



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 $\geq 140 / 90$ mmHg to $\leq 179 / 109$ 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 \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 NEB/AML 5 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 | 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 \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%, patients who could not tolerate one of the mono therapies, or classified as Grade 3 (SBP \geq 180 or DBP \geq 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 | 52.2 | | |
| standard deviation | ± 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 \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 NEB/AML 5 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 |
|----------------------------|---------------------|

| | |
|---------------------------|-----------------------------|
| 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 (\pm 4.35) | 78.2 (\pm 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 occurrences (all) | 0 / 301 (0.00%) 0 | 1 / 279 (0.36%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 301 (0.00%) 0 | 1 / 279 (0.36%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 301 (0.33%) 1 | 7 / 279 (2.51%) 7 | |
| Intracranial aneurysm subjects affected / exposed occurrences (all) | 1 / 301 (0.33%) 1 | 0 / 279 (0.00%) 0 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 2 / 301 (0.66%) 2 | 3 / 279 (1.08%) 3 | |
| Gastrointestinal disorders Toothache subjects affected / exposed occurrences (all) | 0 / 301 (0.00%) 0 | 3 / 279 (1.08%) 3 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 301 (0.00%) 0 | 3 / 279 (1.08%) 3 | |
| Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) | 1 / 301 (0.33%) 1 | 0 / 279 (0.00%) 0 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 301 (0.00%) 0 | 1 / 279 (0.36%) 1 | |
| Erythema subjects affected / exposed occurrences (all) | 0 / 301 (0.00%) 0 | 2 / 279 (0.72%) 2 | |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 301 (0.00%) 0 | 1 / 279 (0.36%) 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: