Clinical trial results: *PHARMACOGENETICS OF HYPERTENSION: A NEW APPROACH TO PERSONALISED MEDICINE*

EudraCT number*	2015-001888-39
Trial protocol	PHARMACOGENETICS OF HYPERTENSION: A NEW APPROACH TO PERSONALISED MEDICINE - PGX-HT
Global end of trial date*	14/11/2018

Trial information

Trial identification Additional study	
Sponsor protocol code*	OSR RF-2011-02347356

Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03249285
WHO universal trial number (UTN)	-

Notes:

Sponsors details*	
Sponsor organisation name	IRCCS Ospedale San Raffaele
Sponsor organisation address	Via Olgettina, 60, Milano, Italy, 20132
Public contact	
Scientific contact	Prof. Lanzani Chiara – 02 2643 5330

Notes:

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

Results analysis stage	
Analysis stage*	Final
Date of final analysis*	04/01/2019
Is this the analysis of the primarycompletion data?*	Yes
Global end of trial reached?*	Yes
Global end of trial date*	14/11/2018
Was the trial ended prematurely?	No

General information about the trial

Main objective of the trial*: the primary objective of the study is confirming a statistically significant difference in terms of reduction in diastolic and systolic blood pressure (BP) values between patients carrying and not carrying the profile genetic specific for each drug, Hydroclorothiazide (HCTZ) or Perindopril (Peri), after 4/8 weeks of treatment.

The secondary objectives are:

1. Implement specific genetic profiles for HCTZ and Peri by identifying new SNPs in genes coding for markers already known to be involved in pressure regulation mechanisms sodium sensitive, but not already included in the profiles indicated.
2. Evaluate the new genetic profiles in the response to Peri and HCTZ drugs in terms of Positive Predictive Value and Specificity.

Actual start date of recruitment*	19/03/2016
Long term follow-up planned*	No
If Yes, rationale:	Safety Efficacy Ethical reason Regulatory reason Scientific research
Duration of the study	2 Years
Independent data monitoring committee(IDMC) involvement?*	No
Protection of trial subjects*:	POLIZZA RC SPERIMENTAZIONE N. ITCANP99992 – OSPEDALE SAN RAFFAELE - STUDIO PGX-HT - SCADENZA 14/11/2018
Background therapy:	No - ESH hypertension guidelines
Evidence for comparator:	NA

Population of trial subjects Subjects enrolled per country

Country:	Italy
Planned number of subjects	300
Actual Number of subjects enrolled*	312
Worldwide total number of subjects	312
EEA total number of subjects	312

Subjects enrolled per age group

In utero*	0
Preterm newborn - gestational age < 37wks*	0
Newborns (0-27 days)*	0
Infants and toddlers (28 days-23months)*	0
Children (2-11 years)*	0
Adolescents (12-17 years)*	0
Adults (18-64 years)*	312
From 65 to 84 years*	0
85 years and over*	0

Subject disposition

Recruitment details: The study involves the enrollment of 300 naïve hypertensive patients with ambulatory blood pressure (BP) ≥ 140/90 and <160/110 mmHg after the exclusion of secondary forms of hypertension and after lifestyle modifications.

Patients will be recruited from 3 centers: Milan (150) (Hypertension Clinic, San Raffaele Hospital), Livorno-Piombino (75) (Health Authority 6 Livorno - Department of Clinical Medicine and Division of Nephrology and Dialysis) and Udine (75) (S. Maria della Misericordia University Hospital - Medical Clinic, Integrated Care Department of Internal Medicine)

The study planned to enroll 150 patients for each study treatment (Perindopril/HCTZ) distributed in the two groups (with and without specific genetic profile) according to a 1:1.5 ratio (60 with profile and 90 without with and without profile).

Pre-assignment - *Screening details*: Patients selected for this pharmacogenomics study (PGX) were naïve hypertensives, i.e. first diagnosed and never treated pharmacologically in order to avoid pharmacological interferences both on hormonal systems (RAAS) and on vascular proteins, and, in consideration of the high variability of the BP response to therapy which is configured as a polygenic trait. Various strategies have been adopted (territorial screening, press campaigns, etc.) to select 312 naïve patients eligible for the PGX-HT study.

Period 1

Period title*	Overall trial
Is this the baseline period?	Yes
Allocation method*	**Randomised – controlled**
Blinding used*	**Not blinded**

Arm title*	**Perindopril/PERI**	**Perindopril/HCTZ**	**HCTZ/HCTZ**	**HCTZ/Perindopril**
Arm description:	Perindopril in patients with genetic profile of Perindopril (PERI)	Perindopril in patients with genetic profile of HCTZ	HCTZ in patients with genetic profile of HCTZ	HCTZ in patients with genetic profile of PERI
Arm type*	Experimental	Experimental	Experimental	Experimental
Investigational medicinal product name*	Perindopril	Perindopril	HCTZ	HCTZ
Investigational medicinal product code	C09AA04	C09AA04	C03AA03	C03AA03
Other name	NA	NA	NA	NA
Pharmaceutical forms*	Tablet	Tablet	Tablet	Tablet
Routes of administration*	Oral	Oral	Oral	Oral
Dosage and administration details*	4 mg initial to be carried to 8 mg final	4 mg initial to be carried to 8 mg final	12,5 mg initial to be carried to 25 mg final	12,5 mg initial to be carried to 25 mg final

Number of subjects in period	PERI/Perindopril	Perindopril/hctZ	HCTZ/HCTZ	HCTZ/Perindopril
Started*	38	33	21	29
Completed*	33	28	21	26

Subject non-completion reason (if applicable)	
AE, non fatal	20
AE, fatal	0
Consent withdrawn by subject	4
Lack of efficacy	0
Lost to follow up	19
Physician decision	12
Pregnancy	0
Protocol Deviation	0
Other	0

Baseline characteristics

Reporting groups* Overall cohort	
Reporting group title*	Overall cohort
Number of subjects at the baseline*	312

Reporting group description:
Baseline characteristics of eligible patients were analyzed across the three collection centers: Milan (Mi), Livorno (Li), Udine (Ud).
A total of 312 patients were included.
The population consisted of 147 males and 165 females.
Overall, the total mean age was 48.15 years (SD ±7.25).
The overall mean BMI was 26.39 kg/m² (SD ±3.21).
The overall mean diastolic BP was 95.51 mmHg (SD ±6.89).
The overall mean systolic BP was 151.62 mmHg (SD ±9.87).
A subset of 121 patients received treatment. Baseline characteristics of this group were also examined by center.

Subject analysis sets

Add a subject analysis set if you wish to report on groups different from the reporting group defined above (repeat if applicable)

Subject analysis set title*	*NA*
Subject analysis set type*	*NA*
Subject analysis set description*	*NA*
Number of subjects in subjects analysis set*	*NA*

Age characteristics*

Complete either the age categorical, age continuous or complete both these characteristics in order to collect values for the reporting groups and optionally the subject analysis sets.

	Characteristic title*	Units*	Age categories*
Age categorical	NA	NA	NA

	Characteristic title*	Units*	Central tendency*	Dispersion type*
Age continuous	Overall cohort	Years	Arithmetic Mean	standard deviation

Gender characteristics*

	Characteristic title*	Units*	Gender categories*
Gender categorical	gender	NA	Female Male

Study specific characteristics

	Characteristic title*	Units*	Categories*	Number of subject for each categories
Study specific categorical	Responder Peri V4	N or %	SBP<140 mmHg at visit 4	44 (62%)
Study specific categorical	Not responder Peri V4	N or %	SBP>140 mmHg at visit 4	27 (38%)
Study specific categorical	Responder HCTZ V4	N or %	SBP<140 mmHg at visit 4	33(59%)
Study specific categorical	Not responder HCTZ V4	N or %	SBP>140 mmHg at visit 4	17 (34%)
Study specific categorical	Responder Peri V5	N or %	SBP<140 mmHg at visit 5	36(59%)

Study specific categorical	Not responder Peri V5	N or %	SBP>140 mmHg at visit 5	25 (41%)
Study specific categorical	Responder HCTZ V5	N or %	SBP<140 mmHg at visit 5	34 (72%)
Study specific categorical	Not responder HCTZ V5	N or %	SBP>140 mmHg at visit 5	13 (28%)

End points

Add subject analysis set if you wish to report on groups different form reporting groups defined above

Subject analysis set title*	**Primary obiective**
Subject analysis set type*	Full Analysis
Subject analysis set description*	The primary objective of the study is to confirm a statistically significant difference in terms of reduction in diastolic and systolic blood pressure values between patients with and without the specific genetic profile for each drug (HCTZ or Peri) after 4/8 weeks of treatment. Specifically, our primary objective is to demonstrate that: - patients carrying the Peri genetic profile (corresponding to the following linear combination of genotypes in the indicated SNPs: presence of SLC12A1 rs6493311 CT+CC and EGFR rs4245566 AA or CPS1 rs17773661 GT+TT and REN rs10900555 TT or PRKG1 rs7897633 AA and ITPR2 rs10506007 TT or MYO16 rs1926507 GG and SIK1 rs229345 TT) show a significantly greater drop in systolic and/or diastolic blood pressure after 4 weeks of therapy with Perindopril (Peri) 4 mg orally compared to non-carriers. - patients carrying the HCTZ genetic profile (corresponding to the following linear combination of genotypes in the indicated SNPs: NKAIN2 rs235679 CG(+CC) or NKAIN3 rs2928389 CC and DRD1 rs4867791 CC, or CYP7A1 rs8192879 AA and NEDD4L rs4149601 AG+GG or WNK1 rs880054 GG and SLC12A3 rs5805 TT) show a significantly greater drop in blood pressure in terms of systolic and/or diastolic blood pressure after 4 weeks of therapy with Hydrochlorothiazide (HCTZ) 12.5 mg per os compared to non-carriers.
Number of subject in subject analysis set *	121

End points definitions

End point title*	Difference in SBP	
		Values
Countable or measurable?*		measurable
If countable, Countable units*:		
If measurable, Measurable units*		mmHg
Measure type*:	Arithmetic Mean	
Precision/dyspersion type*	Standard deviation	
End point title*	responder	
		Values
Countable or measurable?*		countable
If countable, Countable units*:		number
If measurable, Measurable units*		
Measure type*:	NA	

End point type*	Primary

End point timeframe*: 4-8 weeks

Use categories only if the data for the end point can be categorized

Category title

Specify the groups of subjects applicable to this end point

Reporting groups*	**Responder**	**Non responder**	**Responder**	**Non responder**
Period	8 weeks	8 weeks	8 weeks	8 weeks
Arms	perindopril	Perindopril	hctz	Hctz
subject analysis sets	44	27	33	17

Adverse events

Adverse events information

Timeframe for reporting adverse events*: *Enter the time point(s) or time period for AE assessment*

First patient first visit: 19/03/2016
Last recruitment date: 18/09/2018
Study closure: 14/11/2018

Adverse event reporting additional description: *Enter information about the AE collection and provide details about the method of assessment and monitoring*

Assessment type*	Systematic
Frequency threshold for reporting non-serious adverse events*	*At each visit*

Dictionary used

Dictionary name*	MedDRA or CTCAE
Dictionary version*	TCAE v4.03

Adverse events reporting group definition

Use arms from baseline period as reporting groups
OR

Reporting group title*: *Overall cohort*

For this reporting group, provide the following totals:

Subject exposed*	121
Subjects affected by non - SAE*	20
Total number of deaths (all causes)*	0
Total number of deaths resulting from adverse event*	0

Serious adverse event details and values

System organ class*:

Event term*:

Values for serious adverse event per reporting group *

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number	Occurrences causally related to treatment number	Fatalities number	Fatalities causally related to treatment number

Non - Serious adverse event details and values

System organ class*: cardiovascular, respiratory, neurological, gastric, e.coli, hematological, dental, otorhinolaryngology

Event term*: end of study

Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number
Cardiovascular	**3**	**na**	**3**
Respiratory	**8**	**Na**	**8**
neurologicl	**3**	**Na**	**3**
Gastric	**1**	**Na**	**1**
UTI e.coli	**1**	**Na**	**1**
Hematological	**2**	**na**	**2**
Dental	**1**	**na**	**1**
otorhinolaryngology	**1**	**Na**	**1**

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol*? Yes

Date	Amendment
13/11/2024	Amendment became necessary by virtue of the entry into force of the DM 26 January 2023 "Identification of forty territorial ethics committees" and subsequent "Operational indications for the census of Territorial Ethics Committees (CET) / National Ethics Committees (CENs) in OsSC and management of the related transfer of responsibilities of the Coordinating Ethics Committees (CECs) from 7 June 2023" issued by AIFA. The change from CEC Ospedale San Raffaele to CET Lombardia 1 is requested.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial*? No

If Yes, Interruption date

Interruption descrption

Limitations and caveats

None reported

Online references

Enter PubMed identifier (PMID)

CITTERIO L, LANZANI C, BRIONI E, DELLI CARPINI S, SIMONINI M, TENTORI S, CUKA E, FONTANA S, CASAMASSIMA N, MANUNTA P. Pharmacogenomics of hypertension: PGX-HT (EudraCT 2015-001888-39), a new approach for personalized medicine (RF-2011-02347356). OSR Scientific Retreat 2017. 10th-12th March 2017. Baveno, Italy