Clinical trial results:
Antihypertensive effect of different doses of ROSTAFUROXIN in comparison with Losartan, assessed by office and ambulatory blood pressure monitoring in a hypertensive population selected according to a specific genetic profile.

Summary

EudraCT number	2010-022073-34
Trial protocol	IT
Global end of trial date	08 February 2018

Results information

Result version number	v1 (current)
This version publication date	19 September 2020
First version publication date	19 September 2020
Summary attachment (see zip file)	Antihypertensive effect of rostafuroxin in comparison with losartan, by office and ambulatory blood pressure monitoring in a hypertensive population selected according to a specific genetic profile (Summary attachment_PEARL-HT.pdf)

Trial information

Trial identification

Sponsor protocol code	PST2238-DM-10-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01320397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RostaQuo S.p.A
Sponsor organisation address	Via Pontina Km 30,400, Pomezia (Roma), Italy, 00040
Public contact	Clinical Trials Information, RostaQuo S.p.A, 39 06913942103916, rostaquo@legalmail.it
Scientific contact	Clinical Trials Information, RostaQuo S.p.A, 39 06913942103916, rostaquo@legalmail.it
Sponsor organisation name	CVie Therapeutics Company Limited
Sponsor organisation address	No2. Science Park West Avenue, Shatin, Hong Kong,
Public contact	CVie Therapeutics Company Limited, CVie Therapeutics Company Limited, 852 2314 6572, Wy.lam@leespharm.com
Scientific contact	CVie Therapeutics Company Limited, CVie Therapeutics Company Limited, 852 2314 6572, Wy.lam@leespharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2018
Global end of trial reached?	Yes
Global end of trial date	08 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The two primary objectives are as follows :
to demonstrate that the highest two doses of ROSTAFUROXIN (50 microg. and 500 microg.) are able to show a
statistically significant difference on reduction of office sitting systolic blood pressure (OSBP) in comparison to the group of patients treated with Losartan 50 mg in either:
1. the total population bearing a mutation included in the Genetic Profile 1

or

2. the subset of patients of Profile 1 carrying only the Genetic Profile 2

Protection of trial subjects:

This trial involved a subset of newly discovered and never-treated (naïve) hypertensive patients, at an initial grade 1 type of hypertension, who have been selected according to an OSBP level >140 mmHg and ODBP >85 mmHg, and with normal organ functions.
Risks for the patient such as the onset of adverse events that may required the decision on the continuation of the treatment, and the deviation that may affects the validity of the results, were monitored by:

Data and Safety Monitoring Board (DSMB)
Any adverse event which causes the termination of treatment or serious adverse events experienced by the patients was promptly reported to all members of the committee within 24 hours following time of their acknowledgement by the Sponsor.

Case Report Form (CRF)
A Run-In and Treatment Period CRF will be prepared for the study, recording all variables mentioned in the Protocol. The forms for registration of possible adverse events, concomitant medications and any suspension of the Study were placed at the end of the CRF.

Clinical Monitoring
to verify, according to the Sponsor’s requirements, that the study is conducted and documented properly in accordance with the Good Clinical Practice.

Audits
The Auditor has been appointed by the Sponsor to verify the conduct of the Study, having the possibility to perform audits at the investigational site with direct access to the Trial Master File, Case Report Forms, source documents, informed consent and patients’ hospital records.

Inspections
The Investigator/Institution allowed Regulatory Authorities, national and foreign, to carry out inspections. Inspections, on part of one or more Regulatory Authorities, consist in an official revising of documents, structures, recordings and any other source said authorities consider as connected to the

study.

Background therapy: -

Evidence for comparator:

The choice of losartan, as comparator, is supported by two reasons: 1) since this study included an initial run-in period with lifestyle changes, followed by a subsequent study period of two months, a placebo arms could not have been approved by some Ethical Committees; 2) the just completed SOPHIA study on losartan in naïve patients (Frau, Pharmacogenomics, 2014) whose clinical design is similar to that of the previous OASIS-HT study (Lanzani, Science Translational Medicine, 2010), furnished preliminary data for planning the present PEARL-HT study. Standing the well-established relationship between the body sodium and the pressor response to angiotensin II that increases at higher body sodium, the losartan efficacy may also be potentiated by gene variants that, by increasing renal tubular reabsorption, may enhance body sodium. This limits the validity to assess causation from the difference in the BP response, that may also regard any of the available antihypertensive drugs, acting on physiological mechanisms involved in BP regulation.

Actual start date of recruitment	26 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 470
Country: Number of subjects enrolled	Taiwan: 432
Worldwide total number of subjects	902
EEA total number of subjects	470

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)	902
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

PEARL-HT clinical trial, phase 2b multicenter, double-blind, double-dummy, four-arms, parallel group, active comparator-controlled study was conducted in newly discovered and never-treated (naïve) hypertensive patients enrolled in 13 Italian centers and in 15 Taiwanese centres, Italy June 2013-January 2016, Taiwan December 2015-December 2017.

Pre-assignment

Screening details:

The eligibility of the naïve hypertensive patients included: age between 25 and 60 years, being carrier of one or a combination of polymorphisms of the genetic profile P1, with at least 50% of the enrolled patients having a combination of gene variants of the original genetic profile P2. Sitting OSBP 140-169 mmHg, ODBP 85-100 mmHg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Caucasian rostafuroxin 6 microg.

Arm description: -

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

Dosage and administration details:

6 microg. administered orally as one capsule daily

Arm title	Caucasian rostafuroxin 50 microg.

Arm description: -

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

Dosage and administration details:

50 microg. administered orally as one capsule daily

Arm title	Caucasian rostafuroxin 500 microg.

Arm description: -

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

Dosage and administration details:
500 microg. administered orally as one capsule daily

Arm title	Caucasian losartan 50 mg.
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	losartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
50 mg administered orally as one capsule daily

Arm title	Chinese rostafuroxin 50 microg.
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	rostafuroxin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
50 microg. administered orally as one capsule daily

Arm title	Chinese rostafuroxin 500 microg.
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	rostafuroxin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
500 microg. administered orally as one capsule daily

Arm title	Chinese losartan 50 mg.
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	losartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
50 mg administered orally as one capsule daily

Number of subjects in period 1[1]	Caucasian rostafuroxin 6 microg.	Caucasian rostafuroxin 50 microg.	Caucasian rostafuroxin 500 microg.
Started	43	43	43
Completed	38	35	39
Not completed	5	8	4
Patient withdrawn without any treatment	-	1	-
Lost to follow-up	5	7	4

Number of subjects in period 1[1]	Caucasian losartan 50 mg.	Chinese rostafuroxin 50 microg.	Chinese rostafuroxin 500 microg.
Started	43	35	35
Completed	40	33	34
Not completed	3	2	1
Patient withdrawn without any treatment	-	-	-
Lost to follow-up	3	2	1

Number of subjects in period 1[1]	Chinese losartan 50 mg.
Started	37
Completed	34
Not completed	3
Patient withdrawn without any treatment	-
Lost to follow-up	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported at the baseline period (n=279) is different from the worldwide number enrolled in the trial (n=902) because only subjects carrying the genetic profile were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Caucasian rostafuroxin 6 microg.
Reporting group description: -	
Reporting group title	Caucasian rostafuroxin 50 microg.
Reporting group description: -	
Reporting group title	Caucasian rostafuroxin 500 microg.
Reporting group description: -	
Reporting group title	Caucasian losartan 50 mg.
Reporting group description: -	
Reporting group title	Chinese rostafuroxin 50 microg.
Reporting group description: -	
Reporting group title	Chinese rostafuroxin 500 microg.
Reporting group description: -	
Reporting group title	Chinese losartan 50 mg.
Reporting group description: -	

Reporting group values	Caucasian rostafuroxin 6 microg.	Caucasian rostafuroxin 50 microg.	Caucasian rostafuroxin 500 microg.
Number of subjects	43	43	43
Age categorical Units: Subjects			
Adults (25-60 years)	43	43	43
Age continuous Units: years			
arithmetic mean	0	0	0
full range (min-max)	0 to 0	0 to 0	0 to 0
Gender categorical Units: Subjects			
Female	17	18	11
Male	26	25	32
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0

Reporting group values	Caucasian losartan 50 mg.	Chinese rostafuroxin 50 microg.	Chinese rostafuroxin 500 microg.
Number of subjects	43	35	35
Age categorical Units: Subjects			
Adults (25-60 years)	43	35	35
Age continuous Units: years			
arithmetic mean	0	0	0
full range (min-max)	0 to 0	0 to 0	0 to 0

Gender categorical Units: Subjects			
Female	10	16	12
Male	33	19	23
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0

Reporting group values	Chinese losartan 50 mg.	Total	
Number of subjects	37	279	
Age categorical Units: Subjects			
Adults (25-60 years)	37	279	
Age continuous Units: years			
arithmetic mean	0		
full range (min-max)	0 to 0	-	
Gender categorical Units: Subjects			
Female	19	103	
Male	18	176	
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	0		
standard deviation	± 0	-	

Subject analysis sets

Subject analysis set title	Caucasian rostafuroxin 6 microg. - Genetic Profile P2
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 6 microg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - Genetic Profile P2
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Caucasian rostafuroxin 500 microg. - Genetic Profile P2
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 500 microg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Caucasian losartan 50 mg. - Genetic Profile P2
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Chinese rostafuroxin 50 microg. - Genetic Profile P2

Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 50 microg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Chinese rostafuroxin 500 microg. - Genetic Profile P2
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 500 microg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Chinese losartan 50 mg. - Genetic Profile P2
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with losartan 50 mg. and carrying at least one pair of gene variants included in the genetic profile P2.

Subject analysis set title	Caucasian rostafuroxin 6 microg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 6 microg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian rostafuroxin 500 microg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 500 microg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian losartan 50 mg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - LSS AA
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying LSS AA genotype.

Subject analysis set title	Caucasian losartan 50 mg. - LSS AA
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying LSS AA genotype.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - LSS CC
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying LSS CC genotype.

Subject analysis set title	Caucasian losartan 50 mg. - LSS CC
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying LSS CC genotype.

Subject analysis set title	Caucasian rostafuroxin 6 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 6 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Caucasian rostafuroxin 500 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 500 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Caucasian losartan 50 mg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Chinese rostafuroxin 50 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 50 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Chinese rostafuroxin 500 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 500 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Chinese losartan 50 mg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 500 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Reporting group values	Caucasian rostafuroxin 6 microg. - Genetic Profile P2	Caucasian rostafuroxin 50 microg. - Genetic Profile P2	Caucasian rostafuroxin 500 microg. - Genetic Profile P2
Number of subjects	20	17	19
Age categorical Units: Subjects			
Adults (25-60 years)	20	17	19
Age continuous Units: years			
arithmetic mean	49.0	46.7	48.2
full range (min-max)	30 to 59	31 to 56	38 to 56
Gender categorical Units: Subjects			
Female	9	6	5
Male	11	11	14
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	151.9	151.4	151.7
standard deviation	± 6.6	± 7.3	± 6.5

Reporting group values	Caucasian losartan 50 mg. - Genetic Profile P2	Chinese rostafuroxin 50 microg. - Genetic Profile P2	Chinese rostafuroxin 500 microg. - Genetic Profile P2
Number of subjects	23	14	15
Age categorical			
Units: Subjects			
Adults (25-60 years)	23	14	15
Age continuous			
Units: years			
arithmetic mean	50.7	45.5	47.5
full range (min-max)	29 to 62	33 to 57	28 to 60
Gender categorical			
Units: Subjects			
Female	4	4	4
Male	19	10	11
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	150.5	144.7	145.9
standard deviation	± 8.4	± 4.6	± 7.4

Reporting group values	Chinese losartan 50 mg. - Genetic Profile P2	Caucasian rostafuroxin 6 microg. - Genetic Profile P2a	Caucasian rostafuroxin 50 microg. - Genetic Profile P2a
Number of subjects	16	16	15
Age categorical			
Units: Subjects			
Adults (25-60 years)	16	16	15
Age continuous			
Units: years			
arithmetic mean	47.6	48.6	46.9
full range (min-max)	36 to 60	30 to 59	31 to 56
Gender categorical			
Units: Subjects			
Female	8	8	6
Male	8	8	9
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	146.7	150.7	151.0
standard deviation	± 8.1	± 6.7	± 7.7

Reporting group values	Caucasian rostafuroxin 500 microg. - Genetic Profile P2a	Caucasian losartan 50 mg. - Genetic Profile P2a	Caucasian rostafuroxin 50 microg. - LSS AA
Number of subjects	18	20	6
Age categorical			
Units: Subjects			
Adults (25-60 years)	18	20	

Age continuous			
Units: years			
arithmetic mean	48.4	50.3	46.5
full range (min-max)	38 to 56	29 to 62	31 to 61
Gender categorical			
Units: Subjects			
Female	4	4	3
Male	14	16	3
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	151.3	149.8	153.6
standard deviation	± 6.5	± 8.1	± 5.4

Reporting group values	Caucasian losartan 50 mg. - LSS AA	Caucasian rostafuroxin 50 microg. - LSS CC	Caucasian losartan 50 mg. - LSS CC
Number of subjects	6	9	18
Age categorical			
Units: Subjects			
Adults (25-60 years)			
Age continuous			
Units: years			
arithmetic mean	49.8	47.8	50.4
full range (min-max)	41 to 59	35 to 54	35 to 59
Gender categorical			
Units: Subjects			
Female	1	5	2
Male	5	4	16
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	154.6	151.8	150.3
standard deviation	± 7.4	± 8.2	± 6.1

Reporting group values	Caucasian rostafuroxin 6 microg. - Genetic Profile P1	Caucasian rostafuroxin 50 microg. - Genetic Profile P1	Caucasian rostafuroxin 500 microg. - Genetic Profile P1
Number of subjects	36	35	39
Age categorical			
Units: Subjects			
Adults (25-60 years)			
Age continuous			
Units: years			
arithmetic mean	47.9	49.1	49.5
full range (min-max)	30 to 59	31 to 61	29 to 59
Gender categorical			
Units: Subjects			
Female	15	15	10
Male	21	20	29

OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	149.6	151.2	150.4
standard deviation	± 6.1	± 6.2	± 5.9

Reporting group values	Caucasian losartan 50 mg. - Genetic Profile P1	Chinese rostafuroxin 50 microg. - Genetic Profile P1	Chinese rostafuroxin 500 microg. - Genetic Profile P1
Number of subjects	40	30	33
Age categorical			
Units: Subjects			
Adults (25-60 years)			
Age continuous			
Units: years			
arithmetic mean	49.9	46.0	44.7
full range (min-max)	29 to 62	33 to 57	28 to 60
Gender categorical			
Units: Subjects			
Female	9	13	11
Male	31	17	22
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	151.4	146.5	146.2
standard deviation	± 7.5	± 6.5	± 7.2

Reporting group values	Chinese losartan 50 mg. - Genetic Profile P1		
Number of subjects	33		
Age categorical			
Units: Subjects			
Adults (25-60 years)			
Age continuous			
Units: years			
arithmetic mean	44.6		
full range (min-max)	27 to 60		
Gender categorical			
Units: Subjects			
Female	17		
Male	16		
OSBP at baseline			
Office Systolic Blood Pressure (OSBP) at baseline			
Units: mmHg			
arithmetic mean	146.6		
standard deviation	± 7.1		

End points

End points reporting groups

Reporting group title	Caucasian rostafuroxin 6 microg.
Reporting group description: -	
Reporting group title	Caucasian rostafuroxin 50 microg.
Reporting group description: -	
Reporting group title	Caucasian rostafuroxin 500 microg.
Reporting group description: -	
Reporting group title	Caucasian losartan 50 mg.
Reporting group description: -	
Reporting group title	Chinese rostafuroxin 50 microg.
Reporting group description: -	
Reporting group title	Chinese rostafuroxin 500 microg.
Reporting group description: -	
Reporting group title	Chinese losartan 50 mg.
Reporting group description: -	
Subject analysis set title	Caucasian rostafuroxin 6 microg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Caucasian subjects treated with rostafuroxin 6 microg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Caucasian rostafuroxin 50 microg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Caucasian subjects treated with rostafuroxin 50 microg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Caucasian rostafuroxin 500 microg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Caucasian subjects treated with rostafuroxin 500 microg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Caucasian losartan 50 mg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Caucasian subjects treated with losartan 50 mg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Chinese rostafuroxin 50 microg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Chinese subjects treated with rostafuroxin 50 microg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Chinese rostafuroxin 500 microg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Chinese subjects treated with rostafuroxin 500 microg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Chinese losartan 50 mg. - Genetic Profile P2
Subject analysis set type	Per protocol
Subject analysis set description:	
Chinese subjects treated with losartan 50 mg. and carrying at least one pair of gene variants included in the genetic profile P2.	
Subject analysis set title	Caucasian rostafuroxin 6 microg. - Genetic Profile P2a

Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 6 microg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian rostafuroxin 500 microg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 500 microg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian losartan 50 mg. - Genetic Profile P2a
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying at least one pair of gene variants included in the genetic profile P2a.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - LSS AA
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying LSS AA genotype.

Subject analysis set title	Caucasian losartan 50 mg. - LSS AA
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying LSS AA genotype.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - LSS CC
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying LSS CC genotype.

Subject analysis set title	Caucasian losartan 50 mg. - LSS CC
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying LSS CC genotype.

Subject analysis set title	Caucasian rostafuroxin 6 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 6 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Caucasian rostafuroxin 50 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 50 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Caucasian rostafuroxin 500 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with rostafuroxin 500 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Caucasian losartan 50 mg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Caucasian subjects treated with losartan 50 mg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Chinese rostafuroxin 50 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 50 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Chinese rostafuroxin 500 microg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 500 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Subject analysis set title	Chinese losartan 50 mg. - Genetic Profile P1
Subject analysis set type	Per protocol

Subject analysis set description:

Chinese subjects treated with rostafuroxin 500 microg. and carrying at least one gene variant or one pair of gene variants included in the genetic profile P1.

Primary: Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P2a adjusted

End point title	Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P2a adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2a (adjusted for genetic heterogeneity). The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 6 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Primary

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2a, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 6 microg. - Genetic Profile P2a	Caucasian losartan 50 mg. - Genetic Profile P2a		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	20		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-10.8 (-17.48 to -4.01)	-13.2 (-19.22 to -7.15)		

Statistical analyses

Statistical analysis title	P2a rostafuroxin 6 microg. vs losartan- Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 6 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 6 microg. - Genetic Profile P2a v Caucasian losartan 50 mg. - Genetic Profile P2a
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.592
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.61
upper limit	11.48

Primary: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P2a adjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P2a adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2a (adjusted for genetic heterogeneity). The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Primary

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2a, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 50 microg. - Genetic Profile P2a	Caucasian losartan 50 mg. - Genetic Profile P2a		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	20		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-23.0 (-29.91 to -16.0)	-13.2 (-19.22 to -7.15)		

Statistical analyses

Statistical analysis title	P2a rostafuroxin 50 microg. vs losartan- Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 50 microg. - Genetic Profile P2a v Caucasian losartan 50 mg. - Genetic Profile P2a
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.99
upper limit	-0.56

Primary: Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P2a adjusted

End point title	Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P2a adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2a (adjusted for genetic heterogeneity). The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 500 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Primary

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2a, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 500 microg. - Genetic Profile P2a	Caucasian losartan 50 mg. - Genetic Profile P2a		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	20		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-17.4 (-23.74 to -11.03)	-13.2 (-19.22 to -7.15)		

Statistical analyses

Statistical analysis title	P2a rostafuroxin 500 microg. vs losartan-Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 500 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 500 microg. - Genetic Profile P2a v Caucasian losartan 50 mg. - Genetic Profile P2a
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.342
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.98
upper limit	4.57

Other pre-specified: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - LSS AA adjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - LSS AA adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the LSS AA genotype. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying the LSS AA genotype, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 50 microg. - LSS AA	Caucasian losartan 50 mg. - LSS AA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-27.3 (-35.79 to -18.89)	-13.9 (-22.33 to -5.43)		

Statistical analyses

Statistical analysis title	LSS AA - rostafuroxin 50 vs losartan - Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 50 microg. rostafuroxin and 50 mg losartan treatment arms, LSS AA genotype, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect and baseline as covariate. Treatment difference.

Comparison groups	Caucasian losartan 50 mg. - LSS AA v Caucasian rostafuroxin 50 microg. - LSS AA
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.031 [2]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.43
upper limit	-1.49

Notes:

[1] - Comparison of OSBP fall (adjusted for OSBP at baseline) between LSS AA carriers treated with rostafuroxin 50 mcg. and LSS AA carriers treated with losartan 50 mg (9 week-treatment).
[2] - Treatment difference (mmHg), 50 microg. rostafuroxin AA - losartan AA, Caucasian.

Other pre-specified: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - LSS CC adjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - LSS CC adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the LSS CC genotype. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying the LSS CC genotype, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 50 microg. - LSS CC	Caucasian losartan 50 mg. - LSS CC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	18		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-10.3 (-19.51 to -1.13)	-17.7 (-24.14 to -11.17)		

Statistical analyses

Statistical analysis title	LSS CC - rostafuroxin 50 vs losartan - Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 50 microg. rostafuroxin and losartan treatment arms, LSS CC genotype, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect and baseline as covariate. Treatment difference.

Comparison groups	Caucasian rostafuroxin 50 microg. - LSS CC v Caucasian losartan 50 mg. - LSS CC
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.192 [4]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.94
upper limit	18.61

Notes:

[3] - Comparison of OSBP fall (adjusted for OSBP at baseline) between LSS CC carriers treated with rostafuroxin 50 microg. and LSS CC carriers treated with losartan 50 mg (9 weeks treatment).
[4] - Treatment difference (mmHg), 50 microg. rostafuroxin LSS CC - losartan LSS CC, Caucasian

Other pre-specified: Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P2 adjusted

End point title	Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P2 adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 6 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 6 microg. - Genetic Profile P2	Caucasian losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	23		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-8.3 (-14.56 to -2.10)	-13.7 (-19.51 to -7.88)		

Statistical analyses

Statistical analysis title	P2 adj- rostafuroxin 6 microg. vs losartan - Cauca

Statistical analysis description:

ANCOVA / Caucasian - 6 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 6 microg. - Genetic Profile P2 v Caucasian losartan 50 mg. - Genetic Profile P2
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.214
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.17
upper limit	13.89

Other pre-specified: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P2 adjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P2 adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 50 microg. - Genetic Profile P2	Caucasian losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	23		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-22.2 (-28.92 to -15.42)	-13.7 (-19.51 to -7.88)		

Statistical analyses

Statistical analysis title	P2 rostafuroxin 50 microg. vs losartan- Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 50 microg. - Genetic Profile P2 v Caucasian losartan 50 mg. - Genetic Profile P2
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.39
upper limit	0.43

Other pre-specified: Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P2 adjusted

End point title	Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P2 adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to

treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 500 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 500 microg. - Genetic Profile P2	Caucasian losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	23		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-19.5 (-25.88 to -13.11)	-13.7 (-19.51 to -7.88)		

Statistical analyses

Statistical analysis title	P2 rostafuroxin 500 microg. vs losartan- Caucasian

Statistical analysis description:

ANCOVA / Caucasian - 500 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian losartan 50 mg. - Genetic Profile P2 v Caucasian rostafuroxin 500 microg. - Genetic Profile P2
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.44
upper limit	2.84

Other pre-specified: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - LSS AA/CC adjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - LSS AA/CC adjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the LSS AA or LSS CC genotype. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of covariance (ANCOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan, with the continuous fixed covariate of baseline.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two months after randomization - Caucasian subjects carrying the LSS AA or CC genotype, mean change adjusted for OSBP at baseline.

End point values	Caucasian rostafuroxin 50 microg. - LSS AA	Caucasian losartan 50 mg. - LSS AA	Caucasian rostafuroxin 50 microg. - LSS CC	Caucasian losartan 50 mg. - LSS CC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	9	18
Units: mmHg				
arithmetic mean (confidence interval 95%)	-25.2 (-35.38 to -15.02)	-12.9 (-22.30 to -1.78)	-11.1 (-19.35 to -2.83)	-18.6 (-24.51 to -12.68)

Statistical analyses

Statistical analysis title	LSS- rostafuroxin 50 microg. vs losartan-Caucasian

Statistical analysis description:

ANCOVA / Caucasian - LSS AA or CC - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANCOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 50 microg. - LSS AA v Caucasian losartan 50 mg. - LSS AA v Caucasian rostafuroxin 50 microg. - LSS CC v Caucasian losartan 50 mg. - LSS CC
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [5]
Method	ANCOVA
Parameter estimate	Mean difference (net)

Notes:

[5] - Model analysis of OSBP for LSS AA and CC in Caucasians, 50 mcg Rostafuroxin and Losartan.
P value for Treatment x LSS genotype interaction.

Other pre-specified: Chinese OSBP difference between 50 mcg rostafuroxin and Losartan - P2 unadjusted

End point title	Chinese OSBP difference between 50 mcg rostafuroxin and Losartan - P2 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Chinese subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change.

End point values	Chinese rostafuroxin 50 microg. - Genetic Profile P2	Chinese losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	16		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-0.2 (-6.15 to 5.73)	-15.4 (-20.96 to -9.85)		

Statistical analyses

Statistical analysis title	P2 - rostafuroxin 50 microg. vs losartan - Chinese

Statistical analysis description:

ANOVA/ Chinese - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Chinese rostafuroxin 50 microg. - Genetic Profile P2 v Chinese losartan 50 mg. - Genetic Profile P2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.06
upper limit	23.32

Other pre-specified: Chinese OSBP difference between 500 mcg rostafuroxin and Losartan - P2 unadjusted

End point title	Chinese OSBP difference between 500 mcg rostafuroxin and Losartan - P2 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 500 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Chinese subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change.

End point values	Chinese rostafuroxin 500 microg. - Genetic Profile P2	Chinese losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	16		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-4.7 (-10.4 to 1.06)	-15.4 (-20.96 to -9.85)		

Statistical analyses

Statistical analysis title	P2 - rostafuroxin 500 microg. vs losartan- Chinese

Statistical analysis description:

ANOVA/ Chinese - 500 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Chinese rostafuroxin 500 microg. - Genetic Profile P2 v Chinese losartan 50 mg. - Genetic Profile P2
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.75
upper limit	18.72

Other pre-specified: Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P2 unadjusted

End point title	Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P2 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 6 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change.

End point values	Caucasian rostafuroxin 6 microg. - Genetic Profile P2	Caucasian losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	23		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-8.7 (-15.33 to -2.13)	-13.1 (-19.27 to -6.96)		

Statistical analyses

Statistical analysis title	P2 - rostafuroxin 6 microg. vs losartan- Caucasian

Statistical analysis description:

ANOVA/ Caucasian - 6 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 6 microg. - Genetic Profile P2 v Caucasian losartan 50 mg. - Genetic Profile P2
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	13.4

Other pre-specified: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P2 unadjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P2 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change.

End point values	Caucasian rostafuroxin 50 microg. - Genetic Profile P2	Caucasian losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	23		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-22.2 (-29.39 to -15.08)	-13.1 (-19.27 to -6.96)		

Statistical analyses

Statistical analysis title	P2 - rostafuroxin 50 microg. vs losartan-Caucasian

Statistical analysis description:

ANOVA/ Caucasian - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 50 microg. - Genetic Profile P2 v Caucasian losartan 50 mg. - Genetic Profile P2
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.56
upper limit	0.31

Other pre-specified: Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P2 unadjusted

End point title	Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P2 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P2. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 500 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one pair of gene variants included in the genetic profile P2, mean change.

End point values	Caucasian rostafuroxin 500 microg. - Genetic Profile P2	Caucasian losartan 50 mg. - Genetic Profile P2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	23		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-19.7 (-26.48 to -12.95)	-13.1 (-19.27 to -6.96)		

Statistical analyses

Statistical analysis title	P2 -rostafuroxin 500 microg. vs losartan-Caucasian

Statistical analysis description:

ANOVA/ Caucasian - 500 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian losartan 50 mg. - Genetic Profile P2 v Caucasian rostafuroxin 500 microg. - Genetic Profile P2
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.75
upper limit	2.54

Other pre-specified: Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P1 unadjusted

End point title	Caucasian OSBP difference between 6 mcg rostafuroxin and Losartan - P1 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P1. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 6 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one gene variant or one pair of gene variants included in the genetic profile P1, mean change.

End point values	Caucasian rostafuroxin 6 microg. - Genetic Profile P1	Caucasian losartan 50 mg. - Genetic Profile P1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	40		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-5.8 (-10.78 to -0.91)	-17.5 (-22.14 to -12.77)		

Statistical analyses

Statistical analysis title	P1 - rostafuroxin 6 microg. vs losartan -Caucasian

Statistical analysis description:

ANOVA/ Caucasian - 6 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian losartan 50 mg. - Genetic Profile P1 v Caucasian rostafuroxin 6 microg. - Genetic Profile P1
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.81
upper limit	18.41

Other pre-specified: Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P1 unadjusted

End point title	Caucasian OSBP difference between 50 mcg rostafuroxin and Losartan - P1 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P1. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one gene variant or one pair of gene variants included in the genetic profile P1, mean change.

End point values	Caucasian rostafuroxin 50 microg. - Genetic Profile P1	Caucasian losartan 50 mg. - Genetic Profile P1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	40		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-17.3 (-22.31 to -12.30)	-17.5 (-22.14 to -12.77)		

Statistical analyses

Statistical analysis title	P1 - rostafuroxin 50 microg. vs losartan-Caucasian

Statistical analysis description:

ANOVA/ Caucasian - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 50 microg. - Genetic Profile P1 v Caucasian losartan 50 mg. - Genetic Profile P1
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	7.01

Other pre-specified: Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P1 unadjusted

End point title	Caucasian OSBP difference between 500 mcg rostafuroxin and Losartan - P1 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P1. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 500 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Caucasian subjects carrying at least one gene variant or one pair of gene variants included in the genetic profile P1, mean change.

End point values	Caucasian rostafuroxin 500 microg. - Genetic Profile P1	Caucasian losartan 50 mg. - Genetic Profile P1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	40		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-16.0 (-20.74 to -11.26)	-17.5 (-22.14 to -12.77)		

Statistical analyses

Statistical analysis title	P1 -rostafuroxin 500 microg. vs losartan-Caucasian

Statistical analysis description:

ANOVA/ Caucasian - 500 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Caucasian rostafuroxin 500 microg. - Genetic Profile P1 v Caucasian losartan 50 mg. - Genetic Profile P1
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	8.12

Other pre-specified: Chinese OSBP difference between 50 mcg rostafuroxin and Losartan - P1 unadjusted

End point title	Chinese OSBP difference between 50 mcg rostafuroxin and Losartan - P1 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P1. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 50 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Chinese subjects carrying at least one gene variant or one pair of gene variants included in the genetic profile P1, mean change.

End point values	Chinese rostafuroxin 50 microg. - Genetic Profile P1	Chinese losartan 50 mg. - Genetic Profile P1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	33		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-2.7 (-6.69 to 1.23)	-15.9 (-19.72 to -12.17)		

Statistical analyses

Statistical analysis title	P1 - rostafuroxin 50 microg. vs losartan - Chinese

Statistical analysis description:

ANOVA/ Chinese - 50 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Chinese rostafuroxin 50 microg. - Genetic Profile P1 v Chinese losartan 50 mg. - Genetic Profile P1
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.74
upper limit	18.68

Other pre-specified: Chinese OSBP difference between 500 mcg rostafuroxin and Losartan - P1 unadjusted

End point title	Chinese OSBP difference between 500 mcg rostafuroxin and Losartan - P1 unadjusted

End point description:

The change in the office systolic blood pressure (OSBP) over 2 months was measured in carriers of the genetic profile P1. The between group comparison was performed on the change from baseline to treatment of OSBP using an analysis of variance (ANOVA) model. Analysis compared the group treated with 500 mcg rostafuroxin versus the group treated with losartan.

End point type	Other pre-specified

End point timeframe:

Office Systolic Blood pressure (OSBP) change two month-treatment - Chinese subjects carrying at least one gene variant or one pair of gene variants included in the genetic profile P1, mean change.

End point values	Chinese rostafuroxin 500 microg. - Genetic Profile P1	Chinese losartan 50 mg. - Genetic Profile P1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	33		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-4.6 (-8.37 to -0.82)	-15.9 (-19.72 to -12.17)		

Statistical analyses

Statistical analysis title	P1 - rostafuroxin 500 microg. vs losartan -Chinese

Statistical analysis description:

ANOVA/ Chinese - 500 microg. rostafuroxin vs. losartan, Per Protocol Set
ANOVA model with change from baseline to visit 6 as dependent variable, treatment as fixed effect.

Comparison groups	Chinese rostafuroxin 500 microg. - Genetic Profile P1 v Chinese losartan 50 mg. - Genetic Profile P1
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.01
upper limit	16.69

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind, 9 week-period for each patient.
June 26, 2013 - March 28, 2016 for Caucasian
December 18, 2015 - February 8, 2018 for Chinese

Adverse event reporting additional description:

Patients were monitored throughout the study for AEs which were documented and collected on an ongoing basis during the treatment period and the relevant follow up period. In addition, patients were instructed to record any AEs in the Patient Diary.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	6 microg. rostafuroxin Caucasian
Reporting group description: -	
Reporting group title	50 microg. rostafuroxin Caucasian
Reporting group description: -	
Reporting group title	500 microg. rostafuroxin Caucasian
Reporting group description: -	
Reporting group title	50 mg. losartan Caucasian
Reporting group description: -	
Reporting group title	50 microg. rostafuroxin Chinese
Reporting group description: -	
Reporting group title	500 microg. rostafuroxin Chinese
Reporting group description: -	
Reporting group title	50 mg. losartan Chinese

Reporting group description: -

Serious adverse events	6 microg. rostafuroxin Caucasian	50 microg. rostafuroxin Caucasian	500 microg. rostafuroxin Caucasian
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	50 mg. losartan Caucasian	50 microg. rostafuroxin Chinese	500 microg. rostafuroxin Chinese

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	50 mg. losartan Chinese		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	6 microg. rostafuroxin Caucasian	50 microg. rostafuroxin Caucasian	500 microg. rostafuroxin Caucasian
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 42 (11.90%)	5 / 42 (11.90%)	7 / 43 (16.28%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Monoclonal gammopathy			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal submucosal tumour			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Neoplasm			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Female sexual dysfunction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Menstruation irregular			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Rhinitis allergic			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nasal septum deviation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood pressure abnormal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Lymphocyte percentage decreased			

subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 42 (4.76%)	3 / 42 (7.14%)	2 / 43 (4.65%)
occurrences (all)	2	10	2
Dizziness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Loss of consciousness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Tension headache			

subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
VIth nerve paralysis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			

subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Peptic ulcer			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hepatic steatosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pustular psoriasis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			

subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 42 (2.38%)	0 / 43 (0.00%)
occurrences (all)	2	1	0
Muscle spasms			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Bronchitis			

subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Hypercalcaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	50 mg. losartan Caucasian	50 microg. rostafuroxin Chinese	500 microg. rostafuroxin Chinese
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 43 (18.60%)	17 / 35 (48.57%)	21 / 34 (61.76%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Monoclonal gammopathy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal submucosal tumour			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Neoplasm			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 43 (0.00%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Chest discomfort			

subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Female sexual dysfunction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Menstruation irregular			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nasal septum deviation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Anxiety disorder			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences (all)	0	8	1
Anxiety			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood pressure abnormal			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Lymphocyte percentage decreased			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 43 (0.00%)	2 / 35 (5.71%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Left ventricular hypertrophy			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Nervous system disorders			
Headache			
subjects affected / exposed	4 / 43 (9.30%)	2 / 35 (5.71%)	4 / 34 (11.76%)
occurrences (all)	10	2	9
Dizziness			
subjects affected / exposed	1 / 43 (2.33%)	2 / 35 (5.71%)	2 / 34 (5.88%)
occurrences (all)	1	2	2
Tremor			
subjects affected / exposed	1 / 43 (2.33%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Loss of consciousness			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
VIth nerve paralysis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	0 / 43 (0.00%)	2 / 35 (5.71%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Peptic ulcer			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hepatic steatosis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pustular psoriasis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Arthralgia			

subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Tendonitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 43 (2.33%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 43 (0.00%)	5 / 35 (14.29%)	3 / 34 (8.82%)
occurrences (all)	0	5	3
Rhinitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Gastroenteritis viral			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 43 (0.00%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Hyperlipidaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Hyperglycaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1

Non-serious adverse events	50 mg. losartan Chinese		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 35 (57.14%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Monoclonal gammopathy			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Gastrointestinal submucosal tumour			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Neoplasm			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all)	 0 / 35 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Chest discomfort subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 1 / 35 (2.86%) 1 0 / 35 (0.00%) 0 0 / 35 (0.00%) 0 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 2 / 35 (5.71%) 2		
Reproductive system and breast disorders Female sexual dysfunction subjects affected / exposed occurrences (all) Menstruation irregular subjects affected / exposed occurrences (all)	 0 / 35 (0.00%) 0 1 / 35 (2.86%) 1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Nasal septum deviation			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Investigations			
Blood pressure abnormal			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Lymphocyte percentage decreased			

subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Neutrophil count increased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Left ventricular hypertrophy			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	4		
Loss of consciousness			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Tension headache			

subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
VIth nerve paralysis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	2		
Haemorrhoids			

subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Peptic ulcer			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hepatic steatosis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Pustular psoriasis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Skin exfoliation			

subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Bronchitis			

subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastroenteritis viral			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		

Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	Amendment N.1
27 March 2013	Amendment CVT-CV-001 IT3
30 January 2014	Amendment CVT CV-001 IT6
27 May 2014	Amendment CVT CV-001 IT6 v.2
25 June 2015	Amendment N.2.1
11 July 2017	Amendment N.3 V.1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 November 2013	PEARL-HT was interrupted in November 2013 because of the discovery of the mold in the 50 microgr. batch. The appropriate action was taken and approved by AIFA, and the clinical trial restarted in October 2014.	-

Notes:

Limitations and caveats

None reported