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

Summary

EudraCT number	2021-005077-10
Trial protocol	BG PL
Global end of trial date	15 November 2022

Results information

Result version number	v1 (current)
This version publication date	29 November 2023
First version publication date	29 November 2023

Trial information

Trial identification

Sponsor protocol code	MEIN/21/AmNe-Hyp/001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05513937
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, Luxembourg, L-1611
Public contact	Medical Affair & Clinical Operation Director, Menarini, +39 055 5680459, pfabrizzi@menarini.it
Scientific contact	Medical Affair & Clinical Operation Director, Menarini, +39 055 5680459, 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	04 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2022
Global end of trial reached?	Yes
Global end of trial date	15 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antihypertensive efficacy of the extemporaneous combination of nebivolol (NEB) 5 mg with amlodipine (AML) 5 mg or AML 10 mg in lowering the sitting diastolic blood pressure (DBP) between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP, previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4 weeks.

Protection of trial subjects:

This study was performed 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	09 June 2022
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: 70
Country: Number of subjects enrolled	Bulgaria: 231
Worldwide total number of subjects	301
EEA total number of subjects	301

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)	301

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study started on 9 June 2022 and terminated on 15 November 2022
302 patients were screened for the study.
301 patients entered the run-in period and were assigned for monotherapy to Amlodipine (AML) 5 mg or Nebivolol (NEB) 5 mg. All 291 patients that completed monotherapy were assigned to combination therapy and 276 completed the study.

Pre-assignment

Screening details:

302, Grade 1-2 hypertensive patients with blood pressure [BP] ranging from ≥ 140 / 90 mmHg to ≤ 179 / 109 mmHg) in treatment with any beta-blockers (BBs) or calcium channel blockers (CCBs), including NEB 5 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	Nebivolol 5 mg

Arm description:

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

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

Dosage and administration details:

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

Arm title	Amlodipine 5 mg

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 5 mg
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	Nebivolol 5 mg	Amlodipine 5 mg
Started	143	158
Completed	139	152
Not completed	4	6
Consent withdrawn by subject	1	-
Physician decision	1	-
Protocol deviation	2	6

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:

Not blinded

Arms

Arm title	Combination Therapy Nebivolol 5 mg/Amlodipine 5 mg or 10 mg

Arm description:

Patients having uncontrolled BP (SBP/DBP > 130 / 80 mmHg) at Visit 2 (Week 0), were assigned to the extemporaneous combination of NEB 5 mg and AML 5 mg. After 4 Weeks ± 2 days the BP was assessed again (Visit 3, Week 4): controlled patients (SBP/DBP ≤ 130 / 80 mmHg) continued the same extemporaneous combination, while uncontrolled (SBP/DBP > 130 / 80 mmHg) patients were up-tritrated to extemporaneous combination of NEB/AML 5 mg / 10 mg for another 4 weeks ± 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 ≥ 180 or DBP ≥ 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	Nebivolol 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study medication was 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 (Nebivolol/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 Nebivolol 5 mg/Amlodipine 5 mg or 10 mg
Started	279
Completed	276
Not completed	3
Adverse event, non-fatal	2
Protocol deviation	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: 301 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 NEB 5 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 ≤ 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%, patients who could not tolerate one of the mono therapies, or classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertensin were discontinued from the study and excluded from the Assessment Period (12 patients in total).

Baseline characteristics

Reporting groups	
Reporting group title	Assessment

Reporting group description: -

Reporting group values	Assessment	Total	
Number of subjects	279	279	
Age categorical Units: Subjects			
Adults (18-64 years)	279	279	
Age continuous Units: years arithmetic mean standard deviation	 52.2 ± 8.13	 -	
Gender categorical Units: Subjects			
Female	144	144	
Male	135	135	

End points

End points reporting groups

Reporting group title	Nebivolol 5 mg

Reporting group description:

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

Reporting group title	Amlodipine 5 mg

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 Nebivolol 5 mg/Amlodipine 5 mg or 10 mg

Reporting group description:

Patients having uncontrolled BP (SBP/DBP > 130 / 80 mmHg) at Visit 2 (Week 0), were assigned to the extemporaneous combination of NEB 5 mg and AML 5 mg. After 4 Weeks ± 2 days the BP was assessed again (Visit 3, Week 4): controlled patients (SBP/DBP ≤ 130 / 80 mmHg) continued the same extemporaneous combination, while uncontrolled (SBP/DBP > 130 / 80 mmHg) patients were up-tritrated to extemporaneous combination of NEB/AML 5 mg / 10 mg for another 4 weeks ± 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 ≥ 180 or DBP ≥ 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
Subject analysis set type	Modified intention-to-treat

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 %, had at least one dose of combination therapy and had at least baseline [Visit 2 (Week 0)] and Visit 4 (Week 8) assessments with primary efficacy data. .

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 (Week 0) to study Visit 4 (Week 8)

End point values	Combination Therapy Nebivolol 5 mg/Amlodipine 5 mg or 10 mg	Efficacy Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	279	276		
Units: mmHG				
arithmetic mean (standard deviation)	93.3 (± 4.35)	78.2 (± 6.24)		

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 Nebivolol 5 mg/Amlodipine 5 mg or 10 mg v Efficacy Population
Number of subjects included in analysis	555
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Signed Rank Test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Informed Consent signed to final visit

Adverse event reporting additional description:

Safety analyses were carried out using the SAF analysis population, which was defined as all patients in the Enrolled population who received at least one dose of study medication (i.e., monotherapy and/or combination therapy)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Monotherapy

Reporting group description:

Safety Population that received Monotherapy

Reporting group title	Combination Therapy

Reporting group description: -

Serious adverse events	Monotherapy	Combination Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 301 (0.00%)	0 / 279 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Monotherapy	Combination Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 301 (1.99%)	44 / 279 (15.77%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	0 / 301 (0.00%)	2 / 279 (0.72%)	
occurrences (all)	0	2	

Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Lung consolidation			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 301 (0.00%)	2 / 279 (0.72%)	
occurrences (all)	0	2	
Blood creatinine increased			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Blood uric acid increased			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 301 (0.00%)	3 / 279 (1.08%)	
occurrences (all)	0	3	
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 301 (0.33%)	7 / 279 (2.51%)	
occurrences (all)	1	7	
Intracranial aneurysm			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 301 (0.66%)	3 / 279 (1.08%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 301 (0.00%)	3 / 279 (1.08%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	0 / 301 (0.00%)	3 / 279 (1.08%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 301 (0.00%)	2 / 279 (0.72%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	

Endocrine disorders			
Thyroid disorder			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	0 / 301 (0.00%)	6 / 279 (2.15%)	
occurrences (all)	0	6	
Back pain			
subjects affected / exposed	0 / 301 (0.00%)	3 / 279 (1.08%)	
occurrences (all)	0	3	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 279 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 301 (0.00%)	2 / 279 (0.72%)	
occurrences (all)	0	2	
Dehydration			

subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Dyslipidaemia			
subjects affected / exposed	0 / 301 (0.00%)	2 / 279 (0.72%)	
occurrences (all)	0	2	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 279 (0.36%)	
occurrences (all)	0	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 555 patients included in the analysis and not 279 as they effectively are.
555 are indeed the 279 data collected before and the 276 after combined therapy intake.

Notes: