Clinical trial results:
A Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose, Multi-Center Safety and Efficacy Study of Co-Administration of Tesofensine/Metoprolol for 12 weeks in Adult and Adolescent Patients with Prader-Willi Syndrome (PWS), followed by two open label 12 weeks extension periods for Adolescent Patients.

Summary

EudraCT number	2016-003694-18
Trial protocol	CZ HU
Global end of trial date	22 July 2019

Results information

Result version number	v1 (current)
This version publication date	20 July 2022
First version publication date	20 July 2022

Trial information

Trial identification

Sponsor protocol code	TM002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03149445
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 Develovment Officer, Saniona A/S, +45 70 70 52 25, janus.larsen@saniona.com
Scientific contact	Janus Schreiber Larsen, Chief Develovment Officer, Saniona A/S, +45 70 70 52 25, janus.larsen@saniona.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2019
Global end of trial reached?	Yes
Global end of trial date	22 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to investigate the safety and efficacy of co-administration of tesofensine/metoprolol treatment versus placebo in adult and pediatric subjects with Prader-Willi syndrome. The primary objective is to examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS in a study with an open label extension.

Protection of trial subjects:

Any records will be kept and handled in compliance with effective legal regulations (Act XLVII of 1997 and CXII of 2011). The patient's personal data will be processed by administrators who are the sponsor of this study (Saniona, A/S, Smedeland 26B, DK2600 Glostrup) and healthcare service providers, in compliance with Act No 101/2000 Coll., on Personal Data Protection.

The protocol, the informed consent document, relevant supporting information, and all types of patient recruitment or advertisement information were approved by the appropriate IEC prior to study start. The protocol was approved by the competent authorities of the Czech Republic and by the competent authorities in Hungary. Amendments to the protocol were approved, as applicable, by the IEC and competent authorities prior to implementation of any changes in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Hungary: 10
Worldwide total number of subjects	18
EEA total number of subjects	18

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	9
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was planned to be conducted in two steps: Step 1 in adult patients and Step 2 in adolescent patients. Step 2 was initiated following an unblinded analysis of data from Step 1. Participation in a 12-week OLE I was offered to patients who completed Step 2. Participation in a 12 week OLE II was offered to all eligible patients of OLE I.

Pre-assignment

Screening details:

Patients who gave written informed consent were assigned a subject screening number and underwent the screening visit assessments to determine their eligibility for the study, and if found eligible they were randomized on the same day to minimize their travelling to the site.

Period 1

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

Blinding implementation details:

It was a double-blind, placebo-controlled study, i.e. investigators, site staff and patients were blinded as to the treatment allocation. This was achieved by the following procedures:
The IMP blinding was done by third party
The placebo was identical to IMP with regard to size, color, and general appearance

Arms

Are arms mutually exclusive?	Yes
Arm title	Tesomet 0.50/50 mg

Arm description:

Subjects (adults) were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication Tesomet) once daily for 91 days (+2 days after the final assessments with halfdose of metoprolol) during Step 1.

Arm type	Experimental
Investigational medicinal product name	Tesomet (Tesofensine/Metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tesomet (tesofensine/metoprolol): 0.5mg/50mg q.d., per oral

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo matching IMP, q.d.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching IMP, q.d.

Number of subjects in period 1[1]	Tesomet 0.50/50 mg	Placebo
Started	6	3
Completed	2	2
Not completed	4	1
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 9 adult subjects were included in Step 1 (baseline period). After finalization of Step 1, Step 2 was initiated and 9 adolescent subjects were included in Step 2.

Period 2

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

Blinding implementation details:

It was a double-blind, placebo-controlled study, i.e. investigators, site staff and patients were blinded as to the treatment allocation. This was achieved by the following procedures:
The IMP blinding was done by third party
Within Step 2, the placebo matching metoprolol 25 mg was slightly different in size therefore the site staff and CRA were trained in appropriate IMP handling procedures in order to preserve the blinding of the study

Arms

Are arms mutually exclusive?	No
Arm title	Tesomet 0.125/25 mg

Arm description:

Subjects (adolescents) were randomized to receive co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 91 days: +2days after the final assessments with halfdose.

Arm type	Experimental
Investigational medicinal product name	Tesomet (Tesofensine/Metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tesomet (tesofensione/metoprolol) 0.125mg/25mg, q.d., per oral

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo matching IMP, q.d.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching IMP, q.d.

Number of subjects in period 2	Tesomet 0.125/25 mg	Placebo
Started	5	4
Completed	5	4

Period 3

Period 3 title	OLE I
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg

Arm description:

Participation in a 12-week OLE I was offered to patients who completed Step 2. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE I.

Arm type	Experimental
Investigational medicinal product name	Tesomet (Tesofensine/Metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tesomet (tesofensione/metoprolol) 0.125mg/25mg, q.d., per oral

Arm title	Placebo -> Tesomet 0.125/25 mg

Arm description:

Participation in a 12-week OLE I was offered to patients who completed Step 2. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE I.

Arm type	Experimental

Investigational medicinal product name	Tesomet (Tesofensine/Metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tesomet (tesofensine/metoprolol): 0.125mg/25mg q.d., per oral

Number of subjects in period 3	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg
Started	4	4
Completed	4	3
Not completed	0	1
Lost to follow-up	-	1

Period 4

Period 4 title	OLE II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tesomet 0.25/25 mg

Arm description:

Participation in a 12 week OLE II was offered to all eligible patients of OLE I. Patients were receiving co-administration of 0.25 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE II.

Arm type	Experimental
Investigational medicinal product name	Tesomet (Tesofensine/Metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tesomet (tesofensine/metoprolol): 0.25mg/25mg q.d., per oral

Arm title	Tesomet 0.125/25 mg

Arm description:

Participation in a 12 week OLE II was offered to all eligible patients of OLE I. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication) once daily for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Tesomet (Tesofensine/Metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tesomet (tesofensione/metoprolol) 0.125mg/25mg, q.d., per oral

Number of subjects in period 4[2]	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Started	5	1
Completed	3	1
Not completed	2	0
Adverse event, non-fatal	2	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Participation in a 12 week OLE II was offered to all patients who completed OLE I. 7 patients completed OLE I and 6 patients continued to OLE II. The numbers completing OLE I and the numbers starting OLE II are therefore not identical.

Baseline characteristics

Reporting groups	
Reporting group title	Tesomet 0.50/50 mg

Reporting group description:

Subjects (adults) were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication Tesomet) once daily for 91 days (+2 days after the final assessments with halfdose of metoprolol) during Step 1.

Reporting group title	Placebo

Reporting group description: -

Reporting group values	Tesomet 0.50/50 mg	Placebo	Total
Number of subjects	6	3	9
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
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults aged (18-30)	6	3	9
Gender categorical Units: Subjects			
Female	4	2	6
Male	2	1	3

End points

End points reporting groups

Reporting group title	Tesomet 0.50/50 mg
Reporting group description:	
Subjects (adults) were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication Tesomet) once daily for 91 days (+2 days after the final assessments with halfdose of metoprolol) during Step 1.	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tesomet 0.125/25 mg
Reporting group description:	
Subjects (adolescents) were randomized to receive co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 91 days: +2days after the final assessments with halfdose.	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg
Reporting group description:	
Participation in a 12-week OLE I was offered to patients who completed Step 2. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE I.	
Reporting group title	Placebo -> Tesomet 0.125/25 mg
Reporting group description:	
Participation in a 12-week OLE I was offered to patients who completed Step 2. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE I.	
Reporting group title	Tesomet 0.25/25 mg
Reporting group description:	
Participation in a 12 week OLE II was offered to all eligible patients of OLE I. Patients were receiving co-administration of 0.25 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE II.	
Reporting group title	Tesomet 0.125/25 mg
Reporting group description:	
Participation in a 12 week OLE II was offered to all eligible patients of OLE I. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication) once daily for 12 weeks.	

Primary: Percent change from baseline to end of treatment in mean body weight

End point title	Percent change from baseline to end of treatment in mean body weight
End point description:	
Percent change from baseline to end of treatment in body weight. LOCF.	
End point type	Primary
End point timeframe:	
DB Step 1: Day 1 to Day 91 DB Step 2: Day 1 to Day 91 OLE I: Day 91 to Day 181 OLE II: Day 181 to Day 271	

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	5	4
Units: percent				
arithmetic mean (standard deviation)	-4.09 (± 3.73)	-0.38 (± 2.05)	3.56 (± 2.73)	3.00 (± 2.35)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	1
Units: percent				
arithmetic mean (standard deviation)	5.79 (± 2.08)	0.33 (± 3.26)	-1.20 (± 3.80)	-5.51 (± 0)

Statistical analyses

Statistical analysis title	Step 1: Percent change in body weight
Comparison groups	Placebo v Tesomet 0.50/50 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1045 [1]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	1.5

Notes:

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

Statistical analysis title	Step 2: Percent change in body weight
Comparison groups	Tesomet 0.125/25 mg v Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7422 [2]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	5.3

Notes:

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

Statistical analysis title	OLE I: Percent change in body weight
Comparison groups	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg v Placebo -> Tesomet 0.125/25 mg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	11

Notes:

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

Statistical analysis title	OLE II: Percent change in body weight
Comparison groups	Tesomet 0.25/25 mg v Tesomet 0.125/25 mg
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3847 [4]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	17.8

Notes:

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

Secondary: Change from baseline to end of treatment in mean body weight	
End point title	Change from baseline to end of treatment in mean body weight

End point description:

Change from baseline to end of treatment in body weight [kg]. LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	5	4
Units: kilogram(s)				
arithmetic mean (standard deviation)	-4.15 (± 4.82)	-0.77 (± 3.23)	3.10 (± 2.85)	2.25 (± 1.71)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	1
Units: kilogram(s)				
arithmetic mean (standard deviation)	4.75 (± 2.41)	0.45 (± 2.82)	-0.90 (± 3.20)	-3.50 (± 0)

Statistical analyses

Statistical analysis title	Step 1: Change in body weight
Comparison groups	Tesomet 0.50/50 mg v Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1326 [5]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.9
upper limit	2.5

Notes:

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

Statistical analysis title	Step 2: Change in body weight
Comparison groups	Tesomet 0.125/25 mg v Placebo

Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5148 [6]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	5.3

Notes:

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

Statistical analysis title	OLE I: Change in body weight
Comparison groups	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg v Placebo -> Tesomet 0.125/25 mg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0605 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	9.4

Notes:

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

Statistical analysis title	OLE II: Change in body weight
Comparison groups	Tesomet 0.25/25 mg v Tesomet 0.125/25 mg
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5198 [8]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	14

Notes:

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

Secondary: Change from baseline to end of treatment in HQ-CT score

End point title	Change from baseline to end of treatment in HQ-CT score

End point description:

Change from baseline to end of treatment in HQ-CT score. LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	5	4
Units: score on a scale				
arithmetic mean (standard deviation)	-8.50 (± 9.25)	-4.00 (± 7.07)	-3.30 (± 6.82)	-6.75 (± 3.69)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	1
Units: score on a scale				
arithmetic mean (standard deviation)	1.25 (± 5.68)	-1.75 (± 1.50)	-1.00 (± 2.00)	-2.00 (± 0)

Statistical analyses

Statistical analysis title	Step 1: Change in HQ-CT score
Comparison groups	Tesomet 0.50/50 mg v Placebo
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [9]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.5
upper limit	-3.6

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

Statistical analysis title	Step 2: Change in HQ-CT score
Comparison groups	Tesomet 0.125/25 mg v Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5142 [10]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	9.5

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

Statistical analysis title	OLE I: Change in HQ-CT score
Comparison groups	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg v Placebo -> Tesomet 0.125/25 mg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3794 [11]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	11.3

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

Statistical analysis title	OLE II: Change in HQ-CT score
Comparison groups	Tesomet 0.25/25 mg v Tesomet 0.125/25 mg
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.685 [12]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	8.1

Notes:

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

Secondary: Steady state concentrations of tesofensine and metoprolol as measured by trough values

End point title	Steady state concentrations of tesofensine and metoprolol as measured by trough values[13]

End point description:

Steady state concentrations of tesofensine and metoprolol as measured by trough values. Observed values.

End point type	Secondary

End point timeframe:

DB Step 1: Day 29
DB Step 2: Day 29
OLE I: Day 120
OLE II: Day 210

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics were planned for.

End point values	Tesomet 0.50/50 mg	Tesomet 0.125/25 mg	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	3
Units: µg/L				
geometric mean (geometric coefficient of variation)				
Tesofensine	16.29 (± 49.8)	3.34 (± 32.2)	4.14 (± 17.3)	5.06 (± 18.0)
Teso. metab.	2.97 (± 52.6)	0.79 (± 17.1)	1.45 (± 23.3)	1.00 (± 41.9)
Metoprolol	1.61 (± 903.7)	1.97 (± 285.5)	2.81 (± 119.0)	3.32 (± 32.0)

End point values	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: µg/L				
geometric mean (geometric coefficient of variation)				
Tesofensine	4.13 (± 137.5)	6.43 (± 0)		
Teso. metab.	1.56 (± 49.1)	1.98 (± 0)		
Metoprolol	1.76 (± 242.5)	14.50 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in fat- and fat free mass (%) by dual X-ray absorptiometry (DEXA)

End point title	Change from baseline to end of treatment in fat- and fat free mass (%) by dual X-ray absorptiometry (DEXA)[14]

End point description:

Change from baseline to end of treatment in fat- and fat free mass (%) by dual X-ray absorptiometry (DEXA). Observed values.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics were planned for.

End point values	Tesomet 0.50/50 mg	Tesomet 0.125/25 mg	Placebo	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	3
Units: percent				
arithmetic mean (standard deviation)				
Fat mass	-1.27 (± 1.07)	-0.13 (± 0.25)	-0.50 (± 0.85)	1.20 (± 1.74)
Fat free mass	1.19 (± 1.11)	0.137 (± 0.217)	-2.080 (± 4.511)	0.053 (± 2.559)

End point values	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	1	
Units: percent				
arithmetic mean (standard deviation)				
Fat mass	-0.05 (± 0.21)	-1.70 (± 0.1)	-1.50 (± 0)	
Fat free mass	4.290 (± 3.974)	0.000 (± 0.1)	1.470 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in BMD by dual X-ray absorptiometry (DEXA)

End point title	Change from baseline to end of treatment in BMD by dual X-ray absorptiometry (DEXA)[15]

End point description:

Change from baseline to end of treatment in BMD by dual X-ray absorptiometry (DEXA). Observed values.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics were planned for.

End point values	Tesomet 0.50/50 mg	Tesomet 0.125/25 mg	Placebo	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	3
Units: g/cm2				
arithmetic mean (standard deviation)	0.002 (± 0.017)	0.019 (± 0.009)	0.035 (± 0.008)	-0.006 (± 0.008)

End point values	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	1	
Units: g/cm2				
arithmetic mean (standard deviation)	-0.007 (± 0.009)	0.023 (± 0.0)	0.009 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in BMC by dual X-ray absorptiometry (DEXA)

End point title	Change from baseline to end of treatment in BMC by dual X-ray absorptiometry (DEXA)[16]

End point description:

Change from baseline to end of treatment in BMC by dual X-ray absorptiometry (DEXA). Observed values.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics were planned for.

End point values	Tesomet 0.50/50 mg	Tesomet 0.125/25 mg	Placebo	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	3
Units: gram(s)				
arithmetic mean (standard deviation)	9.5 (± 63.8)	74.77 (± 22.46)	35.53 (± 55.37)	-1.12 (± 17.86)

End point values	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	1	
Units: gram(s)				
arithmetic mean (standard deviation)	5.69 (± 66.33)	22.51 (± 46.6)	-21.90 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in HR

End point title	Change from baseline to end of treatment in HR

End point description:

Change from baseline to end of treatment in HR (bpm). LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	5	4
Units: bpm				
arithmetic mean (standard deviation)	8.22 (± 4.26)	7.89 (± 7.88)	5.87 (± 11.01)	2.75 (± 8.96)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	1
Units: bpm				
arithmetic mean (standard deviation)	2.42 (± 15.14)	0.33 (± 8.65)	-9.50 (± 10.86)	-5.67 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in SBP and DBP

End point title	Change from baseline to end of treatment in SBP and DBP

End point description:

Change from baseline to end of treatment in SBP (mmHg) and DBP (mmHg). LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	5	4
Units: mmHg				
arithmetic mean (standard deviation)				
Change in SBP	-2.72 (± 9.96)	0.11 (± 15.22)	-0.13 (± 15.79)	-5.00 (± 9.26)
Change in DBP	0.94 (± 10.72)	-8.89 (± 8.00)	-1.07 (± 7.06)	0.33 (± 2.54)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	1
Units: mmHg				
arithmetic mean (standard deviation)				
Change in SBP	5.67 (± 11.30)	8.08 (± 6.45)	-5.33 (± 2.60)	-9.67 (± 0)
Change in DBP	2.92 (± 10.22)	4.00 (± 5.40)	-6.42 (± 3.95)	1.33 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events
End point description: Incidence of AEs	
End point type	Secondary
End point timeframe: DB Step 1: Day 1 to Day 91 DB Step 2: Day 1 to Day 91 OLE I: Day 91 to Day 181 OLE II: Day 181 to Day 271	

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	5	4
Units: Number of AE/Number of subjects				
Total number of AE	23	10	19	9
Subjects with at least one AE	6	3	5	3
Subjects with at least one SAE	3	0	0	0

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	5	1
Units: Number of AE/Number of subjects				

Total number of AE	11	12	14	5
Subjects with at least one AE	4	4	5	1
Subjects with at least one SAE	0	0	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in ECG parameters

End point title	Change from baseline to end of treatment in ECG parameters

End point description:

Change from baseline to end of treatment in ECG parameters. Observed values

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[17]	2[18]	4[19]	4[20]
Units: ms				
arithmetic mean (standard deviation)				
PR interval	-20.0 (± 0)	0 (± 0)	0.0 (± 0)	20.0 (± 0.0)
QRS duration	-4.0 (± 8.5)	4.0 (± 0.0)	2.0 (± 2.3)	2.0 (± 8.5)
QT interval	-7.0 (± 18.4)	19.0 (± 9.9)	-5.5 (± 27.2)	5.5 (± 27.2)
QTcF	-12.9 (± 4.4)	12.8 (± 19.8)	0.1 (± 24.4)	11.0 (± 20.4)
QTcB	-16.0 (± 2.8)	9.0 (± 25.5)	3.5 (± 31.8)	13.9 (± 21.4)

Notes:

[17] - 2 subjects in all categories except PR interval. 1 subject in PR interval.

[18] - 2 subjects in all categories except PR interval. 0 subjects in PR interval.

[19] - 4 subjects in all categories except PR interval. 1 subject in PR interval.

[20] - 4 subjects in all categories except PR interval. 2 subjects in PR interval.

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[21]	3[22]	2[23]	1
Units: ms				
arithmetic mean (standard deviation)				
PR interval	0.0 (± 0)	-20.0 (± 0)	0 (± 0)	10.0 (± 0)
QRS duration	-1.5 (± 3.0)	0.7 (± 5.0)	-4.0 (± 5.7)	0.0 (± 0)
QT interval	-5.0 (± 19.2)	-13.3 (± 16.2)	7.0 (± 7.1)	-20.0 (± 0)
QTcF	-3.7 (± 14.5)	-10.3 (± 29.3)	17.1 (± 4.5)	-2.9 (± 0)

QTcB	-2.6 (± 22.8)	-8.2 (± 37.3)	23.0 (± 2.9)	8.2 (± 0)

Notes:

[21] - 4 subjects in all categories except PR interval. 1 subject in PR interval.

[22] - 3 subjects in all categories except PR interval. 1 subject in PR interval.

[23] - 2 subjects in all categories except PR interval. 0 subjects in PR interval.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in HbA1c

End point title	Change from baseline to end of treatment in HbA1c

End point description:

Change from baseline to end of treatment in HbA1c (%). LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	5	4
Units: percent				
arithmetic mean (standard deviation)	0.11 (± 0.13)	0.15 (± 0.21)	0.06 (± 0.05)	0.15 (± 0.24)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	1
Units: percent				
arithmetic mean (standard deviation)	0.12 (± 0.26)	0.10 (± 0.17)	0.00 (± 0.12)	0.00 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in insulin

End point title	Change from baseline to end of treatment in insulin

End point description:

Change from baseline to end of treatment in insulin (mIU/L). LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	5	4
Units: mIU/L				
arithmetic mean (standard deviation)	2.67 (± 10.93)	1.50 (± 10.61)	1.95 (± 13.85)	-10.32 (± 17.20)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	1
Units: mIU/L				
arithmetic mean (standard deviation)	13.14 (± 22.15)	4.93 (± 5.25)	-1.35 (± 24.56)	-5.90 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in fasting pl. glucose, triglycerides, LDL and HDL cholesterol

End point title	Change from baseline to end of treatment in fasting pl. glucose, triglycerides, LDL and HDL cholesterol

End point description:

Change from baseline to end of treatment in fasting pl. glucose (mmol/L), triglycerides (mmol/L), LDL and HDL cholesterol (mmol/L). LOCF.

End point type	Secondary

End point timeframe:

DB Step 1: Day 1 to Day 91
DB Step 2: Day 1 to Day 91
OLE I: Day 91 to Day 181
OLE II: Day 181 to Day 271

End point values	Tesomet 0.50/50 mg	Placebo	Tesomet 0.125/25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	5	4
Units: mmol/L				
arithmetic mean (standard deviation)				
Fasting pl. glucose	0.27 (± 0.59)	0.30 (± 0.14)	-0.20 (± 0.58)	-0.30 (± 0.29)
Triglycerides	-0.07 (± 0.29)	-0.02 (± 0.06)	0.56 (± 1.32)	-1.33 (± 1.54)
LDL cholesterol	-0.16 (± 0.44)	-0.12 (± 0.32)	0.16 (± 0.21)	-0.32 (± 0.99)
HDL cholesterol	-0.10 (± 0.20)	-0.17 (± 0.01)	-0.03 (± 0.18)	-0.03 (± 0.17)

End point values	Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	Placebo -> Tesomet 0.125/25 mg	Tesomet 0.25/25 mg	Tesomet 0.125/25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	1
Units: mmol/L				
arithmetic mean (standard deviation)				
Fasting pl. glucose	1.07 (± 1.19)	0.37 (± 0.31)	0.60 (± 0.35)	-0.40 (± 0)
Triglycerides	-0.54 (± 1.23)	0.38 (± 0.14)	-0.13 (± 0.26)	0.13 (± 0)
LDL cholesterol	-0.02 (± 0.43)	-0.01 (± 0.43)	0.10 (± 0.32)	-0.25 (± 0)
HDL cholesterol	0.16 (± 0.22)	0.22 (± 0.11)	-0.05 (± 0.05)	-0.14 (± 0)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to end of study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Step 1 - Tesomet 0.50/50 mg

Reporting group description:

Subjects (adults) were randomized to receive co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication Tesomet) once daily for 91 days (+2 days after the final assessments with halfdose of metoprolol) during Step 1.

Reporting group title	Step 1 - Placebo

Reporting group description: -

Reporting group title	Step 2- Tesomet 0.125/25 mg

Reporting group description:

Subjects (adolescents) were randomized to receive co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 91 days: +2days after the final assessments with halfdose.

Reporting group title	Step 2 - Placebo

Reporting group description: -

Reporting group title	OLE I - Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg

Reporting group description:

Participation in a 12-week OLE I was offered to patients who completed Step 2. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE I.

Reporting group title	OLE I - Placebo -> Tesomet 0.125/25 mg

Reporting group description:

Participation in a 12-week OLE I was offered to patients who completed Step 2. Patients were receiving co-administration of 0.125 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE I.

Reporting group title	OLE II - Tesomet 0.25/25 mg

Reporting group description:

Participation in a 12 week OLE was offered to all eligible patients of OLE I. Patients were receiving coadministration of 0.25 mg tesofensine/25 mg metoprolol (active medication Tesomet) once daily for 12 weeks during OLE II.

Reporting group title	OLE II - Tesomet 0.125/25 mg

Reporting group description:

Participation in a 12 week OLE was offered to all eligible patients of OLE I. Patients were receiving coadministration of 0.125 mg tesofensine/25 mg metoprolol (active medication) once daily for 12 weeks.

Serious adverse events	Step 1 - Tesomet 0.50/50 mg	Step 1 - Placebo	Step 2- Tesomet 0.125/25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Anger			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (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
Hallucination			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (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
Abnormal behaviour			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (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
Infections and infestations			
Retroperitoneal abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Step 2 - Placebo	OLE I - Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	OLE I - Placebo -> Tesomet 0.125/25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Anger			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Retroperitoneal abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	OLE II - Tesomet 0.25/25 mg	OLE II - Tesomet 0.125/25 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Anger			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal behaviour			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Retroperitoneal abscess			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Step 1 - Tesomet 0.50/50 mg	Step 1 - Placebo	Step 2- Tesomet 0.125/25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 3 (100.00%)	5 / 5 (100.00%)
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Arthropod sting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Somnolence			

subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Feeling cold			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Epistaxis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	2 / 5 (40.00%)
occurrences (all)	3	0	2
Affect lability			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Aggression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Delusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Illusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Abnormal behaviour			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Mood swings			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dermatillomania			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hallucination			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Panic attack			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Mood altered			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Negativism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Pain in extremity			

subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Step 2 - Placebo	OLE I - Tesomet 0.125/25 mg -> Tesomet 0.125/25 mg	OLE I - Placebo -> Tesomet 0.125/25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0

Affect lability			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Aggression			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Delusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Illusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Mood swings			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dermatillomania			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Panic attack			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Depressed mood			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Mood altered			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Negativism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	2	1	2
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Osteopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Otitis externa			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	OLE II - Tesomet 0.25/25 mg	OLE II - Tesomet 0.125/25 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	1 / 1 (100.00%)	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Arthropod sting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Feeling cold			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Affect lability			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Aggression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Delusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Illusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Restlessness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Abnormal behaviour			
subjects affected / exposed	2 / 5 (40.00%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Mood swings			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dermatillomania			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hallucination			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Panic attack			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Depressed mood			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Mood altered			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Negativism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nervousness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue			

disorders			
Osteoporosis			
subjects affected / exposed	3 / 5 (60.00%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Osteopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Otitis externa			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Tonsillitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2016	N/A
04 January 2017	For Czech Republic only. SUKL as a Czech RA was added to paragraphs where information about SUKL oversight/approval is needed Dietary instructions for patient suffered from diabetes were added Wording of paragraph „UNBLINDING" was updated
22 March 2017	HQCT questionnaire added, Update of timelines of the clinical trial
10 August 2017	Decrease of dose of tesofensin to 0,25mg Maximum number of randomized patients was increased to 20 Wording of inclusion criteria No.7 was changed to „Growth hormone is allowed; but subject must be on a stable dose of growth hormone ">2 months" Update of timelines of the clinical trial Address of central laboratories was added
04 December 2017	An unblinded interim analysis after Step 1 will be performed by Sponsor and interim analysis will be done, SUKL will be given all the unblided data for review Step 2 will start only after SUKL positive opinion regarding to interim analysis and unblinded dat
28 March 2018	Dose reduction of tesofensine and metoprolol in pediatric patients. Psychiatric examinations are added to each patient visit. Change in Follow up, V15. Data on the duration of the clinical trial were updated. Exclusion criterium No. 7 was extended. The minimum number of patients was adjusted to 5.
10 October 2018	Open Label Phase was added. Visit V14 (last visit of step II) will be simultaneously first visit of OLE Phase for participated patient. To the Protocol Name was added „A 12 Weeks Open Label Extension. New exclusion and inclusion criteria were created. Overall study description was extended. Study procedure for V14-V18 are described in this Protocol. End of OLE was predicted to be in April/May 2019. Manufacture of IMP was changed. Unblinding is not applicable in OLE. For patient in OLE remain the same screening number as in step 2.
06 February 2019	Second Open Label Phase was added. Last visit V17 of OLE will be first visit of OLE II. To the Protocol Name was added „Second 12 Weeks Open Label Extension. Inclusion and exclusion criteria were updated. Estimated end of study is on Jun 2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The administration of tesofensine 0.5mg/metoprolol 50 mg led to unintendedly high plasma levels of tesofensine exceeding efficacious levels by a factor two to three.

Notes: