CLINICAL TRIAL PROTOCOL

Trial Title	Efficacy and safety of GMRx2 (a single pill combination containing telmisartan/amlodipine/indapamide) compared to dual combinations for the treatment of hypertension: An international, multi-center, randomized, double-blind, active-controlled, parallel-group trial
Brief Title	Efficacy and safety of GMRx2 compared to dual combinations for the treatment of hypertension
Phase of Development	Phase III
Trial Drug	GMRx2: Single pill combination of telmisartan/amlodipine/indapamide Dose version 2: telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg Dose version 3: telmisartan 40 mg/amlodipine 5 mg/indapamide 2.5 mg
Trial Number	GMRx2-HTN-2020-ACT1
Indication	Hypertension
Protocol Version	Version 6.0, 10 October 2023
Trial Registration	Clinicaltrials.gov NCT04518293
Sponsor	George Medicines Pty Limited

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP), applicable ethical and regulatory requirements. The Site Investigators will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this trial will have completed ICH-GCP Training.

The protocol, participant information sheet and consent form(s) (PISCF), recruitment materials, and all participant materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the PISCF must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the PISCF will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Alterations to the trial conduct in the context of the coronavirus pandemic
In the context of the COVID-19 pandemic, alterations may be required to trial conduct during the course of the trial. These include home delivery of trial medications, conduct of virtual visits and virtual monitoring as detailed in the trial's COVID-19 Risk Management & Mitigation plan. Any such alterations should be implemented in keeping with the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on May 14, 2020 and any subsequent revisions and any relevant guidance from other regulatory bodies. Any such changes should be documented, according to the procedures in this guidance.

Contents

FIGURES

TABLES

1. CONTACT LIST

1.1. Trial Sponsor

George Medicines

[redacted]

1.2. Academic Coordinating Center

The George Institute for Global Health
Level 5, 1 King Street
Newtown, Sydney, NSW 2042, Australia

[redacted]

2. VERSION HISTORY

Protocol Version	Date	Main reasons for change
Version 1.0	12 August 2020	
Version 2.0	29 October 2020	Addition of exclusion criteria for atrial fibrillation Addition of exclusion criteria for electrolyte abnormalities Addition of standing blood pressure measurement at clinic visits Addition of outcome of any abnormality of sodium or potassium Addition of blood collection for storage and use in substudies Change of home blood pressure machine model Multiple minor clarifications
Version 3.0	9 Feb 2021	Change of home blood pressure cuff specifications in accordance with selected blood pressure machine model Addition of sub-section for early discontinuation of trial medication Addition of provision for verbal consent for fasting and blood collection prior to screening visit Several minor clarifications
Version 4.0	5 Oct 2021	Revision of trial rationale Addition of optional Open-Label extension period Revision of eligibility criteria related to use of BP lowering drugs for other indications, eGFR, and BP eligibility after run-in Clarifications related to timing of blood tests in screening phase and opportunities for re-screening Several minor clarifications
Version 5.0	14 Jan 2022	Update of Roles & Responsibilities Update of Steering Committee members Revision of BP criteria to enter active run-in Revision of criteria to define minimal acceptable adherence to BP measurement protocol during run-in Clarifications related to timing of blood tests in screening phase and opportunities for re-screening For clinic BP assessments, switch to directly entered data Addition of section on management of potential interruptions in supply of study materials to trial centers Several minor clarifications
Version 6.0	10 Oct 2023	Revision of Statistical Methods section to ensure consistency with Statistical Analysis Plan Removal of Open-Label Extension Several minor clarifications

3. ROLES & RESPONSIBILITIES

3.1. Steering Committee

An independent Steering Committee (SC) will provide scientific direction to the trial, approve the trial protocol and any amendments, monitor trial progress and plan dissemination. The SC will meet regularly to discuss the trial progress following the terms of reference in the SC charter.

3.2. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will have overall responsibility for safeguarding the interests of participants by monitoring safety and efficacy data obtained in the trial and making appropriate recommendations to the SC. The DSMB will be operational prior to enrolment of the first participant in the trial. The DSMB composition and its operation will be described in the DSMB charter. Unblinded data will be delivered to the DSMB by the statistical group at the Academic Coordinating Center (ACC).

3.3. Trial Sponsor

George Medicines (GM) is the Sponsor for the trial with ultimate responsibility for the quality and integrity of the trial according to ICH-GCP and applicable ethical and regulatory requirements. GM has the responsibility for the supply of the investigational medicinal product and trial insurance, with the remaining Sponsor responsibilities delegated to the Contract Research Organizations (CROs).

3.4. Contract Research Organizations

GM has delegated responsibility to George Clinical Pty Ltd for global study operations, including database management, study set-up and management, monitoring, safety reporting and endpoint adjudication. Country-specific responsibilities have been delegated to specific CROs according to region.

3.5. Academic Coordinating Center

The George Institute for Global Health is the ACC, which will entail support for the SC and the DSMB, and provision of statistical input into the study design, conduct and analyses.

3.6. Endpoint Adjudication Committee

An independent Endpoint Adjudication Committee (EAC) will review all reported cases of major adverse cardiac events (MACE) or deaths in a blinded fashion. The composition and operation of the EAC are described in the EAC charter.

3.7. Names, Affiliations & Roles of Protocol Contributors

Name	Affiliation	Role
[redacted]	[redacted]	Steering Committee Member, Academic Coordinating Center
		Steering Committee Member, Academic Coordinating Center
		Steering Committee Member, Academic Coordinating Center
		Steering Committee Member (Chair)
		Steering Committee Member
		Steering Committee Member
		Steering Committee Member
		Steering Committee Member
		Steering Committee Member
		Steering Committee Member
		Steering Committee Member
		Steering Committee Member

[redacted]	Steering Committee Member
	Steering Committee Member
	Steering Committee Member
	Academic Coordinating Center
	Steering Committee Member

4. PROTOCOL SYNOPSIS

NAME OF THE SPONSOR: George Medicines Pty Limited	**TRIAL DRUG:** GMRx2: Single pill combinations of telmisartan/amlodipine/indapamide Dose version 2: telmisartan 20mg/amlodipine 2.5mg/indapamide 1.25mg Dose version 3: telmisartan 40mg/amlodipine 5 mg/indapamide 2.5mg
DEVELOPMENT PHASE: III	**INDICATION:** Hypertension

TRIAL TITLE:
Efficacy and safety of GMRx2 compared to dual combinations for the treatment of hypertension.

TRIAL DESIGN:
International, multicenter, randomized, double-blind, active-controlled, parallel-group.

OBJECTIVES:
To investigate the efficacy and safety of GMRx2 compared to the three dual combinations of the component drugs for the treatment of hypertension.

PARTICIPANT ELIGIBILITY:

Key Inclusion Criteria:

At screening visit

1. Provided signed informed consent.
2. Age ≥18 years.
3. Clinic SBP:
   140-179 mmHg on 0 blood pressure (BP)-lowering drugs, or
   130-170 mmHg on 1 BP-lowering drug, or
   120-160 mmHg on 2 BP-lowering drugs, or
   110-150 mmHg on 3 BP-lowering drugs.

At randomization visit

1. Home SBP 110-154 mmHg.
2. Adherence of 80-120% to run-in medication.
3. Tolerated run-in medication.
4. Adhered to home BP monitoring schedule.

Key Exclusion Criteria:

At screening visit

1. Receiving 4 or more BP-lowering drugs.
2. Contraindication to any of the trial medications.

At randomization visit

1. Contraindication to any of the randomized medications.

TRIAL MEDICATIONS & RANDOMIZATION:

A 4-week single-blind active run-in on GMRx2-Dose2 (telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg), followed by a 12-week double-blind period with randomization to one of the following four trial medication groups:

Group	Therapy	N	Treatment
1	Triple - TAI (GMRx2)	600	GMRx2-Dose2 (telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg). At Week 6 visit, forced up-titration to GMRx2-Dose3 (telmisartan 40

			mg/amlodipine 5 mg/indapamide 2.5 mg)
2	Dual - TA	300	telmisartan 20 mg/amlodipine 2.5 mg. At Week 6 visit, forced up-titration to telmisartan 40 mg/amlodipine 5 mg
3	Dual - TI	300	telmisartan 20 mg/indapamide 1.25 mg. At Week 6 visit, forced up-titration to telmisartan 40 mg/indapamide 2.5 mg
4	Dual - AI	300	amlodipine 2.5 mg/indapamide 1.25 mg. At Week 6 visit, forced up-titration to amlodipine 5 mg/indapamide 2.5 mg

T=telmisartan, A=amlodipine, I=indapamide

TRIAL OUTCOMES:

Efficacy Outcomes

Primary

- Difference in change in home SBP from baseline to Week 12

Key secondary efficacy outcomes

- Difference in change in home and clinic BP from baseline to Weeks 6 and 12
- Percentage of participants with hypertension control with home and clinic BP at Weeks 6 and 12

Key Safety Outcomes

- Percentage of participants discontinued trial medication due to an Adverse Event (AEs) or a Serious Adverse Event (SAE) from baseline to Week 12
- Percentage of participants with any SAE from baseline to Week 12

NUMBER OF PARTICIPANTS & TRIAL POWER:

A sample size of 1500 participants (600 in the GMRx2 and 300 in each of the dual combination groups) provides 97% power to detect a minimum difference of 3 mmHg in home seated mean SBP for each of the three comparisons of GMRx2 vs dual therapy, assuming a common standard deviation of 11 mmHg within each group. The overall power for all three comparisons will therefore be over 90%. Randomizing 1500 may necessitate at least 2000 participants entering the run-in phase.

NUMBER OF COUNTRIES & TARGET NUMBERS OF SITES:

Approximately 100 sites in Australia, Czech Republic, New Zealand, Poland, Sri Lanka, South Korea, United Kingdom and the USA.

TRIAL PERIOD:

Participant recruitment period: Approximately 12 months
Active run-in treatment period: 4 weeks
Randomization treatment period: 12 weeks
Safety follow-up period: 4 weeks

5. INTRODUCTION

5.1. Burden of High Blood Pressure and Current Treatment Gaps

High blood pressure (BP) is a leading cause of preventable morbidity and mortality globally.[1] The benefits of BP lowering in reducing cardiovascular (CV) events are well established[2] and there is clear evidence that greater BP lowering confers a greater reduction in CV events.[3-5] However, globally, control of high BP is poor, with only one in three treated patients achieving traditional BP goals.[6,7] Most treated patients receive only monotherapy, despite guidelines recognizing that the large majority of patients require multiple drugs to achieve goal BP.[6] There is broad consensus among leading international authorities that key factors driving this treatment gap are under treatment of hypertension with monotherapy in most patients.[8] In the United States of America (USA), about 40% of treated patients receive monotherapy and this has not changed between 2005 and 2016.[9] Given the recommendations in recent guidelines for target BPs below 130/80 mmHg for high-risk patients, the need for effective, tolerable, and affordable therapy is even more imperative.

5.2. Potential Role of Single Pill Combinations, Including for Initial Treatment

Historically, hypertension management guidelines have recommended initiating pharmacological treatment with monotherapy, with treatment modification (dose up-titration, or adding other drugs) at multiple follow-up visits. However, in practice, most patients remain uncontrolled on monotherapy for numerous reasons, both patient- and physician-related. Lack of adherence to prescribed BP-lowering drugs is a major risk factor for poor BP control[10] and is worsened by the increased number of pills,[11] higher co-payment, adverse drug effects, and a poor patient-provider relationship.[12-14] 'Therapeutic inertia' - the reluctance of physicians to initiate or intensify or modify treatment appropriately has also been identified as an important barrier to hypertension control.[15,16]

Combination therapy has the potential to address many of the aforementioned barriers. A recent systematic review of 13 trials with 13,095 participants demonstrated initial low-dose dual combination therapy improved BP control compared to monotherapy, without an increase in adverse effects.[17] Dual combination therapy achieves about five times more BP-lowering than doubling the dose of monotherapy[18] and adding a third drug is several times more effective than increasing the dose of dual combination.[17] Two pragmatic randomized controlled trials (RCTs) have assessed strategies, rather than mandatory regimens, comparing initial dual combination therapy with monotherapy, with each showing benefits with the former. The STITCH trial compared initial therapies of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) + thiazide diuretic combination with monotherapy and showed improved BP control with combination therapy in a primary care setting.[19] The STRAtegies of Treatment in Hypertension: Evaluation (STRATHE) trial compared initial combination therapy with stepped care and up-titration and showed improved BP control without adverse effects with the initial combination therapy.[20] Furthermore, in the Prevention And Treatment of Hypertension With Algorithm-based Therapy - study 1 (PATHWAY-1) trial,[21] combination of losartan and hydrochlorothiazide (HCTZ) as initial treatment was superior to monotherapy with either drug alone, with no difference in withdrawals due to adverse events (AEs). This trial also demonstrated that the initial combination was uniformly more effective than monotherapy, whether monotherapy was personalized by prediction of each patient's best drug (e.g. using renin levels or age) or by systematic crossover between monotherapy options. Recent hypertension guidelines, including the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guideline,[22] the 2020 International Society of Hypertension Guideline[23] and the 2021 WHO Hypertension Guideline[24] recommend combination therapy as initial treatment for many or most patients and the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline,[25] recommends combination therapy as an initial treatment among patients with BP >140/90 mmHg and average BP more than 20/10 mm Hg above their BP target.

5.3. Potential Role of Triple Low-Dose Combination Therapy

Several observations suggest triple low-dose combination therapy may produce greater BP control without increasing adverse effects:

- A ¼ dose produces about 50-60% of the BP-lowering achieved by a standard dose; a ½ dose achieves 70-80% as much BP reduction as a standard dose; and the dose-response of monotherapies for BP reduction is shallow above ¼ standard dose.[26,27]
- At ¼ or ½ dose, there are little or no drug-specific adverse effects, and drug-specific adverse effects generally rise steeply and steadily as the dose increases, except for ACEIs and ARBs.[26,27]
- There is additivity of effects across drug classes.[18,26,27]
- There is clear evidence of more benefits with more BP reduction.[3,4]
- The incidence of idiosyncratic reactions to each component antihypertensive drug is so low that the risks for a patient simultaneously confronted with three agents will still be acceptably low.[27]

Large and tolerable reductions in BP have been demonstrated by four RCTs of triple or quadruple low-dose combination therapy.[28-31] The three short-term trials (4-12 weeks) are summarized in Table 1, demonstrating large BP reductions compared to placebo or standard-dose monotherapy.

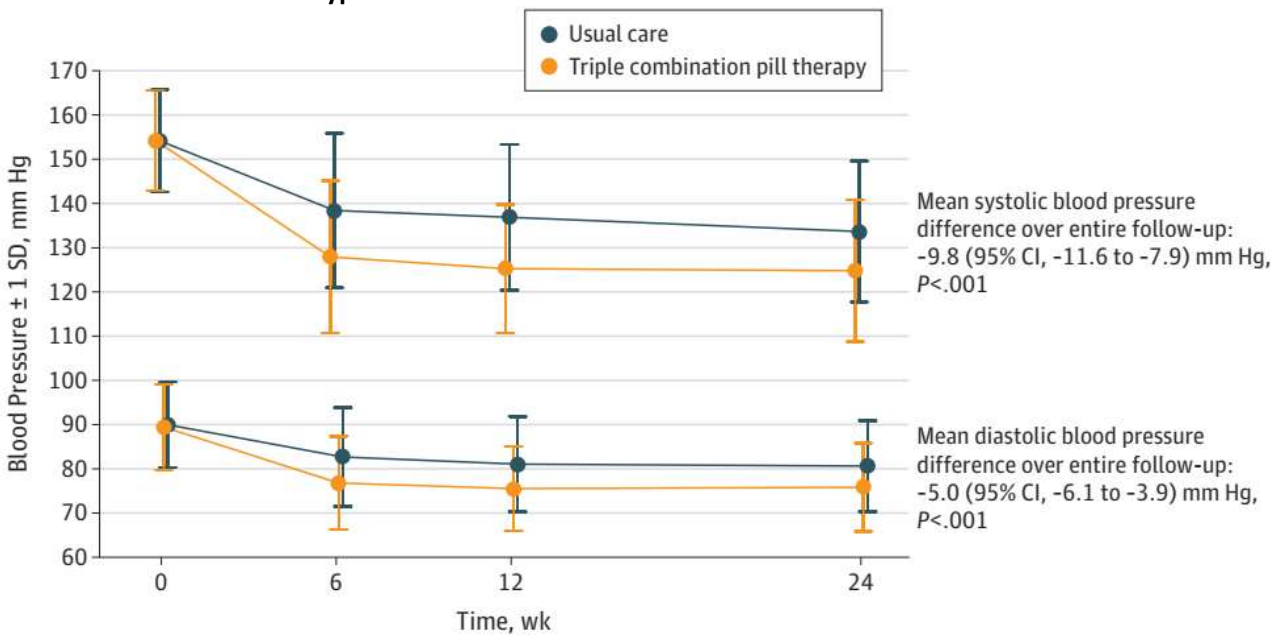
Table 1: Short-term RCTs of triple or quadruple low-dose combination therapy

Trial	Comparison	BP reduction	Tolerability
Mahmud et al 2007[28]	4 x ¼ dose (amlodipine 1.25mg, atenolol 12.5mg, bendroflumethiazide 0.625mg, captopril 25mg, n=22) vs each at standard dose (n=86)	13/8 mmHg (p<0.001)	No SAEs or treatment withdrawals
Wald et al 2012[29]	3 x ½ dose (amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg) vs placebo (n=86 crossover)	18/10 mmHg (P<0.001)	No SAEs or treatment withdrawals
Chow et al 2017[31]	4 x ¼ dose (irbesartan 37.5 mg, amlodipine 1.25 mg, HCTZ 6.25 mg and atenolol 12.5 mg) vs placebo (n=21 crossover)	22/13mmHg p<0.001	No SAEs or treatment withdrawals
Hong et al, 2020[32]	amlodipine, losartan and chlorthalidone at 3 x ½ dose, 3 x ⅓ dose and 3 x ¼ dose (n=107) vs placebo (n=36) for 8 weeks	17/9, 20/10 and 14/8 mmHg, respectively (all p<0.01)	No SAEs, 1 treatment-related withdrawal

5.4. The TRIUMPH Trial of Triple Low-Dose Combination Therapy

The foregoing evidence provided the rationale for the TRIple pill vs Usual care Management for Patients with mild-to-moderate Hypertension (TRIUMPH) RCT.[30] This open-label trial compared a triple low-dose combination (telmisartan 20 mg, amlodipine 2.5 mg, chlorthalidone 12.5 mg) with usual care among adults with blood pressure above goal (systolic BP [SBP] ≥140 mmHg and/or diastolic BP [DBP] ≥90 mmHg; or in patients with diabetes or chronic kidney disease: ≥130 mmHg and/or ≥80 mmHg).[30] Participants were either untreated or were receiving monotherapy at baseline and were enrolled from 11 urban hospital clinics in Sri Lanka. The primary outcome was the proportion of participants achieving target BP at 6 months. This trial demonstrated a large improvement in hypertension control at 6 months with low-dose triple therapy (70% vs 55%, respectively; risk difference, 12.7% [95% confidence interval [CI], 3.2% to 22.0%]; P < 0.001) (Figure 1).[30] There was no increase in withdrawals due to AEs (23/349 [6.6%) vs 24/351 [6.8%), relative risk [RR]: 0.97 [0.56 to 1.70), total AEs (AEs: 38.1% vs 34.8% or SAEs: 7.7% vs 6.0%), although there was an increase in AEs due to dizziness, presyncope, or syncope (5.2% vs 2.8%, P<0.01). For the 413 (59%) of participants who were untreated at baseline, the benefits on the primary outcome of BP control at 6 months were separately significant (BP control: 73% vs 58%, RR: 1.25 [1.08-1.44]) and there was no evidence of an increase in withdrawals due to AEs (5.7% in triple vs 7.8% in usual care group).

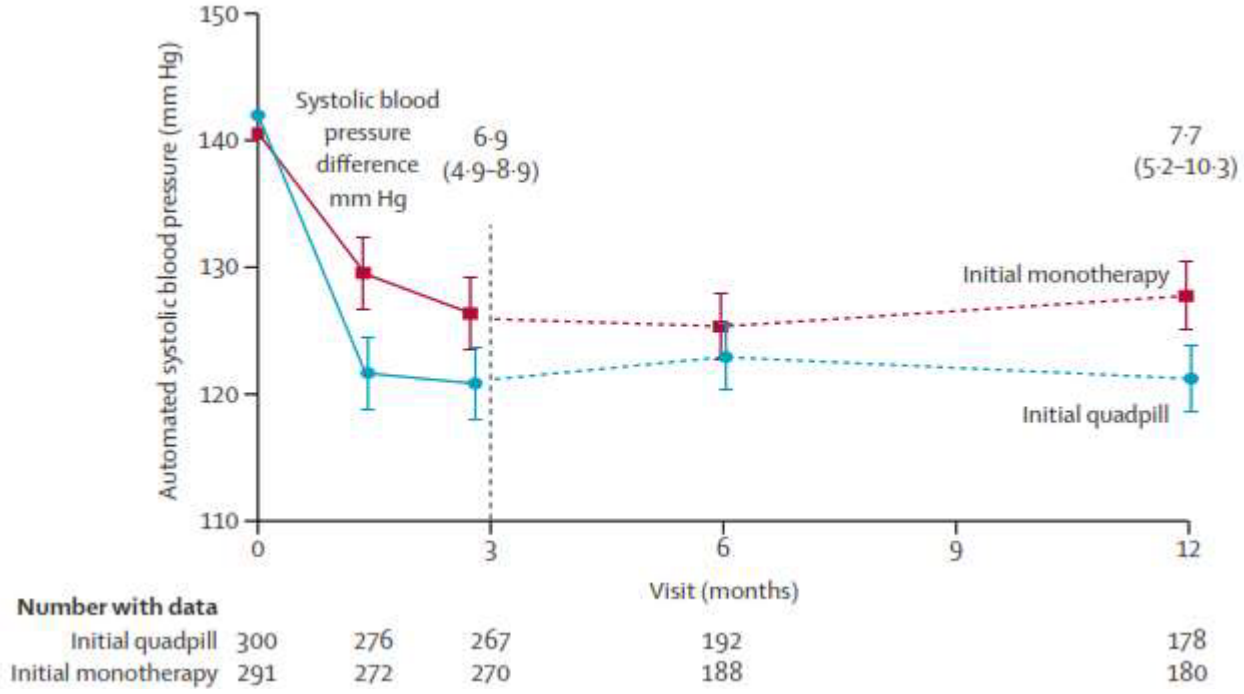
Figure 1: Blood pressure over time in the TRIUMPH trial of triple low-dose combination as initial/early treatment vs usual care for hypertension



5.5. The QUARTET trial of quadruple quarter-dose combination

QUARTET was a multicenter, double-blind, parallel-group, randomized, trial among Australian adults with hypertension, who were untreated or receiving single BP-lowering drug.[33] Participants were randomly assigned to initial quadruple quarter dose (containing irbesartan 37·5 mg, amlodipine 1·25 mg, indapamide 0·625 mg, and bisoprolol 2·5 mg) or monotherapy control (irbesartan 150 mg). Additional medications could be added in both groups among those not at control during follow-up, starting with amlodipine 5 mg. A total

Figure 2: Blood pressure over time in the QUARTET trial of quadruple quarter-dose combination as initial/early treatment vs initial monotherapy for hypertension



of 591 participants were randomized with baseline mean unattended office BP 141/85 mmHg (standard office 153/89 mmHg). By 12 weeks, 44 (15%) of 300 participants had additional BP medications in the intervention group compared with 115 (40%) of 291 participants in the control group. As seen in Figure , SBP was lower by 6·9 mm Hg (95% CI 4·9–8·9; p<0·0001) and BP control was higher in the intervention group compared with control group (76% vs 58%; relative risk [RR] 1·30, 95% CI 1·15–1·47; p<0·0001). There was no difference in adverse event related treatment withdrawals at 12 weeks (intervention 4·0% vs control 2·4%; p=0·27). Among the 417 patients who continued in the randomized groups to 12 months, up-titration occurred more frequently among control participants than intervention participants (p<0·0001). However, at 12 months mean unattended SBP remained lower by 7·7 mm Hg (95% CI 5·2–10·3) and BP control was higher in the intervention group compared with control group (81% vs 62%; RR 1·32, 95% CI 1·16–1·50).

5.6. Need for a New Triple Low-Dose Combination

Currently available triple single pill combinations (SPCs) of BP-lowering drugs are only indicated for substitution among patients already taking all the three-component drugs or as an add-on/switch therapy among patients not adequately controlled on two of the component drugs. [34-36] None of the available triple SPCs are indicated for initial treatment. Furthermore, there are no existing SPC products with low-doses of an ARB, calcium channel blocker (CCB) and a thiazide-like diuretic. To address this unmet need, GM developed a new SPC containing telmisartan, amlodipine and indapamide (GMRx2) in three strengths (10/1.25/0.625 mg, 20/2.5/1.25 mg, and 40/5/2.5 mg, dose versions 1, 2 and 3 respectively).

Hypertension guidelines recommend ACEI, ARB, CCB, and thiazide-like diuretics as first-line therapies for the treatment of hypertension, with some also recommending HCTZ. ARBs are more tolerable than ACEIs given that they do not cause cough and are also about three-times less likely to cause angioedema than ACEIs among black patients.[37] The most reliable comparisons of ARBs with ACEIs are direct randomized comparisons, and these do not show a difference in efficacy in reducing CV events between the two classes but demonstrate reduced AEs with ARBs.[38-40] Telmisartan has the longest half-life (~24 hours) of the ARBs [41] and provides superior or similar BP reduction compared to the commonly used ACEIs.[42] Among CCBs, amlodipine has been used most commonly in CV outcome trials, has fewest interactions with other products (compared, for example, to diltiazem) and has a long half-life (30–50 hours). Thiazide-like diuretics such as indapamide and chlorthalidone are superior to thiazide diuretics in reducing BP without increasing metabolic AEs.[27,43,44] The most consistent and robust evidence of CV events reduction comes from trials involving indapamide or chlorthalidone.[45,46] Compared to HCTZ, indirect comparisons of the results from RCTs indicate a modest additional reduction in CV events and heart failure with thiazide-like diuretics (indapamide and chlorthalidone) compared to thiazide diuretics, after correcting for differences in clinic BP reductions.[47,48] Indapamide has a half-life of 16 to 18 hours,[49] and is widely available internationally.

5.7. Expected Effects of GMRx2

The placebo-corrected systolic BP (SBP)-lowering efficacy of GMRx2 dose versions 1, 2 and 3 from a baseline SBP of 150 mmHg are estimated to be approximately 13 mmHg, 18 mmHg and 25 mmHg, respectively.[4] This would represent a clinically important BP reduction in comparison to standard-dose monotherapy which reduces SBP by 8-9 mmHg, with each doubling of dose conferring only a 1-2 mmHg incremental SBP reduction.[18,27] Dual combinations typically also have a difference of only 1-2 mmHg between neighboring dose versions and a maximum SBP reduction of around 20 mmHg with maximal dose of both drugs.[4,18,27] The reasoning in developing GMRx2 is, therefore, in line with USA Food & Drug Administration (FDA) observations which have stated: “Over the last decade, the Agency has actively discouraged antihypertensive monotherapy and combination doses with effects that were very close together, considering them a nuisance to physicians seeking to get patients to goal.” [50]

RCTs of the lowest-approved dose of monotherapy telmisartan 20 mg, amlodipine 2.5 mg and indapamide 1.25 mg have demonstrated no statistically significant increase in adverse effects compared to placebo (Table

2, below). Telmisartan has no significant differences in tolerability compared to placebo across the dose range.[51-53] Amlodipine 2.5 mg similarly is not expected to cause drug-specific adverse effects, particularly peripheral edema, at such a low dose and particularly when administered with an ARB and a thiazide-like diuretic.[51,54,55] Indapamide 1.25 mg has little or no significant AEs.[56,57] RCTs also demonstrate that telmisartan and indapamide will reduce the most common adverse effects of amlodipine (peripheral edema), and telmisartan will also reduce rates of hypokalemia and dysglycemia associated with diuretic use.[58,59] Hence while adverse effects associated with BP lowering (e.g. dizziness, hypotension) per se may be increased with GMRx2 if it reduces BP significantly, it is expected that there will be fewer drug-specific adverse effects. Overall, therefore, there may not be an increase in drug-specific adverse effects compared to many monotherapy regimens.

Table 2: Adverse events with the lowest approved dose of GMRx2 components vs placebo in previous randomized trials

				Event rate (%)		
Drug dose mg	**RCTs**	**Participants**	**Events**	**Active**	**Placebo**	**RR (95% CI)**
Adverse events						
Amlodipine 2.5	3	784	175	21.9	22.8	0.97 (0.76-1.24)
Telmisartan 20	3	805	163	21.6	19.2	1.16 (0.88-1.52)
Indapamide 1.25	2	426	160	36.2	39.0	0.95 (0.74-1.21)
Withdrawals due to adverse events						
Amlodipine 2.5	4*	890	25	3.9	1.6	2.16 (0.84-5.59)
Telmisartan 20	1	88	2	0.0	4.3	0.22 (0.01-4.43)
Indapamide 1.25	2	426	23	5.6	5.2	1.08 (0.49-2.39)
Treatment-related adverse events						
Amlodipine 2.5	1	524	31	7.7	4.0	1.92 (0.92-3.99)
Telmisartan 20	0					
Indapamide 1.25	2	426	52	12.3	12.3	1.00 (0.60-1.67)

* one study used amlodipine 1.25 to 2.5

More broadly, a systematic review of the AEs showed no significant difference in symptoms between drug classes of the components of GMRx2 and placebo (Table 3).[27]

Table 3: Percentage with symptoms attributable to treatment (treated minus placebo) in previous randomized trials of lowest-dose monotherapy of GMRx2 component drug classes

Drug class	RCTs	Difference between treated and placebo rates (%)	95% CI
Calcium channel blockers	96	1.6%	-3.5 to 6.7%
Angiotensin receptor blockers	44	-1.8%	-10.2 to 6.5%
Thiazides	59	2.0%	-2.2 to 6.3%

6. OBJECTIVES

6.1. Primary Objective

To assess the efficacy of GMRx2 compared to each of the three dual combinations of component drugs of GMRx2 at equivalent doses for lowering BP.

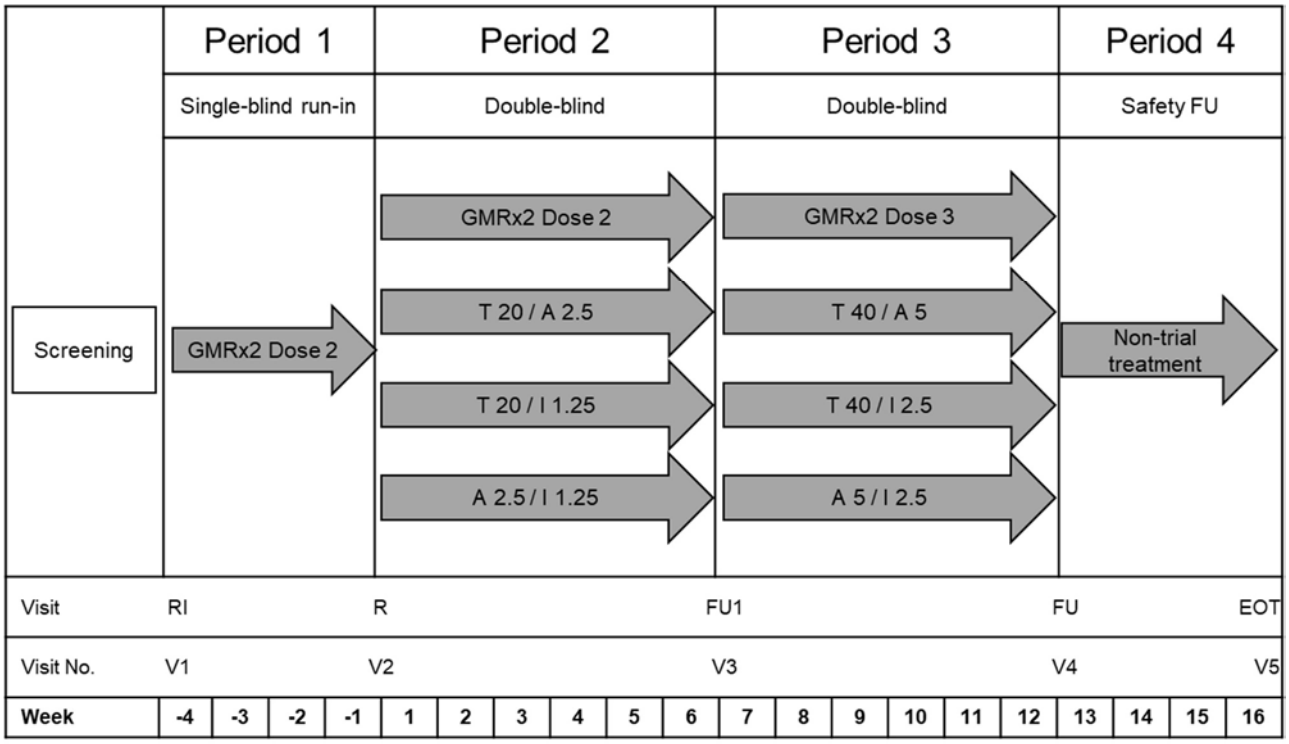
6.2. Secondary Objectives

To assess the safety of GMRx2 compared to each of the three dual combinations of component drugs of GMRx2 at equivalent doses.

7. TRIAL DESIGN

An international randomized, double-blind, active-controlled, parallel-group trial with a 4-week pre-randomization single-blind, active run-in, a 12-week randomized treatment period and a 4-week safety follow-up period. The overall trial design is shown in Figure 2.

Figure 2: Trial design summary



GMRx2 Dose2 = T 20 / A 2.5 / I 1.25; GMRx2 Dose3 = T 40 / A 5 / I 2.5; T = telmisartan; A = amlodipine; I = indapamide; RI = run-in; R=randomization; FU = follow-up; EOT = end of trial; V = visit; Forced up-titration at FU1; EOT will be telephonic. For participants entering the optional Open-Label Extension Period, this will begin after Week 12 and will replace Period 4

7.1. Trial Design Rationale

This trial is designed to investigate the efficacy and safety of GMRx2 for reducing BP in adult participants with high BP compared to dual combinations. The run-in period will assess participant adherence to trial medication and trial procedures, hence maximizing chances of complete follow-up and data collection. The double-blind periods will assess the efficacy and safety of GMRx2 Dose 2 and GMRx2 Dose 3, sequentially, compared to the corresponding three possible dual combinations of the component drugs. This will enable assessment of the contribution of each of the component drugs of GMRx2. The duration of 6 weeks for each double-blind period will enable demonstration of the maximum effects of each regimen. Double-blinding will prevent performance bias for investigators, study staff and trial participants. The safety follow-up period will assess safety after 4 weeks of the discontinuation of the randomized trial medication.

7.2. Sub-studies

Participants will be invited to provide venous blood specimens at the Week 12 visit for use in planned substudy analyses related to measurement of drug metabolite levels. The samples will be immediately processed and

stored at −80°C ± 10°C and shipped during or at the end of the study to a central laboratory for storage until analyses have been completed.

8. METHODS: PARTICIPANTS, INTERVENTION & OUTCOMES

8.1. Trial Setting & Participant Recruitment

Trial participants will be recruited from clinics or hospital-based out-patient departments or primary care centers that provide hypertension care in the participating countries. Based on the recruitment rate and trial timelines, other modes of recruitment that could be used include community resources particularly to target women and minority/under-served populations (also to ensure adequate representation of these groups), referrals from other hospitals/clinics and trial recruitment advertisement in the form of posters, flyers, via social media, etc.

8.2. Participant Eligibility

The guiding principle of participant eligibility is individuals with hypertension who could be appropriately treated with triple or dual combinations, with the component drugs, each at half or standard doses.

8.2.1. Inclusion Criteria

At screening visit

1. Provided signed consent to participate in the trial.
2. Adult of age ≥18 years.
3. Clinic attended automated seated mean SBP (average of 3 measurements):
    a. 140-179 mmHg on 0 BP-lowering drugs, or
    b. 130-170 mmHg on 1 BP-lowering drug, or
    c. 120-160 mmHg on 2 BP-lowering drugs, or
    d. 110-150 mmHg on 3 BP-lowering drugs.

Note: A single tablet containing 2 or 3 different BP lowering agents (i.e. a combination medication) is considered as 2 or 3 BP lowering drugs, respectively.

At randomization visit

1. Home seated mean SBP 110-154 mmHg in the week prior to the randomization visit.
2. Adherence of 80-120% to run-in medication.
3. Tolerated run-in medication.
4. Adherence to home BP monitoring schedule: in the week before randomization, at least 6 measures (e.g. ≥2 sets of triplicate measures, ≥3 sets of duplicate measures) including at least 1 morning and 1 evening each with ≥2 measures
5. Morning is defined as any measure in the am and evening as any measure in the pm. Morning and evening do not have to be same day.

1.

8.2.2. Exclusion Criteria

At screening visit

1. Receiving 4 or more BP-lowering drugs.
2. Receiving any BP lowering drugs for indications other than hypertension e.g. heart failure
3. Pregnant or had a positive pregnancy test or unwilling to undertake a pregnancy test during the trial and up to 30 days after the discontinuation of the trial medication or breastfeeding or of childbearing age and not using an acceptable method of contraception (defined in the Manual of Procedures). Acceptable methods of birth control include Hormonal prescription oral contraceptives, contraceptive

injections, contraceptive patch, intrauterine device, double-barrier method (e.g. condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization. Contraception should be used for at least 1 month before the screening visit and until the end of trial participation.

4. Meets any criteria of local ethical or regulatory requirements related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that would deem participation in a clinical trial unsuitable.
5. Contraindication, including hypersensitivity (e.g. anaphylaxis or angioedema), to the active run-in treatment or to any of the trial medication options in the four randomized groups.
6. Current/history of transient ischemic attack, stroke, or hypertensive encephalopathy.
7. Current/history of acute coronary syndrome, unstable angina, myocardial infarction, percutaneous transluminal coronary revascularization, or coronary artery bypass graft.
8. Current atrial fibrillation. Patients with a history of paroxysmal atrial fibrillation are potentially eligible as long as there has been no episode in the last 3 months, while patients with a history of persistent or permanent atrial fibrillation are not eligible.
9. Current/history of New York Heart Association class III and IV congestive heart failure.
10. Current/history of cardiomyopathy or any other cardiovascular condition of sufficient severity to contraindicate the trial medications or require a contraindicated medication.
11. Current/history of a known secondary cause of hypertension, such as primary aldosteronism, renal artery stenosis, pheochromocytoma, or Cushing's syndrome.
12. Current/history of severe uncontrolled diabetes (HbA1c > 11.0% (> 97 mmol/mol)) within last three months.
13. Current/history of end-stage renal disease or anuria; or current estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2
14. Current electrolyte levels that would be regarded as contraindications for any of the potential treatment arms e.g. serum sodium <132mmol/l or >148 mmol/l or serum potassium <3.1 mmol/l or >5.6mmol/l.
15. Current/history of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal range within 6 months.
16. Current concomitant illness or physical impairment or mental condition that in the judgment of the investigator could interfere with the effective conduct of the trial or constitute a significant risk to the participants' safety or well-being.
17. Arm circumference that is too large or too small for available cuffs to allow accurate measurement of BP. Upper limit is 55cm in all countries, while lower limit is 15cm or 24cm in different countries, depending on available cuff sizes.
18. Currently taking or might need during the trial, a concomitant treatment which is known to interact with one or more of the trial medications: digoxin, lithium, diabetics receiving aliskiren, moderate and strong CYP3A4 inhibitors (e.g. ritonavir, ketoconazole, diltiazem], simvastatin >20 mg/day, immunosuppressants.
19. Might need treatment with drugs that are prohibited during the trial: other antihypertensive drugs, endothelin receptor antagonists, neprilysin inhibitors, or other drugs that may affect BP (see Appendix 5).
20. Current surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of trial drugs such as prior major gastrointestinal tract surgery (e.g. gastrectomy, lap band, or bowel resection) or acute flare of inflammatory bowel disease within one year.
21. Individuals working >2 nightshifts per week.
22. Participated in any investigational drug or device trial within the previous 30 days. This does not include participants in the extended safety follow-up portion of a trial.
23. History of alcohol or drug abuse within 12 months.

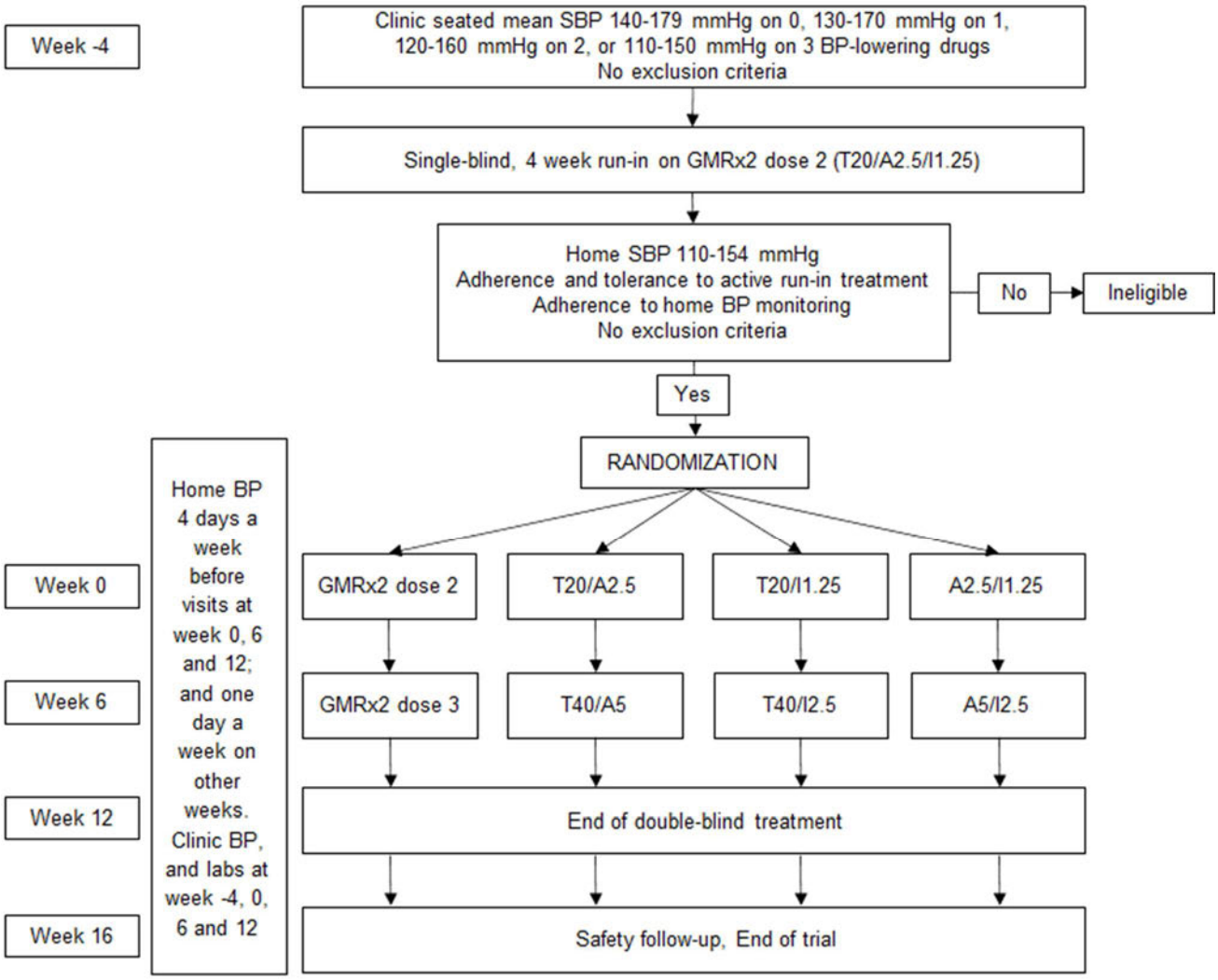
At randomization visit

1. Unable to adhere to the trial procedures during the run-in treatment period.

2. Any of the following which in the investigator's judgment may compromise the safety of the participant if randomized to the trial medications:
   a. High or low clinic BP levels even in the light of the values for home BP that are available for that participant. The exact levels of BP are not specified, since there is clinical uncertainty as to the relevance of BP levels which are high or low in clinic only; for example, the clinical relevance of 'whitecoat hypertension' is uncertain.
   b. High or low home diastolic BP (DBP) levels. The exact levels of DBP is not specified, reflecting clinical uncertainty of the implications of isolated diastolic hypertension. However, home DBP values of >99 mmHg may typically be considered as requiring treatment intensification, and such participants would not be suitable for randomization.
   c. Any abnormal laboratory value which in the judgment of the investigator could interfere with the effective conduct of the trial or constitutes a significant risk to the participants' well-being.
   d. Fulfilling any of the exclusion criteria mentioned for the screening visit, when verified again at randomization visit.

8.3. Trial Schema

Figure 3: Trial schema



GMRx2 Dose 2 = T20/A2.5/I1.25; GMRx2 Dose 3 = T40/A5/I2.5; T=telmisartan; A=amlodipine; I=indapamide; SBP=systolic blood pressure; BP = blood pressure. Participants entering the optional Open-Label Extension Period do so at week 12

8.4. Intervention

8.4.1. Single-Blind Active Run-In Period

During the screening visit, enrolled participants will be asked to discontinue all current BP-lowering drug(s) if applicable and enter a single-blind active run-in period for 4 weeks with GMRx2 dose version 2. Participants will be advised to take the run-in capsule once daily in the morning at approximately the same time each day. For days on which BP is being measured, the run-in capsule should be taken directly after the morning home BP measurement.

8.4.2. Double-Blind Treatment Period

The 4-week single-blind active run-in will be followed by a 12-week double-blind period with randomization to one of the following four treatment groups:

Table 4: Treatment Groups in the Trial

Group	Intervention	N	Treatment
1	Triple - TAI (GMRx2)	600	telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg (GMRx2 dose 2). At Week 6 visit, forced up-titration to telmisartan 40 mg/amlodipine 5 mg/indapamide 2.5 mg (GMRx2 dose 3)
2	Dual - TA	300	telmisartan 20 mg/amlodipine 2.5 mg. At Week 6 visit, forced up-titration to telmisartan 40 mg/amlodipine 5 mg
3	Dual - TI	300	telmisartan 20 mg/indapamide 1.25 mg. At Week 6 visit, forced up-titration to telmisartan 40 mg/indapamide 2.5 mg
4	Dual - AI	300	amlodipine 2.5 mg/indapamide 1.25 mg. At Week 6 visit, forced up-titration to amlodipine 5 mg/indapamide 2.5 mg

T=telmisartan, A=amlodipine, I=indapamide

On the day of randomization visit (W0), all participants will be prescribed and dispensed trial medication to be taken between the randomization and Week 6 visit (period 2). On the day of the Week 6 visit, all participants will be prescribed and dispensed trial medication (the same initial treatment but at double dose) to be taken between Week 6 and Week 12 visit (period 3). **All participants will be up-titrated at Week 6**, unless the investigator believes there is a specific contraindication for a particular participant, such as symptomatic hypotension or is asymptomatic with very low home or clinical BP levels (i.e. SBP <100 mmHg). If a participant is asymptomatic but is judged to be not suitable for dose doubling, then they should be continued on existing trial medication at Week 6. For participants who are not up-titrated at Week 6, up-titration can occur after Week 6 and before Week 12, if appropriate. Week 12 visit date should remain unchanged.

Participants should take trial medication once daily in the morning either before or after breakfast immediately after taking home BP measurement.

8.5. Adherence to Trial Medication

Adherence to trial medication will be assessed during all scheduled trial follow-up visits by counting trial medication capsules returned. Participants in all the groups will be advised of the importance of adhering to BP-lowering drugs for improving BP control and preventing CV events.

8.6. Add-on Treatment for Participants with High BP

The following situations will prompt an urgent clinic visit in an asymptomatic participant for remeasurement of BP in clinic and consideration by the trial investigator of the need to initiate open-label add-on treatment:

1. home seated mean SBP >170 mmHg and/or DBP >105 mmHg on any single day;
2. home seated mean SBP>160 mmHg and/or DBP >100 mmHg on 2 consecutive BP measurement days.

If the trial investigator decides that non-trial BP-lowering medication is warranted after assessment at the site, then they should prescribe the supplied open-label telmisartan 40 mg and/or amlodipine 5 mg on top of existing trial medication, without the need to stop and/or unblind trial medication.

Participants who require add-on treatment during the run-in period are not eligible for randomization, since there is no longer eligibility for randomization to any of the three possible treatment groups. Such participants should therefore cease run-in.

8.7. Down-Titration or Temporary Cessation of Randomized Trial Medication

If, during the randomized period a participant develops a condition or symptom likely to be related to the trial medication (e.g. possible hypotension) that is severe enough to warrant a change in trial medication, then the Investigator can choose to stop study medication temporarily or, if during Weeks 6 to 12, down-titrate to the

trial medication that the participant was receiving between Weeks 0 and 6. There is no need to unblind trial medication in this situation. Consideration should also be given to restarting scheduled medication subsequently, if benefits of restarting outweigh the risks as per the medical condition of the participant. If a participant discontinues medication at his/her own initiative, the reason should be investigated. If medically appropriate, consideration should be given to restarting study medication.

8.8. Early Permanent Discontinuation of Trial Medication

Discontinuation of trial medication occurs when a randomized participant permanently ceases taking the trial medication regardless of the circumstances, before the Week 12 visit and must be reported immediately to the CRO and recorded in the study database. In the case of early discontinuation of a participant from the trial medication, the reason for discontinuation will be recorded and immediately reported in the IBM Clinical Development trial database.

Early permanent discontinuation of trial medication may happen for the following reasons:

- By the participant himself/herself for any reason.
- By the investigator at the request of the participant for any reason.
- By the investigator if the participant's safety or wellbeing is or will be compromised by continued trial medication, including if the participant becomes pregnant
- The trial is terminated (e.g. if in the opinion of the DSMB interim data indicate that it might not be justifiable to continue the trial, the SC may terminate the trial).

In general, unblinding is not required in these situations, see Section 11.4.2 Unblinding of Trial Medication in a Clinical Emergency.

If necessary, the investigator will arrange for an alternative treatment to be prescribed by the treating physician. Participants with early permanent discontinuation of the trial medication are not considered withdrawn from the trial and should continue their participation in the trial as normal, completing all trial visits and assessments until the final trial visit at Week 16. For withdrawal from trial participation, see Section 13, page 34.

8.9. Post-Trial Medication

At the Week 12 visit , the investigator or responsible clinician will provide appropriate continued medical care to participants in line with local guidelines/practice.

9. OUTCOMES

9.1. Efficacy Outcomes

9.1.1. Primary

- Difference in change in home seated mean SBP from randomization to Week 12.

9.1.2. Secondary

- Difference in change in clinic seated mean SBP from randomization to Week 12.
- Difference in change in clinic seated mean SBP from randomization to Week 6.
- Difference in change in clinic seated mean DBP from randomization to Week 12.
- Difference in change in clinic seated mean DBP from randomization to Week 6.
- Percentage of participants with clinic seated mean SBP <140 and DBP <90 mmHg at Week 12.
- Percentage of participants with clinic seated mean SBP <140 and DBP <90 mmHg at Week 6.
- Percentage of participants with clinic seated mean SBP <130 and DBP <80 mmHg at Week 12.

- Percentage of participants with clinic seated mean SBP <130 and DBP <80 mmHg at Week 6.
- Difference in change in home seated mean SBP from randomization to Week 6.
- Difference in change in home seated mean DBP from randomization to Week 12.
- Difference in change in home seated mean DBP from randomization to Week 6.
- Difference in change in trough home seated mean SBP from randomization to week 12
- Difference in change in trough home seated mean SBP from randomization to Week 6
- Percentage of participants with home seated mean SBP <135 and DBP <85 mmHg at Week 12.
- Percentage of participants with home seated mean SBP <135 and DBP <85 mmHg at Week 6.
- Percentage of participants with home seated mean SBP <130 and DBP <80 mmHg at Week 12.
- Percentage of participants with home seated mean SBP <130 and DBP <80 mmHg at Week 6.

9.2. Safety Outcomes

9.2.1. Primary

- Percentage of participants discontinued trial medication due to AE/SAE from randomization to Week 12.

9.2.2. Secondary

- Percentage of participants discontinued trial medication due to AE/SAE from randomization to Week 6.
- Percentage of participants with an SAE from randomization to Week 12.
- Percentage of participants with SAE from randomization to Week 6.
- Percentage of participants with symptomatic hypotension from randomization to Week 12.
- Percentage of participants with symptomatic hypotension from randomization to Week 6.
- Percentage of participants with serum sodium concentration below 135 mmol/l at Week 12.
- Percentage of participants with serum sodium concentration below 135 mmol/l at Week 6.
- Percentage of participants with serum sodium concentration above 145 mmol/l at Week 12.
- Percentage of participants with serum sodium concentration above 145 mmol/l at Week 6.
- Percentage of participants with serum potassium concentration below 3.5 mmol/l at Week 12.
- Percentage of participants with serum potassium concentration below 3.5 mmol/l at Week 6.
- Percentage of participants with serum potassium concentration above 5.5 mmol/l at Week 12.
- Percentage of participants with serum potassium concentration above 5.5 mmol/l at Week 6.
- Percentage of participants with serum sodium <135mmol/l or >145 mmol/l, and/or serum potassium <3.5 mmol/l or >5.5mmol/l at week 6.
- Percentage of participants with serum sodium <135mmol/l or >145 mmol/l, and/or serum potassium <3.5 mmol/l or >5.5mmol/l at week 12.
- Percentage of participants with eGFR drop of over 30% from randomization to Week 12.
- Percentage of participants with eGFR drop of over 30% from randomization to Week 6.
- Percentage of participants with orthostatic hypotension at Week 6,
- Percentage of participants with orthostatic hypotension at Week 12
- Percentage of participants with orthostatic hypertension at Week 6,
- Percentage of participants with orthostatic hypertension at Week 12

9.2.3. Descriptive Safety Outcomes

In addition, descriptive safety data will be reported on:

- Percentage of participants discontinued trial medication due to AE/SAE during the active run-in period

- All SAEs, by severity and by System Organ Class (SOC) criteria during the run-in period, by trial medication group during the randomized period, and safety follow-up period.

10. PARTICIPANT TIMELINE & ASSESSMENTS

10.1. Schedule of Evaluations

Table 5: Trial visits schedule and assessments Randomization Period

Visit Name	SCREEN[10]	Run-in start[11]	Pre-RAND	RAND (Run-in end)	FU1 (Forced up-titration)	FU2 (End of trial medication)	EOT (Telephonic safety FU)
Visit Week	Week -4	Week -4	Week −4 to -1		Week 6	Week 12	Week 16
Visit Day *(Visit window days)*	-28 (±7)	-28 (±7)	During Run-in	0	42 (±7)	84 (±7)	112 (±7)
Written informed consent[1]	✓						
Eligibility (inclusion & exclusion)	✓			✓			
Medical history	✓						
Physical examination[2]	✓						
Demographics	✓						
Height	✓						
Weight	✓					✓	
Clinic BP, standing BP, pulse	✓			✓	✓	✓	
12-lead electrocardiogram (ECG)	✓						
Dispense home BP monitor^		✓					
Home BP monitoring			→	→	→	→	
Home BP monitor brought to clinic				✓	✓	✓	
Blood Collection*							
Results needed before run-in[3]							
Sodium, potassium, chloride, creatinine, liver function	✓						
Pregnancy test if childbearing potential†	✓						
Results needed before randomization[4]							
Fasting glucose			✓			✓	
HbA1c[5]			✓				
Fasting lipid profile[6]			✓			✓	
Complete blood count[7]			✓				
Liver function test[8]			✓			✓	
Sodium, potassium, chloride			✓		✓	✓	
Calcium			✓			✓	
Creatinine with eGFR[9]			✓		✓	✓	
Uric acid			✓			✓	
Thyroid-stimulating hormone			✓				
Other tests							
Blood sample for storage for substudy						✓	

Urine Collection*							
Albumin-creatinine ratio[4]			✓			✓	
Medications							
Discontinue non-trial BP lowering medications		✓					
Allocation of randomized trial medication				✓			
Dispensation of trial medication^		✓		✓	✓		
Return of trial medication				✓	✓	✓	
Adherence to trial medication				✓	✓	✓	
Review of concomitant medications	✓			✓	✓	✓	✓
Safety							
AESI or SAE			→				

[1] At Screening visit, if not collected previously. Written informed consent may be collected pre-screening.
[2] Systems-based examination deemed necessary for the safety of participants by the site investigator
[3] Results must be reviewed for eligibility prior to beginning run-in. If blood tests have been conducted within the past 3 months, these results can be utilized to assess suitability for run-in. If preferred locally, tests can be arranged prior to screening visit, once informed consent is obtained.
[4] Results must be reviewed for eligibility prior to randomization. Tests can be conducted during run-in
[5]For participants with diabetes without a HBA1c in past 3 months, HBA1c can be taken at screening to determine eligibility for randomization at randomization visit;
[6] Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol
[7] Red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, reticulocyte count, white blood cell count, platelet count
[8] Bilirubin, albumin, total protein, gamma-glutamyl transferase, alkaline phosphatase, aspartate transaminase and alanine transaminase
[9] recent eGFR must be known prior to run-in start. If not available in last 3 months, the start of run-in should be delayed until results available from measure taken at the time of screening/run-in blood tests
[10]Screening visit to take place 0-14 days prior to run-in start
[11] Option to extend run-in from 28 to up to 35 days (i.e. by up to 1 week) if there have been technical issues with BP machine use and or measurement protocol
* All laboratory investigations and ECG will be performed at the trial site or local laboratory.
† Serum pregnancy test for women of child-bearing potential. In some jurisdictions, including Czech Republic, Poland and South Korea, women of child-bearing potential will be required to undergo pregnancy testing and the result followed-up every 4 weeks after starting study medication until Week 12, end of randomized treatment period.
^ If respective blood test results are not available by the screening and randomization visits, once eligibility has been confirmed, participants may need to return to the clinic to collect the trial medication and home BP monitor. Alternatively, where feasible, and consent from the participant received, they may be couriered to the participant's home.
EOT=End of trial; FU=Follow up; PRESCREEN=Pre-screening; RAND=Randomization; SCREEN=Screening

10.2. Visit Procedures

10.2.1. Written Informed Consent

No trial procedures are to be carried out until participants have provided written informed consent except where the IRB/IEC has approved verbal consent as the first step in the consent process (See Section 10.2.2). Participants willing to take part in the trial will be consented by trial sites as per the local regulatory and ethical requirements. In brief, participants will be given the PISCF to read and an adequate explanation about the trial and will be given ample time to consider their trial participation. They will be given the opportunity to ask questions about the trial and what their participation involves and will receive full answers from the trial site staff. Before a participant participates in the trial, a written informed consent form (ICF) (using translated versions where appropriate) approved by the relevant IRB/IEC should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion. If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion and must attest an ICF. A copy of the signed ICF will be given to the participant.

10.2.2. Verbal Consent

To enable participants to attend the screening visit in the fasting state for blood sample collection, verbal consent to fast may be obtained. Participants will be provided with a copy of the PISCF to read and an adequate

explanation about the requirement to fast for blood sample collection at the screening visit. They will be given the opportunity to ask questions about the fasting process and will be receive full answers from the trial site staff. Verbal consent can be obtained by telephone and must be clearly documented in participants' trial records. Where feasible and approved by IRB/IEC, the verbal consent process may also be adopted to facilitate collection of screening bloods prior to the screening visit. Prior to performing all other trial procedures participants must provide written informed consent.

10.2.3. Assessment of Participant Eligibility

Each potential participant will be assessed for eligibility to participate in the trial as per the protocol-defined eligibility criteria. Responsible site investigator(s) will ensure that only eligible participants are enrolled in the run-in treatment period and the randomized treatment period of the trial.

10.2.4. Medical History

A detailed medical history will be collected at the screening visit. This will be based on participant medical records and/or self/carer-report. Participant's medical condition will be re-assessed before randomization to confirm eligibility for randomization.

10.2.5. Physical Examination

The physical examination includes elements of a systems-based examination deemed necessary for the safety of participants by the site investigator. Elements of the examination may vary from participant to participant depending upon the health status and symptoms reported, the time and type of visit (initial, follow-up). The physical examination will not be standardized, and information will be captured in the source documents for each participant.

10.2.6. Anthropometric Measurements

Height and weight will be measured as per the prevailing practice at the trial sites, and these measurements will be used for calculating the body mass index.

10.2.7. Clinic BP Measurement

Clinic BP will be measured in the seated position during all scheduled trial visits using a standard procedure (See Appendix 2). To allow flexibility in site visit scheduling and maintenance of participants typical time of taking trial medication, and since all morning home BP measures are to be taken before the next dose of the trial medication, clinic measures are not required to be conducted at trough.

10.2.8. Home BP Measurement

For the days on which home BP is measured, BP measurements should be at the same time in the morning and evening on each measurement day during the following time ranges:

1. morning (ideally between 06:00-10:00 hours) – prior to taking trial medication;
2. evening (ideally between 18:00-22:00 hours).

Participants should aim to have at least 6 hours interval between the morning and evening measurements.
In the week before the Randomization, Week 6 and Week 12 trial visits, BP measurements should be taken on the 4 days immediately prior to the day of the day of the on-site trial visit. In other weeks, measurements should ideally be performed on a single set day. Each home BP measurement should be done as a triplicate i.e., three individual measurements,, following the protocol outlined in Appendix 3, page 42. Telemonitored BP values will be monitored for adherence with measurement schedules and high values (as noted in Section 8.6, page 22), with reporting to the clinic and for medical management as needed.

Participants eligible for run-in medication will be issued with a home BP monitor at the screening visit and will be asked to bring it with them to the randomization visit. If they continue to randomization, they will continue to use the same home BP monitor.

10.2.9. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be obtained at the screening visit to determine the occurrence of silent myocardial infarction, atrial fibrillation, and left ventricular hypertrophy. Site investigators will review ECG reports and comment as either normal or abnormal, and if latter whether clinically significant.

10.2.10. Laboratory Investigations

The 2017 ACC/AHA-recommended laboratory investigations will be performed at the screening visit. These investigations will help in ascertaining participant safety and eligibility for trial participation. For investigations that are to be done in the fasting state, participants will be informed beforehand to fast for blood sample collection. Protocol-required laboratory investigations will be performed at a local laboratory in each participating country following the usual standard procedures of sample collection, analysis, and reporting.
Optional substudy blood samples will be immediately processed and stored at −80°C ± 10°C and shipped during or at the end of the study for storage and future analyses.

10.2.11. Allocation of Trial Medication

During the single-blind run-in period (Week -4 to Week -1 inclusive) all participants will be allocated GMRx2 dose version 2. During the double-blind period (Week 1 to Week 12 inclusive) all participants will be allocated GMRx2 or one of the three dual combinations as per the randomization scheme. Neither the site staff nor the participants will have foreknowledge of the treatment allocation at randomization. After the completion of the double-blind treatment period at Week 12, participants will be switched to non-trial medication as per local guidelines/practice.

10.2.12. Dispensation of Trial Medication

Starting at the screening visit (Week -4), participants will receive sufficient quantities of the trial medication until the next scheduled trial visit. In the case of lost/damaged dispensed treatment, participants will be asked to notify the site immediately and replacement treatment will be dispensed by the site. In circumstances where a participant is unable to return to the site to collect replacement trial medication between two scheduled trial visits, trial medication delivery will be arranged to the participant's location. Delivery of trial medication to participant's location may also occur in other circumstances and where feasible e.g. if blood test results are not available during the screening and randomization visits and randomization and/ or dispensing is delayed or due to pandemic restrictions. Sites will maintain accurate and up-to-date records of all trial medication dispensation to participants. Such records must be available for inspection at all times.

10.2.13. Returning of Trial Medication

Trial participants will return all unused trial medication to the sites during scheduled trial visits (or in between in some circumstances – e.g. discontinuation of treatment). Sites will collect all the returned trial medication and keep an accurate record, to be available for inspection at all times.

10.2.14. Concomitant Treatments

Starting at the screening visit, during all scheduled and unscheduled visits until the end of participation, the investigator/site will review participant concomitant treatments and update the relevant section in source documents and electronic case report form (eCRF) keeping in view the trial allowed and prohibited concomitant treatments. Non-trial BP lowering medication must be ceased prior to starting trial medication and documented in the eCRF. Prescription of non-trial BP-lowering drugs will only be allowed as noted in Section 8.6, page 22. Treatment with other drugs that do not affect BP significantly will be unrestricted and will be at the discretion of the treating physician. For the prescription of concomitant treatments, contraindications and drug-drug interactions should be taken into consideration as per the regulatory-approved prescribing information of drug prescribed. All other medical care should be delivered according to local guidelines/standards by the treating physician.

10.3. Visit Details

10.3.1. Pre-Screening Visit (As Required)

- Can be conducted by telephone.
- Assess potential participant's interest for participation and eligibility for the trial.
- Discuss the trial with the participant, including using the PISCF, and obtain signed informed consent. Participants may be provided time to consider their participation, with a follow-up visit arranged as needed.

- Consider modifying current treatments to facilitate trial eligibility, if clinically appropriate and considered safe. Informed consent must be obtained before the modification of medication(s). If medications are altered, a period of at least 14 days is required between alteration of BP treatment(s) and trial enrolment.
- If locally preferred and/or feasible, Screening Visit blood tests can be pre-arranged following informed consent.

10.3.2. Screening Visit

- Assess the potential participant's interest and eligibility for the trial.
- Discuss the trial with the participant, including using the PISCF, and obtain signed informed consent. This can also be done before the screening visit. The participant can be given the opportunity to consider information and return within the time window for randomization.
- Collect demographic information.
- Collect information on medical history, perform a physical examination.
- Measure height and weight.
- Measure BP and pulse.
- Perform 12-lead ECG.
- Collect blood samples for pre-run-in assessment, including pregnancy, if applicable . If pre run-in blood tests (sodium, potassium, chloride, creatinine, liver function) have been conducted within the past 3 months, these results can be utilized to assess suitability for run-in. Results must be reviewed and eligibility confirmed prior to enrolment into the study and run-in medication start. If laboratory results are not available on the day of the screening visit, the participant may be required to return to the clinic for collection of run-in medication and the home BP monitor as soon as results become available and eligibility has been confirmed. Alternately, if feasible according to local practice and if the participant consents, the home BP monitor and run-in medication may be delivered by courier to the participant's home. A flexible approach in accordance with local logistics and practice is permitted, so long as within local IRC/EC approval.
- In case of a delayed start to run-in medication, a run-in that is ideally 28 days and at least 21 days is still required and therefore the randomization visit may need to be delayed accordingly.
- Arrange laboratory investigations required to be reviewed before randomization, which includes fasting blood sample. This must be done during run-in while receiving run-in treatment.
- Assess eligibility as per the trial inclusion and exclusion criteria.
- Demonstrate home BP measurement and dispense home BP monitor (record serial number) to participant.
- Discontinue non-trial BP lowering medications.
- Dispense run-in medication.

10.3.3. Re-Screening

Participants can be re-screened up to three times in total during the recruitment period. Participants not meeting the eligibility criteria at Pre-Screening or Screening Visit can be re-screened if the reason for non-eligibility was transient (e.g. a short-term illness, abnormal laboratory finding, etc.), or if eligibility is expected to change (e.g. due to an alteration in BP regimen), or a remediable non-medical issue prevented completion of run-in (eg. BP machine malfunction). However, participants cannot be re-screened if they were intolerant of the run-in medication, if they required add-on medication during run-in or if valid home BP measurements did not meet criteria for entering run-in. Before re-screening, a new consent must be signed if more than 2 months have elapsed since signing the consent the first time. All eligibility criteria must be re-assessed on re-screening. Trial-specific laboratory investigations results available from within 30 days of the date of re-screening may be used to assess eligibility for trial participation.

10.3.4. Extended Run-In

The run-in period can be extended by up to 1 week if needed for reasons such as technical issues with the BP

machine or measurement protocol or administrative issues, such as a delay in receiving test results. However, the run-in period cannot be extended if the treatment was not tolerated or if valid home BP measurements did not meet criteria for randomization. If the run-in is extended, participants should measure home BP in the 4 days prior to the new Randomization Visit date.

10.3.5. Pre-Randomization visit

- Collect blood and urine samples for which the results should be available prior to Randomization (see Table 5.

10.3.6. Randomization Visit

- Measure BP and pulse.
- Record any AESIs or SAEs that have occurred since the screening visit.
- Collect unused run-in medication.
- Assess adherence to run-in medication.
- Assess adherence to home BP monitoring schedule.
- Record all medication currently being taken by the participant.
- Review home BP measurement technique.
- Assess eligibility as per the trial inclusion and exclusion criteria.
- Review pre-randomization laboratory results.*
- Confirm that participant is suitable to be randomized.*
- If relevant, discuss with female participants of child-bearing potential the need to conduct home pregnancy tests every 4 weeks during the treatment period and provide pregnancy test kits. *(Applies in some jurisdictions including Czech Republic, Poland and South Korea).*
- Randomize participant.
- Dispense treatment according to the allocated kit number selected by IBM database.
- For participants not suitable to continue, collect home BP monitor.

*If laboratory results are not available for review prior to or on the same day end of run-in /randomization visit, randomization must be delayed until the results are available and eligibility has been confirmed. If eligible, the participant will either be required to return to the clinic for the collection of randomized treatment, or alternatively, if feasible according to local practice and if the participant consents, the randomized medication may be delivered to by courier to the participant's home. Run-in treatment should be continued until randomization, If randomization is delayed.

10.3.7. Week 6 Visit

- Measure BP and pulse.
- Record AESIs or SAEs since the previous visit.
- Collect blood for measurement of electrolytes, creatinine, and eGFR
- Review all medications being taken by the participant.
- Collect unused trial medication.
- Dispense treatment according to the allocated kit number selected by IBM database.

10.3.8. Week 12 Visit

All participants

- Measure BP and pulse.
- Record AESIs or SAEs since the previous visit.
- Review all medications being taken by the participant and update medications.
- Collect unused trial medication and review medication adherence.
- Collect the Week 12 fasting blood and urine samples for laboratory investigations.

- Collect blood sample for storage for substudy (if applicable)

10.3.9. Week 16 visit (End of Trial Visit)

- Contact participant by telephone.
- Record AESIs or SAEs since the previous visit.
- Review all medications being taken by the participant and update medications
- Explain that the trial follow-up is now completed and thank participant

11. METHODS: ASSIGNMENT OF INTERVENTION

11.1. Allocation Sequence Generation

A central, computer-based randomization sequence will be generated, stratified by trial site.

11.2. Allocation Concealment

Randomization sequence will be incorporated into an online electronic data capture (EDC) application by a statistician. Neither the Investigators nor site staff will have access to the randomization sequence.
Participants meeting eligibility for randomization, can be randomized in the online EDC. The EDC application will generate the randomization record with the participant identification number and date and time.

11.3. Blinding (Masking)

Neither the site staff, including those measuring the outcomes nor the participants will be aware of the treatment allocated since all trial medication will be provided in identical capsules. Access to information on allocated treatment will be restricted. Breaking of treatment code (unblinding) will be restricted to situations that necessitate ascertainment of type of medication for a given participant to provide appropriate care. To protect blinding, all medications will have an identical appearance. None of the trial committees will have access to the code list of allocated treatments.

11.4. Unblinding

11.4.1. Unblinding of Trial Medication for Expedited Safety Reporting

Where country regulatory safety reporting requirements mandate the reporting of unblinded data, treatment assignment will be unblinded before they are reported to the Competent Authorities and IRB/IEC in accordance with the local safety reporting requirements. The trial medication assignment will only be made available to the relevant Competent Authorities and IRB/IEC and not be communicated to participants, investigators, or the CRO staff.

11.4.2. Unblinding of Trial Medication in a Clinical Emergency

In general, unblinding will only be required in certain specific circumstances which are expected to be very rare. If a contraindication to trial medication develops after randomization, the trial medication should simply be stopped and usual standard care given. Unblinding should be done only in those rare cases when the clinician believes that clinical management depends importantly upon knowledge of which treatment the participant received. In these cases when urgent unblinding is considered necessary, a 24-hour access service will be available. An unblinding report form should then be completed by the investigator.

12. METHODS: DATA COLLECTION, MANAGEMENT & STATISTICAL ANALYSIS

12.1. Data Collection

The investigator will be responsible for ensuring the accuracy, completeness, and timeliness of the data collected for the trial. All source data should be legible and complete to ensure accurate interpretation.

The trial will use an eCRF for data collection. Trial site staff will be trained on eCRF. Delegated site staff provided with the access (with username, password) will enter data in the eCRF regularly according to instructions for completion and any data queries will be resolved promptly. Data entered in eCRF should be consistent with the source data. For home BP values, the home BP machine is the data originator and the eCRF is regarded as the source record.[60] For BP values measured in clinic in which a paper transcription step is used, then the paper documentation should be retained and made available for inspection.[60] The investigator will sign each participant's eCRF confirming and certifying that the data entered is accurate and complete. All data collected in the eCRF will be securely stored with access restricted to representatives authorized for data management, and data analysis at the end of the trial.

12.2. Data Management

All data entry will be completed via the secure web-based data management system, IBM Clinical Development. Data entry will be performed at the participating sites by authorized site staff who have completed training and been given appropriate role-based access to the system. Data logic and consistency checks will be programmed into the data entry forms so that data entry errors can be caught real time and queries auto-generated. Manual queries may also be generated and listings will be run to perform manual data checks which cannot be programmed. Authorized electronic signatures will be used to lock completed data entry forms once all data queries have been resolved within the system. Data entry and all subsequent changes or deletions will be captured in an accessible audit trail. Coding will be centrally performed either automatically via the IBM coding module or manually. Data will be stored and backed up on the IBM's cloud servers in the USA.

12.3. Sample Size & Power Calculation

A sample size of 1500 participants (600 in GMRx2 and 300 in each of the dual combination groups) provides 97% power to detect a minimum difference of 3 mmHg in home seated mean SBP for each of the three comparisons of GMRx2 vs dual therapy, assuming a common standard deviation of 11 mmHg within each group. The overall power for all three comparisons will therefore be over 90%. Randomizing 1500 may necessitate at least 2000 participants entering the run-in treatment. A systematic review of previous trials of triple vs dual combination therapy demonstrated, on average, a 5.4/3.2 mmHg greater reduction in clinic BP with triple therapy,[61] and it is anticipated that the current trial will have similar rates of drop-in and drop-out as observed in those trials. A systematic review comparing BP reductions from different BP measurement methods indicated that on average reductions in home BP were about 20% less than those seen for clinic BP.[62] In three recent trials that utilized home BP measurement protocols very similar to those planned for this trial, the average SD of change in home SBP was 11 mmHg.[21,63,64]

12.4. Statistical Methods

All analyses will be performed on an intention-to-treat basis. Baseline characteristics by the group will be compared using descriptive analyses. The primary outcome of difference in change in home SBP from baseline to Week 12 will be analyzed using a mixed model for repeated measures with baseline BP, visit, treatment group, and visit by treatment group interaction as a fixed effect and accounting for correlation within participant and clustering at the site level. Other continuous outcomes of difference in change in BP will also be analyzed as the primary outcome. All continuous outcomes will be reported along with 95% CI and the corresponding p-value. The percentage of participants achieving target BP at Week 6 and Week 12 will be summarized descriptively and analyzed using generalized estimating equations with the visit, treatment group, and visit by treatment group interaction as a fixed effect and accounting for correlation within participant and clustering at the site level. Percentages by treatment groups with 95% CI will be presented along with the associated estimated odds ratio and its corresponding p-value. Other binary outcomes of efficacy and safety will be analyzed as the percentage of participants achieving target BP. The primary analysis dataset will be locked after the last participant has reached the 16 week follow-up visit.

13. WITHDRAWAL FROM TRIAL PARTICIPATION

Participants will be informed at the time of consenting and enrolment that; they are free to withdraw from the trial at any time and for any reason without influencing any aspect of their usual medical care. If a participant wishes to withdraw from the study prior to completion and explicitly revokes consent or if the trial investigator decides it is in the best interest of the participant to withdraw from the trial, every effort should be made for the participant to complete a final follow-up assessment to record BP, AESI and SAEs and collect all unused trial medication. Data collected up to the point of withdrawal will be included in trial analyses unless the participant expressly requests their data to be excluded.

14. TRIAL MEDICATION MANAGEMENT

14.1. Manufacturing

The formulation development and manufacturing of GMRx2 will be conducted as per Good Manufacturing Practice and in accordance with the applicable regulatory requirements.

14.2. Packaging, Labelling, Distribution & Storage

Packaging, labeling, quality release, storage, and distribution of the trial medication to the local country depot or directly to participating sites will be conducted as per the local regulatory and set-up requirements. All shipments will be temperature-monitored, and where required, temperature-controlled shipments will be conducted. The CRO will keep accurate records of trial medication supplies to trial sites. At each trial site, the Investigator will be responsible to store and maintain accurate records of trial medication and report to the CRO. Trial sites will store trial medication as per the labeled instructions and will instruct the trial participants accordingly.

14.3. Return & Destruction

At the end of the trial, following the accountability of the returned/unused trial medication, and on the authorization of the ACC, trial medication will be destroyed on-site or returned to the depot for destruction. Once destroyed, a destruction certificate or record will be provided to the site.

15. MANAGING INTERRUPTION OF STUDY MATERIAL SUPPLY TO TRIAL CENTRES

Supply chain-related interruptions of study materials to trial centres may occur, especially in the context of a pandemic, in which case the following strategies should be adopted. If study BP machines are not available at the centre, participants should not be entered into run-in, but asked to return when BP machines are available, which may necessitate re-screening. If study treatment for any trial phase (Run-in/Period 1, Period 2 or Period 3 as in Figure 2) is not available at the centre or not certain to arrive in adequate time, the participant should delay the start of Run-in, which may necessitate rescreening. If a participant is on Run-in/Period 1 and Period 2 and/or 3 study treatment is not available or not certain to arrive in adequate time, then randomization should be delayed, which may necessitate extending or repeating run-in. If a participant is randomised and receiving Period 2 study treatment (see Figure 2, ie. could be receiving GMRx2-dose2, telmisartan 20mg/amlodipine 2.5mg, telmisartan 20mg/indapamide 1.25mg, or amlodipine 2.5mg/indapamide 1.25mg) but Period 3 study treatment is not available, then at the week 6 study visit participants should switch to open-label telmisartan 40mg and amlodipine 5mg. This open-label treatment should be continued until Period 3 study treatment is available at the centre, at which time a repeat clinic visit should be arranged and Period 3 treatment instituted. Home BP monitoring should be continued throughout and any additional tests instituted as required to ensure patient safety. There is no need to unblind. The final clinic visit of the randomised phase should be rescheduled for 6 weeks after the new start date of the Period 3 study treatment.

16. MONITORING

16.1. Data & Safety Monitoring Board

An independent DSMB will monitor the trial data and advise the SC on the continuing safety of trial participants and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

16.2. Data Monitoring

In addition to pre-programmed edit checks in the eCRF, regular remote data monitoring will be conducted by the responsible CRO and designated monitors for confirmation of participant eligibility, identification of missing data, data consistency, and general data quality checks. Automated queries may be generated via programming in the eCRF and can also be manually generated by monitoring staff. On-site monitoring visits will also be conducted to review source documents and to resolve any issues at the site. Full details of monitoring activities will be described in the Trial Monitoring Plan. The investigator should allow the monitors, the persons responsible for the audit, the representatives of the sponsor, the IRB/IEC, and of the Regulatory Authorities to have direct access to source data/documents. The CRO will also undertake regular remote monitoring of data.

17. SAFETY

17.1. Safety Definitions

17.1.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical investigational medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Only AEs that are defined as AESIs will be collected.

17.1.2. Adverse Event of Special Interest

The following AEs are considered AESIs and will be collected:

- Symptomatic hypotension: Dizziness or any other symptom or event possibly related to hypotension
- Abnormal laboratory findings of sodium, potassium, uric acid, glucose, lipids, creatinine or eGFR
- Headache
- Peripheral edema
- Any other symptom or laboratory abnormality that led to permanent discontinuation of trial medication.

17.1.3. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose; results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Hospitalization means the participant has been formally admitted to a hospital for medical reasons. It does not include a presentation at a casualty or emergency room. Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an SAE or AE. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or otherwise meets seriousness criteria, the event is an SAE.

17.1.4. Intensity/Severity of an AESI/SAE

All AESI/SAEs will be graded as mild, moderate, or severe by the investigator based on her/his medical judgment and the following guidance:

- **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate:** limiting age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping for groceries or clothes, using the telephone). Minimal, local or non-invasive intervention indicated.
- **Severe:** Medically-significant but not immediately life-threatening; disabling; limiting self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self); hospitalization or prolongation of hospitalization indicated.

17.1.5. Relationship to the Trial Medication

All AESIs/SAEs will be assessed for causal relationship to the study medication by the investigator and reported as either definitely, probably, possibly, unlikely related, or not related.

17.1.6. Serious Unexpected Suspected Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a suspected adverse reaction related to an investigational medicinal product that is both unexpected and serious. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the information previously described for the trial medication in the Investigator Brochure (IB).

17.2. Safety Reporting

17.2.1. AESI/SAE Data Collection & Follow-Up Period

AESI/SAE data will be collected and followed-up from the time signed informed consent is obtained and up to the Week 16 EOT visit for the double-blind period. Follow-up information on ongoing AESIs/SAEs obtained after the participant's respective EOT visit (as applies) will not be collected in the eCRF but all attempts will made to follow-up SAEs/AESIs until they have resolved or stablised.

17.2.2. Trial Investigator Responsibilities in Reporting AESIs/SAEs

Regardless of the suspected causality, every AESI/SAE must be reported by the site investigators as per the local regulatory and ethical requirements. All SAEs should be reported by completing the paper (Council for International Organizations of Medical Sciences [CIOMS] or relevant form) and eCRF SAE Form. The reports should identify participants by unique identification numbers assigned to the trial participants. SAEs should be promptly reported to the concerned parties and followed-up until resolution as per the local ethical and regulatory requirements. The Investigator should supply additional information (e.g. laboratory results, specialist/hospital letters, and autopsy results, etc.) if required by the CRO. Investigators are responsible for assessing if an AE meets the criteria for reporting as serious, the intensity of the event, and the relationship of the event with the trial medication.

17.2.3. Reporting of AESIs & SAEs

At each trial scheduled visit and unscheduled visits during the trial, site staff will ask participants about the incidence of any AESIs or SAEs since the previous visit. Other AEs will not be recorded since these drugs are well-known and established with widespread use. Site staff may also become aware of the incidence of AEs during a phone call with participants. All SAEs that site staff becomes aware of from the time informed consent is obtained until 30 days after discontinuation of the trial medication must be recorded. The following information will be collected for each AESI and SAE: event name, date of onset, severity, a possible cause of the event, relationship to trial medication, action taken regarding the trial medication, treatment given to manage the event (if applicable), the outcome of event, and date of resolution (if applicable).

An increase in the severity of a previously reported AESI or SAE during the trial will be reported as a new AESI or SAE with higher severity. A decrease in the severity of a previously reported AESI or SAE during the trial, will not require changes to the reported severity. Worsening of a condition, recurrent episodes, and further complications if any are to be reported as a follow-up of the original event.

All SAEs will be reported by the site staff to the sponsor via the eCRF within 24-hours of first becoming aware

of the event. Additional information will be collected including, seriousness criteria, hospitalization date and discharge (if applicable), and procedures performed (if applicable).

17.2.4. Reporting of SUSARs

The Medical Monitor assigned by George Clinical Safety will assess all suspected serious adverse reactions in order to determine expectedness in accordance with the known adverse effects of each investigational drug as listed in the IB. If a suspected serious adverse reaction is determined to be unexpected i.e. a SUSAR, the CRO will report to the applicable regulatory authorities within the required timelines. Follow-up reports will be generated in accordance with applicable regulatory requirements. Reports will also be provided to the overseeing IRB/IEC and Investigators as per country requirements.

17.2.5. Reporting of Pregnancy

Any occurrence of pregnancy in a trial participant during the trial from the time to signing the informed consent until 30 days after discontinuation of the trial medication will be reported by the site staff, using a pregnancy form, to the trial sponsor within 24 hours of the site staff first becoming aware of it. Pregnancy will be followed until final resolution (i.e., delivery or early termination). Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

17.2.6. Reporting of Trial Medication Use Errors or Misuse

Reports of trial medication overdose, abuse, off-label use, misuse, or any other medication error should only be reported as an SAE if they are associated with suspected adverse drug reactions. Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or participant. All trial medication overdose, misuse and other medication errors associated with suspected adverse drug reactions should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, etc.).

18. ETHICAL & REGULATORY COMPLIANCE

This trial will be designed, conducted, analyzed, and reported in compliance with ICH-GCP and local regulatory & ethical requirements.

18.1. Ethical Approval

All participating sites will submit to relevant IRB/IEC the trial protocol, PISCF and other trial-related essential documents, as required by the IRB/IEC, for review and approval. No sites will start the trial before the written approval of the IRB/IEC.

18.2. Regulatory Approval

Where applicable, the trial protocol, PISCF, and other trial-related essential documents will be submitted to the local regulatory agency as per the applicable requirement in the country.

18.3. Confidentiality

All documents and data relating to this trial are strictly confidential. Documents given to the investigators and trial sites by the CRO should not be disclosed to other parties without the written approval of the sponsor. The investigators/sites should maintain the confidentiality of the identification of all trial participants and assure the security and confidentiality of trial data and documents.

18.4. Protocol Amendments

Any change to the protocol will be made through a protocol amendment by the SC. The participating sites will submit the amendment to the relevant IRB/IEC, and the sponsor will submit to the regulatory agencies as per the local requirements.

18.5. Adherence to the Trial Protocol

Investigators/sites will adhere to the trial protocol, comply with the ethical and regulatory requirements for the conduct of the trial. Any deviations from the protocol must not be implemented unless such a deviation is required to prevent/eliminate immediate harm to the trial participant(s). The investigator/site will document protocol deviations along with reasons and notify them to the sponsor/CRO as per the local requirements.

19. ADMINISTRATIVE SECTION

19.1. Insurance

The sponsor provides insurance to cover medical expenses and/or pay compensation in the event of a trial-related injury or death to a trial participant and indemnify (with both legal and financial coverage) the investigator/site against claims arising from the trial, except in the case of claims that arise from malpractice and/or negligence, in compliance with local regulatory and ethical requirements.

19.2. Quality Assurance

Quality assurance will be achieved via compliance with relevant standard operating procedures, regulatory and ethical requirements; database design and data monitoring; training of all study staff on protocol and procedures; documentation of all procedures and processes; communication with stakeholders by the trial coordinating team; and direction and leadership of the trial by the SC.

19.3. Trial Documents Retention

All essential trial documents (as defined by ICH-GCP) will be archived and retained at the trial sites as long as to comply with the requirements of the sponsor (as specified in the agreement between the sponsor and the sites) and the national and international regulations (whichever is the longest period). At the end of such period, the investigator shall notify in writing to the sponsor of the intent to destroy all such documents. If the site investigator is unable to archive or cannot guarantee the archival requirements for some or all the documents, arrangements must be made between the investigator and the sponsor to store documents outside the site, in such a way that they can be accessed in the event of a regulatory inspection. These documents should not be destroyed without prior written approval from the sponsor. In the case of investigator wanting to assign the trial records to another party, or move them to another location, the sponsor must be notified in advance.

For sites using an electronic system to store trial participants medical records and it cannot be confirmed that the electronic system is validated (as per 21 Code of Federal Regulations Part 11 or equivalent standard) or the sponsor representatives or the regulatory inspectors cannot be provided access to the electronic system the site will be requested to print the source documents needed for verification. Such printed copies should be numbered, stapled, and should be certified by the site investigator that they are exact copies with the same information as in the original source record.

19.4. Ownership, Disclosure of Data and Dissemination policy

The Sponsor will have full ownership of the trial data. The sponsor will register the trial and post results on public platforms such as ClinicalTrials.gov within the timelines stipulated by the applicable IRBs/IECs and/or regulatory agencies. The sponsor will develop a clinical trial report documenting results that will be submitted to the regulatory agencies. The SC will be primarily responsible for publications arising from the trial, which will be submitted for presentations at conferences and publications in journals. Authorship on publications will be as per the International Committee of Journal Editors criteria. Draft publications should be shared with the Sponsor, who will provide any comments within 30 days of receipt.

20. APPENDICES

20.1. Appendix 1: List of Abbreviations

Abbreviation	Definition
ACC	Academic Coordinating Center
ACC/AHA	American College of Cardiology/American Heart Association
ACEI	Angiotensin Converting Enzyme Inhibitors
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
BP	Blood Pressure
CCB	Calcium Channel Blocker
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimeters
CRO	Contract Research Organization
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DSMB	Data & Safety Monitoring Board
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EOT	End of Trial
ESC/ESH	European Society of Cardiology/European Society of Hypertension
FDA	USA Food & Drug Administration
GM	George Medicines
GMRx2	Single pill combinations of telmisartan/amlodipine/indapamide
HCTZ	Hydrochlorothiazide
IEC	Institutional Ethics Committee
IB	Investigator's Brochure
ICH-GCP	The International Conference on Harmonization Good Clinical Practice
IRB	Institutional Review Board
MACE	Major Adverse Cardiac Events
mg	Milligram
mmHg	Millimeters of Mercury
PATHWAY-1	Prevention And Treatment of Hypertension With Algorithm-based Therapy - study 1
PISCF	Participant Information Sheet & Consent Form
RCT	Randomized Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SC	Steering Committee

SOC	System Organ Class
SPC	Single Pill Combination
STRATHE	STRAtegies of Treatment in Hypertension Evaluation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRIUMPH	Triple Pill versus Usual Care Management for Patients with Mild-to-Moderate Hypertension
USA	United States of America

20.2. Appendix 2: Procedure for the Measurement of Clinic BP

Procedures for clinic BP measurement are taken from AHA recommendations[65] and will be performed using a supplied FORA D40g BP machine (also known as Medisanté BP800 machine),[66,67] which is a validated, electronic, automatic, digital upper-arm cuff monitor,[68] and the same model as that used for home BP.

1. Ensure the paper clinic BP data collection form is ready with participant's identifying information added and a pen is available so that BP measures can be written down directly on the form, for subsequent transcription to the eCRF. The paper clinic BP data collection form should be retained for monitoring.
2. Participants should be asked to avoid caffeine, smoking and exercise for at least 30 minutes before their BP measurement procedure begins. This preparation is ideal not essential – if not possible, the measurement should still proceed
3. Ensure the participant has emptied his/her bladder.
4. Remove all clothing covering the location of cuff placement. Make sure to avoid rolling up sleeves, this may cause a (partial) tourniquet effect.
5. Support the participant's arm (e.g., resting on a desk).
6. Sit with back straight and supported (e.g. on a straight-backed dining chair).
7. Sit with feet flat on the floor and legs uncrossed.
8. Use the correct cuff size according to arm circumference, from the Small (15 - 24cm, different cuff sizes available in different countries), Medium/Large (M-L = 24 - 43cm) and Extra Large (XL = 38 - 55cm) sizes available, such that the bladder encircles 80-100% of the arm circumference.
9. Position the center of the BP cuff over the upper arm brachial artery at least 1 inch above the crease of the elbow.
10. Position the middle of the cuff on the participant's upper arm at the level of the right atrium (the midpoint of the sternum).
11. Once the participant is prepared, have him/her relax, sitting in a chair with feet flat on the floor and back supported. The participant should be seated for 5 min without talking or moving around before recording the first BP reading.
12. Site staff will initiate BP measurement and will be present until all the measurements are made.
13. Immediately after three seated BP measurements are taken, ask the participant to stand up and take an additional single BP measure after 1 minute of standing.
14. Neither the participant nor the person measuring the BP should talk during the rest period or the measurement.
15. A single press of the on/off button on the bottom right of the FORA D40g device will take a single measure (for initial left arm, right arm BP measures, at screening and re-screening visits only and for standing BP measures) and a single press of the AVG button on the bottom left of the device should be used for all seated measures. This will provide the average of three measurements, each spaced by 1 minute.
16. At the first visit, record a single BP from each the arm. If one arm gives a reading that is more than 10mmHg SBP higher than the other arm, then the arm with the higher measure should be used for all readings throughout the trial. If the SBP difference between arms is 10mmHg or less, a choice of arm should be made and all measures should be taken from the same arm throughout the trial for that participant.
17. Ensure that the BP readings are transcribed from the paper clinic BP data collection form to the eCRF.

20.3. Appendix 3: Procedure for the Measurement of Home BP

Procedures for home BP measurement are taken from AHA recommendations[65] with reference to recent trials and clinical use.[64,69] BP measurements will be performed using a supplied FORA D40g BP machine (also known as Medisanté BP800 machine), which is a validated, electronic, automatic, digital upper-arm cuff monitor, and the same model as that used for clinic BP.

Home BP will be measured according to the following schedule:

- on four consecutive days immediately prior to the trial visit (i.e. Weeks -1, 5, and 11), and ideally on a single set day of participant's preference in other weeks.
- in triplicate in the morning and in the evening, ideally at approximately the same time each morning and evening and between 06:00-10:00 hours and 18:00-22:00 hours. If these time ranges are not possible, measures in the am and pm are sufficient as morning and evening measures, as long as there is at least a 6-hour interval between the morning and evening measurements
- the morning measurements should be immediately before the next trial medication dose

Each participant will be provided a BP monitor for her/his sole use for the duration of the trial. BP readings will be encrypted and transferred automatically to the trial database via SIM connection. Physical recording of BP measurement values by participants will not be required, unless there is a technical failure in data transfer, in which case BP readings should be captured in the BP diaries provided and the BP monitor brought to the trial site for inspection.

Device setting and handover to participant (site staff)

1. Switch on the device.
2. Ensure the supplied cuff is appropriately sized based on the arm circumference such that the bladder encircles 80-100% of the arm circumference. Small (15 - 24cm, available only in some countries), Medium/Large (M-L = 24 - 43cm) and Extra Large (XL = 38 - 55cm) sizes are available.
3. Perform a demonstration measurement following the instructions below and ask participants if they have any queries.
4. Ask participants to contact site staff if they have any questions related to home BP measurement or their device is not functioning properly.

Information and instructions to participants

1. Avoid smoking, caffeinated beverages or exercise within 30 minutes before the BP measurements. This preparation is ideal not essential – if not possible, the measurement should still proceed
2. Urinate to empty the bladder before BP measurements.
3. Start BP measurements after 5 minutes of seated rest.
4. Sit with back straight and supported (e.g. on a straight-backed dining chair).
5. Sit with feet flat on the floor and legs uncrossed.
6. Remove all clothing covering the location of BP measurement cuff placement.
7. Keep arm supported on a flat surface (such as a table), with the upper arm at heart level.
8. Place the bottom of the cuff directly above the antecubital fossa (bend of the elbow).
9. Take BP measurements from the arm advised by the trial site staff.
10. Take 3 BP measurements with a 1-minute interval between each measurement.

20.4. Appendix 4: Trial Organization

Steering Committee

Chair

[redacted]

Members

[redacted]

ACC members – non-voting

[redacted]

Coordination

[redacted]

Data and Safety Monitoring Board

Members

[redacted]

Statisticians

[redacted]

Executive Secretary

[redacted]

Coordination

[redacted]

20.5. Appendix 5: Prohibited Drugs During the Trial

Participants receiving the following drugs are not eligible for participation in the trial, and these drugs should not be initiated during the trial unless clinically essential and treatment cannot be provided with add-on medication as mentioned in Section 8.6, page 22. Past use does not contraindicate eligibility, but any prohibited drug should be ceased at or before the Screening visit and a period of at least 2 weeks or 5 half-lives (whichever is longer) must elapse between permanent drug cessation and randomization.

1. Antihypertensive drugs
    - 1.1. Non-trial angiotensin receptor blockers
    - 1.2. Non-trial calcium channel blocker
    - 1.3. Non-trial diuretics of all types, including thiazide, thiazide-like, loop and potassium sparing diuretics
    - 1.4. Alpha-adrenergic blockers
    - 1.5. Angiotensin-converting enzyme inhibitors
    - 1.6. Beta-adrenergic blockers
    - 1.7. Central alpha-agonists
    - 1.8. Renin-inhibitors
    - 1.9. Reserpine
    - 1.10. Vasodilators

2. Endothelin receptor antagonists

3. Neprilysin inhibitors

4. Other drugs that may affect BP
    - 4.1. Corticosteroids (e.g. cortisone, hydrocortisone) excluding topical inhaled and intranasal use
    - 4.2. Liquorice
    - 4.3. Erythropoiesis stimulating agents (e.g. epoetin alfa)
    - 4.4. Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)
    - 4.5. Sodium-glucose co-transporter-2 (SGLT2) inhibitors (eg. dapagliflozin, empagliflozin, canagliflozin)
    - 4.6. Psychiatric drugs that affect blood pressure:[70] venlafaxine, bupropion, tricyclics, monoamine oxidase inhibitors (MAOis)
    - 4.7. Cocaine, amphetamines or other stimulants, including the appetite suppressant phentermine
    - 4.8. Pseudoephedrine, phenylephrine or other nasal decongestants, excluding topical and intermittent use
    - 4.9. Yohimbine
    - 4.10. Vascular endothelial growth factor pathway inhibitors (e.g. bevacizumab, SORAfenib)

5. Intermittent use of phosphodiesterase (PDE) inhibitors (eg sildafenil) do not constitute a contraindication

20.6. Appendix 6: Protocol Signature Page

The signatures below constitute approval of this protocol by the signatories and provide the assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, applicable ethical and regulatory requirement, laws and ICH-GCP.

Trial Number: GMRx2-HTN-2020-ACT1
Indication: Hypertension

GEORGE MEDICINES CHIEF INVESTIGATOR

Signature [redacted]

Date 8 March 2024

Name [redacted]

Title [redacted]

TRIAL SITE INVESTIGATOR

Trial Site Name

Signature _____

Date _____

Name _____

Title _____

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