Supplementary Online Content


Protocol and Statistical Analysis Plan

This supplementary material has been provided by the authors to give readers additional information about their work.
Clinical Development

Aliskiren/SPP100A

Clinical Study Protocol No. CSPP100A2366

A 104 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy of aliskiren on the progression of atherosclerosis in patients with coronary artery disease when added to optimal background therapy

RAP Module 3 – Detailed Statistical Methodology

<table>
<thead>
<tr>
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<th>Hui Fang, Trial Statistician</th>
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Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Novartis IIS team according to the data analysis section 10 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

Statistical and analytical plans

Most planned analyses are described in Section 9 of the protocol (Appendix 16.1.1). These and additional planned analyses have details given in this section.

Unless otherwise stated, summary tables/figures/listings will be on all subjects included in the population under consideration.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

All centers participating in this study will be pooled into 9 regions according to the geographical locations so that an adequate number of patients for each region would be available for analyses. Regions are mainly consisted of countries, except that United states is separated into two regions east and west; Belgium, France and Germany are pooled into 1 region, Europe central (Table 1); Argentina and Australia are pulled as Rest of the world. Centers in US east are: 529, 519, 509, 510, 512, 527, 574, 557, 579, 507, 545, 546, 548, 563, 530, 531, 539, 518, 521, and 576; all the rest of US sites belong to US west (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Region definition</th>
</tr>
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<tbody>
<tr>
<td>Region Code</td>
<td>Region Description</td>
</tr>
<tr>
<td>1</td>
<td>Hungary</td>
</tr>
<tr>
<td>2</td>
<td>Canada</td>
</tr>
<tr>
<td>3</td>
<td>Italy</td>
</tr>
<tr>
<td>4</td>
<td>Poland</td>
</tr>
<tr>
<td>5</td>
<td>Spain</td>
</tr>
<tr>
<td>Region Code</td>
<td>Region Description</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>6</td>
<td>Europe central</td>
</tr>
<tr>
<td>7</td>
<td>US west</td>
</tr>
<tr>
<td>8</td>
<td>US east</td>
</tr>
<tr>
<td>9</td>
<td>Rest of the world</td>
</tr>
</tbody>
</table>

**Subjects and treatments**

**Screened (SCR)** – All patients who signed the informed consent.

**Enrolled (ENR)** – All patients who enter the single-blind run-in period.

**Randomized (RAN)** — All patients who receive a randomization number, regardless of whether or not the patient receives the trial medication.

**Full Analysis Set (FAS)** — Consists of all randomized patients. Patients will be analyzed according to the treatment that they were assigned at randomization. Mis-randomized patients will be excluded from the FAS. Mis-randomized patients are patients who discontinued the study permanently prior to the randomization visit, but were allocated a randomization number by error.

**Per-Protocol (PP)** — All FAS patients who complete the double blind treatment period without any major protocol deviations that impact on efficacy assessments. The major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses.

**Safety (SAF)** — All enrolled patients who receive at least one dose of double-blind trial medication. Patients will be analyzed according to the treatment that they received.

**Single-blind Safety (SBSAF)** – All patients who receive at least one dose of single-blind trial medication.

**Modified Full Analysis Set for IVUS (mFAS)** – All FAS patients who have a valid baseline and post baseline IVUS measurement and post-baseline IVUS measurement and at least ≥ 72 weeks of treatment (single-blind and double-blind combined).

Patients with major protocol deviations will be excluded from some analysis populations, according to the PD severity codes in the VAP module 3 as follows:

<table>
<thead>
<tr>
<th>Severity Codes</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Exclude from all efficacy analysis (FAS, mFAS and PPS)</td>
</tr>
<tr>
<td>1</td>
<td>Exclude from Per-Protocol analysis (PPS)</td>
</tr>
<tr>
<td>5</td>
<td>Exclude from all safety analyses (SAF)</td>
</tr>
<tr>
<td>6</td>
<td>Exclude from Main Analysis Set (RAN, FAS, mFAS and PPS)</td>
</tr>
</tbody>
</table>
Table 2 provides a detailed list of analysis set and exclusion conditions.

Table 2  
**Rules for subject classification in the analysis sets based on protocol deviations and non-protocol deviation classification criteria**

<table>
<thead>
<tr>
<th>Analysis set</th>
<th>PD severity codes that cause a subject to be excluded</th>
<th>Non-PD criteria that cause a subject to be excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled (ENR)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Randomized (RAN)</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>Single –blind Safety (SBSAF)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Safety Set (SAF)</td>
<td>5, 8</td>
<td>Not receiving any study medication during double blind</td>
</tr>
<tr>
<td>Full Analysis Set (FAS)</td>
<td>0, 6, 8</td>
<td>Mis-randomized and not receiving any study medication</td>
</tr>
<tr>
<td>Modified Full Analysis Set for IVUS</td>
<td>0, 6, 8</td>
<td>Mis-randomized and not receiving any study medication; without post-baseline IVUS or post-baseline IVUS &lt; 72 weeks (single blind and double blind combined)</td>
</tr>
<tr>
<td>Per Protocol set (PPS)</td>
<td>0, 1, 6, 8</td>
<td>Mis-randomized and not receiving any study medication; discontinued from the study per CRF completion panel</td>
</tr>
</tbody>
</table>

Screen failed patients at the end of screening period will be summarized by the screen failure reason for the Screened set. If a patient has multiple screen failure reasons, the patient will be counted once for each of the patient’s multiple screen failure reasons.

The number and percentage of patients who are enrolled and discontinued from the single blind period will be provided for the Enrolled set, discontinuation reason will be presented. The number and percentage of patients, who are randomized, discontinued from the study and discontinued from study drug prematurely as well as discontinuation reasons will be presented for Randomized set by treatment group and by region and treatment group.
The number and percentage of patients included in RAN SAF, FAS, mFAS, and PPS will be summarized by treatment group and the total number of enrolled patients will be provided. The number and percentage of patients in those analysis sets will be summarized by region and treatment as well.

Patients with protocol deviations will be summarized by each protocol deviation and treatment group for the Randomized set. The major protocol deviations leading to patients' exclusion from the SAF, FAS and PPS will be presented in a listing by treatment group. Definitions of protocol deviations are referenced in VAP module 3, and to be finalized prior to the analyses.

**Patient demographics and other baseline characteristics**

The background and demographic characteristics will be summarized for the RAN. These variables include:

- age and age groups (< 65 years, ≥ 65, and ≥ 75 years)
- gender (male or female),
- race (Caucasian, Black, Asian, Native American, Pacific islander , Other),
- ethnicity (Hispanic/Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other)
- height (cm) and weight (kg)
- body mass index (BMI), BMI category (<30, >=30 kg/m²)
- vital signs (msSBP, msDBP, pulse rate)
- pulse pressure
- diabetic status
- history of hypertension
- baseline percent atheroma volume (PAV) and nominal change in normalized total atheroma volume (TAV)
- central aortic pressure
- eGFR category (<60, >=60 ml/min/SA).
- smoking history
- waist and hip circumference

These variables will be analyzed by descriptive statistics (n, mean, standard deviation, median, minimum and maximum) if they are continuous type or summarized with frequency and percentage if they are categorical type. Treatment group comparability will be examined using a chi-square test for categorical baseline characteristics and using an F-test for the continuous baseline characteristics as appropriate. These p-values will be provided for descriptive purposes and not to be considered to define any formal basis of determining factors that should be included in statistical models. If imbalance of treatment group with respect to some variables does occur, supplemental analyses of covariance with addition of these variables may be performed to assess the impact on efficacy as appropriate.

In addition, a summary of baseline therapy (taken prior to Visit 2) will be performed for: alpha blocker, beta blocker, calcium channel blocker, vasodilator, thiazide diuretic, other diuretic, ACE inhibitor, angiotensin receptor blocker, aldosterone receptor blocker, direct renin inhibitor, centrally acting antihypertensive, other antihypertensive
medication, anti-platelet agent, and statin. Summary of CV medical history and summary of risk factors will also be provided.

**Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

The treatment duration will be computed for Safety population (SAF) using the following algorithm:

- Treatment duration (days) in double-blind = last study drug date in the double-blind period - first study drug date (in double-blind period) + 1, if the last date the patient took study drug is known
- Treatment duration (days) in double-blind = last visit date in double-blind period - first study drug date (in double-blind period) + 1, if the last date the patient took study drug is missing or incomplete.
- Treatment duration (days) in single-blind = last study drug date in single-blind period - first study drug date (in single-blind period) + 1, if the last date the patient took study drug is known
- Treatment duration (days) in single-blind = visit 3 date or last visit date (for patient not entering double-blind period) - first study drug date (in single-blind period), if the last date the patient took study drug is missing or incomplete.

Summary statistics [n, mean, standard deviation (SD), median, min, and max] for the duration (in days) of exposure to study drug will be provided by the randomized treatment group during the double blind period.

Prior medications are defined as any medications started prior to the Visit 2 date. Concomitant medications and significant non-drug therapies are defined as any medications or significant non-drug therapies taken after Visit 3 (during the double-blind period). Prior therapy are medication taken prior to Visit 2 date; background therapy are medication taken after the double blind period. It includes medications started after the start of study drug or medications started earlier than the start of study drug and continued after the start of study drug.

Medications and significant non-drug therapies, taken prior to the single-blind period (Visit 2), will be summarized by therapeutic class, preferred term, and treatment group for safety set. Medications and significant non-drug therapies (including specific categories of background therapy (alpha blocker, beta blocker, calcium channel blocker, vasodilator, thiazide diuretic, other diuretic, ACE inhibitor, angiotensin receptor blocker, aldosterone receptor blocker, direct renin inhibitor, centrally acting antihypertensive, other antihypertensive medication, anti-platelet agent, and statin)), taken during the single-blind period and concomitant medications (taken during the double-blind period) will be summarized by therapeutic class, preferred term, and treatment group for safety set.

**Efficacy evaluation**

**The primary variable**
The primary endpoint variable of this study is the change from baseline in percent atheroma volume (PAV) for all matched slices of anatomically comparable segments of the target coronary artery as assessed by IVUS evaluation after 104 weeks of treatment (single-blind and double-blind) as shown in Figure 1-1.

**Figure 1-1  PAV formula**

\[
PAV = \frac{\sum_{All\ Matched\ Slices} (MCSA - LCSA)}{\sum_{All\ Matched\ Slices} MCSA} \times 100
\]

Where:
MCSA = Media Cross Sectional Area
LCSA = Lumen Cross Sectional Area

The percent atheroma volume (PAV) for all matched slices of anatomically comparable segments of the target coronary artery as assessed by IVUS evaluation will be measured at Visit 1 (baseline for IVUS) and at end of study [IVUS measurement at Visit 15 or ≥ 72 weeks of treatment (single-blind and double-blind) for patients who discontinue]. No other post baseline PAV measurements are scheduled. For prematurely discontinued patients with ≥ 72 weeks of exposure to treatment, all efforts will be made to obtain the IVUS at the last visit.

The primary analysis time point will be the Week 104 (Visit 15) endpoint. For each patient, the last post-baseline measurement of PAV at ≥ 72 weeks of treatment (single-blind and double-blind) will be carried forward as the endpoint variable to be analyzed.

The FAS population will be used for the primary efficacy analysis. However, only patients with a baseline and post baseline IVUS taken ≥ 72 weeks of treatment (single-blind and double-blind) will be included in the analysis.

For each patient without a post-baseline PAV measurement, or patient with a post-baseline PAV < 72 weeks of treatment (single-blind and double-blind), the missing values will not be imputed or carried forward for the primary efficacy analysis (IVUS).

The null and alternative hypothesis to be tested for the primary variable, mean change from baseline to endpoint [IVUS measurement at end of study (Visit 15) or ≥ 72 weeks of treatment (single-blind and double-blind) for patients who prematurely discontinue] in PAV are as follows:

\[H_0: \mu_{\text{Aliskiren 300 mg}} = \mu_{\text{Placebo}} \quad \text{vs.} \quad H_a: \mu_{\text{Aliskiren 300 mg}} \neq \mu_{\text{Placebo}}.\]
The primary efficacy variable will be analyzed for the FAS population.

Treatment differences with respect to slowing progression of atherosclerosis by assessment of mean changes in PAV will be estimated by an analysis of covariance (ANCOVA) model with treatment, region and baseline PAV. The treatment comparison between aliskiren and placebo will be performed at endpoint at a two-sided significance level of 0.05. Centers will be pooled into regions as described prior. Least squares mean difference of mean change in PAV from baseline will be provided along with its 95% confidence interval.

If a statistically significant difference in favor of aliskiren is observed then an assessment of regression of atherosclerosis will be carried out within the aliskiren group by assessment of the group means at baseline and endpoint [IVUS measurement at Visit 15 or ≥ 72 weeks of treatment (single-blind and double-blind) for patients who discontinue]. A regression model with change in PAV as depend variable, baseline PAV as covariate will be provided. The time of IVUS is calculated using the IUVS date at post-baseline minus the randomization date (Visit 3) plus one.

Descriptive statistics (n, mean, standard deviation, minimum, median and maximum) of baseline and post baseline value, change from baseline will be summarized by treatment group and visit.

For the primary variable, a supplementary model with treatment-by-region, and treatment-by-baseline PAV added to the primary model, with treatment, region, and prior antihypertensive medication status as factors, and the baseline PAV as a covariate, will be used to assess treatment-by-region and treatment-by-baseline interactions.

For supportive analysis, the above primary efficacy variable will be analyzed for the per protocol population to examine the effect due to premature dropouts and/or major protocol deviation. The precise criteria will be specified prior to the unblinding treatment codes for analysis. After database lock, the subgroup analysis of the primary efficacy endpoint by diabetic status was performed.

A sensitivity analysis will be performed to explore the potential impact of the missing IVUS results on the primary efficacy endpoint. This will include analyses using multiple imputation methods. The PROC MI (Multiple Imputation) procedure in SAS will be used to impute the primary endpoint. The MI procedure assumes that the data are from a continuous multivariate distribution and contain missing values that can occur on any of the variables. Baseline PAV and other baseline characteristics such as age, gender, weight, and waist circumference, baseline systolic and diastolic blood pressure, history of hypertension, history of MI, medications (anti hypertensive medication and statin) and laboratory markers (HDL, LDL, triglycerides), and diabetic status will be used in the imputation procedure. The imputation procedure will only be performed on the primary endpoint.

Descriptive summaries will be provided for the primary efficacy variable by treatment group and each of the demographic subgroups:

- age group (< 65 years, ≥ 65 years, < 75 years and ≥ 75 years),
- gender (male or female),
- race (Caucasian, Black, Asian, Native American, Pacific islander, Other),
- diabetic status,
- eGFR category (< 60 and ≥ 60 (ml/min/1.73 m²)),
- BMI category (< 30 and ≥ 30 kg/m²),
- previously treated with an antihypertensive medication versus treatment naive,
- background anti-hypertensive therapy (ARB, ACE, beta blockers, etc.) the patient received (yes/no)
- prior statin patient receive (yes/no)
- background statin patient receive (yes/no)

**Secondary Variables**

Additional IVUS measurements serving as secondary endpoints to be evaluated include the nominal change in normalized total atheroma volume (TAV).

Treatment differences for change from baseline in normalized total atheroma volume (TAV) will be estimated using the same methods as those for the primary variable. The TAV and the nominal change in normalized TAV are calculated as shown in Figure 1-2.

**Figure 1-2** TAV and normalized TAV formulas

\[
\text{Total Atheroma Volume (TAV, mm}^3\text{)} = \sum (EEM_{area} - Lumen_{area})
\]

\[
\text{Normalized TAV (mm}^3\text{)} = \frac{\sum (EEM_{area} - Lumen_{area})}{\text{Number of Images in Pullback}} \times \text{Median Number of Images}
\]

\[
\text{Nominal Change TAV (mm}^3\text{)} = \text{TAV}_{end\ of\ study} - \text{TAV}_{baseline}
\]

In addition, the proportion of patients in each treatment group with atheroma regression (defined as change from baseline to endpoint in PAV <0) will be compared using a logistic regression model with treatment and region as the factors and the baseline PAV as a covariate at study endpoint (IVUS measurement at Visit 15 or ≥ 72 weeks of treatment for patients who prematurely discontinue).

**Exploratory variables**

Exploratory variables to be analysed include:
- Biomarkers including, but not limited to, hsCRP, PRA, PRC, NT-proBNP, Cystatin-C, F2-isoprostanes, UACR and urine sodium/creatinine ratio.
- Treatment differences in sitting blood pressure, pulse pressure, and central aortic pressure.
- Cardiovascular events: death, stroke, myocardial infarction, hospitalization for ACS, coronary revascularization, resuscitated sudden death and hospitalization for heart failure.

- The correlation between changes in blood pressure and PAV, pulse pressure and PAV, as well as laboratory parameters (LDL and biomarkers listed above) and PAV, and change in central aortic pressure and PAV.

- The correlation between changes in measures of coronary atheroma burden (PAV) and cardiovascular clinical events.

Summary statistics will be provided on the biomarker parameters measured which include, but are not limited to, hsCRP, PRA, PRC, NT-proBNP, Cystatin-C, F2-isoprostanes, urine sodium/creatinine ratio and UACR. Descriptive statistics (n, mean, standard deviation, minimum, median, maximum, geometric mean and 95% confidence interval for the geometric mean) of baseline (using measurements taken before the start of the single blind period, e.g. Visit 2) and post-baseline values, as well as change from baseline will be calculated by treatment group and visit for these biomarkers. The 95% confidence interval for geometric mean will be calculated using the z-distribution. For exploratory analysis, the correlation between change in biomarker parameters and PAV will be calculated.

Treatment differences for the variables assessing change from baseline will be estimated using the same methods as those for the primary variable, an analysis of covariance (ANCOVA) model with treatment and region as factors and baseline as covariate. These variables include change from baseline in mean sitting systolic and diastolic blood pressure (msDBP and msSBP), pulse pressure (defined as the difference of msSBP and msDBP), and central aortic pressure.

Cardiovascular events will be analyzed using the composite event, time to the first cardiovascular event. The time to the first cardiovascular events (listed above) will be calculated in days for each patient using the date of the first event or censoring date (if no event occurs) minus the date of randomization visit (Visit 3 date) plus one. Treatment differences, compared in terms of hazard ratio, for the composite cardiovascular events will be estimated from a Cox proportional hazard model including a term for treatment. The SAS procedure PHREG will be used for this analysis; hazard ratio, confidence limits and the p-value based on Wald test will be presented. The p-value will be derived based on a two-sided test at a 0.05 level. P-values from the log-rank test will also be presented. A plot of Kaplan-Meier estimate for the time to the fist cardiovascular events will be provided by treatment group.

The duration from randomization visit date to the first event will be considered as censored for patients who have no event and at least one of the following applies: withdrawal of study consent, patient’s request to discontinue from study, lost to follow-up. For those patients without events prior to the last visit, the censoring date will be defined as the following (whichever occurs first):

- Date when the patient withdraws informed consent form or requests to discontinue from study
- Date of the patient’s last actual visit
The number and percentage of patients with the composite event, and each of the component CV events will be presented. A patient with multiple events in the same component CV event will be counted only once.

The correlation between the PAV and all the continuous variables listed above (central aortic pressure, blood pressure, etc.) will be performed using Pearson correlation. Correlation between PAV and biomarkers and correlation between PAV and lipids (LDL) will be performed using Spearman correlation. Pearson correlation will be used. The correlation between changes in measures of coronary atheroma burden (PAV) and each of the cardiovascular clinical event, as well as the composite cardiovascular event will be performed using the point-biserial correlation.

For all the Pearson correlation and point-biserial correlation analyses listed above will be stratified by treatment group.

Summary statistics will be provided for mean sitting systolic and diastolic blood pressure (msDBP and msSBP), pulse pressure (defined as the difference of msSBP and msDBP), central aortic pressure. Descriptive statistics (n, mean, standard deviation, minimum, median, maximum,) of baseline and post-baseline values, as well as change from baseline will be calculated by treatment group and visit.

All secondary and exploratory analyses will be done for the FAS population. In addition, analyses including, but not limited to, blood pressure, pulse pressure and biomarkers will be performed in patients with post-baseline (≥ 72 weeks of treatment) IVUS measurements (mFAS set).

In addition, HsTroponin T or other markers of potential use to stratify the patient population for event risk and/or compound efficacy will be measured following database lock if technically feasible.

**Pharmacokinetic evaluations (change / add PD, PK/PD, Biomarkers, as needed)**

NA.

**Safety evaluation**

The assessment of safety will be based mainly on the frequency of adverse events, on the summary of laboratory values and serious adverse events suspected by the investigators to be related to study medications. Vital sign data will be summarized as well.

**Adverse events**

All AEs recorded during the double blind period will be assessed. The double-blind period is defined as from the date of the randomization visit through the last study visit date. All summary tables for safety assessment are for SAF.

Patients with adverse events will be summarized by treatment group, primary system organ class, and preferred term. Patients with adverse events will also be summarized by treatment group, primary system organ class, preferred term, and
severity. The patients with suspected study drug-related adverse events and the patients with AEs leading to permanent discontinuation of study drug will also be summarized by treatment group, primary system organ class and preferred term. The patients with most frequently reported adverse events (≥ 2.0% in any treatment group for each preferred term) will be summarized by treatment group and preferred term in descending frequency order in the aliskiren group. A patient with multiple adverse events in the same body system organ class level and same preferred term will be counted only once in summary tables.

In addition, the patients with serious adverse events (SAEs) and with SAEs leading to permanent discontinuation of study drug will be summarized separately by primary system organ class, preferred term, and treatment group. Similarly a patient with multiple SAEs in the same body system organ class level and same preferred term will be counted only once. Serious adverse events will be narrated.

The incidence of death will be summarized by the treatment group and primary cause of death based on the death site-endpoint form completed by investigators and adjudicated death form separately.

A data listing of all information pertaining to adverse events noted during the double-blind treatment period will be provided by treatment group and patient number for SAF. The listings also include those adverse events reported during the single blind period for the ENR set.

**Laboratory data**

Laboratory data will be summarized in SI units at baseline and during the double-blind period for absolute values and changes from baseline by visit and treatment group. The baseline is the value collected at visit 2. However, if the laboratory value is not available at baseline, the value at latest visit prior to visit 2 will be used as baseline.

For the by visit analysis, only the laboratory values at scheduled visits will be used, and the visit number will be taken from the laboratory dataset. If there are multiple measurements at each visit, the latest measurement at that visit will be used. However all post-baseline laboratory measurements (including those at unscheduled visits) will be included for the assessment of extreme laboratory values during the double blind period.

Occurrence of significant abnormality or notable change in change of laboratory values from baseline will be summarized by treatment group. The incidence of patients with notable RBC count, hematocrit, hemoglobin, WBC count, platelet count, BUN, creatinine, glucose, total bilirubin, ALT(SGPT), SGPT, CK, alkaline phosphatase, sodium, potassium, chloride, calcium, and uric acid values based on pre-specified percent change from baseline (defined in Table 1-2 below) will be summarized by treatment group. The percent increase or percent decrease is relative to baseline values across all post-baseline visits.
In addition, the shift tables from baseline to the post-baseline extreme laboratory value by treatment group will be provided for the biochemistry and hematology parameters.

Listings of patients with notable laboratory values based on pre-specified percent change from baseline (defined in Table 3 below) will be provided by laboratory parameter, treatment group, and patient number for the SAF.

### Table 3  Notable laboratory values based on pre-specified percent change from baseline

<table>
<thead>
<tr>
<th>Laboratory Variables</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC count</td>
<td>&gt;20% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>&gt;20% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;20% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>WBC count</td>
<td>&gt;50% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;50% decrease</td>
<td>&gt;75% increase</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td></td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>&gt;30% increase</td>
</tr>
<tr>
<td>Glucose</td>
<td>&gt;50% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td>&gt;100% increase</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td></td>
<td>&gt;150% increase</td>
</tr>
<tr>
<td>SGPT</td>
<td></td>
<td>&gt;150% increase</td>
</tr>
<tr>
<td>CK</td>
<td></td>
<td>&gt;300% increase</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td>&gt;100% increase</td>
</tr>
<tr>
<td>Sodium</td>
<td>&gt;5% decrease</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>&gt;20% decrease</td>
<td>&gt;20% increase</td>
</tr>
<tr>
<td>Chloride</td>
<td>&gt;10% decrease</td>
<td>&gt;10% increase</td>
</tr>
<tr>
<td>Calcium</td>
<td>&gt;10% decrease</td>
<td>&gt;10% increase</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td>&gt;50% increase</td>
</tr>
</tbody>
</table>

The number and percentage of patients with occurrence of hypokalemia (serum potassium < 3.5 mEq/L) or hyperkalemia (≥ 5.5 mEq/L, > 6.0 mEq/L) as well as an
elevated creatinine (> 176.8 µmol/L) and BUN (> 14.28 mmol/L) at any post baseline assessment will be presented by treatment regimen.

Vital signs
Mean sitting diastolic and systolic blood pressure will be summarized in the efficacy section. For sitting pulse, body weight (kg), hip and waist circumference (male and female), the descriptive statistics (n, mean, standard deviation, median, min, and max) will be provided by treatment group at each visit for absolute values and changes from baseline for SAF. The baseline value is the measurement at Visit 2.

Interim analyses
Interim analyses are planned for safety monitoring and will be performed during the course of the study. Only safety data will be assessed. No efficacy assessments or analyses will be performed. Thus no adjustment of the alpha for the final analysis is needed. Interim results will be evaluated by the DMC independent of study conduct. Details are described in the DMC charter.

Other topics
NA.

Determination of sample size
A sample size of 444 (222 per arm) completed patients is targeted. Assuming a discontinuation rate of 25% due to drop outs [which may include patients who prematurely discontinue from the study after < 72 weeks on study medication for reasons such as, but not limited to, lost to follow-up (LTFU), refusal to undergo the final IVUS procedure or poor IVUS image quality], approximately 592 patients (296 per arm) are to be randomized for this study. This sample size will have at least 80% statistical power to detect a 0.8 % difference for change in PAV. The sample size estimation is based on two-sided test at significance level of 0.05, and standard deviation of 3.0 (Nissen, et al 2008). The sample size computations are based on nQuery.

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The ANCOVA model
For the ANCOVA models for IVUS, SAS procedure PROC MIXED will be used with treatment and region as factors and baseline IVUS values as covariate.

Multiple imputation
SAS procedure PROC MI will be used to impute the missing IVUS values at endpoint, 200 dataset data set will be generated by using seed=7397.
Two stage multiple imputation (MI) will be used. The first MI uses multivariate normal multiple imputation on the continuous baseline variables (age, gender, weight, waist circumference, baseline systolic and diastolic blood pressure, and laboratory markers (HDL, LDL, triglycerides)); the second MI uses a regression model to impute the final outcome. The first stage takes care of the non-monotone patterns and the second stage allows discrete baseline covariates to be included with a monotone imputation.

**Cox regression model for primary and secondary efficacy variables**

Cox proportional hazards model will be used to estimate hazard ratio and to obtain the CI and p-value. The PROC PHREG will be used as follows

```
Proc phreg data=dataset_name;
    Model response*status(1)=treatment / ties=efron RL=WALD;
    Ods output parameterestimates=dataset_name;
Run;
```

Where in the above SAS procedure

- *response* is the time to the first CV event
- *status* is the variable to indicate the status of censoring (0=event, 1=censoring)
- *treatment* is the treatment assignment (1=aliskiren, 0=placebo)

**References**