CLINICAL TRIAL PROTOCOL

Trial Title	Efficacy and safety of GMRx2 (a single pill combination containing telmisartan/amlodipine/indapamide) compared to placebo for the treatment of hypertension: An international, multi-center, randomized, double-blind, placebo-controlled, parallel-group trial
Brief Title	Efficacy and safety of GMRx2 compared to placebo for the treatment of hypertension
Phase of Development	Phase III
Trial Drug	GMRx2: Single pill combination of telmisartan/amlodipine/indapamide Dose version 1: telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg Dose version 2: telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
Trial Number	GMRx2-HTN-2020-PCT1
Indication	Hypertension
Protocol Version	Version 6.0, 22 December 2023
Trial Registration	Clinicaltrials.gov NCT04518306
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.

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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 ABPM measurements for a subset of participants Addition of standing blood pressure measurement at clinic visits Addition of outcome of any abnormality of sodium or potassium Addition of blood and urine 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	14 Jan 2022	Update of Roles & Responsibilities Update of Committee members Revision of trial rationale Revision of BP criteria to enter placebo run-in Revision of eligibility criteria related to use of BP lowering drugs for other indications and eGFR 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 Addition of optional Open-Label Extension Period Several minor clarifications
Version 5.0	17 Apr 2023	Clarification of important medical event definition Several other minor clarifications and administrative corrections
Version 6.0	22 Dec 2023	Revision of Statistical Methods section to ensure consistency with Statistical Analysis Plan 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 certain global study operations, including database management, study set-up and management, 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) and 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
	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 1: telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg Dose version 2: telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
DEVELOPMENT PHASE: III	**INDICATION:** Hypertension

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

TRIAL DESIGN:
International, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, followed by an optional Open-Label Extension Period

OBJECTIVES:
To investigate the efficacy and safety of GMRx2 compared to placebo for the treatment of hypertension.

PARTICIPANT ELIGIBILITY:

Key Inclusion Criteria:

At screening visit

1. Provided signed consent to participate in the trial.
2. Adult aged ≥18 years.
3. Low calculated cardiovascular risk according to local guidelines such that pharmacological BP-lowering treatment is not mandatory: E.g. Pooled Cohorts Equation 10-years ASCVD risk <10% in the USA.
4. Likely diagnosis of hypertension, defined as:
    - automated SBP at this clinic visit of ≥130mmHg on no BP lowering medicines or ≥120mmHg on 1 BP lowering medicine that will be stopped at this visit, OR
    - documentation in last 6 months of office SBP ≥ 140 mmHg and/or DBP ≥ 90mmHg on no BP lowering medicines or SBP ≥ 130 and/or DBP ≥ 85mmHg on 1 BP lowering medicine that will be stopped at this visit, OR
    - documentation in last 6 months of home SBP ≥ 130 mmHg and/or DBP ≥ 80mmHg on no BP lowering medicines or SBP ≥ 120 mmHg and/or DBP ≥ 75mmHg on 1 BP lowering medicine that will be stopped at this visit, OR
    - documentation in last 6 months of ambulatory daytime SBP ≥ 130 mmHg and/or DBP ≥ 80mmHg on no BP lowering medicines or SBP ≥ 120 mmHg and/or DBP ≥ 75mmHg on 1 BP lowering medicine that will be stopped at this visit

At randomization visit

1. Home SBP 130-154 mmHg.
2. Adherence of 80-120% to run-in medication.
3. Tolerated run-in medication.
4. Adhered to home BP monitoring schedule.

At week 4 (for optional Open-Label Extension Period)

1. Provided signed informed consent.
2. Completed randomized treatment and willing to continue GMRx2-based regimen for 12 months

Key Exclusion Criteria:

At screening visit

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

At randomization visit

1. Contraindication to any of the randomized medications including placebo

At week 4 (for optional Open-Label Extension Period)

1. Contraindication to any of the open-label GMRx2-based BP-lowering treatment regimen.

TRIAL MEDICATIONS:

A 2-week single-blind placebo run-in followed by a 4-week double-blind period with randomization to one of the following three trial medication groups:

Group	Intervention	N	Treatment
1	GRMx2 Dose version 1: Triple ¼	100	telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg
2	GRMx2 Dose version 2: Triple ½	100	telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
3	Placebo	50	placebo

An optional 12-month Open-Label Extension Period will commence at Week 4

TRIAL OUTCOMES:

Efficacy Outcomes

Primary

- Difference in change in home SBP from baseline to Week 4

Key secondary efficacy outcomes

- Difference in change in home DBP and clinic BP from baseline to Week 4.
- Percentage of participants with hypertension control with home and clinic BP at Week 4.

Key Safety Outcomes

- Adverse events (AEs)/serious AEs leading to discontinuation of trial medication from baseline to Week 4.
- Serious AEs from baseline to Week 4

In addition, descriptive, non-comparative data on mean BP, BP control, and safety outcomes will be reported on the cohort of participants entering the optional Open-Label Extension Period.

NUMBER OF PARTICIPANTS & TRIAL POWER:

A total of 250 participants will be randomized, which may necessitate over 300 entering the placebo run-in treatment period. For the comparison of triple ¼ vs placebo at Week 4, a sample size of 150 participants at a ratio of 2:1 will provide 90% power to detect a difference of at least 9 mmHg in mean home SBP, assuming a standard deviation of 11 mmHg.

NUMBER OF COUNTRIES & TARGET NUMBERS OF SITES:

Approximately 25-30 sites in Australia, Sri Lanka, Nigeria, UK and USA.

TRIAL PERIOD:

Placebo run-in treatment period: 2 weeks
Randomization treatment period: 4 weeks
Safety follow-up period: 4 weeks
Optional Open-Label Extension Period: 12 months (selected countries only)

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 BP 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.

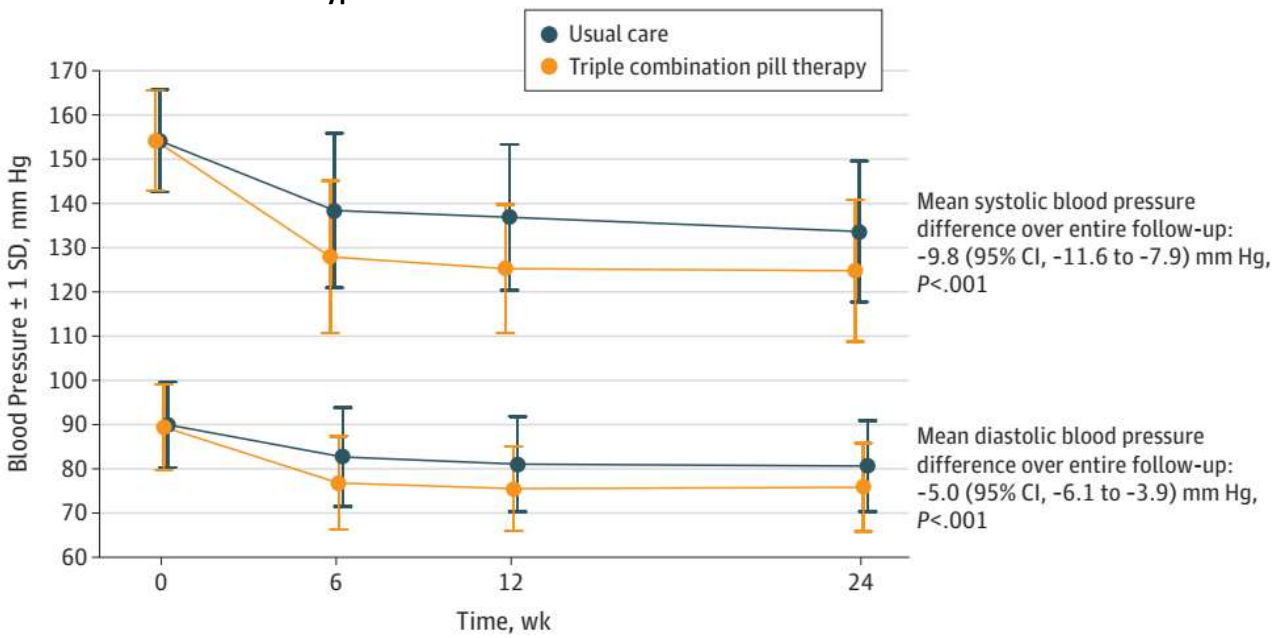
Table 1: Short-term RCTs of triple or quadruple low-dose combination therapy

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).

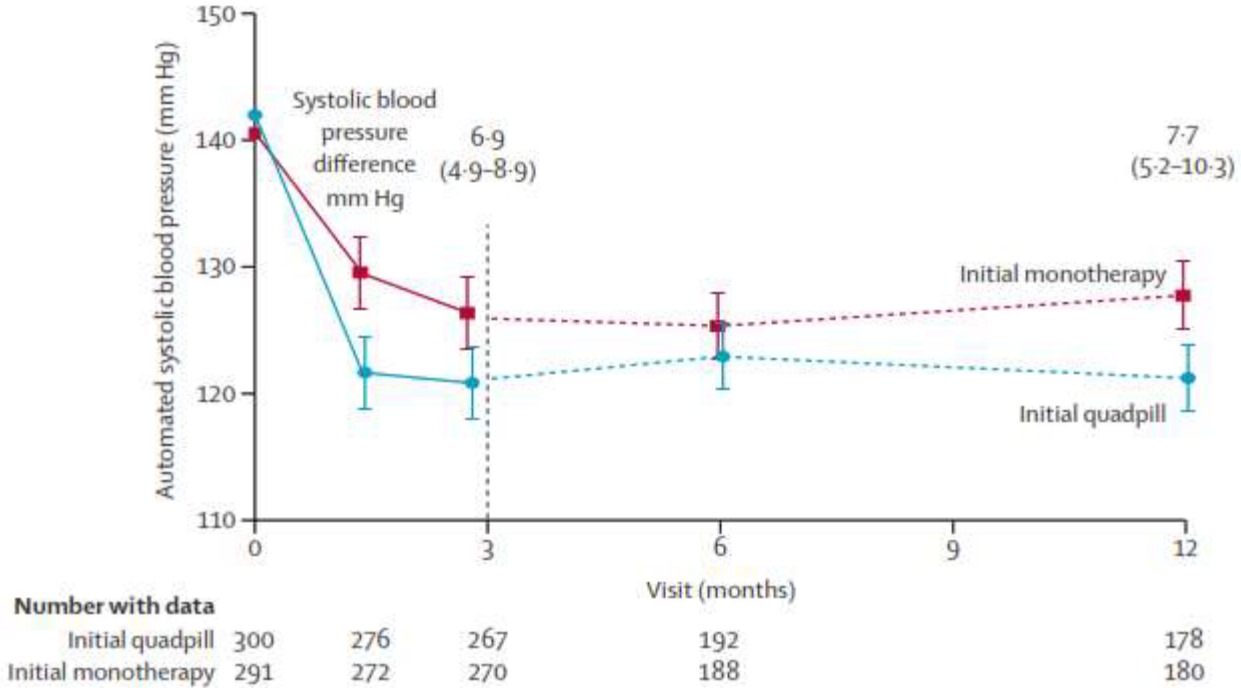
Figure 1: Blood pressure over time in the TRIUMPH trial of triple low-dose combination as initial/early treatment vs usual care for hypertension



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 2**, 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 placebo for lowering BP in adults with hypertension.

6.2. Secondary objectives

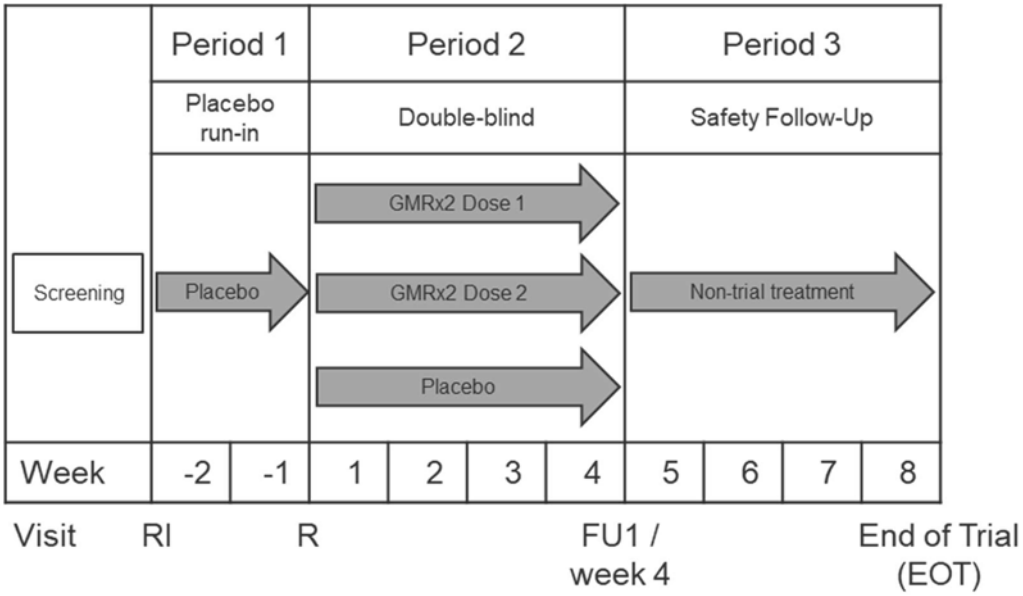
To assess the safety of GMRx2 compared to placebo for the treatment of hypertension in adults.

To assess the longer-term efficacy and safety of GMRx2 in the optional Open-Label Extension Period.

7. TRIAL DESIGN

An international randomized, double-blind, placebo-controlled, parallel-group trial with a 2-week pre-randomization placebo run-in, a 4-week randomized treatment period and a 4-week safety follow-up period or an optional Open-Label Extension period. The overall study design is shown in Figure 3 and 4.

Figure 2: Study design summary



GMRx2 Dose1 = T 10 / A1.25 / I 0.625; GMRx2 Dose2 = T 20 / A 2.5 / I 1.25; T=telmisartan; A=amlodipine; I=indapamide; R = randomization; RI = Run-in; FU = Follow-up. For participants entering the optional open-label extension period, this will begin after week 4 and replace Period 3

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 placebo, i.e. the full effects of GMRx2 compared to no BP-lowering medications. The run-in period will assess participant's adherence to taking medication and completing trial procedures and therefore will enhance the power of the trial to detect difference between GMRx2 and placebo. The double-blind period will assess the efficacy and safety of GMRx2 dose 1 and GMRx2 dose 2 compared to placebo. Double-blinding will avoid any performance bias by investigators and trial participants. The safety follow-up period will assess safety over a 30-day period after discontinuation of the trial medication. The optional Open-Label Extension Period will assess efficacy and tolerability over a one-year period.

7.2. Sub-studies

Participants will be invited to provide venous blood and urine specimens at baseline, 4 weeks and if applicable at 8 weeks visits for use in planned substudy analyses. These samples will be analysed for renal biomarkers[60] and drug metabolite levels.[61, 62] The samples will be immediately processed and stored at −80°C ± 10°C and shipped during or at the end of the study to designated central laboratories for storage until analyses have been completed. In addition, some centers will participate in a sub-study of ambulatory BP measurement and provide participants the option of joining this substudy.

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 poster or flyer, via social media etc.

8.2. Participant Eligibility

The guiding principle of participant eligibility is patients with hypertension who could appropriately be treated with GMRx2 dose version 1 or GMRx2 dose version 2 or placebo.

8.2.1. Inclusion Criteria

At screening visit

1. Provided signed consent to participate in the trial.
2. Adult aged ≥18 years.
3. Low calculated CV risk according to local guidelines such that pharmacological BP-lowering treatment is not mandatory: e.g. Pooled Cohorts Equation 10-years ASCVD risk <10% in the USA.
4. Likely diagnosis of hypertension, defined as one or more of:
   - automated SBP at this clinic visit according to trial methods (see Appendix 2) of ≥130mmHg on no BP lowering medicines or ≥120mmHg on 1 BP lowering medicine that will be stopped at this visit, OR
   - documentation in last 6 months of office SBP ≥ 140 mmHg and/or DBP ≥ 90mmHg on no BP lowering medicines or SBP ≥ 130 mmHg and/or DBP ≥ 85mmHg on 1 BP lowering medicine that will be stopped at this visit, OR
   - documentation in last 6 months of home SBP ≥ 130 mmHg and/or DBP ≥ 80mmHg on no BP lowering medicines or SBP ≥ 120 mmHg and/or DBP ≥ 75mmHg on 1 BP lowering medicine that will be stopped at this visit, OR
   - documentation in last 6 months of ambulatory daytime SBP ≥ 130 mmHg and/or DBP ≥ 80mmHg on no BP lowering medicines or SBP ≥ 120 mmHg and/or DBP ≥ 75mmHg on 1 BP lowering medicine that will be stopped at this visit
5. No contraindication to trial medications, including 2-weeks placebo run-in and 4-weeks randomized treatment period with GMRx2 (dose version 1 or 2) or placebo.

At randomization visit

1. Home seated mean SBP 130-154 mmHg in the week before the randomization visit.
2. Adherence of 80-120% to placebo run-in.
3. Tolerated placebo run-in.
4. Adherence to home BP monitoring schedule: in the week before randomization, at least 6 measures (e.g. ≥2 sets of triplicate measures) including at least 1 morning and 1 evening each with ≥2 measures. 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.

At week 4 (for optional Open-Label Extension Period)

1. Provided signed informed consent.
2. Completed randomized treatment and willing to continue GMRx2-based treatment regimen for 12 months.

8.2.2. Exclusion Criteria

At screening visit

1. Receiving 2 or more 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.
2. Clinic seated mean SBP ≥160 mmHg and/or DBP ≥100 mmHg.
3. 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.
4. Contraindication, including hypersensitivity (e.g. anaphylaxis or angioedema), to the placebo run-in treatment or to any of the trial medications in the three randomized groups.
5. Current/history of transient ischemic attack, stroke, or hypertensive encephalopathy.
6. Current/history of acute coronary syndrome, unstable angina, myocardial infarction, percutaneous transluminal coronary revascularization, or coronary artery bypass graft
7. 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.
8. Current/history of New York Heart Association class III and IV congestive heart failure
9. Current/history of cardiomyopathy or any other cardiovascular condition of sufficient severity to contraindicate the trial medications or require a contraindicated medication.
10. Current/history of a known secondary cause of hypertension, such as primary aldosteronism, renal artery stenosis, pheochromocytoma, or Cushing's syndrome.
11. Current/history of severe uncontrolled diabetes (HbA1c > 11.0% (> 97 mmol/mol)) within the last three months.
12. Current/history of end-stage renal disease or anuria.
13. 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 constitutes a significant risk to the participants' safety or well-being.
14. 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.
15. Currently taking or might need during the trial, a concomitant treatment which is known to interact significantly with the trial medication: digoxin, lithium, diabetics receiving aliskiren, moderate and strong CYP3A4 inhibitors (e.g. ritonavir, ketoconazole, diltiazem], simvastatin >20 mg/day, immunosuppressants.
16. 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).
17. 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.
18. Individuals working >2-night shifts per week.
19. 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.
20. History of alcohol or drug abuse within 12 months.

At randomization visit

1. Unable to adhere to the trial procedures during the run-in period.
2. Any of the following which in the investigator's judgment may compromise the safety or wellbeing 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/low in clinic only; for example, the clinical relevance of 'whitecoat hypertension' is uncertain.

b. High or low home DBP levels. The exact levels of DBP are 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.

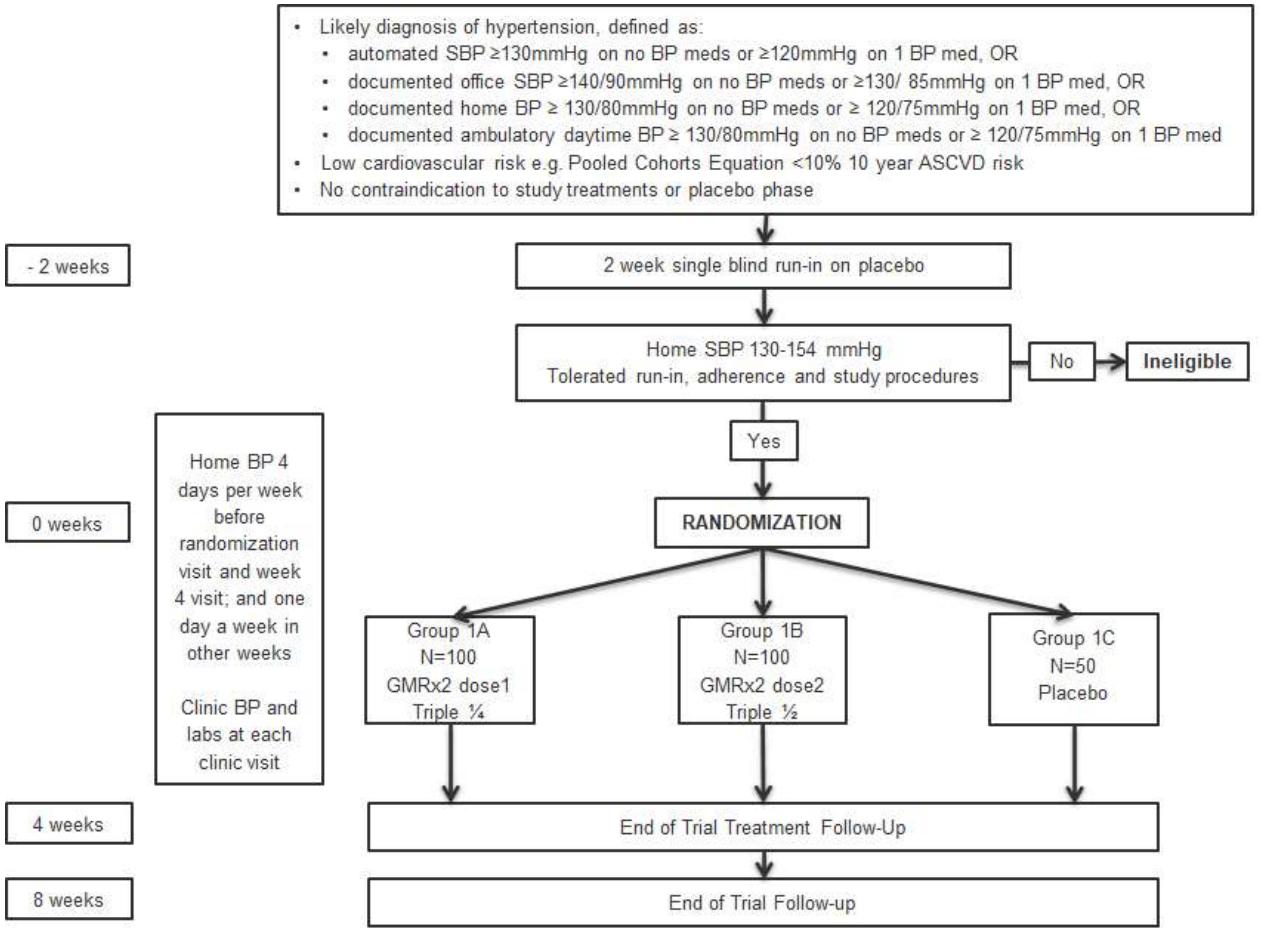
3. Pregnant or had a positive pregnancy test or unwilling to undertake a pregnancy test during the trial and up to 30 days after the discontinuation of the trial medication or breastfeeding or of childbearing age and not using an acceptable method of contraception (defined in the Manual of Procedures). 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 Randomization visit and until the end of trial participation.
4. Current estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m.^{2}
5. 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.
6. Current/history of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal range within 6 months.
7. 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' safety or well-being.
8. Fulfilling any of the exclusion criteria mentioned for the screening visit, when verified again at the randomization visit.

At week 4 (for optional Open-Label Extension Period)

1. Contraindication to open-label GMRx2-based BP-lowering treatment.

8.3. Trial Schema

Figure 43: Trial schema



GMRx2 Dose2 = T20 / A2.5 / I1.25; GMRx2 Dose3 = 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 4

8.4. Intervention

8.4.1. Single-Blind Placebo Run-In Period

During the screening visit, enrolled participants will be asked to discontinue their current BP-lowering drug if applicable and undergo a single-blind placebo run-in period for 2 weeks. 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 2-week single-blind placebo run-in will be followed by a 4-week double-blind period with randomization to one of the following three treatment groups:

Table 4: Treatment groups in the trial

Group	Intervention	N	Treatment
1	GRMx2 Dose version 1: Triple ¼	100	telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg
2	GRMx2 Dose version 2: Triple ½	100	telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
3	Placebo	50	placebo

On the day of randomization visit, all eligible participants will be prescribed and dispensed trial medication to be taken between the randomization and Week 4 visits. Participants will be advised to take one capsule of trial medication once daily in the morning at approximately the same time each day, either before or after breakfast, immediately after taking morning home BP measurement.

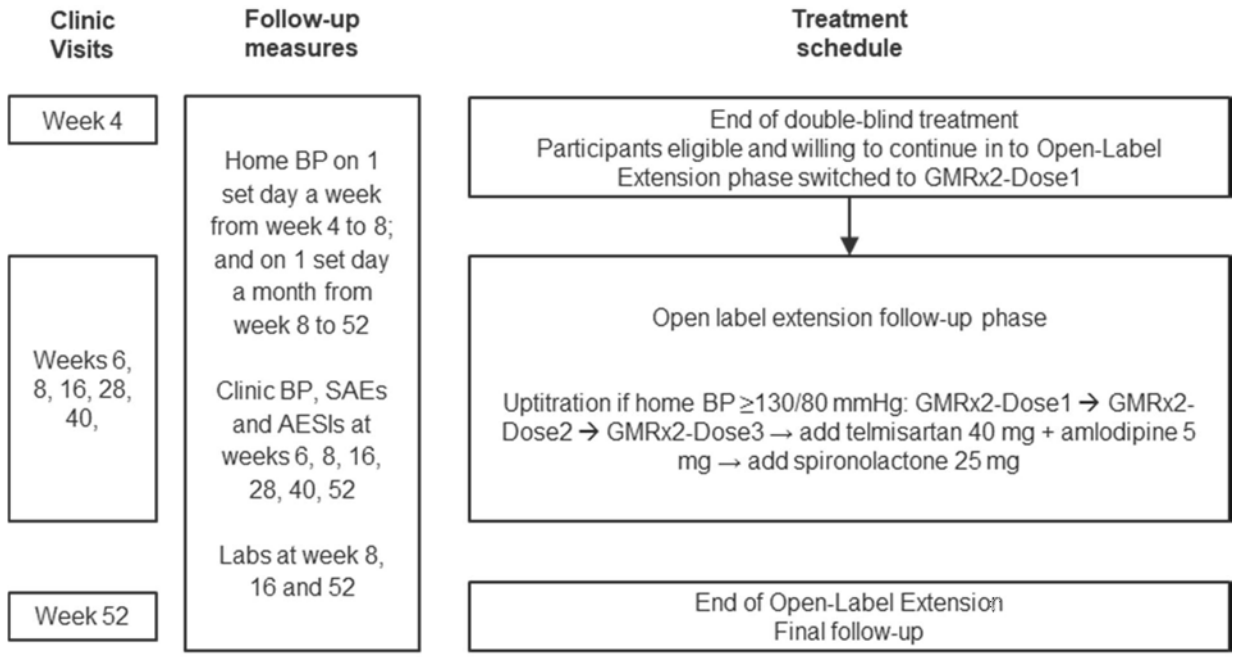
8.4.3. Optional Open-Label Extension Period

In a subset of sites, participants who are still receiving study medication at Week 4 will be invited to continue on to an optional Open-Label Extension Period with the aim to assess effectiveness, safety and adherence over a 52-week period. Willing participants will enter the Open-Label Extension Period at the Week 4 visit, at which time they will be allocated open-label GMRx2-Dose version 1. Follow-up visits will be conducted at Week 6, 8, 16, 28, 40, and end of Open-Label Extension Period visit at week 52 (See Table 6). Participants will continue to monitor BP at home, once per week until the Week 8 visit, and thereafter on a set day every month (e.g. 1st day of the month) until the week 52 visit. Home BP measurements will be made using a validated, electronic, automatic, digital upper-arm cuff and recorded in a home BP diary, as specified in the Blood Pressure Monitoring Manual of Procedures. During follow-up visits, if home BP from the most recent measurement is above 130 mm Hg for SBP and/or above 80 mmHg for DBP, BP-lowering therapy will be up-titrated in the following order: GMRx2-Dose1 → GMRx2-Dose2 → GMRx2-Dose3 (telmisartan 40mg/amlodipine 5mg/indapamide 2.5mg) → GMRx2-Dose3 plus telmisartan 40 mg/amlodipine 5 mg → GMRx2-Dose3 plus telmisartan 40 mg/amlodipine 5 mg plus spironolactone 25 mg. The rationale for this regimen is based on the evidence indicating that:

- About 80% of the maximum BP-lowering effects of BP-lowering regimens are achieved by 2 weeks[60]
- US hypertension guidelines recommend a home BP target of <130/80 mmHg[25]
- Up-titration steps should provide clinically meaningful BP reductions – the BP reductions of only 2-3/1-2 mmHg achieved by increasing the dose of a single drug are likely to be only modestly effective and such steps can act as barriers to effectively achieving BP goals.[50] Doubling the dose of telmisartan 40 mg/amlodipine 5 mg achieves an additional 5/4 mmHg reduction,[61] and the use of concomitant ARB therapy reduces the incidence of pedal oedema associated with higher dose amlodipine.[59,61] The Pathway-2 trial demonstrated that a mineralocorticoid receptor antagonist is superior to a beta-blocker or an alpha-blocker in patients not controlled on maximal doses of three drugs.[62]

If necessary, participants can be stepped down to a lower dose option; or switched to other treatment or withdrawn from all BP-lowering treatment, temporarily or permanently. If there is a delay in receiving OLE IMP at site, participants can temporarily switch to open label telmisartan until the OLE IMP arrives.

Figure 4: Schema for Open-Label Extension



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.

During the randomized treatment period, 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. due to possible hypotension) that is severe enough to warrant discontinuation of the trial medication, then the Investigator can choose to discontinue the trial medication temporarily. The reason for discontinuation will be recorded. There is no need to unblind trial medication in this situation. Consideration should also be given to restarting trial 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 the Trial Medication

Discontinuation of trial medication occurs when a randomized participant permanently ceases taking the trial medication, regardless of the circumstances, before the Week 4 visit. Early discontinuation must be reported immediately to the CRO and recorded in the study database, including the reason for discontinuation. 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 8. For withdrawal from trial participation, see Section 13, page 35.

8.9. Post-Trial Medication

At either the Week 4 visit or after the Open-Label Extension Period, 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 4.

9.1.2. Secondary

- Difference in change in clinic seated mean SBP from randomization to Week 4.
- Difference in change in home seated mean DBP from randomization to Week 4.
- Difference in change in clinic seated mean DBP from randomization to Week 4.
- Percentage of participants with clinic seated mean SBP <140 and DBP <90 mmHg at Week 4.
- Percentage of participants with clinic seated mean SBP <130 and DBP <80 mmHg at Week 4.
- Difference in change in trough home seated mean SBP from randomization to week 4.
- Difference in change in trough home seated mean DBP from randomization to week 4.
- Percentage of participants with home seated mean SBP <135 and DBP <85 mmHg at Week 4.
- Percentage of participants with home seated mean SBP <130 and DBP <80 mmHg at Week 4.

9.2. Safety Outcomes

9.2.1. Primary

- Percentage of participants discontinued trial medication due to AEs/SAEs from randomization to Week 4.

9.2.2. Secondary

- Percentage of participants with an SAE from randomization to Week 4.
- Percentage of participants with symptomatic hypotension from randomization to Week 4.
- Percentage of participants with serum sodium concentration below 135 mmol/l at Week 4.
- Percentage of participants with serum sodium concentration above 145 mmol/l at Week 4.
- Percentage of participants with serum potassium concentration below 3.5 mmol/l at Week 4.
- Percentage of participants with serum potassium concentration above 5.5 mmol/l at Week 4.
- 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 4.
- Percentage of participants with eGFR drop of over 30% from randomization to Week 4.
- Percentage of participants with postural hypotension at Week 4
- Percentage of participants with postural hypertension at Week 4

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 placebo run-in period.
- All AESI and SAEs, by severity and by System Organ Class (SOC) criteria during the run-in period, by trial medication group during the randomized treatment period, and safety follow-up period or Open-Label Extension Period.

9.3. Outcomes for those participating in the Open-Label Extension Period

- Descriptive, non-comparative data on mean BP, BP control and the safety outcome measures outlined in Sections 9.1 and 9.2 will be reported on the cohort of participants entering the Open-Label Extension Period.

10. PARTICIPANT TIMELINE & ASSESSMENTS

10.1. Schedule of Evaluations

Table 5 outlines the trial visits schedule and assessments for participants in the trial who do not enter the optional Open-Label extension period; for those who do enter the Open-Label Extension period, **Table 6** outlines the visits schedule from Week 4 onwards. It should be noted that there is flexibility in the timing of blood and urine collection tests before randomization as noted in **Table 5**, to suit participant preferences and local clinic feasibility and ease of scheduling, with the proviso that all of the requirements for eligibility at Screening and Randomization are met, as outlined in Section 8.2.

Table 5: Trial visits schedule and assessments: Randomization and Safety Follow-up Periods

Visit Name	PRE-SCREEN (Optional)	SCREEN (Run-in start)	RAND (Run-in end)	FU1 (End of trial medication)	EOT[5] (Telephone safety FU)
Visit Week	Week -4	Week -2		Week 4	Week 8
Visit Day *(Visit window days)*	-28	-14 *(-12 to -21)**		28 (±7)*	56 (±7)*
Written informed consent[1]	✓	✓			
Eligibility (inclusion & exclusion)	✓	✓	✓		
Medical history	✓	✓			
Physical examination[2]		✓			
Demographics		✓			
Anthropometrics – Height, weight		✓			
Clinic BP, standing BP, pulse		✓	✓	✓	
12-lead electrocardiogram (ECG)		✓			
Cardiovascular risk assessment		✓			
Dispensing of home BP monitor		✓			
Home BP monitoring		→	→	→	
Home BP monitor brought to clinic			✓	✓	
24-hour ambulatory BP measurement if participating in substudy				✓	
Blood Collection					
Study bloods[3]		✓		✓	
Follow-up creatinine with eGFR[4]					✓[4]
Pregnancy test if childbearing potential		✓			
Blood sample for storage for substudy		✓		✓	
Urine Collection[3]					
Albumin-creatinine ratio		✓		✓	✓[4]
Urine sample for storage for substudy		✓		✓	✓[4]
Medications					
Discontinue BP lowering medication (if applicable)	✓	✓			
Dispensation of run-in medication		✓			
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 at pre-screening.

[2] Systems-based examination deemed necessary for the safety of participants by the site investigator

[3] The following blood and urine tests should be taken at a time most suitable for the participant at Screening visit or during run-in so that results are available for review at the RAND visit, and during Week 4 (ie. at the week 4 final visit or in the preceding week):

- Fasting glucose
- Fasting lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol)
- HBA1c - for participants with diabetes without a HBA1c in past 3 months; repeat measure not required at Week 4
- Complete blood count (red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, reticulocyte count, white blood cell count, platelet count)
- Liver function (bilirubin, albumin, total protein, gamma-glutamyl transferase, alkaline phosphatase, aspartate transaminase and alanine transaminase)

- Sodium, potassium, chloride
- Calcium
- Creatinine with eGFR
- Uric acid
- Thyroid-stimulating hormone; repeat measure not required at Week 4
- Blood sample for storage for substudy (if participating)
- Urine albumin-creatinine ratio
- Urine sample for storage for substudy (if participating)

All laboratory investigations and ECG will be performed at the trial site or local laboratory. If blood test results are not available on the same day as the 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, trial medication and home BP monitor may be couriered to the participant's home once eligibility is confirmed.

[4] At Week 8, only for participants who have had ≥30% reduction in eGFR and/or ≥30% increase in serum creatinine between RAND and Week 4 visits

[5] If participating in Open-Label extension phase, see Table 6 for additional assessments at Week 4 and thereafter

* If a screening visit is rescheduled, then the randomization date should be scheduled/rescheduled so that the length of the run-in period remains at least 12 days. Option to extend run-in by up to 1 week if there have been technical or administrative issues with BP machine use and or measurement protocol. Ideally there should not be a gap between the end of Run-in period and Randomization. Post-randomization visit dates should not be altered i.e. should remain at the scheduled time since randomization.

EOT=End of trial; FU=Follow up; PRESCREEN=Pre-screening; RAND=Randomization; SCREEN=Screening

Table 6: Trial visits schedule and assessments for participants in Open-Label Extension Period

Visit Name	Commence Open-Label Extension	OLE FU1	OLE FU2	OLE FU3	OLE FU4	OLE FU5	OLE EOT
Visit Week	Week 4	Week 6	Week 8	Week 16	Week 28	Week 40	Week 52
Visit window days	*(±7)*	*(±7)*	*(±7)*	*(±14)*	*(±14)*	*(±14)*	*(±14)*
Written informed consent	✓						
Eligibility for open-label period	✓						
Clinic BP, standing BP, pulse		✓	✓	✓	✓	✓	✓
Home BP monitoring		→	→	→	→	→	→
Home BP monitor brought to clinic		✓	✓	✓	✓	✓	✓
Blood Collection*							
Fasting glucose							✓
Fasting lipid profile[1]							✓
Sodium, potassium, chloride			✓	✓			✓
Creatinine with eGFR			✓	✓			✓
Uric acid							✓
Urine Collection*							
Albumin-creatinine ratio			✓[2]				✓
Urine sample for storage for substudy			✓[2]				
Medications							
Dispensation of trial medication	✓	✓	✓	✓	✓	✓	
Return of trial medication		✓	✓	✓	✓	✓	✓
Adherence to trial medication		✓	✓	✓	✓	✓	✓
Review of concomitant medications		✓	✓	✓	✓	✓	✓
Safety							
AESI or SAE		→	→	→	→	→	→

[1] Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol

[2] At Week 8, only for participants who have had ≥30% reduction in eGFR and/or ≥30% increase in serum creatinine between baseline and Week 4 visits

* All laboratory investigations will be performed at the trial site based local laboratory. Local practice can be followed whether the blood draws are done before, at or following each clinic visit. Any other investigations at discretion of site investigator
EOT=End of trial; FU=Follow up

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 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. 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 measurement should be at the same time in the morning and evening on each measurement day and 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 and Week 4 trial visits, BP measurements should be taken on the 4 days immediately prior to the day of the on-site Randomization visit. In other weeks, measurements should 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 44. Telemonitored BP values will be monitored for adherence with measurement schedules and high values (as noted in Section 8.6, page 23), with reporting to the clinic 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 continue to use the same home BP monitor.

10.2.9. 24-hour ambulatory BP measurement

24-hour ABPM will be performed prior to Week 4 visit for participants in the ABPM substudy. Accordingly, participants will be asked to visit trial site 1 to 7 days before the end of trial medication visit for the placement of ABPM device on the participant for 24-hours.

10.2.10. Cardiovascular Risk Assessment

Cardiovascular risk assessment will be conducted by the study investigator, in accordance with the local guideline recommended algorithm or estimator. For example, the ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) to estimate 10-year risk of atherosclerotic CVD (ASCVD) recommended by the 2017 ACC/AHA hypertension guideline. Note if a patient input value is out of range for the calculator, use the nearest value and clinical judgement eg. when using the ACC/AHA calculator for an 18 year old, enter age 20 years and use clinical judgement that this will be a slight overestimate of absolute risk.

10.2.11. 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.

10.2.12. 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. Blood and urine sample collected for urinary biomarkers and adherence will be stored and shipped to a central laboratory for analysis.

10.2.13. Allocation of Trial Medication

During the single-blind run-in period (Week -2 and Week -1, inclusive) all participants will be allocated placebo. During the double-blind period (Week 1 to Week 4, inclusive) all participants will be allocated GMRx2 dose version 1(Triple ¼), GMRx2 dose version 2 (Triple ½) or placebo. 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 4, participants not entering the Open Label Extension Period will be switched to non-trial medication as per local guidelines/practice.

10.2.14. Dispensation of Trial Medication

Starting at the screening visit (Week -2), participants will receive sufficient quantities of the trial medication until the next scheduled trial visit. In the case of dispensed treatment lost/damaged, 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 the two scheduled trial visits, trial medication delivery will be arranged to the participant's location. Delivery of trial medication to the participant's location may also occur in other circumstances and where feasible e.g. if blood test results are not available at the time of the randomization visit 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.

10.2.15. Returning of Trial Medication

Trial participants will return all unused randomized trial medication to the sites at Week 4 (or prior in some circumstances – e.g. discontinuation of treatment) and at respective visits for the open label extension period. Sites will collect all the returned trial medication and keep an accurate record for inspection at all times.

10.2.16. 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. Prescription of non-trial BP-lowering drugs will only be allowed as noted in Section 8.6, page 23. 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 over the phone.
- Assess potential participant's interest for participation and eligibility for the trial.
- Discuss the trial with the potential participant, including using the PISCF, and obtain signed informed consent. Potential participants may be provided time to consider their participation, with a follow-up visit arranged as needed.
- Consider stopping current BP monotherapy to facilitate trial eligibility, if clinically appropriate and considered safe. Informed consent must be obtained before the modification of medication.
- If locally preferred and/or feasible, blood tests can be pre-arranged following informed consent.
- The pre-screening visit can be repeated up to 3 times, as needed

10.3.2. Screening Visit

- Assess the potential participant's interest and eligibility for the trial.
- Discuss the trial with the potential participant, including using the PISCF, and obtain signed informed consent. This can also be done before the screening visit. The potential 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.
- Review all medication currently being taken.
- Measure height and weight.
- Measure BP and pulse.

- Perform 12-lead ECG.
- Collect blood and urine samples, including for pregnancy, (if applicable) or arrange for these tests to be completed during the run-in period. Results must be reviewed and eligibility confirmed prior to randomization, but are not required for review prior to the beginning of the placebo run-in.
- Collect sub-study blood and urine samples (if applicable) – these can also be collected during run-in or at the randomization visit if preferred.
- Assess eligibility as per the trial inclusion and exclusion criteria.
- Consider stopping current BP monotherapy to facilitate trial eligibility, if clinically appropriate and considered safe. Informed consent must be obtained before the modification of medication. If medication is altered, a period of at least 14 days is required between alteration of BP treatment and trial randomization (ie the minimum placebo run-in duration is 14 days). In situations in which it is not deemed clinically appropriate to stop BP monotherapy for the trial duration, such participants should be regarded as ineligible.
- Demonstrate home BP measurement and dispense home BP monitor (record serial number) to participant.
- Dispense run-in medication as soon as possible.

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 randomization. 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. Randomization Visit

- Measure BP and pulse.
- Record any AESIs/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 laboratory results. If laboratory results are not available for review prior to or on the same day end of the 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 by courier to the participant's home.

- Collect sub-study urine and blood for storage (if applicable and not collected during the run-in period).
- Review home BP measurement technique.
- Assess eligibility as per the trial inclusion and exclusion criteria.
- Confirm that participant is suitable to be randomized. If not, collect home BP monitor and thank for participation. If suitable, randomize participant.
- Dispense treatment according to the allocated kit number selected by IBM database (eCRF).
- Advise participant to visit the site 1 or 7 days before the Week 4 visit for the placement of the ABPM device, if participating in ABPM substudy.

10.3.6. ABPM Device Placement Prior to Week 4 Visit (if applicable)

- To be conducted 1-7 days prior to Week 4 Visit
- Initialize and program the ABPM device, place on the participant and provide instructions on use.
- Instruct the participant to return the device to the site after completing 24 hours of ABPM.

10.3.7. Week 4 Visit

All participants

- If applicable, collect the ABPM device, download the data, check if 24-hour ABPM was successful. If unsuccessful, repeat within 48 hours and delay the Week 4 visit.
- Measure BP and pulse.
- Record AESIs/SAEs since the previous visit.
- Collect fasting blood and urine samples.
- Collect sub-study urine and blood for storage (if applicable)
- Review all medications being taken by the participant and update concomitant medications.
- Collect unused trial medication and review medication adherence

If the site is participating in Open-Label extension, invite all participants still receiving trial medication to participate.

Participants continuing in the Open-Label Extension period – go to Section 10.3.9

Participants not continuing in the Open-Label Extension period:

- Collect home BP monitor.
- Ask participants to report any AEs during the next 4 weeks after the end of trial medication.
- Record AESIs/SAEs since the previous visit.
- Collect blood and urine sample
- Review all medications being taken by the participant and update concomitant medications.
- Stop trial medication and prescribe alternate BP-lowering treatment in line with local guidelines/practice.
- Explain that the trial follow-up is now completed and thank participant.

10.3.8. Week 8 visit (End of Trial Visit for participants not continuing in the Open-Label Extension Period)

- Contact participant by telephone.
- Record AESIs or SAEs since the previous visit.
- Review all medications being taken by the participant and update medications.
- Arrange blood and urine for participants who have had ≥30% reduction in eGFR and/or ≥30% increase in serum creatinine between baseline and week 4 visits
- Explain that the trial follow-up is now completed and thank participant.

10.3.9. Week 4 Commence Open-Label Extension Period (selected sites only)

- Obtain consent for Open-Label Extension Period
- Switch from randomized treatment to Open-Label GMRx2 Dose1, as outlined in 8.4.3, page 22.

- Fora device will be collected and new BP monitor will be issued

10.3.10. Week 6, 8, 16, 28, 40 (for Open-Label Extension Period only)

- Measure clinic BP and pulse.
- Record AESIs/SAEs since the previous visit.
- Arrange blood and urine for participants who have had ≥30% reduction in eGFR and/or ≥30% increase in serum creatinine between baseline and week 4 visits (Week 8 only)
- Collect blood sample (Week 16, 28).
- Review all medications being taken by the participant.
- Collect unused study medication (if applicable).
- Continue medication as is or titrate according to GMRx2 treatment regimen
- Dispense study medication (if applicable).

10.3.11. Week 52 Visit (for Open-Label Extension Period only)

- Measure clinic BP and pulse.
- Record AESIs/SAEs since the previous visit.
- Collect blood and urine samples.
- Review all medications being taken by the participant.
- Collect unused study medication (if applicable).
- Stop study medication and prescribe alternate BP-lowering treatment in line with local guidelines/practice.
- Ask participants to report any AESIs/SAEs during 14 days after the end of study medication
- 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.[63] 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.[63] 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 total of 250 participants will be randomized, with a 2:2:1 ratio of triple ¼: triple ½ : placebo, which is likely to necessitate over 300 entering the placebo run-in treatment period. Assuming a common standard deviation of 11 mmHg, this sample size will provide >90% power to detect differences in mean home SBP of 9 mmHg and 13 mmHg respectively for the comparisons of triple ¼ vs placebo and triple ½ vs placebo, respectively. For the comparison of triple ¼ vs triple ½ there will be >80% power to detect a difference of at least 4.5 mmHg in mean home SBP.

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 4 will be analyzed using a mixed model with baseline BP and treatment group as fixed effect and accounting for 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 4 will be summarized descriptively and analyzed using a generalized estimating equation to account for clustering at the site level. Percentages by treatment groups with 95% CI will be presented along with the associated estimated RR 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 8-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 (Period 1 (Run-in) or Period 2 as in Figure 3) is not available at the centre, the participant should delay the start of Run-in, which may necessitate rescreening. If a participant is on Run-in but Period 2 study treatment is not available, then randomization should be delayed, which may necessitate extending or repeating run-in.

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 8 EOT visit for the double-blind period. For participants continuing in the Open-Label Extension Period, AESIs/SAEs will be collected up to and including the Week 52 visit. Follow-up information on ongoing AESIs/SAEs obtained after the participant's respective EOT visit (as applies) will not be collected in the eCRF.

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 monitored by the Sponsor, including 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; and input by the Steering Committee.

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[64] and will be performed using a supplied FORA D40g BP machine (also known as Medisanté BP800 machine),[65, 66] which is a validated, electronic, automatic, digital upper-arm cuff monitor,[67] 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 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.
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, available only in some 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 at all clinic visits) 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 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[64] with reference to recent trials and clinical use.[68, 69] During the run-in and randomised treatment periods, 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. During the OLE period, BP measurements will be performed using a supplied validated, electronic, digital upper-arm cuff, with measurements recorded in a home BP diary.

During the run-in and randomised treatment periods, home BP will be measured according to the following schedule:

- on four consecutive days immediately prior to the trial visit (i.e. Weeks -1, and 3), 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.

During the OLE period, home BP will be measured according to the following schedule:

- once per week until the Week 16 visit, and thereafter on a set day every month (e.g., 1st day of the month) until the Week 52 visit.
- 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 BP measurements should be immediately before the next trial medication dose.

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 23. Past use does not contraindicate eligibility as long as a period of at least 2 weeks or 5 half-lives (whichever is longer) has elapsed 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 (e.g. 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-PCT1
Indication: Hypertension

GEORGE MEDICINES CHIEF INVESTIGATOR

Signature [redacted]

Date 3 Jan 2024

Name [redacted]

Title [redacted]

TRIAL SITE INVESTIGATOR

Trial Site Name

Signature _____

Date _____

Name _____

Title _____

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