



Clinical trial results:

Interventional clinical trial to assess efficacy and safety of the extemporaneous combination of Zofenopril calcium and amlodipine in grade 1-2 hypertensive patients versus each monotherapy

Summary

EudraCT number	2021-000745-40
Trial protocol	IT
Global end of trial date	28 April 2022

Results information

Result version number	v1 (current)
This version publication date	14 May 2023
First version publication date	14 May 2023

Trial information

Trial identification

Sponsor protocol code	MEIN/20/ZoAm-Hyp/001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05279807
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	Medical Affairs & Clinical Operation Director Paolo Fabrizio, Menarini , +39 055568091, pfabrizzi@menarini.it
Scientific contact	Medical Affairs & Clinical Operation Director Paolo Fabrizio, 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	24 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2022
Global end of trial reached?	Yes
Global end of trial date	28 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: To assess the anti-hypertensive efficacy of the extemporaneous combination of ZOF 30 mg with AML 5 mg or AML 10 mg in lowering the sitting diastolic BP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with ZOF (30 mg) or AML (5 mg) 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	15 October 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	Hungary: 270
Country: Number of subjects enrolled	Russian Federation: 7
Worldwide total number of subjects	277
EEA total number of subjects	270

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)	277

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study started on 15 October 2021 and terminated on 28 April 2022

290 patients were screened for the study.

277 patients entered the run-in period and were assigned for monotherapy to Amlodipine (AML) 5 mg or Zofenopril (ZOF) 30 mg. All 271 completed patients in monotherapy were assigned to combination therapy and 269 completed the study.

Pre-assignment

Screening details:

290, Grade 1-2 hypertensive patients with blood pressure [BP] ranging from $\geq 140 / 90$ mmHg to $\leq 179 / 109$ mmHg) in treatment with any ACE-I or CCBs, including ZOF 30 mg or AML 5 mg (only dosage allowed) for at least one month prior to Visit 1 (Week -4), were screened for eligibility.

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 30mg

Arm description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit. Patients previously receiving ZOF 30 mg continued the same treatment, patients receiving any other ACE-i were switched to ZOF 30 mg

Arm type	Active comparator
Investigational medicinal product name	Zofenopril 30mg
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 administered with a glass of water once daily

Arm title	Amlodipine 5mg
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Arm description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit. Patients previously receiving AML 5 mg continued the same treatment, while patients receiving any other CCBs were switched to AML 5 mg

Arm type	Active comparator
Investigational medicinal product name	Amlodipine 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 30mg	Amlodipine 5mg
Started	144	133
Completed	142	132
Not completed	2	1
Consent withdrawn by subject	1	-
Laboratory Abnormal Results	1	1

Period 2

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

Arms

Arm title	Combination Therapy Zofenopril 30mg/Amlodipine 5mg or 10mg
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Arm description:

Patients having uncontrolled BP (SBP/DBP > 130 / 80 mmHg) at Visit 2 (Week 0), were assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. After 4 Weeks \pm 2 days the BP was assessed again (Visit 3, Week 4): controlled patients (SBP/DBP \leq 130 / 80 mmHg) continued the same extemporaneous combination, while uncontrolled (SBP/DBP > 130 / 80 mmHg) patients were up-titrated to extemporaneous combination of ZOF/AML 30 mg / 10 mg for another 4 weeks \pm 2 days (Visit 4, Week 8). At Visit 2 (Week 0) and Visit 3 (Week 4) patients with SBP/DBP value classified as Grade 3 (SBP \geq 180 or DBP \geq 110 mmHg) hypertension were withdrawn from the study. To correctly evaluate additional effect of the combination therapy, the number of patients with uncontrolled BP on AML or ZOF monotherapy needed to be balanced at Week 0. Weekly evaluations were performed to maintain a 1:1 ratio during the assessment period 2. Corrective measures were initiated in case of 5% differences between the two groups.

Arm type	Experimental
Investigational medicinal product name	Zofenopril 30mg
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 administered with a glass of water once daily

Investigational medicinal product name	Amlodipine 5/10 mg
Investigational medicinal product code	Amlodipine besylate
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.

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/Amlodipine) 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/Amlodipine 5mg or 10mg
Started	271
Completed	269
Not completed	2
Consent withdrawn by subject	1
Laboratory Abnormal Results	1

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: 277 patients are enrolled patients that are included in the study and start the Run-in period (Period 1). Period 1 is not the baseline period. The baseline period is Period 2 (Assessment) where patients start to take the combination therapy ZOF 30 mg/AML 5 mg /AML 10 mg

[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 \leq 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 (3 patients in total)

Baseline characteristics

Reporting groups

Reporting group title	Assessment
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Reporting group description: -

Reporting group values	Assessment	Total	
Number of subjects	271	271	
Age categorical			
Units: Subjects			
Adults (18-64 years)	271	271	
Age continuous			
Units: years			
arithmetic mean	52.3		
standard deviation	± 9.83	-	
Gender categorical			
Units: Subjects			
Female	151	151	
Male	120	120	

End points

End points reporting groups

Reporting group title	Zofenopril 30mg
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Reporting group description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit. Patients previously receiving ZOF 30 mg continued the same treatment, patients receiving any other ACE-i were switched to ZOF 30 mg

Reporting group title	Amlodipine 5mg
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Reporting group description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit. Patients previously receiving AML 5 mg continued the same treatment, while patients receiving any other CCBs were switched to AML 5 mg

Reporting group title	Combination Therapy Zofenopril 30mg/Amlodipine 5mg or 10mg
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Reporting group description:

Patients having uncontrolled BP (SBP/DBP > 130 / 80 mmHg) at Visit 2 (Week 0), were assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. After 4 Weeks \pm 2 days the BP was assessed again (Visit 3, Week 4): controlled patients (SBP/DBP \leq 130 / 80 mmHg) continued the same extemporaneous combination, while uncontrolled (SBP/DBP > 130 / 80 mmHg) patients were up-titrated to extemporaneous combination of ZOF/AML 30 mg / 10 mg for another 4 weeks \pm 2 days (Visit 4, Week 8). At Visit 2 (Week 0) and Visit 3 (Week 4) patients with SBP/DBP value classified as Grade 3 (SBP \geq 180 or DBP \geq 110 mmHg) hypertension were withdrawn from the study. To correctly evaluate additional effect of the combination therapy, the number of patients with uncontrolled BP on AML or ZOF monotherapy needed to be balanced at Week 0. Weekly evaluations were performed to maintain a 1:1 ratio during the assessment period 2. Corrective measures were initiated in case of 5% differences between the two groups.

Subject analysis set title	Efficacy Population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All study participants who signed informed consent, met all screening criteria, were enrolled and received at least one dose of the assigned treatment during run-in period, completed the 4-week run-in period and met criteria at Visit 2 (Week 0) [uncontrolled BP (sitting SBP/DBP > 130 / 80 mmHg)], tolerated treatment, had treatment adherence between 80 – 120 % and had at least one available post baseline primary efficacy assessment [(from Visit 3 (Week 4) or Visit 4 (Week 8))].

Primary: Change in mean sitting DBP

End point title	Change in mean sitting DBP
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End point description:

End point type	Primary
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End point timeframe:

8 weeks of combination therapy treatment. From study Visit 2 (Week 0) to study Visit 4 (Week 8)

End point values	Combination Therapy Zofenopril 30mg/Amlodipine 5mg or 10mg	Efficacy Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	269 ^[1]	271 ^[2]		
Units: mmHG				

arithmetic mean (standard deviation)	78.9 (\pm 6.46)	92.4 (\pm 5.78)		
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Notes:

[1] - Values collected here are DBP measurement at the end of the study

[2] - Only 271 patients have valid DBP measurement at baseline. Values collected here are baseline ones

Statistical analyses

Statistical analysis title	DBP at Visit 2 (Week 0) vs Visit 4 (Week 8)
Statistical analysis description:	
Change from Baseline in the Diastolic Blood Pressure (DBP).	
Comparison groups	Combination Therapy Zofenopril 30mg/Amlodipine 5mg or 10mg v Efficacy Population
Number of subjects included in analysis	540
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24
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Reporting groups

Reporting group title	Combination Therapy Zofenopril 30mg/Amlodipina 5mg or 10mg
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Reporting group description:

Patients having uncontrolled BP (SBP/DBP > 130 / 80 mmHg) at Visit 2 (Week 0), were assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. After 4 Weeks \pm 2 days the BP was assessed again (Visit 3, Week 4): controlled patients (SBP/DBP \leq 130 / 80 mmHg) continued the same extemporaneous combination, while uncontrolled (SBP/DBP > 130 / 80 mmHg) patients were up-titrated to extemporaneous combination of ZOF/AML 30 mg / 10 mg for another 4 weeks \pm 2 days (Visit 4, Week 8). At Visit 2 (Week 0) and Visit 3 (Week 4) patients with SBP/DBP value classified as Grade 3 (SBP \geq 180 or DBP \geq 110 mmHg) hypertension were withdrawn from the study. To correctly evaluate additional effect of the combination therapy, the number of patients with uncontrolled BP on AML or ZOF monotherapy needed to be balanced at Week 0. Weekly evaluations were performed to maintain a 1:1 ratio during the assessment period. Corrective measures were initiated in case of 5% differences between the two groups.

Serious adverse events	Combination Therapy Zofenopril 30mg/Amlodipina 5mg or 10mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 271 (0.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Oesophageal food impaction			
subjects affected / exposed	1 / 271 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Combination Therapy Zofenopril 30mg/Amlodipina 5mg or 10mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 271 (7.01%)		

Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	5 / 271 (1.85%) 5		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all)	3 / 271 (1.11%) 3 8 / 271 (2.95%) 8		
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 271 (1.11%) 3		

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 540 patients included in the analysis and not 271 as they effectively are.

540 are indeed the 271 data collected before and the 269 after combined therapy intake

Notes: