STATISTICAL ANALYSIS PLAN

Quadruple UltrA-low-dose tReaTment for hypErTension

An investigator initiated and conducted, multicentre, randomised double blind controlled trial to assess the effectiveness and tolerability of ultra-low-dose quadruple combination therapy ('LDQT') in patients with hypertension

Final version 1.0
18th of March 2021

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Study: QUARTET

Title:

An investigator initiated and conducted, multicentre, double blind randomised controlled trial to assess the effectiveness and tolerability of ultra-low-dose quadruple combination therapy ('LDQT') in participants with hypertension – QUARTET

Version: 1.0 (Final)
Version date: 18MAR2021

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas. The principal author also finds this plan to be in compliance with ICH-E9 as well as The George Institute's SOP ST-SOP-04.

DocuSigned by:
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29 March 2021

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THE UNIVERSITY OF SYDNEY

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1. Modification history

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Draft 0.1	10MAR2020	Sandrine Stepien	N/A – First Version
Draft 1.0	30MAR2020	Sandrine Stepien	Removed ECG and EQ5D from the SAP.
Draft 2.0	28SEP2020	Sandrine Stepien	Integrate Anthony's comments Reorganize the outcome sections Clarify primary outcome derivation
Draft 3.0	22OCT2020	Sandrine Stepien	Integrate steering committee members comments and clean up the SAP
Draft 3.1	05NOV2020	Sandrine Stepien	Clarify BP Variation variable and including tipping point analysis added AE of special interest
Draft 4.0	23NOV2020	Sandrine Stepien	
Draft 4.1	29JAN2021	Sandrine Stepien	Clarify method for absolute risk difference Update "normal" load values Review of tolerability assessment
Final 1.0	18MAR2021	Sandrine Stepien	Replaced UK coef for EQ5D5L with Australian coeficients Revised tolerability outcomes : definition, analysis, shells

2. Introduction

This document describes the intended statistical analyses to be performed on data collected in the QUARTET trial. It describes, in detail, the data and variables to be summarized and analysed, including specifics of the statistical analyses to be performed. This document is based on the protocol version 8.0 – 8th April 2018.

It is intended to be stand-alone from the protocol and adhere to the main points in the analysis summary specified in the protocol. However, the Statistical Analysis Plan can undergo revision outside of the protocol version 8.0 – 8th April 2018.

The analysis plan also outlines the proposed layout of tables and figures that will be presented.

3. Study objectives

This trial has been designed to investigate in a double blind randomised controlled trial whether initiating treatment with ultra-low-dose quadruple-combination therapy ('LDQT') will lower blood pressure more effectively, and with fewer side effects, compared to initiating standard dose monotherapy as per current guidelines in patients with hypertension.

3.1. Primary objective

The primary objective of this study is to determine whether a combination pill comprising four types of blood pressure lowering medications each at ¼ standard doses will lower blood pressure more effectively after 12 weeks of treatment than initiating patients with standard dose monotherapy as per current guideline-recommended therapy.

3.2. Secondary objectives

Secondary objectives of this study are to assess:

- If this LDQT approach is safe and has fewer side effects compared to standard care including long term tolerability to 12 months;
  - The effectiveness of BP control at later time points,
  - The self-reported BP lowering medication use (adherence),
- the cost effectiveness of such strategy,

and finally, to investigate the acceptability to clinicians and patients.

3.3. Process Evaluation

The acceptability and feasibility of the process will be examined to help identify which factors are important to patients and health providers in blood pressure reduction. Analyses for this component of the study are not described in this statistical analysis plan (SAP) but will be specified separately.

3.4. Economic evaluation

A cost-effectiveness analysis, taking a health system perspective, will compare the LDQT strategy with usual care. See separate analysis plan for the economic evaluation analysis.

4. Study design

4.1. General Description

The QUARTET trial is a double-blind randomized controlled trial with 12 weeks of follow-up. The study is conducted in Australia and New Zealand, recruiting participants with previous documentation of hypertension or high blood pressure from GP, pharmacist or health care professional from community, primary care centres and hospital outpatient clinics.

Either LDQT (intervention) or irbesartan 150 mg (standard care/control) have been randomly allocated, in a 1:1 ratio, to 650 patients who consented to participate to the trial and who are either treatment naïve or on monotherapy requiring initiation or intensification of pharmacological treatment.

- The control group follows that recommended by the current Australian Hypertension guidelines
- The intervention group commences intervention treatment with of one capsule containing the selected quarter standard doses (with standard dose defined as the most reported usual maintenance dose recorded by the British National Formulary (BNF), Martindale and Monthly Index of Medical Specialties (MIMS)) of the following:
  - ✓ Irbesartan 37.5mg
  - ✓ Amlodipine 1.25mg
  - ✓ Indapamide 0.625mg
  - ✓ Bisoprolol 2.5mg

4.2. Control/Intervention Groups

4.2.1. Description

Patients who are on monotherapy when screened will be asked to stop their treatment while they are taking the study treatment.

The control group will receive irbesetan 150mg and at 6 weeks, if the BP is greater than 140/90 mmHg, the study clinician can consider adding amlodipine 5mg. This approach is in line with the current Australian Hypertension guidelines,[31] i.e. initiating with an ACE-I or ARB, and if BP not controlled adding a CCB in combination. This approach is also consistent with the 2011 NICE Hypertension Guidelines, and among the preferred treatment options in the 2013 JNC-8 Guidelines and the 2013 ESC/ESH Guidelines. Irbesartan was chosen as it has a long half-life and amlodipine is the most commonly prescribed CCB in Australia for blood pressure management includes prescribed drugs as per usual practice.

The intervention group (LDQT)will receive a combination pill of Irbesartan 37.5mg/ Amlodipine 1.25mg/ Indapamide 0.625mg/ Bisoprolol 2.5mg and at 6 weeks, if the BP is

greater than 140/90 mmHg, the study clinician can consider adding amlodipine 5mg.

4.2.2. Method of Assigning Patients to Control/Intervention Groups

Randomisation is accessible through a central, computer-based randomisation service, and is stratified by site. The random allocation sequence is 1:1 (control:intervention) allocation ratio.

4.2.3. Blinding

This study is double blind which means the trial participants are blinded to study treatment allocation as well as study team members. Only the nominated unblinded statistician and the manufacturer of the investigational products will have access to the randomisation schedule.

4.3. Outcomes

4.3.1. Efficacy Outcomes

4.3.2. Primary Outcomes

The primary outcome will be difference between groups in mean automated office systolic blood pressure at 12 weeks adjusted for baseline values

4.3.3. Secondary Outcomes

24-hour ambulatory blood pressure measures

a) **Difference between groups in mean 24-hour SBP and DBP at 12 and 52 weeks**
b) Difference between groups in mean change in 24-hour SBP and DBP from 0 to 12 weeks, 0 to 52 weeks and 12 to 52 weeks
c) Difference between groups in mean daytime SBP and DBP at 12 and 52 weeks
d) Difference between groups in mean night-time SBP and DBP at 12 and 52 weeks
e) Difference between groups in daytime, night-time, and 24-hour BP load (percentage area under the blood pressure curve above normal day, night, and 24-hour values as per NHFA Guide to diagnosis and management of hypertension in adults 2016)
f) Difference between groups in the proportion of non-dippers (night-time BP is not more than 10% lower than average daytime BP as per NHFA Guide to diagnosis and management of hypertension in adults 2016) and coefficient of variability of BP

Other blood pressure measures in LDQT vs control groups:

a) **Difference between groups in mean automated office systolic (52 weeks) and diastolic blood pressure (12 and 52 weeks)**
b) **Difference between groups in standard clinic SBP and DBP at 12 and 52 weeks**

c) Hypertension control (% with SBP <140 mmHg and DBP <90 mmHg and tight BP control, defined as % with SBP <130 mmHg and DBP<80 mmHg) at 6, 12, 26 and 52 weeks

d) Percentage requiring step-up treatment at 6 weeks

e) Percentage requiring step-up blood pressure lowering treatment over 52 weeks

f) Percentage with both BP control (as defined above) and no adverse events

g) Difference between groups in SBP and DBP variability, defined as difference in SD and coefficient of variability .{Parati, 2013 #5732; Chowdhury, 2019 #5733}.

4.3.4. Tolerability Outcomes

a) Difference between groups in any potentially related side-effects.

b) Difference between groups in common potentially related side-effects

c) Difference between groups in mean potassium, mean sodium, uric acid, blood glucose, cholesterol and fractions, ALT, AST, UACR (Urine albumin-to-creatinine ratio) and creatinine levels

d) Difference between groups in participant withdrawals from treatment for any reason and withdrawals due to a treatment-related AE or SAE.

In addition – we will report

e) Differences between groups in any hypotension, symptomatic hypotension, asymptomatic (or unknown) hypotension.

f) Difference in any bradycardia, symtomatic bradycardia, asymptomatic (or unknown) bradycardia.

4.3.5. Safety Outcomes

Proportion of participants with any serious adverse event

4.3.6. Other Outcomes

Self-reported medication adherence

Pill count

4.4. Determination of Sample Size

The assumptions are as follow:

- ✓ Irbesartan 150mg and up-titration in 75% with the addition of amlodipine will give an average reduction of 12mmHg in the control group from an average baseline SBP of 150mmHg,
- ✓ The quadruple combination therapy is expected to reduce SBP by at least 16mmHg (Based on the information presented in section 3.2.1 of the protocol)

A sample size of 650 patients would provide 90% power at p=0.05 to detect a difference of 4 mmHg in the primary outcome, assuming an SD of 15mmHg. A sample of 650 would also

have 85% power to detect a 3mmHg difference in average 24hr SBP (SD 12 mmHg) and 85% power to detect a 25% increase in proportion with controlled blood pressure (RR of 1.25) assuming 50% will be controlled in the control group. All calculations allow for a 10% dropout or data loss rate.

4.5. Changes in the Conduct of the Study or Planned Analyses

4.5.1. Changes in the Conduct of the Study

Not applicable.

4.5.2. Changes in Planned Analysis

Regarding other blood pressure measures, from the protocol, hypertension control was looking at the following ranges: SBP <140 mmHg and DBP <90 mmHg. A tight BP control was added in this SAP (see section 4.3.1.2).

5. Statistical Methods

5.1. General Methodology

SAS version 9.4 or any relevant recognized statistical software for academic studies will be used in the statistical analysis.

No visit window will be applied to determine the inclusion of the visit assessment in the analysis. Any visits outside the visit window range will be reported in the protocol deviation listing.

All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. All intervention evaluations will be performed on the principle of 'intention to treat' unless otherwise specified.

Methods of handling missing data for the primary and secondary endpoints are described section 6.2 of this SAP. No adjustments for multiplicity are planned for the primary and secondary endpoints.

Summaries of continuous baseline variables will be presented as means and standard deviations together with medians and inter-quartile ranges. Minimum and maximum values may also be provided in order to check for extreme values or data issues. Categorical variables will be presented as frequencies and percentages.

Mock tabular are shown in the Appendix of this document.

5.2. Handling of Dropouts or Missing Data

Dropouts will not be replaced in this study.

The percentage of missing data at baseline and week 12 for the on clinic automated BP and as well the percentage of dropouts for the primary outcome will be investigated in order to confirm the power of the analysis being retained at over 90%.

Two different imputation methods will be used to assess the possible impact of missing data

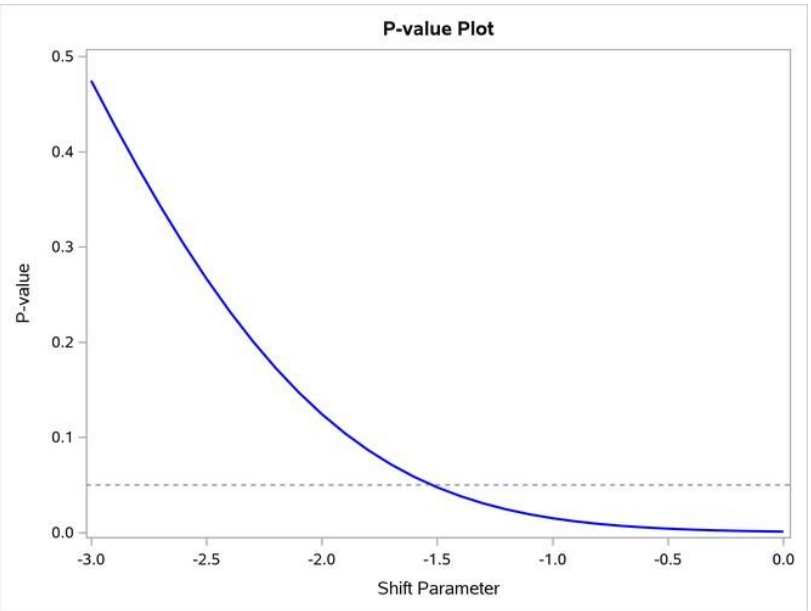
on the primary outcome analysis using different assumptions.

A multiple imputation technique (FCS) will be used to investigate the impact of missing data based on the missing at random (MAR) assumption. [Section 7. References 6, 7, 8]

A tipping point analysis will be exploring the influence of missingness on the overall conclusion by adding an incremental shift to the imputed missing values in order to assess a wide spectrum of assumptions regarding the missingness mechanism (from less conservative to more conservative).

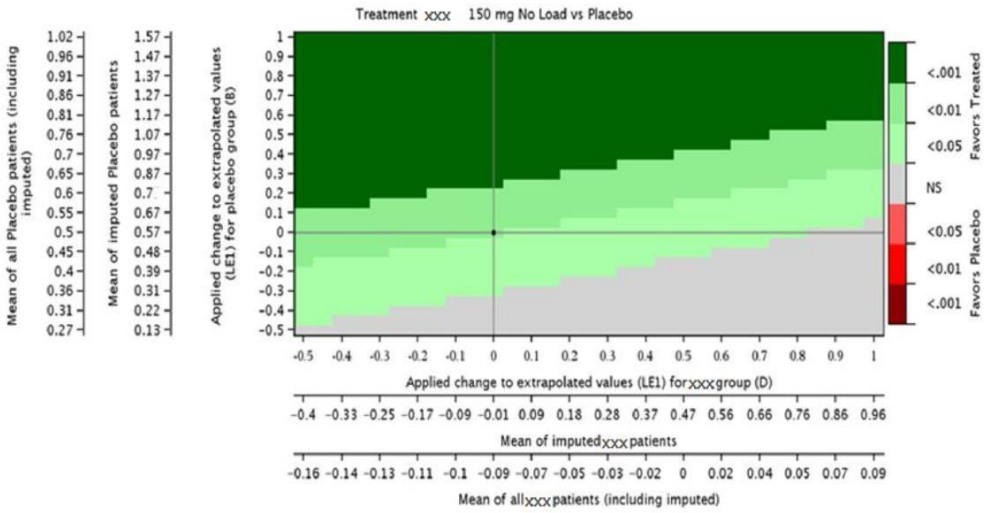
The analysis finds a (tipping) point, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified while the result is no longer statistically significant. This imputation analysis used a specified sequence of shift parameters, which adjust the imputed values for observations in both the intervention group and in the usual care group. The tipping point can be identified while the result is no longer statistically significant. [Section 7. References 9, 10, 11]

Below are examples for your reference



- The values on two axis are delta (shift values).
- The yellow highlighted area is the safe area (with all significant p values).
- The area on the right of the boundary is the dangerous area, which includes p values corresponding to all combinations of shifts from the imputed values (under MAR) for dropout subjects in treatment and placebo groups that would overturn significant treatment effect.

Figure 16.1.9-2.4 (Page 1 of 3)
Tipping point analysis of joint structural damage total sharp score change from baseline at Week 24
Full Analysis Set



5.3. Adjustments for Covariates

No adjusted analysis is planned.

5.4. Interim Analyses

No interim analysis was planned for this study.

5.5. Multicenter Studies

This study is stratified by centre and as a consequence the primary analysis will be adjusted by centre.

5.6. Multiple Comparisons/Multiplicity

No multiple comparison adjustments will be made.

5.7. Examination of Subgroups

The following pre-specified subgroup analyses will be conducted on the primary efficacy variable:

- Age (split by tertiles)
- Sex
- Diabetes
- Education (high/low) where high education is anything beyond secondary school
- Systolic blood pressure at baseline into tertiles
- Diastolic blood pressure at baseline into tertiles
- By BP lowering treatment at baseline (no treatment vs monotherapy)
- Participants with cardiovascular disease (yes/no)

For each subgroup analysis a model will include the subgroup variable along with its interaction with treatment. A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term. The results of these subgroup analyses will be treated with caution as this study was not powered for these analyses. Forest plots will be prepared for ease of presentation.

6. Statistical Analysis

6.1. Disposition of Subjects

All subjects screened and randomised will be accounted for. All post-randomisation discontinuations will be summarised overall and by time of discontinuation. Reason for discontinuation will also be summarised.

Subject disposition will be based on the screened set and tabulated for the following categories:

- Total number of subjects screened
- Total number of subjects randomised
- Number (percentage) of subjects completing the study
- Number (percentage) of subjects prematurely discontinuing from the study
- Primary reason for premature discontinuation

The flow of subjects will be presented using a consort diagram.

6.2. Selection of Subjects to be included in the Analyses

All randomised patients will be included in the analysis following the Intent-to-treat (ITT) principles.

We will also look at the following set of patients:

- Received at least one dose of LDQT for the Intervention arm
- Some post-randomisation data of SBP and DBP are available for both intervention and control arm

and if it differs from the randomised set by more than 10% we will look at baseline summaries on both randomized and ITT sets.

Another analysis set will be investigated, including all participants who have been assessed at week 52.

6.3. Baseline Characteristics

Baseline demographic variables such as:

- age,
- sex,
- ethnicity,
- country of birth,
- height,
- weight,
- body mass index (BMI),
- systolic blood pressure,
- diastolic blood pressure,
- heart rate,
- lifestyle status: smoking, drinking, exercise and eating habit,

- socio economics,
- hypertension and other medical history: hypertension, CVD, diabetes, …,
- baseline treatment status: treatment naïve, currently not on treatments (4 weeks), currently taking on BP lowering drug,
- baseline medications: Blood pressure lowering, other cardiovascular medications, any alternative medicine for hypertension or CVD,
- pregnancy status

will be summarised per group (control/intervention) on the randomised population.

See the Appendix for a list of tables that will be used for presenting baseline characteristics.

Systolic and diastolic blood pressure recorded by automatic machine as well as heart rate values summarised in the descriptive tables will be the simple unweighted average value of all the consecutive automated measurements.

6.4. Medications

6.4.1. Variable descriptions/derivations

Medications will be classified into the following categories: antiplatelet, cholesterol lowering, BP lowering, other.

Concomitant medications are all medications that started or were ongoing from randomisation (Week 0) to the end of study.

6.4.2. Analysis

Concomitant medications will be summarised descriptively and presented by treatment group and drug category.

6.5. Analysis of Efficacy

6.5.1. Primary Analysis

6.5.2. Variable descriptions/derivations

Using a validated automated digital blood pressure monitor, 3 measurements will be programmed and assessed as follow:

- ✓ start the 1st measurement after 5 minutes of rest,
- ✓ the 2nd measurement 1 minute after 1st measurement
- ✓ the 3rd measurement 1 minute after the 2nd measurement.

Patients should be seated in a quiet room, and the researcher should press the button to start the 3 measurements prior to leaving the room.

The 3 measurements and the corresponding average are then recorded into the database. The averaged value will be the value used for the analysis described below.

6.5.3. Analysis

The average value of the systolic blood pressure values recorded at week 12 as well as the corresponding change from baseline will be summarised descriptively by treatment group. An analysis of covariance on the change from baseline values will be presented as follow:

- For each treatment group, the adjusted change from baseline means and corresponding 95% confidence intervals (CI)
- the estimated mean difference between treatments on the change from baseline and its corresponding p-value.

Those estimates will be extracted from a mixed model with SBP baseline as a fixed effect and site as a random effect.

6.5.4. Secondary Analyses

6.5.5. Variable descriptions/derivations

a) 24-hour ambulatory blood pressure measures

- mean 24-hour SBP and DBP at 12 and 52 weeks,

b) Other blood pressure measures

- mean automated office systolic (52 weeks) and diastolic blood pressure (12 and 52 weeks),
- observed standard clinic SBP and DBP at 12 and 52 weeks,
- proportion of participants with hypertension control (% with SBP <140 mmHg and DBP <90 mmHg and % with SBP <130 mmHg and DBP <80 mmHg)) at 6, 12, 26 and 52 weeks (clinical measurement).

6.5.6. Analysis

Secondary blood pressure measures will be similarly analysed using an analysis of covariance as per the primary outcome. Excluding the 24h ABPM, other BP measures will be additionally analysed including 6-week, 12-week, 26-week and 52-week measurements in a longitudinal analysis of change from baseline BP. The overall mean per treatment arm and overall difference (and 95% confidence interval) between treatment arms will be calculated using a repeated-measure linear mixed model with a fixed effect of treatment, a fixed categorical effect of time (study visit), a fixed interaction between treatment and time, a fixed continuous effect of baseline SBP, a random site effect (to model within-site correlations) and a random patient effect (to model within-patient correlations). The different visit intervals will be taken into account into the model. The mean difference between intervention and control and corresponding 95% CI for each post baseline visit will be estimated with the above model by using the appropriate coefficients and contrasts.

The proportion of participants achieving BP control target at the different post baseline visits will be summarized descriptively as well as analysed using log-binomial regression with treatment group as fixed effects and center entered as random effect. Proportions by treatment groups with 95% Confidence Intervals (CI) will be presented along with the

associated estimated relative risk and its corresponding p-value. Absolute risk difference (RD) with 95% CI will be estimated using a binomial identity model (similar model as above but replacing the log link by the identity link). The RD and the standard error (SE) will be extracted from the model. The normal approximation for the 95 % confidence intervals (CIs) for the RD will be as follow: RD $\pm 1.96 \times SE_{\text{model fitted}}$ (Wald formula). If the model does not converge, a Poisson GEE model with identity link will be applied to estimate RD and corresponding 95% CI (using SE and Wald formula).

6.5.7. Other efficacy analysis

6.5.8. Variable descriptions/derivations

a) <u>24-hour ambulatory blood pressure measures</u>

- **mean change in 24-hour SBP and DBP from 0 to 12 weeks, 0 to 52 weeks and 12 to 52 weeks**:
  From the received files (one per patient and per visit), the total systolic mean variable and the total diastolic mean variable at week 12 and week 0 will be extracted to compute the change from week 0 to week 12 for each participant. Same process for change from week 0 to week 52 and change from week 12 to week 52.

- **mean daytime SBP and DBP at 12 and 52 weeks**:
  From the received files (one per patient and per visit), the awake systolic mean variable and the awake diastolic mean variable at week 12 and week 52 will be extracted.
  We will derive 2 different variables for awake BP mean variables:
  1. *The primary approach will use the diary entry for sleep/awake time and if missing a standard awake time period will be applied (from 7am to 11pm). The corresponding BP values will be averaged per participants and per visits over the awake time period provided by the participant.*
  2. *the secondary approach will be to apply to all ambulatory BP values the standard awake time disregarding the participant diary entry and averaging the BP values over the standard time period.*

- **mean night-time SBP and DBP at 12 and 52 weeks**:
  From the received files (one per patient and per visit), the asleep systolic mean variable and the asleep diastolic mean variable at week 12 and week 52 will be extracted.
  We will derive 2 different variables for asleep BP mean variable:
  1. *The primary approach will use the diary entry for sleep/awake time and if missing a standard asleep time period will be applied (from 11pm to 7 am). The corresponding BP values will be averaged per participants and per visits over the asleep time period provided by the participant.*
  2. *the secondary approach will be to apply to all ambulatory BP the standard asleep time disregarding the participant diary entry and*

averaging the BP values over the standard time period.

- **daytime, night-time, and 24-hour BP load**:
  "Total Sys Load", "Awake Sys Load"; "Asleep Sys Load", "Total Dia Load", "Awake Dia Load"; "Asleep Dia Load" which will be extracted from the different received files but also rederived the same way as BP measures described previously. The systolic and diastolic load refers to the percentage of ambulatory BP measurements above threshold set as (xx/xxx bpm), and is calculated automatically, in the analyzing software. BP load (percentage time during which BP readings exceed hypertension threshold over 24 h) should ideally be less than 20% Loads. Loads in excess of 20% will be considered abnormal. (Section 7. References 5.)

- **proportion of participants with non-dippers**:
  A dip is defined as the difference between the mean systolic pressure in the day and mean systolic pressure during the night, expressed as a percentage of the daytime mean, with the accepted normal between 10% and 20%. Non-dippers are participants with a dip lower than 10%.

- **coefficient of variability of BP**.
  For each patient and each visit, the standard deviation of the 24h ambulatory BP measurement divided by its mean is then used as a continuous variable.

b) Other blood pressure measures

- **proportion of participants requiring step-up treatment at 6 weeks**:
  At 6 weeks if the BP is greater than 140/90 mmHg in either treatment group, the study clinician will consider adding amlodipine 5mg.

- **proportion of participants requiring step-up blood pressure lowering treatment over 52 weeks**:
  (note: week 6 step-up will be included in the total number of step-up of BP lowering treatment).

- **proportion of participants with both BP control and no potentially related side-effects**:
  At week 6, observed standard clinic BP control defined as SBP <140 mmHg and DBP <90 mmHg (repeat analysis with SBP <130 mmHg and DBP <80 mmHg) with no potentially related side-effects (common or other) new or ongoing at the time of assessment. It will also be looked at week 12, 24, 36 and 52 .

- **proportion of participants with both BP control (as defined above) and no treatment related withdrawal due to Severe Adverse Events**.

- **SBP and DBP variability**

BP variability, derived for each individual as for each individual as the standard deviation of the 24h ambulatory BP measurement.

6.5.9. Analysis

Continuous BP variables will be descriptively summarised and similarly analysed as the primary and secondary endpoints (see section 7.3.1.2).

Binomial variables will be analysed using a log-binomial regression as described in section 7.5.2.2.

6.5.10. Subset Analyses

The subset population of all participants who have completed Week 52 will be looked at for the primary and secondary efficacy outcomes.

6.6. Tolerability Assessments

6.6.1. Variable descriptions/derivations

- **laboratory parameters**:
  plasma biochemistry (Na+, K+, Cl-, bicarbonate, urea, serum creatinine, eGFR, uric acid), liver function test (ALT, AST, ALP, GGT, albumin & bilirubin), UACR (Urine albumin-to-creatinine ratio), LDL, HDL, total cholesterol , triglycerides, fasting glucose and hemoglobin.

- **Any potentially related side-effects:** .
  either reported including dizziness, any hypotention, any bradycardia, heart failure, ankle oedema, skin rash, itching, other (e.g. blurred vision, syncope/ collapse/ fall, chest pain/ angina, shortness of breath, cough, wheeze, gout, or any other reported) or measured – i.e. hyperkalaemia, hypokalaemia, hyponatraemia)

- **Common potentially related side-effects: .**
  reported in Adverse Events of Special Interest list (p33, V8 protocol and Table 9.2, page 39-45) - (dizziness, hypotension, pedal oedema, headache, muscle cramps, bradycardia, heart failure, hypersensitivity reactions (skin rashes, itching), gastrointestinal complaints, musculoskeletal trauma)

- **proportion of participants withdrawing from treatment**:
  - the proportion of patient who withdrew treatment for any reasons
  - the proportion of patient who withdrew treatment due to a treatment-related SAE

6.6.2. Analysis

Laboratory parameters will be analysed descriptively onlyusing actual and change from baseline values will be summarised.

A negative binomial regression with site as random effect and the log of follow-up time as an

offset will be used to compare the number of potentially related side-effects (“any” or “common”), from baseline to Week 52.

The same model will be applied on the proportion of participant who withdrew from treatment.

Overall rate and rates of each separate “Common potentially related side-effects” (or AESI) will presented in a table. The total number of AESI by visit, type and treatment groups will also be presented on the same graph.

Hypotension and bradycardia will be summarized descriptively only. (table 19b)

6.7. Analysis of Safety

All safety analysis will be descriptive only.

6.7.1. Adverse Events and Serious Adverse Events

6.7.2. Variable descriptions/derivations

Any new or ongoing AEs (“Other” category) at the time of visit has been recorded in the CRF. AESIs status: presence (new or ongoing) or absence have also been collected at each visits.

A Serious Adverse Event (SAE) is any AE that meets 1 or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Medically significant event.

Causality to treatment for all SAEs has been evaluated by an independent medical monitoring group and classified into: unrelated or possibly related to treatment. AEs/AESIs causality has not been collected.

6.7.3. Analysis

Number of events and numbers and proportions of subjects experiencing AEs will be tabulated by treatment group received and overall. SAEs will be classified according to the MeDRA vxx.xx (Medical Dictionary for Regulatory Activities) system and summarized by system organ class and preferred term and treatment group. SAEs will also be summarized by causality to treatment.

No inferential statistics will be used to compare proportions between treatment groups.

Mock tables 20 to 22 show how AEs should be summarized and displayed in each output.

6.8. Other analysis

6.8.1. Variable descriptions/derivations

- Pill count
  Medication adherence expressed in percentage will be calculated as follow: (number of pills dispensed – number of pill returned) / expected number of pills taken for the duration the participant was "on-study) x 100
  We will look at the following categories:
  =0 to 79%; 80% to 100%; above 100%

  Note: every 3 monthly visit including the first randomisation visit, participants were dispensed kits. Each kit contains 3 bottles containing 33 tablets in each bottle.

- Self-reported medication adherence
  Adherence is defined as the participant taking the drug for at least 4 out of the last 7 days. This information is self-reported.

- EQ-5D-5L: health state, EQ VAS and index value derived using the Australian coefficients (see appendix 13).

6.8.2. Analysis

The analysis will be descriptive only for pill count and EQ-5D-3L.

The self-reported adherence (Yes/No) at end of follow up visit (patient last visit) will be analysed using the descriptive statistics and analysed using a log binomial model as described in section 7.5.2.2. This will be repeated for week 12 and 52.

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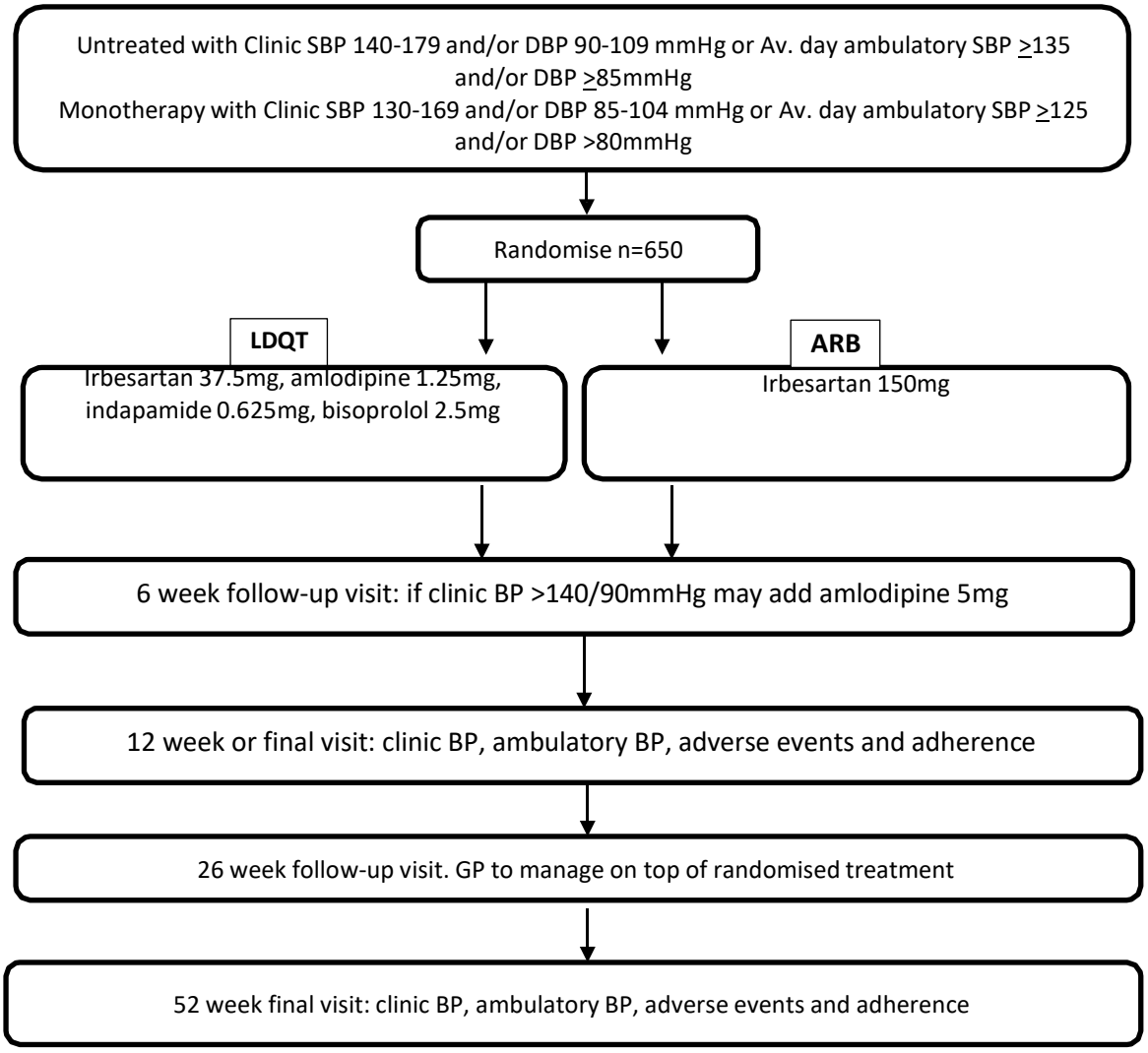
8. List of tables

9. List of listings

10. Appendix 1: Schedule of Evaluations



11. Appendix 2: Schedule of Events

Study Periods	Baseline	Randomisation	Treatment		Extension	
Study Week	-2 to 0	0	6	12	26	52
Study Visit Window from Randomisation	+/- 14 days	N/A	+/- 5 days	+/- 5 days	+/- 14 days	+/- 14 days
Evaluation						
Informed Consent	X					
Inclusion/ Exclusion Criteria	X	X				
Randomisation		X				
Study Drug dispensed		X	X[1]	X	X	
Status of participant			X	X	X	X
Study Drug returns and Pill counts			X[2]	X	X	X
Demographics (DOB, Sex, Ethnicity)	X					
Hypertension History	X					
Medical History	X					
Lifestyle (smoking/alcohol)	X					
Anthropometrics (Height, Weight, BMI)	X					
Socio-economics	X					
Vital Signs (heart rate, clinic BP x 1, automated office blood pressure x 3)	X		X	X	X	X
Plasma Biochemistry (Na+, K+, Cl-, bicarbonate, urea, serum creatinine, eGFR, uric acid)	X[3]		X[4]	X	X[4]	X
Liver Function Tests (ALT, AST, ALP, GGT, albumin & bilirubin)	X[3]		X[4]	X	X[4]	X
Urine albumin creatinine ratio	X[3]		X[4]	X	X[4]	X
Fasting glucose	X[3]		X[4]	X	X[4]	X
LDL, HDL, total cholesterol & triglycerides	X[3]		[4]	X[4]	X[4]	X[4]
Haematology (Haemoglobin)	X[3]		[4]	X[4]	X[4]	X[4]
12- lead ECG	X[3]		X[5]	X[5]	X[5]	X
Medication Adherence	X			X		X
24hr ABPM	X			X		X

Study Periods	**Baseline**	**Randomisation**	**Treatment**		**Extension**	
Study Week	-2 to 0	0	6	12	26	52
Study Visit Window from Randomisation	+/- 14 days	N/A	+/- 5 days	+/- 5 days	+/- 14 days	+/- 14 days
Evaluation						
Health Service Utilisation			X	X	X	X
Quality of life	X			X		X
AEs and SAEs			X	X	X	X
Concomitant Medications	X		X	X	X	X

1. *At 6 weeks if the BP is > 140/90 mmHg, the study clinician will consider adding amlodipine 5mg*
2. *If participant withdraws from study count returned drugs required*
3. *If the participant has had laboratory including ECG and urine assessments conducted within 3 months of the screening/ enrolment visit, these tests are not required to be repeated.*
4. *Only repeat laboratory/urine assessments that were outside of the laboratories normal reference ranges at visit 1 and/ or were considered clinically significant by the study investigator(s)*
5. *Repeat ECG only if required as per current guidelines*

12. Appendix 3 – 24-hour Ambulatory Blood Pressure Measure File and variables

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Asleep_Central_Pulse_Pressure_Ma	Asleep Central Pulse Pressure Max	$	10	
Asleep_Central_Pulse_Pressure_Me	Asleep Central Pulse Pressure Mean	$	2	
Asleep_Central_Pulse_Pressure_Mi	Asleep Central Pulse Pressure Min	$	10	
Asleep_Central_Pulse_Pressure_St	Asleep Central Pulse Pressure Std Dev	$	3	
Asleep_Dia_Above_Threshold_Count	Asleep Dia Above Threshold Count	$	1	
Asleep_Dia_Load	**Asleep Dia Load**	**$**	**1**	**Y**
Asleep_Dia_Max	Asleep Dia Max	$	10	
Asleep_Dia_Mean	**Asleep Dia Mean**	**$**	**2**	**Y**
Asleep_Dia_Min	Asleep Dia Min	$	10	
Asleep_Dia_Std_Dev	Asleep Dia Std Dev	$	3	
Asleep_Dia_Threshold	Asleep Dia Threshold	$	2	
Asleep_HR_Max	Asleep HR Max	$	10	
Asleep_HR_Mean	Asleep HR Mean	$	2	
Asleep_HR_Min	Asleep HR Min	$	10	
Asleep_HR_Std_Dev	Asleep HR Std Dev	$	3	
Asleep_MAP_Max	Asleep MAP Max	$	10	
Asleep_MAP_Mean	Asleep MAP Mean	$	2	
Asleep_MAP_Min	Asleep MAP Min	$	10	
Asleep_MAP_Std_Dev	Asleep MAP Std Dev	$	3	
Asleep_Pulse_Pressure_Max	Asleep Pulse Pressure Max	$	10	

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Asleep_Pulse_Pressure_Mean	Asleep Pulse Pressure Mean	$	2	
Asleep_Pulse_Pressure_Min	Asleep Pulse Pressure Min	$	10	
Asleep_Pulse_Pressure_Std_Dev	Asleep Pulse Pressure Std Dev	$	1	
Asleep_Sys_Above_Threshold_Count	Asleep Sys Above Threshold Count	$	1	
Asleep_Sys_Load	**Asleep Sys Load**	**$**	**2**	**Y**
Asleep_Sys_Max	Asleep Sys Max	$	11	
Asleep_Sys_Mean	**Asleep Sys Mean**	**$**	**3**	**Y**
Asleep_Sys_Min	Asleep Sys Min	$	11	
Asleep_Sys_Std_Dev	Asleep Sys Std Dev	$	3	
Asleep_Sys_Threshold	Asleep Sys Threshold	$	3	
Asleep_cAIX_75_Max	Asleep cAIX@75 Max	$	10	
Asleep_cAIX_75_Mean	Asleep cAIX@75 Mean	$	2	
Asleep_cAIX_75_Min	Asleep cAIX@75 Min	$	10	
Asleep_cAIX_75_Std_Dev	Asleep cAIX@75 Std Dev	$	4	
Asleep_cAIX_Max	Asleep cAIX Max	$	10	
Asleep_cAIX_Mean	Asleep cAIX Mean	$	2	
Asleep_cAIX_Min	Asleep cAIX Min	$	10	
Asleep_cAIX_Std_Dev	Asleep cAIX Std Dev	$	4	
Asleep_cAIx_Threshold	Asleep cAIx Threshold	$	1	
Asleep_cAP_Max	Asleep cAP Max	$	10	
Asleep_cAP_Mean	Asleep cAP Mean	$	2	
Asleep_cAP_Min	Asleep cAP Min	$	10	
Asleep_cAP_Std_Dev	Asleep cAP Std Dev	$	1	

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Asleep_cAP_Threshold	Asleep cAP Threshold	$	1	
Asleep_cDia_Max	Asleep cDia Max	$	10	
Asleep_cDia_Mean	Asleep cDia Mean	$	2	
Asleep_cDia_Min	Asleep cDia Min	$	10	
Asleep_cDia_Std_Dev	Asleep cDia Std Dev	$	3	
Asleep_cHR_Max	Asleep cHR Max	$	10	
Asleep_cHR_Mean	Asleep cHR Mean	$	2	
Asleep_cHR_Min	Asleep cHR Min	$	10	
Asleep_cHR_Std_Dev	Asleep cHR Std Dev	$	3	
Asleep_cMAP_Max	Asleep cMAP Max	$	10	
Asleep_cMAP_Mean	Asleep cMAP Mean	$	2	
Asleep_cMAP_Min	Asleep cMAP Min	$	10	
Asleep_cMAP_Std_Dev	Asleep cMAP Std Dev	$	3	
Asleep_cPP_Threshold	Asleep cPP Threshold	$	1	
Asleep_cSys_Above_Threshold_Coun	Asleep cSys Above Threshold Count	$	1	
Asleep_cSys_Load	Asleep cSys Load	$	1	
Asleep_cSys_Max	Asleep cSys Max	$	11	
Asleep_cSys_Mean	Asleep cSys Mean	$	3	
Asleep_cSys_Min	Asleep cSys Min	$	10	
Asleep_cSys_Std_Dev	Asleep cSys Std Dev	$	3	
Asleep_cSys_Threshold	Asleep cSys Threshold	$	1	
Awake_Central_Pulse_Pressure_Max	Awake Central Pulse Pressure Max	$	10	
Awake_Central_Pulse_Pressure_Mea	Awake Central Pulse Pressure Mean	$	2	

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Awake_Central_Pulse_Pressure_Min	Awake Central Pulse Pressure Min	$	10	
Awake_Central_Pulse_Pressure_Std	Awake Central Pulse Pressure Std Dev	$	3	
Awake_Dia_Above_Threshold_Count	Awake Dia Above Threshold Count	$	1	
Awake_Dia_Load	**Awake Dia Load**	**$**	**1**	**Y**
Awake_Dia_Max	Awake Dia Max	$	11	
Awake_Dia_Mean	**Awake Dia Mean**	**$**	**2**	**Y**
Awake_Dia_Min	Awake Dia Min	$	10	
Awake_Dia_Std_Dev	Awake Dia Std Dev	$	4	
Awake_Dia_Threshold	Awake Dia Threshold	$	2	
Awake_HR_Max	Awake HR Max	$	10	
Awake_HR_Mean	Awake HR Mean	$	2	
Awake_HR_Min	Awake HR Min	$	10	
Awake_HR_Std_Dev	Awake HR Std Dev	$	3	
Awake_MAP_Max	Awake MAP Max	$	11	
Awake_MAP_Mean	Awake MAP Mean	$	2	
Awake_MAP_Min	Awake MAP Min	$	10	
Awake_MAP_Std_Dev	Awake MAP Std Dev	$	4	
Awake_Pulse_Pressure_Max	Awake Pulse Pressure Max	$	10	
Awake_Pulse_Pressure_Mean	Awake Pulse Pressure Mean	$	2	
Awake_Pulse_Pressure_Min	Awake Pulse Pressure Min	$	10	
Awake_Pulse_Pressure_Std_Dev	Awake Pulse Pressure Std Dev	$	4	
Awake_Sys_Above_Threshold_Count	Awake Sys Above Threshold Count	$	1	
Awake_Sys_Load	**Awake Sys Load**	**$**	**1**	**Y**

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Awake_Sys_Max	Awake Sys Max	$	11	
Awake_Sys_Mean	**Awake Sys Mean**	**$**	**3**	**Y**
Awake_Sys_Min	Awake Sys Min	$	10	
Awake_Sys_Std_Dev	Awake Sys Std Dev	$	4	
Awake_Sys_Threshold	Awake Sys Threshold	$	3	
Awake_cAIX_75_Max	Awake cAIX@75 Max	$	10	
Awake_cAIX_75_Mean	Awake cAIX@75 Mean	$	2	
Awake_cAIX_75_Min	Awake cAIX@75 Min	$	9	
Awake_cAIX_75_Std_Dev	Awake cAIX@75 Std Dev	$	4	
Awake_cAIX_Max	Awake cAIX Max	$	10	
Awake_cAIX_Mean	Awake cAIX Mean	$	2	
Awake_cAIX_Min	Awake cAIX Min	$	10	
Awake_cAIX_Std_Dev	Awake cAIX Std Dev	$	4	
Awake_cAIx_Threshold	Awake cAIx Threshold	$	1	
Awake_cAP_Max	Awake cAP Max	$	10	
Awake_cAP_Mean	Awake cAP Mean	$	2	
Awake_cAP_Min	Awake cAP Min	$	9	
Awake_cAP_Std_Dev	Awake cAP Std Dev	$	4	
Awake_cAP_Threshold	Awake cAP Threshold	$	1	
Awake_cDia_Max	Awake cDia Max	$	10	
Awake_cDia_Mean	Awake cDia Mean	$	2	
Awake_cDia_Min	Awake cDia Min	$	10	
Awake_cDia_Std_Dev	Awake cDia Std Dev	$	3	

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Awake_cHR_Max	Awake cHR Max	$	10	
Awake_cHR_Mean	Awake cHR Mean	$	2	
Awake_cHR_Min	Awake cHR Min	$	10	
Awake_cHR_Std_Dev	Awake cHR Std Dev	$	1	
Awake_cMAP_Max	Awake cMAP Max	$	11	
Awake_cMAP_Mean	Awake cMAP Mean	$	2	
Awake_cMAP_Min	Awake cMAP Min	$	10	
Awake_cMAP_Std_Dev	Awake cMAP Std Dev	$	4	
Awake_cPP_Threshold	Awake cPP Threshold	$	1	
Awake_cSys_Above_Threshold_Count	Awake cSys Above Threshold Count	$	1	
Awake_cSys_Load	Awake cSys Load	$	1	
Awake_cSys_Max	Awake cSys Max	$	11	
Awake_cSys_Mean	Awake cSys Mean	$	3	
Awake_cSys_Min	Awake cSys Min	$	10	
Awake_cSys_Std_Dev	Awake cSys Std Dev	$	4	
Awake_cSys_Threshold	Awake cSys Threshold	$	1	
Dia_Asleep_Dip__	**Dia Asleep Dip %**	**$**	**3**	**Y**
Sys_Asleep_Dip__	**Sys Asleep Dip %**	**$**	**3**	**Y**
Total_Central_Pulse_Pressure_Max	Total Central Pulse Pressure Max	$	10	
Total_Central_Pulse_Pressure_Mea	Total Central Pulse Pressure Mean	$	2	
Total_Central_Pulse_Pressure_Min	Total Central Pulse Pressure Min	$	10	
Total_Central_Pulse_Pressure_Std	Total Central Pulse Pressure Std Dev	$	3	
Total_Dia_Load	**Total Dia Load**	**$**	**1**	**Y**

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Total_Dia_Max	Total Dia Max	$	11	
Total_Dia_Mean	**Total Dia Mean**	**$**	**2**	**Y**
Total_Dia_Min	Total Dia Min	$	10	
Total_Dia_Std_Dev	**Total Dia Std Dev**	**$**	**4**	**Y**
Total_HR_Max	Total HR Max	$	10	
Total_HR_Mean	Total HR Mean	$	2	
Total_HR_Min	Total HR Min	$	10	
Total_HR_Std_Dev	Total HR Std Dev	$	3	
Total_MAP_Max	Total MAP Max	$	11	
Total_MAP_Mean	Total MAP Mean	$	2	
Total_MAP_Min	Total MAP Min	$	10	
Total_MAP_Std_Dev	Total MAP Std Dev	$	4	
Total_Pulse_Pressure_Max	Total Pulse Pressure Max	$	10	
Total_Pulse_Pressure_Mean	Total Pulse Pressure Mean	$	2	
Total_Pulse_Pressure_Min	Total Pulse Pressure Min	$	10	
Total_Pulse_Pressure_Std_Dev	Total Pulse Pressure Std Dev	$	4	
Total_Sys_Load	**Total Sys Load**	**$**	**2**	**Y**
Total_Sys_Max	Total Sys Max	$	11	
Total_Sys_Mean	**Total Sys Mean**	**$**	**3**	**Y**
Total_Sys_Min	Total Sys Min	$	10	
Total_Sys_Std_Dev	**Total Sys Std Dev**	**$**	**4**	**Y**
Total_cAIX_75_Max	Total cAIX@75 Max	$	10	
Total_cAIX_75_Mean	Total cAIX@75 Mean	$	2	

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Total_cAIX_75_Min	Total cAIX@75 Min	$	9	
Total_cAIX_75_Std_Dev	Total cAIX@75 Std Dev	$	4	
Total_cAIX_Max	Total cAIX Max	$	10	
Total_cAIX_Mean	Total cAIX Mean	$	2	
Total_cAIX_Min	Total cAIX Min	$	10	
Total_cAIX_Std_Dev	Total cAIX Std Dev	$	4	
Total_cAP_Max	Total cAP Max	$	10	
Total_cAP_Mean	Total cAP Mean	$	2	
Total_cAP_Min	Total cAP Min	$	9	
Total_cAP_Std_Dev	Total cAP Std Dev	$	2	
Total_cDia_Max	Total cDia Max	$	10	
Total_cDia_Mean	Total cDia Mean	$	2	
Total_cDia_Min	Total cDia Min	$	10	
Total_cDia_Std_Dev	Total cDia Std Dev	$	3	
Total_cHR_Max	Total cHR Max	$	10	
Total_cHR_Mean	Total cHR Mean	$	2	
Total_cHR_Min	Total cHR Min	$	10	
Total_cHR_Std_Dev	Total cHR Std Dev	$	3	
Total_cMAP_Max	Total cMAP Max	$	11	
Total_cMAP_Mean	Total cMAP Mean	$	2	
Total_cMAP_Min	Total cMAP Min	$	10	
Total_cMAP_Std_Dev	Total cMAP Std Dev	$	4	
Total_cSys_Load	Total cSys Load	$	1	

NAME	LABEL	FORMAT	FORMATL	Included in efficacy analysis
Total_cSys_Max	Total cSys Max	$	11	
Total_cSys_Mean	Total cSys Mean	$	3	
Total_cSys_Min	Total cSys Min	$	10	
Total_cSys_Std_Dev	Total cSys Std Dev	$	4	
cDia_Asleep_Dip__	cDia Asleep Dip %	$	3	
cSys_Asleep_Dip__	cSys Asleep Dip %	$	3	

13. Appendix 4 – EQ5D5L coefficients

coefficients to apply to health state scores

EQ-5D-3L value set for Australia		Example: the value health state of 12133
constant	1	Constant = 1
Mobility=2	-0.072	
Mobility=3	-0.091	
Mobility=4	-0.276	
Mobility=5	-0.302	
Self care=2	-0.072	- 0.072
Self care=3	-0.079	
Self care=4	-0.218	
Self care=5	-0.301	
Usual activities=2	-0.116	
Usual activities=3	-0.120	
Usual activities=4	-0.283	
Usual activities=5	-0.283	
Pain/discomfort=2	-0.079	
Pain/discomfort=3	-0.089	-0.089
Pain/discomfort=4	-0.259	
Pain/discomfort=5	-0.333	
Anxiety/depression=2	-0.140	
Anxiety/depression=3	-0.246	-0.246
Anxiety/depression=4	-0.398	
Anxiety/depression=5	-0.398	
any dimension of the EQ-5D-5L at level 5	0.059	
		State 12133 = 0.593

14. Appendix 5 – Table shells

Table 1a: Disposition of subjects at End of Study

Number of patients	Intervention	Control	Total
Screened			
Randomised			
Completed			
Discontinued			
Reason for discontinuation			
AE			
Protocol non-compliance			
Lost to follow-up			
Investigator decision			
Withdrew consent/participant decision			
Death			
Other			

Note:
Percentages for randomised, completed and discontinued are based on the number of randomised patients
Percentages of the different reasons for discontinuation are based on the number of patients who discontinued from the study
The AEs recorded at the last available visit will be considered as the reason for discontinuation due to AE.In case of multiple reasons for discontinuation due to AE, a patient is counted at most once within each category/row but could contribute to more than one category/row.

Table 1b: Disposition of subjects at End of Study – by study center

Number of patients	Intervention	Control	Total
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C□□ □□□□d	□□□ □□□□□ □	□□□ □□□□□ □	□□□ □□□□□ □
D□c□□□□□□d	□□ □□□□ □	□□ □□□□ □	□□ □□□□ □
R□a□□□ □r d□c□□□□a□□□			
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Repeat for all centers…

Note:
Percentages for randomised, completed and discontinued are based on the number of randomised patients
Percentages of the different reasons for discontinuation are based on the number of patients who discontinued from the study

Table 2: Overall subject disposition

Visit Status	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Week 6 visit			
Visit done (1)	□□□□□□ □□□□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □
□□□□□□ □□□c□□ □□□d □2□	□□□□□□ □□□□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □
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Reason assessment not completed (3)			
□a□□ □□ c□□ac□□ar□c□a□□□□□□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □
□a□□□□d□c□a□□d	□□□□□□ □□□□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □
□ar□c□a□□□ □hdra□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □	□□□□□□ □□□□ □
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M□a□ □D□	□□□ □□□□□	□□□ □□□□□	□□□ □□□□□
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Visit Status	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
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Note:

(1) Percentages for "visit done" are based on the number of randomised patients,
(2) Percentages for "assessment completed/not completed" are based on the number of subjects with a "visit done,
(3) Percentages for "Reason assessment not completed" are based on the number of subjects with an assessment not completed
(4) Percentages for "type of info withdrawn" are based on the the number of participant who withdrew consent
(5) Percentages for outside window visits " are based on the number of subjects with a "visit done

Table 3: Data available for primary endpoint analysis – Randomised population

Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
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Note:
Percentages are based on the number of patients in the randomised population

Table 4: Data available – Randomised population

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Visit Forms	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
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Note:
Percentages are based on the number of patients assessed for the visit.

Table 5: Baseline characteristics – Randomised population

Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
Age (yrs)			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Gender			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Ethnicity			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Country of birth			
[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
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Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
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Current smoker	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
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Average e-cigarettes smoked / day			
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Average cigars smoked / day			
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Average times pipe smoked / day			
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Years being a smoker			
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Former smoker	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
Average cigarettes smoked / day			
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Average e-cigarettes smoked / day			
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Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
Average times pipe smoked / day			
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Years being a smoker			
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Years since quit smoking			
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Currently drinking alcohol once/more a week	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
Average standard drinks of wine / week			
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□ □□ □a□	□□ □□	□□ □□	□□ □□
Average standard drinks of spirits / week			
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Average standard drinks of beer / week			
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Currently drinking caffeinated drinks	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
Average number of caffeinated drinks per week			
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Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
Number of days eating fruit per week			
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□ □□ □a□	□□ □□	□□ □□	□□ □□
Number of servings of fruit per day			
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Number of servings of fruit per week			
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□ □□ □a□	□□ □□	□□ □□	□□ □□
Number of days eating uncooked vegetables per week			
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Number of servings of uncooked vegetables per day			
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Number of servings of uncooked vegetables per week			
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Number of days eating cooked vegetables per week			
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Number of servings of cooked vegetables per day			
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Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
Number of servings of cooked vegetables per week			
Number of servings of vegetables (uncooked and cooked) per week			
Number of days eating fish per week			
Number of servings of fish per day			
Number of servings of fish per week			
Number of days of moderate / vigorous exercise per week			
Minutes of moderate / vigorous exercise per day			
Number of days of mild exercise per week			

Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
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□ □□ □a□	□□ □□	□□ □□	□□ □□
Minutes of mild exercise per day			
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Time spent sitting or reclining on a typical day (hours)			
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Holding healthcare concession card	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
Holding a DVA card	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
Holding a private health insurance	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □
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Characteristics	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
Main lifetime occupation			
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(1) Baseline value using an automated BP machine output – average of the 3 measured

(2) high SBP - automated BP machine:
   a. In treatment naïve (i.e. never treated) or in patients currently not on treatment (not taken in last 4 weeks) : SBP 140-179mmHg

b. In patients currently taking one BP lowering drug ‘monotherapy: SBP 130-169mmHg

(3) high DBP - automated BP machine:
   a. In treatment naïve (i.e. never treated) or in patients currently not on treatment (not taken in last 4 weeks) : DBP 90-109mmHg
   b. In patients currently taking one BP lowering drug ‘monotherapy: DBP 85-104mmHg

(4) Baseline value using a 24h ambulatory BP monitoring device – daytime average

(5) high SBP - daytime average:
   a. In treatment naïve (i.e. never treated) or in patients currently not on treatment (not taken in last 4 weeks) : SBP ≥135mmHg
   b. In patients currently taking one BP lowering drug ‘monotherapy: SBP ≥125mmHg

(6) high DBP - daytime average:
   a. In treatment naïve (i.e. never treated) or in patients currently not on treatment (not taken in last 4 weeks) : DBP ≥85mmHg
   b. In patients currently taking one BP lowering drug ‘monotherapy: DBP ≥80mmHg

Note to programmer:

If more convenient possible to separate the baseline characteristics output by sections as per CRF. eg

- Baseline characteristics
- Life style status
- Socio economic characteristics

Table 6: Hypertension and other medical history – Randomised population

Medical history	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
Diagnosed with hypertension (months)			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Currently treated with blood pressure medications	[illegible]	[illegible]	[illegible]
[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Modified lifestyle to treat blood pressure			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Try to control salt/ sodium intake			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Do you have a home blood pressure monitor?			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Do you use it regularly			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Coronary artery disease	[illegible]	[illegible]	[illegible]
Heart Failure	[illegible]	[illegible]	[illegible]
Atrial Fibrillation	[illegible]	[illegible]	[illegible]
Stroke	[illegible]	[illegible]	[illegible]
Type of Stroke			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Medical history	Intervention (N=xxx)	Control (N=xxx)	Total (N=xxx)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Peripheral vascular disease	[illegible]	[illegible]	[illegible]
Chronic obstructive pulmonary disease	[illegible]	[illegible]	[illegible]
Asthma	[illegible]	[illegible]	[illegible]
Sleep apnoea	[illegible]	[illegible]	[illegible]
Chronic kidney disease	[illegible]	[illegible]	[illegible]
Diabetes	[illegible]	[illegible]	[illegible]
Age at diagnosis (yrs)			
[illegible]	[illegible]	[illegible]	[illegible]
M[illegible]	[illegible]	[illegible]	[illegible]
M[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Type of Diabetes			
[illegible] 1	[illegible]	[illegible]	[illegible]
[illegible] 2	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
History of depression	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Family history of heart disease/stroke in a first degree relative	[illegible]	[illegible]	[illegible]

Note: describe any denominator for % when ambiguous.

Table 7: Baseline medications – Randomised population

Medication	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Table 8: Concomitant medications – Randomised population

Medication	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
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Table 9: Step-up care - Randomised population

	Intervention	Control	Total
Amlodipine dispensed	**(N = xxx)**	**(N = xxx)**	**(N = xxx)**
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Note: counts the study dispensed step-up for BP lowering treatment.

Table 10: Step-up blood pressure lowering treatment - Randomised population

	Intervention	Control	Total
BP lowering treatment	**(N = xxx)**	**(N = xxx)**	**(N = xxx)**
Treatment adjustment: Any increase			
Week 0 to Week 6			
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Week 6 to Week 12			
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Week 12 to Week 26			
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Week 26 to Week 52			
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Note: Count includes study dispensed or the patient's clinician initiated BP medicine

Table 11: Vital signs – Descriptive statistics – Actual values - Randomised population

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Systolic blood pressure (mmHg) - (Observed clinic measure)			
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Systolic blood pressure (mmHg) – (24h ABPM)			
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Systolic blood pressure (mmHg) – (24h ABPM) – Awake time

Repeat for all visits: baseline, week 12, week 52

Systolic blood pressure (mmHg) – (24h ABPM) – Sleep time

Repeat for all visits: baseline, week 12, week 52

Systolic blood pressure load (24h ABPM)

Repeat for all visits: baseline, week 12, week 52

Systolic blood pressure load (24h ABPM) – Awake time

Repeat for all visits: baseline, week 12, week 52

Systolic blood pressure load (24h ABPM) - Sleep time

Repeat for all visits: baseline, week 12, week 52

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Diastolic blood pressure (mmHg)

(as above)

Heart rate (bpm)

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Figure 1: Vital signs– Mean plot over time – Actual values - Randomised population

Present mean plots over time for SBP, DBP by treatment group on the same graph. Each measurement type will be provided on a different graph (observed clinical, automatic office, 24h-ABPM).

Present mean plots over time for SBP, DBP by treatment group on the same graph for 24h-ABPM measurements: 24h, awake and sleep time.

Another graph will present HR by treatment group

Table 12: Vital signs – Descriptive statistics – Change from baseline - Randomised population

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Systolic blood pressure (mmHg) - (Observed clinic measure)			
[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]
Mean (SD)	[illegible]	[illegible]	[illegible]
[illegible] 12			
[illegible]	[illegible]	[illegible]	[illegible]
Mean (SD)	[illegible]	[illegible]	[illegible]
[illegible] 2			
[illegible]	[illegible]	[illegible]	[illegible]
Mean (SD)	[illegible]	[illegible]	[illegible]
[illegible] 2			
[illegible]	[illegible]	[illegible]	[illegible]
Mean (SD)	[illegible]	[illegible]	[illegible]
R[illegible]a[illegible]r **automated office measure** a[illegible]d [illegible]r **24h ABPM** [illegible]2[illegible]h[illegible]a[illegible]a[illegible] [illegible] [illegible] [illegible] [illegible]			
R[illegible]a[illegible]r **Systolic blood pressure load** [illegible]2[illegible]h[illegible]a[illegible]a[illegible] [illegible] [illegible] [illegible]			
Diastolic blood pressure (mmHg) *(as above)*			
Heart rate (bpm) [illegible] [illegible] [illegible]r[illegible]d c[illegible]c [illegible] a[illegible]r[illegible]r HR			

Note: average of the last 2 recordings for that visit. Done at resting, sitting position.

Figure 2: Vital signs - Mean plot over time – Change from baseline - Randomised population

Present mean plots over time for SBP, DBP by treatment group on the same graph as well as the different type of measurements (observed clinical, automatic office, 24h-ABPM).

Present mean plots over time for SBP, DBP by treatment group on the same graph for 24h-ABPM measurements: 24h, awake and sleep time.

Another graph will present HR by treatment group

Table 13a: Analysis of covariance on Blood pressure - change from baseline values – Randomised population

Visit	Statistics	Intervention (N = xxx)	Control (N = xxx)	Mean Difference	P-value
Systolic BP (mmHg) - observed office measure					
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Systolic BP (mmHg) - automated office measure					
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Systolic BP (mmHg) – 24h ABPM – Awake time					
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Systolic BP (mmHg) – 24h ABPM – Sleep time					
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Visit	Statistics	Intervention (N = xxx)	Control (N = xxx)	Mean Difference	P-value
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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Systolic BP load – 24h ABPM

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Systolic BP load – 24h ABPM – Awake time

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Systolic BP load – 24h ABPM – Asleep time

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Repeat for Diastolic BP (mmHg) and the 3 different types of measures
(as above)

Note:
(1) primary endpoint.
For each visit, the p-value was extracted using a mixed model on the change from baseline with baseline as a covariate, treatment as fixed effect and site as random effect.

Table 13b: Analysis of covariance on Blood pressure - change from baseline values – Completed Week 52 population

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Table 14: Longitudinal analysis of blood pressure on change from baseline values – Completed Week 52 population

Parameter Timepoint	Intervention (N = xxx) Mean (95% CI)	Control (N = xxx) Mean (95% CI)	Mean difference (95% CI)	P for the difference
Systolic BP (mmHg) - observed office measure				
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Note: 24h ABPM parameters are not included in this analysis

Repeat for
Diastolic BP (mmHg)
(as above)

Note: A longitudinal analysis of change from baseline BP over time including the following terms: treatment group, visit as a categorical variable, a treatment-by-visit interaction, the baseline value (i.e. baseline SBP, baseline DBP) as fixed effects, as well as center as random effect. All results presented in this table come from the model.

Table 15: Hypertension control – Randomised population

Visit	Intervention (N = xxx) [1]	Control (N = xxx) [1]	Absolute risk difference (95% CI) [2]	Relative risk (95% CI) [3]	P-value)
Achieving BP target (4) (5) **Using observed clinic measure**					
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(1) Descriptive statistics (top rows)
(2) Absolute risk difference and 95% CI defined using the XXXX method.
(3) Relative risks and 95% CI extracted from the log-binomial regression described in note (5).
(4) For all participants :: SBP < 140 mmHg and DBP < 90 mmHg.
(5) Log-binomial regression with treatment group as fixed effects and center entered as random effect

Table 16a: Hypertension control with no potentially related side-effects – Randomised population

Visit	Intervention (N = xxx) (1)	Control (N = xxx) (1)	Absolute risk difference (95% CI) (2)	Relative risk (95% CI) (3)	P-value)
Achieving BP target (4) (5) without any AE **Using observed clinic measure and potentially related side-effects**					
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(1) Descriptive statistics (top rows)
(2) Absolute risk difference and Newcombe 95% CI.
(3) Relative risks and 95% CI extracted from the log-binomial regression described in note (5).
(4) For all participants :: SBP < 140 mmHg and DBP < 90 mmHg.
(5) Log-binomial regression with treatment group as fixed effects and center entered as random effect

Table 16b: Hypertension control with no treatment related withdrawal due to Severe Adverse Events – Randomised population
Repeat 16a

Table 17: Change in blood and urine values - Randomised population

Laboratory Measurement Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N=xxx)
Sodium (mmol/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Potassium (mmol/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Chloride (mmol/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Bicarbonate (mmol/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			

Laboratory Measurement Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N=xxx)
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Urea (mmol/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Uric acid (mg/dL)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Creatinine (mg/dL)			
Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
eGFR (mg/dL)			
Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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Laboratory Measurement Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N=xxx)
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
ALT (IU/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
AST (IU/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
GGT (IU/L)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
ALP (IU/L)			
Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□

Laboratory Measurement Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N=xxx)
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Albumin			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Bilirubin			
Baseline			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
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M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
UACR (mg/dL)			
Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□
Week 12 - Baseline			
□	□□□	□□□	□□□
M□a□ □□D□	□□□□ □□□□	□□□□ □□□□	□□□□ □□□□

R□□□a□□□r □DH□HD□□□□a□ch□□□□□r□□□r□□□c□r□d□□□a□□□□ □□c□□□ a□d h□□ □□□□□□

Table 18a: Potentially related side-effects and treatment withdrawal - Randomised population

	Intervention (N = xxx) [1]	Control (N = xxx) [1]	Relative risk (95% CI) [2]	P-value [3]
Any Potentially related side effects	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □		
M□d□□□□□□□ a□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□ □□□□□□ □	0□□□□□
Common Potentially related side effects	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □		
M□d□□□□□□□ a□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□ □□□□□□ □	0□□□□□
Withdrew treatment for any reasons	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □		
M□d□□□□□□□ a□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□ □□□□□□ □	0□□□□□
Withdrew treatment due to a treatment-related SAE	□□□□□□□ □□□□□□ □	□□□□□□□ □□□□□□ □		
M□d□□□□□□□ a□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□□□□□	□□□□ □□□□□□ □□□□□□ □	0□□□□□

[1] Descriptive statistics (top rows)
[2] Relative risks and 95% CI extracted from the log-binomial regression described in note (5).

[3] Negative log-binomial regression with treatment group as fixed effects and center entered as random effect

Table 18b: Hypertension and Bradycardia - Randomised population

	Statistics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Any hypotension	□□ □ □□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □
□□□ □□□□ a□c	□□ □ □□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □
□□□□ □□□□ a□c □□r □□□□□□□ □□	□□ □ □□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □
Any bradycardia	□□ □ □□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □
□□□ □□□□ a□c	□□ □ □□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □
□□□□ □□□□ a□c □□r □□□□□□□ □□	□□ □ □□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □	□□□ □□□ □□□□□ □

Note:
the number and percentage represent subjects with at least one event (one subject is counted at most once within a category). The denominator is the number of patients randomised

Table 19: Adverse events summary - Randomised population

	Statistics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
AEs of special interest				

Note:
the number and percentage represent subjects with at least one event (one subject is counted at most once within a category). The denominator is the number of patients randomised

Table 20: Serious adverse events - Randomised population

	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Note:
In case of multiple seriousness criteria, a patient is counted at most once within each category/row but could contribute to more than one category/row. The denominator is the number of patients randomised.
In case of multiple causality, a patient is counted at most once within each category/row but could contribute to more than one category/row. The denominator is the number of patients randomised.

Table 21: Causes of deaths - Randomised population

	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Note:
The denominator is the number of patients randomised

Table 22: Serious Adverse Events by System Organ Class and Prefered Term - Randomised population

System Organ Class Preferred Term	Statistics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Any events	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □
SOC1	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □
□□1	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □
□□2	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □
SOC2	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □
□□1	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □
□□2	□□ □ □□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □	□□ □□ □□□□□ □

Note:
For each SOC or PT, the number and percentage represent subjects with at least one event (one subject is counted at most once within a SOC or PT). The denominator is the number of patients randomised

Table 23: Pill count and adherence – Randomised population

Visit	Intervention (N = xxx)	Control (N = xxx)
□□□ □□r □□□□□□□□ □a□□□	□ M□a□ □□D□ M□d□a□ □□1□□3□ □ □□ □a□	
□dh□r□□c□ □□ □	0□ □□ □□□ □0□ □□ 100□ □100□ □dh□r□□□ □□□□	

Table 24: Self-reported adherence – Randomised population

Visit	Intervention (N = xxx)	Control (N = xxx)	RR (95% CI)	P for the difference
□ □□□ 12	□□□ □□□□□ □	□□□ □□□□□ □	□□□□ □□□□□ □□□□□ □	0□□□□
□ □□□ □2	□□□ □□□□□ □	□□□ □□□□□ □	□□□□ □□□□□ □□□□□ □	0□□□□
□□d □□□□□□□ □□□	□□□ □□□□□ □	□□□ □□□□□ □	□□□□ □□□□□ □□□□□ □	0□□□□

Note (2) log-binomial regression with treatment group as fixed effect and center entered as random effect.
End of follow up corresponds to last patient visit.