Clinical trial results:
A PHASE II, PARTIAL-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, 5-WAY CROSS-OVER CLINICAL PHARMACOLOGY STUDY TO EVALUATE THE PHARMACODYNAMICS OF BDP/B17MP AND FORMOTEROL ACROSS TWO DIFFERENT DOSE LEVELS OF CHF 1535 NEXThaler® DPI AND CHF 1535 pMDI (BOTH FIXED COMBINATION OF BECLOMETHASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN ADULT COPD PATIENTS.

Summary

EudraCT number	2013-002966-38
Trial protocol	GB
Global end of trial date	11 April 2014

Results information

Result version number	v1 (current)
This version publication date	11 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	CCD-01535BC1-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02000609
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo, 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency Manager, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency Manager, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.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	11 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2014
Global end of trial reached?	Yes
Global end of trial date	11 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the average heart rate over 4 hours after administration of BDP and Formoterol using CHF 1535 100/6 NEXThaler® DPI and CHF 1535 100/6 pMDI at two different dose levels

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements . Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2013
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	United Kingdom: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	26
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty-nine COPD patients were randomised and received the study drug. Forty-five (91.8%) randomised and treated patients completed the study. Four (8.2%) patients discontinued the study; 1 (2.0%) patient withdrew consent and 3 (6.1%) patients discontinued due to an AE.

Pre-assignment

Screening details:

One hundred and six patients were screened. Fifty-seven patients were not randomised (i.e., screening failures), of whom 43 patients were not eligible to enter the study, 4 patients withdrew consent and 3 patients had an AE during run-in. Seven patients were not randomised for other reasons.

Period 1

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

Blinding implementation details:

A partial-blind treatment allocation approach was applied, meaning that patients and also the Investigator and the Sponsor were aware of the formulation they had taken (CHF 1535 100/6 NEXThaler® or CHF 1535 100/6 pMDI) but did not know the dosage.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence T1-T2-P-R1-R2

Arm description:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Arm type	experimental - placebo - active comparator
Investigational medicinal product name	CHF1535 Nexthaler DPI (BDP+FF)
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 200 µg BDP and 12 µg FF.
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 800 µg BDP and 48 µg FF.

Investigational medicinal product name	CHF1535 mDPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. Total dose: 200 µg BDP and 12 µg FF.

- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. Total dose: 800 µg BDP and 48 µg FF.

Investigational medicinal product name	CHF 1535 Nexthaler DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment P: single dose administration via NEXThaler DPI containing placebo.

Arm title	Sequence T2-P-T1-R2-R1

Arm description:

- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Arm type	experimental - placebo - active comparator
Investigational medicinal product name	CHF1535 Nexthaler DPI (BDP+FF)
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Routes of administration	Inhalation use

Dosage and administration details:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 200 µg BDP and 12 µg FF.
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 800 µg BDP and 48 µg FF.

Investigational medicinal product name	CHF1535 mDPI
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Other name	beclomethasone dipropionate, formoterol fumarate
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- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Investigational medicinal product name	CHF 1535 Nexthaler DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Arm title	Sequence R1-R2-T2-T1-P

Arm description:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Arm type	active comparator - experimental - placebo
Investigational medicinal product name	CHF1535 Nexthaler DPI (BDP+FF)
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 200 µg BDP and 12 µg FF.
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 800 µg BDP and 48 µg FF.

Investigational medicinal product name	CHF1535 mDPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Investigational medicinal product name	CHF 1535 Nexthaler DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Arm title	Sequence R2-T1-R1-P-T2

Arm description:

- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
-Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg

Arm type	active comparator - experimental - placebo
Investigational medicinal product name	CHF1535 Nexthaler DPI (BDP+FF)
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 200 µg BDP and 12 µg FF.
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 800 µg BDP and 48 µg FF.

Investigational medicinal product name	CHF1535 mDPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Investigational medicinal product name	CHF1535 Nexthaler DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Arm title	Sequence P-R1-R2-T2-T1

Arm description:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg-
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
-Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg

Arm type	placebo - active comparator - experimental
Investigational medicinal product name	CHF1535 Nexthaler DPI (BDP+FF)
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 200 µg BDP and 12 µg FF.
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. Total dose: 800 µg BDP and 48 µg FF.

Investigational medicinal product name	CHF1535 mDPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Investigational medicinal product name	CHF 1535 Nexthaler DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder

Routes of administration	Inhalation use

Dosage and administration details:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Number of subjects in period 1	Sequence T1-T2-P-R1-R2	Sequence T2-P-T1-R2-R1	Sequence R1-R2-T2-T1-P
Started	10	10	10
Completed	10	9	10
Not completed	0	1	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Sequence R2-T1-R1-P-T2	Sequence P-R1-R2-T2-T1
Started	9	10
Completed	7	9
Not completed	2	1
Consent withdrawn by subject	-	-
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups

Reporting group title	Sequence T1-T2-P-R1-R2

Reporting group description:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Reporting group title	Sequence T2-P-T1-R2-R1

Reporting group description:

- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Reporting group title	Sequence R1-R2-T2-T1-P

Reporting group description:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Reporting group title	Sequence R2-T1-R1-P-T2

Reporting group description:

- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
-Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg

Reporting group title	Sequence P-R1-R2-T2-T1

Reporting group description:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg-
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
-Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg

Reporting group values	Sequence T1-T2-P-R1-R2	Sequence T2-P-T1-R2-R1	Sequence R1-R2-T2-T1-P
Number of subjects	10	10	10
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	61.3	61.8	62.2
standard deviation	± 9.56	± 8.6	± 9.46
Gender categorical			
Units: Subjects			
Female	6	5	7
Male	4	5	3

Reporting group values	Sequence R2-T1-R1-P-T2	Sequence P-R1-R2-T2-T1	Total
Number of subjects	9	10	49
Age categorical			
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	61.8	67	
standard deviation	± 7.38	± 6.31	-
Gender categorical			
Units: Subjects			
Female	3	6	27
Male	6	4	22

End points

End points reporting groups

Reporting group title	Sequence T1-T2-P-R1-R2

Reporting group description:

- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Reporting group title	Sequence T2-P-T1-R2-R1

Reporting group description:

- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg

Reporting group title	Sequence R1-R2-T2-T1-P

Reporting group description:

- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo

Reporting group title	Sequence R2-T1-R1-P-T2

Reporting group description:

- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg
- Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
-Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg

Reporting group title	Sequence P-R1-R2-T2-T1

Reporting group description:

- Treatment P: single dose administration of CHF 1535 100/6 NEXThaler® DPI placebo
- Treatment R1: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 200 µg / FF 12 µg
- Treatment R2: single dose administration of CHF 1535 100/6 pMDI via standard actuator. total dose: BDP 800 µg / FF 48 µg-
- Treatment T2: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 800 µg / FF 48 µg
-Treatment T1: single dose administration of CHF 1535 100/6 via NEXThaler® DPI. total dose: BDP 200 µg / FF 12 µg

Subject analysis set title	Treatment T1 - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who received at least one dose of study medication.

Subject analysis set title	Treatment T2 - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who received at least one dose of study medication.

Subject analysis set title	Treatment R1 - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who received at least one dose of study medication.

Subject analysis set title	Treatment R2 - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who received at least one dose of study medication.

Subject analysis set title	Treatment P - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who received at least one dose of study medication.

Subject analysis set title	Treatment T1 - PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD analysis. PD population included all patients from the safety population with available primary endpoint and without any major protocol deviations

Subject analysis set title	Treatment T2 - PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD analysis. PD population included all patients from the safety population with available primary endpoint and without any major protocol deviations

Subject analysis set title	Treatment R1 - PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD analysis. PD population included all patients from the safety population with available primary endpoint and without any major protocol deviations

Subject analysis set title	Treatment R2 - PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD analysis. PD population included all patients from the safety population with available primary endpoint and without any major protocol deviations

Subject analysis set title	Treatment P - PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD analysis. PD population included all patients from the safety population with available primary endpoint and without any major protocol deviations

Primary: Average HR0-4h

End point title	Average HR0-4h

End point description:

End point type	Primary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - PD	Treatment T2 - PD	Treatment R1 - PD	Treatment R2 - PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	45	44	45
Units: bpm				
least squares mean (confidence interval 95%)	69.31 (68.492 to 70.137)	75.47 (74.659 to 76.282)	69.52 (68.701 to 70.345)	74.88 (74.077 to 75.681)

End point values	Treatment P - PD			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: bpm				
least squares mean (confidence interval 95%)	67.83 (67.031 to 68.638)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - PD v Treatment R1 - PD
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7188
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.349
upper limit	0.932

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - PD v Treatment R2 - PD
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.303
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.538
upper limit	1.521

Statistical analysis title	Treatment T2 vs Treatment T1
Comparison groups	Treatment T2 - PD v Treatment T1 - PD
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	6.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.022
upper limit	7.289

Statistical analysis title	Treatment R2 vs Treatment R1
Comparison groups	Treatment R1 - PD v Treatment R2 - PD
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	5.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.222
upper limit	6.49

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - PD v Treatment P - PD

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0114
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.338
upper limit	2.622

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment T2 - PD v Treatment P - PD
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	7.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.512
upper limit	8.759

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - PD v Treatment R1 - PD
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0038
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.554
upper limit	2.823

Statistical analysis title	Treatment R2 vs Treatment P

Comparison groups	Treatment P - PD v Treatment R2 - PD
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	7.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.908
upper limit	8.181

Secondary: Average HR0-1h

End point title	Average HR0-1h

End point description:

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	46
Units: bpm				
arithmetic mean (standard deviation)	70.2 (± 9.81)	74.8 (± 10.22)	69.1 (± 9.6)	73.1 (± 11.32)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	68.1 (± 9.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average HR1-2h

End point title	Average HR1-2h

End point description:

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	46
Units: bpm				
arithmetic mean (standard deviation)	69.2 (± 9.76)	75.3 (± 10.77)	68.4 (± 9.77)	73.9 (± 12.15)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	66.9 (± 9.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average HR2-3h

End point title	Average HR2-3h

End point description:

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	46
Units: bpm				
arithmetic mean (standard deviation)	68.7 (± 9.56)	74.6 (± 10.55)	68.2 (± 9.45)	73.8 (± 11.33)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	67 (± 9.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average HR3-4h

End point title	Average HR3-4h

End point description:

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	46
Units: bpm				
arithmetic mean (standard deviation)	69.6 (± 9.82)	74.8 (± 9.9)	69.2 (± 9.52)	75.3 (± 10.98)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	67.9 (± 9.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum HR0-4h

End point title	Maximum HR0-4h

End point description:

End point type	Secondary

End point timeframe:
At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	46
Units: bpm				
arithmetic mean (standard deviation)	100 (± 13.23)	104.5 (± 14.65)	100.2 (± 14.59)	103.8 (± 15.4)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	98.6 (± 12.75)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4763
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.447
upper limit	2.085

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8215
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.907
upper limit	3.658

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6849
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.576
upper limit	3.912

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment T2 - Safety v Treatment P - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	5.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.683
upper limit	9.181

Statistical analysis title	Treatment R1 vs Treatment P

Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2663
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.424
upper limit	5.122

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	5.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.273
upper limit	8.839

Secondary: Average HR0-9 h

End point title	Average HR0-9 h
End point description:	
End point type	Secondary
End point timeframe:	
At each visit from Visit 1 (screening) to Visit 6	

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	46	45	44
Units: bpm				
arithmetic mean (standard deviation)	76.4 (± 9.74)	80.7 (± 10.19)	75.8 (± 9.99)	80.1 (± 10.87)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	75.1 (± 10.32)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9628
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.286
upper limit	1.226

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8994
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.191
upper limit	1.354

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1082
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.227
upper limit	2.268

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	5.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.423
upper limit	6.903

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0988
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.199
upper limit	2.299

Statistical analysis title	Treatment R2 vs Treatment P

Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	5.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.308
upper limit	6.855

Secondary: Average HR0-12h

End point title	Average HR0-12h

End point description:

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	46	45	44
Units: bpm				
arithmetic mean (standard deviation)	77.7 (± 9.78)	81.7 (± 9.76)	77.3 (± 9.92)	81.2 (± 10.83)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
arithmetic mean (standard deviation)	77 (± 10.32)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7786
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.218
upper limit	0.914

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8884
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.157
upper limit	1.004

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2816
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	1.639

Statistical analysis title	Treatment T2 vs Treatment P

Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	4.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.709
upper limit	5.814

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1749
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.329
upper limit	1.792

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	4.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.758
upper limit	5.919

Secondary: HR at 5 min post-dose

End point title	HR at 5 min post-dose

End point description:

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	45	45	44
Units: bpm				
arithmetic mean (standard deviation)	78.72 (± 11.209)	80.29 (± 11.986)	75.86 (± 9.802)	77.18 (± 11.117)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: bpm				
arithmetic mean (standard deviation)	77.87 (± 11.481)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0333
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.176
upper limit	4.225

Statistical analysis title	Treatment T2 vs Treatment R2

Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0145
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.513
upper limit	4.595

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6364
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.541
upper limit	2.514

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0101
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	4.669

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0948
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.728
upper limit	0.3

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9228
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	2.151

Secondary: PR

End point title	PR

End point description:

PR, QRS, QTcF were measured at the following time points:
45, 30, 15 minutes pre-dose, 5, 10, 20, 30, 45 minutes post-dose and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 hours post-dose.
Only data referring to 5 minutes post-dose are reported here.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	44	45	44
Units: msec				
arithmetic mean (standard deviation)	153.55 (± 23.937)	153.4 (± 20.534)	156.41 (± 21.649)	155.71 (± 20.831)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: msec				
arithmetic mean (standard deviation)	154.87 (± 22.006)			

Statistical analyses

No statistical analyses for this end point

Secondary: QRS

End point title	QRS

End point description:

PR, QRS, QTcF were measured at the following time points:
45, 30, 15 minutes pre-dose, 5, 10, 20, 30, 45 minutes post-dose and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 hours post-dose.
Only data referring to 5 minutes post-dose are reported here.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	45	45	44
Units: msec				
arithmetic mean (standard deviation)	97.45 (± 10.21)	97.98 (± 10.513)	97.71 (± 10.371)	97.74 (± 10.884)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: msec				

arithmetic mean (standard deviation)	97.3 (± 10.608)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in QTcF

End point title	Change from baseline in QTcF

End point description:

PR, QRS, QTcF were measured at the following time points:
45, 30, 15 minutes pre-dose, 5, 10, 20, 30, 45 minutes post-dose and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 hours post-dose.
Only data referring to 5 minutes post-dose are reported here.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	45	45	44
Units: msec				
arithmetic mean (standard deviation)	415.71 (± 19.23)	416.69 (± 19.413)	415.8 (± 19.282)	145.53 (± 17.871)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: msec				
arithmetic mean (standard deviation)	414.83 (± 17.997)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3064
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.759
upper limit	3.24

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1172
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.097
upper limit	3.928

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.168
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.324
upper limit	3.654

Statistical analysis title	Treatment T2 vs Treatment p

Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0136
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.005
upper limit	4.967

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment R1 - Safety v Treatment P - Safety
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7244
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.564
upper limit	2.414

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.383
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.954
upper limit	3.094

Secondary: Premature atrial contractions (PAC) burden 0-12 h

End point title	Premature atrial contractions (PAC) burden 0-12 h

End point description:

PAC burden was calculated 1 hour pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 hours post-dose, and over the 0-12 hour post-dose interval. Only data regarding this latter are reported here.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: percent				
arithmetic mean (standard deviation)	-0.0001 (± 0.00188)	-0.0002 (± 0.00552)	0.0002 (± 0.00314)	0.0005 (± 0.00393)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: percent				
arithmetic mean (standard deviation)	-0.0008 (± 0.00273)			

Statistical analyses

No statistical analyses for this end point

Secondary: Premature ventricular contractions (PVC) burden 0-12 h

End point title	Premature ventricular contractions (PVC) burden 0-12 h

End point description:

PVC burden was calculated 1 hour pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 hours post-dose, and over the 0-12 hour interval. Only data regarding this latter are reported here.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: percent				
arithmetic mean (standard deviation)	0.00197 (± 0.003047)	0.0024 (± 0.004905)	0.00109 (± 0.001671)	0.00141 (± 0.003765)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: percent				
arithmetic mean (standard deviation)	0.00145 (± 0.003322)			

Statistical analyses

No statistical analyses for this end point

Secondary: DBP AUC0-8h/8h

End point title	DBP AUC0-8h/8h

End point description:

SBP and DBP were measured at screening and at Visit 2 to Visit 6, at 45 and 30 min pre-dose, 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h post-drug administration by automated machine.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6.

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: bpm				
least squares mean (confidence interval 95%)	68.66 (67.667 to 69.659)	65.93 (64.926 to 66.928)	68.54 (67.519 to 69.56)	66.3 (65.32 to 67.272)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
least squares mean (confidence interval 95%)	70.37 (69.394 to 71.354)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8631
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.287
upper limit	1.534

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5998
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.754
upper limit	1.016

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0158
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.096
upper limit	-0.326

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-4.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.826
upper limit	-3.069

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0102
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.228
upper limit	-0.441

Statistical analysis title	Treatment R2 vs Treatment P

Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-4.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.461
upper limit	-2.695

Secondary: SBP AUC0-8h/8h

End point title	SBP AUC0-8h/8h

End point description:

SBP and DBP were measured at screening and at Visit 2 to Visit 6, at 45 and 30 min pre-dose, 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h post-drug administration by automated machine.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: bpm				
least squares mean (confidence interval 95%)	120.58 (119.295 to 121.859)	119.16 (117.856 to 120.463)	120.17 (118.843 to 121.494)	119.24 (117.959 to 120.517)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
least squares mean (confidence interval 95%)	123.18 (121.906 to 124.461)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6565
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	2.216

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9319
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.888
upper limit	1.731

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0046
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	-0.814

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.821
upper limit	-2.227

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0012
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.827
upper limit	-1.203

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-3.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.756
upper limit	-2.135

Secondary: DBP AUC0-12h/12h

End point title	DBP AUC0-12h/12h

End point description:

SBP and DBP were measured at screening and at Visit 2 to Visit 6, at 45 and 30 min pre-dose, 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h post-drug administration by automated machine.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: bpm				
least squares mean (confidence interval 95%)	68.78 (67.793 to 69.772)	66.44 (65.447 to 67.436)	68.56 (67.542 to 69.57)	66.55 (65.584 to 67.522)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: bpm				
least squares mean (confidence interval 95%)	70.07 (69.101 to 71.047)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7505
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.175
upper limit	1.628

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8729
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.488
upper limit	1.264

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0656
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.667
upper limit	0.084

Statistical analysis title	Treatment T2 vs Treatment P

Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.002
upper limit	-2.263

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0319
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.902
upper limit	-0.133

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-3.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.895
upper limit	-2.146

Secondary: SBP AUC0-12h/12h

End point title	SBP AUC0-12h/12h

End point description:

SBP and DBP were measured at screening and at Visit 2 to Visit 6, at 45 and 30 min pre-dose, 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h post-drug administration by automated machine.

End point type	Secondary

End point timeframe:

At each visit from Visit 1 (screening) to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: mmHg				
least squares mean (confidence interval 95%)	121.22 (119.95 to 122.496)	120.44 (119.141 to 121.73)	120.85 (119.533 to 122.165)	119.88 (118.609 to 121.148)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: mmHg				
least squares mean (confidence interval 95%)	123.34 (122.074 to 124.61)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6816
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.422
upper limit	2.169

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5414
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	2.354

Statistical analysis title	Treatment T1 vs Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0199
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.899
upper limit	-0.339

Statistical analysis title	Treatment T2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0016
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.691
upper limit	-1.123

Statistical analysis title	Treatment R1 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0069
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.292
upper limit	-0.694

Statistical analysis title	Treatment R2 vs Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.262
upper limit	-1.666

Secondary: Serum potassium AUC0-4

End point title	Serum potassium AUC0-4

End point description:

Collection of blood for glucose and potassium determination in serum were performed at the scheduled time: pre-dose, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4 h post-drug administration.

End point type	Secondary

End point timeframe:

At each visit from Visit 2 to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: mmol*h/L				
geometric mean (confidence interval 95%)	16 (15.6 to 16.4)	15.5 (15.1 to 15.9)	16.2 (15.8 to 16.6)	15.4 (15 to 15.8)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: mmol*h/L				
geometric mean (confidence interval 95%)	16.4 (16 to 16.8)			

Statistical analyses

Statistical analysis title	Treatment T1 / Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.4999
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	98.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	95.57
upper limit	102.25

Notes:

[1] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.7257
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	100.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	97.28
upper limit	104.03

Notes:

[2] - pairwise comparison

Statistical analysis title	Treatment T1/ Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.1442
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	97.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	94.32
upper limit	100.87

Notes:

[3] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0006
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	94.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	91.17
upper limit	97.46

Notes:

[4] - pairwise comparison

Statistical analysis title	Treatment R1 / Treatment P

Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.4339
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	98.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	95.41
upper limit	102.05

Notes:

[5] - pairwise comparison

Statistical analysis title	Treatment R2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0002
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	93.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	90.61
upper limit	96.89

Notes:

[6] - pairwise comparison

Secondary: Serum potassium Cmin

End point title	Serum potassium Cmin

End point description:

Collection of blood for glucose and potassium determination in serum were performed at the scheduled time: pre-dose, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4 h post-drug administration.

End point type	Secondary

End point timeframe:

At each visit from Visit 2 to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: mmol/L				
geometric mean (confidence interval 95%)	3.79 (3.65 to 3.94)	3.57 (3.44 to 3.72)	3.77 (3.63 to 3.93)	3.56 (3.43 to 3.7)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: mmol/L				
geometric mean (confidence interval 95%)	3.9 (3.75 to 4.05)			

Statistical analyses

Statistical analysis title	Treatment T1 / Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.8896
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	100.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	95.14
upper limit	105.91

Notes:

[7] - pairwise comparison

Statistical analysis title	Treatment T2/ Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.8651
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	100.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	95.22
upper limit	106

Notes:

[8] - pairwise comparison

Statistical analysis title	Treatment T1/ Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.2989
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	97.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	92.18
upper limit	102.55

Notes:

[9] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.0017
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	91.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	86.98
upper limit	96.79

Notes:

[10] - pairwise comparison

Statistical analysis title	Treatment R1 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.2438
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	96.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	91.78
upper limit	102.22

Notes:

[11] - pairwise comparison

Statistical analysis title	Treatment R2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.001
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	91.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	86.56
upper limit	96.36

Notes:

[12] - pairwise comparison

Secondary: Serum potassium Tmin

End point title	Serum potassium Tmin

End point description:

Collection of blood for glucose and potassium determination in serum were performed at the scheduled time: pre-dose, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4 h post-drug administration.

End point type	Secondary

End point timeframe:

At each visit from Visit 2 to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: hours				
median (standard deviation)	1.53 (± 0)	1.53 (± 0)	1.55 (± 0)	1.53 (± 0)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: hours				
median (standard deviation)	1.03 (± 0)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.3057
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.37

Notes:

[13] - Pairwise comparison

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.7033
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.48

Notes:

[14] - Pairwise comparison

Secondary: Serum glucose AUC0-4h

End point title	Serum glucose AUC0-4h

End point description:

Collection of blood for glucose and potassium determination in serum were performed at the scheduled time: pre-dose, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4 h post-drug administration.

End point type	Secondary

End point timeframe:

At each visit from Visit 2 to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: mg*h/dL				
geometric mean (confidence interval 95%)	375 (363 to 388)	415 (402 to 429)	377 (364 to 390)	413 (400 to 426)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: mg*h/dL				
geometric mean (confidence interval 95%)	371 (359 to 383)			

Statistical analyses

Statistical analysis title	Treatment T1 / Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.8539
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	99.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	95.07
upper limit	104.28

Notes:

[15] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.7948
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	100.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.09
upper limit	105.34

Notes:

[16] - pairwise comparison

Statistical analysis title	Treatment T1 / Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.5978
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	101.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.69
upper limit	106

Notes:

[17] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	112.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	107.1
upper limit	117.35

Notes:

[18] - pairwise comparison

Statistical analysis title	Treatment R1 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.4772
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	101.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	97.1
upper limit	106.47

Notes:

[19] - pairwise comparison

Statistical analysis title	Treatment R2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	111.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	106.43
upper limit	116.66

Notes:

[20] - pairwise comparison

Secondary: Serum glucose Cmax

End point title	Serum glucose Cmax

End point description:

Collection of blood for glucose and potassium determination in serum were performed at the scheduled time: pre-dose, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4 h post-drug administration.

End point type	Secondary

End point timeframe:

At each visit from Visit 2 to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: mg/dL				
geometric mean (confidence interval 95%)	102 (99.6 to 104)	112 (110 to 114)	101 (99.2 to 104)	112 (110 to 115)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: mg/dL				
geometric mean (confidence interval 95%)	102 (99.9 to 104)			

Statistical analyses

Statistical analysis title	Treatment T1 / Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.8142
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	100.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	97.46
upper limit	103.32

Notes:

[21] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.8395
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	99.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.83
upper limit	102.65

Notes:

[22] - pairwise comparison

Statistical analysis title	Treatment T1 / Treatment P
Comparison groups	Treatment T1 - Safety v Treatment P - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.8543
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	99.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.88
upper limit	102.66

Notes:

[23] - pairwise comparison

Statistical analysis title	Treatment T2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment T2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	109.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	106.73
upper limit	113.12

Notes:
[24] - pairwise comparison

Statistical analysis title	Treatment R1 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.6776
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	99.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.51
upper limit	102.34

Notes:
[25] - pairwise comparison

Statistical analysis title	Treatment R2 / Treatment P
Comparison groups	Treatment P - Safety v Treatment R2 - Safety
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	least square mean ratio
Point estimate	110.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	107.04
upper limit	113.47

Notes:
[26] - pairwise comparison

Secondary: Serum glucose Tmax

End point title	Serum glucose Tmax

End point description:

Collection of blood for glucose and potassium determination in serum were performed at the scheduled time: pre-dose, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4 h post-drug administration.

End point type	Secondary

End point timeframe:

At each visit from Visit 2 to Visit 6

End point values	Treatment T1 - Safety	Treatment T2 - Safety	Treatment R1 - Safety	Treatment R2 - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	45	47
Units: Hours				
median (standard deviation)	0.18 (± 0)	1.91 (± 0)	0.18 (± 0)	2.03 (± 0)

End point values	Treatment P - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: Hours				
median (standard deviation)	0 (± 0)			

Statistical analyses

Statistical analysis title	Treatment T1 vs Treatment R1
Comparison groups	Treatment T1 - Safety v Treatment R1 - Safety
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.2641
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0

Notes:

[27] - Pairwise comparison

Statistical analysis title	Treatment T2 vs Treatment R2
Comparison groups	Treatment T2 - Safety v Treatment R2 - Safety
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.2742
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate of shift
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0

Notes:

[28] - Pairwise comparison

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each Visit from visit 0 (pre-screening) and visit 1 (screening) to Visit 6 and afterward at the follow-up (phone call)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Treatment T1- safety population
Reporting group description: -	
Reporting group title	Treatment T2 - safety population
Reporting group description: -	
Reporting group title	Treatment R1 - safety population
Reporting group description: -	
Reporting group title	Treatment R2 - safety population
Reporting group description: -	
Reporting group title	Treatment P - safety population
Reporting group description: -	

Serious adverse events	Treatment T1- safety population	Treatment T2 - safety population	Treatment R1 - safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	0 / 45 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	0 / 45 (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

Serious adverse events	Treatment R2 - safety population	Treatment P - safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Prostatitis			

subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment T1- safety population	Treatment T2 - safety population	Treatment R1 - safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 47 (12.77%)	16 / 46 (34.78%)	8 / 45 (17.78%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Muscle injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Suture related complication			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 47 (2.13%)	5 / 46 (10.87%)	2 / 45 (4.44%)
occurrences (all)	1	5	2
Migrane			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Post herpetic neuralgia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 47 (0.00%)	3 / 46 (6.52%)	0 / 45 (0.00%)
occurrences (all)	0	3	0
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Local swelling			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0

Abdominal pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Increased upper airway secretion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	1	0	1
Muscle spasms			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Infected bites			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Rash pustular			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 46 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	0 / 45 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Treatment R2 - safety population	Treatment P - safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 47 (29.79%)	14 / 47 (29.79%)	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Excoriation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Muscle injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Suture related complication			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Headache			

subjects affected / exposed	3 / 47 (6.38%)	3 / 47 (6.38%)	
occurrences (all)	3	3	
Migrane			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Local swelling			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Dyspepsia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	1 / 47 (2.13%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Increased upper airway secretion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Wheezing			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			

subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Infected bites			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Rash pustular			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 47 (2.13%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Sinusitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

There are no limitations or caveats to this summary of results

Notes: