Clinical trial results:
A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE-DOSE, TWO-CENTRE, SAFETY AND EFFICACY STUDY OF CO-ADMINISTRATION OF TESOFENSINE/METOPROLOL TREATMENT IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Summary

EudraCT number	2015-005522-19
Trial protocol	DE
Global end of trial date	22 November 2016

Results information

Result version number	v1 (current)
This version publication date	30 December 2017
First version publication date	30 December 2017

Trial information

Trial identification

Sponsor protocol code	TM001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02737891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Saniona A/S
Sponsor organisation address	Baltorpvej 154 , Ballerup , Denmark, 2750
Public contact	Jørgen Drejer, PhD CEO and founder, Saniona, A/S, +45 20289705, jd@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	24 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 November 2016
Global end of trial reached?	Yes
Global end of trial date	22 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of co-administration of tesofensine/ metoprolol treatment vs. placebo on 24-hour mean heart rate

Protection of trial subjects:

All available measures were implemented per local EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2016
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	Germany: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	54
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects from general population in Neuss and Mainz were recruited for the study.

Pre-assignment

Screening details:

Subjects who gave the written informed consent were screened for the study. For subjects on any anti-diabetic medications, treatment with all anti-diabetic medications except metformin was washed out. The subjects returned for a baseline visit at the end of the washout period (1-4 weeks).

Period 1

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

Blinding implementation details:

Randomization and blinding was used in order to avoid bias introduced through an association between allocation order of IMP and subject characteristics. Subjects were also stratified based on their background anti-diabetic therapy – on metformin vs. metformin + further anti-diabetic agent.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo tesofensine/metoprolol

Arm description:

Each subject was randomly allocated to one of two treatment arms. Treatment arm 1 was tesofensine 0.5 mg + metoprolol 100 mg administered once a day, in the morning with a meal (the first 2 days a loading dose of 1.0 mg/d of tesofensine was given) and treatment arm 2 was placebo tablets matching oral tesofensine + metoprolol administered once a day, in the morning with meal (the first 2 days a loading dose of 1.0 mg/d of placebo tesofensine was given). Each tablet was formulated separately; a currently available commercial formulation of metoprolol, MetoHEXAL® 100 mg retard, was used.

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

Dosage and administration details:

0.5mg placebo

Investigational medicinal product name	placebo metoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg placebo

Arm title	Tesofensine/Metoprolol

Arm description:

Each subject was randomly allocated to one of two treatment arms. Treatment arm 1 was tesofensine 0.5 mg + metoprolol 100 mg administered once a day, in the morning with a meal (the first 2 days a loading dose of 1.0 mg/d of tesofensine was given) and treatment arm 2 was placebo tablets matching oral tesofensine + metoprolol administered once a day, in the morning with meal (the first 2 days a loading dose of 1.0 mg/d of placebo tesofensine was given). Each tablet was formulated separately; a

currently available commercial formulation of metoprolol, MetoHEXAL® 100 mg retard, was used.

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

Dosage and administration details:
0.5mg

Investigational medicinal product name	metoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
100mg

Number of subjects in period 1	Placebo tesofensine/metoprolol	Tesofensine/Metoprolol
Started	30	30
Completed	28	30
Not completed	2	0
one withdrawn consent and second SAE	2	-

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	60	60	
Age categorical			
inclusion criteria: 18-70 years of age			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	54	54	
From 65-84 years	6	6	
85 years and over	0	0	
Adult	0	0	
Gender categorical			
Randomisation			
Units: Subjects			
Female	21	21	
Male	39	39	

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was based on the intention-to-treat principle and it included all randomized subjects

Reporting group values	FAS		
Number of subjects	60		
Age categorical			
inclusion criteria: 18-70 years of age			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	54		
From 65-84 years	6		
85 years and over	0		
Adult	0		
Gender categorical			
Randomisation			
Units: Subjects			
Female	21		
Male	39		

End points

End points reporting groups

Reporting group title	Placebo tesofensine/metoprolol

Reporting group description:

Each subject was randomly allocated to one of two treatment arms. Treatment arm 1 was tesofensine 0.5 mg + metoprolol 100 mg administered once a day, in the morning with a meal (the first 2 days a loading dose of 1.0 mg/d of tesofensine was given) and treatment arm 2 was placebo tablets matching oral tesofensine + metoprolol administered once a day, in the morning with meal (the first 2 days a loading dose of 1.0 mg/d of placebo tesofensine was given). Each tablet was formulated separately; a currently available commercial formulation of metoprolol, MetoHEXAL® 100 mg retard, was used.

Reporting group title	Tesofensine/Metoprolol

Reporting group description:

Each subject was randomly allocated to one of two treatment arms. Treatment arm 1 was tesofensine 0.5 mg + metoprolol 100 mg administered once a day, in the morning with a meal (the first 2 days a loading dose of 1.0 mg/d of tesofensine was given) and treatment arm 2 was placebo tablets matching oral tesofensine + metoprolol administered once a day, in the morning with meal (the first 2 days a loading dose of 1.0 mg/d of placebo tesofensine was given). Each tablet was formulated separately; a currently available commercial formulation of metoprolol, MetoHEXAL® 100 mg retard, was used.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was based on the intention-to-treat principle and it included all randomized subjects

Primary: 24-hour heart rate

End point title	24-hour heart rate

End point description:

In the FAS, the primary endpoint, mean 24-hour heart rate, was reduced on average by 4.3 beats/minute in subjects treated with tesofensine/metoprolol compared to an average decline of 0.2 beats/minute in subjects dosed with placebo. The reduction was statistically significant for treatment with tesofensine/metoprolol compared with placebo (LSM difference -3.8 beats/minute, 95% CI (-6.36; -1.29), p=0.004). The result was confirmed by the analysis based on the PPP (LSM difference -4.1 beats/minute, 95% CI (-6.66; -1.54), p=0.002).

End point type	Primary

End point timeframe:

from the baseline to Week 12

End point values	Placebo tesofensine/metoprolol	Tesofensine/Metoprolol	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	30	60	
Units: beats/min				
arithmetic mean (standard deviation)	70.08 (± 9.115)	67.70 (± 7.186)	0 (± 0)	

Statistical analyses

Statistical analysis title	Repeated measures ANCOVA

Statistical analysis description:

Efficacy endpoints (primary, secondary and exploratory endpoints apart from PHQ scores) were analysed with a parametric model, i.e. compared between treatment arms by means of an analysis of covariance (ANCOVA) model (proc MIXED) using change from baseline to the end of treatment as dependent variable, treatment and study site as fixed effects and the value from baseline as covariate. The residual errors were assumed independent and identically distributed (i.i.d.) and normally distributed.

Comparison groups	Placebo tesofensine/metoprolol v Tesofensine/Metoprolol
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.05 [2]
Method	ANCOVA

Notes:

[1] - Efficacy endpoints were checked for normal distribution via a Shapiro-Wilk test. In case of normally distributed parameter, an additional analysis was performed without study site as fixed effect, if this effect was not significant (24-hour heart rate, waist circumference).

[2] - Within the model least square mean (LS-mean) for each treatment as well as the difference of the means between the treatment arms, the corresponding 95% confidence intervals (CIs) and p-values were calculated.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to Day 91

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Gastrointestinal disorders

Reporting group description: -

Serious adverse events	Gastrointestinal disorders		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
cholelithiasis	Additional description: One not treatment-emergent SAE occurred in a subject of the placebo arm, a cholelithiasis of moderate intensity not reported as medical history that led to repeated hospitalization (removal of a gallstone in the distal hepatic duct and cholecystectom		
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Gastrointestinal disorders		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 60 (26.67%)		
Gastrointestinal disorders			
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		

Abnormal faeces	Additional description: Abnormal faeces		
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Dental caries	Additional description: Dental caries		
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Gastric disorder	Additional description: Gastric disorder		
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Impaired gastric emptying	Additional description: Impaired gastric emptying		
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Nausea	Additional description: Nausea		
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	9		
Toothache	Additional description: Toothache		
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2016	Two amendments to the study documentation were generated. Amendment 1 was generated because of the conditional approval of the clinical study by the Competent Authority, German Federal Institute for Drugs and Medical Devices, [Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)] and entailed a change of the study protocol (final version 4.0, dated 09 Mar 2016, Appendix 16.1.1), the IB, the SI/IC Form and the subject diary. This amendment was substantial for the IEC. On 29 Mar 2016, the leading IEC approved amendment 1 and the corresponding study documents prior to study start.
29 March 2016	T Amendment 2 concerned minor corrections of the study protocol and was non-substantial for the IEC. Non-substantial amendments did not require a favourable opinion by the IEC and the respective IEC was not to be notified according to local requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported