STATISTICAL ANALYSIS PLAN

Trial Title	Efficacy and safety of GMRx2 (a single pill combination containing telmisartan/amlodipine/indapamide) compared to placebo for the treatment of hypertension: An international, multi-center, randomized, double-blind, placebo-controlled, parallel-group trial
Brief Title	Efficacy and safety of GMRx2 compared to placebo for the treatment of hypertension
Phase of Development	Phase III
Trial Drug	GMRx2: Single pill combination of telmisartan/amlodipine/indapamide Dose version 1: telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg Dose version 2: telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
Trial Number	GMRx2-HTN-2020-PCT1
Indication	Hypertension
Trial Registration	Clinicaltrials.gov NCT04518306 Universal Trial Number (UTN) U1111-1262-2232
Funder	George Medicines Pty Limited

Amendment

SAP Amendment Number	Amendment date
2.0	08 December 2023

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1 ADMINISTRATIVE INFORMATION

1.1 Trial Identifiers

- **Protocol Number**: GMRx2-HTN-2020-PCT1, **Version: 6.0, Date: 10 October 2023**

1.2 Revision History

Version	Date	Details
0.1 (draft)	11AUG2020	First draft by Sandrine Stepien
1.0	17AUG2020	CKD-epi formula for eGFR. Graph example added Re-order of secondary outcomes
1.1	06FEB2023	Revise SAP according to protocol version 4. Various changes to document body and TLFs to ensure compatibility with ACT trial.
1.3	14JUN2023	Added estimands to analyses Miscellaneous minor refinements to TLFs
2.0	08DEC2023	The Statistical Analysis Plan was updated following a 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 • Revision of tipping point analysis • Additional editorial modifications to align with Protocol updates to Version 6.0

1.3 Contributors to The Statistical Analysis Plan

Name	Affiliation	Responsibility
[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, placebo-controlled trial to investigate the efficacy and safety of GMRx2 compared to placebo 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-PCT1. 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 patients with hypertension who could appropriately be treated with GMRx2 dose version 1 or GMRx2 dose version 2 or placebo.

2.2.1 Inclusion Criteria

At screening visit:

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

At randomization visit:

- Home seated mean SBP 130-154 mmHg in the week before the randomization visit.
- Adherence of 80-120% to placebo run-in.
- Tolerated placebo run-in.
- Adherence to home BP monitoring schedule: in the week before randomization, at least 6 measures (e.g. ≥2 sets of triplicate measures) including at least 1 morning and 1 evening each with ≥2 measures. Morning is defined as any measure in the am and evening as any measure in the pm. Morning and evening do not have to be same day.

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

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

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:

- Receiving 2 or more BP-lowering drugs. Note: A single tablet containing 2 or 3 different BP lowering agents (i.e. a combination medication) is considered as 2 or 3 BP lowering drugs, respectively.
- Contraindication, including hypersensitivity (e.g. anaphylaxis or angioedema), to the placebo run-in treatment or to any of the trial medications in the three randomized groups.

At randomization visit:

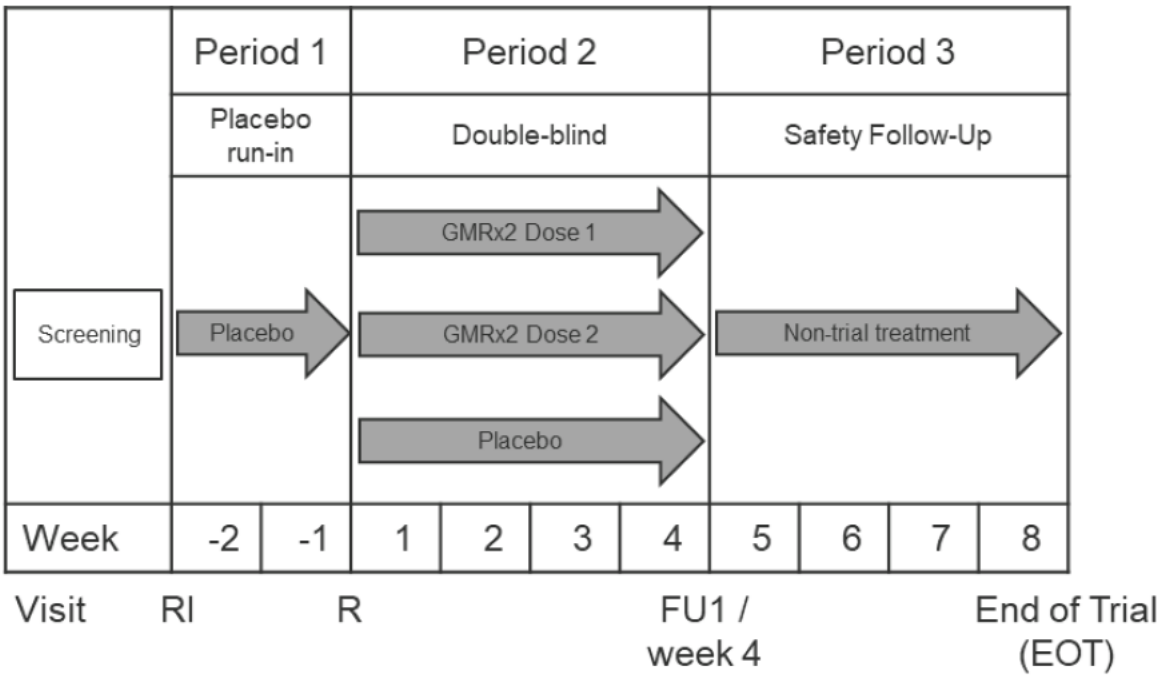
- Unable to adhere to the trial procedures during the run-in period.
- Any of the following which in the investigator's judgment may compromise the safety or wellbeing of the participant if randomized to the trial medications:
    - High or low clinic BP levels even in the light of the values for home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

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

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

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

This study is designed to investigate the efficacy and safety of GMRx2 for reducing BP in adult participants with high BP compared to placebo. The study initiates with a two week single-blind placebo run-in period where the participants are blinded to treatment (except in the UK, where regulatory authorities required participants to be informed that run-in was on placebo). After run-in, eligible participants are randomized (at Visit R), to receive GMRx2 dose 1, GMRx2 dose 2, or Placebo in 2:2:1 treatment allocation. The primary analysis timepoint is Follow-up Visit 1 (FU1)/Week 4 after randomization. Preceding this visit, participants will be requested to perform extra home BP measurements in the week running up to the clinic visit. At FU1/Week 4, the participant will complete the double-blind part of the trial and continue on non-trial treatment in a safety follow-up period. Although time periods have been nominated (4 weeks for FU1) 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 a 2-week single-blind placebo run-in, followed by a 4-week double-blind period with randomization to one of the following three treatment groups:

1. **Triple ¼** (GMRx2 dose 1): telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg
2. **Triple ½** (GMRx2 dose 2): telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
3. **Placebo**

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 allocated to receive either placebo or one of the GMRx2 doses. The ratio of randomization will be 2:2:1, as shown below:

1. **Triple ¼** (GMRx2 dose 1): N=100
2. **Triple ½** (GMRx2 dose 2): N=100
3. **Placebo:** N=50

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

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. 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 (Endpoints)

2.4.1.1 Primary

Difference in change in home seated mean SBP from randomization to Week 4.

2.4.1.2 Secondary

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

2.4.2 Safety Outcomes (Endpoints)

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 Week 4.

2.4.2.2 Secondary

- Percentage of participants with an SAE from randomization to Week 4.

- Percentage of participants with symptomatic hypotension from randomization to Week 4.
- Percentage of participants with serum sodium concentration below 135 mmol/l at Week 4
- Percentage of participants with serum sodium concentration above 145 mmol/l at Week 4
- Percentage of participants with serum potassium concentration below 3.5 mmol/l at Week 4
- Percentage of participants with serum potassium concentration above 5.5 mmol/l at Week 4
- Percentage of participants with serum sodium <135mmol/l or >145 mmol/l, and/or serum potassium <3.5 mmol/l or >5.5mmol/l at Week 4.
- Percentage of participants with eGFR drop of over 30% from randomization to Week 4
- Percentage of participants with orthostatic (postural) hypotension at Week 4
- Percentage of participants with orthostatic (postural) hypertension at Week 4

In addition, descriptive safety data will be reported on:

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

2.5 Sample Size

A total of 250 participants will be randomized: 100 for each of the GMRx2 doses and 50 for placebo group. As noted in Section 12.3 of the protocol, for the comparison of triple ¼ vs placebo at week 4, a sample size of 150 participants at a ratio of 2:1 will provide 99.7% power to detect a difference of at least 9 mmHg in mean home SBP, assuming a standard deviation of 11 mmHg. Similarly for the comparison of triple ½ vs placebo at week 4, a sample size of 150 participants at a ratio of 2:1 will provide 100.0% power to detect a difference of at least 13 mmHg in mean home SBP, assuming a standard deviation of 11 mmHg. Therefore, the power for the two comparisons versus placebo will be 99.7% (since 0.997 × 1.0 = 0.997). Note that this is a simple, conservative sample size calculation by intention – the actual experimental design and subsequent statistical modelling approach will provide greater power than this.

2.6 Changes in the Conduct of the Study or Planned Analyses

2.6.1 Changes in the Conduct of the Study

A total sample size of 250 participants was planned; however due to a number of high recruiting centres starting at a similar time towards the end of the study a total of 295 participants were randomized.

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 endpoints

3 STATISTICAL ANALYSIS

3.1 Interim Analyses

No formal, unblinded interim analysis was planned. Observed standard deviation of the home BP measurements on the overall sample were computed to support updated power calculations periodically

through the study. No modifications to the study were made.

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 for 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 both of the GMRx2 dose versions versus placebo comparisons simultaneously for the designated primary endpoint (i.e., each GMRx2 dose has to be statistically significantly superior at two-sided $p<0.05$ to placebo 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, 2022'.

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 placebo 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 adjust 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 and primary conclusions of the trial.

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. Participants will be grouped according to the treatment assigned. If the Randomized Set and the FAS are very similar in size (≤ 5% difference), 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). Major protocol deviations are defined in Section 3.9.3.

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 (screening) and on-treatment (run-in and post-randomization) study days are numbered relative to the day of the first dose of single-blind placebo 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 placebo. In Period 2, the planned treatment group is randomly assigned to be:

1. **Triple ¼ (GMRx2):** telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg
2. **Triple ½ (GMRx2):** telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg
3. **Placebo**

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 safety summaries, Period 1 (placebo run-in period) will be summarized separately from the randomized treatment period and follow-up. Efficacy summaries will not be created for Period 1.

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 placebo run-in 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 3-2.

3.5.3 Study Period for Analysis

The study is planned with 3 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, FU1 may not occur at 4 weeks exactly and screening visit is not always exactly 2 weeks before Randomization visit, due to protocol-specified visit windows and administrative issues such as scheduling issues for participants. Therefore, the analysis periods will be defined:

- Period 1: From Week -2 to Randomization, defined as from screening to Randomization and Baseline Visit,
- Period 2: From Randomization to Week 4, defined as from Randomization and Baseline Visit to FU1/Week 4 visit,
- Period 3: From Week 4 to Week 8, defined as from FU1/Week 4 to EOT/Week 8,
- Post-Randomization Period: From Randomization to Week 8, defined as from Randomization and Baseline Visit to FU2 (Period 2 and Period 3).

Analysis of the optional Open-Label Extension Study will be described in a separate analysis plan.

3.6 Subject Disposition

All participants screened who met study inclusion criteria for placebo run-in (Period 1) 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 4, Visit FU1)
- Number (%) of participants completing the trial, including safety follow-up
- Number (%) of participants prematurely and permanently discontinuing the study treatment 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 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 groups, 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)
- Change from Screening Visit to Randomization in Clinic BP (SBP and DBP)
- Average home BP at Randomization (end of Period 1 SBP; See Table 3-2 for derivations)
- Change in average home BP from first to last week of Period 1

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 ACT code level 1 and preferred term
- Number (%) of participants with at least one concomitant medication during Period 1, by ACT code level 1 and preferred term
- Number (%) of participants with at least one concomitant medication post-Randomization, by ACT 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. Adherence to trial medication will be computed overall and separately for each randomized group.

Trial medication adherence will be computed separately for the 2-week run-in period and the post-randomization treatment period (from randomization to FU1/Week 4) and 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 measured via pill counts and numbers 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 dates 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 in a separate 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, 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 Randomization and Week 4 trial visits, BP measurements should be taken on the 4 days immediately prior to the day of 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 and unblinding, 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 teams. The number of major protocol deviations will be summarized by type of deviations. All protocol deviations will be listed.

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

- Randomized even though ineligible (not including minor non-safety related reasons such as miscalculation of run-in adherence)
- Received the wrong treatment
- Non-adherence to study treatment (adherence < 80% or > 120%), for reasons known to be unrelated to tolerability or efficacy eg. 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 randomization or follow-up visit 1.

A summary table will present the tabulations by major protocol deviation on the Screened Set. All protocol deviations will be listed.

3.10 Analysis of the Efficacy Endpoints

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 home measured SBP after Week 4 of treatment post-randomization and the home measured SBP in the week 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)
- Discontinuation from the study treatment for reasons related to the study protocol or study treatment, such as lack of efficacy, tolerability, or adverse event.

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 3.10.2.6). 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 for repeated measures (MMRM). 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 3.10.2.5).

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 methods (analysis to be performed if samples differ by >5%)
2) Complete cases with Clinic BP Substitution: Participants with missing pre-Randomization or Week 4 home BP assessment 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 4 assessments without an in-clinic assessment at the designated visit will be excluded.
3) Per Protocol Analysis Set: Excluding any participants with an intercurrent event or major protocol deviation.

3.10.1.2 Secondary Estimand

The population for the secondary estimands includes adults (aged ≥18 years) with hypertension. 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 endpoint values will be assumed to have not achieved the endpoint (i.e., missing data will be singly imputed as “failure”).

Table 3-1 Estimands

Estimand Label	Treatment Comparison	Population	Population-level summary	Analysis Population	Handling of Intercurrent events
Primary Analysis	GMRx2-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs Placebo Analysis will be performed using 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 – Adjusted Analysis	GMRx2-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs Placebo Analysis will be performed using MMRM with Multiple Imputation, adjusted for covariates	Randomized Set	Treatment policy strategy with intercurrent events only used as part of missing data imputation strategy
Primary Estimand, Sensitivity Analysis – Adjusted Analysis	GMRx2-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs Placebo Analysis will be performed using 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-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs Placebo 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-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs Placebo 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

Estimand Label	Treatment Comparison	Population	Population-level summary	Analysis Population	Handling of Intercurrent events
Primary Estimand, Supplemental Analysis	GMRx2-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Difference in change in home SBP, for GMRx2 vs Placebo 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-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	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 Week 4 results reported. Complete cases only with no imputation for missing data.
Secondary Estimands, Binary Endpoints	GMRx2-dose 1 vs Placebo and GMRx2-dose 2 vs Placebo at week 4	Adults with hypertension	Binary 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 endpoint data will be imputed as “failure”.

3.10.2 Primary Efficacy Analysis

3.10.2.1 Definition – Home BP

Home seated systolic and diastolic measurements will be averaged as described in Table 3-2 and the following endpoints will be derived:

- Average home SBP during the 7 days prior to Randomization and FU1/Week 4
- Average home DBP during the 7 days prior to Randomization and FU1/Week 4
- Average trough (i.e., measurement taken before morning dose) home SBP during the 7 days prior to Randomization and FU1/Week 4

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.

Table 3-2 Definitions of Home Blood Pressure Derivations

Measure	Rules
Randomization and week 4 home BP	• Defined as home BP in the week before randomization and FU visit 1 (Week 4).
Individual BP measurement	• Each BP measurement must consist of valid SBP and DBP values (ie. 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. • Home BP are expected on at least 4 consecutive days immediately prior to the trial visits (i.e., Week -1, Week 4) 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 allocated 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 4 are averages (as defined above) 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 3-2.

3.10.2.2 Main Analysis

Blood pressure values will be summarized using descriptive statistics, including actual values and changes from Baseline (week prior to Randomization) to Week 4, by timepoint and treatment groups. Graphical presentations of group means over time will be presented on the Randomized Set by treatment group. Additional summaries may be presented.

The difference in change from Baseline to Week 4 will be analyzed using MMRM. The endpoint will be the FU1/Week 4 home SBP values with fixed effects for treatment group and Baseline home SBP. The variance will be estimated using a Huber-White sandwich estimator, with the model accounting for correlation within site. 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 placebo will be performed at Week 4. The comparisons at Week 4 will serve as the primary endpoint analysis. As an exploratory assessment, a comparison between GMRx2 dose levels will also be presented.

Sample SAS Code:

```
PROC MIXED DATA = ADEFF EMPIRICAL METHOD = REML;
      CLASS SITEID SUBJID VISIT TRTP;
      MODEL AVAL = BASE TRTP / CL;
      REPEATED / SUBJECT = SITEID TYPE = CS;
      WHERE VISIT IN ('WEEK4');
      LSMEANS TRTP / DIFF CL ALPHA=0.05;
      RUN;
```

Where ADEFF is the ADaM dataset for efficacy, AVAL represents the Week 4 home SBP measurement, BASE is the Baseline SBP value and TRTP is the planned treatment.

Superiority of the triple combination over the placebo will be shown if the 2 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 3.10.2.6).

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) Complete Cases with Clinic BP Substitution
3) Per Protocol Set excluding participants with intercurrent events or major protocol deviations

3.10.2.3 Sensitivity Analysis Pooled GMRx2

The primary analysis methods (Section 3.10.2.2) will be repeated comparing pooled GMRx2 to Placebo. The imputation from the primary analysis and primary analysis methods will otherwise remain unchanged.

3.10.2.4 Adjusted Analyses

Adjusted analyses will be performed as a sensitivity analysis by adding 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 least square mean difference and 95% confidence interval.

3.10.2.5 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 (USA; Other)
- Placebo run-in single-blinded (yes/no)*
- Baseline (at Randomization) home SBP category (<140, 140-149, ≥150 mmHg) and DBP category (<80, 80-89, ≥90 mmHg)
- Number of BP medications at Screening (0, 1)
- Hypertension status at Screening – office BP <140/90 mmHg, ≥140/90 mmHg; office BP <130/80 mmHg, ≥130/80 mmHg
- Orthostatic (postural) hypotension at Randomization (measured at clinic BP): see Section 3.10.3.2 for definitions.

* UK authorities required unblinded run-in period, non-UK centres had single blinded run-in period.

Subgroup analyses will be performed by inclusion of the subgroup main effect as well as two- way interaction terms as fixed effects with treatment within the MM. Heterogeneity of treatment effect between subgroups will be evaluated using contrast statements, to test whether the LS Mean difference between GMRx2 and placebo group differs between levels of the subgroup. Comparisons will be performed separately for each GMRx2 dose level against placebo. A comparison of combined GMRx2 doses against placebo by subgroups will also be performed. LS Means, LS Mean Differences 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 overall 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 TRTP|SEX / CL;
      REPEATED / SUBJECT = SITEID TYPE = CS;
      WHERE VISIT IN ('WEEK4');
      LSMEANS TRTP*SEX / DIFF CL ALPHA=0.05;
      lsmestimate trtP*sex "(TS11-TS31)-(TS12-TS32)"
        [1, 1 1] [-1, 3 1] [-1, 1 2] [1, 3 2]; *TRTP=1 vs TRTP=3;
      lsmestimate trtP*sex "(TS21-TS31)-(TS22-TS32)"
        [1, 2 1] [-1, 3 1] [-1, 2 2] [1, 3 2]; *TRTP=2 vs TRTP=3;
      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 or 1 medications. As such, a graphical descriptive analysis of blood pressure changes during run-in on placebo will be presented separately for different blood pressure regimens participants were receiving at screening, noting participants could be on 0-1 antihypertensives at the time, before being switched to placebo. Additional descriptive analyses will be conducted according to hypertension control status and number of antihypertensives at screening, including:

- Clinic BP at screening < 140/90 and 0 antihypertensives at screening
- Clinic BP at screening < 140/90 and 1 antihypertensive at screening
- Clinic BP at screening ≥ 140/90 and 0 antihypertensives at screening
- Clinic BP at screening ≥ 140/90 and 1 antihypertensive at screening

3.10.2.6 Treatment of Missing Data

For the primary endpoint requiring a valid weekly average home BP value preceding the Randomization and Week 4 visits, if a participant does not have a valid endpoint measure, that value will be flagged as missing and requiring imputation. In all cases it is the final 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 4 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: Participants who received the wrong treatment and have missing

Week 4 results will have results imputed from the sample of participants who received the same treatment.

b. 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 placebo.

3) Participants non-adherent to study treatment: Participants who were non-adherent to study treatment during Period 2 with missing Week 4 home BP measurement will be imputed from the sample of participants with intercurrent events and randomly assigned to placebo.
4) Participants with missing Week 4 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 4 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
2) Analysis: 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   ROUND = . . . . . 1
     MAXIMUM = . . . . . 200  MINMAXITER = 5000 SIMPLE NOPRINT;
     FCS REG(BASE = TRTPN AGE SEX RACE BMI ETHNIC SMK ALC/ DETAILS);
     FCS REG(SBP4 = TRTPN AGE SEX RACE BMI ETHNIC SMK ALC BASE / DETAILS);
     CLASS TRTPN SEX RACE ETHNIC SMK ALC;
     VAR TRTPN AGE SEX RACE BMI ETHNIC SMK ALC BASE SBP4;
     RUN;
*SBP2 will be reformatted into an analysis dataset, here titled ADEFF with
each observation 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 TRTP;
     MODEL AVAL = BASE TRTP / CL;
     REPEATED / SUBJECT = SITEID TYPE = CS;
     WHERE VISIT IN ('WEEK4');
     LSMEANS TRTP / DIFF CL ALPHA=0.05;
     ODS OUTPUT COVPARMS = CP LSMEANS = LSM DIFF = DIFFS;
     RUN;
PROC SORT DATA = DIFF;
     BY TRTP _TRTP;
     RUN;
PROC MIANALYZE DATA = DIFF ALPHA = 0.05;
     BY TRTP _TRTP;
     WHERE TRTP NE 3 AND _TRTP = 3;
     *TRTP = 3 corresponds to placebo 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 and SBP4 is the average SBP value at FU1/Week 4. 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 3.10.1.2).

3.10.2.7 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 groups with missing Week 4 data will be imputed separately from the trajectories from the placebo control treatment group with missing Week 4 data. A shift parameter, delta, will be added to each imputed value. The placebo control treatment groups will be imputed with a shift of 0. The shift parameter applied to the GMRx2 treatment groups 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.

3.10.2.8 Descriptive figures

The following graphical displays are planned:

- Plot of the LS Mean home SBP with 95% CI derived from the MM 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 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 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 3-2). The Randomization Period will begin on the first day of randomized treatment and will extend until the earliest of: FU1/Week 4 visit, End of Study visit, or 7 weeks of post-randomized BP home measurements.

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 Endpoints

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. 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 DBP from baseline to Week 4,
- Difference in change in trough home mean SBP from baseline to Week 4,
- Difference in change in trough home mean DBP from baseline to Week 4.

Additional exploratory analyses, including longitudinal models for all home SBP measurements collected through Week 4, may be performed.

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

- Weekly averaged home SBP <135 and DBP <85 mmHg at Week 4,
- Weekly averaged SBP <130 and DBP <80 mmHg at Week 4

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 4 will be summarized by treatment group by:

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

Binary secondary endpoints will also be analyzed using Generalized Estimating Equations (GEE) to account for clustering at the site level. For the regression analysis, participants with missing endpoint data (Week 4) will be imputed as "failure". The GEE regression analyses will be performed on the Randomized Set. The

endpoint will be the post-Baseline occurrence of the event at Week 4 with fixed effects for treatment group and Baseline home SBP. The variance will be estimated using a sandwich estimator and the model will account for correlation within site. 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. The odds ratios and 95% confidence intervals 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. Pairwise comparisons between GMRx2 doses and placebo will be performed.

Sample SAS Code:

```
PROC GENMOD DATA = ADEFF;
     CLASS SITEID TRTP;
     MODEL AVAL = BASE TRTP / DIST = BIN CL;
     REPEATED / SUBJECT = SITEID TYPE = EXCH;
     WHERE VISIT IN ('WEEK4);
     LSMEANS TRTP / DIFF CL ALPHA=0.05;
     RUN;
```

Risk differences and 95%CI for comparisons between the occurrence of events in GMRx2 dose levels versus Placebo will be computed using the Predictive Margins and Average Marginal Effects SAS Macro (https://support.sas.com/kb/63/038.html). Risk differences and 95%CI between GMRx2 dose levels will also be computed. Sample SAS code with implementation to simulated data is provided in Appendix 3.

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 Week 0. Standing clinic BP measurements will also be summarised descriptively.

Analysis

In clinic BP endpoints listed below:

- Difference in change in clinic SBP from baseline to Week 4,
- Difference in change in clinic DBP from baseline to Week 4,
- Percentage of participants with clinic SBP <140 and DBP <90 mmHg at Week 4,
- Percentage of participants with clinic SBP <130 and DBP <80 mmHg at Week 4
- Percentage of participants with orthostatic hypotension at Week 4
- Percentage of participants with orthostatic hypertension at Week 4

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 on complete cases only. Continuous endpoints will be summarized using descriptive statistics. Binary endpoints will be summarized with frequency and proportions by treatment groups 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. Comparisons will be made between GMRx2 dose levels and Placebo. Exploratory comparisons between GMRx2 dose levels will also be computed.

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 cases 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% CI will be computed for comparisons between GMRx2 dose levels and placebo. Missing values at Week 4 will be imputed as "failures" for the analysis.

3.11 Analysis of Safety Endpoints

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 an 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 endpoints 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) system (version 24.0, March 2021) and summarized by system organ class and preferred term.

Treatment periods for AE summary include: Period 1/Run-in Period, Period 2, Period 3 and Post-Randomization (Periods 2 and 3). 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

Note: Clinical laboratory values noted as out of range at Week 4 that were also noted as out of range at screening will not be considered emergent AESI.

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; DOI: 10.1177/0962280211415469), to evaluate each GMRx2 dose levels against Placebo. Risk differences will also be computed between GMRx2 dose levels for exploratory comparison. 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 dose levels versus Placebo. Risk differences will also be computed between GMRx2 dose levels for exploratory comparisons.

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 4 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 4
- 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 dose levels against Placebo 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
MMRM	Mixed Model for Repeated Measures
mmHg	Millimeters of Mercury
(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: Schedule of Assessment

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

[1] At Screening visit, if not collected previously. Written informed consent may be collected at pre-screening.
[2] Systems-based examination deemed necessary for the safety of participants by the site investigator
[3] The following blood and urine tests should be taken at a time most suitable for the participant at Screening visit or during run-in so that results are available for review at the RAND visit and during week 4 (ie. at the week 4 final visit or in the preceding week):

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

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

All laboratory investigations and ECG will be performed at the trial site based local laboratory. If blood test results are not available on the same day as the randomization visits, once eligibility has been confirmed, participants may need to return to the clinic to collect the trial medication and home BP monitor. Alternatively, where feasible and consent from the participant received, trial medication and home BP monitor may be couriered to the participant's home once eligibility is confirmed.

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

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

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

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

Appendix 3: 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 100;
      trtpn = 1;
      week = 1;
            x1 = rand('UNIFORM');x1 = rand('UNIFORM');
            if x1 > 0.4 then resp = 1;
            else resp = 0;
            output;
            end;
      do i = 101 to 200;
      trtpn = 2;
      week = 1;
            x1 = rand('UNIFORM');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 ,
        response   = RESP,
        roptions   = event='1',
        dist       = BINOMIAL,
        model      = trtpn,
        geesubject = i,
        margins    = trtpn,
        options    = diff cl,
        diff       = all);
```