Clinical trial results:
A 24-week phase 2, double-blind, randomized, placebo-controlled, single-centre safety and efficacy study to evaluate overall safety and tolerability of co-administration of tesofensine and metoprolol in subjects with hypothalamic injury-induced obesity (HIO), and with a 24-week open-label extension, in total 48 weeks

Summary

EudraCT number	2018-003672-12
Trial protocol	DK
Global end of trial date	16 October 2020

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	TM005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03845075
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Saniona
Sponsor organisation address	Smedeland 26B, Glostrup, Denmark, 2600
Public contact	Janus Schreiber Larsen Chief Development Office, Saniona A/S, +45 70 70 52 25, janus.larsen@saniona.com
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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	16 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2020
Global end of trial reached?	Yes
Global end of trial date	16 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To examine overall safety and tolerability of co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment over 24 weeks in subjects with HIO

Protection of trial subjects:

None

Background therapy:

HIO develops in approx 50% of patients undergoing surgery for suprasellar tumors including craniopharyngeomas. There is no approved therapy for HIO and conventional overweight treatment inclding food restriction has no or limited effect.

Evidence for comparator:

As there is no approved therapy for HIO, placebo is the choice for comparator. All subjects were offered dietetic councelling.

Actual start date of recruitment	25 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	19
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

21 subjects were recruited within the period of 28Feb2019 to 01Oct2019. Subjects recruited in Denmark only.

Pre-assignment

Screening details:

35 subjects were screened; 13 subjects were screen failures. A total of 21 unique subjects were assigned 22 randomization numbers. One subject was a screen failure who was randomized in error, and withdrawn after receiving 1 dose of Tesofensine/metoprolol; this subject was later rescreened and rerandomized to placebo.

Period 1

Period 1 title	Part 1 - DB
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	Tesofensine/Metoprolol

Arm description:

Subjects were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily for 24 weeks during Part 1.

Arm type	Experimental
Investigational medicinal product name	Tesofensine/Metoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg tesofensine and 50 mg metoprolol - once daily for 24 weeks during Part 1.

Arm title	Placebo

Arm description:

Subjects were randomized to receive matching placebo tesofensine and placebo metoprolol tablets once daily for 24 weeks during Part 1.

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

Dosage and administration details:

Matching placebo tesofensine and placebo metoprolol tablets once daily for 24 weeks during Part 1.

Number of subjects in period 1	Tesofensine/Metoprolol	Placebo
Started	14	8
Completed	12	6
Not completed	2	2
Consent withdrawn by subject	1	1
screen failure, but got 1 dose of drug in error	1	-
Adverse event, non-fatal	-	1

Period 2

Period 2 title	Part 2 - OLE
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tesofensine/Metoprolol -> Tesofensine/Metoprolol

Arm description:

Subjects who received co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily for 24 weeks during Part 1 and continued to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol once daily for an additional 24 weeks in Part 2.

Arm type	Experimental
Investigational medicinal product name	Tesofensine/Metoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg tesofensine and 50 mg metoprolol - once daily for 24 weeks during Part 2.

Arm title	Placebo -> Tesofensine/Metoprolol

Arm description:

Subjects who received matching placebo tesofensine and placebo metoprolol tablets once daily for 24 weeks during Part 1 were switched to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol once daily for an additional 24 weeks in Part 2.

Arm type	Experimental
Investigational medicinal product name	Tesofensine/Metoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg tesofensine and 50 mg metoprolol - once daily for 24 weeks during Part 2.

Number of subjects in period 2	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol
Started	12	6
Completed	12	6

Baseline characteristics

Reporting groups	
Reporting group title	Tesofensine/Metoprolol
Reporting group description:	
Subjects were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily for 24 weeks during Part 1.	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomized to receive matching placebo tesofensine and placebo metoprolol tablets once daily for 24 weeks during Part 1.	

Reporting group values	Tesofensine/Metoprolol	Placebo	Total
Number of subjects	14	8	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	6	18
From 65-84 years	2	2	4
85 years and over	0	0	0
Age continuous Units: years			
median	51	43	
full range (min-max)	26 to 70	25 to 67	-
Gender categorical Units: Subjects			
Female	11	6	17
Male	3	2	5
Weight Units: kg			
median	120.3	111.5	
full range (min-max)	86.1 to 144.4	80.4 to 163.1	-

End points

End points reporting groups

Reporting group title	Tesofensine/Metoprolol

Reporting group description:

Subjects were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily for 24 weeks during Part 1.

Reporting group title	Placebo

Reporting group description:

Subjects were randomized to receive matching placebo tesofensine and placebo metoprolol tablets once daily for 24 weeks during Part 1.

Reporting group title	Tesofensine/Metoprolol -> Tesofensine/Metoprolol

Reporting group description:

Subjects who received co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily for 24 weeks during Part 1 and continued to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol once daily for an additional 24 weeks in Part 2.

Reporting group title	Placebo -> Tesofensine/Metoprolol

Reporting group description:

Subjects who received matching placebo tesofensine and placebo metoprolol tablets once daily for 24 weeks during Part 1 were switched to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol once daily for an additional 24 weeks in Part 2.

Primary: Frequency of Treatment Emergent Adverse Events

End point title	Frequency of Treatment Emergent Adverse Events[1]

End point description:

Number and percentage of adverse events in each of the two treatment arms

End point type	Primary

End point timeframe:

from Baseline to week 24

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: No statistical analyses have been specified for this primary end point. Only descriptive analyses were planned for

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: count of participants				
Frequency of Treatment Emergent Adverse Events	12	7		

Statistical analyses

No statistical analyses for this end point

Primary: Severity of Treatment Emergent Adverse Events

End point title	Severity of Treatment Emergent Adverse Events[2]

End point description:

Number and percentage of mild, moderate and severe adverse events in each of the two treatment arms

End point type	Primary

End point timeframe:

from Baseline to week 24

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: No statistical analyses have been specified for this primary end point. Only descriptive analyses were planned for

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: count of participants				
At least one mild AE	11	7		
At least one moderate AE	10	5		
At least one severe AE	2	2		

Statistical analyses

No statistical analyses for this end point

Primary: Frequency and Type of Serious Adverse Events

End point title	Frequency and Type of Serious Adverse Events[3]

End point description:

Number, percentage and type of serious adverse events in each of the two treatment arms

End point type	Primary

End point timeframe:

from Baseline to week 24

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: No statistical analyses have been specified for this primary end point. Only descriptive analyses were planned for

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: count of participants				
At least one SAE	2	1		
Preferred Term: Anxiety	1	0		
Preferred Term: Craniopharyngioma	1	0		
Preferred Term: Hyponatraemia	0	1		
Preferred Term: Post procedural complication	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety as Assessed by Systolic Blood Pressure [mmHg]

End point title	Safety as Assessed by Systolic Blood Pressure [mmHg]

End point description:

Systolic blood pressure in mmHg measured at each visit in each of the two treatment arms

End point type	Primary

End point timeframe:

from Baseline to week 24

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[4]	8[5]		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	124.0 (± 9)	134.5 (± 16)		
Week 4	126.6 (± 12)	131.8 (± 17)		
Week 8	129.2 (± 17)	126.3 (± 23)		
Week 12	126.3 (± 13)	126.2 (± 14)		
Week 16	123.9 (± 14)	126.0 (± 17)		
Week 20	127.3 (± 12)	129.2 (± 18)		
Week 24	125.3 (± 16)	130.5 (± 22)		

Notes:

[4] - number of participants at baseline/W4/W8/W12/W16/20/W24: 13/13/12/12/12/12/12

[5] - number of participants at baseline/W4/W8/W12/W16/20/W24: 8/8/6/6/6/6/6

Statistical analyses

Statistical analysis title	1 for Safety as Assess. by Systolic blood press

Statistical analysis description:

Week 4; Safety set LOCF

Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4671 [6]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	3.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.58
upper limit	13.78

Notes:

[6] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	2 for Safety as Assess. by Systolic blood press
Statistical analysis description:	
Week 8; Safety set, LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1808 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	10.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.14
upper limit	25.36

Notes:

[7] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	3 for Safety as Assess. by Systolic blood press
Statistical analysis description:	
Week 12; Safety set; LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4171 [8]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.08
upper limit	16.33

Notes:

[8] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	4 for Safety as Assess. by Systolic blood press
Statistical analysis description:	
Week 16; Safety set; LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3116 [9]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	5.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.43
upper limit	16.1

Notes:

[9] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	5 for Safety as Assess. by Systolic blood press
Statistical analysis description:	
Week 20; Safety set; LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2353 [10]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.12
upper limit	15.72

Notes:

[10] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	6 for Safety as Assess. by Systolic blood press
Statistical analysis description:	
Week 24; Safety set; LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3037 [11]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	5.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.76
upper limit	17.48

Notes:
[11] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Primary: Safety as Assessed by Diastolic Blood Pressure [mmHg]

End point title	Safety as Assessed by Diastolic Blood Pressure [mmHg]

End point description:
Diastolic blood pressure in mmHg measured at each visit in each of the two treatment arms

End point type	Primary

End point timeframe:
from Baseline to week 24

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[12]	8[13]		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	83.2 (± 14)	85.9 (± 8)		
Week 4	84.2 (± 8)	86.8 (± 8)		
Week 8	84.5 (± 9)	86.0 (± 9)		
Week 12	81.5 (± 10)	86.5 (± 8)		
Week 16	81.4 (± 9)	80.3 (± 13)		
Week 20	84.3 (± 9)	85.7 (± 9)		
Week 24	83.1 (± 9)	84.2 (± 13)		

Notes:
[12] - number of participants at baseline/W4/W8/W12/W16/20/W24: 13/13/12/12/12/12/12
[13] - number of participants at baseline/W4/W8/W12/W16/20/W24: 8/8/6/6/6/6/6

Statistical analyses

Statistical analysis title	1 Safety as assessed by Diastolic Blook Pressure

Statistical analysis description:
Week 4; Safety set LOCF

Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6543 [14]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.33
upper limit	4.72

Notes:
[14] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	2 Safety as assessed by Diastolic Blook Pressure
Statistical analysis description: Week 8; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7941 [15]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	8.38

Notes:

[15] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	3 Safety as assessed by Diastolic Blook Pressure
Statistical analysis description: Week 12; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5937 [16]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.72
upper limit	5.73

Notes:

[16] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	4 Safety as assessed by Diastolic Blook Pressure
Statistical analysis description: Week 16; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5423 [17]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.11
upper limit	11.23

Notes:

[17] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	5 Safety as assessed by Diastolic Blook Pressure
Statistical analysis description:	
Week 20; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7226 [18]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.77
upper limit	8.16

Notes:

[18] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	6 Safety as assessed by Diastolic Blook Pressure
Statistical analysis description:	
Week 24; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7912 [19]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.85
upper limit	10.16

Notes:

[19] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Primary: Safety as Assessed by Heart Rate [Bpm]

End point title	Safety as Assessed by Heart Rate [Bpm]

End point description:

Heart rate measured in beats per minute (bpm) at each visit in each of the two treatment arms

End point type	Primary
End point timeframe: from Baseline to week 24	

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[20]	8[21]		
Units: bpm				
arithmetic mean (standard deviation)				
Baseline	75.5 (± 8)	78.9 (± 11)		
Week 4	71.9 (± 9)	75.9 (± 12)		
Week 8	72.7 (± 8)	76.0 (± 13)		
Week 12	74.2 (± 10)	73.3 (± 8)		
Week 16	73.8 (± 13)	74.8 (± 6)		
Week 20	74.8 (± 11)	77.2 (± 13)		
Week 24	73.6 (± 10)	71.5 (± 9)		

Notes:

[20] - number of participants at baseline/W4/W8/W12/W16/20/W24: 13/13/12/12/12/12/12

[21] - number of participants at baseline/W4/W8/W12/W16/20/W24: 8/8/6/6/6/6/6

Statistical analyses

Statistical analysis title	1 Safety as assessed by Heart Rate
Statistical analysis description: Week 4; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7023 [22]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.67
upper limit	5.97

Notes:

[22] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	2 Safety as assessed by Heart Rate
Statistical analysis description: Week 8; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9012 [23]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.58
upper limit	7.61

Notes:

[23] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	3 Safety as assessed by Heart Rate
Statistical analysis description:	
Week 12; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6138
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.63
upper limit	10.92

Statistical analysis title	4 Safety as assessed by Heart Rate
Statistical analysis description:	
Week 16; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7889 [24]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.26
upper limit	10.72

Notes:
[24] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	5 Safety as assessed by Heart Rate
Statistical analysis description: Week 20; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9536 [25]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.34
upper limit	10.94

Notes:
[25] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	6 Safety as assessed by Heart Rate
Statistical analysis description: Week 24; Safety set LOCF	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5551 [26]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.72
upper limit	12.12

Notes:
[26] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Primary: Safety as Assessed by Hematology Parameters

End point title	Safety as Assessed by Hematology Parameters[27]
End point description: Number and percentage of deviations from normal range for hemoglobin, platelet counts, white cells count, differential counts at baseline, week 12 and week 24 in each of the two treatment arms	
End point type	Primary
End point timeframe: from Baseline to week 24	

Notes:

[27] - 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: No statistical analyses have been specified for this primary end point. Only descriptive analyses were planned for

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[28]	8[29]		
Units: counts of participants				
Hemoglobin: Baseline - Low	0	0		
Hemoglobin: Baseline - High	0	1		
Hemoglobin: Week 12 - Low	0	0		
Hemoglobin: Week 12 - High	0	0		
Hemoglobin: Week 24 - Low	1	0		
Hemoglobin: Week 24 - High	0	0		
Platelets: Baseline - Low	0	0		
Platelets: Baseline - High	1	0		
Platelets: Week 12 - Low	0	0		
Platelets: Week 12 - High	1	0		
Platelets: Week 24 - Low	0	0		
Platelets: Week 24 - High	1	0		
WBC: Baseline - Low	0	0		
WBC: Baseline - High	3	2		
WBC: Week 12 - Low	0	0		
WBC: Week 12 - High	5	1		
WBC: Week 24 - Low	0	0		
WBC: Week 24 - High	0	1		
Neutrophils: Baseline - Low	1	0		
Neutrophils: Baseline - High	1	1		
Neutrophils: Week 12 - Low	0	0		
Neutrophils: Week 12 - High	4	1		
Neutrophils: Week 24 - Low	1	0		
Neutrophils: Week 24 - High	1	1		
Monocytes: Baseline - Low	0	0		
Monocytes: Baseline - High	0	0		
Monocytes: Week 12 - Low	0	0		
Monocytes: Week 12 - High	1	0		
Monocytes: Week 24 - Low	0	0		
Monocytes: Week 24 - High	1	0		
Lymphocytes: Baseline - Low	0	1		
Lymphocytes: Baseline - High	1	2		
Lymphocytes: Week 12 - Low	0	1		
Lymphocytes: Week 12 - High	0	0		
Lymphocytes: Week 24 - Low	0	0		
Lymphocytes: Week 24 - High	1	0		

Notes:

[28] - Number of participants at baseline/week 12/week 24: 14/13/12

[29] - Number of participants at baseline/week 12/week 24: 8/8/6

Statistical analyses

No statistical analyses for this end point

Primary: Safety as Assessed by Electrolytes and Creatinine

End point title	Safety as Assessed by Electrolytes and Creatinine[30]

End point description:

Number and percentage of deviations from normal range for sodium, potassium, creatinine at each visit in each of the two treatment arms

End point type	Primary

End point timeframe:

from Baseline to week 24

Notes:

[30] - 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: No statistical analyses have been specified for this primary end point. Only descriptive analyses were planned for

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[31]	8[32]		
Units: counts of participants				
Sodium: Baseline - Low	0	0		
Sodium: Baseline - High	2	2		
Sodium: Week 4 - Low	0	0		
Sodium: Week 4 - High	0	0		
Sodium: Week 8 - Low	0	0		
Sodium: Week 8 - High	1	1		
Sodium: Week 12 - Low	0	0		
Sodium: Week 12 - High	1	0		
Sodium: Week 16 - Low	0	0		
Sodium: Week 16 - High	1	0		
Sodium: Week 20 - Low	0	0		
Sodium: Week 20 - High	2	2		
Sodium: Week 24 - Low	1	0		
Sodium: Week 24 - High	0	1		
Potassium: Baseline - Low	0	0		
Potassium: Baseline - High	0	1		
Potassium: Week 4 - Low	2	1		
Potassium: Week 4 - High	0	1		
Potassium: Week 8 - Low	2	0		
Potassium: Week 8 - High	0	0		
Potassium: Week 12 - Low	1	0		
Potassium: Week 12 - High	0	0		
Potassium: Week 16 - Low	1	0		
Potassium: Week 16 - High	0	1		
Potassium: Week 20 - Low	1	0		
Potassium: Week 20 - High	0	0		
Potassium: Week 24 - Low	0	1		
Potassium: Week 24 - High	0	0		
Creatinine: Baseline - Low	3	2		
Creatinine: Baseline - High	0	0		
Creatinine: Week 4 - Low	2	4		
Creatinine: Week 4 - High	0	0		

Creatinine: Week 8 - Low	2	3		
Creatinine: Week 8 - High	0	0		
Creatinine: Week 12 - Low	2	2		
Creatinine: Week 12 - High	0	0		
Creatinine: Week 16 - Low	3	2		
Creatinine: Week 16 - High	0	0		
Creatinine: Week 20 - Low	4	2		
Creatinine: Week 20 - High	0	0		
Creatinine: Week 24 - Low	3	1		
Creatinine: Week 24 - High	0	0		

Notes:

[31] - number of participants: at baseline/W 4/W 8/W 12/W 16/W 20/W 24: 14/13/13/12/12/12/12

[32] - number of participants: at baseline/W 4/W 8/W 12/W 16/W 20/W 24: 8/8/7/6/6/6/6

Statistical analyses

No statistical analyses for this end point

Primary: Safety as Assessed by Liver and Kidney Function Tests

End point title	Safety as Assessed by Liver and Kidney Function Tests[33]

End point description:

Number and percentage of deviations from normal range for gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), glomerular filtration rate (GFR),
and urea at baseline, week 12, and week 24 in each of the two treatment arms

End point type	Primary

End point timeframe:

from Baseline to week 24

Notes:

[33] - 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: No statistical analyses have been specified for this primary end point. Only descriptive analyses were planned for

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: counts of participants				
GGT: Baseline - Low	0	0		
GGT: Baseline - High	5	1		
GGT: Week 12 - Low	0	1		
GGT: Week 12 - High	5	2		
GGT: Week 24 - Low	0	0		
GGT: Week 24 - High	4	0		
AST: Baseline - Low	0	0		
AST: Baseline - High	0	0		
AST: Week 12 - Low	0	0		
AST: Week 12 - High	0	0		
AST: Week 24 - Low	0	0		
AST: Week 24 - High	0	0		
ALT: Baseline - Low	0	0		
ALT: Baseline - High	0	0		
ALT: Week 12 - Low	0	0		

ALT: Week 12 - High	1	0		
ALT: Week 24 - Low	0	0		
ALT: Week 24 - High	0	0		
ALP: Baseline - Low	0	0		
ALP: Baseline - High	1	0		
ALP: Week 12 - Low	0	0		
ALP: Week 12 - High	2	0		
ALP: Week 24 - Low	0	0		
ALP: Week 24 - High	1	0		
GFR: Baseline - Low	0	0		
GFR: Baseline - High	0	0		
GFR: Week 12 - Low	0	0		
GFR: Week 12 - High	0	0		
GFR: Week 24 - Low	0	0		
GFR: Week 24 - High	0	0		
Urea: Baseline - Low	1	1		
Urea: Baseline - High	0	0		
Urea: Week 12 - Low	2	0		
Urea: Week 12 - High	0	0		
Urea: Week 24 - Low	1	0		
Urea: Week 24 - High	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Satiety Score (CSS)

End point title	Composite Satiety Score (CSS)

End point description:

Change in satiety and appetite using the CSS from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 measured at each visit for each of the two treatment arms
Full name of the scale: composite satiety score (CSS), sometimes referred to as “appetite suppression score”. Range of values is 0-100; lower the value, hungrier a person is. CSS = (satiety + fullness + [100 − hunger] + [100 − prospective food consumption]) / 4. The four variables included are measured by visual analog scales (0-100 mm)

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline to Week 24	4.5 (± 20.6)	6.5 (± 19.3)		
Baseline to Week 48	4.2 (± 15.1)	11.2 (± 14.3)		

Week 24 to Week 48	-0.3 (± 14.4)	4.7 (± 12.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Composite Satiety Score
Statistical analysis description:	
Baseline to week 24	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7782 [34]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.23
upper limit	16.2

Notes:

[34] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for Composite Satiety Score
Statistical analysis description:	
Baseline to Week 48	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313 [35]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-7.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.09
upper limit	7.56

Notes:

[35] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 3 for Composite Satiety Score
Statistical analysis description:	
Week 24 to Week 48	

Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4033 [36]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-5.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.92
upper limit	8.47

Notes:

[36] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Body Weight

End point title	Body Weight

End point description:

Change in body weight (kg) from baseline to week 24, from baseline to 48 and from week 24 to week 48 measured at each visit for each of the two treatment arms

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: kg				
arithmetic mean (standard deviation)				
Baseline to Week 24	-7.93 (± 6.59)	-0.15 (± 4.74)		
Baseline to Week 48	-6.53 (± 7.36)	-5.65 (± 8.90)		
Week 24 to Week 48	1.40 (± 4.05)	-5.50 (± 6.20)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Body Weight

Statistical analysis description:

Baseline to Week 24

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0325 [37]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.29
upper limit	-0.71

Notes:

[37] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 2 for Body Weight
Statistical analysis description:	
Baseline to Week 48	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9394 [38]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.04
upper limit	8.4

Notes:

[38] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 3 for Body Weight
Statistical analysis description:	
Week 24 to Week 28	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135 [39]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	6.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	12.18

Notes:

[39] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Body Composition - Fat Mass

End point title	Body Composition - Fat Mass

End point description:

Change in body fat mass as measured in kg by DXA scan measured at baseline, week 24 and week 48 for each of the two treatment arms - (mITT observed values).

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[40]	6[41]		
Units: kilogram(s)				
arithmetic mean (standard deviation)				
Baseline to Week 24	-5.31 (± 5.34)	-1.04 (± 3.75)		
Baseline to Week 48	-4.87 (± 5.31)	-3.77 (± 5.81)		
Week 24 to Week 48	0.44 (± 3.50)	-2.73 (± 3.37)		

Notes:

[40] - number of participants at baseline/w24/w48: 13/12/12

[41] - number of participants at baseline/w24/w48: 13/12/12

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Body Composition - Fat

Statistical analysis description:

Baseline to Week 24; last observation carried forward (LOCF) approach (mITT observed).

Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1048 [42]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-4.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.31
upper limit	0.98

Notes:

[42] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for Body Composition - Fat

Statistical analysis description:

Baseline to Week 48; last observation carried forward (LOCF) approach (mITT LOCF).

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7189 [43]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.75
upper limit	4.77

Notes:

[43] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 3 for Body Composition - Fat

Statistical analysis description:

Week 24 to Week 48; last observation carried forward (LOCF) approach (mITT LOCF).

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1053 [44]
Method	ANCOVA
Parameter estimate	LS Mean difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	6.91
Variability estimate	Standard deviation

Notes:

[44] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Body Composition - Lean Tissue Mass

End point title	Body Composition - Lean Tissue Mass

End point description:

Change in lean body mass as measured in kg by DXA scan measured at baseline, week 24 and week 48 for each of
the two treatment arms (mITT observed values).

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[45]	6[46]		
Units: kilogram(s)				
arithmetic mean (standard deviation)				
Baseline to Week 24	-2.85 (± 1.88)	0.55 (± 1.32)		
Baseline to Week 48	-1.81 (± 2.18)	-1.87 (± 3.36)		
Week 24 to Week 48	1.04 (± 1.18)	-2.42 (± 3.51)		

Notes:

[45] - number of participants at baseline/w24/w48: 13/12/12

[46] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Lean Tissue Mass

Statistical analysis description:

Baseline to Week 24; mITT observed.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033 [47]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.02
upper limit	-1.21

Notes:

[47] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for Lean Tissue Mass

Statistical analysis description:

Baseline to Week 48; mITT LOCF.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6663 [48]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	3.41

Notes:

[48] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 3 for Lean Tissue Mass

Statistical analysis description:

Week 24 to Week 48; mITT LOCF

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [49]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	3.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	5.98

Notes:

[49] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Secondary: Glycemic Control - HbA1c

End point title	Glycemic Control - HbA1c

End point description:

Change in HbA1c from baseline to week 24, baseline to week 48 and week 24 to week 48 measured at baseline, week
14, week 24, week 36 and week 48 for each of the two treatment arms

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48 (mITT observed values).

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[50]	6[51]		
Units: mmol/mol				
arithmetic mean (standard deviation)				
Baseline to Week 24	-6.00 (± 15.39)	-0.17 (± 2.40)		
Baseline to Week 48	-5.33 (± 14.79)	-0.17 (± 2.23)		
Week 24 to Week 48	0.67 (± 1.30)	0.00 (± 0.63)		

Notes:

[50] - number of participants at baseline/w24/w48: 13/12/12

[51] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Glycemic Control - HbA1
Statistical analysis description: Baseline to Week 24; mITT observed	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0713 [52]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.34
upper limit	0.3

Notes:

[52] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for Glycemic Control - HbA1
Statistical analysis description: Baseline to Week 48: mITT LOCF	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1457 [53]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.92
upper limit	0.96

Notes:

[53] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 3 for Glycemic Control - HbA1
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.1837 [55]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	2.15
Variability estimate	Standard deviation

Notes:

[54] - Statistical analysis description: Week 24 to Week 48: mITT LOCF

[55] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Glycemic Control - Fasting Plasma Glucose

End point title	Glycemic Control - Fasting Plasma Glucose

End point description:

Change in fasting plasma glucose from baseline to week 24, baseline to week 48 and week 24 to week 48 measured at
each visit for each of the two treatments arms

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48 (mITT observed values).

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[56]	6[57]		
Units: mmmol/L				
arithmetic mean (standard deviation)				
Baseline to Week 24	-0.29 (± 0.64)	-0.28 (± 0.57)		
Baseline to Week 48	-0.11 (± 0.53)	-0.08 (± 0.37)		
Week 24 to Week 48	0.18 (± 0.46)	0.37 (± 0.59)		

Notes:
[56] - number of participants at baseline/w24/w48: 13/12/12

[57] - number of participants at baseline/w24/w48: 6/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Glycemic Control - Fast

Statistical analysis description:
Baseline to Week 24; mITT LOCF

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7926 [58]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.33

Notes:
[58] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 2 for Glycemic Control - Fast

Statistical analysis description:
Baseline to Week 48; mITT LOCF

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2124 [59]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.17
Variability estimate	Standard deviation

Notes:
[59] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 for Glycemic Control - Fast

Statistical analysis description:	
Week 24 to Week 48; last observation carried forward (LOCF) approach	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6084 [60]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.43
Variability estimate	Standard deviation

Notes:

[60] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Craving for Something Sweet, Salty, Meat/Fish, or Fatty

End point title	Craving for Something Sweet, Salty, Meat/Fish, or Fatty

End point description:

Change in craving for something sweet, salty, meat/fish, or fatty by the use of visual analogue scales (VAS) from baseline to week 24, from baseline to week 48, and from week 24 to week 48
The VAS consisted of a 100-mm horizontal line; subjects placed a vertical line on the VAS to indicate the level of intensity of their food craving. The VAS value is the distance in mm (0-100 mm) from the left end of the line to the
subject's vertical line (higher value represents less craving). (mITT observed values).

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[61]	6[62]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Desire for something sweet from baseline to W 24	9.0 (± 36.6)	16.2 (± 30.8)		
Desire for something sweet from baseline to W 48	2.1 (± 35.8)	35.3 (± 32.9)		
Desire for something sweet from week 24 to week 48	-6.9 (± 20.2)	19.2 (± 30.7)		
Desire for something salty from baseline to W 24	-2.3 (± 27.9)	13.2 (± 21.5)		
Desire for something salty from baseline to W 48	-3.4 (± 28.8)	33.3 (± 30.9)		
Desire for something salty from W 24 to W 48	-1.2 (± 8.5)	20.2 (± 22.7)		

Desire for meat/fish from baseline to week 24	7.3 (± 42.6)	8.8 (± 34.0)		
Desire for meat/fish from baseline to week 48	14.0 (± 44.1)	35.0 (± 34.6)		
Desire for meat/fish from week 24 to week 48	6.8 (± 18.6)	26.2 (± 34.2)		
Desire for something fatty from baseline to W24	18.2 (± 22.6)	2.2 (± 11.3)		
Desire for something fatty from baseline to W48	5.2 (± 25.7)	22.5 (± 26.3)		
Desire for something fatty from W24 to W48	-13.0 (± 15.6)	20.3 (± 28.0)		

Notes:

[61] - number of participants at baseline/w24/w48: 13/12/12

[62] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 Desire for something fatty
Statistical analysis description:	
Baseline to week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0905 [63]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	34.85

Notes:

[63] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 Desire for meat/fish
Statistical analysis description:	
Baseline to Week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6285 [64]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	6.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.05
upper limit	35.36

Notes:

[64] - P-value from ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 3 Desire for something salty
Statistical analysis description:	
Baseline to Week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5884 [65]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-6.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.05
upper limit	19.43

Notes:

[65] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 4 Desire for something sweet
Statistical analysis description:	
Baseline to Week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8533 [66]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.73
upper limit	36.68

Notes:

[66] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 5 Desire for something fatty

Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1529 [67]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-17.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.87
upper limit	7.2

Notes:

[67] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 6 Desire for meat/fish
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.3399 [69]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-11.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.15
upper limit	13.65

Notes:

[68] - Baseline to Week 48; mITT LOCF.

[69] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 7 Desire for something salty
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0673
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.0673

Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.84
upper limit	1.93

Statistical analysis title	Statistical Analysis 8 Desire for something sweet
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1657 [70]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-22.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.65
upper limit	10.46

Notes:

[70] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 9 Desire for something fatty
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0108 [71]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-30.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.31
upper limit	-8.06

Notes:

[71] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 10 Desire for meat/fish

Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171 [72]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-14.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.71
upper limit	7.13

Notes:

[72] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 11 Desire for something salty
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083 [73]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-19.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	-5.93

Notes:

[73] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 12 Desire for something sweet
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0631 [74]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-22.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.39
upper limit	1.43

Notes:

[74] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Thirst

End point title	Thirst

End point description:

Change in thirst by the use of a visual analog scale (VAS) from baseline to week 24, from baseline to week 48, and from week 24 to week 48
The VAS consisted of a 100-mm horizontal line; subjects placed a vertical line on the VAS to indicate the level of intensity of their thirst. The VAS value is the distance in mm (0-100 mm) from the left end of the line to the subject's vertical line (higher value represents an increase in perception of thirst). mITT observed values

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[75]	6[76]		
Units: score on a scale				
arithmetic mean (standard deviation)				
From baseline to week 24	-2.4 (± 28.9)	-18.8 (± 23.2)		
From baseline to week 48	-6.3 (± 25.8)	-16.7 (± 18.8)		
From week 24 to week 48	-3.8 (± 16.5)	2.2 (± 20.5)		

Notes:

[75] - number of participants at baseline/w24/w48: 13/12/12

[76] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Thirst

Statistical analysis description:

Baseline to Week 24; mITT observed.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8082 [77]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.65
upper limit	19.53

Notes:

[77] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for Thirst
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9034 [78]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.94
upper limit	23.1

Notes:

[78] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 for Thirst
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4658 [79]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.93
upper limit	12.93
Variability estimate	Standard deviation

Notes:

[79] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Waist Circumference

End point title	Waist Circumference

End point description:

Change in waist circumference from baseline to week 24, from baseline to week 48, and from week 24 to week 48. mITT observed values

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[80]	6[81]		
Units: cm				
arithmetic mean (standard deviation)	-7.08 (± 6.93)	-1.17 (± 4.40)		

Notes:

[80] - number of participants at baseline/w24/w48: 13/12/12

[81] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Waist Circumference

Statistical analysis description:

Baseline to Week 24; mITT LOCF.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0537 [82]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-5.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.46
upper limit	0.1

Notes:

[82] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for Waist Circumference

Statistical analysis description:

Baseline to Week 48; mITT LOCF.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3772 [83]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.98
upper limit	3.61

Notes:

[83] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 for Waist Circumference

Statistical analysis description:

Week 24 to week 48; mITT LOCF.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1171 [84]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	6.91

Notes:

[84] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Secondary: Lipid Profile

End point title	Lipid Profile

End point description:

Change in lipid profile from baseline to week 24, from baseline to week 48, and from week 24 to week 48. mITT observed values

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[85]	6[86]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Change in total cholesterol from baseline to W24	-0.17 (± 0.46)	-0.17 (± 0.45)		
Change in total cholesterol from baseline to W48	-0.01 (± 0.60)	-0.22 (± 0.75)		
Change in total cholesterol from W24 to W48	0.16 (± 0.48)	-0.05 (± 0.69)		
Change in HDL cholesterol from baseline to week 24	0.04 (± 0.21)	-0.02 (± 0.37)		
Change in HDL cholesterol from baseline to week 48	0.09 (± 0.26)	0.03 (± 0.25)		
Change in HDL cholesterol from week 24 to week 48	0.05 (± 0.24)	0.05 (± 0.16)		
Change in LDL cholesterol from baseline to week 24	-0.23 (± 0.39)	-0.20 (± 0.43)		
Change in LDL cholesterol from baseline to week 48	-0.15 (± 0.38)	-0.32 (± 0.53)		
Change in LDL cholesterol from week 24 to week 48	0.08 (± 0.28)	-0.12 (± 0.45)		
Change in triglycerides from baseline to week 24	-0.08 (± 0.77)	-0.30 (± 0.76)		
Change in triglycerides from baseline to week 48	-0.07 (± 0.77)	-0.48 (± 0.28)		
Change in triglycerides from week 24 to week 48	0.01 (± 0.69)	-0.18 (± 0.66)		

Notes:

[85] - number of participants at baseline/w24/w48: 13/12/12

[86] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 Change in total cholesterol
Statistical analysis description: Baseline to Week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8623 [87]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.5

Notes:
[87] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 2 Change in HDL cholesterol
Statistical analysis description:	
Baseline to Week 24; mITT observed.	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8327 [88]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.3

Notes:
[88] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 Change in LDL cholesterol
Statistical analysis description:	
Baseline to Week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.808 [89]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.42

Notes:
[89] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 4 Change in triglycerides
Statistical analysis description:	
Baseline to Week 24; mITT observed.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5791
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	1.07

Statistical analysis title	Statistical Analysis 5 Change in cholesterol
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9337 [90]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.77

Notes:

[90] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 6 Change in HDL cholesterol
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9305 [91]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.23

Notes:

[91] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 7 Change in LDL cholesterol
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.691 [92]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.59

Notes:

[92] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 8 Change in triglycerides
Statistical analysis description:	
Baseline to Week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2688 [93]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.01

Notes:

[93] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 9 Change in cholesterol

Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8262 [94]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.67

Notes:

[94] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 10 Change in HDL cholesterol
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8293 [95]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.17

Notes:

[95] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 11 Change in LDL cholesterol
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5486 [96]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.49

Notes:

[96] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 12 Change in triglycerides

Statistical analysis description:

Week 24 to week 48; mITT LOCF.

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3226 [97]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.75

Notes:

[97] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: Quality of Life - SF-36

End point title	Quality of Life - SF-36

End point description:

Change in quality of life by use of the Short Form 36 Health Survey (SF-36) scores from baseline to week 24, from baseline to week 48, and from week 24 to week 48
The physical component summary score includes the aggregated scores for scales of physical functioning, rolephysical, bodily pain, and general health. The mental health component summary score includes the aggregated scores for scales of vitality, social functioning, role-emotional, and mental health. Scores range from 0 to 100; higher score indicates better health. mITT observed values

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[98]	6[99]		
Units: score on scale				
arithmetic mean (standard deviation)				

Physical component from baseline to week 24	0.90 (± 7.59)	1.36 (± 3.74)		
Physical component from baseline to week 48	0.70 (± 5.98)	2.41 (± 4.82)		
Physical component from week 24 to week 48	-0.21 (± 6.80)	1.05 (± 3.64)		
Mental component from baseline to week 24	-3.08 (± 11.44)	-0.49 (± 2.02)		
Mental component from baseline to week 48	-1.46 (± 7.74)	0.49 (± 1.74)		
Mental component from week 24 to week 48	1.62 (± 11.46)	0.98 (± 2.29)		

Notes:

[98] - number of participants at baseline/w24/w48: 13/12/12

[99] - number of participants at baseline/w24/w48: 8/6/6

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Physical component sco
Statistical analysis description:	
From baseline to week 24; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.842
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.55
upper limit	6.73

Statistical analysis title	Statistical Analysis 2 for Mental component score
Statistical analysis description:	
From baseline to week 24; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6693 [100]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.15
upper limit	6.67

Notes:

[100] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 for Physical component scor
Statistical analysis description:	
From baseline to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5444 [101]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.12
upper limit	4.46

Notes:

[101] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 4 for Mental component score
Statistical analysis description:	
From baseline to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5595 [102]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.47
upper limit	4.76

Notes:

[102] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 5 for Physical component scor

Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4331 [103]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.54
upper limit	3.41

Notes:

[103] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 6 for Mental component score
Statistical analysis description:	
Week 24 to week 48; mITT LOCF.	
Comparison groups	Placebo -> Tesofensine/Metoprolol v Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6427 [104]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	5.03

Notes:

[104] - P-value from an ANCOVA model with treatment as factor and baseline as covar

Secondary: Frequency of Adverse Events and Serious Adverse Events - Open-label Extension

End point title	Frequency of Adverse Events and Serious Adverse Events - Open-label Extension
End point description:	
Number and frequency of adverse events and serious adverse events reported from week 24 to week 48	
End point type	Secondary
End point timeframe:	
from week 24 to week 48	

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	6		
Units: counts of participants				
Infections and infestations	6	4		
Gastrointestinal disorders	5	3		
Musculoskeletal and connective tissue disorders	7	1		
Nervous system disorders	3	4		
General disorders and administration site conditio	4	0		
Psychiatric disorders	2	2		
Cardiac disorders	0	3		
Injury, poisoning and procedural complicati	1	1		
Vascular disorders	0	2		
Blood and lymphatic system disorders	1	0		
Investigations	1	0		
Respiratory, thoracic and mediastinal disorders	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Heart Rate and Blood Pressure (Change)

End point title	Heart Rate and Blood Pressure (Change)

End point description:

Change in heart rate and blood pressure from baseline to week 24, from baseline to week 48, and from week 24 to
week 48

End point type	Secondary

End point timeframe:

from baseline to week 24, from baseline to week 48 and from week 24 to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: mmHg (BP) / bpm (HR)				
arithmetic mean (standard deviation)				
Change in Systolic BP from baseline to week 24	2.0 (± 13)	-4.2 (± 8)		
Change in Systolic BP from baseline to week 48	5.8 (± 14)	9.7 (± 13)		

Change in Systolic BP from week 24 to wek 48	5.0 (± 11)	-5.5 (± 14)		
Change in Diastolic BP from baseline to week 24	2.8 (± 11)	-2.0 (± 11)		
Change in Diastolic BP from baseline to week 48	6.5 (± 12)	-1.0 (± 13)		
Change in Diastolic BP from week 24 to week 48	4.2 (± 9)	1.0 (± 10)		
Change in Heart Rate from baseline to week 24	-2.4 (± 11)	-7.0 (± 12)		
Change in Heart Rate from baseline to week 48	0.1 (± 7)	0.7 (± 20)		
Change in Heart Rate from week 24 to week 48	4.2 (± 8)	7.7 (± 10)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Heart Rate and Blood Pr
Statistical analysis description:	
From baseline to week 24; safety set LOCF. (Change in systolic blood pressure)	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3037 [105]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	5.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.76
upper limit	17.48
Variability estimate	Standard deviation

Notes:

[105] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 2 for Heart Rate and Blood Pr
Statistical analysis description:	
From baseline to week 48; safety set LOCF. (Change in systolic blood pressure)	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7912 [106]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.85
upper limit	10.16
Variability estimate	Standard deviation

Notes:

[106] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 for Heart Rate and Blood Pr

Statistical analysis description:

From baseline to week 24; safety set LOCF. (Change in heart rate)

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.551 [107]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.72
upper limit	12.12
Variability estimate	Standard deviation

Notes:

[107] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 4 for Heart Rate and Blood Pr

Statistical analysis description:

From baseline to week 48; safety set LOCF. (Change in systolic blood pressure)

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1773 [108]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	10.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.25
upper limit	25.83
Variability estimate	Standard deviation

Notes:

[108] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 5 for Heart Rate and Blood Pr
Statistical analysis description:	
From baseline to week 48; safety set LOCF. (Change in diastolic blood pressure)	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.798 [109]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.55
upper limit	12.2
Variability estimate	Standard deviation

Notes:

[109] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 6 for Heart Rate and Blood Pr
Statistical analysis description:	
From baseline to week 48; safety set LOCF. (Change in heart rate)	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7256 [110]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.88
upper limit	10.63
Variability estimate	Standard deviation

Notes:

[110] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 7 for Heart Rate and Blood Pr
Statistical analysis description:	
From week 24 to week 48; safety set LOCF. (Change in systolic blood pressure)	
Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158 [111]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	7.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	18.94
Variability estimate	Standard deviation

Notes:

[111] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 8 for Heart Rate and Blood Pr

Statistical analysis description:

From week 24 to week 48; safety set LOCF. (Change in diastolic blood pressure)

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7021 [112]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.36
upper limit	10.64
Variability estimate	Standard deviation

Notes:

[112] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 9 for Heart Rate and Blood Pr

Statistical analysis description:

From week 24 to week 48; safety set LOCF. (Change in heart rate)

Comparison groups	Tesofensine/Metoprolol -> Tesofensine/Metoprolol v Placebo -> Tesofensine/Metoprolol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4822 [113]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-3.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.05
upper limit	6.48
Variability estimate	Standard deviation

Notes:

[113] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Secondary: 24 Hours Blood Pressure

End point title	24 Hours Blood Pressure

End point description:

Changes in 24 hours blood pressure from baseline to week 12 and baseline to week 24

End point type	Secondary

End point timeframe:

from baseline to week 12 and baseline to week 24

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic BP mean change from baseline to week 12	-8.0 (± 20)	0.7 (± 14)		
Systolic BP mean change from baseline to week 24	2.3 (± 20)	-8.4 (± 17)		
Diastolic BP mean change from baseline to W12	0.2 (± 9)	3.7 (± 8)		
Diastolic BP mean change from baseline to W24	3.7 (± 8)	-2.8 (± 9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for 24 Hours Blood Pressure

Statistical analysis description:

From baseline to week 24; mITT LOCF. (Change in systolic blood pressure mean)

Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8728 [114]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.17
upper limit	21.18
Variability estimate	Standard deviation

Notes:

[114] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Statistical analysis title	Statistical Analysis 2 for 24 Hours Blood Pressure

Statistical analysis description:

From baseline to week 24; mITT LOCF. (Change in diastolic blood pressure mean)

Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5714 [115]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.61
upper limit	11.54
Variability estimate	Standard deviation

Notes:

[115] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 3 for 24 Hours Blood Pressure

Statistical analysis description:

From baseline to week 12; mITT LOCF. (Change in systolic blood pressure mean)

Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2322 [116]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-10.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.51
upper limit	7.22
Variability estimate	Standard deviation

Notes:

[116] - P-value from an ANCOVA model with treatment as factor and baseline as covariate.

Statistical analysis title	Statistical Analysis 4 for 24 Hours Blood Pressure

Statistical analysis description:	
From baseline to week 12; mITT LOCF. (Change in diastolic blood pressure mean)	
Comparison groups	Tesofensine/Metoprolol v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4321 [117]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.61
upper limit	5.68
Variability estimate	Standard deviation

Notes:

[117] - P-value from an ANCOVA model with treatment as factor and baseline as covariate

Secondary: Plasma Trough Concentrations

End point title	Plasma Trough Concentrations

End point description:

Plasma trough concentrations of tesofensine, metabolite NS2360 and metoprolol for the active arm (the first 24 weeks
and then continuously up to week 48) and placebo arm (start of treatment at week 25 and then continuously up to week
48)

The placebo arm did not start treatment before week 25 and values are therefore 0 for week 12 and week 24

End point type	Secondary

End point timeframe:

baseline to week 48

End point values	Tesofensine/Metoprolol -> Tesofensine/Metoprolol	Placebo -> Tesofensine/Metoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	6		
Units: µg/L				
geometric mean (geometric coefficient of variation)				
Tesofensine Week 12	12.03 (± 38.6)	0 (± 0)		
Tesofensine Week 24	12.34 (± 55.4)	0 (± 0)		
Tesofensine Week 36	11.01 (± 54.4)	19.10 (± 56.1)		
Tesofensine Week 48	6.78 (± 394.7)	15.11 (± 70.2)		
NS2360 metab. Week 12	3.39 (± 48.5)	0 (± 0)		
NS2360 metab. Week 24	3.96 (± 71.9)	0 (± 0)		
NS2360 metab. Week 36	3.39 (± 57.1)	6.51 (± 56.3)		
NS2360 metab. Week 48	2.44 (± 157.3)	6.02 (± 67.7)		

Metoprolol Week 12	10.83 (± 120.8)	0 (± 0)		
Metoprolol Week 24	9.07 (± 281.4)	0 (± 0)		
Metoprolol Week 36	8.97 (± 309.6)	10.62 (± 206.0)		
Metoprolol Week 48	7.29 (± 156.9)	7.30 (± 578.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: 48 Hours Heart Rate and QT Interval at Baseline, Week 12 and Week 24

End point title	48 Hours Heart Rate and QT Interval at Baseline, Week 12 and Week 24

End point description:

For Part 1, 48 hours HR and QT interval from week 12 to week 24 were not recorded in the database and analysis of
changes not evaluated. Instead, abnormal findings over visits were summarized.
An abnormal ECG assessment at any post-baseline time point was recorded for 3 subjects (23% of 13) treated with
Tesomet and for none (0% of 8) receiving Placebo. Abnormal ECG findings detected in the three Tesomet treated
subjects are:
• QTc prolongation (466 ms)
• Bradycardia (56 bpm)
• QTc prolongation (460 ms) All were considered not clinically significant.

End point type	Secondary

End point timeframe:

baseline, week 12 and week 24

End point values	Tesofensine/Metoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: counts of participants				
ECG interretation baseline	14	8		
ECG interretation at week 12	12	6		
ECG interretation at week 24	12	6		
48 hour heart rate at baseline	13	8		
48 hour heart rate at week 12	12	6		
48 hour heart rate at week 24	12	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1 (DB): From the first dose of double-blind study drug during Part 1 until the last dose during Part 1 (24 W duration).
Part 2 (OLE): From the first dose of open-label study drug during Part 2 until the last dose during Part 2 (24 W duration)

Adverse event reporting additional description:

Safety Analysis Set incl. all subjects receiving at least one dose of study drug (active or placebo). For Part 2 (OLE I and OLE II) only new events staring in Part 2 are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Tesofensine/Metoprolol

Reporting group description:

Subjects were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily for 24 weeks during Part 1.

Reporting group title	Placebo

Reporting group description:

Subjects were randomized to receive matching placebo tablets once daily for 24 weeks during Part 1.

Reporting group title	Tesofensine/Metoprolol -> Tesofensine/Metoprolol

Reporting group description:

Subjects who received co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) once daily
for 24 weeks during Part 1 continued to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol once
daily for an additional 24 weeks in Part 2.

Reporting group title	Placebo -> Tesofensine/Metoprolol

Reporting group description:

Subjects who received matching placebo tablets once daily for 24 weeks during Part 1 were switched to receive
co-administration of 0.5 mg tesofensine/50 mg metoprolol once daily for an additional 24 weeks in Part 2.

Serious adverse events	Tesofensine/Metoprolol	Placebo	Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	1 / 8 (12.50%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Craniopharyngioma			

subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (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
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (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

Serious adverse events	Placebo -> Tesofensine/Metoprolol		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Craniopharyngioma			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 6 (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 %

Non-serious adverse events	Tesofensine/Metoprolol	Placebo	Tesofensine/Metoprolol -> Tesofensine/Metoprolol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	7 / 8 (87.50%)	11 / 11 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Orthostatic hypotension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Energy increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Influenza like illness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nasal discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hallucination, auditory			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Paranoia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	7 / 14 (50.00%)	1 / 8 (12.50%)	2 / 11 (18.18%)
occurrences (all)	7	1	2
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	3
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 14 (42.86%)	3 / 8 (37.50%)	1 / 11 (9.09%)
occurrences (all)	6	6	1
Dyskinesia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Headace			
subjects affected / exposed	5 / 14 (35.71%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	6	0	1
Paraesthesia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
lymphadenopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 14 (21.43%)	3 / 8 (37.50%)	0 / 11 (0.00%)
occurrences (all)	3	5	0
Constipation			
subjects affected / exposed	2 / 14 (14.29%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	2	0	2
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	2 / 8 (25.00%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Dry mouth			
subjects affected / exposed	6 / 14 (42.86%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	6	0	0
Faeces hard			
subjects affected / exposed	2 / 14 (14.29%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 14 (14.29%)	2 / 8 (25.00%)	2 / 11 (18.18%)
occurrences (all)	3	2	3
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	2 / 8 (25.00%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	3 / 14 (21.43%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Night sweats			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	4 / 11 (36.36%)
occurrences (all)	0	0	4
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Myalgia			

subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Eye infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Gastroenteritis viral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Gingivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Onychomycosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Oral herpes			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Viral tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 8 (25.00%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1

Non-serious adverse events	Placebo -> Tesofensine/Metoprolol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Energy increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nasal discomfort			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hallucination, auditory			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Paranoia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Blood pressure increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Wound			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dyskinesia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Headace			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Restless legs syndrome subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Blood and lymphatic system disorders lymphadenopathy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Faeces hard subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 2 / 6 (33.33%) 2 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		
Hepatobiliary disorders			

Cholecystitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Skin and subcutaneous tissue disorders Hyperhydrosis subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Joint stiffness subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 2 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		
Infections and infestations			

Eye infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastroenteritis viral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gingivitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Onychomycosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Tonsillitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			

Viral tonsillitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2019	Exclusion criterion 23 was original included to ensure that no subjects with depression are included into the study, and read as follows: PHQ-9 (Patient Health Questionnaire) score ≥ 10 or any score > 0 on question 9 at screening and baseline. In connection with the recruitment of subjects to the TM005 study it became evident, that a high proportion of the subjects was classified as screening failures due to a high score in the PHQ-9. This was due to an overlap between the terms and scoring in the questionnaire, and frequent symptoms of the HIO disease.
05 September 2019	Saniona wishes to also analyse for the trough value of the Tesofensine metabolite N-desmethylmetabolite NS2360. This analysis can be done on samples already taken for analysis of Tesofensine and metoprolol. Analysis of N-desmethyl-metabolite NS2360 has not previous been included in the protocol. BP values to be used for evaluation of exclusion criteria 1 has been clarified.
10 December 2019	Saniona wish to add Adverse Events of Special Interest to the protocol. Further a section regarding Water Retention and/or Hyponatremia has been added. The section regarding water retention and/or hyponatremia is added based on mechanism of action of Tesofensine, as a non-selective inhibitor of serotonin reuptake. Hence, it may be anticipated that an additive antidiuretic effect of Tensofensine may lead to increased risk of water retention and/or hyponatremia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported