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Efficacy and Safety of a Novel Low-Dose Triple Single-Pill Combination Compared With Placebo for Initial Treatment of Hypertension

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ABSTRACT

BACKGROUND Single-pill combinations of 3 or more low-dose blood pressure (BP)–lowering drugs hold promise for initial or early treatment of hypertension.

OBJECTIVES The authors conducted a placebo-controlled trial of a new single-pill combination containing low doses of telmisartan, amlodipine, and indapamide in 2 dose options to assess efficacy and safety.

METHODS This international, randomized, double-blind, placebo-controlled, parallel-group trial enrolled adults with hypertension receiving 0 to 1 BP-lowering drugs. After a 2-week placebo run-in during which any BP-lowering medication was stopped, participants were eligible if home systolic BP (SBP) was 130 to 154 mm Hg. Participants were randomized in a 2:2:1 ratio to GMRx2 $^1/_4$ dose (telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg), GMRx2 $^1/_2$ dose (telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg), or placebo. The primary efficacy outcome was difference in change in home SBP from randomization to week 4, and primary safety outcome was treatment discontinuation due to an adverse event.

RESULTS From June 14, 2021 to October 18, 2023, a total of 295 participants (mean age: 51 years; 56% female) were randomized and 96% completed the trial. Baseline mean home BP was 139/86 mm Hg and clinic BP was 138/86 mm Hg after placebo run-in. The placebo-corrected least square mean differences in home SBP at Week 4 were −7.3 mm Hg (95% CI: −4.5 to −10.2) for GMRx2 $^1/_4$ dose and −8.2 mm Hg (95% CI: −5.2 to −11.3) for GMRx2 $^1/_2$ dose; reductions for clinic BP were 8.0/4.0 and 9.5/4.9 mm Hg. At Week 4, clinic BP control (<140/90 mm Hg) was 37%, 65%, and 70% for placebo, GMRx2 $^1/_4$ dose, and GMRx2 $^1/_2$ dose, respectively (both doses $P < 0.001$ vs placebo). Placebo, GMRx2-triple $^1/_4$, and GMRx2 $^1/_2$ treatment discontinuation due to an adverse event occurred in 1 (1.6%), 0, and 6 (5.1%), respectively; out of normal range serum sodium or potassium was observed in 4 (6.3%), 12 (10.6%), and 12 (10.1%), respectively, but no participant had a serum sodium <130/>150 mmol/L or potassium <3.0/>6.0 mmol/L. Serious adverse events were reported by 2 participants in the placebo and GMRx2 $^1/_2$ groups and none in the GMRx2 $^1/_4$ group.

CONCLUSIONS In a population with mild-to-moderate BP elevation, both dose versions of the novel low-dose triple single-pill combination showed good tolerability and clinically relevant BP reductions compared with placebo. (Efficacy and Safety of GRMx2 Compared to Placebo for the Treatment of Hypertension: NCT04518306)
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ABBREVIATIONS AND ACRONYMS

AE = adverse events

AESI = adverse event of special interest

BP = blood pressure

CV = cardiovascular

DBP = diastolic blood pressure

GMR = telmisartan/amlodipine/indapamide combination

SAE = serious adverse event

SBP = systolic blood pressure

Hypertension treatment guidelines have historically recommended initial treatment with a single blood pressure (BP)-lowering agent. However, current guidelines generally recommend starting with dual combinations for many or most adults with hypertension and lower BP targets to significantly reduce the risk of cardiovascular (CV) events.[1,2] Recent evidence has emerged indicating that low-dose combinations with 3 or more BP-lowering agents are a potentially useful initial or early treatment strategy.[3] For example, 2 trials have shown such a strategy quickly achieves 80% BP control and is more effective than usual care.[4,5]

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Low-dose combination treatment with multiple drug classes may achieve greater BP control without increasing adverse effects for several reasons.[6] First, much of the BP-lowering efficacy of any monotherapy is achieved at low doses and efficacy dose-response curves are typically shallow above one-quarter of the standard dose.[6,7] Second, at low doses there are few or no adverse effects, but for many classes, adverse effects increase steeply and steadily as the dose increases.[6,7] Third, the incidence of idiosyncratic reactions (such as anaphylaxis) to BP-lowering drugs is so low that the risks for a patient simultaneously taking 3 drugs is acceptably low.[6] Finally, there is additivity of effects across drug classes that target different pathophysiological pathways.[6-8] Therefore, use of 3 antihypertensives at low doses in a single-pill combination could potentially be an effective and tolerable treatment option for the initial or early treatment of hypertension.

There is broad consensus that evaluation for novel hypertension treatments should include comparison with placebo[9] to assess the full effects for both efficacy and tolerability. Without placebo, it is impossible to differentiate true treatment effect regression to the mean,[10] which is inevitable but variable in size. Assessing the size of BP reduction is important also because this determines most or all clinical benefits.[11-13] Placebo control is also critical to assess what proportion of adverse events (AEs) may be due to treatment. Past trials also had numerous shortcomings, such as few comparisons of different dose options and use of "research-only" formulations that could not be used in clinical practice. We therefore conducted a placebo-controlled trial of 2 new low-dose single-pill combinations containing telmisartan, amlodipine, and indapamide (GMRx2).[14]

METHODS

STUDY DESIGN. This was an international, randomized, double-blind, placebo-controlled, parallel-group trial. This trial was designed to investigate the efficacy and safety of GMRx2 at 2 dose levels compared with placebo in adult participants with high BP. GMRx2 contains telmisartan (T), amlodipine (A), and indapamide (I), with GMRx2 $^{1}/_{4}$ dose containing T 10/A 1.25/I 0.625 mg and the GMRx2 $^{1}/_{2}$ dose containing T 20/A 2.5/I 1.25 mg. During a 2 week run-in period, all participants were allocated placebo and any existing monotherapy was stopped. This run-in was single blind, except in the United Kingdom, where the local regulator required specification that this phase was placebo for all participants. Eligible participants were randomized in a 2:2:1 ratio to 4 weeks of double-blind treatment with GMRx2 $^{1}/_{4}$, GMRx2 $^{1}/_{2}$, or placebo. The study received ethics approval at all participating centers.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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PARTICIPANTS. Participants were eligible if aged ≥18 years, provided signed informed consent, and had low calculated CV risk according to local guidelines such that pharmacologic BP-lowering treatment is not mandatory (eg, pooled cohorts equation 10 years atherosclerotic CV disease risk <10% in the United States). At an initial screening visit participants had to have a likely diagnosis of hypertension, defined by home, ambulatory, and/or clinic BP during the prior 6 months, and be either untreated or receiving only monotherapy. Potentially eligible participants underwent a 2-week placebo run-in, during which any monotherapy was discontinued. Participants were eligible for randomization if their home systolic blood pressure (SBP) was 130 to 154 mm Hg at the end of the run-in; adherence to the run-in medication was 80% to 120%; run-in was tolerated; and the participant adhered to a home BP monitoring schedule. Exclusion criteria are outlined in full in the study protocol (Supplemental Appendix), but briefly included: receiving 2 or more BP-lowering drugs; and contraindication to placebo run-in or any of the trial medications. Participants were recruited at clinics or hospital-based out-patient departments or primary care centers that provided hypertension care in Australia, Nigeria, Sri Lanka, the United States, and the United Kingdom.

INTERVENTION AND CONTROL. All trial treatments were double-blinded using identical capsules. Participants were advised to take 1 trial capsule daily in the morning, at approximately the same time each day (before or after breakfast) immediately after taking their morning home BP measurements. For randomization, the random sequence was incorporated into an online electronic data capture application by the unblinded study statistician. Neither the investigators nor site staff had access to the randomization sequence. The electronic data capture application generated the randomization record with the participant identification number, date, and time. After completion of the double-blind treatment period at Week 4, participants were either switched to nontrial medication as per local guidelines/practice or enrolled in a 1-year open label extension of the GMRx2 regimen.

PROCEDURES. Starting at the beginning of the run-in period until the end of the double-blind period, participants measured BP at home, following procedures informed by the American Heart Association recommendations[15] with reference to recent trials and clinical use.[16,17] Each participant was supplied a FORA D40g BP machine (also known as Medisanté BP800 machine, Taidoc Technology Corporation), which is a validated, electronic, automatic, digital upper-arm cuff monitor. BP readings were encrypted and transferred automatically to the trial database via SIM connection. Home BP measurement schedule had the following key features: on 4 consecutive days immediately before a trial visit and once a week on other weeks; in triplicate in the morning and in the evening; and the morning measurements immediately before the next trial medication dose. BP was measured in the seated position during all scheduled trial visits using the same machine and a standard procedure.

OUTCOMES. The primary efficacy outcome was difference in change in mean home SBP from randomization to Week 4 between GMRx2 triple $^{1}/_{4}$, $^{1}/_{2}$, and placebo. At the outset of the trial the primary outcome was clinic BP, but this was switched to home BP at the beginning of the COVID-19 pandemic. Secondary efficacy outcomes were corresponding differences in change in clinic BP, home diastolic blood pressure (DBP), and the percentage of participants with BP control (clinic BP <140/90 and <130/80 mm Hg; home BP <135/85 and <130/80 mm Hg, including at trough), at Week 4. The primary safety outcome was the percentage of participants who discontinued trial medication due to an AE from randomization to Week 4. The secondary safety outcomes were: percentage with serious adverse event (SAE), symptomatic hypotension, hyponatremia/hypernatremia, hypokalaemia/hyperkalaemia, reduction in estimated glomerular filtration rate of >30%, and orthostatic hypotension or hypertension at Week 4. Other than SAEs, only data on adverse events of special interest (AESIs) were collected given the well-established safety profile of the component medicines. An AESI was defined as the following set of AEs: symptomatic hypotension; abnormal laboratory findings of sodium, potassium, uric acid, glucose, lipids, creatinine, or estimated glomerular filtration rate; headache; peripheral edema; or any other symptom or laboratory abnormality that led to permanent discontinuation of trial medication.

STATISTICAL ANALYSIS. A total of 250 participants was planned to ensure each comparison of GMRx2 vs placebo was well powered—for each comparison, a sample size of 150 participants at a ratio of 2:1 would provide >95% power to detect a difference of at least 9 mm Hg in mean home SBP, assuming a SD of 11 mm Hg. Due to a number of high recruiting centers starting at a similar time toward the end of the study, a total of 295 participants were randomized.

All tests were 2-sided with a nominal level of α set at 5%. Because the purpose of the trial is to

demonstrate effects on both designated primary efficacy endpoint comparisons simultaneously (ie, superiority was required for both GMRx2 vs placebo comparisons for the trial to be regarded as positive), there was no need for adjustment of the type I error for the primary endpoint.[18] Additionally, the secondary efficacy parameters measure different aspects of the same underlying treatment effect, that is the effect of GMRx2 compared with placebo on BP, and do not demonstrate additional new treatment effects of the drug, but rather clarified the effect already demonstrated in the primary analysis. No type I error adjustment was therefore conducted to account for multiplicity for secondary efficacy endpoint analyses.

An independent Data and Safety Monitoring Board had responsibility for safeguarding the interests of the study participants by reviewing interim safety and efficacy data. A statistical analysis plan was finalized and published before database lock (Supplemental Appendix, Statistical Analysis Plan). The estimand framework[19] was used, with a treatment policy strategy as a primary estimand, which most closely aligns to an intention to treat analysis, where all available and imputed data contribute toward the estimated treatment effects irrespective of intercurrent events. The population for the primary estimand included adults with hypertension, the variable of interest was difference between baseline and week 4 home SBP, with the primary analysis performed on the randomized set that included all participants who were randomized to treatment. Intercurrent events (that is postrandomization events that affect either the interpretation or existence of outcome data) were defined ahead of datalock in the statistical analysis plan.

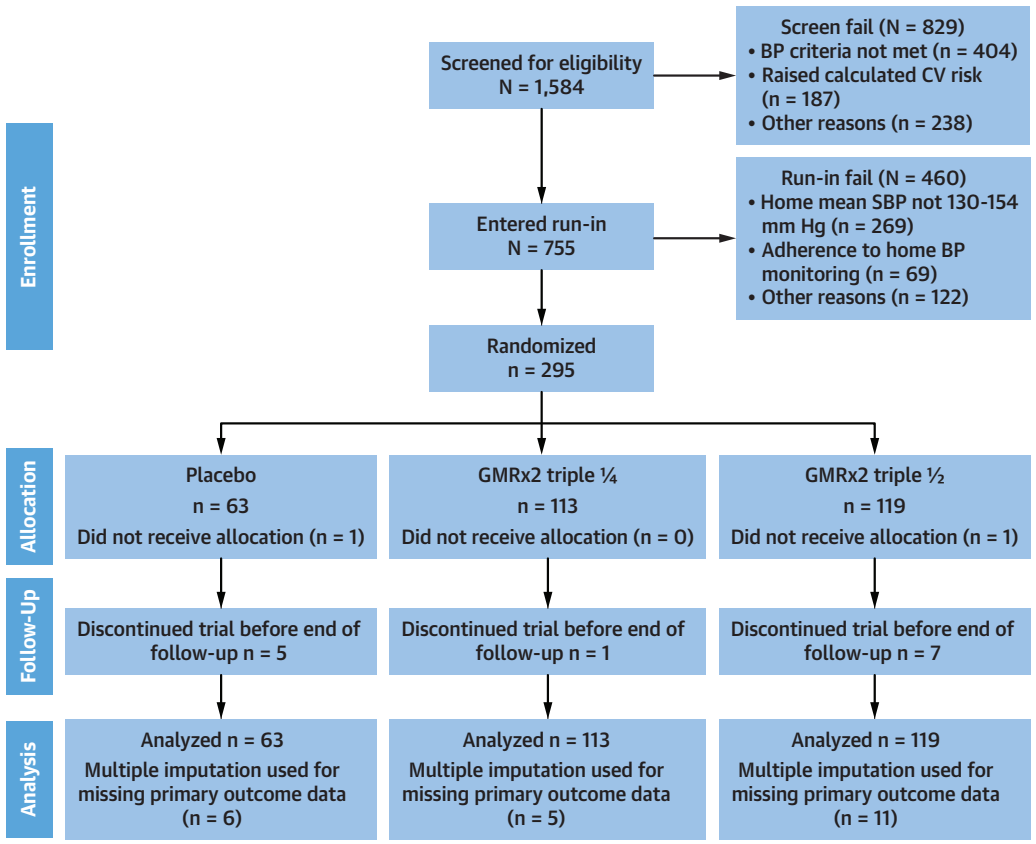
Baseline characteristics by treatment group were summarized descriptively. To calculate home BP averages, the first measurement from each of the home BP triplicates was dropped and the remaining measurements were averaged for each participant (full details available in the statistical analysis plan). The primary analysis was performed using a mixed model with repeated measures, including Week 4 measurements with baseline BP, visit, treatment group, and visit by treatment group interaction as fixed effects, accounting for correlation within participants and clustering at the site level and variance estimated using a Huber-White sandwich estimator. For participants with missing primary outcome data a Retrieved Data Multiple Imputation approach was used, with missing data imputed only from participants who were concordant with presence or absence of an intercurrent event. A total of 100 imputed datasets were used. Sensitivity analyses included: analysis adjusted for covariates; complete cases with clinic BP substitution for missing home BP values; and a per protocol analysis, excluding any participants with an intercurrent event or major protocol deviation. A supplemental 2-dimensional multiple imputation tipping point analysis was conducted to evaluate the impact of missing data under the assumption of data not missing at random.[20] This involved imputing missing Week 4 data for both the GMRx2 and placebo groups, applying a shift parameter to assess when statistical significance was lost ($P > 0.05$) for at least 1 pairwise comparison. Other continuous outcomes of difference in change in BP were analyzed as per the primary outcome. All continuous outcomes were reported along with 95% CI and the corresponding P value. The percentage of participants with BP control was summarized descriptively and analyzed using generalized estimating equations with the visit, treatment group, and visit by treatment group interaction as fixed effects and accounting for correlation within participant and clustering at the site level. Percentages by treatment groups with 95% CI were presented along with the associated estimated odds ratio or risk differences and corresponding P value. Other binary outcomes of efficacy and safety were analyzed as per the percentage of participants with BP control. Statistical analyses were conducted with SAS 9.4 and R software (SAS Institute, Inc).

RESULTS

From June 14, 2021 to October 18, 2023, 1,584 participants were screened, 755 of whom entered into the 2-week run-in period, and 295 were randomized to 1 of the 3 study treatment groups: 63 to placebo, 113 to GMRx2 triple $^1/_4$, and 119 to GMRx2 triple $^1/_2$ (**Figure 1**). The large majority of screen and run-in fails were due to not meeting BP criteria, or being at sufficiently low CV risk (**Figure 1**). The mean age of those randomized was 51 years, 56% were female, and baseline characteristics were similar in all 3 groups (**Table 1**). Home and clinic BP were 139/86 and 138/86 mm Hg, respectively, at randomization. All but 2 randomized participants commenced study treatment and 96% completed the trial. Adherence, defined as the percentage of planned randomized treatment that was taken and ascertained by pill count, was high: 99%, 98%, and 97% in the placebo, GMRx2 $^1/_4$, and GMRx2 $^1/_2$ groups, respectively.

The primary efficacy outcome, placebo-corrected least square mean difference in change in home seated SBP from randomization to Week 4 was −7.3 mm Hg (95% CI: −10.2 to −4.5 mm Hg) for

FIGURE 1 **CONSORT Patient Flow Chart**



CONSORT = Consolidated Standards of Reporting Trials.

GMRx2 triple $^1/_4$ and −8.2 mm Hg (95% CI: −11.3 to −5.2 mm Hg) for the GMRx2 triple $^1/_2$ group (both $P < 0.0001$) (**Central Illustration**). The findings were not materially altered in all sensitivity analyses, including a tipping point analysis (Supplemental Appendix). The corresponding mean difference in home seated DBP was −4.0 mm Hg (95% CI: −6.0 to −2.0 mm Hg) ($P = 0.0002$) for GMRx2 triple $^1/_4$, and −5.5 mm Hg (95% CI: −7.3 to −3.7 mm Hg) ($P < 0.0001$) for GMRx2 triple $^1/_2$ (**Table 2**). At Week 4, placebo-corrected reductions of 8.0/4.0 and 9.5/4.9 mm Hg were also observed in clinic SBP/DBP for the GMRx2 triple $^1/_4$ and GMRx2 triple $^1/_2$ groups, respectively (all $P < 0.002$) (**Central Illustration**). Most of the treatment effect was apparent within 2 weeks of randomization (**Figure 2**).

Findings for home SBP reduction were broadly consistent across predefined subgroups (Supplemental Figure 1). Although there was statistically significant heterogeneity across some subgroups for home SBP, these were not replicated for clinic SBP, for example, for treatment effects by region (Supplemental Figure 2). Compared with average home BP, similar reductions in trough home seated SBP/DBP of 6.8/3.9 and 8.7/5.4 mm Hg for GMRx2 triple $^1/_4$ and triple $^1/_2$, respectively, indicated the treatment effect was maintained to the end of the interdosing interval.

For participants in the placebo, GMRx2 triple $^1/_4$, and GMRx2 triple $^1/_2$ groups, proportions with clinic BP <140/90 mm Hg were 37%, 65% and 70%, respectively (**Central Illustration**). Absolute increases in the proportion of GMRx2-dose participants achieving BP below a certain threshold at Week 4 ranged from 17% to 36%, according to the definition of the threshold (**Table 2**). All improvements in BP control rates were statistically significant ($P < 0.01$).

TABLE 1 Baseline Characteristics of Randomized Participants

	GMRx2 $^1/_4$ (N = 113)	GMRx2 $^1/_2$ (N = 119)	Placebo (N = 63)
Age, y	50 ± 12	51 ± 10	51 ± 13
Female	68 (60)	61 (51)	36 (57)
Race			
American Indian or Alaskan Native	2 (2%)	0 (0)	1 (2)
Black or African American	18 (16)	20 (17)	11 (18)
Native Hawaiian or other Pacific Islander	1 (1%)	0 (0)	0 (0)
White	66 (58)	72 (61)	43 (68)
Asian	26 (23)	27 (23)	8 (13)
Ethnicity			
Non-Hispanic/Latino	70 (62)	76 (64)	38 (60)
Hispanic/Latino	40 (35)	42 (35)	23 (37)
Country			
Australia	15 (13)	16 (13)	11 (18)
Nigeria	2 (2)	5 (4)	3 (5)
Sri Lanka	19 (17)	18 (15)	6 (10)
United States	59 (52)	65 (55)	33 (52)
United Kingdom	18 (16)	15 (13)	10 (16)
BMI, kg/m^2	30.9 ± 6.0	30.4 ± 6.7	30.0 ± 5.7
Health conditions			
Mild congestive heart failure (NYHA functional class I or II)	1 (1)	0 (0)	0 (0)
Diabetes mellitus type 2	8 (7)	10 (8)	3 (5)
Dyslipidemia	25 (22)	33 (28)	17 (27)
Obstructive sleep apnea	5 (4)	3 (3)	3 (5)
Thyroid disease	7 (6)	7 (6)	3 (5)
Chronic obstructive pulmonary disease	0 (0)	1 (1)	0 (0)
Smoking			
Never	90 (80)	79 (66)	47 (75)
Former	15 (13)	28 (24)	12 (19)
Current	8 (7)	12 (10)	4 (6)
Alcohol consumption			
Currently drink alcohol once a week or more	38 (34)	50 (42)	25 (40)
No. of BP-lowering medications at screening			
0	69 (61)	58 (49)	30 (48)
1	44 (39)	61 (51)	33 (52)
Hypertension status			
Clinic BP ≥140/90 mm Hg at screening	66 (58)	70 (59)	37 (59)
Clinic BP ≥140/90 mm Hg at randomization	57 (50)	59 (50)	35 (56)
Clinic BP ≥130/80 mm Hg at screening	104 (92)	110 (92)	58 (92)
Home BP ≥135/85 mm Hg at randomization	92 (81)	102 (86)	45 (71)
Clinic BP at randomization			
SBP, mm Hg	137 ± 12	138 ± 11	139 ± 10
DBP, mm Hg	85 ± 9	86 ± 9	87 ± 9
Home BP at randomization			
SBP, mm Hg	138 ± 7	139 ± 6	139 ± 7
DBP, mm Hg	85 ± 7	87 ± 7	86 ± 9

Values are n (%) or mean ± SD.
BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

There was no statistically significant difference in the primary safety outcome of discontinuation of study treatment due to AE from randomization to Week 4 (Table 3). However, the numbers discontinuing due to an AE were very low in all groups: 1 (1.6%), 0, and 6 (5.1%) participants in the placebo, GMRx2 triple $^1/_4$, and GMRx2 triple $^1/_2$ groups, respectively. The risk difference for GMRx2 triple $^1/_4$ vs placebo was −1.6 (95% CI: −9.8 to 2.8) and for GMRx2 triple $^1/_2$ vs placebo was 3.5 (95% CI: −5.3 to 9.8). Only 4 SAEs were reported during the randomized phase, 1 nonfatal stroke in the GMRx2 triple $^1/_2$ group, and 3 cases of COVID-19. No deaths were reported.

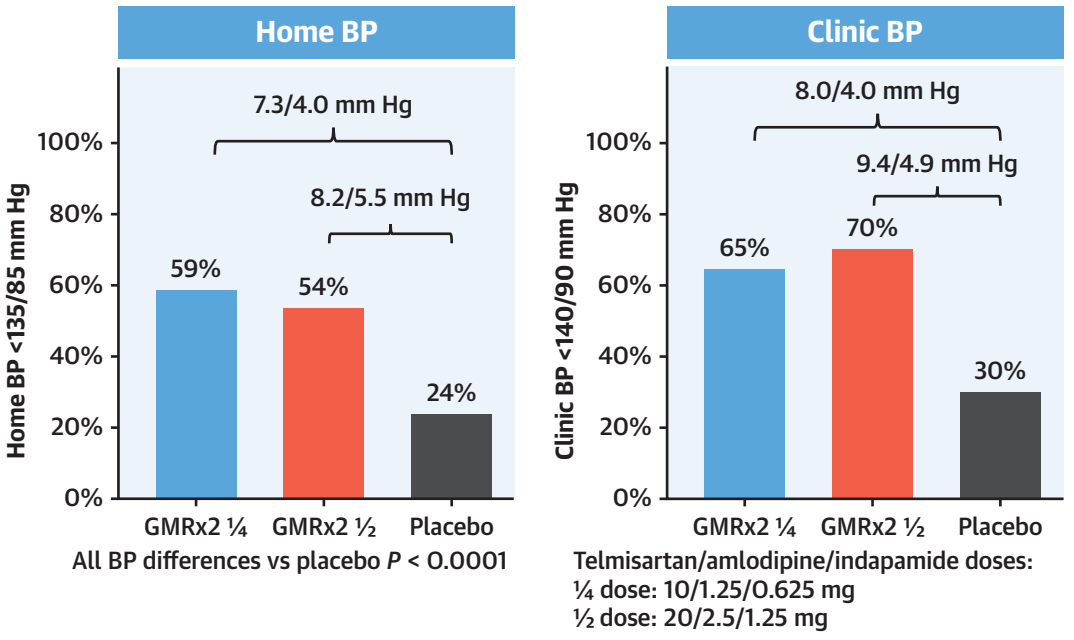
During the randomized phase the frequency of AESIs was numerically higher in the GMRx2 triple groups than in the placebo group but these differences were not statistically significant—the absolute numbers (%) were 14 (12.4%), 21 (17.8%) and 6 (9.7%) in the GMRx2 triple $^1/_4$ and GMRx2 triple $^1/_2$ dose and placebo groups, respectively (Table 3). As shown in Tables 3 and 4, higher numbers of GMRx2 participants reported symptoms of hypotension (4 [3.5%] vs 6 [5.1%] vs 0 [0%]) and electrolyte abnormalities (12 [10.6%] vs 12 [10.1%] vs 4 [6.3%]) and fewer numbers had headache (2 [1.8%] vs 2 [1.7%] vs 4 [6.5%]) for GMRx2 triple $^1/_4$, vs $^1/_2$ vs placebo, respectively, however, the differences with placebo were not statistically significant for any of them.

DISCUSSION

This is the first trial to assess the efficacy of triple $^1/_4$ dose and triple $^1/_2$ dose combination of telmisartan, amlodipine, and indapamide compared with placebo for the treatment of hypertension. The trial assessed treatment initiation at lower BP levels than previous studies and demonstrated that both dose versions significantly improved mean home and clinic BP and control rates. Tolerability was good, with no increase in treatment discontinuation due to adverse effects.

Strengths of this trial included randomization, double blinding, and a placebo control. Placebo-controlled trials are essential components in the evaluation of new treatments,[9] facilitating more reliable attribution of BP changes and AEs to the new treatment as opposed to those that would have happened anyway.[10] Given the benefits of BP lowering are most or all dependent on the amount of BP reduction,[13] it is important to assess degree of efficacy not just establish a difference from placebo. Although the sample size was not very large, the trial provided precise assessment of the efficacy of each dose option, with high-quality measures, for both home and clinic BP. In addition, this was the first international trial in the area and included a broad sample of adults with hypertension. Finally, the trial provided evidence at BP levels considerably lower than those studied in previous trials,[3] with a

CENTRAL ILLUSTRATION **Effects on Home and Clinic Blood Pressure**



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BP = blood pressure.

mean baseline clinic BP of 138/86 mm Hg, and, hence, of relevance to lower thresholds for initiating treatment.

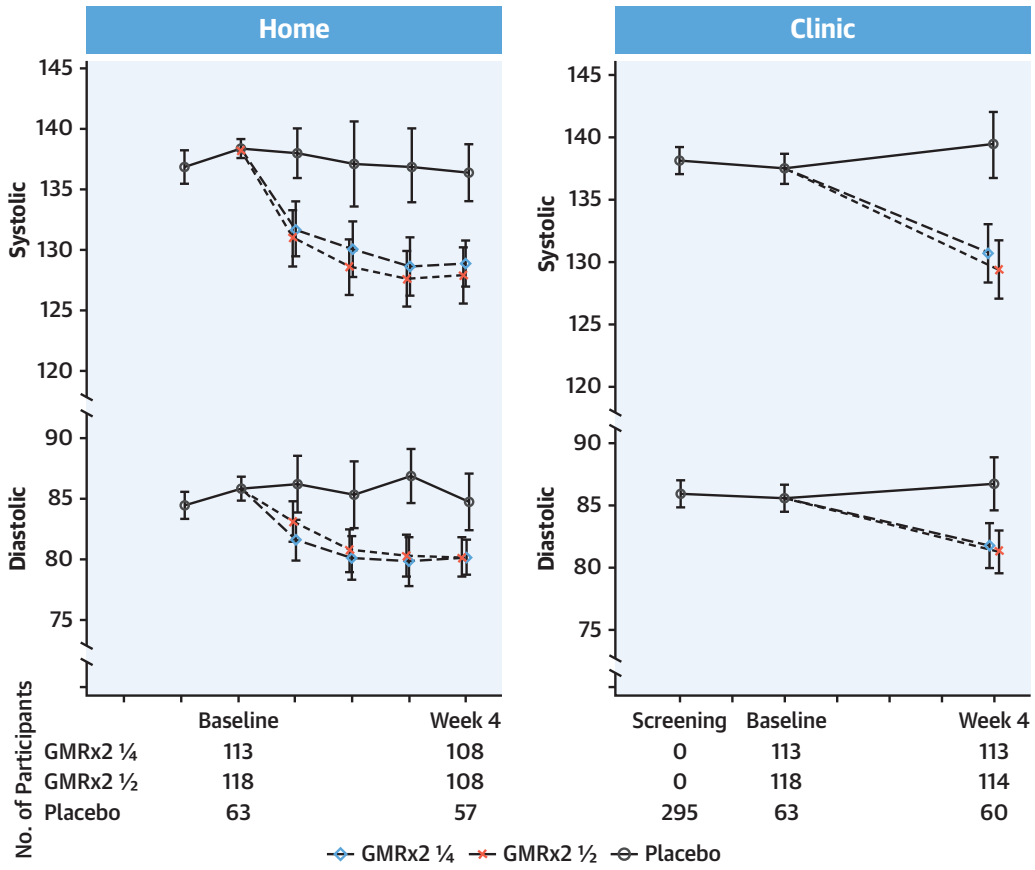
STUDY LIMITATIONS. There were limitations of the trial, mostly arising from accommodations to allow use of placebo. Follow-up was short, to minimize duration of placebo use. There were few patients with highly elevated BP, among whom single pill combination therapy may be preferentially used and for whom treatment effects are larger.[3,6] Similarly, the inability to include higher CV risk patients in a placebo-controlled trial limits applicability, although

TABLE 2 **Home and Clinic BP Levels and Differences at Week 4**

				GMRx2 ¼ vs Placebo		GMRx2 ½ vs Placebo	
	GMRx2 ¼ (n = 113)	GMRx2 ½ (n = 119)	Placebo (n = 63)	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Home BP							
SBP, mm Hg	129 ± 10	128 ± 12	136 ± 9	−7.3 (−10.2 to −4.5)	<0.0001	−8.2 (−11.3 to −5.2)	<0.0001
DBP, mm Hg	81 ± 8	80 ± 8	85 ± 9	− 4.0 (−6.0 to −2.0)	0.0002	−5.5 (−7.3 to −3.7)	<0.0001
Control <130/80 mm Hg	32 (28)	40 (34)	7 (11)	17 (4-28)	0.003	23 (9-34)	0.0001
Control <135/85 mm Hg	67 (59)	64 (54)	15 (24)	36 (20-49)	<0.0001	30 (14-43)	<0.0001
Clinic BP							
SBP, mm Hg	131 ± 13	129 ± 12	139 ± 10	−8.0 (−11.3 to −4.7)	<0.0001	−9.5 (−13.6 to −5.4)	<0.0001
DBP, mm Hg	82 ± 10	81 ± 9	87 ± 9	−4.0 (−6.4 to −1.6)	0.002	−4.9 (−7.1 to −2.6)	<0.0001
Control <130/80 mm Hg	23 (20)	36 (30)	2 (3)	17 (6-26)	<0.0001	27 (15-37)	<0.0001
Control <140/90 mm Hg	73 (65)	83 (70)	23 (36)	28 (12-42)	0.0002	33 (17-47)	<0.0001

Values are n (%) or mean ± SD, unless otherwise indicated. Absolute mean differences reported are for either mean BP values (mm Hg) or mean BP control (%).
Abbreviations are as in Table 1.

FIGURE 2 Clinic and Home Mean SBP Over Time



SBP = systolic blood pressure.

TABLE 3 Treatment Discontinuation due to AEs, ARSIs, and SAE, Baseline to Week 4

	GMRx2 ¼ (n = 113)	GMRx2 ½ (n = 119)	Placebo (n = 63)
Treatment discontinuation due to AEs	0 (0)	6 (5.1)	1 (1.6)
AESIs	14 (12.4)	21 (17.8)	6 (9.7)
Symptomatic hypotension	4 (3.5)	6 (5.1)	0 (0)
Abnormal laboratory findings[a]	9 (8.0)	12 (10.2)	2 (3.2)
Headache	2 (1.8)	2 (1.7)	4 (6.5)
Peripheral edema	1 (0.9)	0 (0)	0 (0)
At least 1 SAE	0 (0)	2 (1.7)	2 (3.2)

Values are n (%). Results are for people with one or more event type in randomized phase.
[a]Abnormalities of sodium, potassium, uric acid, glucose, lipids, creatinine, or estimated glomerular filtration rate.

AE = adverse event; AESI = adverse events of special interest; SAE = serious adverse event.

generally CV risk levels do not affect the size of BP reductions per se just the absolute benefits they confer.[12] The screen and run-in failure rates were moderately high, mainly due to challenges in finding participants in the correct BP range who were able to follow the home BP measurement protocol. An additional limitation is the absence of 24-hour BP measurements, although morning home trough BP data were available to show maintenance of effect to the end of the dosing interval and weekly data showed almost all effects were realized within 2 weeks, which is in keeping with previous findings.[21]

Comparison with the few previous trials of low-dose combinations is challenging, given the relatively low BP in this population and close dependence of degree of BP elevation with amount of BP

reduction.[6,22] Furthermore, reductions in home BP tend to be slightly smaller than those for clinic BP.[21] The extent of the BP reduction observed was somewhat lower than that predicted,[11] as was the difference between triple $^1/_4$ and triple $^1/_2$ efficacy, and whether this was due to greater attenuation of effect at lower BP levels or an additional factor is unclear. The relevance of subgroup findings is uncertain given the relatively large number of subgroup analyses conducted and the lack of consistency with the subgroup results for home and clinic BP reduction. A few excess AEs were observed, but overall, the data on tolerability was consistent with previous findings, with no statistically significant increase in AEs warranting treatment discontinuation. However, there was a likely increase in milder symptoms of hypotension and minor electrolyte abnormalities and so standard clinical and laboratory monitoring are therefore required. The trend to reduced headache is consistent with previous reviews.[23,24]

Placebo-controlled trials are necessary but not sufficient for testing new interventions; this trial is part of a program,[14] with additional trials recently completed: one assessing the contribution of each component to efficacy and safety, and another comparing this strategy to usual care in Nigeria. Other ongoing trials include a stroke prevention trial among people with a history of hemorrhagic stroke.[25] Further research is required to assess the comparative efficacy of this new treatment option compared with usual care strategies, in a range of different clinical settings and in populations at higher CV risk. Three trials have been completed with other formulations, comparing a low-dose combination of 3 or 4 drugs to usual care in those with high BP, whether untreated or on monotherapy.[4,5,26] Collectively those trials demonstrated a large benefit for low-dose combination therapy-based care, without an increase in treatment discontinuation due to adverse effects. These findings were seen despite much more frequent up-titration in usual care groups in these trials.[26-28] However, these trials were conducted with "research only" formulations not available for clinical use, while the current formulation is intended to be available on the market widely. Although 1 trial,[5] which was a key rationale for this development program, had similar components (using chlorthalidone instead of indapamide), further direct evidence with this formulation is required. These trials should ideally assess this new paradigm of care in the context of other approaches likely to improve hypertension outcomes such as team-based care[29] and evidence-based up-titration strategies, based on evidence that mean clinic SBP has to be around 125 mm Hg to achieve 80% BP control at 140/90 mm Hg.[30-32]

TABLE 4 Other Safety and Tolerability Outcomes

	GMRx2 $^1/_4$ (n = 113)	GMRx2 $^1/_2$ (n = 119)	Placebo (n = 63)
Sodium <135 mmol/L	4 (3.5)	1 (0.8)	0 (0)
Sodium >145 mmol/L	4 (3.5)	5 (4.2)	3 (4.8)
Potassium <3.5 mmol/L	4 (3.5)	6 (5.0)	1 (1.6)
Potassium >5.5 mmol/L	1 (0.9)	0 (0)	0 (0)
Sodium <135 or >145 mmol/L, and/or potassium <3.5 or >5.5 mmol/L	12 (10.6)	12 (10.1)	4 (6.3)
eGFR decrease of >30%	0 (0)	0 (0)	1 (1.6)
Orthostatic hypotension	7 (6.2)	4 (3.4)	3 (4.8)
Orthostatic hypertension	19 (16.8)	31 (26.1)	13 (20.6)

Data are n (%). eGFR decrease from baseline to Week 4, other outcomes at Week 4. No participants had sodium <130 mmol/L or > 150 mmol/L or potassium <3.0 mmol/L or > 6 mmol/L. Orthostatic hypotension and hypertension defined as decrease and increase, respectively, of ≥20/10 mm Hg from sitting to standing measure.
eGFR = estimated glomerular filtration rate.

CONCLUSIONS

The clinical and public health significance of these findings are considerable because many millions of people initiate treatment for high BP globally each year, and most do not achieve BP control.[33] This strategy could provide an effective and well-tolerated option for the initial or early management of hypertension; in this trial population, it provided 60% to 70% BP control at 140/90 mm Hg in a single step. In addition, it becomes a consideration for initial treatment of mild to moderate hypertension followed by titration using higher-dose versions as needed. To achieve long-term control rates higher than seen here further research is needed on the best strategy to intensify therapy while maintaining acceptable tolerability and ease of use. The increasing evidence of benefits for BP lowering to achieve sustained mean SBP <130 mm Hg [34,35] suggests such strategies would be needed for many individuals.

In conclusion, a novel triple single-pill combination containing telmisartan, amlodipine, and indapamide at quarter and half doses was effective in lowering BP and was well tolerated. This presents a new therapeutic option for the initial management of hypertension.

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Documentation about the analyses presented here will be made available to qualified scientific and

medical researchers, upon researcher's request, as necessary for conducting legitimate research. Patient data will be deidentified and will be shared via a secure means. Requests for data will only be reviewed after approval of the product in the United States and the European Union, and after George Medicines approval of its Data Access Request and receipt of its executed Data Sharing Agreement. A request form can be obtained by email to the corresponding author or to info@george-medicines.com.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.