STATISTICAL ANALYSIS PLAN SIGNATURE FORM

Protocol Title: A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)

Protocol Number: RLY5016-207

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The individuals signing below have reviewed and approve this statistical analysis plan.

Prepared by:

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Protocol Number:	RLY5016-207
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GLOSSARY OF ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin to creatinine ratio
AE	adverse event
ANCOVA	analysis of covariance
AOBP	automated office blood pressure
ARB	angiotensin II receptor blocker
BID	twice daily
BP	blood pressure
CBC	complete blood count
BPM	beats per minute
CI	confidence interval
CKD	chronic kidney disease
DBP	diastolic blood pressure
DSMC	data safety monitoring committee
EDC	electronic data capture
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	early termination
FU	Follow-up Visit
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GCP	good clinical practices
HbA1c	hemoglobin A1c
HBP (7dHBP)	home blood pressure (seven-day home blood pressure)
HF	heart failure
HR	heart rate

ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
K+	potassium
MedDRA	Medical Dictionary for Regulatory Activities
MRA	mineralocorticoid receptor antagonist
NSAIDs	non-steroidal anti-inflammatory drugs
QD	once daily
RAASi	renin-angiotensin aldosterone system (inhibitor)
S1	Screening Visit 1
S2	Screening Visit 2
S3	Screening Visit 3
S4	Screening Visit 4
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SMBP	subject-measured blood pressure performed at the study site using the HBP monitor
TEAE	treatment-emergent adverse event
TID	three times daily
WBC	white blood cell count

1   INTRODUCTION

This document presents the statistical analysis plan (SAP) for protocol RLY5016-207, entitled "A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)".

Results obtained from the analyses outlined in this document will provide the basis of the Clinical Study Report (CSR) for this study. The statistical rationale and analysis methods specified in this document take precedence over those described in the protocol, should there be any differences.

2   STUDY OBJECTIVES AND STUDY DESIGN

2.1   Study Objectives

The objective of the study is to determine whether patiromer treatment of CKD subjects receiving spironolactone for the treatment of resistant hypertension will result in:

- More persistent use of spironolactone through prevention of hyperkalemia
- Improved blood pressure control through more persistent use of spironolactone

2.2   Study Design

This study is a randomized, double-blind, placebo-controlled, parallel group study of patiromer or placebo treatment (patiromer/placebo) in conjunction with spironolactone in subjects with resistant hypertension and CKD. Approximately 290 subjects will be randomized.

Screening for this study includes 4 visits and lasts up to 4 weeks. Subjects who meet all eligibility criteria are randomized to receive either spironolactone and patiromer or spironolactone and placebo. The active treatment period runs for 12 weeks. A follow-up visit is scheduled 2 weeks after completion of the Week 12 or Early Termination (ET) Visit.

Study periods are as follows:

- Screening Period (4 Visits)
  Screening Visit 1 (S1), Screening Visit 2 (S2), Screening Visit 3 (S3) and Screening Visit 4 (S4) occur one week apart (at least 4 days but no more than 10 days). If the subject meets all eligibility criteria at the final screening visit (S4), the visit becomes the Randomization/Baseline Visit.

- Double-Blind Treatment/Observation Period (12 weeks)
   At the Randomization/Baseline Visit, each subject is randomized to either spironolactone + patiromer or spironolactone + placebo, and is instructed to begin study drug on the following day, which then becomes Day 1 of the study.

The Double-Blind Treatment/Observation Period consists of 8 scheduled visits at Weeks 1, 2, 3, 4, 6, 8, 10, and 12. The intent is to observe all subjects for the entire 12 weeks of this period, whether or not they have discontinued study drug.

- Follow-up Period
Two weeks after the subject has completed either the Week 12 Visit or ET Visit, the subject returns for a Follow-up (FU) Visit.

The Schedule of Events for this study is presented in Appendix A.

The initial dose of spironolactone will be 25 mg QD for all subjects, and the initial dose of patiromer/placebo will be 2 packets QD. If a subject's blood pressure and potassium assessments allow, the dose of spironolactone will be increased to 50 mg QD at Week 3. Detailed titration rules for spironolactone and patiromer/placebo are specified in the protocol in Appendix B (patiromer/placebo) and Appendix C (spironolactone).

The overall design of the study is presented schematically below in Figure 1.

Figure 1. Study Schema
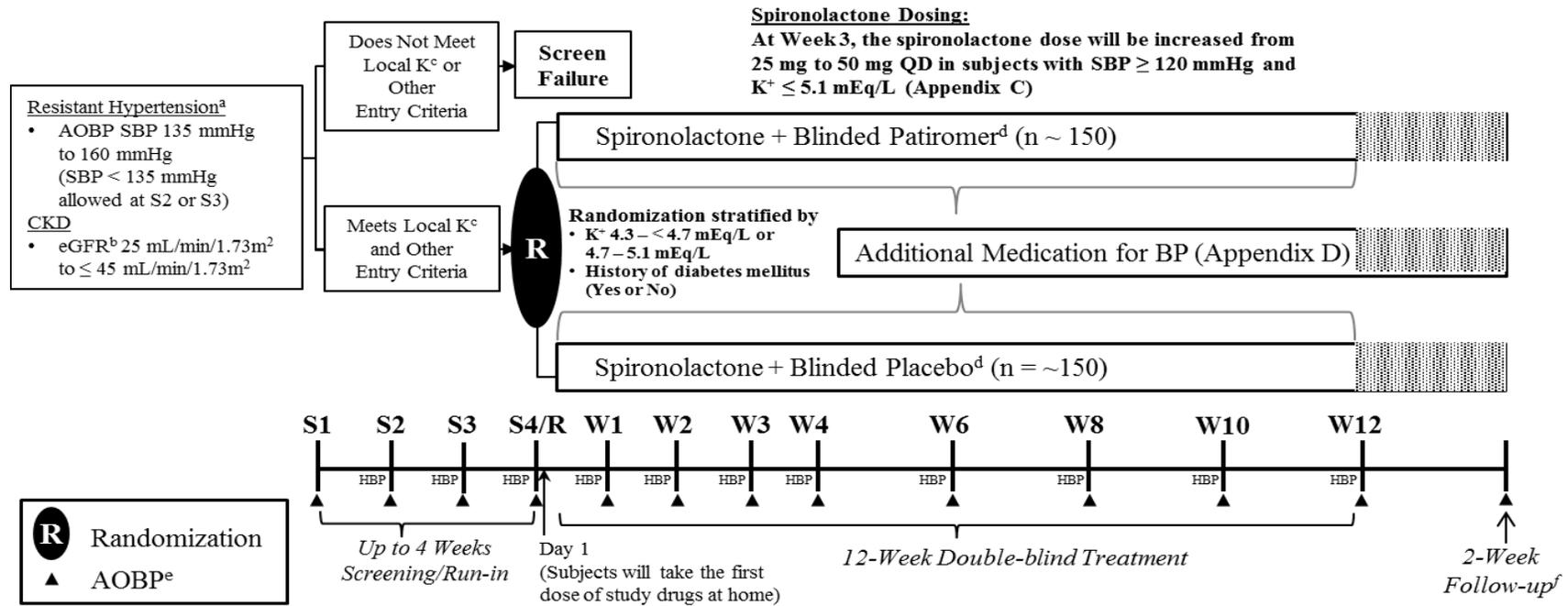
AOBP = automated office blood pressure; HBP = home blood pressure; eGFR = estimated glomerular filtration rate; K^+ = potassium measurement; R = Randomization/Baseline (Day 0) Visit; S = Screening Visit; SBP = systolic blood pressure; W = week

[a]   Receiving at least three antihypertension drugs including diuretic. ACE inhibitors or ARBs should be included among these three antihypertensive medications, unless previously not tolerated or contraindicated (see Inclusion Criteria)..

[b]   Mean (calculated by the IWRS) of two values measured at Visits S1 and S3 (or 7 to 28 days apart) during the Screening/Run-in Period.

[c]   Qualifying local laboratory K^+ measurements of 4.3 – 5.1 mEq/L obtained at Visits S1, S3 and S4 (all measurements must be within range)

[d]   Subjects who develop hyperkalemia ($K^+ \geq 5.5$ mEq/L) that cannot be managed with blinded patiromer/placebo escalation according to the treatment algorithm will discontinue spironolactone and patiromer/placebo, but still remain in the study. Hyperkalemia may be treated using standard of care

[e]   Performed both by a designated oscillometric BP monitoring device that will automatically measure subject's BP in triplicate after 5 minutes of sitting quietly without the aid of study staff, AOBP, and by the subject using their issued HBP device (triplicate measurements).

[f]   Two (2) weeks after the Week 12 (+ 7 days) or ET Visit (note, no subject measured office BP at this Visit). Subjects who complete the Follow-up Visit prior to 2 Weeks will receive a Follow-up Phone Call at 2 weeks (+ up to 7 days) after Week 12 or ET Visit.

Note: The reference to Appendix C for dosing is referring to the Protocol Appendix C. For subjects with study drug (spironolactone or patiromer/placebo) modifications based on BP assessments or potassium levels, an Unscheduled Visit will be conducted within 1 week after this modification unless the next scheduled visit is within 1 week of the study drug modification, in which case, the subject will return at the next scheduled visit. For all study visit windows, refer to the Schedule of Events.

2.3   Sample Size Determination

This study will randomize approximately 290 subjects, to ensure that at least 280 subjects will be available for the primary analysis. This allows for the possibility that up to 10 subjects are randomized but never take study medication. A sample size of 280 subjects has 90% power to detect a difference between treatment groups of 20% or more in the proportion of subjects remaining on spironolactone at Week 12, at $\alpha = 0.05$.

3   RANDOMIZATION AND BLINDING

At Screening Visit 4, eligible subjects will be randomized 1:1 to spironolactone + patiromer or spironolactone + placebo. Randomization will be stratified by the Visit S4 locally measured potassium value (4.3 to < 4.7 mEq/L or 4.7 to 5.1 mEq/L) and by history of Type 1 or 2 diabetes mellitus (Yes or No).

To minimize the potential for bias, subjects, site personnel, and sponsor and vendor staff will remain blinded to treatment assignments, with the exception of unblinded staff required for the development of the final randomization schedule and for production of unblinded materials for the Data Safety Monitoring Committee (DSMC). Drug safety staff may also be unblinded where this is necessary to comply with regulatory requirements.

For production of DSMC materials, an unblinded sponsor biostatistician and unblinded sponsor programmer(s) will be identified.

The final randomization schedule will be produced by unblinded staff at Endpoint, the IWRS vendor for this study, and will be reviewed by the sponsor DSMC unblinded biostatistician.

The study will be unblinded after database lock.

4   INTERIM ANALYSES

No interim efficacy analysis is planned for this study. Safety will be evaluated by the DSMC on an ongoing basis.

5   ANALYSIS SETS

5.1   Intent-to-treat Population (ITT)

The Intent-to-Treat (ITT) Population includes all subjects who have been randomized and have taken at least one dose of spironolactone and at least one dose of patiromer/placebo.

All efficacy analyses will be performed on the ITT population, analyzed by planned treatment group assignment. In addition, the primary and secondary endpoints will also be performed using the Per-protocol Population.

5.2   Per-protocol Population (PP)

The per-protocol population includes ITT subjects who have been compliant with dosing of both spironolactone and patiromer/placebo and who do not have any important protocol deviations (see Section 5.4).

Dosing compliance is defined as having taken 80-120% of the prescribed dose.

The primary and secondary endpoints will be performed using the PP Population, in addition to the ITT Population.

5.3   Safety Population (SAF)

The safety population will include all randomized subjects who have taken at least one dose of spironolactone or patiromer/placebo, analyzed according to the actual treatment received.

All safety analyses will be performed on the SAF population.

5.4   Protocol Deviations

Prior to database lock, all protocol deviations will be compiled. Important protocol deviations will be identified and used to determine, prior to database lock, the per protocol population.

The following deviations are considered, a priori, to be important protocol deviations:

- Violations of initial informed consent

- Enrolled in violation of the entry criteria

- Site errors in randomization assignment

- Administration of a prohibited medication to a study subject potentially affecting the primary and secondary efficacy endpoints

- Study subjects not discontinuing study medication when they met protocol criteria for stopping study treatment

- Dosing with study drug after a study subject's withdrawal from the study

6   ENDPOINTS AND VISIT WINDOWS

6.1   Efficacy Endpoints

6.1.1   Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the proportion of subjects remaining on spironolactone at Week 12.

Subjects who terminate from the study early or discontinue study spironolactone prior to Week 12, for any reason, will be considered as not having remained on spironolactone until Week 12.

6.1.2   Secondary Efficacy Endpoint

The secondary efficacy endpoint is change from Baseline in AOBP SBP at Week 12 or last available AOBP SBP prior to addition of any new BP medications or increase from any baseline BP medications.

6.1.3   Other Efficacy Endpoints

The following other efficacy endpoints were specified by the protocol:

- Change in AOBP SBP from baseline to Week 12

- Potassium levels over time (measured both centrally and locally)

- Proportion of subjects with serum $K^+ \geq 5.5$ mEq/L

- Average daily dose and cumulative dose of spironolactone

- Time to discontinuation of spironolactone

- Change in albuminuria (urine albumin to creatinine ratio [ACR]) from baseline to Week 12

- EQ-5D-5L questionnaire results at Baseline and Week 12/ET

In addition to the endpoints specified in the protocol, the following additional endpoints will be examined:

- Change in AOBP SBP from baseline to Week 12 in the subgroup of patients remaining on spironolactone at Week 12

- Change in AOBP SBP/DBP over time

6.1.4   Exploratory Efficacy Endpoint

- Change in 7dHBP SBP/DBP over time

6.2   Safety Endpoints

Safety endpoints will consist of:

- Adverse events, including newly observed clinically significant physical examination abnormalities and events of interest (e.g. gastrointestinal events, renal events)

- Clinical laboratory test results and changes over time, including Spironolactone level and NT-pro-BNP.

- Vital signs

- ECG findings and changes

- Reasons for discontinuing patiromer/placebo/spironolactone

- Deaths

Adverse events will be coded using MedDRA 18.1.

6.3   Study Day and Visit Windows

6.3.1   Study Day

The first date of dosing with any study medication (either spironolactone or patiromer/placebo) will be used as the Reference Date for Study Day calculation.

The Study Day for date of first dosing is Day 1. The Study Day for all other study events is defined as follows:

- If a date is prior to the Reference Date, Study Day is defined as [date] - [Reference Date], so the Study Day for the day before date of first dose (typically the randomization day) is defined as Day -1.

- If a date is on or after the Reference Date, Study Day is defined as [date] - [date of randomization] +1; hence, the Study Day for the day after first dose is defined as Day 2.

6.3.2   Visit Windows

The protocol specified windows for scheduled visits are shown in the Schedule of Events (Appendix A).

Unless otherwise specified, analyses by visit will use the visit weeks reported in the database and include results collected at scheduled visits.

Analyses not limited to visits (e.g. incidence of laboratory test values within a given range, and time to event analyses), will include all available values of the variable of interest, irrespective of whether it was collected at a scheduled or unscheduled visit.

For central laboratory data, the visit information from the central laboratory will be used to determine whether a visit is scheduled or unscheduled.

6.3.3   Baseline

For all analysis variables, unless otherwise specified, baseline is the last non-missing value of the variable on or before the first dose of any study medication.

6.4   Key Considerations for Blood Pressure

Blood pressure is measured in three ways in this study:

- AOBP: Automated Office Blood Pressure

- SMBP: Subject-Measured Blood Pressure (performed at the study site using the HBP monitor)

- 7dHBP: 7-day Home Blood Pressure

The AOBP is an unwitnessed measurement taken at the clinic using an automatic office device that collects 3 measures of SBP/DBP. The mean of the three values is used for titration of study medication, and is the value that will be used for most analyses.

The SMBP is an unwitnessed measurement taken at the clinic using the subject's home blood pressure device. The home blood pressure device takes 3 readings automatically, and the mean of the three is used. If an AOBP is unavailable at a visit, for whatever reason, the SMBP will be used in its place to determine titration of study medications.

The HBP device is used by the subject outside the clinic to take measurements twice a day. At each sitting, 3 readings are taken automatically and uploaded to the Bioclinica database. The 7-day home blood pressure (7dHBP) is calculated from these measurements as follows:

1. Morning average = average of all measurements with time stamp midnight to before noon on given day

2. Evening average = average of all measurements with time stamp noon to before midnight on given day

3. Daily average = average of morning and evening averages

4. 7-day HBP (7dHBP) = average of daily averages for prior 7 days

The morning/evening averages include all values within the specified timeframes. If there are no valid readings during the morning time period, the morning average is missing, and the daily average will be based on the available values during the evening period, and similarly if there are no valid readings in the evening period. If there are no valid readings in either the morning or evening period, the daily average will be missing for that day. The 7dHBP is calculated using as many daily averages as are available for the previous 7 days. A valid 7dHBP requires that there be, at an absolute minimum, at least one valid reading for each of the prior 3 days. Readings taken with the HBP device while at the clinic are excluded from the calculation of the 7dHBP. Because the calculation requires averages of averages, rounding should not be done until the final 7dHBP result has been calculated.

For summaries of the 7dHBP by visit, the value of the 7dHBP at a visit will be calculated using the 7 days prior to the visit, and will not include any readings taken on the day of the visit.

7   HANDLING OF DROPOUTS AND MISSING DATA

7.1   Dropouts

In this study, every effort is made to retain all subjects through Week 12, whether or not they are still on study medication.

For the primary endpoint (percentage of subjects remaining on spironolactone at Week 12), any subject who terminates early is defined as not having remained on spironolactone. All ITT subjects will be included in the analysis.

7.2   Missing AOBP

If the AOBP SBP is missing at a scheduled visit, the SMBP SBP for that visit will be used in analysis.

7.3   Missing Information for Adverse Events

For subjects with the missing information for adverse events, the following imputation rules will be applied:

- An adverse event with onset date equivalent to the first dosing date will be considered to be treatment-emergent unless there is evidence to conclude that it is not.

- An adverse event with missing severity will be assigned to the highest severity observed for the subject, among all events with the same preferred term; if there are no other AEs with same preferred term and non-missing severity, the adverse event will be counted as severe.

- An adverse event with missing relationship to study drug (patiromer/placebo or spironolactone) will be assigned to possible relationship (i.e. related).

7.4   Missing Dates or Partially Missing Dates

Missing or partially missing dates will be imputed conservatively for concomitant medications, procedures and adverse events (AEs). Specific rules for handling missing or partially missing dates are provided in the Appendix B.

No imputations for other missing safety data will be undertaken.

8   STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1   General Considerations and Statistical Methods

Efficacy analyses will be performed by planned treatment (i.e. as randomized), and safety analyses by actual treatment received.

For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation (SD), standard error (SE), median, 25th, 75th percentiles, minimum and maximum.

For categorical variables, descriptive statistics will include frequencies and percentages in each category.

For time-to-event variables, the descriptive statistics will include the median, 95% CI, $25^{th}/75^{th}$ percentiles, minimum and maximum. Counts of events and of number censored will also be provided.

When mean change from baseline is summarized, subjects will be included in the analysis if they have both a baseline value and a post-baseline value at the time point of interest.

All statistical tests will be conducted at a two-sided alpha level of 0.05, and 95% confidence intervals will be utilized, unless otherwise stated.

Detailed statistical methods are specified in sections below.

8.2   Subject Disposition

The number and percentage of subjects randomized, subjects who receive study drug, and subjects who complete study (or are terminated early) will be summarized by treatment group and overall. The number and percentage of subjects terminating from the study early will be presented by reason. The ITT, PP, and Safety Populations will also be summarized by treatment group and overall. If populations do not differ (e.g. ITT and Safety Populations) then the summary will be presented only once.

In addition, the number and percentage of subjects who signed informed consent, screen failures and screen failure reasons will be summarized.

Listings of subject disposition and screening will be provided.

8.3   Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the ITT, PP and Safety Populations (if they differ from ITT), by treatment group and overall.

The summary of demographic information will include age, sex, race and ethnicity. The summary of patient characteristics at baseline will include, but is not limited to, weight, height, BMI, baseline medical history (including chronic kidney disease, diabetes types, hypertension, heart failure including NYHA class, ejection fraction (EF), myocardial infarction, baseline serum potassium and eGFR).

Listings of demographics and baseline characteristics will be provided.

8.4   Medical History

General medical history will be coded in accordance with MedDRA 18.1 and will be summarized by body system (or procedure), for each treatment group and overall.

A listing of general medical history will be provided.

8.5   Prior and Concomitant Medications

All prior and concomitant medications will be coded using the current version of the World Health Organization Drug dictionary (WHO Drug Sep2016).

Prior medications are defined as medications with start date before the date of first dose of study medication. Concomitant medications are those taken during the study period, and are defined as medications with start date on or before the date of last dose of study medication and end date on or after the date of first dose of study medication, or no end date.

Prior and concomitant medications will be separately summarized by treatment and overall. Additional summaries will be provided for concomitant medications of interest, including all antihypertensive agents and medications for diabetes mellitus (Type 1 or 2). Summaries will be presented by treatment group and overall.

Listings of all prior and concomitant medications will be provided.

8.6   Exposure to Study Drug

Exposure to study drug will be summarized separately for spironolactone and patiromer/placebo. Summaries will be provided, by treatment group, for:

- Duration: calculated as [last dose date]-[first dose date]+1.

- Total dose: calculated for each subject as the total dosage received

- Mean daily dose: calculated for each subject as the total dose divided by the duration of study drug exposure

- Number and type of titrations (up or down)

In addition, for patiromer/placebo, the number of non-zero dose days will be summarized.

Separate listings will be provided for spironolactone and patiromer/placebo exposure.

8.7   Compliance

Study drug compliance will be assessed separately for spironolactone and patiromer/placebo. Summaries will be presented by treatment group.

Dose compliance will be derived from the total dose of study drug taken by a subject divided by the prescribed total dose over the treatment period, multiplied by 100.

Descriptive statistics will be provided for dose compliance. In addition, counts (%) will be provided for compliance categories 80-120%, < 80%, and > 120%.

A listing of compliance for each study drug by subject will be provided.

8.8   Protocol Deviations

The number and percentage of subjects with protocol deviations will be summarized by category of deviation, for each treatment group and overall. A listing of important protocol deviations will be provided.

8.9   Efficacy Analyses

8.9.1   Primary Efficacy Analysis

The primary efficacy endpoint for this study is the proportion of subjects remaining on spironolactone at Week 12.

A subject is defined as having remained on spironolactone until Week 12 if the End of Study Treatment eCRF confirms the subject has completed the full 12-week course of study treatment and the subject had not discontinued spironolactone early. Subjects who terminate from the study early or discontinue spironolactone early, for any reason, will be defined as not having remained on spironolactone until Week 12. The number and percentage of subjects remaining on spironolactone at Week 12, and the 95% CI, will be provided by treatment group. Confidence intervals will be obtained using the exact (Clopper-Pearson) method.

The percentage of subjects remaining on spironolactone at Week 12 will be compared between treatment groups (spironolactone + patiromer versus spironolactone + placebo) using a Cochran-Mantel-Haenszel (CMH) test, at α-level 0.05. The test will be stratified by baseline potassium category (4.3 to < 4.7 mEq/L or 4.7 to 5.1 mEq/L) and Type 1 or 2 diabetes mellitus (Yes or No).

The primary analysis will be performed using the ITT and PP Populations.

8.9.2   Secondary Efficacy Analysis

The secondary efficacy endpoint is change from Baseline in AOBP SBP at Week 12 or last available AOBP SBP on or prior to the first date of addition of any new BP medications or increases from any baseline BP medications.

Baseline AOBP is defined as the latest available AOBP on or before the date of first dose date.

Changes/additions to baseline BP medications are recorded on the Antihypertensive Medications eCRF. The earliest date of any recorded increase/addition will be compared to the date of the Week 12 AOBP, and the rules below will be applied. Note that only dates of BP medication increases/additions with start date on or before the upper limit of the Week 12 window will be considered.

- If the earliest date of BP medication increase/addition is on or after the date of the Week 12 AOBP, or there is no record of any increase/addition, the Week 12 AOBP SBP will be used for analysis.

- If the earliest date of BP medication increase/addition is prior to the Week 12 AOBP, or when the Week 12 visit should have occurred if there is no Week 12 AOBP, then the AOBP on or before and closest to the earliest date of change will be used for analysis.

- If a subject has no Week 12 AOBP and no record of any BP medication changes/additions, the subject will not be included in this analysis.

In above rules, the SMBP, if available, may be used in place of a missing AOBP at the same visit.

The secondary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model, with baseline AOBP SBP as a continuous covariate and factors for treatment group, baseline serum potassium (K^+ 4.3 – < 4.7 or 4.7 – 5.1 mEq/L), and Type 1 or 2 diabetes mellitus (Yes or No).

The analysis will be performed using the ITT and PP Populations. A sensitivity analysis will be performed using the last observation carried forward, when a subject has no Week 12 AOBP and no record of any BP medication changes/additions.

8.9.3   Additional Efficacy Analyses

Additional analyses will be provided for blood pressure, potassium, spironolactone exposure and quality of life measures as outlined in subsections below.

8.9.3.1   Blood Pressure

Change in AOBP SBP from baseline to Week 12

Treatment groups will be compared for change in AOBP SBP at Week 12 regardless of increase in antihypertensives by using both ANCOVA and repeated measures methods.

An ANCOVA analysis will be carried out using a model that includes baseline AOBP SBP as a continuous covariate and factors for treatment group, baseline serum potassium (K^+ 4.3 to < 4.7 or 4.7 to 5.1 mEq/L), and Type 1 or diabetes mellitus (Yes or No). This analysis will include only ITT subjects who have AOBP SBP (or SMBP if AOBP is missing) at both Baseline and Week 12.

In addition, a repeated measures mixed model analysis will be performed using all ITT subjects who have an AOBP SBP (or SMBP if AOBP is missing) assessment at Baseline and at least one post-baseline assessment at Week 1 or later. The model will include baseline AOBP SBP as a continuous covariate and factors for treatment group, time, baseline serum potassium (K^+ 4.3 to < 4.7 or 4.7 to 5.1 mEq/L), and Type 1 or 2 diabetes mellitus (Yes or No).

AOBP over time

Summaries of AOBP SBP/DBP will be provided at each visit and for change from Baseline, by treatment group. SMBP SBP/DBP may be used for missing AOBP SBP/DBP. Summaries of change at each post-baseline time point will include only subjects who have non-missing values at baseline and at the post-baseline time point of interest.

Mean SBP/DBP and mean change from baseline will be presented graphically.

The change from Baseline in AOBP SBP over time prior to the first date of addition of any new BP medications or increases from any baseline BP medications will also be presented for the subjects who remained on spironolactone through Week 12.

8.9.3.2   Potassium

Central serum potassium levels and change from Baseline will be summarized, by treatment group, at each scheduled visit.

Central serum potassium over time will be presented graphically.

Number and percentage of subjects who have experienced no $K^+ \geq 5.5$ mEq/L will be presented by visit. All central laboratory potassium values will be used for this analysis.

Local laboratory potassium values from serum samples will be included in listings.

8.9.3.3   Spironolactone

Treatment groups will be compared for spironolactone duration, total dose and mean daily dose using ANCOVA models with baseline AOBP as a continuous covariate, and including factors for treatment group, baseline serum potassium (K^+ 4.3 to < 4.7 or 4.7 to 5.1 mEq/L), and history of Type 1 or 2 diabetes mellitus (Yes or No).

The number and percentage of subjects at each spironolactone dose will be presented by treatment group and visit. Dose at a visit is defined to be the investigator prescribed dose at that visit.

Time to discontinuation of spironolactone will be estimated using Kaplan-Meier methods, and will be compared between treatment groups using the log rank test.

8.9.3.4   Change in albuminuria (urine albumin to creatinine ratio [ACR]) from Baseline to Week 12 (ET)

Albuminuria will be summarized, by treatment group, at Baseline and Week 12, as well as change in albuminuria from Baseline to Week 12. The analysis will also be conducted for the subgroup of subjects whose ACR was elevated at baseline.

8.9.3.5   EQ-5D-5L Quality of Life questionnaire results at Baseline and Week 12/ET

The EQ-5D-5L Quality of Life (QOL) instrument is collected at Randomization/Baseline and Week 12/ET.

The EQ-5D-5L QOL instrument consists of 5 dimensions of quality of life (mobility, self care, usual activities, pain/discomfort, and anxiety/depression) and the EQ visual analogue (EQ VAS) measure of "how good or bad your health is today".

For each of the 5 dimensions, subjects choose between 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). Answers are scored from 1 (no problems) to 5 (extreme problems). The EQ VAS is measured from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine").

The EQ-5D-5L questionnaire is collected at Randomization/Baseline and Week 12/ET. Summaries of the number and percentage of subjects at each level in each dimension will be presented at the two time points. Summary statistics will be provided for the EQ VAS at Randomization/Baseline and Week 12/ET, and for change from Baseline to Week 12/ET.

8.9.4   Subgroups

The primary and secondary analyses will be performed for the following subgroups:

- Sex (male versus female)

- Age (< 65 versus ≥ 65 years)

- Type 1 or Type 2 diabetes mellitus (presence versus absence at baseline)

- Baseline potassium category (4.3 to < 4.7 mEq/L versus 4.7 to 5.1 mEq/L) from central lab

- Region (Group A versus Group B)

- History of heart failure (presence versus absence at baseline)

- Baseline eGFR (< 30 versus ≥ 30 mL/min/1.73 m^2)

The test for interaction between treatment and a subgroup will be performed.

8.9.5   *Exploratory Efficacy Analysis*

7dHBP over time

Summaries of 7dHBP SBP/DBP will be provided at each visit and for change from Baseline, by treatment group. Summaries of change at each post-baseline time point will include only subjects who have non-missing values at baseline and at the post-baseline time point of interest.

Mean SBP/DBP and mean change from baseline will be presented graphically.

8.10   Safety Analyses

8.10.1   *Adverse Events*

AEs and SAEs will be coded to system organ class (SOC) and preferred term (PT) in accordance with MedDRA 18.1. Adverse event analyses will include only treatment-emergent AEs (TEAEs). A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of study drug administration. If the onset date of an AE is missing, the AE will be considered treatment-emergent unless there is evidence to conclude that it is not. AE listings will include all AEs.

Central laboratory serum pregnancy tests will be done at S1 and Week 12/ET. Local urine pregnancy tests will be done at Randomization/Baseline. Pregnancy is not considered an AE but is reported separately (please see Protocol Amendment 2 Section 8.4 regarding Procedures for Reporting Pregnancy Exposure and Birth Events).

The incidence of TEAEs will be summarized by system organ class (SOC), preferred term (PT) and severity. For those TEAEs that occur more than once during the study period, the maximum severity will be used in the summary by severity.

Descriptive statistical summaries (frequencies and percentages) will be provided by treatment group for the followings:

- Overall summary of TEAEs, including summaries of severity, TEAEs related to study drug, SAEs, SAEs related to study drug, TEAEs leading to study drug modification and TEAEs leading to study drug discontinuation

- Summary of all TEAEs by SOC, PT and severity

- Summary of TEAEs related to study drug by SOC, PT, separately for spironolactone and patiromer/placebo

- Summary of TEAEs leading to study drug modification by SOC, PT, separately for spironolactone and patiromer/placebo

- Summary of TEAEs leading to early study drug discontinuation by SOC, PT, separately for spironolactone and patiromer/placebo

- Summary of SAEs by SOC, PT, and severity

- Summary of SAEs related to study drug by SOC, PT, separately for spironolactone and patiromer/placebo

- Summary of TEAEs of special interest (e.g. allergic reactions, gastrointestinal events, renal events)

A listing for all AEs will be provided, including verbatim term, PT, SOC, severity, whether serious, relationship to each study drug, onset and end date, action taken and outcome of event will be provided. Listings of SAEs and TEAEs leading to study drug modification and to early study drug discontinuation will be provided. Listings will also be provided for events of special interest.

8.10.2   Emergency Room Visits and Revascularization Procedures

Listings will be provided for all reported emergency room visits and revascularization procedures.

8.10.3   Death

A listing of all deaths will be provided. The listing will include date of death, primary cause of death and any associated AE.

8.10.4   Clinical Laboratory Tests

Clinical laboratory tests to be performed in this study are listed in detail in Appendix C.

For central laboratory test summaries by visit, the central laboratory measurements at scheduled visits will be used if available. The visit information from the central laboratory will be used to determine whether a visit is scheduled or unscheduled.

If a laboratory result from a visit is retested and the central laboratory subsequently determines the original result to be valid, the original result for that visit will be used in analysis, and the second (i.e. 'retested') value will be ignored. Otherwise, if the central laboratory detects an error through the retesting, the retested value will be used in analysis as the measurement for that visit.

The baseline central laboratory value is defined as the last non-missing central laboratory value collected on or before the date of the first dose of study medication.

8.10.4.1   Serum Chemistry

Serum chemistry tests will be performed at S1, S3, Randomization/Baseline and all scheduled visits during the study, including the FU Visit. Tests may also be done at unscheduled visits.

All serum chemistry results will be summarized by treatment group with descriptive statistics at each scheduled visit, and for the change from baseline to the corresponding time points.

The incidence of laboratory test results in ranges of interest will be summarized by treatment group. These summaries will include but are not limited to the following:

- Serum potassium < 3.0, < 3.5, < 3.8, > 5.0, and ≥ 5.5 mEq/L

- Serum magnesium < 1.4, < 1.2, and < 1.0 mg/dL

- Serum calcium > 10.2 mg/dL

Laboratory shift tables from Baseline to End of Treatment will be provided for selected laboratory results.

Listings will be provided for all serum chemistry parameters. Listings will include test results at both scheduled and unscheduled visits.

8.10.4.2   Hematology

Hematology tests will be performed at S1, Randomization/Baseline, Week 4 and Week 12/ET. Tests may also be done at unscheduled visits.

All hematology results will be summarized by treatment group with descriptive statistics at Randomization/Baseline, Week 4, and at Week 12/ET, and for the change from Baseline at each time point.

A listing of hematology will be provided. The listing will include test results at both scheduled and unscheduled visits.

8.10.4.3   Special Laboratory Tests

The following special laboratory tests will be conducted for this study: NT-proBNP; aldosterone and plasma renin activity; spironolactone level.

Special laboratory test results will be summarized by treatment group with descriptive statistics at each time point at which they were collected, and for change from Baseline to each post-baseline time point.

A listing for special laboratory tests will be provided.

8.10.4.4   24-hour Urine

24-hour urine for sodium, potassium, creatinine, and albumin tests will be performed at Randomization/Baseline.

Raw test results will be adjusted to correct for the actual observed duration of the collection time in hours. The 24-hour-adjusted values for sodium, potassium, creatinine, and albumin will be calculated as:

24-hour-adjusted value = [(raw test value) / (sample collection time in hours)] × 24

The 24-hour ACR will be calculated as:

$$\text{24-hour ACR} = (\text{24-hour albumin} / (\text{24-hour creatinine})$$

Descriptive summary statistics will be presented at Baseline, by treatment group, for the following variables:

- 24-hour-adjusted sodium, potassium, creatinine, and albumin

- Ratio of 24-hour urine albumin and creatinine

A listing for 24-hour urine results will be provided.

8.10.4.5   Spot Urine (ACR)

Spot urine will be collected for measuring ACR at Randomization/Baseline, Week 4, Week 8, and Week 12/ET. At Randomization/Baseline spot urine samples will be from 2 first morning voids, collected 1 and 2 days prior to the Randomization/Baseline Visit. At Weeks 4, 8, and 12, spot urine samples will be from 3 first morning voids collected on the day of the visit and on 1 and 2 days prior to the visit.

Mean values will be calculated for albumin and creatinine over the spot urine samples collected for each visit. The value of ACR at a visit will be the mean albumin value divided by the mean creatinine value.

Spot urine ACR will be summarized by treatment group with descriptive statistics at Randomization/Baseline, Week 4, Week 8, and Week 12. Note that change in ACR from Randomization/Baseline to Week 12/ET is an efficacy endpoint in this study (see Section 6.1.3).

A listing for spot urine results will be provided.

8.10.5   Vital Signs

Blood pressure summaries have been described in Section 8.9.

Heart rate will be summarized, by treatment group, with descriptive statistics for each scheduled visit, and for the change from baseline to the corresponding time points.

Height is assessed only at S1 and will be summarized as part of the baseline characteristics.

Weight is assessed at S1, Randomization/Baseline, and at Week 12/ET. Weight will be summarized, by treatment group, with descriptive statistics for Randomization/Baseline and Week 12/ET, and for the change from baseline to Week 12/ET.

A listing for vital signs, weight and height will be provided.

8.10.6   Physical Examination

Physical examinations will be performed at S1 and Week 12/ET.

Abnormalities found in physical examinations will be summarized by treatment group at Screening and at Week 12/ET. Clinically significant abnormalities after the start of study drug are reported as AEs and summarized as described in Section 8.10.

A listing for physical examination will be provided.

8.10.7   12-lead Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed in all subjects at the S1 and Week 12/ET. Number and percentage of subjects with normal/abnormal and clinically significant abnormal ECG findings will be summarized at S1 and Week 12/ET.

A listing for 12-lead ECG will be provided.

8.10.8   Pregnancy Test

A listing for all pregnancy tests will be provided.

9   REFERENCES

1. International Conference on Harmonization (ICH) E6, "Guideline for Good Clinical Practice"; 1996.

2. International Conference on Harmonization (ICH) E9, "Statistical Principles for Clinical Trials"; 1998.

3. van Reenen M, Janssen B. EQ-5D-5L User Guide Version 2.1, April 2015

4. RLY5016-301 Statistical Analysis Plan, Amendment 1, Dated 20 March 2013.

5. Williams B, MacDonald T, et al. Spironolactone Versus Placebo, Bisoprolol, and Doxazosin to Determine the Optimal Treatment for Drug-Resistant Hypertension (PATHWAY-2): a Randomised, Double-blind, Crossover Trial. Lancet, 386[10008], 2059-2068, 2015.

APPENDIX A: SCHEDULE OF EVENTS

Study Period	Screening/Run-in Period			Screening/ Randomization	Double-Blind Treatment								Follow-Up[a]	Unscheduled Visit
Visit/Day/Week	S1	S2	S3	S4/BL(D0)[b]	W1	W2	W3	W4	W6	W8	W10	W12 or ET Visit	2W after W12 or ET Visit	
Window	1 week ($\geq$ 4 d but $\leq$ 10 d) apart				±3 d	±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	+7 d	
Study Activity														
Informed Consent	X													
IWRS Entry	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X
Inclusion Exclusion Criteria	X			X[d]										
Demographics	X													
Medical History	X													
Heart Rate (resting for 5 minutes)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X			X[d]								X		X, optional
Physical Examination	X											X		X, optional
12-lead Electrocardiogram	X											X		X, optional
AOBP performed onsite (triplicate measurements)[e]	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X
SMBP performed onsite and HBP training, as necessary (triplicate measurements)[g]	X	X	X	X	X	X	X	X	X	X	X	X		X, if available
SMBP performed at home (triplicate measurements)[h]		X	X	X	X	X	X	X	X	X	X	X		X, if available
Potassium[i]	L&C		L&C	L&C[d]	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L&C	L&C	L&C
Serum Chemistry (including creatinine, eGFR)	C		C	C[d]	C	C	C	C	C	C	C	C	C	C, optional
Hematology	C			C[d]				C				C		C, optional
Serum Pregnancy	C											C		
NT-proBNP				C[d]								C		

Schedule of Events (Cont'd)

Study Period	Screening/Run-in Period			Screening/ Randomization	Double-Blind Treatment								Follow-Up[a]	Unscheduled Visit
Visit/Day/Week	S1	S2	S3	S4/BL(D0)[b]	W1	W2	W3	W4	W6	W8	W10	W12 or ET Visit	2W after W12 or ET Visit	
Window	1 week (≥ 4 d but ≤ 10 d) apart				±3 d	±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	+7 d	
Study Activity														
Aldosterone and plasma renin activity				C[d]										
Spironolactone Level					C			C		C		C		
Urinalysis	C			C[d]								C		
24 hr urine collection container (dispense and train)			X											
24 hr urine for sodium, potassium, creatinine, albumin (for ACR)				C[d]										
ACR urine sample collection cups (dispense and train)			X				X		X		X			
Urine ACR (3 first morning void samples)				C[d,k]				C		C		C		
Urine pregnancy test				X[d]										
EQ-5D-5L Questionnaire[l]				X[d]								X		
IWRS Randomization to Patiromer / Placebo				X[d]										
Patiromer/placebo Dispensing[m]				X[d]	X	X	X	X	X	X	X			X, optional
Spironolactone Dispensing[n]				X[d]	X	X	X	X	X	X	X			X, optional
Drug Accountability					X	X	X	X	X	X	X	X		X, optional
Dietary Counselling	X	X	X	X[d]	X	X	X	X	X	X	X	X		X

Schedule of Events (Cont'd)

Study Period	Screening/Run-in Period			Screening/ Randomization	Double-Blind Treatment								Follow-Up[a]	Unscheduled Visit
Visit/Day/Week	S1	S2	S3	S4/BL(D0)[b]	W1	W2	W3	W4	W6	W8	W10	W12 or ET Visit	2W after W12 or ET Visit	
Window	1 week (≥ 4 d but ≤ 10 d) apart				±3 d	±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	+7 d	
Study Activity														
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AOBP = automated office blood pressure; ACR = albumin to creatinine ratio; AE = adverse event; BP = blood pressure; C = central laboratory; D (or d) = day; D0 = Day 0; ET = Early Termination Visit; hr = hour; IWRS = Interactive Web Response System; L = local; R = Randomization; S = Screening Visit; SMBP = subject-measured blood pressure.

[a] If a subject completes the Follow-up Visit prior to 2 Weeks, the subject will receive a Follow-up Phone Call at 2 weeks after Week 12 or ET Visit (+ up to 7 days)

[b] If hemolysis of the local sample is detected or is suspected), subject is not randomized at S4, and a repeat of the potassium measurement from a separate blood draw will be performed within 1 day. If subject qualifies they will be randomized and this Visit will be the Randomization/Baseline (Day0) Visit. All assessments at S4, aside from the repeat potassium level, will be considered the baseline.

[c] For subjects who meet all inclusion criteria, this Visit becomes the Randomization/Baseline Visit (Day0). For subjects who screen fail at this visit, this is Visit S4.

[d] Assessment or event will occur only if subject meets all inclusion criteria.

[e] Measured automatically using office device (while unobserved by the study staff) after 5 minutes of quiet seating prior to triplicate measures.

[f] Review AOBP results and adjust study medications according to titration rules.

[g] HBP device issued on Visit S1 and measured by subject using their issued HBP device (while unobserved by the study staff) after 5 minutes of quiet seating prior to triplicate measures . HBP monitors are collected from subjects at the Visit Week-12.

[h] HBP will be measured by subject twice daily (e.g., at approximately 08:00 hrs and 20:00 hrs) after sitting quietly for at least 5 minutes. The subject will perform triplicate measures, 1 minute apart. HBP training will be performed at the first screening visit and retraining can be performed at any Visit, as needed. HBP monitors are collected from subjects at the Visit Week-12.

[i] If hemolysis of the local sample is detected or is suspected, the sample must repeated within 1 .day for reassessment of potassium.

[j] Review potassium results and adjust study medications according to titration rules..

[k] One of the ACR measurements will be from the 24-hour urine collection.

[l] Subjects will complete the EQ-5D-5L questionnaire before study staff performs any clinic or study assessments to avoid biasing the subjects' responses.

[m] On Day1 patiromer/placebo two packets QD will be taken at home with food and at least 3 hours before or 3 hours after other oral medications including spironolactone.

[n] On Day 1 spironolactone (25 mg QD) will be taken at home and increased to 50 mg at Week 3 for subjects with blood pressure ≥ 120 mmHg..

APPENDIX B: IMPUTATION OF DATES

1   Imputation of Missing/Partially Missing Adverse Event Dates

1.1   Incomplete Start Date:

Partially missing AE start/stop dates will be imputed in the ADaM dataset for AEs, according to the rules below. However, listings of AE data will present the date as is, with missing date components left blank.

If the AE end date is complete with no missing year, month, or day, and a partially missing start date imputed by the rules below is after the AE end date, then the imputed start date will be equal to the end date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.

- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.

- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.

- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.

- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as TEAE.

1.2   Incomplete Stop Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.

- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

2   Imputation of Dates for Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. However, listings of prior/concomitant medications/procedures data will present the date as is, with missing date components left blank.

For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

3.   Imputation of Dates for Pre-specified Medical History

Partially missing start dates for pre-specified medical history will be imputed in the ADaM dataset for pre-specified medical history. However, listings of pre-specified medical history data will present the date as is, with missing date components left blank.

Partially missing pre-specified medical history start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

APPENDIX C: LIST OF CENTRAL LABORATORY ASSAYS

Serum Chemistry Panel:	Hematology:
Alanine aminotransferase	White blood cell count (WBC)
Albumin	Red blood cell count
Alkaline phosphatase	Hemoglobin
Amylase	Hematocrit (Packed Cell Volume)
Aspartate aminotransferase	Mean cell volume
Bicarbonate	Mean cell hemoglobin
Bilirubin (total)	Mean cell hemoglobin concentration
Blood Urea Nitrogen	Platelet count
Calcium	Differential WBC
Creatine kinase	**Urine:**
Creatinine (with eGFR)	Specific gravity
Glucose	pH
Inorganic phosphate	Protein
Iron	Glucose
Lactate dehydrogenase	Creatinine
Magnesium	Ketones
Potassium	Blood
Sodium	Urobilinogen
Total cholesterol	Leukocytes
Total protein	Leukocyte esterase
Uric acid	Nitrites
Other:	Bilirubin
Serum pregnancy	24-hour urine collection for sodium, creatinine, albumin (for ACR)
NT-proBNP	
Aldosterone and plasma renin activity	Spot urine for albumin and creatinine (for ACR)
Spironolactone level	Urine pregnancy