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ORIGINAL ARTICLE

Efficacy and Safety of the Extemporaneous Combination Nebivolol/Amlodipine in Patients with Hypertension Uncontrolled on Monotherapy: The BOTTICELLI Study

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Abstract

Introduction Hypertension is the leading cause of cardiovascular disease, and its complications are preventable with blood pressure (BP)-lowering treatment. Combination treatment with 2 or more antihypertensive agents achieves sustained BP reductions. Nebivolol (NEB), a highly β1-selective beta-blocker with vasodilating properties, and amlodipine (AML), a dihydropyridine calcium channel blocker, are widely prescribed as monotherapies or in combination.

Aim To evaluate efficacy and safety of extemporaneous combination at fixed doses of NEB/AML in adults with hypertension uncontrolled on monotherapy.

Methods This phase 4, open-label, multicentre study enrolled adults with hypertension uncontrolled on monotherapy. After 4-week run-in on NEB 5 mg or AML 5 mg, patients with uncontrolled BP initiated NEB/AML 5/5 mg. Those still uncontrolled after 4 weeks were up-titrated to NEB/AML 5/10 mg, while controlled patients continued NEB/AML 5/5 mg for the full 8-week period. The primary endpoint was the change from baseline in mean sitting DBP after 8 weeks of treatment. Secondary endpoints included the change from baseline in mean sitting SBP, the proportion of patients achieving guideline-recommended BP targets, and safety.

Results A total of 301 patients, mean age 52.1 (± 8.5) years, entered the run-in period; of these, 276 completed the study, with 182 achieving goal BP on NEB/AML 5/5 mg and 94 up-titrated to NEB/AML 5/10 mg. Overall, mean sitting DBP decreased by −15.2 (± 8.3) mmHg and SBP by −24.2 (± 11.8) mmHg (both $p<0.001$) over the treatment period. At study end, 63.0% of patients achieved BP <130/80 mmHg. NEB/AML dose regimens were well tolerated, and no serious treatment-emergent adverse events were reported.

Conclusion This study adds to the existing evidence supporting the efficacy and safety of the NEB/AML combination at two dose levels in managing hypertension and bringing patients at target goal.

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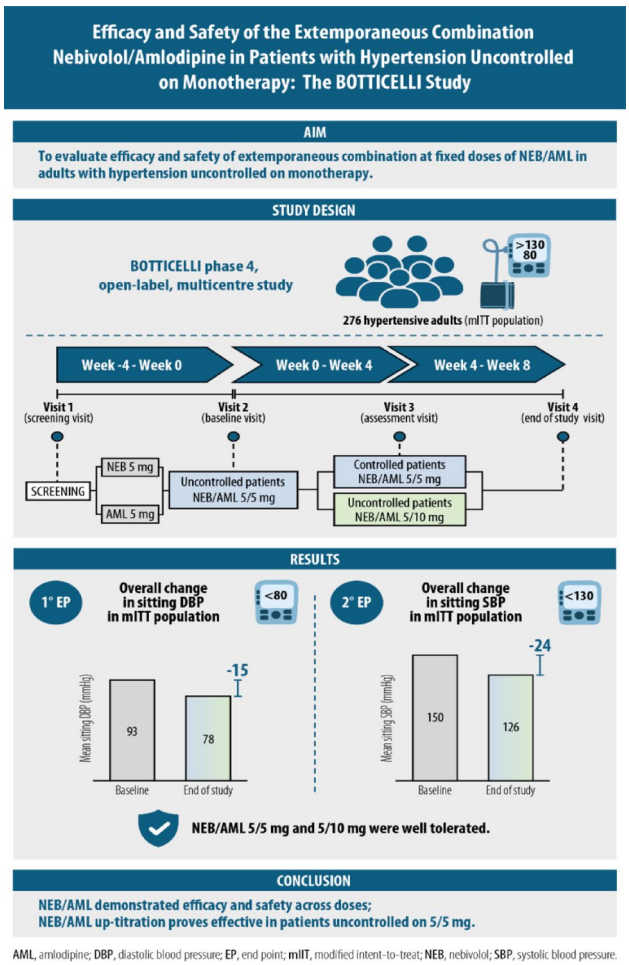
Graphical abstract



AML, amlodipine; DBP, diastolic blood pressure; EP, end point; mITT, modified intent-to-treat; NEB, nebivolol; SBP, systolic blood pressure.

Keywords Amlodipine · Antihypertensive agent combination · Blood pressure target · Extemporaneous combination · Nebivolol · Uncontrolled hypertension

1 Introduction

Hypertension is the leading cause of cardiovascular (CV) disease and one of the most preventable health conditions worldwide [1]. Over the past 20 years, its prevalence has increased markedly, affecting more than one billion adults [1]. With less than half of treated patients achieving blood pressure (BP) control, and even lower proportions when applying the current <130/80 mmHg target, BP control remains unsatisfactory [2].

Uncontrolled hypertension is associated with several adverse outcomes, including coronary heart disease, stroke, heart failure (HF), atrial fibrillation (AF), dementia, renal disease and death [3], all of which can be mitigated by effective BP-lowering treatment [3, 4]. Thus, improving hypertension control is at the core of national and global guidelines and strategies [2].

Since 2018, European guidelines have recommended monotherapy for low-risk grade 1 hypertension [3]. They also introduced a recommendation for combination therapy as the initial treatment for most hypertensive patients. These recommendations were reaffirmed in the 2023 European Society of Hypertension (ESH) guidelines [5], and again in the 2024 European Society of Cardiology (ESC) guidelines [6]. In particular, the 2023 ESH guidelines emphasised that initial combination therapy should not only target different pathophysiologic pathways, but also enable faster BP reduction, providing earlier protection for patients at high CV risk [5]. Both ESC and ESH guidelines encourage the use of single-pill combinations (SPCs) as the preferred initial strategy, particularly to support treatment adherence [5, 6]. In principle, drugs belonging to any of the five major antihypertensive classes – angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs),

beta-blockers (BBs), calcium channel blockers (CCBs) and thiazide/thiazide-like diuretics – can be combined, with the exception of the combination of ARBs and ACEIs [5]. 2023 ESH Guidelines state that BBs, either alone or in combination with other classes, may be used at initiation or at any subsequent step of treatment. ESC guidelines mentioned the importance of BBs when specific indications are present such as post myocardial infarction, tachy-arrhythmias, ischemic heart disease, HF with reduced or preserved ejection fraction and AF) [5]. Both the ESH and ESC guidelines clearly indicate that when a BB is selected, a vasodilating agent, including nebivolol (NEB), is preferred [5–7]. Thus, the combination of BBs with other first-line antihypertensive drugs such as CCBs represents a viable therapeutic option, targeting different pathophysiologic pathways and achieving additive BP-lowering effects [8–10].

Both NEB, a third-generation BB, and amlodipine (AML), a dihydropyridine CCB, are widely used antihypertensive drugs used either as monotherapies or in combination therapy in routine clinical practice [8, 11, 12]. Differently from other members of the BBs class, NEB is a highly selective β1-adrenoreceptor antagonist and is the only BB known to induce vascular nitric oxide production, thereby mediating endothelial vasodilation [13, 14]. AML is a widely used CCB that primarily acts by inhibiting extracellular calcium influx at both cardiac and vascular smooth muscle cell levels [15]. Moreover, both NEB and AML have a neutral metabolic profile and positive endothelial effects [16–18], further supporting their use in BP management, also in patients with or at risk for metabolic disorders. In the BENEFIT KOREA study, the combination of NEB with a CCB achieved the largest BP reduction among the regimens evaluated, with pronounced decreases in both SBP and DBP when NEB was added to existing CCB-based therapy [19]. Taken together, these findings suggest that this dual combination may offer meaningful advantages in patients requiring intensified BP control.

The extemporaneous combination at fixed doses of NEB and AML is commonly prescribed by European physicians for the management of hypertension, according to a retrospective analysis of seven European databases of patient medical records and prescriptions, where use of the combination ranged from 2.9% to 9.9% of all patients with a prescription of NEB or AML [20].

The BOTTICELLI study (Open-laBel, multicentre, 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; NCT05513937) was a phase 4 trial conducted to assess the efficacy and safety of the extemporaneous combination of NEB 5 mg and AML 5 mg or 10 mg in hypertensive patients uncontrolled on BB or CCB monotherapy, with the aim of strengthening the scientific rationale for the development of a NEB and AML fixed-dose combination.

2 Methods

2.1 Study Design

BOTTICELLI was a phase 4, open-label, multicentre, multinational, interventional clinical trial performed at 19 European centres in Bulgaria and Poland between June and November 2022 (ClinicalTrials.gov identifier: NCT05513937).

This study enrolled adults (aged ≥18 and <65 years) with grade 1 or 2 hypertension based on 2018 ESC/ESH guidelines [3], i.e. mean sitting systolic blood pressure (SBP) ≥140 mmHg and ≤179 mmHg and/or mean sitting diastolic blood pressure (DBP) ≥90 mmHg and ≤109 mmHg. Patients were required to receive monotherapy treatment either with BBs or CCBs for at least 4 weeks before screening, to be compliant with all study procedures and the drug regimen, and to be able to understand and provide written informed consent. Female patients were eligible to participate if not pregnant or not breastfeeding and if they refrained from donating or storing oocytes.

Exclusion criteria included serious disorders that could limit the ability to evaluate the efficacy or safety of the tested medications; secondary hypertension; and severe renal impairment defined as creatinine clearance <30 mL/min or renal transplant. Patients contraindicated according to NEB or AML summary of product characteristics were ineligible. Further exclusion criteria included patients with aortic stenosis or a history of CV conditions within the last 6 months (myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, bypass surgery, HF, hypertensive encephalopathy, valve replacement, stroke or transient ischaemic attack). Patients with diseases that, in the opinion of the investigator, prevented protocol adherence were also ineligible.

The study was performed in accordance with International Council for Harmonisation Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki, and local regulatory requirements and laws.

2.2 Procedures

The study duration was 12 weeks, including a run-in period of 4 weeks and an 8-week assessment period (Fig. 1). At screening visit (Visit 1), patients with hypertension who were on treatment with any BBs or study-allowed CCBs, including NEB 5 mg or AML 5 mg, for at least one month

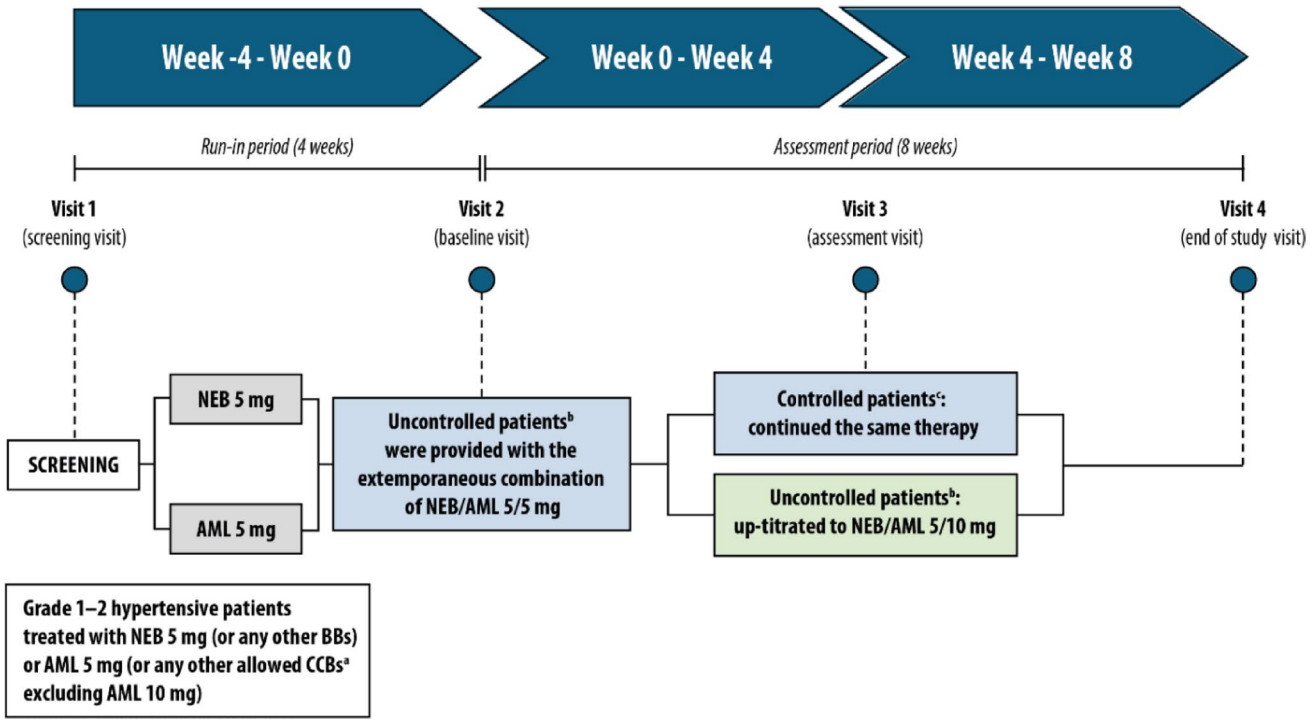


Fig. 1 Schematic representation of study design. Grade 1 to 2 hypertensive patients: Patients with SBP/DBP ranging from ≥140/90 mmHg to ≤179/109 mmHg. [a] Allowed CCBs at screening included felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine. Patients treated with AML or NEB in dosages higher than 5 mg/daily were not eligible. [b] Uncontrolled: patients with sitting SBP ≥130 and DBP ≥80 mmHg. Patients with SBP ≥80 or DBP ≥110 mmHg were withdrawn from the study at Visit 2 and Visit 3. [c] Controlled: patients with sitting SBP/DBP <130/80 mmHg. Abbreviations: AML, amlodipine; BBs, beta-blockers; CCBs, calcium channel blockers; DBP, diastolic blood pressure; NEB, nebivolol; SBP, systolic blood pressure.

prior, were screened for the study. The other CCBs allowed at screening were felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and nisoldipine.

On the same day of the screening visit, the eligible patients entered a run-in period of 4 weeks. Patients receiving NEB 5 mg or AML 5 mg continued the same therapy for 4 weeks. Otherwise, patients on any other BBs were switched to NEB 5 mg, and those on other CCBs were switched to AML 5 mg, balanced as per the study protocol.

BP was measured in both arms at Visit 1 (screening visit) to detect possible between-arm differences. The arm with the higher mean DBP was identified at screening and used in all subsequent visits for BP monitoring. BP was measured at approximately the same time of day (between 7:00 AM to 12:00 PM), on the same arm, by the same personnel and using the same calibrated automated device at each visit. BP measurements were collected according to the European Guideline on clinical investigation of medicinal products in the treatment of hypertension [21], with three BP measurements recorded. The mean of the three sitting recordings was used as the BP value for that visit.

After the 4-week run-in period of monotherapy, BP was further assessed at Visit 2 (baseline visit). Patients with uncontrolled sitting BP (≥130/80 mmHg), treatment adherence ranging from 80% to 120%, and adequate treatment tolerance, entered the assessment period and were assigned to the extemporaneous combination at fixed doses of NEB/AML 5/5 mg. Those with controlled sitting BP (<130/80 mmHg) and/or those who did not tolerate the treatment or had an adherence range below 80% or above 120% were withdrawn from the study. After the first 4 weeks of the assessment period (Visit 3), BP was further evaluated: patients with controlled BP levels (sitting SBP/DBP <130/80 mmHg) continued with the same extemporaneous combination of NEB/AML 5/5 mg, while uncontrolled patients were up-titrated to NEB/AML 5/10 mg for 4 weeks. At the end of the assessment period, after 8 weeks of treatment, outcomes were evaluated at Visit 4 (end of study). Adverse events (AEs) and serious adverse events (SAEs) were recorded at all visits.

2.3 Endpoints

The primary efficacy endpoint was the change in mean sitting DBP from Visit 2 (baseline - start of the assessment period) to Visit 4 (end of study). DBP was selected as the primary endpoint because it exhibits lower visit-to-visit variability. Secondary endpoints included changes in mean sitting SBP

over the same period, changes in mean sitting DBP and SBP from Visit 3 (after the first 4 weeks of the assessment period) to Visit 4 (end of study) in patients receiving NEB/AML 5/5 mg versus patients up-titrated to NEB/AML 5/10 mg, and the number and proportion of patients achieving BP <130/80 mmHg at Visits 2, 3 and 4. Treatment adherence was measured through treatment compliance and calculated as the percentage of actual doses taken versus the number of doses to be taken. This parameter was assessed at each visit and derived by counting the number of tablets in the returned blister. Safety and tolerability of monotherapies and combinations (NEB 5 mg + AML 5 or 10 mg) were evaluated through AEs, SAEs and any significant changes in vital signs, electrocardiograms (ECGs) and laboratory parameters.

Exploratory analyses of the following groups were conducted to assess change in mean sitting DBP and SBP across the different study visits: patients who were on NEB 5 mg and AML 5 mg at Visit 1 and continued to be on the same therapies, and those who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1. Additional subgroup analyses were conducted based on key cardiovascular risk factors [22], such as hypertension grade, diabetes and hypercholesterolaemia. Exploratory analyses also examined BP changes between Visits 2 and 3, and a post hoc analysis assessed the number and proportion of patients achieving the BP goal <140/90 mmHg between Visits 2, 3 and 4.

2.4 Statistical Analysis

The primary endpoint was assessed on the modified intent-to-treat (mITT) population and the per-protocol population (PP) using a paired t-test. The mITT population included all enrolled patients who received at least one dose of combination therapy and had both baseline and end of study assessments with primary efficacy data. The PP population included all patients from the safety population who had no major protocol deviations affecting the primary efficacy analysis and had both baseline and end of assessment period primary endpoint data. A total of 216 patients were enrolled to provide a DBP reduction of ≥4 mmHg, with 90% power at a two-tailed 5% significance level, assuming a 25% drop out rate. As this was a single-arm study, no randomisation was required.

The assumption of normality was assessed using the Shapiro-Wilk test. For non-normally distributed data, the Wilcoxon signed-rank test was applied. Repeated measures were analysed using a general linear model to assess covariate effects and interactions. Covariates included treatment, age, sex, body mass index and baseline DBP.

Other continuous secondary and exploratory endpoints were analysed across different study visits using paired or independent t-tests, as appropriate. The proportions of patients achieving the BP target at Visit 2 (start of assessment period after run-in) and Visit 4 (end of study) were assessed in both the mITT and PP populations with corresponding 95% confidence intervals (CIs) using the Clopper Pearson approach. Comparisons of paired proportions were made using the Exact McNemar test for Visit 2 versus Visit 3 (after the first 4 weeks in the assessment period) and Visits 2 and 4.

AEs were coded by using the Medical Dictionary for Regulatory Activities version 25.1. Treatment-emergent AEs (TEAEs) were presented based on the date of onset relative to the first dose of combination therapy. Safety data were summarised for the overall population and by treatment group; no formal statistical comparisons were performed for safety outcomes.

All analyses were conducted using SAS Enterprise Guide 8.2 (SAS Institute Inc., Cary, NC, USA).

2.5 Ethics

The study was conducted in accordance with the protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, EU-Directives and Regulations (applicable for the 2 countries), and national requirements of the participating countries. Approval was granted by the Republic of Bulgaria Ministry of Health Ethics Committee for Clinical Trials (20 April 2022, No. ЕКК/СТ 004) and by the Bioethics Committee at the District Medical Council of the Wielkopolska Medical Chamber in Poznań (16 March 2022, No. 92/2022), which acted as the Lead Committee for Poland, issuing a single opinion. Although local ethics committees retained the right to raise objections, no objections were raised by any local committee.

3 Results

3.1 Patients Distribution, Demographic, and Baseline Characteristics

A total of 302 patients were screened, of whom 301 entered the run-in period and received monotherapy with either NEB 5 mg (n=143) or AML 5 mg (n=158; Fig. 2). Following the run-in period, 8 patients achieved BP control in monotherapy and 14 were excluded for various reasons, while 279 patients-initiated combination therapy (Fig. 2). Of these, 276 completed the study and were therefore included in the mITT population. The PP population comprised 260 patients.

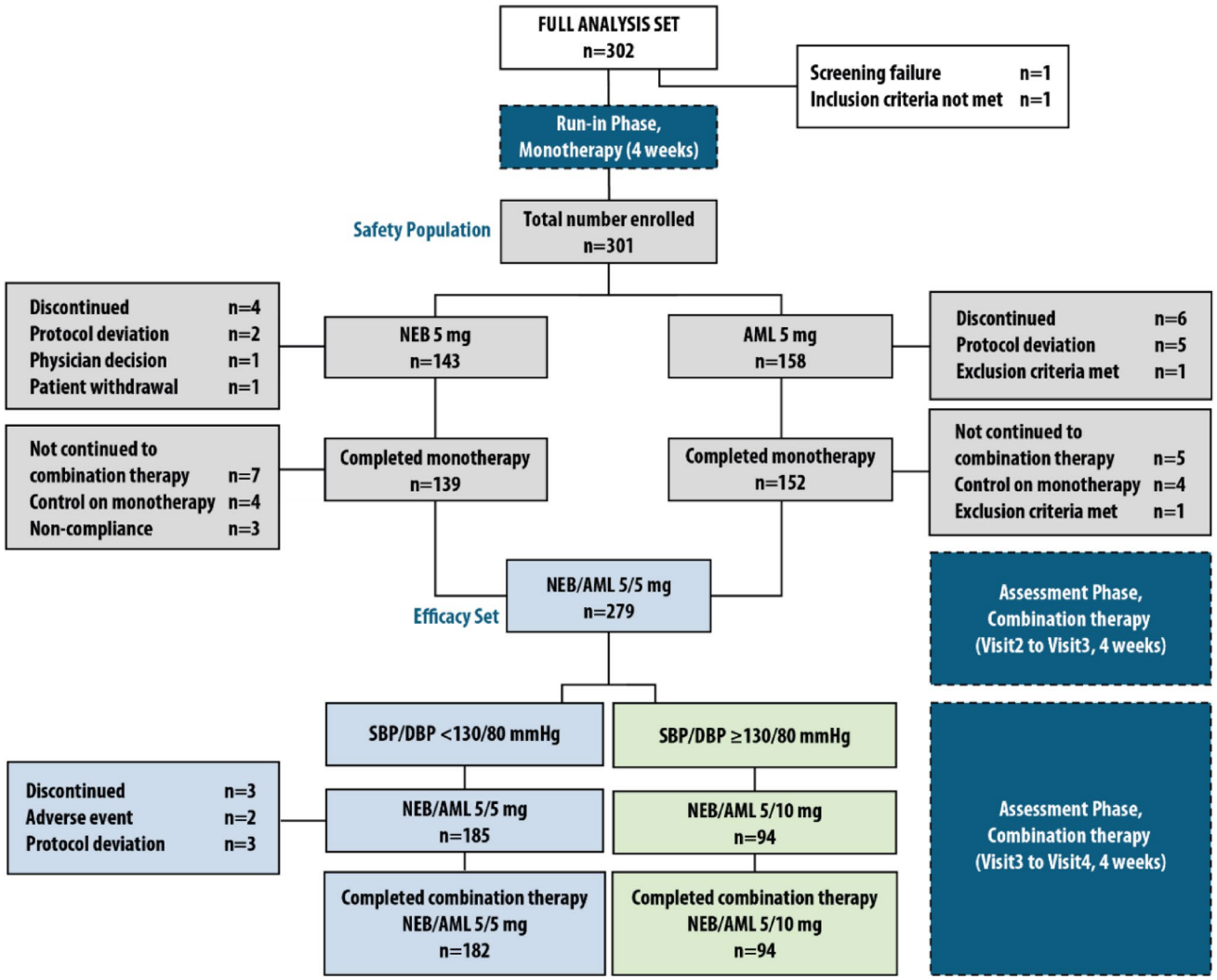


Fig. 2 Patient flowSix screened patients did not meet the inclusion/exclusion criteria. However, these patients received study treatment and were included in the enrolled population and safety analysis. Abbreviations: AML, amlodipine; DBP, diastolic blood pressure; NEB, nebivolol; SBP, systolic blood pressure.

At screening, the mean (± standard deviation [SD]) age was 52.1 (± 8.4) years and 50.8% were female (Table 1); 258 patients (85.7%) were already on either NEB 5 mg or AML 5 mg monotherapy. At screening, the mean (± SD) sitting DBP was 96.3 (± 5.0) mmHg and the mean ± SD sitting SBP was 155.1 (± 10.1) mmHg; 166 patients (55.1%) had SBP 140–159 mmHg or DBP 90–99 mmHg (grade 1 hypertension), and 134 (44.5%) had SBP 160–179 mmHg or DBP 100–109 mmHg (grade 2 hypertension). Hypercholesterolaemia was present in 32.9% of patients and type 2 diabetes was present in 10.0%.

At baseline, in patients initiating combination therapy, the mean (± SD) age was 52.2 (± 8.1) years and 51.6% were female (Table 1). The mean ± SD sitting DBP was 93.3 (± 4.35) mmHg and the mean ± SD sitting SBP was 149.7 (± 9.6) mmHg. At baseline, 148 patients (53.0%) had SBP 140–159 mmHg or DBP 90–99 mmHg (grade 1), and 131 (47.0%) had SBP 160–179 mmHg or DBP 100–109 mmHg (grade 2). In terms of metabolic comorbidities, 94 patients (33.7%) had hypercholesterolaemia and 29 (10.4%) had type 2 diabetes.

Of the 276 patients who completed the study, 182 remained on NEB/AML 5/5 mg and 94 required up-titration to NEB/AML 5/10 mg at Visit 3.

3.2 Efficacy

The primary endpoint was met, with a mean (± SD) sitting DBP reduction of −15.2 (± 8.3) mmHg from Visit 2 (baseline) to Visit 4 (end of study), which was statistically significant ($p<0.001$; Table 2) in the mITT population. The same result was confirmed in the PP population. In the mITT population, patients treated with NEB/AML 5/5 mg achieved a mean (± SD) sitting DBP of 76.4 (± 4.5) mmHg at Visit 4

Table 1 Patient demographics and characteristics in the enrolled population.

	At screening (Visit 1)			At baseline (Visit 2)		
	NEB 5 mg (n=143)	AML 5 mg (n=158)	Total (n=301)	NEB/AML 5/5 mg (n=185)	NEB/AML 5/10 mg (n=94)	Total (n=279)
Age, years, mean ± SD	51.5 ± 8.9	52.6 ± 7.8	52.1 ± 8.4	51.5 ± 8.1	53.4 ± 8.0	52.2 ± 8.1
Age group, n (%)						
<40 years	17 (11.9)	9 (5.7)	26 (8.6)	17 (9.2)	6 (6.4)	23 (8.2)
≥40 years	126 (88.1)	149 (94.3)	275 (91.4)	168 (90.8)	88 (93.6)	256 (91.8)
Sex, n (%)						
Female	80 (55.9)	73 (46.2)	153 (50.8)	99 (53.5)	45 (47.9)	144 (51.6)
Male	63 (44.1)	85 (53.8)	148 (49.2)	86 (46.5)	49 (52.1)	135 (48.4)
Hypertensive medication status at screening, n (%)						
NEB 5 mg or AML 5 mg	112 (78.3)	146 (92.4)	258 (85.7)	159 (85.9)	84 (89.4)	243 (87.1)
NEB 5 mg[a]	112 (100.0)	0	112 (43.4)	69 (43.4)	34 (40.5)	103 (42.4)
AML 5 mg[a]	0	146 (100.0)	146 (56.6)	90 (56.6)	50 (59.5)	140 (57.6)
Other BBs or CCBs	31 (21.7)	12 (7.6)	43 (14.3)	26 (14.1)	10 (10.6)	36 (12.9)
Other BBs[b]	31 (100.0)	5 (41.7)	36 (83.7)	23 (88.5)	7 (70.0)	30 (83.3)
Other CCBs[b]	0	7 (58.3)	7 (16.3)	3 (11.5)	3 (30.0)	6 (16.7)
BMI[c], kg/m^2, mean ± SD	27.6 ± 4.7	28.1 ± 4.6	27.9 ± 4.7	26.8 ± 4.0	29.9 ± 5.2	27.8 ± 4.7
Presence of type 2 diabetes at screening, n (%)						
Yes	15 (10.5)	15 (9.5)	30 (10.0)	14 (7.6)	15 (16.0)	29 (10.4)
No	128 (89.5)	143 (90.5)	271 (90.0)	171 (92.4)	79 (84.0)	250 (89.6)
Hypertension grade at screening[d], mmHg, n (%)						
140≤SBP<160 or 90≤DBP<100	80 (55.9)	86 (54.4)	166 (55.1)	105 (56.8)	43 (45.7)	148 (53.0)
160≤SBP<180 or 100≤DBP<110	62 (43.4)	72 (45.6)	134 (44.5)	80 (43.2)	51 (54.3)	131 (47.0)
Presence of hypercholesterolaemia at screening, n (%)						
Yes	46 (32.2)	53 (33.5)	99 (32.9)	54 (29.2)	40 (42.6)	94 (33.7)
No	97 (67.8)	97 (67.8)	97 (67.8)	131 (70.8)	54 (57.4)	185 (66.3)
Sitting DBP at baseline, mmHg[c], mean ± SD	96.1 ± 5.3	96.5 ± 4.7	96.3 ± 4.97	93.8 ± 3.7	92.4 ± 5.3	93.3 ± 4.4
Sitting SBP at baseline, mmHg[c], mean ± SD	154.8 ± 10.3	155.4 ± 9.9	155.1 ± 10.1	150.4 ± 9.5	148.4 ± 8.9	149.7 ± 9.4

NEB/AML 5/5 mg includes the patients receiving NEB/AML 5/5 mg at Visit 2 (start of the assessment period) and continuing the same during the study. NEB/AML 5/10 mg includes the patients up-titrated to NEB/AML 5/10 mg at Visit 3 (after the first 4 weeks of the assessment period). Note: Percentages are based on the total number of patients in the analysis population for each treatment group.

[a]Percentages are based on the total number of patients with NEB 5 mg or AML 5 mg as hypertensive medication status at Visit 1 (screening).

[b]Percentages are based on the total number of patients with other BBs or CCBs as hypertensive medication status at Visit 1 (screening).

[c]DBP, SBP, and BMI values collected at Visit 1 (screening) are considered as baseline under monotherapy. Baseline is defined as the last non-missing measurement taken the same day or prior to reference start date (including unscheduled assessments) before the first dose of study medication (combination therapy).

[d]Out of 143 patients on NEB 5 mg monotherapy, one patient had missing values for hypertension grading.

Abbreviations: AML, amlodipine; BBs, beta-blocker; BMI, body mass index; CCBs, calcium channel blockers; DBP, diastolic blood pressure; Max, maximum; Min, minimum; NEB, nebivolol; SBP, systolic blood pressure; SD, standard deviation.

(end of study), corresponding to a −17.4 (± 6.4) mmHg change from baseline (p<0.001; Table 2, Fig. 3). Sequential up-titration from NEB/AML 5/5 mg to NEB/AML 5/10 mg in the 94 patients who had not reached the BP target at Visit 3 was also effective. Patients up-titrated to NEB/AML 5/10 mg reached a mean (± SD) sitting DBP of 81.6 (± 7.5) mmHg at Visit 4 (end of study), with a −7.4 (± 9.8) mmHg reduction from baseline (p<0.001; Table 2, Fig. 3).

The secondary endpoint was also met, with a mean change in sitting SBP from Visit 2 (baseline) to Visit 4 (end of study) of −24.2 (± 11.8) mmHg in the mITT population (p<0.001; Table 2) with consistent findings in the PP population. Patients who remained on NEB/AML 5/5 mg reached a mean (± SD) sitting SBP of 123.2 (± 5.5) mmHg at Visit 4 (end of study), corresponding to a −27.2 (± 9.5) mmHg change from baseline (p<0.001; Table 2, Fig. 4). Those up-titrated to NEB/AML 5/10 mg achieved a mean (± SD) sitting SBP of 130.0 (± 10.4) mmHg, with a −18.4 (± 13.4) mmHg reduction from baseline (p<0.001; Table 2, Fig. 4).

Overall, among the 276 patients with uncontrolled BP at Visit 2 (baseline) who initiated combination therapy, 174 (63.0%; 95% CI 57.1-68.8) achieved the target SBP/DBP of <130/80 mmHg by Visit 4 (end of study). Specifically, of the 182 patients starting NEB/AML 5/5 mg at Visit 2 (baseline),

Table 2 Summary and change in mean sitting diastolic and systolic blood pressure in the modified intent-to-treat population.

	NEB/AML 5/5 mg (n=182)	NEB/AML 5/10 mg (n=94)	Total (n=276)
Sitting DBP, mmHg, mean ± SD			
Week 0 (Visit 2)	93.8 ± 3.8	92.4 ± 5.3	93.3 ± 4.4
Week 4 (Visit 3)	76.3 ± 3.3	88.2 ± 5.3	80.3 ± 7.0
Week 8 (Visit 4)	76.4 ± 4.5	81.6 ± 7.5	78.2 ± 6.3
Change from Week 0 to Week 8	–17.4 ± 6.4	–10.8 ± 9.8	–15.2 ± 8.3
p-value	<0.001	<0.001	<0.001
Sitting SBP, mmHg, mean ± SD			
Week 0 (Visit 2)	150.4 ± 9.5	148.4 ± 8.9	149.7 ± 9.3
Week 4 (Visit 3)	123.9 ± 4.9	139.6 ± 7.7	129.2 ± 9.6
Week 8 (Visit 4)	123.2 ± 5.5	130.0 ± 10.4	125.5 ± 8.2
Change from Week 0 to Week 8	–27.2 ± 9.5	–18.4 ± 13.4	–24.2 ± 11.8
p-value	<0.001	<0.001	<0.001

NEB/AML 5/5 mg includes the patients receiving NEB/AML 5/5 mg at Visit 2 (start of the assessment period) and continuing the same during the study. NEB/AML 5/10 mg includes the patients up-titrated to NEB/AML 5/10 mg at Visit 3 (after the first 4 weeks of the assessment period).

p-values calculated using paired t-test or Wilcoxon signed-rank test.

Abbreviations: AML, amlodipine; DBP, diastolic blood pressure; NEB, nebivolol; SBP, systolic blood pressure; SD, standard deviation.

144 (79.1%; 95% CI 72.5-84.8) achieved the target sitting SBP/DBP of <130/80 mmHg by Visit 4 (end of study). Among the 94 patients who were up-titrated at Visit 3 due to uncontrolled BP, 30 (31.9%; 95% CI 22.7-42.3) reached the target sitting SBP/DBP of <130/80 mmHg by Visit 4 (end of study). In both groups, the difference between the proportion of patients achieving the BP target at Visit 4 (end of study) versus the proportion of patients achieving BP target at Visit 2 (baseline) was significant (p<0.001). Other subgroup analyses based on baseline BP levels and presence or absence of diabetes and hypercholesterolaemia are reported in Table 3. The results consistently support the effectiveness of the combination therapy in achieving BP target, regardless of these baseline variables.

In a post-hoc analysis, the proportions of patients achieving a sitting SBP/DBP <140/90 mmHg increased from 82.6% (95% CI 77.7-86.6) at Visit 3 (4 weeks after initiating combination therapy) to 93.5% (95% CI 89.9-95.8) at Visit 4 (end of study) versus Visit 2 (baseline), and both differences were statistically significant (p<0.001).

Adherence to monotherapy was high, with a mean (± SD) compliance of 99.4% (± 6.5) overall; 98.9% (± 7.3) in the NEB 5 mg and 99.9% (± 5.7) in the AML 5 mg group. At Visit 3, four-weeks after initiating combination therapy, mean (± SD) adherence to combination treatment was 99.7% (± 3.1), increasing to 100.4% (± 9.2) by Visit 4 (end of study). The high adherence to mono- or combination therapy is expected, given the low-intervention nature of the study, with an 8-week follow-up and four scheduled

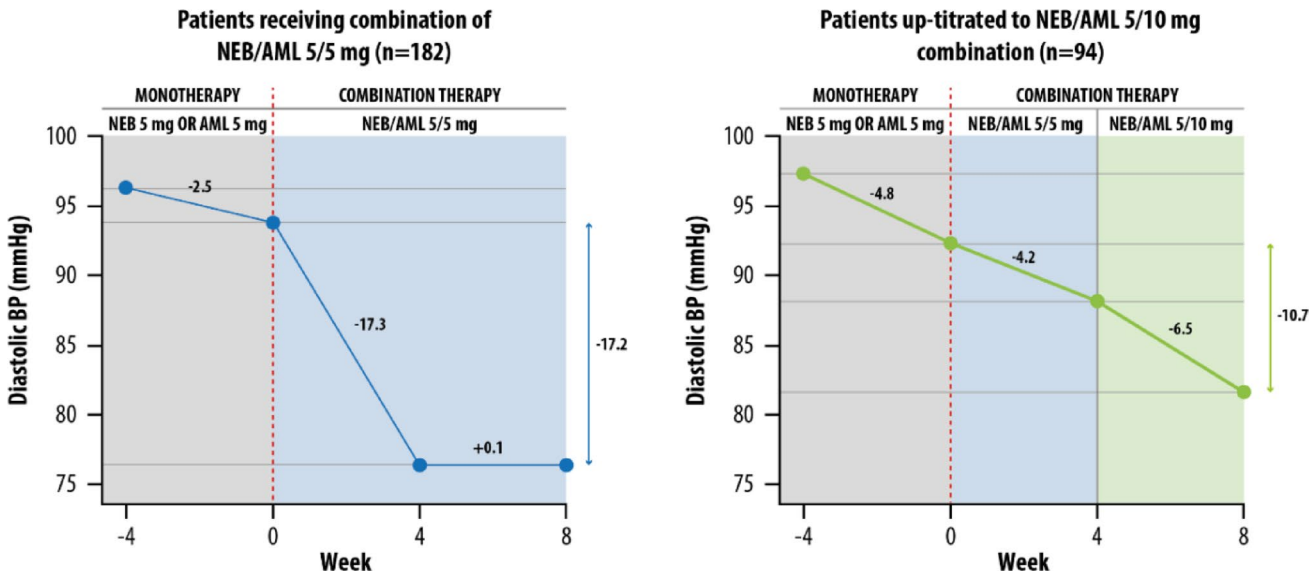


Fig. 3 Mean change in sitting diastolic blood pressure (primary endpoint) in patients (A) receiving nebivolol/amlodipine 5/5 mg (n=182) or (B) up-titrated to nebivolol/amlodipine 5/10 mg (n=94), in the modified intent-to-treat population. Treatment trajectories should not be interpreted as a direct comparison between treatment groups, as patients receiving NEB/AML 5/10 mg represent the subgroup who remained uncontrolled after the initial treatment period. BP goal considered: BP <130/80 mmHg. Abbreviations: AML, amlodipine; BP, blood pressure; NEB, nebivolol.

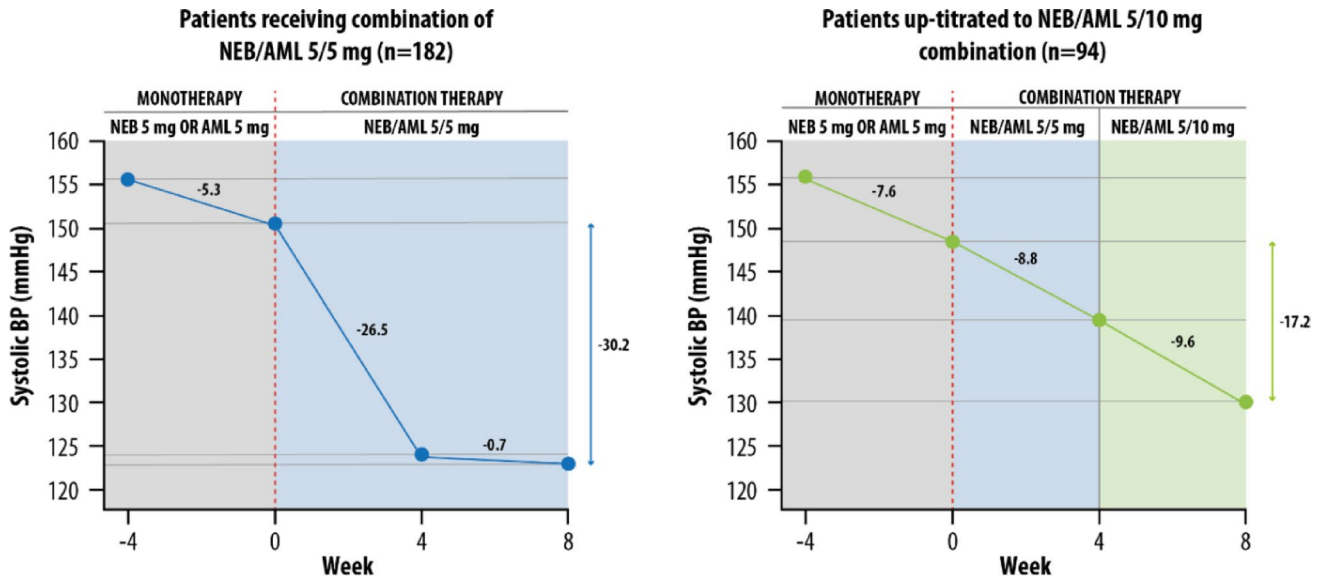


Fig. 4 Mean change in sitting systolic BP (secondary endpoint) in patients (A) receiving nebivolol/amlodipine 5/5 mg (n=182) or (B) up-titrated to nebivolol/amlodipine 5/10 mg (n=94), in the modified intent-to-treat population. Treatment trajectories should not be interpreted as a direct comparison between treatment groups, as patients receiving NEB/AML 5/10 mg represent the subgroup who remained uncontrolled after the initial treatment period. BP goal considered is BP <130/80 mmHg. Abbreviations: AML, amlodipine; BP, blood pressure; NEB, nebivolol.

Table 3 Proportion of patients achieving the blood pressure goal (<130/80 mmHg) by subgroups.

n (%)	N	Visit 3 (assessment)	Visit 4 (end of study)
BP measurement at screening			
140≤SBP<160 or 90≤DBP<100, mmHg	146	93 (63.7)	85 (58.2)
160≤SBP<180 or 100≤DBP<110, mmHg	130	79 (60.8)	89 (68.5)
Presence of diabetes			
Yes	28	13 (46.4)	17 (60.7)
No	248	159 (64.1)	157 (63.3)
Presence of hypercholesterolaemia			
Yes	93	51 (54.8)	51 (54.8)
No	183	121 (66.1)	123 (67.2)
Presence of diabetes and/or hypercholesterolaemia			
Yes	105	56 (53.3)	58 (55.2)
No	171	116 (67.8)	116 (67.8)

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

visits, in contrast with the adherence levels usually reported in real-world clinical practice.

In exploratory subgroup analyses, patients who were on NEB 5 mg or AML 5 mg at Visit 1 (screening visit) and continued on the same monotherapy until Visit 2 (baseline) showed statistically significant mean (± SD) reductions in DBP of −3.1 (± 5.0) mmHg, −16.3 (± 8.3) mmHg, and −19.0 (± 7.4) mmHg from Visit 1 to Visits 2, 3 and 4, respectively ($p<0.001$). Similarly, patients who switched to NEB 5 mg or AML 5 mg from other BBs or CCBs at Visit 1 (screening visit) had significant mean (± SD) reductions in DBP of −4.3 (± 5.8) mmHg, −16.1 (± 7.7) mmHg, and −14.9 (± 10.8) mmHg across the same timepoints ($p<0.001$ for all). SBP reductions followed similar patterns and were also statistically significant ($p<0.001$).

3.3 Safety

During the run-in period, six patients (2.0%) reported at least one TEAE: four (2.8%) in the NEB 5 mg group and two (1.3%) in the AML 5 mg group. Ten patients discontinued monotherapy treatment, of whom one reported a TEAE leading to discontinuation (hyperhidrosis). All TEAEs during the run-in period were mild (4 patients [1.3%]) or moderate (2 [0.7%]) and were evenly distributed between NEB 5 mg and AML 5 mg monotherapies. All TEAEs reported with monotherapy were classified as non-serious.

During the combination therapy period, TEAEs were reported in 35 patients (12.5%) receiving NEB/AML 5/5 mg and in nine (9.6%) receiving NEB/AML 5/10 mg, and all were classified as non-serious (Table 4). All AEs were either mild (32 patients [11.5%] in the NEB/AML 5/5 mg group and 8 [8.5%] in the NEB/AML 5/10 mg group) or moderate (3 patients [1.1%] in the NEB/AML 5/5 mg group and 1 [1.1%] in the NEB/AML 5/10 group). The most frequently

Table 4 Incidence of treatment-emergent adverse events by system organ class and preferred term in the safety population.

System Organ Class Preferred Term	NEB/AML 5/5 mg (n=279)	NEB/AML 5/10 mg (n=94)
Number of patients with at least one TEAE*	35 (12.5)	9 (9.6)
Musculoskeletal and connective tissue disorders	9 (3.2)	0
Arthralgia	6 (2.2)	0
Back pain	3 (1.1)	0
Nervous system disorders	7 (2.5)	0
Headache	7 (2.5)	0
Investigations	6 (2.2)	3 (3.2)
Hepatic enzyme increased	0	3 (3.2)
Gastrointestinal disorders	5 (1.8)	1 (1.1)
Toothache	3 (1.1)	0
Diarrhoea	<1%	1 (1.1)
Infections and infestation	4 (1.4)	1 (1.1)
Upper respiratory tract infection	<1%	1 (1.1)
Ear and labyrinth disorders	3 (1.1)	0
Vertigo	3 (1.1)	0
Metabolism and nutrition disorders	3 (1.1)	3 (3.2)
Dyslipidaemia	<1%	1 (1.1)
Hypercholesterolaemia	0	1 (1.1)
Hyperuricaemia	0	1 (1.1)
General disorders and administration site conditions	<1%	1 (1.1)
Feeling hot	<1%	1 (1.1)
Skin and subcutaneous tissue disorders	<1%	1 (1.1)
Erythema	<1%	1 (1.1)
Cardiac disorders	<1%	1 (1.1)
Tachycardia	0	1 (1.1)

*TEAEs are defined as new AEs that occur on or after the date/time of the first administration of study medication or worsen if an AE started prior to the start of first administration of study medication.

Percentages are based on the total number of patients in the analysis population for each treatment group. TEAEs with an incident <1% are not reported in the table.

Abbreviations: AE, adverse event; AML, amlodipine; NEB, nebivolol; TEAE, treatment-emergent adverse event.

reported TEAEs with NEB/AML 5/5 mg were headache (7 patients [2.5%]), arthralgia (6 patients [2.2%]), and back pain, toothache and vertigo (3 patients [1.1%] each). One patient (0.4%) in the NEB/AML 5/5 mg group experienced peripheral oedema, one had an increased heart rate and one discontinued treatment due to headache. In the NEB/AML 5/10 mg group, the most frequently reported TEAE was a mild-to-moderate increase in hepatic enzymes (3 patients [3.2%]). No bradycardia (heart rate <60 bpm), erectile dysfunction or dyspnoea were reported in either combination therapy group.

4 Discussion

The BOTTICELLI study results suggest that the extemporaneous combination at fixed doses of NEB and AML effectively reduced BP in hypertensive patients who remained uncontrolled on either BB or CCB monotherapy. After 8 weeks of treatment, both mean sitting DBP (primary endpoint) and SBP (secondary endpoint) were significantly reduced from baseline, with a large proportion of patients achieving the target BP of <130/80 mmHg. The magnitude of BP reduction seen in this study is notable, particularly considering that enrolled patients constituted a population insufficiently controlled on first-line therapy. Furthermore, in patients who did not reach the target after 4 weeks of NEB/AML 5/5 mg, up-titration to NEB/AML 5/10 mg resulted in additional BP reduction, with 31.9% achieving BP control at the end of the study. These findings suggest the efficacy of an up-titration strategy before considering the addition of a third antihypertensive agent. A likely explanation for the higher proportion of patients achieving the BP target in the NEB/AML 5/5 mg group is that patients who required up-titration to NEB/AML 5/10 mg, patients remained uncontrolled after the first 4 weeks of treatment with NEB/AML 5/5 mg, indicating that they entered up-titration with a more resistant or more severe hypertensive profile. Consequently, these patients were expected to have more difficulty achieving the BP target.

Our results build on previous evidence supporting the use of NEB/AML combination therapy in hypertension management. A study comparing NEB/AML 5/10 mg with AML 10 mg/valsartan 160 mg found NEB/AML to be superior in reducing central BP [12], which is considered a more reliable predictor of CV outcomes than peripheral pressure [23].

The BOTTICELLI study expands upon these findings by including a large population and implementing an up-titration protocol. It also supports the efficacy of increasing the AML dose within the NEB/AML combination for patients uncontrolled on the NEB/AML 5/5 mg regimen.

The combination of BBs and CCBs is a well-established strategy in hypertension management, with bisoprolol/AML being one of the most studied BB/CCB fixed-dose combinations [24, 25]. The AMCOR trial, which evaluated bisoprolol/AML 5/5 mg, reported that 62% of patients achieved a target BP <140/90 mmHg after 4 weeks [24]. In comparison, the BOTTICELLI study showed that 83.2% of patients on NEB/AML 5/5 mg achieved this same target at Visit 3 (4 weeks after initiating combination therapy), which might indirectly suggest a potential advantage, although no direct head-to-head comparison is available. NEB is highly β1-selective and has unique vasodilatory properties due to nitric oxide release, which may confer additional vascular and metabolic benefits [13]. Indeed, previous randomised

trials in patients with hypertension treated with NEB have demonstrated improvements in endothelial and sexual function, has a neutral or beneficial effect on glucose metabolism, insulin resistance and lipid profile, and no worsening of respiratory function in patients with concomitant stable, mild-to-moderate chronic obstructive pulmonary disease, suggesting a possible use for NEB-based therapy in selected populations [13, 26, 27].

The safety profile of the NEB/AML combination in this study was consistent with the safety data from NEB and AML monotherapy [8, 13]. Both NEB/AML dose regimens were well tolerated, with no serious TEAEs and no cases of bradycardia, erectile dysfunction or dyspnoea – events sometimes associated with β-blocker therapy. [28, 29]. Only one case of peripheral oedema occurred in this study. Although amlodipine is effective for BP reduction, it is well known to cause dose-dependent peripheral oedema [30]. Nebivolol's nitric oxide–mediated vasodilatory effects [13] could theoretically counteract the precapillary vasodilation induced by amlodipine, which may potentially be reducing the incidence of swelling. Further studies are needed to confirm this mechanism.

Our results support the NEB/AML combination as a viable option for patients with hypertension who remain uncontrolled on NEB or AML monotherapy, particularly those with CV or metabolic comorbidities. Given its favourable tolerability, safety and metabolic profile, NEB may be especially suitable for patients with endothelial dysfunction or metabolic risk.

This study also reinforces the importance of up-titration before introducing a third antihypertensive agent. The significant BP reductions observed with NEB/AML 5/10 mg align with the 2023 ESH guidelines [5], which recommend maximising the dose of two-drug combinations before initiating triple therapy. A stepwise dose increase may enhance BP control without increasing pill burden, thus supporting long-term adherence. Real-world data also show that extemporaneous NEB/AML is used across Europe, but adherence to the two-pill regimen remains suboptimal, reinforcing the potential value of a single-pill combination to simplify therapy and improve persistence [20].

The main limitation of this study is the lack of a control arm and randomisation. All eligible patients were ultimately switched to combination therapy, preventing direct comparison with alternative treatment strategies or with continued monotherapy. The study also assessed only surrogate blood pressure endpoints, and a restricted follow-up window was assessed as long-term BP control, and CV outcomes could not be further evaluated.

However, the structured run-in period ensured that only patients truly uncontrolled on NEB or AML monotherapy were included in the assessment, strengthening the internal validity of the observed BP reductions. Further validation in larger, prospective, multicentre cohorts is warranted, and future studies employing randomised, controlled designs with longer follow-up and extended endpoints will be important to expand these findings and clarify the mechanisms underlying the observed effects.

Overall, the BOTTICELLI study provides compelling support for the use of a single pill combination with NEB/AML, in line with current ESH and ESC recommendations promoting simplified pill strategies to improve long-term adherence in hypertension management [5, 6].

5 Conclusion

The combination of NEB and AML showed clinically significant SBP/DBP reduction, with a high proportion of patients achieving the guidelines' recommended target BP of <130/80 mmHg after 8 weeks of treatment with NEB/AML. The combination was well tolerated in patients uncontrolled on BB or CCB monotherapy. Up-titration to NEB/AML 5/10 mg provided further BP reduction and control, supporting a stepwise management approach prior to the addition of a third agent. These findings reinforce the efficacy and safety of NEB/AML combination therapy, highlight its role in optimising BP management strategies, and supports the future development of a fixed-dose combination of NEB and AML to reduce pill burden, in line with the 2023 ESH and 2024 ESC hypertension guidelines.

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Author Contributions MV, GD, SB, SM, PF, LM helped design the study. MV, RD, PVDB, GM participated in the interpretation of the data. GR participated in the analysis and interpretation of the data. All authors contributed to the writing and development of the drafts.

The manuscript was critically reviewed, revised, and approved by all authors.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest MV has received honoraria for speakers' bureau or Advisory Boards from Astra Zeneca, Diasorin, GSK, Menarini Int, Neopharmed, Novartis, Pfizer, Polpharma, Sanofi, Sequirus, Servier. GD has received honoraria for speaking activities and advisory board participation from Menarini and Servier. RD has received honoraria and travel funding from Menarini. PVDB has received compensation for consultancy, advisory board, and speaker activities with Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Lilly, Menarini, Novartis, Novo Nordisk, and Sanofi, performed on behalf of ULB–HUB Erasme Hospital (Brussels). GR declares to be a consultant for Menarini. GM, in the past 24 months, has received compensations as speaker/chairman/consultant from: Berlin Chemie, IPCA Laboratories, Medtronic Inc USA, Menarini Int, Merck Healthcare KGaA, Omnicuris, Recordati, Sanofi, Servier, Sun Laboratories. SB, SM, PF, LM declare to be employees of Menarini Group.

Ethical approval The study was conducted in accordance with the protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, EU-Directives and Regulations (applicable for the 2 countries), and national requirements of the participating countries. Approval was granted by the Republic of Bulgaria Ministry of Health Ethics Committee for Clinical Trials (20 April 2022, No. ЕКК*И*/СТ 004) and by the Bioethics Committee at the District Medical Council of the Wielkopolska Medical Chamber in Poznań (16 March 2022, No. 92/2022), which acted as the Lead Committee for Poland, issuing a single opinion. Although local ethics committees retained the right to raise objections, no objections were raised by any local committee.

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