Clinical trial results:
Open-label, multicenter, multinational, interventional clinical trial to assess effectiveness and safety of the extemporaneous combination of nebivolol and zofenopril calcium in grade 1 to 2 hypertensive patients versus each monotherapy

Summary

EudraCT number	2020-002340-23
Trial protocol	IT
Global end of trial date	22 December 2021

Results information

Result version number	v1 (current)
This version publication date	07 January 2023
First version publication date	07 January 2023

Trial information

Trial identification

Sponsor protocol code	MEIN/19/ZoNe-HYP/001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05257148
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini International Operation Luxembourg SA
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg, L-1611
Public contact	Clinical Operation Director, Menarini, +39 055568091, pfabrizzi@menarini.it
Scientific contact	Clinical Operation Director, Menarini, +39 055568091, pfabrizzi@menarini.it

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2021
Global end of trial reached?	Yes
Global end of trial date	22 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antihypertensive effect of the extemporaneous combination of nebivolol 5 mg and zofenopril calcium 30 mg in lowering sitting diastolic blood pressure (DBP) after 8 weeks of treatment, in patients with uncontrolled blood pressure (BP) who were previously treated with nebivolol or zofenopril calcium monotherapies for at least 4 weeks

Protection of trial subjects:

The study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP), including the archiving of essential documents as well as the ethical principles of the Declaration of Helsinki.

Background therapy:

No Background Therapy

Evidence for comparator: -

Actual start date of recruitment	08 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 267
Country: Number of subjects enrolled	Italy: 16
Worldwide total number of subjects	283
EEA total number of subjects	283

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)	283

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study started on 26 May 2021 and terminated on 22 December 2021
296 patients were screened for the study.
283 patients entered the run-in period and were assigned for monotherapy to Nebivolol (NEB) 5 mg or Zofenopril (ZOF) 30 mg. Of the 269 completed patients in monotherapy, 246 were assigned to combination therapy and 238 competed the study

Pre-assignment

Screening details:

296 patients male and female Caucasian uncontrolled hypertensive patients ≥ 18 and < 65 years of age on monotherapy either with ACE-i or BBs since at least 1 month and with mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg and / or mean sitting DBP ≥ 90 mmHg and ≤ 109 mmHg, were screened.

Period 1

Period 1 title	Run-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open-label study, not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Zofenopril 30 mg

Arm description:

Patients in therapy with ACE-i, were assigned to monotherapy with ZOFENOPRIL 30 mg for 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Zofenopril 30 mg
Investigational medicinal product code	Zofenopril calcium
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study drug was administered with a glass of water once daily

Arm title	Nebivolol 5 mg

Arm description:

Patients in therapy with Beta Blockers, were assigned to monotherapy with Nebivolol 5 mg for 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Nebivolol 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study drug was administered with a glass of water once daily

Number of subjects in period 1	Zofenopril 30 mg	Nebivolol 5 mg
Started	137	146
Completed	130	139
Not completed	7	7
Lost to follow-up	2	5
Protocol deviation	5	2

Period 2

Period 2 title	Assessment
Is this the baseline period?	Yes[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open-label study, not blinded

Arms

Arm title	Combination Therapy Zofenopril 30mg/Nebivolol 5mg

Arm description:

During the assessment period of 8 weeks, the eligible patients (uncontrolled hypertension with sitting BP of SBP/DBP > 130/80 mmHg, who tolerated the treatment and whose adherence to the therapies ranged from 80% to 120%) received a combination of NEB 5 mg and ZOF 30 mg to be taken orally once daily.

Arm type	Experimental
Investigational medicinal product name	Nebivolol 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study drug was administered with a glass of water once daily

Investigational medicinal product name	Zofenopril 30 mg
Investigational medicinal product code	Zofenopril calcium
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study drug was administered with a glass of water once daily

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the Run-in period. The objective of the study is to evaluate the effectiveness and safety of the combination therapy (Zofenopril/Nebivolol) versus the monotherapy. Hence the baseline period starts on Period 2, with the assessment of blood pressure after the run-in period and the intake of the combination therapy.

Number of subjects in period 2[2][3]	Combination Therapy Zofenopril 30mg/Nebivolol 5mg
Started	246
Completed	238
Not completed	8
Consent withdrawn by subject	4
Adverse event, non-fatal	2
Protocol deviation	2

Notes:

[2] - 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: 283 patients are enrolled patients that are included in the Run-in period (Period 1). Period 1 is not the baseline period. Patients

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: After the Run-in Period, Patients with controlled BP (sitting SBP / DBP ≤ 130/80 mmHg) at Week 0 (Visit 2), patients with uncontrolled BP (sitting SBP / DBP > 130/80 mmHg) whose adherence to the treatment was not included from 80% to 120%, or patients who could not tolerate one of the mono therapies were discontinued from the study and excluded from the Assessment Period (23 patients in total)

Baseline characteristics

Reporting groups	
Reporting group title	Assessment

Reporting group description: -

Reporting group values	Assessment	Total	
Number of subjects	246	246	
Age categorical Units: Subjects			
Adults (18-64 years)	246	246	
Gender categorical Units: Subjects			
Female	106	106	
Male	140	140	

End points

End points reporting groups

Reporting group title	Zofenopril 30 mg
Reporting group description:	
Patients in therapy with ACE-i, were assigned to monotherapy with ZOFENOPRIL 30 mg for 4 weeks	
Reporting group title	Nebivolol 5 mg
Reporting group description:	
Patients in therapy with Beta Blockers, were assigned to monotherapy with Nebivolol 5 mg for 4 weeks	
Reporting group title	Combination Therapy Zofenopril 30mg/Nebivolol 5mg
Reporting group description:	
During the assessment period of 8 weeks, the eligible patients (uncontrolled hypertension with sitting BP of SBP/DBP > 130/80 mmHg, who tolerated the treatment and whose adherence to the therapies ranged from 80% to 120%) received a combination of NEB 5 mg and ZOF 30 mg to be taken orally once daily.	
Subject analysis set title	Intention to treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all patients who were enrolled and received at least 1 dose of study drug (combination therapy) and have at least 1 post baseline safety assessment.	

Primary: Change in mean sitting DBP

End point title	Change in mean sitting DBP
End point description:	
End point type	Primary
End point timeframe:	
8 weeks of combination therapy treatment. From study visit 2 to study visit 3.	

End point values	Combination Therapy Zofenopril 30mg/Nebivolol 5mg	Intention to treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	241[1]	241[2]		
Units: mmHG				
arithmetic mean (standard deviation)	91.8 (± 5.5)	82.5 (± 7.91)		

Notes:

[1] - Only 241 patient have valid SBP measurement at baseline. Values collected here are baseline ones

[2] - Values collected here are SBP measurement at the end of the study

Statistical analyses

Statistical analysis title	Monotherapy vs Combination in DBP after 8 weeks
Statistical analysis description:	
Change from Baseline in the Diastolic Blood Pressure (DBP).	
Comparison groups	Combination Therapy Zofenopril 30mg/Nebivolol 5mg v Intention to treat population

Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Informed Consent signed to final visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	Combination Therapy Zofenopril 30mg/Nebivolo l 5mg

Reporting group description: -

Serious adverse events	Combination Therapy Zofenopril 30mg/Nebivolo l 5mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 246 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Combination Therapy Zofenopril 30mg/Nebivolo l 5mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 246 (0.81%)		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 246 (0.41%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 246 (0.41%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Note that due to technical limits in the portal the statistical analysis reports 482 patients included in the analysis and not 241 as they effectively are.
482 are indeed the 241 data collected before and the 241 after combined therapy intake

Notes: