George Medicines

STATISTICAL ANALYSIS PLAN

Trial Title	Efficacy and safety of GMRx2 (a single pill combination containing telmisartan/amlodipine/indapamide) compared to dual combinations for the treatment of hypertension: An international, multi-center, randomized, double-blind, active-controlled, parallel-group trial
Brief Title	Efficacy and safety of GMRx2 compared to dual combinations for the treatment of hypertension
Phase of Development	Phase III
Trial Drug	GMRx2: Single pill combination of telmisartan/amlodipine/indapamide Dose version 2: telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg Dose version 3: telmisartan 40 mg/amlodipine 5 mg/indapamide 2.5 mg
Trial Number	GMRx2-HTN-2020-ACT1
Indication	Hypertension
Version	Version 2.0, 18 November 2023
Trial Registration	Clinicaltrials.gov NCT04518293
Funder	George Medicines Pty Limited

Amendment

SAP Amendment Number	Amendment date
2.0	18 November 2023

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Appendices

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1 ADMINISTRATIVE INFORMATION

1.1 Trial Identifiers

- Protocol Number: GMRx2-HTN-2020-ACT1, Version 6.0, Date 10 October 2023

1.2 Revision History

Version	Date	Details
0.1 (draft)	25JUN2020	First draft by Sandrine Stepien
0.2 (draft)	31JUL2020	Analysis sets updated Multiplicity adjustment updated Incorporate comments Add table shells
0.3 (draft)	14AUG2020	Add some shells, reference tables in text, list of listing added
1.0	17AUG2020	CKD-epi formula for eGFR. Graph example added Re-order of secondary outcomes
1.1 (draft)	23JUN2021	Revise SAP according to protocol version 3.0 including: exclusion criteria, addition of standing blood pressure measurement at clinic visits, addition of outcome of any abnormality of sodium or potassium, change of home blood pressure weekly derivation revision of imputation method and added description align table shells with latest SAP
1.2 (draft)	05NOV2021	Revise SAP according to protocol version 4.0.
1.3 (draft)	10MAY2022	Revise SAP according to protocol version 5.0 Added sensitivity analysis adjusting for relevant baseline covariates. Added single interim power analysis using the observed standard deviation and targeted treatment effect. Changed from endpoint analyses with timing based on calendar week to timing based around clinic visits.
1.4	24AUG2022	Added fields to listings (and removed duplicates) Consistently referred to amlodipine and indapamide as “AI”, not “IA””
1.5	24JAN2023	Added estimands to analyses Miscellaneous minor refinements to TLFs
1.6	14JUN2023	Modified definitions of analysis sets and estimand framework. Added further clarification on approach for primary outcome analyses. Miscellaneous minor refinements to TLFs.
2.0	17NOV2023	The Statistical Analysis Plan was updated following Type C meeting and correspondence with the US FDA (02Aug2023): • Editorial changes for increased clarity, including sections for general methods, computing environment, baseline derivations, and an expanded plan for analysis of baseline assessments • Expansion of Sample Size calculations • Clarifications of estimands, multiple imputations, primary endpoint analysis methods, including Mixed Models for Repeated Measures, and secondary endpoint analysis methods • Addition of tipping point analysis

		Additional editorial modifications were made to align with Protocol updates to Version 6.0

1.3 Contributors to The Statistical Analysis Plan

Name	Affiliation	Responsibility
[redacted]	[redacted]	Prior trial statistician (until November 2021)
		Principal (blinded) statistician
		Blinded statistician
		Steering Committee member
		Steering Committee member
		Blinded statistician

1.3.1 Approvals

The undersigned have reviewed this statistical analysis plan (SAP) and approve it as final.

Signature	**Date**
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

2 INTRODUCTION

2.1 Trial Objective

This trial is an international, multi-center, parallel-group, double-blind, randomized, controlled trial to investigate the efficacy and safety of GMRx2, a fixed-dose combination of telmisartan, amlodipine and indapamide compared to three dual combinations of the component drugs for the treatment of hypertension.

Section 5 of the Protocol introduces the history and development of combination therapies for treatment of hypertension and describes the potential role of triple low-dose combination and expected effects.

This statistical analysis plan (SAP) defines derivations, algorithms, key components, and statistical analysis methods to be applied in the analysis and summary of data collected in the study GMRx2-HTN-2020-ACT1. Sample SAS programming code is provided for a select group of statistical models. This code is provided as example and may require modifications to accommodate the data collected.

2.2 Trial Population

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

2.2.1 Inclusion Criteria

At screening visit:

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

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

At randomization visit:

- Home seated mean SBP 110-154 mmHg in the week prior to the randomization visit.
- Adherence of 80-120% to run-in medication.
- Tolerated run-in medication.
- 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.

2.2.2 Exclusion Criteria

Section 8.2.2 of the protocol delineates exclusion criteria at screening visit and at randomization visit. Key exclusion criteria as follows.

At screening visit:

1. Receiving 4 or more BP-lowering drugs.
2. Receiving any BP lowering drugs for indications other than hypertension e.g. heart failure.
3. Pregnant or had a positive pregnancy test or unwilling to undertake a pregnancy test during the trial and up to 30 days after the discontinuation of the trial medication or breastfeeding or of childbearing age and not using an acceptable method of contraception. Acceptable methods of birth control include Hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g. condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization. Contraception should be used for at least 1 month before the screening visit and until the end of trial participation.
4. Meets any criteria of local ethical or regulatory requirements related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that would deem participation in a clinical trial unsuitable.
5. Contraindication, including hypersensitivity (e.g. anaphylaxis or angioedema), to the active run-in treatment or to any of the trial medication options in the four randomized groups.
6. Current/history of transient ischemic attack, stroke, or hypertensive encephalopathy.
7. Current/history of acute coronary syndrome, unstable angina, myocardial infarction, percutaneous transluminal coronary revascularization, or coronary artery bypass graft.
8. Current atrial fibrillation. Patients with a history of paroxysmal atrial fibrillation are potentially eligible as long as there has been no episode in the last 3 months, while patients with a history of persistent or permanent atrial fibrillation are not eligible.
9. Current/history of New York Heart Association class III and IV congestive heart failure.
10. Current/history of cardiomyopathy or any other cardiovascular condition of sufficient severity to contraindicate the trial medications or require a contraindicated medication.
11. Current/history of a known secondary cause of hypertension, such as primary aldosteronism, renal artery stenosis, pheochromocytoma, or Cushing's syndrome.
12. Current/history of severe uncontrolled diabetes (HbA1c > 11.0% (> 97 mmol/mol)) within last three months.
13. Current/history of end-stage renal disease or anuria; or current estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2.
14. Current electrolyte levels that would be regarded as contraindications for any of the potential treatment arms e.g. serum sodium <132mmol/l or >148 mmol/l or serum potassium <3.1 mmol/l or >5.6mmol/l.
15. Current/history of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal range within 6 months.
16. Current concomitant illness or physical impairment or mental condition that in the judgment of the investigator could interfere with the effective conduct of the trial or constitutes a significant risk to the participants' safety or well-being.
17. Arm circumference that is too large or too small for available cuffs to allow accurate measurement of BP. Upper limit is 55cm in all countries, while lower limit is 15cm or 24cm in different countries, depending on available cuff sizes.
18. Currently taking or might need during the trial, a concomitant treatment which is known to interact with one or more of the trial medications: digoxin, lithium, diabetics receiving aliskiren, moderate and strong CYP3A4 inhibitors (e.g. ritonavir, ketoconazole, diltiazem], simvastatin >20 mg/day, immunosuppressants.
19. Might need treatment with drugs that are prohibited during the trial: other antihypertensive drugs, endothelin receptor antagonists, neprilysin inhibitors, or other drugs that may affect BP.
20. Current surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of trial drugs such as prior major gastrointestinal tract surgery (e.g. gastrectomy, lap band, or bowel resection) or acute flare of inflammatory bowel disease within one

year.

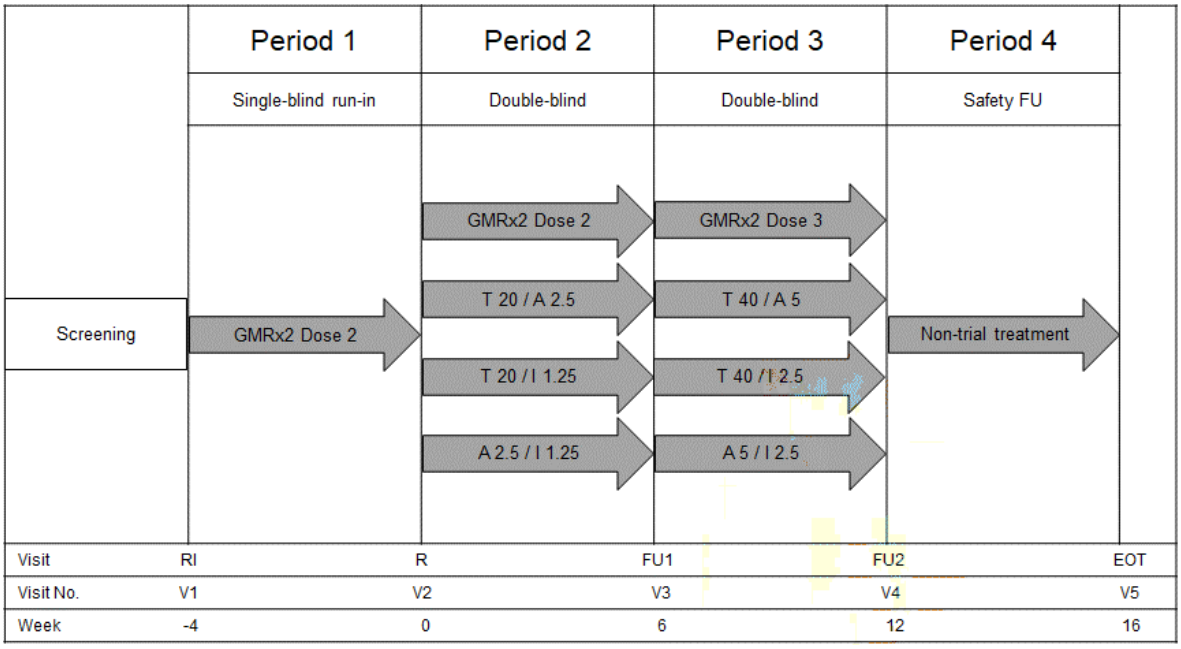
21. Individuals working >2 nightshifts per week.
22. Participated in any investigational drug or device trial within the previous 30 days. This does not include participants in the extended safety follow-up portion of a trial.
23. History of alcohol or drug abuse within 12 months.

At randomization visit:

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

2.2.3 Trial design

The trial design is described in detail in Section 7 of the protocol, with the following figure summarising the overall design:



GMRx2 Dose2 = T 20 / A 2.5 / I 1.25; GMRx2 Dose3 = T 40 / A5 / I 2.5; T = telmisartan; A = amlodipine; I = indapamide; RI = run-in; R = randomization; FU = follow-up; EOT = end of trial; V = visit; Forced up-titration at FU1; EOT will be telephonic.

Of particular note are the two study visits Week 6/Follow-up 1 (FU1) and Week 12/Follow-up 2 (FU2). Preceding both visits, participants will be requested to perform extra home BP measurements in the week running up to the clinic visit. At FU1, all participants are expected to be up-titrated to the higher level of study drug, unless there is a specific contraindication, such as symptomatic hypotension. At FU2, the participant will complete the double-blinded part of the trial and continue on non-trial treatment in a safety follow-up period. Although time periods have been nominated (6 weeks for FU1 and 12 weeks for FU2) these are indicative only and actual time periods may vary within an expected window, as specified within the study protocol.

2.3 Intervention

2.3.1 Treatment Groups

The trial will comprise an approximately 4-week single-blind active run-in on GMRx2 dose version 2 (telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg), followed by a double-blind period (targeted at 12 weeks) with randomization to one of the following four treatment groups:

1. **Triple – TAI: (GMRx2)** telmisartan (T) 20 mg/amlodipine (A) 2.5 mg/indapamide (I) 1.25 mg.
   At Follow-up visit 1, forced up-titration to
   telmisartan 40 mg/amlodipine 5 mg/indapamide 2.5 mg
2. **Dual – TA:** telmisartan 20 mg/amlodipine 2.5 mg.
   At Follow-up visit 1, forced up-titration to telmisartan 40 mg/amlodipine 5 mg
3. **Dual – TI:** telmisartan 20 mg/indapamide 1.25 mg.
   At Follow-up visit 1, forced up-titration to telmisartan 40 mg/indapamide 2.5 mg
4. **Dual – AI**: amlodipine 2.5 mg/indapamide 1.25 mg.
   At Follow-up visit 1, forced up-titration to amlodipine 5 mg/indapamide 2.5 mg

2.3.2 Randomization

Randomization (permuted with variable block sizes and stratified by trial site) will be conducted via a password-protected, secure website/interactive voice response service. Following successful randomization, each participant will be assigned a unique 'participant study number' and be assigned to receive either GMRx2 or one of the three dual combination of Blood Pressure (BP) lowering drugs. The ratio of randomization will be 2:1:1:1, i.e. GMRx2 assigned to twice more participants than each of the dual combinations:

1. **Triple – TAI** (GMRx2): N=600
2. **Dual – TA:** N=300
3. **Dual – TI:** N=300
4. **Dual – AI**: N=300

Study participants, treating clinicians, study investigators and data collectors will be blinded to treatment group allocation.

2.3.3 Changes & Additions on Trial Medication

Sections 8.6, 8.7 and 8.8 of the protocol describe the different possible changes and additions on trial medication:

1. Add-on non-study treatments for participants with high BP,
2. Down-titration or temporary cessation of trial medication,
3. Temporary change from investigational medicinal product (IMP) to open label therapy arising from

pandemic-related IMP supply shortages,
4. Early discontinuation of the trial medication.

Add-on non-study treatments, down-titration and temporary cessation as described in the protocol will aim to retain participants on trial medication while addressing symptoms and/or out of range blood pressure levels. For early discontinuation of trial medication, the participant will be followed-up until the end of the trial unless the participant withdraws consent. In all these scenarios, there is no need to unblind the participants – the specific scenarios for unblinding are referred to in the protocol Section 11.4.

2.4 Outcomes

2.4.1 Efficacy Outcomes

2.4.1.1 Primary

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

2.4.1.2 Secondary

- Difference in change in clinic seated mean SBP from randomization to follow-up Week 12.
- Difference in change in clinic seated mean SBP from randomization to follow-up Week 6.
- Difference in change in clinic seated mean DBP from randomization to follow-up Week 12.
- Difference in change in clinic seated mean DBP from randomization to follow-up Week 6.
- Percentage of participants with clinic seated mean SBP <140 and DBP <90 mmHg at follow-up Week 12.
- Percentage of participants with clinic seated mean SBP <140 and DBP <90 mmHg at follow-up Week 6.
- Percentage of participants with clinic seated mean SBP <130 and DBP <80 mmHg at follow-up Week 12.
- Percentage of participants with clinic seated mean SBP <130 and DBP <80 mmHg at follow-up Week 6.
- Difference in change in home seated mean SBP from randomization to follow-up Week 6.
- Difference in change in home seated mean DBP from randomization to follow-up Week 12.
- Difference in change in home seated mean DBP from randomization to follow-up Week 6.
- Difference in change in trough home seated mean SBP from randomization to follow-up Week 12.
- Difference in change in trough home seated mean SBP from randomization to follow-up Week 6.
- Percentage of participants with home seated mean SBP <135 and DBP <85 mmHg at follow-up Week 12.
- Percentage of participants with home seated mean SBP <135 and DBP <85 mmHg at follow-up Week 6.
- Percentage of participants with home seated mean SBP <130 and DBP <80 mmHg at follow-up Week 12.
- Percentage of participants with home seated mean SBP <130 and DBP <80 mmHg at follow-up Week 6.

2.4.2 Safety Outcomes

2.4.2.1 Primary

Percentage of participants discontinued trial medication due to an Adverse Event (AE) or a Serious Adverse Event (SAE) from randomization to follow-up Week 12.

2.4.2.2 Secondary

- Percentage of participants discontinued trial medication due to AE/SAE from randomization to follow-up Week 6.
- Percentage of participants with an SAE from randomization to follow-up Week 12.
- Percentage of participants with an SAE from randomization to follow-up Week 6.

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

In addition, descriptive safety data will be reported on:

- Percentage of participants discontinued trial medication due to AE/SAE during the active run-in period.
- All SAEs, by severity and by System Organ Class (SOC) criteria in the run-in period and by trial medication group in the randomized period and safety follow-up period.

2.5 Sample Size

As noted in Section 12.3 of the protocol, a sample size of 1500 participants randomized (600 in GMRx2 and 300 in each of the dual combination groups) provides 97% power with a two-sided type I error rate of 5% to detect a minimum difference of 3 mmHg in home seated mean SBP for each of the three pairwise comparisons of GMRx2 vs dual therapy, assuming a common standard deviation of 11 mmHg within each group. Efficacy can be claimed only if all three comparisons are statistically significant at the two-sided 5% level. The overall, family-wise power for all three comparisons will therefore be over 90%.

The study was planned using a simple, conservative sample size calculation by intention. The actual experimental design and subsequent statistical modelling approach is expected to provide greater power than this. Additional calculations are specified in Appendix 2.

An updated power analysis was performed mid-trial using the observed overall standard deviation and hypothesized treatment effect for the DSMB and Steering Committee. Calculations of the standard deviation were based on the pooled sample, not requiring unblinding or any efficacy calculations.

2.6 Changes in the Conduct of the Study or Planned Analyses

2.6.1 Changes in the Conduct of the Study

Recruitment to the study was terminated before randomizing 1500 participants. Details are provided in Appendix 2.

2.6.2 Changes in Planned Analysis

Multiple analysis sections have been expanded within this document from the protocol-specified analyses. Clarifications and expansions include:

- The addition of an estimands section
- Detailed descriptions of mixed models for repeated measures and multiple imputations
- Clarified calculation methods for derivation of primary endpoint
- Use of multiple populations for analysis, including the use of supportive and sensitivity analysis
- Expansion of analysis methods to be used for secondary efficacy and secondary safety endpoint analysis

3 STATISTICAL ANALYSIS

3.1 Interim Analyses

The DSMB met periodically throughout the duration of the trial for data review. No analyses on unblinded efficacy results were performed. Observed standard deviation of the home BP measurements on the overall sample informed updated power calculations periodically through the study: see Appendix 2.

3.2 Multi-Center Trials

Analysis of demographic and baseline characteristics, efficacy and safety data will be pooled across all sites.

For the primary analysis, mixed models with repeated measures (MMRM) will be applied accounting for correlation between observations within site.

3.3 Multiplicity Adjustment

All tests are to be two-sided with a nominal level of α set at 5%. Since the purpose of the trial is to demonstrate effects on all three of the designated primary efficacy endpoint comparisons simultaneously (i.e. GMRx2 has to be statistically significantly superior at two-sided $p<0.05$ to each of the possible dual combinations for the trial to be regarded as positive), there is no need for adjustment of the Type I error for the primary endpoint, according to ICH E9 Guidance and FDA Guidance 'Multiple Endpoints in Clinical Trials. Guidance for Industry, 2017'. The impact on Type II error and sample size has been carefully considered, in that the estimated power for each separate comparison is >97% and so the power for all three comparisons is >91% (i.e., $0.97^3 = 0.91$).

The secondary efficacy parameters measure different aspects of the same underlying treatment effect evaluated in the primary efficacy endpoint, that is the effect of GMRx2 compared to dual combinations on blood pressure, and do not demonstrate additional new treatment effects of the drug, but rather clarify the effect already demonstrated by the primary analysis. No type I error adjustment is proposed to account for multiplicity for secondary efficacy endpoint analyses.

3.4 Populations for Analysis

3.4.1 Screened Set

The Screened Set includes all participants who have provided consent and have a screening number, regardless of whether they have been randomized or treated with study treatment.

3.4.2 Safety Set

The Safety Set is defined as all participants who took at least one dose of study treatment, including during Period 1 single-blind run-in. For the analysis of the safety endpoints, participants will be analyzed in the treatment group they actually received.

3.4.3 Efficacy Populations

For all efficacy analyses, participants will be analyzed in the treatment group to which they have been randomized.

The Randomized Set will be the set of reference for reporting primary and secondary endpoints to preserve the intention-to-treat (ITT) principle. The Full Analysis Set (FAS) and other strategies proposed will be used to evaluate the robustness of the results.

3.4.3.1 Randomized Set

The Randomized Set includes all participants who have been randomized. Participants will be analyzed in the treatment group to which they have been randomized.

3.4.3.2 Full Analysis Set

The FAS is defined as all participants in the randomized set who have taken at least one dose of randomly assigned treatment. If the Randomized Set and the FAS are very similar (≤5% difference) in size, the efficacy analysis will not be rerun on the FAS set as a sensitivity analysis.

3.4.3.3 Per Protocol Set

The Per Protocol Set is defined as all randomized participants who did not experience an intercurrent event or major protocol deviation. Intercurrent events are defined within the Estimand Statements (Section 3.10.1). Protocol deviations are defined within Section 3.9.3. As receipt of an incorrect study treatment (wrong study treatment kid dispensed) is a major protocol deviation, participants will be grouped according to the treatment received.

3.5 General Methods

All data listings that contain an evaluation date will contain a relative study day. Two relative study days will be defined: Period 1 Relative Day (P1 Rel Day) and Post-Randomization Relative Day (PR Rel Day). For Period 1 Relative Day, pre-treatment and on-treatment study days are numbered relative to the day of the first dose of single-blind study treatment which is designated as P1 Day 1. The preceding day is P1 Day -1, the day before that is P1 Day -2, etc. Post-Randomization Relative Day will be numbered relative to the day of the first dose of the randomized medication which is designated as PR Day 1.

The planned treatment group for all participants in Period 1 is GMRx2. In Period 2, the planned treatment group is randomly assigned to be:

1. Triple – TAI (GMRx2) : telmisartan (T) 20 mg/amlodipine (A) 2.5 mg/indapamide (I) 1.25 mg.
2. Dual – TA: telmisartan 20 mg/amlodipine 2.5 mg.
3. Dual – TI: telmisartan 20 mg/indapamide 1.25 mg.
4. Dual – AI: amlodipine 2.5 mg/indapamide 1.25 mg.

Up-titration is planned to occur prior to Period 3, resulting in planned treatment at increased dose levels; however, the up-titration may not occur for reasons as specified in the protocol (Section 8.4.2). Therefore, treatments in period 3 include:

Table 3-1 Planned Treatment Assignments Period 2 and Period 3

Treatment Group	Period 2: Treatment (Planned)	Period 3: With Up-titration (Planned)	Period 3: No Up-Titration
Triple – TAI	telmisartan (T) 20 mg/ amlodipine (A) 2.5 mg/ indapamide (I) 1.25 mg. (GMRx2 Dose2)	telmisartan 40 mg/ amlodipine 5 mg/ indapamide 2.5 mg (GMRx2 Dose3)	same as in Period 2
Dual – TA	telmisartan 20 mg/ amlodipine 2.5 mg	telmisartan 40 mg/ amlodipine 5 mg	same as in Period 2
Dual – TI	telmisartan 20 mg/ indapamide 1.25 mg	telmisartan 40 mg/ indapamide 2.5 mg	same as in Period 2
Dual – AI	amlodipine 2.5 mg/ indapamide 1.25 mg	amlodipine 5 mg/ indapamide 2.5 mg	same as in Period 2

All output will be incorporated into Microsoft Word or Adobe Acrobat PDF files, sorted and labelled according to the ICH recommendations, and formatted to the appropriate page size(s).

Tables will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tables of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Summarizations will be presented by treatment group and overall. For efficacy and safety summaries, Period 1 (active run-in period) will be summarized separately from the randomized treatment period and follow-up.

3.5.1 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software using version 9.4 or higher, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 (or higher, as up-versioning may occur). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2021 version (or later, as up-versioning may occur).

3.5.2 Baseline Definitions

For Period 1, Baseline for safety and in-clinic assessments is defined as the most recent measurement prior to the first administration of study treatment.

For in-clinic efficacy parameters including change from baseline measurements at post-Randomization timepoints, Baseline is the last Clinic BP measurement occurring prior to the first dose with randomized study treatment.

Baseline for home SBP measurements is defined as measures taken during the week prior to Randomization,

with derivation defined in Table 3-3.

3.5.3 Study Period for Analysis

The study is planned with 4 periods (Section 2.2.3) with varying treatment assigned in both trial medication and dose level during the specified periods. For a minority of participants, Follow-Up visits 1 and 2 may not occur at 6 and 12 weeks, respectively and screening visit is not always 4 weeks before baseline visit, due to protocol-specified visit windows and IMP supply interruptions. Therefore, the analysis periods will be defined:

- Period 1: From Week -4 to Randomization, defined as from screening to Randomization and Baseline Visit,
- Period 2: From Randomization to Week 6, defined as from Randomization and Baseline Visit to Follow-up Visit 1,
- Period 3: From Week 6 to Week 12, defined as from Follow-up Visit 1 to Follow-up Visit 2,
- Randomized Period: From Randomization to Week 12, defined as from Randomization and Baseline Visit to Follow-up Visit 2 (Period 2 and Period 3),
- Period 4: From Week 12 to Week 16, defined as from Follow-up Visit 2 to end of study (Week 16).

3.6 Subject Disposition

All participants screened who met study inclusion criteria for Period 1 (active run-in) will be accounted for. The number of participants who were randomized; and reasons for exclusion for non-randomized participants will be summarized.

Subject disposition will be tabulated for the following categories and will include all participants in the Screened Set:

- Number (%) of participants screened
- Number (%) of participants entered run-in period
- Number (%) of participants randomized
- Number (%) of participants randomized, ineligible for randomization
- Number (%) of participants randomized but did not receive study treatment
- Number (%) of participants completing Period 2 (defined as attending Week 6, Visit FU1)
- Number (%) of participants completing Period 3 (defined as attending Week 12, Visit FU2)
- Number (%) of participants completing the trial, including safety follow-up (defined as attending Week 12, Visit FU2 and Week 16, Visit EOT)
- Number (%) of participants prematurely and permanently discontinuing the trial medications and reasons
- Number (%) of participants prematurely and permanently discontinuing from the trial and reasons
- Number (%) of participants in each analysis population (Section 3.4).

3.7 Baseline Characteristics

Description of the participant baseline characteristics will be presented by treatment group and overall. Baseline characteristics will be summarized on the Safety Set by treatment group, Safety Set by Randomization Eligibility and Randomized Set by treatment group, including the below parameters:

- Demographic characteristics: age (years), sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), country/region, education
- Lifestyle: Smoking status and alcohol consumption
- 12-lead ECG: Interpretations will be tabulated

- Screening visit number of prior BP medications

The following parameters will be summarized:

- Demographic characteristics, lifestyle, and 12-lead ECG
- Screening visit clinic BP (SBP and DBP)
- Average home BP at Randomization (last week of Period 1 SBP) (see Section 3.10.2 for derivations)
- Change in clinic BP from Screening Visit to Randomization visit
- Change in home BP from 1st to last week of Period 1 will be summarized by Randomization Eligibility

Medical history will be provided in by-participant data listings. Summaries may also be presented.

3.8 Prior/Concomitant Medications

Prior and concomitant medications will be summarized by treatment group. Prior medications are medications that were being taken at the time of screening. Concomitant medications are medications that started or were ongoing from run-in period to the end of trial. Concomitant medications will be summarized separately for medications taken during Period 1 (pre-Randomization) and post-Randomization.

Prior/Concomitant medication will be summarized using descriptive statistics:

- Number (%) of participants with at least one prior medication, by ATC code level 1 and preferred term
- Number (%) of participants with at least one concomitant medication during Period 1, by ATC code level 1 and preferred term
- Number (%) of participants with at least one concomitant BP lowering medication during Period 1, by ATC code level 1 and preferred term
- Number (%) of participants with at least one concomitant medication post-Randomization, by ATC code level 1 and preferred term
- Number (%) of participants with at least one concomitant BP lowering medications post-randomization, by ATC code level 1 and preferred term

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) term according to the WHO Drug Dictionary (WHO DD) (March 2021 version or later if up-versioning occurs) used for drug coding (https://www.whocc.no/atc_ddd_index/).

3.9 Adherence

3.9.1 Adherence to Trial Medication

The planned daily dose is 1 pill per day. Low and standard doses are dispensed in separate bottles. Adherence to trial medication will be computed overall (across both low and standard doses).

Trial medication adherence over the run-in period will be presented as below:

- Adherence to active run-in treatment specified as the number of pills taken compared to the planned number of pills for the period, expressed in percentage. The planned number of pills for the period will be determined as the expected number of days of treatment between the Period 1 first dose date and Period 1 last dose date. The number of pills taken is determined as the difference between number of pills dispensed and the number of pills returned. For participants with missing pill-return data, 100% adherence will be assumed for the associated period.

Trial medication adherence over the randomized period (from randomization to Week 12) will be assessed

using the following parameters:

- Denominator: Planned number of pills for the period is defined as the number of days between the scheduled first and last treatment intake. The medication log CRF will be used to determine the number of expected days by computing the number of days between the start and stop dates for each record and summing across all records reported for each participant. Note, if there is a gap between the stop and start records for sequential medication logs, gap days will be assigned an expected count of 0.
- Numerator: The number of pills taken is determined as the difference between number of pills dispensed and the number of pills returned. For participants with missing pill-return data, it will be assumed that the number of pills taken equals the minimum of the number of pills dispensed for that period and the number of days between the logged start and stop date for the corresponding trial medication log.

Adherence to trial medication will be calculated as numerator ÷ denominator and expressed in percentage. Adherence is confirmed if ≥80% and ≤120%.

Additional details surrounding the calculations of numbers of pills dispensed and adherence will be described within a specifications document.

3.9.2 Adherence to Home BP Measurement

As per Section 8.2.1 in the protocol, adherence to home BP monitoring schedule will be assessed at the randomization visit. In the week before randomization (week -1), at least 6 measures (e.g., ≥2 sets of triplicate measures, ≥3 sets of duplicate measures) are required 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.

Following randomization, a minimally valid half-day of BP measurements is defined as one that has either:

- ≥1 BP values in the morning (earlier than 12:00 hours), or
- ≥1 BP values in the evening (12:00 hours or later).

Study protocol Section 10.2.8 instructs that in the week before the Randomization, Week 6, and Week 12 trial visits, BP measurements should be taken on the 4 days immediately prior to the day of the on-site trial visit. In other weeks, measurements should be performed on a single day.

Adherence to home BP measurement will be evaluated by looking at the number of minimally valid half-days and will be summarized by counting the number of minimally valid AM and PM periods of BP measurements per week of follow-up, by treatment group and overall.

3.9.3 Protocol Deviations

Over a blind review meeting, before database lock, the different protocol deviations will be classified as minor or major and categorized by type (e.g. non-compliance to treatment, prohibited medication etc.) by the clinical team. The number of major protocol deviations will be summarized by type of deviations.

Major protocol deviation categories include, but are not limited to:

- Randomized even though ineligible.
- Received the wrong treatment.
- Non-adherence to study treatment (adherence < 80% or > 120%), for reasons known to be unrelated

to tolerability or efficacy e.g. participant moved overseas.

- Interruption to study treatment as a result of supply chain issues in which protocol-specified procedures were not followed.
- Insufficient valid home BP measurements for home blood pressure calculation at one or more of: baseline, Week 6 Follow-up Visit 1, Week 12 Follow-up Visit 2.
- Up-titration at Week 6 Follow-up Visit 1 was not performed for reasons other than those specified in the protocol.
- Other

A summary table will present the tabulations by major protocol deviation on the Safety Set. All protocol deviations (recorded or programmed) will be listed.

3.10 Analysis of the Efficacy Outcomes

3.10.1 Estimand

3.10.1.1 Primary Estimand

The population for the primary estimand includes adults (aged ≥18 years) with hypertension. The variable of interest is the difference between the home measured SBP during Week 12 of treatment post-randomization and the home measured SBP immediately prior to randomization. The primary analysis will be performed on the Randomized set including all participants who were randomized to treatment.

Intercurrent events for the primary analysis are listed below:

- Received the wrong treatment (i.e., a treatment other than the randomly assigned treatment)
- IMP interruption for supply-related reasons
- Up-titration at Week 6 was not performed for reasons not allowed by study protocol
- Discontinuation from the study treatment for reasons related to the study protocol or study treatment (e.g., due to safety findings, adverse event, disease worsening, or lack of efficacy)

For the primary analysis, the Treatment Policy Strategy will be applied where intercurrent events that do not result in missing BP measurements are considered irrelevant and data will be analyzed regardless of the occurrence of the event. The use of a Treatment Policy Strategy most closely aligns to an ITT analysis, where all available and imputed data contribute toward the estimated treatment effects. Participants with intercurrent events and missing data will have imputations performed from those participants with intercurrent events and non-missing data. (Section 3.10.2.7) Participants without intercurrent events and missing data will have imputations performed from those participants without intercurrent events and non-missing data.

The primary analysis will be performed using a mixed model with repeated measures (MMRM), including Week 6 and Week 12 assessments. A sensitivity analysis will be performed using the same methods applied to Week 12 home BP results only (Section 3.10.2.3). Additional sensitivity analyses adjusted for covariates are planned for the primary endpoint (Section 3.10.2.3). Subgroup analyses will also be performed among the primary analysis set (Section 3.10.2.6).

Supplemental analyses will be performed among the following analysis sets:

1) Full Analysis Set, including participants who have taken at least 1 dose of study treatment post-randomization and applying imputation methods in the same manner as the primary analysis method (analysis to be performed if samples differ by >5%)

2) Randomized Set excluding participants with IMP interruptions for supply-related reasons
3) Complete cases with Clinic BP Substitution: Participants with missing Baseline, Week 6, or Week 12 Home BP assessments with Clinic BP recorded will have their clinic measured value substituted for the missing Home BP assessment at the respective visit. Any participants with missing Baseline or Week 12 assessments without an in-clinic assessment at the designated visit will be excluded.
4) Per Protocol Analysis Set: Excluding any participants with an intercurrent event or major protocol deviation.

3.10.1.1 Secondary Estimands

The population for the secondary estimands includes adults (aged ≥18 years) with hypertension. Participants in the trial will complete a 4-week single-blind active run-in on the experimental product GMRx2-Dose2 and then be randomized to treatment. The variables of interest are listed in Section 2.4.1.2.

Hypothesis testing is not planned for secondary endpoints and, therefore, the results of the planned analyses are considered exploratory. Statistical analyses for continuous secondary endpoints will be performed on Complete Cases only. Statistical analyses for binary secondary endpoints will be performed on the Randomized Set, where participants with missing endpoints values will be assumed to have not achieved the endpoint (i.e., missing data will be singly imputed as “failure”).

Table 3-2 Estimands

Estimand Label	Treatment Comparison	Population	Population-level summary	Analysis Population	Handling of Intercurrent events
Primary Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using Mixed Model with Repeated Measures (MMRM) with Multiple Imputation	Randomized Set	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy
Primary Estimand, Sensitivity Analysis – Week 12 only	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using Mixed Model with Repeated Measures (MMRM) with Multiple Imputation, Week 12 results only	Randomized Set	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy
Primary Estimand, Sensitivity Analysis – Adjusted Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using Mixed Model with Repeated Measures (MMRM) with Multiple Imputation, adjusted for covariates	Randomized Set	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy

Estimand Label	Treatment Comparison	Population	Population-level summary	Analysis Population	Handling of Intercurrent events
Primary Estimand, Sensitivity Analysis – Subgroup Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using Mixed Model with Repeated Measures (MMRM) with Multiple Imputation, with interaction terms for specified subgroups	Randomized Set	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy
Primary Estimand, Supplemental Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using MMRM with Multiple Imputation	Full Analysis Set	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy
Primary Estimand, Supplemental Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using MMRM with Multiple Imputation	Randomized Set excluding participants with IMP interruptions for supply-related reasons	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy, excluding participants with IMP interruptions due to supply-related reasons
Primary Estimand, Supplemental Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using MMRM with Clinic BP Substitution	Randomized Set, Complete Cases with Clinic BP Substitution	Treatment policy strategy with substitution of missing home BP assessments with clinic BP assessment values (participants missing both home and clinic BP values will be excluded from analysis)

Estimand Label	Treatment Comparison	Population	Population-level summary	Analysis Population	Handling of Intercurrent events
Primary Estimand, Supplemental Analysis	GMRx2 vs dual combinations at week 12	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs each dual combination separately Analysis will be performed using MMRM	Per Protocol Set	All participants with intercurrent events and major protocol deviations excluded from analysis
Secondary Estimands, Continuous Endpoints	GMRx2 vs dual combinations at specified timepoints	Adults with hypertension	Continuous Endpoints: Analysis will be performed using MMRM, Summary variable will be LS Means and LS Mean Difference	Randomized Set	Treatment Policy Strategy for intercurrent events with results reported. Complete cases only with no imputation for missing data.
Secondary Estimands, Binary Endpoints	GMRx2 vs dual combinations at specified timepoints	Adults with hypertension	Dichotomous Endpoints: Analysis will be performed using GEE, Summary variable will be Odds Ratios, Risk Difference, and corresponding confidence intervals (CIs)	Randomized Set	Treatment Policy Strategy for intercurrent events with results reported. Missing data will be imputed as “failure”.

3.10.2 Primary Efficacy Analysis

3.10.2.1 Definition – Home BP

Home seated systolic and diastolic BP measurements will be averaged as described in Table 3-3 and the following endpoints will be derived:

- Average home SBP during the 7 days prior to Randomization visit, Week 6 FU1 visit and Week 12 FU2 visit
- Average home DBP during the 7 days prior to Randomization visit, Week 6 FU1 visit and Week 12 FU2 visit
- Average trough (i.e. measurement taken before morning dose) home SBP during the 7 days prior to Randomization visit, Week 6 FU1 visit and Week 12 FU2 visit

Note that trough will be assumed to be any BP measure taken in the morning, as participants are instructed to perform the BP measurement prior to taking their daily medication and to take that medication in the morning.

Table 3-3 Definitions of Home Blood Pressure Derivations

Measure	*Rules*
Randomization, week 6 and week 12 home BP	• Defined as the home BP in the week before randomization, FU visit 1 (scheduled at Week 6) and FU visit 2 (scheduled at Week 12), respectively. FU visits 1 and 2 may not occur exactly at 6 and 12 weeks, respectively.
Individual BP measurement	• Each BP measurement must consist of valid SBP and DBP values. (i.e., SBP>60 mmHg and <250 mmHg and DBP>40mmHg and <150mmHg). If valid SBP and DBP are not recorded, the entire measure will be discarded. • Recommended home BP measurements were for 4 consecutive days immediately prior to the trial visits (i.e. Week -1, Week 5, Week 11) and on a single set day of the participant's preference in other weeks.
Grouping of measurements into sessions	• Individual BP measurements must be grouped into 5-minute "sessions". • To group individual BP measurements into sessions, the start of a 5-minute period is at the time of the first measurement with all BP measurements in those 5 minutes being assigned to the single session. • A new session starts at the first BP measure encountered after the completion of an existing session. • If more than two measures are captured in a session then, as with three measures, the second and third measures with be flagged for use. The first and any measures after the third are ignored. • In the case of fewer than three BP measures in a session, all measures will be flagged for use.
Selection of a single session per half-day period	• Each day is divided into two half-days – AM and PM. • If more than one session occurs in one period e.g., two sessions in the AM period of a given day, one session only will be selected for use using two prioritisation steps:

	– Sessions containing three or more BP measures will be prioritised over those with two. Those with only one BP measure will be used as a last resort. – If the first step does not uniquely select one session for the period, the earliest session of those selected in the first step will be used.
Calculation of averages	• To calculate an average, perform a simple, unweighted mean of the flagged BP measurements in the selected sessions for the period of interest. – At Randomization: A minimum of 6 measures (e.g. ≥2 sets of triplicate measures or ≥3 sets of duplicate measures) are expected, including at least 1 morning and 1 evening, each with ≥2 measures per protocol-specified eligibility criteria. – Post-Randomization: At least 4 consecutive calendar days (8 measurement sessions, 24 BP readings) were recommended. – Calculations: For all timepoints, calculations of averages will be performed if there is at least 1 valid BP measurement. • The home BP values for the purpose of Baseline, FU visit 1 Week 6 and FU visit 2 Week 12 are averages (as defined above) across up to 7 calendar days immediately preceding each in-clinic visit. – Each of the up to 2 selected sessions per day (1 morning and 1 evening) may be included in the calculation. – Days with no valid measures reported will be excluded from the calculation (i.e., only days with SBP measurements recorded will be included in average).

In addition, for descriptive plots of SBP and DBP measurements post-randomization, weekly average BP will be computed where Week is defined in relation to the randomization date with Week 1 initiating on Day 1, the first treatment with randomized trial medication:

$$Week = (date\ of\ BP\ measurement - date\ of\ first\ dose\ of\ randomized\ treatment)/7$$

Week is rounded up to the nearest integer. Averages will otherwise be calculated in the same manner as described in Table 3-3.

3.10.2.2 Main Analysis

Blood pressure values will be summarized using descriptive statistics, including actual values and changes from baseline to Week 6 and Week 12, by timepoint and treatment groups. Graphical presentations of group means over time will be presented. Summaries will be presented on the Safety Set by Randomization Status and Randomization Set. Additional summaries may be presented.

The difference in change of home SBP from Baseline to Week 12 will be analyzed using a MMRM. The outcome will be the post-Baseline home SBP values with fixed effects for treatment group, time (visit as categorical variable), treatment by time (visit) interaction, and Baseline home SBP. The variance will be estimated using a Huber-White sandwich estimator and the model will account for correlation within participant and within site. An unstructured covariance matrix for within participant observations will be used with fall-backs to first a compound symmetry (exchangeable) matrix and finally an independent matrix if the model does not converge. A compound symmetry covariance matrix will account for correlation within site with a fall back of an independent matrix if the model does not converge. Least Square Means and corresponding standard errors will be estimated for each post-Baseline visit and treatment group. Pairwise comparisons between GMRx2 and dual treatments will be performed at Week 6 and Week 12. The comparisons at Week 12 will serve as the

primary endpoints analysis.

Sample SAS Code:

```
PROC MIXED DATA = ADEFF EMPIRICAL METHOD = REML;
      CLASS SITEID SUBJID VISIT TRTP;
      MODEL AVAL = BASE VISIT TRTP VISIT*TRTP / CL;
      REPEATED VISIT SUBJID / SUBJECT = SITEID TYPE = UN@CS;
      WHERE VISIT IN ('WEEK6','WEEK12');
      LSMEANS VISIT*TRTP / DIFF CL ALPHA=0.05;
      RUN;
```

Where ADEFF is the ADaM dataset for efficacy, AVAL represents the Week 6 or Week 12 home SBP measurement, BASE is the Baseline value, VISIT is the visit (Week 6 or Week 12), TRTP is the planned treatment, and VISIT*TRTP is the interaction between visit and planned treatment.

Superiority of the triple combination over the dual combinations will be shown if the 3 comparisons listed above are statistically significant (when the null hypothesis of equal adjusted means is rejected).

The main analysis of the primary endpoint will be performed using multiple imputation to account for missing data (Section 3.10.1.1; Section 3.10.2.7).

Supportive analyses will be performed on:

1) The Full Analysis Set (if the analysis set differs from the Randomized set by at least 5%) using the same multiple imputation rules as the primary analysis
2) The Randomized set excluding participants with IMP interruptions for supply-related reasons using the same multiple imputation rules as the primary analysis
3) Complete Cases with Clinic BP Substitution
4) Per Protocol Set using no imputations

3.10.2.3 Sensitivity Analysis at Week 12 Only

The primary analysis methods (Section 3.10.2.2) will be repeated including Week 12 only (excluding Week 6 from the MMRM). The variance will be estimated using a Huber-White sandwich estimator and the model will account for correlation within site. The handling of intercurrent events and imputation methods will be the same as the primary analysis.

Sample SAS Code:

```
PROC MIXED DATA = ADEFF EMPIRICAL METHOD = REML;
      CLASS SITEID SUBJID TRTP;
      MODEL AVAL = BASE TRTP / CL;
      REPEATED SUBJID / SUBJECT = SITEID TYPE = CS;
      WHERE VISIT IN ('WEEK12');
      LSMEANS TRTP / DIFF CL ALPHA=0.05;
      RUN;
```

3.10.2.4 Sensitivity Analysis Pooled Control

The primary analysis methods (Section 3.10.2.2) will be repeated comparing GMRx2 to a pooled control group, inclusive of all three dual control treatment groups. The imputation from the primary analysis and primary analysis methods will otherwise remain unchanged.

3.10.2.5 Adjusted Analyses

Adjusted analyses will be performed as a sensitivity analysis by adding (as a group of variables) the following

covariates: age (continuous), sex, race, BMI category, diabetes, and number of treatments at screening. The adjusted treatment effect will be reported as the adjusted mean difference and 95% CI.

3.10.2.6 Subgroup and Additional Analyses

Pre-specified subgroup analyses will be carried out irrespective of whether there is a statistically significant treatment effect on the primary endpoint. Subgroups are defined as follows:

- Sex (Male; Female)
- Age (<55; 55-65; > 65 years)
- Race (black; non-black)
- BMI (<30,>=30 kg/m^2)
- Diabetic; non-diabetic
- Region (US; Other)
- Baseline (at Randomization) home SBP category (<130, 130-139, >=140 mmHg)
- Number of BP medications at Screening (0, 1, 2, 3)
- Hypertension status at Screening – office BP <140/90 mmHg, ≥140/90 mmHg; office BP <130/80 mmHg, ≥130/80 mmHg
- Orthostatic hypotension at Randomization (measured at clinic BP): see Section 3.10.3.2 for definitions.

Subgroup analyses will be performed by inclusion of the subgroup main effect as well as two- and three-way interaction terms as fixed effects with visit and treatment within the MMRM. Heterogeneity of treatment effect between subgroups will be evaluated using contrast statements, to test whether the LS Mean difference between GMRx2 and each dual control treatment group differs between levels of the subgroup. Comparisons will be performed separately for each dual control treatment group. A comparison of GMRx2 against a combined dual control treatment group will also be performed. Assessments of heterogeneity will be performed at Week 6 and Week 12 timepoints. LS Means, LS Mean Differences between GMRx2 and dual control treatment groups and 95% CIs will be reported for each category of subgroup. If any subgroup does not have sufficient participants for statistical modelling (i.e., model convergence), descriptive statistics will be provided. A forest plot will also be provided to visualize the subgroup analysis.

Sample SAS Code accounting for Sex as Subgroup:

```
PROC MIXED DATA = ADEFF EMPIRICAL METHOD = REML;
      CLASS SITEID SUBJID VISIT TRTP SEX;
      MODEL AVAL = BASE VISIT|TRTP|SEX / CL;
      REPEATED VISIT SUBJID / SUBJECT = SITEID TYPE = UN@CS;
      WHERE VISIT IN ('WEEK6','WEEK12');
      LSMEANS VISIT*TRTP*SEX / DIFF CL ALPHA=0.05;
      lsmestimate VISIT*trtP*sex "(VTS211-VTS221)-(VTS212-VTS222)"
        [1, 2 1 1] [-1, 2 2 1] [-1, 2 1 2] [1, 2 2 2]; *TRTP=1 vs TRTP=2;
      lsmestimate VISIT*trtP*sex "(VTS211-VTS231)-(VTS212-VTS232)"
        [1, 2 1 1] [-1, 2 3 1] [-1, 2 1 2] [1, 2 3 2]; *TRTP=1 vs TRTP=3;
      lsmestimate VISIT*trtP*sex "(VTS211-VTS241)-(VTS212-VTS242)"
        [1, 2 1 1] [-1, 2 4 1] [-1, 2 1 2] [1, 2 4 2]; *TRTP=1 vs TRTP=4;
      RUN;
```

There is clinical interest in the effects of BP lowering by time of day, particularly trough BP in the morning. The telemonitored home BP devices provide a timestamp of each BP measurement taken. Additional analyses will be completed analysing difference between study arms of home SBP by AM and PM time periods.

The clinical use of GMRx2 is expected to involve use in participants who were previously on 0-3 medications.

As such, a graphical descriptive analysis of blood pressure changes during run-in on GMRx2 will be presented separately for different blood pressure regimens participants were receiving at screening, noting participants could be on 0-3 antihypertensives at the time, before being switched to GMRx2-dose 2. Additional descriptive analyses will be conducted according to hypertension control status and number of antihypertensives at screening.

3.10.2.7 Treatment of Missing Data

For the primary endpoint requiring a valid weekly average home BP value preceding the Randomization and Week 12 visits, if a participant does not have a valid endpoint measure, that value will be flagged as missing and requiring imputation. Imputation will also be performed for missing Week 6 results. In all cases it is the BP weekly average that will be imputed for each time interval, not each component measure used to calculate the average. Imputations will be performed separately by analysis set, as required (i.e., Randomized Set, Per Protocol).

For missing Baseline (prior to Randomization) SBP results, missing data are considered missing at random and a multiple imputation will be applied.

For post-Randomization missing data, a Retrieved Data Multiple Imputation will be applied to account for the occurrence of intercurrent events which aligns to the Treatment Policy Strategy for handling of Intercurrent Events:

1) Participants with missing Baseline measurements will be assumed to have data missing at random and will have results imputed from the full baseline sample of participants (pre-randomization).
2) Participants with missing Week 6 or Week 12 home BP assessments and experiencing intercurrent events will have their result imputed for the primary analysis using multiple imputation. Participants with intercurrent events will have their missing result based on other participants with intercurrent events within the same treatment group.
    a. Receive Wrong Treatment:
        i. Participants who received the wrong treatment and have missing Week 12 results will have results imputed from the sample of participants who received the same treatment they received during Period 3. The participants will be grouped as randomized for the primary analysis.
        ii. Participants who received the wrong treatment and have missing Week 6 results will have results imputed from the sample of participants who received the same treatment they received during Period 2. The participants will be grouped as randomized for the primary analysis.
    b. Participants with IMP interruption for supply-related reasons will have missing Week 6 or Week 12 results imputed from the sample of participants with intercurrent events and assigned the same randomized treatment.
    c. Participants with missing Week 12 who do not have up-titration at Week 6 will have results imputed from the sample of participants randomly assigned to the same treatment and have an intercurrent event. Week 6 results will be used to impute the Week 12 timepoint.
    d. Participants who discontinue treatment for reasons related to study treatment or study procedures will be imputed using a control-based imputation from the sample of participants with intercurrent events and randomly assigned to one of the control groups (AI, TA, TI).
2) Participants non-adherent to study treatment:
    a. Participants who were non-adherent to study treatment during Period 2 with missing Week 6 home BP measurement will be imputed from the sample of participants with intercurrent events and randomly assigned to one of the control groups (AI, TA, TI).
    b. Participants who were non-adherent to study treatment during Period 3 with missing Week

12 home BP measurements will be imputed from the sample of participants with intercurrent events and randomly assigned to one of the control groups (AI, TA, TI).

3) Participants with missing Week 6 or Week 12 home BP assessments who were adherent to study treatment and did not experience intercurrent events will have their results imputed for the primary analysis using multiple imputation. Participants without intercurrent events will have their missing result based on other participants also without intercurrent events and within the same treatment group.

If there is not a sufficient sample size to perform multiple imputations as described, participants with and without intercurrent events will be included in the source sample for imputation.

Multiple imputation (MI) will be applied, replacing each missing average SBP home assessment with a set of plausible values from the identified subsample, listed above. This will represent the uncertainty of the correct value based on the observed results. The multiply imputed datasets will be analyzed using standard procedures for complete data with their results combined with a variance-adjustment. The multiple imputation will be computed as follows:

1) Imputation:
    a. For missing baseline, a regression method will impute missing data from the overall randomized sample.
    b. For missing Week 12 SBP results, a regression method will impute missing data from the respective subsample with or without intercurrent events, as specified above, and within the respective treatment group. Imputation will be performed using a Fully Conditional Specification (FCS) model using the regression method and will include the following factors:
        - Age, sex, race, BMI, and ethnicity
        - Patient smoking and alcohol consumption
        - Baseline (at Randomization) average home SBP, Week 6 average home SBP
2) Analyzing: The final multiple imputed datasets will be analyzed using Ruben's Rule.

Proc MI and Proc MIANALYZE in SAS will be used to generate the datasets and run the analyses.

Sample SAS Code:

```
PROC MI DATA = SBP OUT = SBP2 SEED = 20231010 NIMPUTE = 100
     MINIMUM = . . . . . 80 80 80     ROUND = . . . . . 1 1 1
     MAXIMUM = . . . . . 200 200 200  MINMAXITER = 5000 SIMPLE NOPRINT;
     FCS REG (BASE = TRTPN AGE SEX RACE BMI ETHNIC SMK ALC/ DETAILS);
     FCS REG (SBP6 = TRTPN AGE SEX RACE BMI ETHNIC SMK ALC BASE/ DETAILS)
     FCS REG (SBP12 = TRTPN AGE SEX RACE BMI ETHNIC SMK ALC BASE SBP6/
              DETAILS)
     CLASS TRTPN SEX RACE ETHNIC SMK ALC;
     VAR TRTPN AGE SEX RACE BMI ETHNIC SMK ALC BASE SBP6 SBP12;
     RUN;
*SBP2 will be reformatted into an analysis dataset, here titled ADEFF with
each observation is on a separate line;
*Note that in actual implementation, the imputations will be done separately
for those with intercurrent events and those without intercurrent events.
Note also that baseline values will be imputed from all observations;

PROC MIXED DATA = ADEFF EMPIRICAL METHOD = REML;
      BY IMPUTNUM;
      CLASS SITEID SUBJID VISIT TRTP;
      MODEL AVAL = BASE VISIT TRTP VISIT*TRTP / CL;
      REPEATED VISIT SUBJID / SUBJECT = SITEID TYPE = UN@CS;
```

```
        WHERE VISIT IN ('WEEK6','WEEK12');
        LSMEANS VISIT*TRTP / DIFF CL ALPHA=0.05;
        ODS OUTPUT COVPARMS = CP LSMEANS = LSM DIFF = DIFFS;
        RUN;
PROC SORT DATA = DIFF;
     BY TRTP _TRTP VISIT _VISIT;
     RUN;
PROC MIANALYZE DATA = DIFF ALPHA = 0.05;
     BY TRTP _TRTP VISIT _VISIT;
     WHERE TRTP = 1 AND _TRTP NE 1 AND VISIT = _VISIT;
     *TRTP = 1 corresponds to GMRx2 in this example;
     MODELEFFECTS ESTIMATE;
     STDERR STDERR;
     ODS OUTPUT PARAMETERESTIMATES=SBP_PROP;
     RUN;
```

TRTPN is the planned treatment group, SEX is the sex of the participant, RACE is participant race, ETHNIC is participant ethnicity, SMK is participant smoking status, ALC is alcohol use. BASE is the baseline (at Randomization) average SBP value, SBP6 is the average SBP value at Week 6 (Visit 1), and SBP12 is the average SBP value at Week 12 (Visit 2). The minimum and maximum values for SBP imputation may be modified according to the observed minimum and maximum within the sample. If the multiple imputation models cannot converge, model reduction (excluding covariates) may be performed.

For binary endpoints with missing results, a single value imputation of “failure” will be performed for analysis (Section 3.10.1.1).

3.10.2.8 Tipping point analysis

If the primary analysis is statistically significant in favor of GMRx2, a MI tipping point analysis may be performed in the Randomized Population to assess the impact of missing data under the assumption that data are not missing at random. A two-dimensional tipping point analysis will be performed where the trajectories of participants in the GMRx2 treatment group with missing Week 12 data will be imputed separately from the trajectories from the active control treatment groups with missing Week 12 data. A shift parameter, delta, will be added to each imputed value. The three active control treatment groups will be imputed with a shift of 0. The shift parameter applied to the GMRx2 treatment group will be applied across a range of values. Successively larger deltas will be imposed on the imputed values of GMRx2 treatment group until statistical significance is lost, i.e. two-sided p-value is >0.05 and no longer in favor of GMRx2 for at least one of the pairwise comparisons.

3.10.2.9 Descriptive figures

The following graphical displays are planned:

- Plot of the LS Mean home SBP with 95% CI derived from the MMRM for the primary analysis will be presented.
- Results from the tipping point analysis will be presented graphically.
- Forest plots of the LS Means, 95%CI and p-values for determining heterogeneity by subgroup will be presented.
- Descriptive scatter plots to display the average weekly SBP post-randomization, where Week 1 begins at first treatment post-randomization, Week 2 begins at Day 8 of treatment post-randomization, etc.
- Descriptive scatter plots to display the change in average weekly SBP from randomization through the Randomization Period. Randomization will be defined as the 7 calendar days prior to the Randomization clinic visit (Table 3-3). The Randomization Period will begin on the first day of randomized treatment and will extend until the earliest of: Week 12 visit, End of Study visit, or 14

weeks of post-randomized BP home measurements.

- Descriptive scatter plots to display the change in average weekly SBP from end of Phase 2/FU1 visit through Period 3. End of Phase 2/FU1 visit will be defined as the 7 calendar days prior to the FU1 Week 6 clinic visit (Table 3-3). Period 3 will begin on the first day of treatment following FU1 Week 6 clinic visit and will extend until the earliest of: Week 12 visit, End of Study visit, or 7 weeks of Period 3 BP home measurements.

Scatter plots may be presented for the treatment groups overall as well as by subgroups, as appropriate. Similar plots may be presented for home DBP, as appropriate.

3.10.3 Analysis of Secondary Efficacy Outcomes

3.10.3.1 Home Blood Pressure

Analysis of home SBP and DBP secondary continuous endpoint analysis on change from baseline (randomization) will be performed on Complete Cases only, including all data available. Summary statistics, including number with missing observations, at each timepoint will be presented. Mixed models with repeated measures (MMRM) will be applied for continuous variables using the same approach as the primary endpoint (with no imputations applied).

- Difference in change in mean home SBP from randomization to Week 6,
- Difference in change in mean home DBP from randomization to Week 12,
- Difference in change in mean home DBP from randomization to Week 6,
- Difference in change in trough (i.e. before morning dose) home mean SBP from randomization to Week 12,
- Difference in change in trough (i.e. before morning dose) home mean SBP from randomization to follow-up Week 6

Additional exploratory analyses, including longitudinal models for all home SBP measurements collected during Week 6 and Week 12 may be performed.

Descriptive summaries of binary endpoints will include the number and percentage of participants with controlled BP, i.e.:

- weekly averaged SBP <135 and DBP <85 mmHg at Week 12,
- weekly averaged SBP <135 and DBP <85 mmHg at Week 6,
- weekly averaged SBP <130 and DBP <80 mmHg at Week 12,
- weekly averaged SBP <130 and DBP <80 mmHg at Week 6

Frequency of missing data will be reported.

Data will be summarized as reported, including only complete cases. Estimated proportions by treatment groups with exact Clopper-Pearson 95% CI will be presented along with the associated estimated risk difference, risk ratio, and corresponding p-values. The number and percentage with 95% CI of participants with controlled BP at Week 12 will be summarized by treatment group by:

- Number of prior therapies at enrolment
- Controlled or uncontrolled BP status at Randomization

Binary secondary endpoints will be analyzed using Generalized Estimating Equations (GEE) to account for repeated measures. For the regression analysis, participants with missing endpoint data (Week 6 or Week 12) will be imputed as “failure” at the respective timepoint(s). The GEE regression analyses will be performed on the Randomized Set. The outcome will be the post-Baseline occurrence of the event at Week 6 and Week 12 with fixed effects for treatment group, time (visit as categorical variable), treatment by time (visit) interaction,

and Baseline home SBP. The variance will be estimated using a sandwich estimator and the model to account for correlation within participant and within site. A compound symmetry covariance matrix will account for correlation within participant and site, with a fall back of an independent matrix if the model does not converge. The odds ratios and 95% CIs for the occurrence of the events will be estimated for each post-Baseline visit and treatment group. In addition, risk differences and 95% CI will be computed for each post-Baseline visit to evaluate pairwise differences between GMRx2 and dual treatments at Week 6 and Week 12.

Sample SAS Code:

```
PROC GENMOD DATA = ADEFF;
     CLASS SITEID SUBJID VISIT TRTP;
     MODEL AVAL = BASE VISIT TRTP VISIT*TRTP / DIST = BIN CL;
     REPEATED SUBJECT = SUBJID(SITEID) / TYPE = EXCH;
     WHERE VISIT IN ('WEEK6','WEEK12');
     LSMEANS VISIT*TRTP / DIFF CL ALPHA=0.05;
     RUN;
```

Risk differences and 95%CI for comparisons between the occurrence of events in GMRx2 group versus each dual control will be computed using the Predictive Margins and Average Marginal Effects SAS Macro (https://support.sas.com/kb/63/038.html). Sample SAS code with implementation to simulated data is provided in Appendix 4.

3.10.3.2 In Clinic Blood Pressure

At each scheduled trial visit, triplicate BP measurements will be performed "in clinic" after 5 minutes of seated rest and with a 1-minute interval between measurements. The last two measurements will be averaged. If only two measures were taken, both will be averaged, and if only 1 measure is taken that value will be used. The Baseline value for clinic BP measurement is the value recorded at Randomization.

As per the home BP measurements, any zero SBP or DBP values will be treated as missing.

In clinic BP endpoints are listed below:

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

Orthostatic hypotension is defined as a decrease from measured in clinic sitting to standing blood pressure of ≥20 mmHg SBP or ≥10 mmHg DBP. Orthostatic hypertension is defined as an increase from measured in clinic sitting to standing blood pressure of ≥20 mmHg SBP or ≥10 mmHg DBP.

Descriptive statistics will be used to summarize secondary endpoints by visit on complete cases only.

Continuous endpoints will be summarized using descriptive statistics. Binary endpoints will be summarized with frequency and proportions by treatment group with exact Clopper-Pearson 95% CIs along with associated estimated risk difference, risk ratio, and corresponding p-values. Frequency of missing data will be presented.

Mixed models with repeated measures (MMRM) will be applied for continuous endpoints using the same approach as the primary endpoint (with no imputations applied). Results will be presented in a similar fashion as home BP. Standing clinic BP measurements will be summarised descriptively by visit. Complete case analysis will be performed with no imputations for continuous endpoints.

Binary secondary endpoints will be analyzed using GEE regression methods in the same manner as home BP endpoints. Risk differences and 95% confidence intervals will be computed for comparisons between GMRx2 and dual control treatments. Missing values at Week 6 and Week 12 will be imputed as "failures" for the analysis.

3.11 Analysis of Safety Outcomes

3.11.1 Adverse Events of Special Interest

3.11.1.1 Definitions & Derivations

An Adverse Event (AE) is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial medications.

Drug-related AEs are AEs with a causality to drug being possibly, probably, definitely related or with a missing causality.

The only non-serious Adverse Events to be recorded are Adverse Events of Special Interest (AESIs). An AESI is the subset of AEs that are due to:

- Dizziness or any other symptom or event possibly related to hypotension,
- Abnormality detected in laboratory assessments of sodium, potassium, uric acid, glucose, lipids, creatinine or eGFR,
- Symptom of pedal edema reported by the participant,
- Any other symptom or laboratory abnormality that led to treatment withdrawal.

AESI include events occurring during Run-in, Randomization Period, and Follow-up.

A Serious Adverse Event (SAE) is any AE that meets one or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in 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.

AESIs and SAEs will be recorded from time of informed consent up to 30 days after trial medication discontinuation.

3.11.1.2 Adverse Event Summaries

For the summary of safety parameters, AEs will be classified according to the treatment period and treatment received as of the start date of the AE (Section 3.5.3). If an AE is ongoing at the time of randomization, it will be allocated to the Period 1 treatment. If a treatment ongoing at randomization worsens following randomization, the AE worsening will be allocated to the Period 2 treatment.

AESIs and SAEs will be classified according to the MedDRA (Medical Dictionary for Regulatory Activities) system (version 24.0, March 2021) and summarized by system organ class and preferred term.

Treatment periods for AE summary include: Period 1, Period 2, Period 3, Randomization Period, and Period 4. The total number of events and incidence of participants experiencing AESIs will be tabulated by treatment group and overall for the specified study periods.

For each period, any AESI or SAEs that emerges or worsens during the period of interest will be summarized:

- Adverse Events of Special Interest,
- Serious AE,
- Related AESIs – defined as those judged by the investigator to be 'possibly', 'probably' or 'definitely' related
- Related SAEs – defined as those judged by the investigator to be 'possibly', 'probably' or 'definitely' related,
- AE leading to trial medication discontinuation
- AE leading to trial discontinuation – defined as a request by the participant to withdraw from future follow-up visits

AESIs of abnormality detected in laboratory assessments for Period 1 will only include those whose lab value for that parameter was in the normal range at baseline. Summaries of AESI and SAEs occurring during the Randomized Period will include risk differences with 95% CI, computed using the Newcombe hybrid score method (with continuity correction; https://pubmed.ncbi.nlm.nih.gov/21996567/), to evaluate GMRx2 against each dual control treatment group and overall. System organ classes and preferred terms with events occurring in at least 1% of the sample will be included.

In addition, the frequency and percentage of participants discontinuing treatment due to an AE will be reported with risk differences between treatment groups computed using the Newcombe hybrid score method (with continuity correction) to evaluate the primary safety endpoint among GMRx2 treatment participants compared to each dual control treatment group, and overall.

3.11.2 Laboratory Parameters: Hematology, Biochemistry & Urine

Blood hematology, biochemistry and urine parameters will be collected according to the schedule of events. Only scheduled visit results will be presented in summary tabulations. Unscheduled visits will be included in data listings only. The baseline value for each parameter will be the latest non-missing value recorded before randomization (i.e., prior to Period 2).

Estimated Glomerular Filtration Rate (eGFR) results provided by the various pathology laboratories across study may be calculated by different equations; however any differences are expected to be balanced across randomized treatment groups and no adjustments will be made.

Actual values and changes from baseline for all laboratory parameters will be descriptively summarized by

treatment group. A subset by-participant listing of out-of-range values will be presented.

In addition, tabular descriptive summaries will present the number and percentage of participants at Week 6 and 12 with:

- serum sodium concentration below 135 mmol/l
- serum sodium concentration above 145 mmol/l
- serum potassium concentration below 3.5 mmol/l
- serum potassium concentration above 5.5 mmol/l
- serum sodium <135mmol/l or >145 mmol/l, and/or serum potassium <3.5 mmol/l or >5.5mmol/l at week 6
- serum sodium <135mmol/l or >145 mmol/l, and/or serum potassium <3.5 mmol/l or >5.5mmol/l at week 12
- eGFR (estimated GFR) drop of over 30% from baseline

Frequencies and proportions, including frequency of missing data will be presented. Risk differences with 95% CI, computed using the Newcombe hybrid score method (with continuity correction), to evaluate GMRx2 against each dual control treatment group will be performed. The analysis of binary secondary safety endpoints will be performed on the Safety Analysis Set, limited to those participants who were randomized. Participants will be grouped as treated.

3.11.3 Other Safety Analysis

Weight and BMI will be summarized descriptively using at actual values and changes from baseline by treatment groups.

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Appendix 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
CI	Confidence Interval
cm	Centimeters
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EOT	End of Trial
EU	European Union
FAS	Full Analysis Set
FCS	Fully Conditional Specification
FDA	USA Food & Drug Administration
GEE	Generalized Estimating Equation
GM	George Medicines
GMRx2	Single pill combinations of telmisartan/amlodipine/indapamide
ICH	The International Conference
LOCF	Last Observation Carried Forward
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mg	Milligram
mmHg	Millimeters of Mercury
MMRM	Mixed Model with Repeated Measures
(Q1-Q3)	Interquartile limits
RCT	Randomized Controlled Trial
RR	Risk ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard deviation
SOC	System Organ Class
STEAE	Serious Treatment-Emergent Adverse Event
TE	Treatment-Emergent
USA	United States of America
WHO	World Health Organization

Appendix 2: Additional Power Calculations

As noted in Section 2.5, the initial power calculation presented is a very conservative calculation, which is based on a simple comparison of mean values and a common standard deviation of the actual SBP values i.e., T-test of sample means with equal variances. Our modelling approach – a multivariable mixed model – is similar to an ANCOVA (Analysis of Covariance) type of analysis which will explicitly consider an adjustment for the baseline SBP values. A sample size calculation based on the ANCOVA (which would be more powerful than the simple and more conservative t-test approach used above) and on the same assumption as before (allocation ratio of 2:1 of GMRx2 vs dual, alpha 0.05, equal SD across arms of 11) would lead to the following power: 98% if regressing the SBP values to the specific covariate set the R^2 (proportion of variance explained) achieved is 10%, 99% if R^2 is 20%, 99.6% if R^2 is 30% with overall power respectively 95%, 97% and 99%. These R^2 values were considered to be conservative, since two similar, completed BP trials (TRIUMPH and QUARTET) each had R^2 values over 40% in mixed models on SBP data using treatment, time, their interaction and SBP at baseline and compared with the null model.

Supply chain and logistics issues, substantial recruitment delays related to the COVID-19 pandemic and other unanticipated issues caused unplanned and significant trial conduct interruptions. As a result of these delays, a re-supply of IMP became infeasible. In addition, there had been independent review of study power at two Steering Committee meetings (6 Dec 2022 and 14 Feb 2023), based on the prespecified statistical approach of a mixed model repeated measures and blinded standard deviation of the overall sample, that the trial likely would have more statistical power than the univariate approach on which initial powering was modelled, as detailed above. These estimates were made without any reference to unblinded data. The Sponsor informed the Steering Committee of the pending IMP supply situation at their meeting on 11 April 2023, and given these challenges and blinded study power assessment that indicated the trial already had as much power as originally planned, the Steering Committee chair consulted the Data Safety Monitoring Board. Following deliberation between the two committees, the Steering Committee Chair wrote to the Sponsor on 21 April 2023 recommending a premature termination of recruitment. Based on the foregoing, the Company decided to terminate recruitment to the study. The final number of patients randomized was over 90% of the planned sample size.

Appendix 3: Schedule of Assessment

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

Return of trial medication				✓	✓	✓	
Adherence to trial medication				✓	✓	✓	
Review of concomitant medications	✓			✓	✓	✓	✓
Safety							
AESI or SAE				→			

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

Appendix 4: Predictive Margins and Average Marginal Effects Macro and Implementation

SAS documentation on the Predictive Margins and Average Marginal Effects SAS Macro is available here: https://support.sas.com/kb/63/038.html.

Sample implementation code using simulated data:

```
data test;
      do i = 1 to 300;
      trtpn = 1;
      week = 1;
            x1 = rand('UNIFORM');
            if x1 > 0.3 then resp = 1;
            else resp = 0;
            output;
      week = 2;
            x1 = rand('UNIFORM');
            if x1 > 0.4 then resp = 1;
            else resp = 0;
            output;
            end;
      do i = 301 to 600;
      trtpn = 2;
      week = 1;
            x1 = rand('UNIFORM');
            if x1 > 0.4 then resp = 1;
            else resp = 0;
            output;
      week = 2;
            x1 = rand('UNIFORM');
            if x1 > 0.5 then resp = 1;
            else resp = 0;
            output;
            end;
      run;

proc freq data = test;
      table week*resp*trtpn / riskdiff;
      run;

%include "P:\George Medicines\ACT\macros\margins.sas";
%Margins(data      = test,
        class      = i trtpn week,
        response   = RESP,
        roptions   = event='1',
        dist       = BINOMIAL,
        model      = trtpn|week,
        geesubject = i,
        margins    = trtpn*week,
        options    = diff cl,
        diff       = all);
```