Week 1 then up-titrated to 100 mg in Week 2, 200 mg in Week 3 and continued taking STM 300 mg as a target dose until Week 15.

Serious adverse events	Placebo	STM 100 mg	STM 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 75 (2.67%)	2 / 74 (2.70%)	3 / 74 (4.05%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Meniscus injury			

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Trigeminal nerve disorder			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Somatic symptom disorder			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	STM 300 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 75 (1.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Trigeminal nerve disorder			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
Abdominal pain			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Psychiatric disorders</b>			
Somatic symptom disorder			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Influenza			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Placebo	STM 100 mg	STM 200 mg
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	33 / 75 (44.00%)	36 / 74 (48.65%)	55 / 74 (74.32%)
<b>Vascular disorders</b>			
Hypertension			
subjects affected / exposed	3 / 75 (4.00%)	6 / 74 (8.11%)	1 / 74 (1.35%)
occurrences (all)	3	6	1
<b>Nervous system disorders</b>			
Paraesthesia			
subjects affected / exposed	7 / 75 (9.33%)	16 / 74 (21.62%)	32 / 74 (43.24%)
occurrences (all)	8	17	38
Headache			
subjects affected / exposed	7 / 75 (9.33%)	5 / 74 (6.76%)	14 / 74 (18.92%)
occurrences (all)	9	5	15
Dizziness			

subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	2 / 74 (2.70%) 3	4 / 74 (5.41%) 4
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	5 / 74 (6.76%) 5	4 / 74 (5.41%) 4
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2  3 / 75 (4.00%) 3	1 / 74 (1.35%) 1  5 / 74 (6.76%) 6	4 / 74 (5.41%) 4  5 / 74 (6.76%) 7
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	0 / 74 (0.00%) 0	1 / 74 (1.35%) 1
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	1 / 74 (1.35%) 1	4 / 74 (5.41%) 4
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3  10 / 75 (13.33%) 10	4 / 74 (5.41%) 5  4 / 74 (5.41%) 4	7 / 74 (9.46%) 7  7 / 74 (9.46%) 7
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)  Glucose tolerance impaired subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0  5 / 75 (6.67%) 5	4 / 74 (5.41%) 5  3 / 74 (4.05%) 3	0 / 74 (0.00%) 0  2 / 74 (2.70%) 2

<b>Non-serious adverse events</b>	STM 300 mg		
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Total subjects affected by non-serious adverse events subjects affected / exposed	60 / 75 (80.00%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3		
Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)	43 / 75 (57.33%) 53  11 / 75 (14.67%) 13  2 / 75 (2.67%) 2		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 6		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 7  3 / 75 (4.00%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3		
Infections and infestations			

COVID-19			
subjects affected / exposed	11 / 75 (14.67%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	7 / 75 (9.33%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	3		
Glucose tolerance impaired			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2022	Amendment 1 <ul style="list-style-type: none"><li>- An exclusion criterion was added to exclude subjects who are kept in an institution or who might not consent entirely voluntarily</li><li>- Guidance was added about study withdrawal or continuation regarding patients with an active SARS-CoV-2 infection</li><li>- SAE reporting timelines were updated according to German ordinance</li></ul>
29 March 2022	Amendment 2 <ul style="list-style-type: none"><li>- The "FLOW" logo and study name were added for consistency with other study-related material</li><li>- Inclusion criterion #3 was updated in the synopsis to exactly match inclusion criterion #3 in Section 8.1.</li><li>- Errors regarding the number of weeks of treatment and weeks on target dose related to the PSG sleep studies at Visit 5 were corrected.</li><li>- Determination of PLMAI for exclusion criterion #3 was clarified.</li><li>- Exclusion criterion #22 was updated to include patients with infections to be more precise; accordingly, exclusion criterion #24 was removed.</li><li>- Because of the variability of the COVID-19 situation in different countries, COVID-19 testing will be done per applicable local requirements. The mandatory PCR test at screening was removed. Exclusion criterion #24 (previously #25) was updated accordingly.</li><li>- To reduce patient burden, the sample frequency for specific laboratory tests was reduced.</li><li>- Further clarifications were added to the schedule of assessments (Section 10.1).</li><li>- It was clarified that capillary blood gas analysis will be done locally at selected sites (Section 14).</li><li>- For consistency with the statistical analysis plan, it was clarified that demographic and baseline characteristics include country and not region (Section 15.4).</li><li>- The record retention period was changed from 25 years to a minimum of 15 years to account for various country-specific requirements (Section 16.4).</li></ul>
15 December 2022	Amendment 3 The purpose of this amendment was to decrease the sample size.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported