| **STATISTICAL ANALYSIS PLAN** | |
|---|---|
| Study Code | D9480C00001 |
| Edition Number | 3.0 |
| Date | 24-Oct-2022 |

# A phase 3 multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (sodium zirconium cyclosilicate), in patients with hyperkalemia (HARMONIZE Asia)

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| AZ | AstraZeneca |
| BMI | Body Mass Index |
| BP | Blood pressure |
| BUN | Blood Urea Nitrogen |
| c-lab | Central laboratory |
| CI | Confidence Interval |
| CKD | Chronic kidney disease |
| CM | Concomitant medication |
| COVID-19 | Coronavirus Disease 2019. |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CRO | Clinical Research Organization |
| CSP | Clinical Study Protocol |
| DBL | Database lock |
| DM | Diabetes mellitus |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| EOS | End of Study |
| FAS | Full Analysis Set |
| FAS-OLP | Full Analysis Set for the Open-Label Initial Phase |
| FAS-RTP | Full Analysis Set for the 28-day Randomized Treatment Study Phase |
| GFR | Glomerular Filtration Rate |
| GGT | Gamma-glutamyl transferase |
| Hb | Haemoglobin |
| HCG | Human chorionic gonadotropin |

| Abbreviation or special term | Explanation |
|---|---|
| HF | Heart failure |
| HL | Hy's law |
| ICH | International Conference on Harmonization |
| IP | Investigational Product |
| IPD | Important protocol deviations |
| ITT | Intent-to-Treat |
| LSMEAN | Least Square Mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple imputation |
| OLP | Open-label initial phase |
| PO | Per Os |
| P-Renin | Plasma-Renin |
| PT | Preferred Term |
| qd | Once daily |
| RAAS | Renin-Angiotensin-Aldosterone System |
| RBC | Red Blood Cell |
| REML | Restricted maximum likelihood method |
| RTP | 28-day randomized treatment study phase |
| S-Aldo | Serum-Aldosterone |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAF-OLP | Safety Analysis Set for the Open-Label Initial Phase |
| SAF-RTP | Safety Analysis Set for the 28-day Randomized Treatment Study Phase |
| SAP | Statistical Analysis Plan |
| S-Ca | Serum calcium |
| S-HCO3 | Serum bicarbonate |
| S-K | Serum potassium |
| S-Mg | Serum magnesium |
| S-Na | Serum sodium |
| S-PO4 | Serum phosphate |
| SD | Standard deviation |

| Abbreviation or special term | Explanation |
|---|---|
| SOC | System Organ Class |
| TFL | Tables, Figures and Listings |
| TID | Three times a day |
| ULN | Upper limit of normal |
| VS | Vital Sign |
| WBC | White Blood Cell |
| WHO | World Health Organization |
| WHODrug | World health Organization Drug Dictionary |
| ZS | Sodium Zirconium Cyclosilicate |

# AMENDMENT HISTORY

| **CATEGORY** Change refers to: | **Date** | **Description of change** | **In line with CSP?** | **Rationale** |
|---|---|---|---|---|
| **N/A** | 27-Sep-2021 | Initial approved SAP | N/A | N/A |
| **Section 3.2.1.1.** | 04-Apr-2022 | Definition of FAS-OLP updated to be in line with CSP | Yes | Update SAP to be in line with CSP |
| **Section 3.3** | 04-Apr-2022 | Added convention used for rounding | NA | Consistency in outputs. |
| **Section 3.3.1.1** | 04-Apr-2022 | Removed timing for the two pre-dose measurements used to derive baseline for OLP.<br>Added that baseline values can also be replaced.<br>Added a sentence to confirm that measures taken on the same day as first IP are assumed to be pre-dose if time is missing. | Yes | Clarifying the logic for imputing missing Clab values with i-STAT values. |
| **Section 3.3.1.2** | 04-Apr-2022 | Added definition of 'on-treatment' | Yes | Clarifying the definition for consistency in outputs and summaries. |
| **Section 3.3.2.1** | 04-Apr-2022 | Updated/added hypotheses for exponential rate of change. | No | Defining two time points (24/48 hr) as not all subjects will have 48h time point |
| **Section 3.3.3** | 04-Apr-2022 | Table 2 (Analysis visit windows) updated. | Yes | |
| **Section 3.3.5** | 22-Apr-2022 | Section added to summarise how to handle missing S-K data | Yes | Consistency in how this handled for all efficacy outcomes. |
| **Section 4** | 04-Apr-2022 | Removed quartiles from summary statistics | Yes | Quartiles are not required for the summaries. |
| **Section 4.1.5** | 04-Apr-2022 | Serum potassium added as a baseline characteristic | NA | To improve assessment of baseline characteristics |
| **Section 4.1.7.1** | 04-Apr-2022 | Definition of prior and concomitant added. Updated imputation of missing dates to coincide with Section 3.3.1.3 | Yes | Clarifying the definition for consistency in outputs and summaries. |
| **Section 4.2.1.3** | 04-Apr-2022 | Adding a time constraint to imputing missing values with i-STAT | Yes | Add an additional rule as to when it is appropriate to impute value. |

| | | | | |
|---|---|---|---|---|
| | | Information added for the seed, number of burn-ins and variance structure for the multiple imputation | | To provide further details on how the multiple imputation should be carried out. |
| **Section 4.2.1.5** | 04-Apr-2022 | Supplementary analysis of primary endpoint updated to be stop date of disallowed medication + 7 days. | Yes | To align the supplementary analyses for disallowed medications. |
| **Section 4.2.1.6** | 04-Apr-2022 | Added a specification of the number of observations required to conduct the subgroup analyses | Yes | To ensure enough observations to generate robust estimates. |
| **Section 4.2.3.6** | 04-Apr-2022 | Updated handling of missing data to be in line with the primary end point. | Yes | Clarifies that all RTP endpoint should be based on the imputed data. |
| **Section 4.3.2** | 04-Apr-2022 | Removed summary of AEs leading to discontinuation and most common AEs. Removed study specific AEs. Added summary by decreasing frequency. | Yes | To removed summaries of AEs that are not required and to update the AE table to present by decreasing frequency rather than selecting the most common to give a most robust overview of AEs. |
| **Section 4.3.3** | 04-Apr-2022 | Removed Hy's Law definitions and updated the elevated liver test summary | Yes | To condense the overview of elevated liver tests. |
| **Section 4.3.6** | 04-Apr-2022 | Added baseline versus maximum on-treatment summary for vital signs. | Yes | To provide additional analyses of the vital signs. |
| **Section 3.3.1.3** | 12-Aug-2022 | Added definition of 'treatment-emergent' | Yes | Clarifying the definition for consistency in outputs and summaries. |
| **Section 4.2.2.1** | 12-Aug-2022 | Updated list of time points at which the proportion of subjects who achieve normokalemia are assessed during the OLP | Yes | End of OLP timepoint was missing from list |
| **Section 4.2.3.2** | 12-Aug-2022 | Added derivation for the number of days subjects remain normokalemic | Yes | To provide further clarification on the logic of the derivation |
| **Section 4.2.3.3** | 12-Aug-2022 | Added additional description for the summaries required for time to hyperkalemia | Yes | To align with requirements in output To align with requirements in output |

| | | | | |
|---|---|---|---|---|
| **Section 4.2.3.5** | 12-Aug-2022 | Updated the minimum number of subjects required per subgroup analysis | Yes | To allow for a lower threshold for the subgroup analysis to be performed |
| **Section 4.3.3.2** | 12-Aug-2022 | Updated to use "treatment-emergent" in derivation description | Yes | To align with the definition of treatment-emergent added in Section 3.3.1.3 |
| **Section 4.3.6.2** | 12-Aug-2022 | Updated to use "treatment-emergent" in derivation description | Yes | To align with the definition of treatment-emergent added in Section 3.3.1.3 |
| **Section 4.3.8.2** | 12-Aug-2022 | Added that QTcF values above 450 ms at baseline should be summarised | Yes | To align with requirements in output |
| **Section 3.3.1.4** | 18-Oct-2022 | Added sentence to derivation of missing start/end dates for concomitant medications and AEs | Yes | To provide further logic on the imputation of missing dates. |
| **Appendix A** | 24-Oct-2022 | Updated IPD master file | Yes | To align with the most recent version of the IPD master file. |

# 1 INTRODUCTION

The purpose of this document is to give details for statistical analysis of study D9480C00001 supporting the clinical study report. The reader is referred to the clinical study protocol (CSP) for details of study conduct.

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the CSP for the Harmonize Asia study and is based on version 6.0 of the CSP.

This SAP applies to the phase 3, multicentre, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (sodium zirconium cyclosilicate), in patients with hyperkalemia (HARMONIZE Asia).

# 2 CHANGES TO PROTOCOL PLANNED ANALYSES

The text referring to a 2-sample t-test in section 8.5 of the CSP, ("Where applicable, comparisons between each active dose treatment group vs. placebo control group will be performed using a 2-sample t-test.") has been removed as needed in the SAP, as this referred to the descriptive tabulations of data, and this is no longer part of the planned descriptive tabulation of the study.

The structure of the model used for the main analysis of the primary endpoint has been amended to include visit, treatment, as well as visit-by-treatment interaction as fixed effects, to reflect the corresponding analysis done in the Harmonize Global study. In addition, rather than incorporating a random intercept within subject explicitly in the model, an unstructured marginal covariance matrix will be used. This is to provide better potential for achieving good model fit (note that a model with a random intercept within subject and an e.g. scaled identity as conditional covariance matrix is a special case of this approach).

The subgroup analysis of the primary endpoint has been amended to assess all subjects, rather than those with hyperkalemia (S-K $\geq$ 5.1mmol/L). This reflects the corresponding analysis in the Harmonize Global study and aligns with the primary analysis of the primary outcome.

Change from baseline in the OLP has been amended to use a one-sample, two-sided, t-test instead of a paired, two-sided, t-test. This allows a comparison of the mean change from baseline to the null hypothesis of zero (i.e. no change from baseline) rather than assessing the difference between the paired observations. This also aligns with the approach taken in the Global Harmonize study.

To better reflect the Intent-to-Treat (ITT) approach defined to the efficacy analyses the secondary endpoint reading:

- "Proportion of subjects who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomized treatment study phase at Study Days 29/Exit"

has been changed to:

- "Proportion of subjects who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomized treatment study phase at Study Days 29".

To reflect the flexibility of the duration of the open label phase introduced in the later versions of the CSP the endpoint reading:

- "Open-label phase mean change from baseline of S-K 48 hours after first dose of ZS 10g"

has been clarified to state:

- "Open-label phase mean change from baseline of S-K to the end of OLP after first dose of ZS 10g".

To clarify the definition of the full analysis set in the open label initial phase, a subject is considered to have been registered into the OLP if they received at least 1 dose of study medication in the open label initial phase.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 Timing of Analyses

The primary analysis will be performed after database lock (DBL). No interim analysis is planned for this study.

## 3.2 Analysis Populations

Two main analysis populations are defined for two different periods of this study, the full analysis set (FAS) and the safety analysis set (SAF).

### 3.2.1 Full analysis set

All efficacy analyses, unless otherwise specified, will be performed using the full analysis set (FAS), which is based on ITT principle. That is, subjects allocated to a treatment group will be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment.

#### 3.2.1.1 Full analysis set in Open-label initial phase (FAS-OLP)

For the open-label initial phase (OLP), the full analysis set will include all subjects who received at least 1 dose of study medication in the open-label initial phase.

#### 3.2.1.2 Full analysis set in Randomized treatment study phase (FAS-RTP)

For the randomized treatment study phase (RTP), the full analysis set will include all subjects who are randomized to the 28-day randomized treatment phase, regardless of whether they took study medication or not.

In this set, subjects will be analyzed according to their randomized treatment assignment.

### 3.2.2 Safety analysis set

All safety analyses will be performed using the SAF. Safety analyses will be performed for each study phase, OLP and RTP.

#### 3.2.2.1 Safety analysis set in Open-label period (SAF-OLP)

For the OLP, the safety analysis set will include all subjects who receive at least 1 dose of study medication in the initial phase.

#### 3.2.2.2 Safety analysis set in randomized treatment study phase (SAF-RTP)

For the subsequent RTP, the safety analysis set will include all subjects in the FAS-RTP who receive at least 1 dose of study medication in the RTP. Subjects with erroneous treatment are analyzed according to that treatment only if they only received the erroneous treatment and none of the correct treatment. Subjects who receive more than one treatment are analysed according to their randomized treatment.

The analysis sets used for each outcome are provided in Table 1.

**Table 1 Summary of outcome variables and analysis populations**

| Outcome variable | Analysis set |
|---|---|
| **Efficacy data** | |
| Primary endpoint/variables | FAS-RTP |
| Secondary endpoints/variables for open label phase | FAS-OLP |
| Secondary endpoints/variables for randomized treatment phase | FAS-RTP |
| **Study population** | |
| Demography characteristics | FAS-OLP and FAS-RTP |
| Baseline and disease characteristics | FAS-OLP and FAS-RTP |
| Important protocol deviations | FAS-OLP and FAS-RTP |
| Medical/surgical history | FAS-OLP and FAS-RTP |
| Concomitant medications | FAS-OLP and FAS-RTP |
| Study drug compliance | FAS-OLP and FAS-RTP |
| **Safety data** | |
| Exposure | SAF-OLP and SAF-RTP |

| Outcome variable | Analysis set |
|---|---|
| AEs | SAF-OLP and SAF-RTP |
| Laboratory measurements | SAF-OLP and SAF-RTP |
| Vital signs | SAF-OLP and SAF-RTP |
| ECG | SAF-OLP and SAF-RTP |

## 3.3 General Considerations

All efficacy analyses will be performed separately for the open-label initial phase and the 28-day randomized treatment study phase using their respective full analysis sets. Safety data will be separately summarized in a descriptive manner on the safety analysis sets for the OLP and the RTP, respectively.

All efficacy data will be listed by subject and will include S-K assessments data and efficacy response (achieve normokalemia) data. Study population listings will include disposition, protocol deviations, subjects excluded from efficacy analysis, demographic and baseline characteristics, and safety listings will include treatment compliance, adverse events, individual laboratory measurements, vital signs, physical examinations, and electrocardiograms (ECG).

Unless otherwise stated, percentages will be calculated out of the population total and for each treatment group and will be rounded to 1 decimal place. For continuous data, the mean and median will be rounded to one additional place compared to the original data, the standard deviation (SD) and standard error (SE) will be rounded to 2 additional places, and the minimum and maximum will be displayed to the same accuracy as the original data. If the number of decimal places of the original data is > 3, then the minimum and maximum will be assigned 3 decimal places, the mean and median 4 decimal places, and the SD and SE 5 decimal places.

Results of all statistical analyses will be presented using a 95% confidence interval (CI) and two-sided p-value, unless otherwise stated. All p-values will be presented to 3 decimal places. All p-values less than 0.001 will be presented as '< 0.001' and p-values greater than 0.999 will be presented as '> 0.999'.

SAS® version 9.4 or higher will be used for all analyses.

### 3.3.1 General Study Level Definitions

#### 3.3.1.1 Definition of Baseline

**Efficacy Baseline**

**For the OLP**: The baseline Serum Potassium (S-K) will be established on the OLP Study Visit 3 (pre-dose) by taking the mean of 2 different S-K values.

**For the RTP**: The baseline S-K, S-Aldo and P-Renin will be established based on the last pre-randomization measurement for S-K, S-Aldo and P-Renin, respectively, obtained during the OLP.

If baseline S-K C-lab values are missing, the i-STAT data will be used to replace them as described in Section 4.2.1.3. Subjects with missing values at baseline will be excluded from the relevant efficacy analysis.

**Safety Baseline**

Safety analyses will be performed separately for OLP and RTP. For change from baseline tabulations (laboratory measurements, vital signs, ECG and weight) the baseline will be defined as follows:

**For OLP:** Baseline will be the last non-missing measurement taken prior to first IP administration during OLP. If a measurement was taken on the date of first IP administration and no time is recorded, it is assumed that the measurement was taken pre-dose and will be considered a candidate for baseline.

**For RTP:** Same as OLP baseline, i.e. the last non-missing measurement taken prior to first IP administration during OLP.

#### 3.3.1.2 Definition of On-Treatment

**For OLP**: Any measurements that have an onset day on or after the date of first dose of open-label study treatment and no later than the date of last dose of open-label study treatment + 1 day.

**For RTP**: Any measurements with an onset date more than one day after the day of last dose of open label study medication, and either on or after the day of first dose of randomized study medication, and no later than the day of last dose of study medication +1 day.

#### 3.3.1.3 Definition of Treatment-emergent

**For OLP**: Any measurements reported as ‘abnormal’ whilst on-treatment (defined as per Section 3.3.1.2),but were previously reported as ‘normal’ at OLP Baseline (defined as per Section 3.3.1.1)

**For RTP**: Any measurements reported as 'abnormal' whilst on-treatment (defined as per Section 3.3.1.2),but were previously reported as 'normal' at RTP Baseline (defined as per Section 3.3.1.1)

#### 3.3.1.4 Handling of missing dates

Missing adverse event (AE) and concomitant medication (CM) start and end dates will be imputed as follows:

For partial or missing start dates:

- Missing day: impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing day and month: impute 1st January, unless the year is the same as first dose date and the end date does not suggest it could have started prior to first dose (i.e. end date is before first dose date), then impute first dose date.
- Completely missing: impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

For partial or missing end dates:

- Missing day: impute the last day of the month unless month is same as month of first dose of study drug then impute last dose date.
- Missing day and month: impute 31st December unless year is the same as first dose date then impute last dose date.
- Completely missing: need to look at whether the AE or CM is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE or CM is still present (i.e. do not impute a date). If the AE or CM has stopped and start date is prior to first dose date then impute the last dose date, if it started on or after first dose date then impute a date that is after the last dose date.

### 3.3.2 Hypotheses

#### 3.3.2.1 Primary hypotheses

**Endpoint:** Mean S-K level between placebo and each ZS treatment group (high to low) during the 28-day randomized treatment study phase Days 8-29.

**The null hypothesis**: No treatment difference in the mean S-K levels during RTP (Days 8-29) compared to placebo as follows (two null hypotheses):

For this endpoint the null hypothesis is that during RTP (Days 8-29) there is no treatment difference in the mean S-K levels; and the alternative is compared to placebo there is a difference in the mean S-K levels:

$$H_0: \mu_{sk}(ZS_{10g}) = \mu_{sk}(Placebo) \text{ vs. } H_A: \mu_{sk}(ZS_{10g}) \neq \mu_{sk}(Placebo)$$

$$H_0: \mu_{sk}(ZS_{5g}) = \mu_{sk}(Placebo) \text{ vs. } H_A: \mu_{sk}(ZS_{5g}) \neq \mu_{sk}(Placebo)$$

#### 3.3.2.2 Secondary hypotheses

**For the OLP, the following hypotheses will be tested versus two-sided alternatives:**

**Endpoint:** Exponential rate of change in S-K levels (blood) at 24 hours and 48 hours during OLP.

**The null hypothesis:**

$$H_0: Exponential\ rate_{\Delta S-K}(24\ hours) = 0 \text{ vs. } H_A: Exponential\ rate_{\Delta S-K}(24\ hours) \neq 0$$

$$H_0: Exponential\ rate_{\Delta S-K}(48\ hours) = 0 \text{ vs. } H_A: Exponential\ rate_{\Delta S-K}(48\ hours) \neq 0$$

This is evaluated by the parameter estimate of time (in hours) from a mixed effects model as described in Section 4.2.2.4. Note that the exponential rate of change refers to the degree of decline in SK values over time, which is assumed to follow an exponential trend.

**Endpoint:** Mean change (absolute and percent (%) change) from baseline in S-K levels

**The null hypotheses:**

$$H_0: \mu_{\Delta\,S-K}(24\ hours) = 0 \text{ vs. } H_A: \mu_{\Delta\,S-K}(24\ hours) \neq 0$$

$$H_0: \mu_{\Delta\,S-K}(End\ of\ OLP) = 0 \text{ vs. } H_A: \mu_{\Delta\,S-K}(End\ of\ OLP) \neq 0$$

The end of OLP can be 24 or 48 hours depending on the duration of OLP, as subjects who did not achieve normokalemia at 24 hours are evaluated again at 48 hours.

There will be a similar hypothesis for the mean percent change of S-K at 24 and 48 hours.

**For the RTP, the following hypotheses will be tested:**

**Endpoint:** Proportion of subjects who remain normokalemic at the end of the RTP and during the RTP.

**The null hypotheses**:

$$H_0: OR\left(ZS_{10g} vs\ Placebo\right) = 1. \text{ vs. } H_A: OR\left(ZS_{10g}\ vs\ Placebo\right) \neq 1$$

$$H_0: OR\left(ZS_{5g} vs\ Placebo\right) = 1. \text{ vs. } H_A: OR\left(ZS_{5g}\ vs\ Placebo\right) \neq 1$$

For each of the treatment arm comparisons, two tests will be done: one aiming at evaluating the odds of being normokalemic Day 8-29, performed by means of a generalized random effects model as described in Section 4.2.3, and another aiming at evaluating the probability of being normokalemic at Day 29 in particular, performed by means of a logistic regression model.

**Endpoint:** Number of days subjects remain normokalemic during the RTP.

**The null hypotheses:**

$H_0: \mu_{\text{days of normokalemic}}\left(ZS_{10g}\right) = \mu_{\text{days of normokalemic}}(Placebo)$ vs.
$H_A: \mu_{\text{days of normokalemic}}\left(ZS_{10g}\right) \neq \mu_{\text{days of normokalemic}}(Placebo)$

$H_0: \mu_{\text{days of normokalemic}}\left(ZS_{5g}\right) = \mu_{\text{days of normokalemic}}(Placebo)$ vs.
$H_A: \mu_{\text{days of normokalemic}}\left(ZS_{5g}\right) \neq \mu_{\text{days of normokalemic}}(Placebo)$

**Endpoint:** Time to hyperkalemia.

**The null hypotheses**:

$$H_0: HR\left(ZS_{10g} vs\ Placebo\right) = 1. \text{ vs. } H_A: HR\left(ZS_{10g}\ vs\ Placebo\right) \neq 1$$

$$H_0: HR\left(ZS_{5g} vs\ Placebo\right) = 1. \text{ vs. } H_A: HR\left(ZS_{5g}\ vs\ Placebo\right) \neq 1$$

**Endpoint:** The mean changes in S-Aldo and P-Renin levels during RTP

**The null hypotheses**:

$$H_0: \mu_{Aldo}(ZS_{10g}) = \mu_{Aldo}(Placebo) \text{ vs. } H_A: \mu_{Aldo}(ZS_{10g}) \neq \mu_{Aldo}(Placebo)$$

$$H_0: \mu_{Aldo}(ZS_{5g}) = \mu_{Aldo}(Placebo) \text{ vs. } H_A: \mu_{Aldo}(ZS_{5g}) \neq \mu_{Aldo}(Placebo)$$

$$H_0: \mu_{Renin}(ZS_{10g}) = \mu_{Renin}(Placebo) \text{ vs. } H_A: \mu_{Renin}(ZS_{10g}) \neq \mu_{Renin}(Placebo)$$

$$H_0: \mu_{Renin}(ZS_{5g}) = \mu_{Renin}(Placebo) \text{ vs. } H_A: \mu_{Renin}(ZS_{5g}) \neq \mu_{Renin}(Placebo)$$

### 3.3.3 Visit Window

In the absence of nominal visits, visits windows will apply. Measurements will be assigned to exhaustive visit windows based on study day such that measurements taken at any time point can be accounted for and used in summaries and/or analyses. If an unscheduled visit occurred in the same window, then the measurement from the scheduled visit will be used in the analysis. If there are multiple unscheduled visits in the same visit window, then the visit closest to the scheduled visit day will be used. If there are multiple records on the same day the last measurement will be used.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment is used (regardless of where it falls in an interval).
- Listings display all values contributing to a time point for a subject.
- For visit-based summaries
    - If there is more than one scheduled value per subject within a time window then the closest value to the scheduled visit date is summarized. If the scheduled values are equidistant from the nominal visit date, then the earlier value is used. Data listings will highlight the values used in the summary table, wherever feasible.
    - Note: in summaries of extreme values (i.e. when assessing the minimum/maximum on-treatment values), all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date and appears in the corresponding visit-based summary.

Visit windows are described in **Table 2**.

**Table 2 Time windows for allocation of data to visits for statistical analysis**

| Study Visit (Target Day) | Nominal Target Day | Study Visit Window (Days) | |
|---|---|---|---|
| | | Lower | Upper |
| **Pre Screening Phase and Screening Phase**[1] | | | |
| Visit 1 (Pre-screen) | --- | --- | --- |
| Visit 2 (Screening) | --- | --- | 1[1] |
| **Open Label Phase** | | | |
| OLP-Day 1 | 1 | 1 | 1 |
| OLP-Day 2 [2] | 2 | 2 | 2 |
| OLP-Day 3 [3] | 3 | 3 | 3 |
| End of OLP (24 hours or 48 hours) [4] | 2 or 3 | --- | --- |
| End of Study Visit (OLP-Day 9) [5] | 9 | 4 | 16 |
| **Randomized Treatment Phase** | | | |
| Randomization (RTP-Day 1) | 1 | 1 | 1 |
| Visit 6 (RTP-Day 2) | 2 | 2 | 2 |
| Visit 7 (RTP-Day 5) | 5 | 3 | 6 |
| Visit 8 (RTP-Day 8) | 8 | 7 | 9 |
| Visit 9 (RTP-Day 12) | 12 | 10 | 13 |
| Visit 10 (RTP-Day 15) | 15 | 14 | 17 |
| Visit 11 (RTP-Day 19) | 19 | 18 | 20 |
| Visit 12 (RTP-Day 22) | 22 | 21 | 24 |
| Visit 13 (RTP-Day 26) | 26 | 25 | 27 |
| Visit 14 (RTP-Day 29) | 29 | 28 | 31 |
| End of Study Visit (RTP-Day 35)[6] | 35 | 32 | 43 |

1. The screening phase lasts up to the date and time when the open label initial phase is initiated, i.e. date and time of the first dose.
2. Potassium is measured predose and 1 hour post dose. The predose measure is considered as the 24-hour measurement for all analyses. Patients who achieve normokalemia at 24 hours will proceed to the Randomization (RTP-Day 1) visit.
3. Potassium is measured predose and this measure is considered as the 48-hour measurement for all analyses.
4. End of OLP (24 hours or 48 hours) the latest treatment day of open label initial phase only for patients who complete 24 hours or 48 hours OLP treatment.
5. End of Study Visit (OLP-Day 9) in open label initial phase only for patients NOT entering the 28-day randomized treatment study phase and occurs 7±1 day after the last administration of IP.
6. End of Study Visit (RTP-Day 35) occurs 7±1 day after last planned administration of IP in RTP.

### 3.3.4 Handling of Unscheduled Visits

Unscheduled visits are included in the method of assigning data to scheduled visits described in the rules in Section 3.3.3 above. Unscheduled visits are not included as a separate visit in the summary tables, but they will be included in all listings of study data.

### 3.3.5 Handling of Missing Serum Potassium (S-K) Data

The S-K levels used for all analyses will be based on the central laboratory (c-lab) measurements. If the S-K c-lab data points are missing, the i-STAT data will be used to replace missing data by adjusting for the average paired difference between the c-lab and i-STAT levels collected at the same visit and with the same calibration method for the potassium assay. If the time difference between the SK c-lab and i-STAT measurements is greater than 15 minutes, the SK measure for that time point will be set as missing.

### 3.3.6 Mixed Model: Terms and Estimation

The form of the linear mixed effects model employed in the analyses in this study is as follows:

$$\ln\,(SK\ level)_{ij} = X_{ij}\beta + Z_i b_i + \varepsilon_{ij}$$

where:

1. $\ln\,(SK\ level)_{ij}$ is the S-K level in the natural log scale for the $j^{th}$ measurement for the $i^{th}$ subject.
2. $X_{ij}$ is the matrix of fixed effects covariates.
3. $\beta$ is a vector containing the fixed-effects regression coefficients.
4. $Z_i$ represents the random effects covariates.
5. $b_i$ is a normally distributed random effect parameter.
6. $\varepsilon_{ij}$ is a normally distributed random error term.

Variance components will be estimated using a restricted maximum likelihood method (REML) and an unstructured marginal covariance structure will be assumed. If the specified model fails to converge, the final covariance structure will be determined by Akaike's information criteria: Toeplitz, first-order autoregressive and compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

For the analysis of primary endpoint, the model will include S-K data values (natural log scale) assigned to the scheduled visits between Days 8-29 as response variables, and the following fixed effects: eGFR baseline, OLP and RTP baseline S-K values, visit, treatment, visit-by-treatment interaction, as well as age (<55, 55-64, >64 years) and baseline binary indicators for renin-angiotensin-aldosterone system (RAAS) inhibitors, chronic kidney disease, heart failure, and diabetes mellitus.

### 3.3.7 Multiplicity/Multiple Comparisons

A sequential closed testing procedure will be used in OLP and RTP to maintain an overall Type I error rate of 5%.

Treatment testing will proceed from high dose (ZS 10g) to low dose (ZS 5g) relative to placebo, with statistical significance (two-sided p-value $\leq 0.05$) required for the high dose vs. placebo control in order to proceed to the low dose vs. placebo control.

P-values for tests not included in the sequential closed testing procedure are not adjusted for multiplicity and will not be called significant and are considered exploratory.

Specifically, the following fixed hierarchical sequence will be employed: progression to the next test in the sequence will continue until a 2-sided p-value of $> 0.05$ is encountered, at which any point further testing will cease. Explicitly, Table 3 will be implemented.

**Table 3. Overview of the variables/endpoints and multiplicity testing order**

| | Endpoints/Variables | Phase | Treatment Comparison | Testing Order in Hierarchy |
|---|---|---|---|---|
| Primary | Mean serum potassium [S-K] level | RTP[ii] | ZS 10g QD vs. Placebo | 2 |
| Primary | Mean serum potassium [S-K] level | RTP[ii] | ZS 5g QD vs. Placebo | 3 |
| Secondary | Proportion of subjects who remain normokalemic[iv] at the end of RTP[iii] | RTP[ii] | ZS 10g QD vs. Placebo | 4 |
| Secondary | Proportion of subjects who remain normokalemic at the end of RTP | RTP[ii] | ZS 5g QD vs. Placebo | 5 |
| Secondary | Number of days that subjects are normokalemic | RTP[ii] | ZS 10g QD vs. Placebo | 6 |
| Secondary | Number of days that subjects are normokalemic | RTP[ii] | ZS 5g QD vs. Placebo | 7 |
| Secondary | Time to hyperkalemia[v] | RTP[ii] | ZS 10g QD vs. Placebo | 8 |
| Secondary | Time to hyperkalemia | RTP[ii] | ZS 5g QD vs. Placebo | 9 |
| Secondary | Mean serum potassium [S-K] change from baseline after first dose | OLP[i] | NA | 1 |

[i] OLP refers to the 24 or 48 hours Open Label Phase.
[ii] RTP refers to the 28 days Randomized Treatment Phase, and Days 8-29 is of interest for the endpoints.
[iii] End of RTP in the maintenance day refers to the planned day of last dose of study treatment, Day 29.
[iv] Normokalemic/Normokalemia is defined as having [S-K] level within the range of 3.5-5.0 mmol/L, inclusive.
[v] Hyperkalemia is defined as having [S-K] level greater equal than 5.1 mmol/L.

### 3.3.8 Handling of Protocol Deviations in Study Analysis

There is no defined Per Protocol population for this study and all efficacy analyses will be based on the FAS. Therefore, protocol deviations will not imply exclusion from analyses.

According to ICH E3 (ICH 1995) guidelines,

> "Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety or well-being."

Important protocol deviations relating to subject-level and subject-visit level events are defined in the Non-Compliance Handling Plan and presented in Appendix A: IPD Master List. They will be reviewed by appropriate medical, clinical, data management, and statistical personnel and will be documented prior to database lock.

A full list of subject inclusion and exclusion criteria is provided in the study protocol.

### 3.3.9 COVID-19 Impact

If a study participant is unable to attend more than two consecutive clinic visits either due to quarantine for being infected with or suspected for COVID-19 or due to site closure for COVID-19, the investigational product should be discontinued after discussed with AZ.

# 4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation per domain.

For all domains, descriptive statistics presented will depend on the type of variable analyzed and will include n (number of subjects included in the analysis), mean, standard deviation (SD), median, minimum and maximum. For categorical variables, they will consist of the number of observations in the respective category, as well as the corresponding percentages.

## 4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medications, and study drug compliance.

The majority of the presentations in this domain, with the exception of the overview of the analysis sets and recruitment, will consist of summary statistics provided for each of the treatment arms, and for the treatment arms combined.

### 4.1.1 Subject Disposition and Completion Status

#### 4.1.1.1 Definitions and Derivations

Subject accounting will be provided for but not limited to the following:

- Subjects included in the OLP
- Subjects included in the RTP
- Non-randomized subjects
- Subjects who received treatment in the OLP and in the RTP
- Subjects who were randomized but did not receive any treatment in RTP
- Subjects who completed treatment in the OLP
- Subjects who discontinued treatment in the OLP
- Randomized subjects who completed treatment in the RTP
- Randomized subjects who discontinued treatment in the RTP
- Randomized subjects who completed the study
- Randomized subjects who withdrew from the study
- Randomized subjects who discontinued treatment due to global/country situation
- Randomized subjects who withdrew from the study due to global/country situation

#### 4.1.1.2 Presentation

The number and percentage of subjects in the above categories will be presented separately for OLP and RTP.

The subject recruitment will be presented by center for each treatment group.

Disposition listings will include subject ID, age, gender and race, and will be presented sorted by treatment group, subject ID, and date/time of observation.

### 4.1.2 Analysis Sets

#### 4.1.2.1 Definitions and Derivations

Refer to Section 3.2 for definition of analysis sets.

#### 4.1.2.2 Presentation

The number of subjects included in the FAS and SAF for OLP and RTP, along with the reasons for exclusion from either of the analysis sets where relevant, will be summarized.

A listing of subjects excluded from any analysis set will include subject ID, age, gender and race, and will be presented sorted by treatment group, subject ID, and date/time of observation.

### 4.1.3 Protocol Deviations

#### 4.1.3.1 Definitions and Derivations

Refer to section 3.3.7 for definition of protocol deviations.

#### 4.1.3.2 Presentation

Important protocol deviations will be listed and summarized separately for the FAS-OLP and FAS-RTP.

The number and percentage of subjects with any IPD will be summarized for each IPD category. Subjects with more than one deviation in the same IPD category will be counted once for that IPD category. Any subjects who have deviations in more than one IPD category will be counted once in the overall summary.

The number and percentages of subjects within each important protocol deviation type will be summarized by study phase, OLP and RTP, respectively. In the RTP, summaries will be presented overall and by treatment group. All individual subjects with important protocol deviations will be listed as well for OLP and RTP, respectively.

Similarly, COVID-related IPD will be summarized.

### 4.1.4 Demographics

#### 4.1.4.1 Definitions and Derivations

Demographics are comprised of age, age group, sex, race and ethnicity.

#### 4.1.4.2 Presentation

Demographics will be listed for all subjects enrolled and summarized respectively for the FAS-OLP and FAS-RTP. This listing will include subject ID, age, gender, ethnicity and race, and will be presented sorted by treatment group and subject ID.

In addition to being summarized as a continuous variable, age will be summarized as the age group categorical variable (<55, 55–64, >64 years).

## 4.1.5 Baseline Characteristics

### 4.1.5.1 Definitions and Derivations

Baseline characteristics include height (m), weight (kg) and BMI (kg/m$^2$), baseline serum potassium (S-K), baseline eGFR, baseline binary indicators for RAAS, chronic kidney disease, heart failure and diabetes mellitus.

Baseline parameters are measured/collected up to 1 day prior to administration of the 1st dose of study drug on the open-label initial phase Day 1 (Visit 3).

BMI is calculated as: Weight (kg) / [Height (m)]$^2$.

eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2009) for each time-point where creatinine is measured, using central laboratory creatinine:

$$eGFR = 141 * min(S_{Cr}/K, 1)^{\alpha} * max(S_{Cr}/K, 1)^{-1.209} * 0.993^{Age} * 1.018 * 1.159\ [if\ patient\ is\ black]$$

Where:

1. $S_{Cr}$ is the standardized serum creatinine in mg/dL
2. $K$ = 0.7 (females) or 0.9 (males)
3. $\alpha$ = -0.329 (females) or -0.411 (males)
4. $Age$ is in years.

### 4.1.5.2 Presentation

Baseline characteristics will be listed for all subjects enrolled and summarized respectively for the FAS-OLP and FAS-RTP. This listing will include subject ID, age, gender and race, and will be presented sorted by treatment group and subject ID.

## 4.1.6 Medical History and Concomitant Disease

### 4.1.6.1 Definitions and Derivations

Medical and surgical history are collected up to one day prior to administration of study drug on Day1 (Visit 3) are classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

### 4.1.6.2 Presentation

Medical history and surgical history are grouped by MedDRA system organ class and preferred term and are summarized by System Organ Class (SOC) and Preferred Term (PT), for all subjects in FAS-OLP and in FAS-RTP.

They will be listed for all subjects enrolled and summarized respectively for the FAS-OLP and FAS-RTP. This listing will be presented sorted by treatment group, subject ID, and date/time of the event.

### 4.1.7 Prior and Concomitant Medications

#### 4.1.7.1 Definitions and Derivations

Medications will be classified according to the latest version of the WHO Drug coding dictionary. Prior medication is any medication that started and stopped prior to treatment with investigational product. Concomitant medication is any medication that is taken concurrently with investigational product regardless of the start date of the medication. Concomitant medications include allowed and disallowed medications taken by the subjects during the respective phases (i.e. a medication can be concomitant for the OLP but not RTP, or RTP but not OLP). Missing medication start and stop dates will be imputed according to Section 3.3.1.4.

For the definition of disallowed medications, see Appendix B.

#### 4.1.7.2 Presentation

Prior and concomitant medications (allowed and disallowed) and procedures will be listed respectively for all subjects in the SAF-OLP and SAF-RTP, and will be presented sorted by treatment group and subject ID.

Concomitant medications and procedures listed in Section 7.7 of the CSP will be summarized by chemical subgroup (ATC 4th level) and preferred WHO name respectively for the SAF-OLP and SAF-RTP. Subjects with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than one (chemical and/or therapeutic) subgroup will be presented in each subgroup. A medical review may also be done.

Disallowed medications will be similarly summarized, separately.

### 4.1.8 Study Drug Compliance

#### 4.1.8.1 Definitions and Derivations

Treatment compliance is obtained by summing up the total number of sachets taken and dividing it by the expected number of sachets to be taken, multiplied by 100%, where the expected number of sachets is calculated over the subject’s actual duration in the trial and not the planned duration. Subjects who did not receive IP will have their treatment compliance set to missing.

#### 4.1.8.2 Presentation

Treatment compliance will be summarized separately for the OLP and the RTP, overall and by treatment group.

### 4.1.9 COVID-19 Impact

#### 4.1.9.1 Definitions and Derivations

See section 3.3.9 for the definition.

#### 4.1.9.2 Presentation

Depending on the extent of any impact, summaries of data relating to subjects diagnosed with COVID-19, and the impact of COVID-19 on study conduct may be generated including

- Disposition (discontinued IP due to COVID-19 and withdrew study due to COVID-19)
- Deviations (overall deviations plus if due to COVID-19 and not due to COVID-19)
- Summary of COVID-19 disruptions (visit impact, drug impacted)

Listing for subjects affected by the COVID-19 pandemic will also be produced.

## 4.2 Endpoint/Variable Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Efficacy analyses will be undertaken for the open-label initial phase and the 28-day randomized treatment study phase on the respective full analysis sets unless otherwise stated.

| Statistical category | Endpoint | Analysis set | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| **Primary objective:** To evaluate the efficacy of two different doses (5 and 10 g) of ZS orally administered once daily (qd) for 28 days in maintaining normokalemia (serum potassium [S-K] between 3.5-5.0 mmol/L, inclusive) in normokalemic subjects, following treatment in the open-label initial phase, for hyperkalemic subjects (two consecutive i-STAT potassium values ≥ 5.1 mmol/L, taken 60 minutes apart) at baseline. | | | | | |
| Primary | Mean S-K level between placebo and each ZS treatment group (high to low) during the 28-day randomized treatment study phase Days 8-29. | FAS-RTP | Treatment policy: intercurrent events ignored | Difference in mean S-K values between each of the active treatment groups (ZS 10g and ZS 5g) and placebo, during RTP Days 8-29, estimated using a longitudinal mixed model. | 4.2.1.4 |
| Sensitivity | Mean i-STAT level between placebo and each ZS treatment group (high to low) during the 28-day randomized treatment study phase Days 8-29. | FAS-RTP | Treatment policy: intercurrent events ignored | Difference in mean i-STAT values between each of the active treatment groups (ZS 10g and ZS 5g) and placebo, during RTP Days 8-29, estimated using a longitudinal mixed model. | 4.2.1.5 |
| Supplementary | Mean S-K level between placebo and each ZS treatment group (high to low) during the 28-day randomized treatment study phase Days 8-29. | FAS-RTP | Hypothetical strategy for disallowed medications: measurements obtained while a subject was using disallowed medication are excluded from the analysis. | Difference in mean S-K values between each of the active treatment groups (ZS 10g and ZS 5g) and placebo, during RTP Days 8-29, estimated using a longitudinal mixed model. | 4.2.1.6 |
| **Secondary objective 1 (OLP):** To evaluate the proportion of subjects who achieve normokalemia after the completion of open-label initial phase treatment | | | | | |
| Secondary | 1- Proportion of subjects who achieve normokalemia (3.5 – 5.0 mmol/L) during and at the end of OLP (classification of each screened subject as | FAS-OLP | Treatment policy: intercurrent events ignored. This policy will be used for all four of the endpoints in this section. | 1- Probability of subjects achieving normokalemia, at 24 h and at the end of OLP, estimated as proportion of responders, with 95% two-sided Clopper-Pearson exact CIs.<br>2- The time effect derived from | 4.2.2.4 |

| Statistical category | Endpoint | Analysis set | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| | either a “responder” or a “non-responder”)<br>2- Exponential rate of change in S-K levels during OLP 24 hours post-dose<br>3- Mean change (absolute and percent change) in S-K level at all post-dose time intervals during OLP<br>4- Time to normalization in S-K levels during OLP | | | a longitudinal mixed model including all SK measurements up to 24 hours post-dose<br>3- Mean change (absolute and percent change) in S-K level from baseline to each of the planned measurement occasions during OLP, as well as end of OLP, analyzed using one sample, two-sided t-tests<br>4- The CDF of time to S-K normalization estimated using Kaplan-Meier life table curves | |
| Supplementary | Proportion of subjects who achieve normokalemia without use of disallowed medications during and at the end of OLP | FAS-OLP | Composite strategy: Intercurrent event (use of disallowed medication) is included as part of a composite endpoint, where subjects can only be counted as a "success" (responder) if they did not receive any disallowed medication before the measurement occasion and if they are normokalemic (S-K between 3.5-5.0 mmol/L). | Probability of subjects achieving normokalemia without usage of disallowed medications, estimated as proportion of responders, with 95% two-sided Clopper-Pearson exact CIs. | 4.2.2.5 |
| Supplementary | Mean change in S-K level from baseline to 24h and end of OLP | FAS-OLP | Hypothetical strategy: measurements obtained post usage of disallowed medications are removed from the analysis | Mean change in S-K level from baseline to 24h and end of OLP, analyzed using one sample, two-sided t-tests | 4.2.2.5 |
| Supplementary | Exponential rate of change in S-K levels during OLP 48 hours | FAS-OLP | Treatment policy: intercurrent events ignored. | The time effect derived from a longitudinal mixed model including all SK measurements | 4.2.2.5 |

| Statistical category | Endpoint | Analysis set | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| | post-dose | | | up to 48 hours post-dose | |
| **Secondary objective 2 (RTP):** To evaluate the efficacy of ZS in subjects with hyperkalemia for the following subgroups as applicable:<br>- chronic kidney disease (CKD)<br>- diabetes mellitus (DM)<br>- heart failure (HF)<br>- those on renin-angiotensin-aldosterone system (RAAS) inhibitors. | | | | | |
| Secondary | 1- Proportion of subjects who remain normokalemic during and at the end of RTP<br>2- The number of days subjects remain normokalemic during RTP<br>3- Time to hyperkalemia<br>4- Mean change (absolute and percent change) in S-K level at all post-dose time intervals during RTP | FAS-RTP | Treatment policy: intercurrent events ignored. This policy will be used for all four of the endpoints in this section. | 1- Odds ratio of being normokalemic on Day 29, and between Day 8 and 29, compared between each of the active treatment groups (ZS 10g and ZS 5g) and placebo using a logistic regression model (generalized random effect model)<br>2- The least square mean of number of the days will be compared between each of the active treatment groups (ZS 10g and ZS 5g) and placebo using a linear regression model<br>3- Hazard ratio for median time (days) to hyperkalemia between each of the active treatment groups (ZS 10g and ZS 5g) and placebo obtained from Cox proportional hazards model<br>4- Mean change (absolute and percent change) in S-K level from baseline to each of the planned measurement occasions | 4.2.3.3 |

| Statistical category | Endpoint | Analysis set | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| | | | | during RTP, analyzed using one sample, two-sided t-tests | |
| Supplementary | Proportion of subjects who remain normokalemic at the end of RTP | FAS-RTP | Composite strategy: Intercurrent event (use of disallowed medication) is included as part of a composite endpoint, where subjects can only be counted as a "success" (responder) if they did not receive any disallowed medication before the measurement occasion and if they are normokalemic (S-K between 3.5-5.0 mmol/L). | Odds ratio of being normokalemic on Day 29 compared between each of the active treatment groups (ZS 10g and ZS 5g) and placebo using a logistic regression model | 4.2.3.4 |
| **Secondary objective 3 (RTP):** To evaluate the effect of ZS on serum-Aldosterone (S-Aldo) and Plasma-Renin (P-Renin) levels. | | | | | |
| Secondary | The mean changes in S-Aldo and P-Renin levels during RTP | FAS-RTP | Treatment policy: intercurrent events ignored. | Mean difference in values between each of the active treatment groups (ZS 10g and ZS 5g) and placebo estimated using a longitudinal mixed model. | 4.2.3.3 |

### 4.2.1 Primary Endpoint

The primary efficacy variable is serum potassium [S-K] level during the RTP, Days 8-29, using c-lab, or adjusted i-STAT for visits where c-lab is not available.

#### 4.2.1.1 Definition

Several intercurrent events of concern have been identified in this setting, namely the use of disallowed medications, changes in treatment, including discontinuations, and death. For the main analysis of the primary endpoint a treatment policy approach to all the identified intercurrent events will be used (except for death, for which such an approach is not applicable).

However, a supplementary analysis aimed at evaluating the impact of disallowed medication use is included. In this analysis, the S-K (or i-STAT, if applicable) measurements obtained while a subject was receiving disallowed medication are excluded, reflecting a hypothetical scenario where disallowed medication is not available to subjects (i.e. a "hypothetical strategy" type of approach, see ICH E9 (R1) 2017 p. 18).

#### 4.2.1.2 Derivations

See section 3.3.1.1 for definition of baseline for the efficacy analyses.

#### 4.2.1.3 Handling of Dropouts and Missing Data

The S-K levels used for the primary analysis will be based on the c-lab measurements obtained during the RTP. Missing S-K c-lab values will be replaced as described in Section 3.3.5.

For the supplementary analysis aimed at evaluating the impact of usage of disallowed medications, if a subject is missing both the central laboratory and i-STAT values they will be imputed using multiple imputation (MI). Note that MI will not be used for the main analysis, as it is expected that, after i-STAT imputation, the amount of missing data will be minimal, and the missing pattern will be MAR, and would be sufficiently explained by the covariates included in the model.

**Multiple imputation for the supplementary analysis**

Multiple imputation (MI) will be done where imputation of unavailable c-lab values with i-STAT values not possible.

Missing S-K values will be imputed using the Fully Conditional Specification (FCS) method (Brand 1999; Van Buuren 2007). The covariates to be included in the imputation model are; the available c-lab data obtained post randomization visit (RTP Day 1) with baseline

covariates for the open-label initial phase eGFR, the open-label initial phase S-K values, the 28-day randomized treatment study phase S-K values as well as age (<55, 55-64, >64 years), baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, diabetes and treatment arm. The imputation will be performed using the log-transformed S-K values. M=100 will be chosen as the number of imputed data sets, the seed will be set as 22438 and the default 20 burn-ins will be used. An unstructured marginal covariance structure will be assumed. If the specified model fails to converge, alternative structures will be used as described in Section 3.3.6.

**Analysis:**

Once M complete data sets have been constructed using MI, the statistical analysis will be conducted on each of the M complete data sets. Explicitly, a linear mixed models will be applied, see Section 4.2.1.4.

**Pooling:**

Rubin's rules will be implemented for combining estimates and standard errors across the imputed data sets and conducting the analysis. Suppose $\hat{Q}_i$ and $\hat{W}_i$ are the point and variance estimates from the i[th] imputed data set, i = 1, 2, . . . , 100. Then the combined point estimate for Q from multiple imputation is the average of the 100 complete-data estimates:

$$\bar{Q} = \frac{1}{100}\sum_{i=1}^{100} \hat{Q}_i$$

$\bar{W}$ is the within-imputation variance, which is the average of the m complete-data estimates:

$$\bar{W} = \frac{1}{m}\sum_{i=1}^{100} \hat{W}_i$$

B is the between-imputation variance:

$$B = \frac{1}{100-1}\sum_{i=1}^{100} (\hat{Q}_i - \overline{Q})^2$$

Then the variance estimate associated with $\bar{Q}$ is the total variance is:

$$T = (1+x)^n = \bar{W} + \left(1 + \frac{1}{100}\right)B$$

The statistic $(\hat{Q}_i - \overline{\mathrm{Q}})T^{-(\frac{1}{2})}$ is approximately distributed as t with $V_m$ degrees of freedom

$$V_{100} = (100-1)\left(\left[1 + \frac{\bar{W}}{(1+100^{-1})B}\right]\right)^2$$

No imputation will be done for missing covariates in the models.

#### 4.2.1.4 Main Analysis of Primary Endpoint

To address the primary objective, a comparison between placebo and each ZS treatment group (high to low) with regards to the mean S-K level during the 28-day randomized treatment study phase Days 8-29 will be made.

Descriptive statistics will be presented for S-K values at randomization visit (RTP Day 1) through Visit 14 (RTP Day 29), and the EOS visit. Mean change (absolute and percent change) from baseline will be summarized by treatment groups (ZS 5g, ZS 10g and placebo). In addition, a box plot of S-K values by visit will be presented.

The primary efficacy endpoint will be analyzed using a longitudinal mixed model (SAS PROC MIXED). The model will include all S-K data values (natural log scale) collected at the scheduled visits between Days 8-29 as response variables, and treatment, visit, treatment-by-visit interaction, baseline eGFR, OLP and RTP baseline S-K values as well as age (<55, 55-64, >64 years) and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, and diabetes mellitus as fixed effects, patients are random effect term.

The p-value from least square mean (LSMEAN) (two-sided) will be provided to compare the overall mean difference in S-K values between each active treatment (ZS 10g and ZS 5g) and placebo (the second and third tests in the sequential closed testing procedure).

The estimated mean difference in log-transformed S-K values between each of the active treatment groups (ZS 10g and ZS 5 g) relative to the placebo treatment group will be provided along with accompanying 2-sided 95% confidence intervals. The relative difference in back-transformed S-K, ZS 10g and ZS 5 g vs placebo, will also be presented, along with the corresponding 2-sided 95% CI.

#### 4.2.1.5 Supplementary and Sensitivity Analyses of Primary Endpoint

A sensitivity analysis will be conducted to assess the potential discrepancy in observed effect as assessed through by c-lab potassium, as opposed to i-STAT. This will be performed by using the same longitudinal model as was used for the main analysis of the primary endpoint on subjects Day 8 to Day 29 i-STAT measurements.

A supplementary analysis, aimed at evaluating the impact of the usage of disallowed medications on the efficacy results, will also be conducted. This will be done by means of removing the potassium measurements that occurred while a subject was receiving a disallowed medication (between medications start date and stop date, plus 7 days), replacing them using a MI approach, and replicating the main analysis on each of the resulting data sets. See Section 4.2.1.3 for details on the MI procedure.

#### 4.2.1.6 Subgroup Analysis

The primary efficacy endpoint will be evaluated in several sub-groups, in order to explore the consistency of the treatment effect, as follows:

- chronic kidney disease status (yes/no)
- diabetes mellitus status (yes/no)
- heart failure status (yes/no)
- those on RAAS inhibitors (yes/no).

For the subgroup analysis to be conducted, a minimum of 10 subjects per treatment-subgroup combination is required, since this is the generally accepted minimum number. A single model will be fitted, this model including a treatment by subgroup interaction term in addition to the covariates in the original analysis (See section 4.2.1). Estimates of the treatment effect for each subgroup will be provided, with corresponding confidence intervals. A p-value for the interaction term will also be given. Additionally, LSMEAN for the combinations of treatment by subgroup levels will be presented with corresponding confidence intervals.

### 4.2.2 Secondary Endpoints for OLP phase

#### 4.2.2.1 Definition

The secondary efficacy endpoints for OLP phase will include the following:

1. Proportion of subjects who achieve normokalemia during the OLP at 24 hours (OLP Day 2) and at the end of the OLP. Each subject is classified into a responder or a non-responder category (i.e. a 0-1 type of response for subjects who achieve normokalemia or subjects who do not achieve normokalemia), with a subject being a responder if they have S-K between 3.5 and 5.0 mmol/L, inclusive. The following 7 time points during the OLP phase will be considered:

    - OLP Day 1, at 1, 2 and 4 hours post first dose
    - OLP Day 2, pre-dose and 1 hour post dose
    - OLP Day 3, pre-dose
    - End of OLP

    **Note:** not all subjects will have OLP Day 2, 1 hour post dose and OLP Day 3 pre-dose visit.

2. Exponential rate of change in S-K levels (blood) at 24 hours during OLP

3. Mean change (absolute and percent (%) change) from baseline in S-K levels at all measured time intervals post-dose during OLP listed above.

4. Time to normalization in S-K levels (normalization defined as first time S-K levels between 3.5-5.0 mmol/L, inclusive, are achieved) during OLP

#### 4.2.2.2 Derivations

See section 3.3.1.1 for definition of baseline for the efficacy endpoints.

Time to normalization is defined as the number of hours from the first administration of IP in OLP to the date-time of normalization = (date-time of normalization – date-time of first IP administration). For analysis of time to normalization, subjects who fail to achieve normalization will be censored at the time of last SK measurement in the OLP.

For analysis of the exponential rate of change, time (in hours) from first dose of IP will be derived as (datetime of SK measurement – datetime of first dose of IP)/3600.

#### 4.2.2.3 Handling of Dropouts and Missing Data

Missing S-K c-lab values will be replaced as described in Section 3.3.5.

#### 4.2.2.4 Primary Analysis of Secondary Endpoints (OLP)

Descriptive statistics will be presented for S-K levels at baseline, OLP Day 1 (1, 2 and 4 hours post first dose) and OLP Day 2 (pre-dose and 1 hour post the first dose in the day), OLP Day 3 (pre-dose) and end of OLP, including the mean change (absolute and percent change) from baseline. In addition, a box plot of S-K values by timepoint will be presented.

Similarly, descriptive statistics tabulating the proportion of subjects who achieve normokalemia at each of the timepoints specified above will be presented.

**Proportion of subjects who achieve normokalemia**

The observed proportions of subjects achieving normokalemia at 24 hours (OLP Day 2) and end of OLP will be provided along with 95% two-sided Clopper-Pearson exact confidence intervals.

**Exponential rate of change**

The exponential rate of change in S-K levels will be derived from a longitudinal mixed model (SAS PROC MIXED, see Section 3.3.5) of log-transformed S-K levels during the OLP. Measurements up to and including 24 hours post-dose will be used as the response variable. The model will include OLP baseline eGFR, OLP baseline S-K values as well as age (<55, 55-64, >64 years), time (in hours) and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, and diabetes mellitus as fixed effects terms. A random intercept and slope (for time) will be used in the model. The exponential rate of change will correspond

to the estimate of the parameter describing the SK decline over time, i.e. the slope in terms of log SK. It will be presented with corresponding standard error, 95% confidence interval and p-value.

**Mean change (absolute and percent change) from baseline**

For changes and percent changes from baseline in S-K levels at 24 hours (OLP Day 2) (and end of OLP, one sample, two-sided t-tests will be applied to test the null hypotheses that the means are equal zero. The estimates, corresponding SD, 95% 2-sided CI and p-values will be presented.

**Time to normalization in S-K values**

The time to normalization in S-K levels will be summarized using Kaplan-Meier life table curves and associated 95% CI points will be provided at 1, 2, 4, 24 and 48 hours post first dose of IP.. All S-K assessments during OLP will be used.

#### 4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

#### 4.2.2.6 Supplementary Analyses of the Secondary Endpoint

Two supplementary analyses, aiming at evaluating the impact of use of disallowed medication, will be performed. The first one will consider the proportion of subjects that achieved normokalemia at 24 hours (OLP Day 2) and at the end of OLP without use of rescue medication. That is, the analysis of the proportion of normokalemic subjects described above will be replicated, with endpoint re-defined so that a subject is considered to be a responder only if they achieved normokalemia and did not use disallowed medications prior to the relevant timepoint, which would constitute a composite strategy with respect to the intercurrent event of disallowed medication usage.

The second analysis will exclude all SK measurements in the OLP obtained post usage of disallowed medications and replicate the analysis of the mean change in SK at 24 hours (OLP Day 2) and at the end of OLP as compared to baseline on the resulting data. This would constitute a hypothetical strategy with respect to the intercurrent event of disallowed medication usage, with the hypothetical scenario being that disallowed medications are not available to subjects.

Disallowed medications are listed in Appendix B: Disallowed Medications.

A third supplementary analysis will be performed assessing the exponential rate of change up to 48 hours post-dose. The exponential rate of change in S-K levels will be derived from a longitudinal mixed model (as described in Section 4.2.2.4) of log-transformed S-K levels

during the OLP. Measurements up to and including 48 hours post-dose will be used as the response variable.

#### 4.2.2.7 Subgroup Analyses

Not applicable

### 4.2.3 Secondary Endpoints for RTP phase

#### 4.2.3.1 Definition

The secondary efficacy endpoints for RTP phase will include the following:

1. The proportion of subjects who remain normokalemic (as defined by S-K levels between 3.5-5.0 mmol/L, inclusive) at the end of the RTP and during the RTP (Day 8 to Day 29).

2. The number of days subjects remain normokalemic during the RTP (Day 8 to Day 29).

3. The time to the first instance of hyperkalemia (defined as S-K ≥5.1 mmol/L).

4. The mean changes in S-Aldo and P-Renin levels.

#### 4.2.3.2 Derivations

See section 3.3.1.1 for definition of baseline for the efficacy endpoints.

The number of days subjects remain normokalemic is calculated as the sum of the length of each period of normokalemia a subject has. The length of a period of normokalemia is calculated as the stop date of normokalemia – start date of normokalemia + 1. For subjects who have a period of normokalemia lasting for a single visit, the duration of this period is set to 1. For subjects who have a time point missing in between two visits where the subject was recorded as being normokalemic, it can be assumed that the subject remained normokalemic and extend the period of normokalemia to the next, non-missing time point. For subjects with no record of being normokalemic during the RTP, the number of days subjects remain normokalemic is set to 0.Time to hyperkalemia is defined as the number of days from randomization to the date of hyperkalemia = (date of hyperkalemia -date of randomization) +1.

For analysis of time to hyperkalemia, subjects who discontinue treatment in RTP due to high S-K levels (i-STAT potassium levels > 6.2 mmol/l at the 90-minute post dose 2 blood draw) will be treated the same as the subjects who developed hyperkalemia (event). Subjects who do not become hyperkalemic during RTP will be censored at the time of the last S-K measure available for the RTP.

#### 4.2.3.3 Primary Analysis of Secondary Endpoints for RTP

Descriptive statistics will be presented for S-K levels for all timepoints for each S-K was scheduled to be measured, as well as OLP baseline. The statistics will include the mean change (absolute and percent change) from baseline. In addition, a plot of S-K values by timepoint will be presented.

Similarly, the proportion of subjects who remain normokalemic will be presented by study visit.

**Proportion of subjects normokalemic at Study Day 29**

For the Day 29, the likelihood of being normokalemic will be compared using a logistic regression model containing the same baseline covariates as for the primary efficacy endpoint with the exception of visit and the visit-by-treatment interaction (see Section 4.2.1.4). The estimated odds ratios corresponding to the difference between the treatment arms, 95% 2-sided CI and p-values will be provided.

**Proportion of subjects normokalemic during the RTP**

The likelihood of being normokalemic during RTP will be analyzed using a generalized mixed model (SAS PROC GLIMMIX), which includes a random intercept and logit link. The model will include all S-K data values collected at the scheduled visits between Days 8-29, dichotomized as normal and abnormal, as response variables, and the same covariates as the model used for the main analysis of the primary endpoint (See Section 4.2.1.4).Similarly, to the approach used for the primary analysis, the model will attempt to incorporate different (unstructured) degree of dependence between the repeated observations and, if issues with model fit are observed, switch to simplified dependence structures (see Section 3.3.6). The estimated odds ratios corresponding to the difference between the treatment arms, 95% 2-sided CI and p-values will be provided.

**Number of days subjects remain normokalemic**

The number of normokalemic days during the RTP, inclusive of Days 8-29, will be calculated assuming that the time interval between assessments is normokalemic only if both the beginning and end assessments for that time interval display normal S-K values.

The number of normokalemic days will be analyzed using a linear regression model with the same baseline covariates as for the primary efficacy endpoint, with the exception of visit and the visit-by-treatment interaction (see Section 4.2.1.4). The results will be presented per treatment arm. The p-value (two-sided) will be provided to compare the LSMEAN of the normokalemic days between each active treatment versus placebo.

**Time to hyperkalemia**

The time to hyperkalemia (days) will be summarized using Kaplan-Meier life table curves and associated 95% CI points will be provided at Days 2, 5, 8, 12, 15, 19, 22 and 29 during the RTP. Kaplan-Meier curves of the time to hyperkalemia (days) will be displayed for each treatment group.

A Cox proportional hazards model (SAS PROC PHREG) will be used with the same baseline covariates as for the primary efficacy endpoint analysis, with the exception of visit and the visit-by-treatment interaction (see Section 4.2.1.4). The hazard ratio between each active treatment versus placebo will be reported along with a 95% confidence interval and a p-value.

**Mean changes in S-Aldo and P-Renin levels**

Descriptive statistics will be presented for nominal values, change and percent change from baseline in S-Aldo and P-Renin levels during the RTP at Randomization (Day 1), Day 15, Day 29, and EOS for each.

This endpoint will also be analyzed using a longitudinal mixed model (SAS PROC MIXED) respectively for S-Aldo and P-Renin levels. The model will include all S-Aldo and P-Renin data values collected at the scheduled visits on Days 15 and 29 as response variables, and RTP baseline values for S-Aldo and P-Renin (respectively), baseline OLP eGFR, age (<55, 55-64, >64 years) and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure and diabetes mellitus as covariates.

The p-value from LSMEAN (two-sided) will be provided to compare the overall mean difference in S-Aldo and P-Renin values between each active treatment (ZS 10g and ZS 5g) and placebo. The estimated mean difference in S-Aldo and P-Renin values between each of the active treatment groups (ZS 10g and ZS 5 g) relative to the placebo treatment group will be provided along with accompanying 95% confidence intervals.

#### 4.2.3.4 Supplementary Analyses of the Secondary Endpoint

One supplementary analysis, aimed at evaluating the impact of disallowed medications use on the likelihood of being normokalemic at the end of RTP, will be performed. The intercurrent event of disallowed medication is again incorporated through a composite endpoint where subjects who receive disallowed medication are classed as “non-responders”. The analysis described above will then be replicated using this endpoint.

#### 4.2.3.5 Subgroup Analyses

The secondary efficacy endpoint of the proportion of subjects who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase will be evaluated in order to explore the consistency of the treatment effect for the following subgroups:

- chronic kidney disease status (yes/no)
- diabetes mellitus status (yes/no)
- heart failure status (yes/no)
- those on RAAS inhibitors (yes/no).

A minimum of 10 responses in total for both arms combined are required for a subgroup analysis to be performed. A single model will be fitted, this model including a treatment by subgroup interaction term in addition to the covariates in the original analysis. Estimates of the treatment effect for each subgroup will be provided, with corresponding confidence intervals. A p-value for the interaction term will also be given.

#### 4.2.3.6 Handling of Dropouts and Missing Data

The S-K levels used for all secondary analyses will be based on the c-lab measurements obtained during the RTP. Missing S-K c-lab values will be replaced as described in Section 3.3.5.

For the number of days subjects remain normokalemic, if an intermediate assessment time point is missing, the time interval will be extended until the next non-missing time point.

## 4.3 Safety Analyses

The respective safety analysis will be undertaken on the safety analysis sets, separately for the OLP and for the RTP. Safety and tolerability data will be presented by treatment arm and listed, unless otherwise stated.

Safety endpoints will include adverse events (AEs), vital signs (VS), ECGs, clinical laboratory evaluations, and other electrolytes (specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

### 4.3.1 Exposure

#### 4.3.1.1 Definitions and Derivations

Duration of exposure is defined as the number of days between the first and the last dose of IP + 1 day, for each treatment period. Duration of exposure for subjects on every other day dosing is defined as the number of days between the first and the last dose of IP where subjects have a planned dose of IP + 2 days.

**Actual Exposure**

Actual exposure for each subject will be obtained by summing up the days for which at least one dose of the drug was taken, excluding dose interruptions, and for each treatment arm and overall.

#### 4.3.1.2 Presentation

Individual subject data for study drug administration will be listed for all subjects respectively in the SAF-OLP and SAF-RTP.

Duration of exposure and actual exposure will be summarized for the OLP and the RTP, overall and by treatment group.

### 4.3.2 Adverse Events

#### 4.3.2.1 Definitions and Derivations

On-treatment adverse events are defined as per Section 3.3.1.2.

The derivations for the following parameters will be the difference between the two dates stated below + 1 day (where first dose date is for either the OLP or RTP first dose date as applicable).

- Time from start of treatment to onset of AE (days)
- Time from last dose to death (days)
- Time from first dose to death (days)
- Time from last dose to onset of AE (days) - Calculated for AEs starting after the discontinuation of the study treatment.
- Time from start of treatment to AE becoming serious (days)
- Time from start of treatment to discontinuation of investigational product (due to adverse event) (days).

MedDRA (using the latest or current version) is used to code AEs apart from hypokalemia. The identified risk of hypokalaemia is defined by laboratory values and not by specific MedDRA terms.

**Oedema**

Oedema related events will be defined by the following MedDRA PT terms: Hypervolaemia Fluid retention, Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling.

#### 4.3.2.2 Presentation

Adverse Events will be presented separately for the OLP and the RTP. The analyses will mainly be focused on on-treatment AEs, but some tables will be replicated for all AEs occurring during a study period. All adverse events will be summarized by SOC and PT. All AEs, including those not considered on-treatment, will be included in safety listings but excluded from the summary tables.

The onset date of the AE determines the phase in which the AE will be summarized. This is in order to have a consistent "worst case" allocation of AEs, because it will not be possible to distinguish AEs occurring before or after the actual intake of randomized IP.

**Overall Summary of Adverse Events**
AEs will be summarised by treatment group for the OLP and RTP and will include the following:

- the number and percentage of subjects experiencing an AE
- the number and percentage of subjects experiencing an AE with an outcome of death
- the number and percentage of subjects experiencing a SAE
- the number and percentage of subjects experiencing an AE leading to treatment withdrawal

This table will be done both on-treatment and using all AEs that occurred during RTP.

**AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)**
The number and percentage of subjects with AEs and SAEs will be summarised by SOC and PT, by treatment group. A subject with more than one type of AE in a particular SOC will be counted only once in the total of subjects experiencing AEs in that particular SOC. Since a subject could have more than one type of AE within a particular SOC, the sum of subjects experiencing different AEs within the SOC could be larger than the total number of subjects experiencing AEs in that SOC. Similarly, a subject who has experienced an AE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs.

**AEs by PT and frequency**
The number and percentage of subjects with AEs will be summarised by PT and treatment group and sorted by descending frequency on PT level.

**Possibly related AEs and SAEs by SOC and PT**
The number and percentage of subjects with possibly related AEs and SAEs will be summarised by SOC, PT, and treatment group.

**AEs by SOC, PT, and maximum severity**
The number and percentage of subjects with AEs will be summarised by SOC, PT and maximum intensity, and treatment group.

**Deaths**
The number and percentage of subjects with SAEs or AEs with outcome of death will be

summarised by SOC, PT, and treatment group. Subject listings of all deaths and their causes will be provided.

**Oedema**
The number and percentage of subjects with oedema related events will be presented by treatment group, separately for OLP and RTP.

### 4.3.3 Clinical Laboratory, Blood Sample

#### 4.3.3.1 Definitions and Derivations

A full list of parameters (including other electrolytes) is provided in Appendix C: Laboratory Safety Variables.

These will be evaluated fasting at OLP Day 1, End of OLP and EOS for subjects not entering the RTP and at RTP Randomization visit, Visit 10, Visit 14 and EOS for those entering the RTP.

The date, time of collection and results (values, units and reference ranges) will be recorded in the appropriate eCRF module.

The clinical chemistry and hematology will be performed at a central laboratory.

**Elevated liver test results**

- ALT >3x, >5x, and >10x ULN during the study.
- AST >3x, >5x, and >10x ULN during the study.
- Total bilirubin >=2x ULN during the study.

**Hypokalemia**
Hypokalemia is determined as potassium values <3.5 mmol/L.

#### 4.3.3.2 Presentations

Descriptive statistics by time of assessment will be presented for each laboratory parameter including other serum electrolytes separately for OLP and RTP. All laboratory values will be classified as low, normal, or high based on normal ranges supplied by the central laboratory. For purposes of analyses, laboratory results based upon standardized units will be used.

For each summary of continuous variables, the number of non-missing observations, mean, median, standard deviation, minimum, and maximum values will be presented by study phase and treatment group for OLP and RTP.

Absolute values and change from baseline for all continuous haematology and clinical chemistry parameters will be summarized for OLP and RTP by treatment arm and scheduled visit.

Box plots of absolute values by scheduled visit, and box plots of change from baseline by visit, may be presented for certain parameters if warranted after data review.

Any treatment-emergent laboratory data reported as abnormal according to reference values as well as individuals with treatment-emergent, abnormal serum laboratory values will be summarized and listed for the relevant safety analysis set by treatment group presented separately for the OLP and the RTP.

Additionally, subject listings and summary of all on-treatment hematology and chemistry changes will be provided for OLP and RTP by treatment group.

**Elevated liver test results**
Maximum on-treatment ALT and AST versus maximum total bilirubin will be presented. Listings of liver biochemistry test results will be provided, separately for OLP and RTP.

**Hypokalemia**
Tabulation of the number and percentage of subjects with hypokalemia (<2.5 mmol/L, <3 mmol/L, <3.5 mmol/L) at any point during a phase (OLP and RTP), while on treatment, will be presented by treatment group.

### 4.3.4 Clinical Laboratory, Urinalysis

#### 4.3.4.1 Definitions and Derivations

A full list of the urinalysis parameters for this study (including other electrolytes) is provided in Appendix C: Laboratory Safety Variables

These will be evaluated fasting at OLP Day 1, End of OLP and EOS for subjects not entering the RTP and at RTP Randomization visit, Visit 10, Visit 14 and EOS for those entering the RTP.

The date, time of collection and results (values, units and reference ranges) will be recorded in the appropriate eCRF module.

The urinalysis will be performed at a central laboratory.

#### 4.3.4.2 Presentations

Absolute values and change from baseline for all continuous urinalysis will be summarized for OLP and RTP by treatment arm and visit.

Urinalysis baseline versus maximum value on treatment shift table will be provided for categorical urinalysis parameters.

If applicable, urinalysis values will be classified as low, normal, or high based on normal ranges supplied by the central laboratory and presented in a shift table as described above. For purposes of analyses and where applicable, urinalysis results based upon standardized units will be used.

### 4.3.5 Other Laboratory Evaluations

#### 4.3.5.1 Definitions and Derivations

In addition to the urinalysis urine-HCG will also be collected during the study. The OLP Day 1 urine pregnancy test for women of childbearing potential is performed as part of the screening procedure prior to any IP administration and is repeated at the last visit of the study, either on the OLP EOS visit, or on the RTP EOS visit.

#### 4.3.5.2 Presentations

These data will be listed only, no summary tables will be produced.

### 4.3.6 Vital Signs

#### 4.3.6.1 Definitions and Derivations

Pulse rate and systolic and diastolic blood pressure (BP) will be assessed at OLP Day 1, End of OLP and EOS for subjects not entering the RTP and at RTP Randomization visit, Visit 10, Visit 14 and EOS for those entering the RTP.

#### 4.3.6.2 Presentations

Summary statistics for vital signs will be calculated for absolute values and change from baseline to each subsequent planned visit where applicable. For each summary, the number of non-missing observations, mean, median, standard deviation, minimum, and maximum will be presented by treatment group for each study phase (OLP and RTP).

Baseline versus maximum value on treatment shift table will be provided for all vital sign parameters.

Any treatment-emergent, abnormal vital signs will be summarized and listed for the safety analysis set by treatment group for each study phase (OLP and RTP).

### 4.3.7 Physical examinations

#### 4.3.7.1 Definitions and Derivations

Any new or aggravated clinically relevant abnormal medical findings at a physical examination as compared with the baseline assessment will be reported as an AE.

#### 4.3.7.2 Presentations

No separate analyses for Physical Examinations will be provided.

### 4.3.8 Electrocardiogram

#### 4.3.8.1 Definitions and Derivations

ECG mean heart rate, P wave duration and QRS durations, PR and QTc intervals aggregate will be recorded at OLP Day 1, Day 2, End of OLP and EOS for subjects not entering the RTP, and at RTP Randomization Visit (RTP Day 1), Visits 5, 8, 10, 12, 14, and EOS for those entering the RTP.

**QTc intervals**

QTc intervals will be calculated using the Fridericia formula:

$$QTcF = \frac{QT(msec)}{(RR(msec)/1000)^{1/3}}$$

Where:

1. $RR(msec) = (60/HR) * 1000$
2. $RR$ = RR interval
3. $HR$ = Heart rate.

#### 4.3.8.2 Presentations

Overall ECG evaluations will be presented in a shift table showing baseline classification against last on-treatment (OLP and RTP) classification, by treatment group.

The following ECG variables will be descriptively summarized by treatment group and visit to include change from baseline to each subsequent visit: ECG mean heart rate, P wave duration, PR interval aggregate, QRS duration aggregate, QT interval aggregate and QTcF interval aggregate. The summaries will be presented for OLP and RTP, separately.

A listing of subjects with overall ECG evaluation reported as abnormal or borderline abnormal will also be provided.

**QTc intervals**

Number and percentage of subjects for QTcF for the following categories will be provided for OLP and RTP, by treatment group.

- QTcF value above 450 ms at baseline (>450 ms, 480 ms and > 500 ms):

- QTcF value above 450 ms at any time during treatment (>450 ms, 480 ms and > 500 ms):

- QTcF increase by more than 30 ms at any time during treatment (>30 ms, >60 ms and >90 ms)

- QTcF value above 450 ms and QTcF increase [a] by more than 30 ms at any time during treatment [(value > 450 ms and increase >30 ms and (value > 500 ms and increase >60 ms)]

- QTcF decrease by more than 30 ms at any time during treatment (>30 ms, >60 ms and >90 ms).

### 4.3.9 Other Safety Assessments

Not applicable.

# 5 INTERIM ANALYSIS

Not applicable.

# 6 REFERENCES

This Statistical Analysis Plan (SAP) is based on ZS-Harmonize Asia Protocol Version 6, dated 19 August 2020.

[1] SAS/STAT® 9.3 User's Guide. The FREQ Procedure: Odds Ratio and Relative Risks for 2 x 2 Tables, viewed Jan 2019, https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_freq_a0000000565.htm

[2] Ann Intern Med. 2009;150(9):604-612. A New Equation to Estimate Glomerular Filtration Rate. https://annals.org/aim/article-abstract/744469/new-equation-estimate-glomerular-filtration-rate

[3] ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017, Committee for Human Medicinal Products

[4] Brand, J. P. L. (1999). Development, Implementation, and Evaluation of Multiple Imputation Strategies for the Statistical Analysis of Incomplete Data Sets. Ph.D. thesis, Erasmus University.

[5] Van Buuren (2007). Multiple imputation of discrete and continuous data by fully conditional specification. Statistical Methods in Medical Research, (16), 3, 219–242

[6] Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc

# 7 APPENDIX

## 7.1 Appendix A: IPD Master List

| IPD Code | IPD | CSP Version and Date | Identification method | Source for identification |
|---|---|---|---|---|
| 1 | **Inclusion Criteria Deviations** - Subjects who were enrolled or randomized but did not meet critical inclusion criteria. | | | |
| **1.1** | Provision of informed consent (pre-screening consent - as applicable) prior to any study specific procedures. | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Manual CRA review | DM: CONSENT1, VISIT2 |
| **1.2** | Male and female subjects aged 18 to 90 years, inclusive | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Manual CRA review | DM |
| **1.3** | Provision of informed consent prior to any study specific procedures | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Manual CRA review | DM: CONSENT, VISIT1 |
| **1.4** | Two consecutive i-STAT potassium values, measured 60-minutes (± 10 minutes) apart, both ≥ 5.1 mmol/L and measured within 1 day of the first ZS dose on open-label initial phase Day 1 | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- B&I Programming<br>- Source Data review | DM: LB, EX |
| **1.5** | Ability to have repeated blood draws or effective venous catheterization | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **1.6** | Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of ZS/matching placebo to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used | CSP v6.0 (19-Aug-2020) | - Source Data review | |

| | | | | |
|---|---|---|---|---|
| **1.7** | Randomized to the 28-day randomized treatment study phase, even though not fulfilling randomization criteria: The i-STAT potassium value is within the normal range (3.5 to 5.0 mmol/L, inclusive).<br>Refer to CSP sec. 4.3 for details about randomization criteria | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- B&I Programming<br>- Source Data review | DM: LB2 |
| **2** | **Exclusion Criteria Deviations -** Subjects who were enrolled or randomized even though they fulfilled the critical exclusion criteria. | | | |
| **2.1** | Participation in another clinical study with an investigational product during the last 3 months | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.2** | Presence of any condition which, in the opinion of the investigator, places the patient at undue risk or potentially jeopardizes the quality of the data to be generated | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.3** | Pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen due to excessive fist clenching to make veins prominent, difficult or traumatic venepuncture, or history of severe leukocytosis or thrombocytosis | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.4** | Patients treated with lactulose, xifaxan (rifaximin) or other non-absorbed antibiotics for hyperammonemia within 7 days prior to the first dose of study drug | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data review | CM: EX |
| **2.5** | Patients treated with resins (such as sevelamer acetate or sodium polystyrene sulfonate [SPS; e.g. Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within 7 days prior to the first dose of study drug | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data review | CM: EX |
| **2.6** | Patients with a life expectancy of less than 3 months | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.7** | Patients who are severely physically or mentally incapacitated and who in the opinion of investigator are unable to perform the subjects' tasks associated with the protocol | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.8** | Female patients who are pregnant, lactating, or planning to become pregnant | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Source Data review | DM: PREG: VISIT |
| **2.9** | Patients with diabetic ketoacidosis | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data review | MH |
| **2.10** | Known hypersensitivity or previous anaphylaxis to ZS or to components thereof | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.11** | Patients with cardiac arrhythmias that require immediate | CSP v6.0 | - Source Data review | |

| | | | | |
|---|---|---|---|---|
| | treatment | (19-Aug-2020) | | |
| **2.12** | History of QT prolongation associated with other medications that required discontinuation of that medication | CSP v6.0 (19-Aug-2020) | - Source Data review<br>- B&I Programming | |
| **2.13** | Congenital long QT syndrome | CSP v6.0 (19-Aug-2020) | - Source Data review<br>- B&I Programming | MH |
| **2.14** | Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **2.15** | QTc(f) > 550 msec | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Source Data review | DM: EG,EG1,EG2,EG3 |
| **2.16** | Patients on dialysis | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3** | **Discontinuation Criteria for study product met but patient not withdrawn from study treatment** | | | |
| **3.1** | Patient Decision to discontinue treatment but patient not withdrawn from study treatment | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Source Data review | DM: EX: EX1: DOSDISC |
| **3.2** | Adverse Event requiring IP discontinuation but patient not withdrawn from study treatment | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Source Data review | DM: EX: EX1: DOSDISC |
| **3.3** | Severe non-compliance with the study protocol *(as assessed by Investigator and/or AZ)* | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3.4** | Patient not discontinued from study medication although Risk to subjects was judged by the investigator | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3.5** | Pregnancy is confirmed | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- Source Data review | DM: PREG: DOSDISC |
| **3.6** | Require treatment with medications prohibited or contraindicated for use due to safety concerns with ZS | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3.7** | Start dialysis while in the study | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3.8** | Patient unblinded due to emergency | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3.9** | Patients who change or switch RAAS inhibitor and/or diuretic dose during the study | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **3.10** | Patient develops severe hypokalaemia (i-STAT potassium | CSP v6.0 | - EDC Automatic Check | DM: |

| | | | | | |
|---|---|---|---|---|---|
| | values <3.0 mmol/L) at any time during the study or has i-STAT level > 6.2 mmol/L during the 28-day randomized treatment study phase (confirmed by taking a second potassium measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug discontinuation rule). | | (19-Aug-2020) | - Source Data review | LB,LB1,LB2,LB3: EX: EX1: DOSDISC |
| **3.11** | Patient has a clinically significant cardiac arrhythmia (see below) at any time in the 28-day randomized treatment study phase, the patient should immediately receive appropriate medical treatment and be discontinued from study drug. Any of the following cardiac events will result in immediate discontinuation from the study drug (independent of whether it is in the open-label initial phase or the 28-day randomized treatment study phase): | | CSP v6.0 (19-Aug-2020) | | |
| | **3.11.1** | *- Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, new paroxysmal supraventricular tachycardia [other than sinus tachycardia], new 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])* | | - EDC Automatic Check<br>- Source Data review | DM: AE:DOSIDISC |
| | **3.11.2** | *- Acute heart failure* | | - B&I Programming - Source Data review | DM: EG2, EG3: DOSDISC |
| | **3.11.3** | *- Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block), widening of the QRS complex (>140 msec in the absence of pre-existing bundle branch block) or new onset peaked T-wave.* | | - EDC Automatic Check - Source Data review | DM: EG, EG2,EG3: DOSDISC |
| | **3.11.4** | *- An absolute QTc >550msec, or an increase in QTc interval > 60msec from baseline to more than 500msec. All patients meeting the QTc>500ms criterion should immediately have potassium assessed by i-STAT and central lab, if not already done within 1 hour of the collection of the ECG. The QTc(f) algorithm (QT interval corrected by the* | | - EDC Automatic Check for QTcF only<br>- B&I Programming - Source Data review | DM: AE: DOSDISC |

| | | | | | |
|---|---|---|---|---|---|
| | | *Fridericia method) is recommended.* | | | |
| **4** | **Discontinuation Criteria for overall study withdrawal met but patient not withdrawn from study** | | | | |
| **4.1** | Voluntary discontinuation by the patient | | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **4.2** | Severe non-compliance to protocol as judged by the Investigator and/or Sponsor | | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **5** | **Investigational Product (IP) Deviation** | | | | |
| **5.1** | Participant received incorrect IP **(corporate IPD):**Subject received incorrect IP to that to which they were randomised. | | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **5.2** | Subjects who were randomised but did not receive IP | | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data review | DS: DS1: IE1;<br>EX1: DOSDISC |
| **5.3** | *Incorrect Dose Adjustment during Open Label Phase:*<br>If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive, during the open-label initial phase, but patient takes more ZS during the rest of that day. **(refer to CSP sec. 7.2)** | | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data review | LB: LB1: EX |
| **5.4** | *Incorrect dose adjustment during 28-Day Randomized Treatment Phase:* If a patient develops **i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L,** inclusive (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval), during the 28-day randomized treatment study phase, dosing is not reduced from qd to qod for the remainder of the study. | | CSP v6.0 (19-Aug-2020) | - Source Data review | - |
| **5.5** | *Incorrect dose adjustment during 28-Day Randomized Treatment Phase:*<br>After dosing reduced from qd to qod, if a patient i-STAT potassium value is back to normal (**3.5 – 6.2 mmol/L inclusive**), during the 28-day randomized treatment study phase, dosing is increased back from qod to qd for the remainder of the study. | | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **5.6** | Use of expired IP | | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **6** | **Excluded Medications taken** | | | | |

| | | | | |
|---|---|---|---|---|
| **6.1** | Subject received concomitant medication defined as prohibited in the CSP (corporate IPD).<br>*Administration of prohibited concomitant medication or non-drug therapy as outlined in CSP sec 7.7)* | CSP v6.0 (19-Aug-2020) | - Manual Physician Review based on CMR/GPR reports<br>- B&I Programming<br>- Source Data Review | CM |
| **7.** | **Deviations to study procedure** | | | |
| **7.1** | Two or more **successive** visits missed or not performed according to the protocol | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data Review | VISIT, VISIT1 |
| **7.2** | Any of the following visits missed:<br>For those patients randomized (with patient randomization number) on Day 2 and get randomized same day, they should complete:<br>- Enrolment/screening visit<br>- Open label initial phase Day 1<br>- Randomization visit<br><br>For those patients randomized (with patient randomization number) on Day 3, they should complete:<br>- Enrolment/screening visit<br>- Open label initial phase Day 1<br>- Open label initial phase Day 2<br>- Randomization visit<br><br>For those patients who failed OLP, they should complete:<br>- Enrolment/screening visit<br>- Open label initial phase Day 1<br>- Open label initial phase Day 2<br>- Open label initial phase Day 3 | CSP v6.0 (19-Aug-2020) | - B&I Programming<br>- Source Data Review | VISIT, VISIT1 |
| **7.3** | Patient is not fasting for any of the following visits as per protocol for K sample for i-STAT or central lab for open-label initial phase:<br>- Day 1 – 0min (1st potassium sample for assessment, pre-dose)<br>- Day 1 – 60 min (2nd potassium sample for assessment, pre-dose)<br>- Day 2 or Day 3 or Randomization – 0 min (pre-dose) | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check for Local Labs only<br>- Source Data Review | DM: LB, LB1,LB2 |

| | | | | |
|---|---|---|---|---|
| **7.4** | Missing ALL of the following i-STAT and central lab potassium samples (as applicable) for Open-label initial phase:<br>- Day 1 – 0min *(1st potassium sample for assessment, pre-dose)*<br>- Day 1 – 60 min *(2nd potassium sample for assessment, pre-dose)* | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check for Local Labs only<br>- Source Data Review | DM: LB |
| **7.5** | Missing the i-STAT and central lab potassium samples for Randomization Visit (open-label initial phase Day 2 or Day 3) – 0 min (pre-dose) | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check for Local Labs only<br>- Source Data Review | DM: LB1, LB2 |
| **7.6** | Patient is not fasting for any of the following visits as per protocol for S-K sample for i-STAT or central lab for Randomized Treatment Phase – Day 1, 15, 29, 35 | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check for Local Labs only<br>- Source Data Review | DM: LB2 |
| **7.7** | For subjects randomized and not withdrawn before Day 8 of the 28-day randomized treatment study phase, missing BOTH the i-STAT and central lab potassium samples from Day 8 to Day 28 | CSP v6.0 (19-Aug-2020) | - EDC Automatic Check<br>- B&I Programming<br>- Source Data review | DM: LB2, ASMPERF: DS1: DS: VISIT |
| **7.8** | Missing any of two consecutive i-STAT potassium values, measured ± 10 minutes apart during study drug adjustment or patient discontinuation | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **8** | **Other Important Protocol Deviations (including missing PI eCRF signature [corporate IPD], others to be agreed by Study Team)** | | | |
| **8.1** | Any deviation considered important that was not predicted or prespecified. | CSP v6.0 (19-Aug-2020) | - Source Data review | |
| **8.2** | Add study specific IPDs that are not covered by any category above. | CSP v6.0 (19-Aug-2020) | - Source Data review | |

## 7.2 Appendix B: Disallowed Medications

Disallowed medications in the study broadly consist of two classes: potassium binders and RAASi / diuretics. For the former, any use of while on IP is to be considered as an instance of disallowed medication usage. For the latter, as per the CSP, the addition of a new RAAS inhibitor and/or diuretic, or change of the dose, discontinuation, or switch of these drugs, is to be considered as an instance of usage of disallowed mediation.

The exact method by which such instances of usage can be identified in the database will be documented separately.

## 7.3 Appendix C: Laboratory Safety Variables

| **Haematology** | **Clinical Chemistry (serum)** |
|---|---|
| B-Hemoglobin (Hb) | S-Total Protein |
| B-Hematocrit | S-Albumin |
| B-Erythocyte count (RBC) | S-Bicarbonate |
| B-Total leukocyte count (WBC) | S-Blood Urea Nitrogen |
| B-Leukocyte differential count (absolute count) | S-Creatinine |
| B-Platelet count | S-Bilirubin, total |
| | S-Alkaline phosphatise (ALP) |
| **Urinalysis** | S-Glucose |
| U-PH | S-Sodium |
| U-Specific gravity | S-Potassium[1] |
| U-Glucose | S-Inorganic phosphate |
| U-Ketones | S-Calcium, total |
| U-Bilirubin | S-Magnesium |
| U-Urobilinogen | S-Gamma-glutamyl transferase (GGT) |
| U-Blood | S-Aspartate transaminase (AST) |
| | S-Alanine transaminase (ALT) |
| U- Human chorionic gonadotropin (HCG) (only for females of childbearing potential) [2] | S-Aldosterone[3] |
| | P-Renin [3] |

1. Blood potassium will be measured only by i-STAT at the optional Pre-screening visit. Blood potassium will be measured by i-STAT and Serum potassium will be measured by C-lab for Visit 2 to EOS Visit.

2. Urine-HCG will be measured at clinic, used the tube provided by Central Laboratory.

3. Subjects need to be either standing or seated upright for at least 2 hours before sample collection for S-Aldosterone and P-Renin assessment.