Official Title: An exploratory, randomized, double-blind, placebo-controlled, parallel arm trial of the safety and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure

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STATISTICAL ANALYSIS PLAN

An exploratory, randomized, double-blind, placebo-controlled, parallel arm trial of the safety and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure

SAR439954 - PDY15079

STATISTICIAN: [redacted] – [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine transaminase
BMI:	body mass index
CSR:	clinical study report
DBP:	diastolic blood pressure
DMC:	data monitoring committee
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
IMP:	investigational medicinal product
IRT:	interactive response technology
PCSA:	potentially clinically significant abnormalities
PD:	pharmacodynamic
PK:	pharmacokinetic
PV:	plasma volume
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SGLT2:	sodium-glucose cotransporter type 2
TEAE:	treatment-emergent adverse event
ULN:	upper laboratory normal

1 OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical techniques to be used to analyze data for SAR439954 study protocol PDY15079 approved on 05 Jul 2017 amended on 14 Mar 2018. The purpose of the SAP is to ensure the credibility of the study findings by prespecifying the statistical approaches to the analysis of study data prior to database lock.

1.1 STUDY DESIGN AND RANDOMIZATION

This is a phase 2, multi-center, multinational, randomized, double-blind, placebo-controlled, parallel arm trial of the safety, tolerability and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure. An initial cohort of patients (Cohort 1) will receive sotagliflozin 200mg (n=approximately10) or placebo (n= approximately 5) for fourteen days. Following safety monitoring and review by thedata monitoring committee (DMC), Cohort 2 will receive sotagliflozin 400mg (n= approximately 10) or placebo (n= approximately 5) orally for fourteen days. Following completion of Cohort 2 and review of safety and tolerability by the DMC, patients in Cohort 3 will be allocated to sotagliflozin 200 mg, (n= approximately 17) 400 mg (n= approximately 17) or placebo (n= approximately 17) orally for fourteen days. This is summarized in Table 1.

Table 1 - Cohort randomization and allocation scheme

Cohort	Randomization	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Total N
1	2:1	10	0	5	15
2	2:1	0	10	5	15
3	1:1:1	17	17	17	51
Total N		27	27	27	81

Patients are randomized to receive either sotagliflozin or placebo, according to the randomization scheme for each Cohort as described below:

- Cohort 1: Sotagliflozin 200 mg : Placebo = 2:1
- Cohort 2: Sotagliflozin 400 mg : Placebo = 2:1
- Cohort 3: Sotagliflozin 200 mg : Sotagliflozin 400 mg : Placebo = 1:1:1

For each randomized patient, the IRT will allocate a treatment package number corresponding to the treatment group assigned.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to assess the safety and tolerability of sotagliflozin, added to the standard of care treatment, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

A co-primary objective of this trial is the estimation of the effect of sotagliflozin, when added to the standard of care treatment, on changes in plasma volume, as assessed by direct (indicator dilution) and indirect (hemoconcentration) methods, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

1.2.2 Secondary objectives

The main secondary objectives of this study are:

- To explore the effect of sotagliflozin, added to standard of care treatment, on erythropoiesis, as assessed by changes in plasma erythropoietin levels, in hemodynamically stable patients with worsening of heart failure, compared to placebo.
- To explore the effect of sotagliflozin, added to standard of care treatment, on changes in plasma NT-proBNP levels, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

1.2.3 Exploratory objective

The exploratory objectives of this study are to explore the effect of sotagliflozin compared to placebo treatment, in hemodynamically stable patients with worsening of heart failure, on the following endpoints:

- Change in total body water from baseline to 14 days
- Change in uric acid from baseline to 14 days
- Change in beta-hydroxybutyrate from baseline to 14 days
- Change in total blood volume from baseline to 14 days
- Change in red cell mass from baseline to 14 days
- Percentage of patients within 15% of ideal blood volume on study day 14
- Blood pressure, sitting (SBP and DBP), at day 14 compared to baseline

1.3 DETERMINATION OF SAMPLE SIZE

The sample size determination and the statistical power are estimated based on the main PD endpoint of plasma volume. The following assumptions are used for the estimation of the sample size, based on published data of the plasma volume (PV) response following 12 weeks of treatment with SGLT2 inhibition, relative to the placebo response, in non-HF patients:

- 10% reduction in plasma volume from baseline, with an averaged value of 0.47 liters difference for the sotagliflozin group to the end of 2-week treatment between the sotagliflozin and placebo groups, respectively;
- The placebo response might be highly variable in this population. In the study by Lambers Heerspink et al, PV increased by approximately 2% at the end of the 12 week treatment period in the non-HF population. For the purpose of sample size estimation in this study, the assumption is that PV will be reduced by 1% in the placebo group.
- A common standard deviation (SD) of 0.8 liters for the reductions from baseline to the end of 2-week treatment in plasma volume for both groups;
- A t-test at 1-sided α=0.05; or equivalently, 2-sided α=0.10;

Based on the above assumptions, it is estimated that, with a total of 81 patients with complete evaluations, or 27 patients per arm, the study will have a 71% power to detect an approximately 9 percentage point difference (10% vs 1%) in the reduction from baseline in plasma volume at the end of 2-week treatment for the main comparison of the pooled sotagliflozin (200 mg and 400 mg) group versus placebo. With 60 evaluable patients, or 20 patients per group, the study power is 60%. The calculated sample size refers to the size of completers who have plasma volume values at both baseline and end of the 2-week treatment.

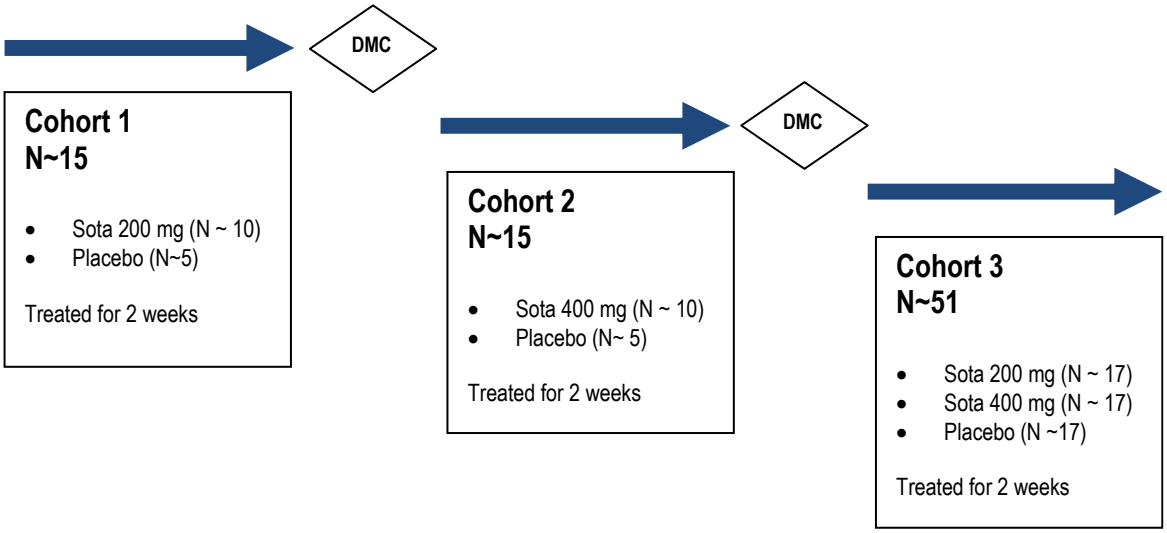
Furthermore, interim analyses will be performed following Cohort 2 and during Cohort 3 for the purpose of exploratory analyses of pharmacodynamic, pharmacokinetic or safety variables, and sample size re-estimation, partly based on the observed variability of changes in plasma volume and/or hemoconcentration. Exploratory analyses may also be performed earlier for safety reasons, or if requested by the DMC or institutional ethics committees. In that case, the analysis will not result to any changes to the protocol.

The study population will consist of at least 30% diabetic patients.

1.4 STUDY PLAN

The following figure describes an overview of the design of the study:

Figure 1 – Study Design



The study consists of:

- Screening period will be up to 21 days
- Treatment period is 14±1 days
- Follow up period will be 14±2 days
- Total study duration will approximately be 26-51 days

1.5 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

This SAP describes updated standard analyses as planned in the new BTD-009094.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable

2 STATISTICAL AND ANALYTICAL PROCEDURE

2.1 SUBJECT DESCRIPTION

2.1.1 Disposition of subjects

A detailed description of patient accountability will be generated by treatment group, including count of:

- Screened patients (i.e. having signed the informed consent);
- Screen failure patients and reason for screen failure;
- Patients randomized and treated (i.e. randomized patients with a treatment number assigned and recorded and received at least one administration of IMP);
- Patients who permanently discontinued the IMP with the main reason for permanent treatment discontinuation,
- Patients who requested permanent treatment discontinuation.

Patients treated without being randomized will not be considered as randomized and will not be included in any analysis population for which being randomized is required. The safety data of patients treated but not randomized will be reported separately, and these patients will not be in the safety population.

Additionally a count of screened patients including number of screened patients, screen failure and inclusion/exclusion criteria met will be provided.

A listing of patients with treatment discontinuation or screen failure will be provided sorted by treatment group and patients, including patients status at the end of the study with the date of last IMP administration, date of last available information and method of contact, reason for permanent treatment discontinuation, and whether the blind was broken on site at time of discontinuation. All withdrawals from the study, taking place on or after IMP administration, will be fully documented in the body of the clinical study report (CSR).

In case of code broken for medical and accidental reasons on site, a listing of concerned patients will be provided, specifying the reason (AE/SAE or other), the date and time of code breaking, and the person who broke the code.

A listing of all comments done by the Investigator on the electronic case report form (eCRF) will be provided by treatment group, if any.

2.1.2 Protocol deviations

During the blinded review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment or dosing compliance, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the study team before database lock and listed in the Data Review and Surveillance Report, including missing data and study drug discontinuations, and classified as critical, major or minor deviations.

Critical or major deviations resulting in exclusion for the pharmacodynamics analyses and any other critical or major deviations will be summarized by treatment group.

2.2 ANALYSIS POPULATIONS

The number of patients included in each study population (safety population, pharmacokinetic population, pharmacodynamic population, pharmacokinetic/pharmacodynamic population) will be provided by treatment group. All exclusions from any analysis populations (pharmacodynamic, pharmacokinetic, and/or safety) will be fully documented in the clinical study report.

2.2.1 Pharmacodynamic population

For the main PD endpoints of plasma volume and hemoconcentration, the PD population will consist of all randomized and treated patients who have valid values of the main PD parameters both at baseline and at Day 14/EOT.

2.2.2 Safety population

All randomized patients who are exposed to IMP (regardless of the amount of treatment administered) will be included in the safety population. For safety analyses, patients will be included in the treatment group as actually received. Non-randomized and treated patients will not be part of the safety population, but their safety data will be summarized separately.

2.2.3 Pharmacokinetic population

The PK population will consist of all patients in the safety population who have at least one non-missing and eligible plasma concentration data.

Only patients with no major or critical deviations related to IMP (eg, vomiting just after drug administration), and for whom PK data are considered sufficient and interpretable, will be included in the pharmacokinetic population.

Patients will be analyzed according to the treatment actually received. Patients having received only placebo will not be included in the pharmacokinetic population.

2.2.4 Pharmacokinetic/Pharmacodynamic population

All patients being included in both the pharmacokinetic and the pharmacodynamic populations will be included in the pharmacokinetic/pharmacodynamic population. In addition, patients being included in the pharmacodynamic population and having received only placebo will also be included in the pharmacokinetic/pharmacodynamic population.

2.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

2.3.1 Subject demographic characteristics, medical history, and diagnoses

The response to IMP might be affected by several variables, including continuous variables (e.g., age, height, weight, body mass index (BMI) and qualitative variables (gender, race and/or ethnicity). BMI can be described both quantitatively and qualitatively (Underweight: BMI is less than 18.5; Normal weight: BMI is 18.5 to 24.9; Overweight: BMI is 25 to 29.9; Obese: BMI is 30 or more). The following variables will be summarized by descriptive statistics for the safety population and for additional population if relevant:

- Age (years)
- Weight (Kg)
- Height (cm)
- Body mass index (Kg/m^2)
- Race and/or ethnicity
- Gender
- eGFR

Medical history will be coded according to MedDRA (last version available before database lock). Specific medical history (Diabetes, cardiovascular events – including but not limited to stroke, myocardial infarction, atrial fibrillation – and previous cardiac interventions (eg angioplasty)) will be summarized by treatment group and overall, and presented by primary SOC and High Level Term (HLT) on the safety population. The events will be sorted by SOC internationally agreed order and decreasing frequency of HLT.

2.3.2 Baseline pharmacodynamic parameters

Baseline values of PD parameters are defined to be those taken or measured approximately one to three (3) hours prior to the first dosing of study treatment on Day 1.

All baseline PD parameters will be summarized and presented by treatment group as with all other baseline patient characteristics. In addition, for the main PD parameters such as plasma volume and hemoconcentration, the mean baseline values of the PD parameters will also be summarized along with the mean Day 14/EOT values and mean change from baseline values.

2.3.3 Baseline safety parameters

Baseline for safety parameters will be defined as the last available and evaluable parameter value before and closest to the first IMP dosing for laboratory data, vital sign parameters, and for 12 lead ECG parameters.

Baseline definitions specific to each type of safety parameter will be detailed in corresponding Section 2.7.2 to Section 2.7.5

Baseline safety values will be presented along with subsequent safety values assessed during or after dosing.

2.4 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

The extent of study treatment exposure (ie, duration of IMP exposure during the study) will be defined as the total number of days of IMP administrations, ignoring temporary drug discontinuations and will be calculated as:

(Date of the last study drug administration - date of the first study drug administration) + 1.

The duration of IMP exposure during the study will be summarized categorically (counts and percentages) by treatment group, on the safety population using the following categories: between 1 and 7 days; between 8 and 11 days; between 10 and 12 (excluded) days; between 12 and 15 days.

The following listings will be provided:

- Patients receiving IMP from specified batch
- Randomization scheme.

2.5 PRIOR/CONCOMITANT MEDICATION/THERAPY

Medications will be coded according to the World Health Organization Drug Dictionary (Drug Dictionary (WHO-DD), last available version before database lock). Summary of concomitant medications with the IMP will be provided by anatomic class and therapeutic class.

2.6 ANALYSIS OF PHARMACODYNAMIC VARIABLES

All the pharmacodynamic analyses will be performed using the pharmacodynamic population.

2.6.1 Description of pharmacodynamic variables

The following pharmacodynamic variables will be analyzed:

Primary PD variables

- Change in hemoconcentration from baseline to D14/EOT as assessed by changes in hematocrit, hemoglobin, albumin and total protein.
- Change in plasma volume in milliliters from baseline to D14/EOT as assessed by the indicator dilution method using ^{131}I-labelled human albumin.

Secondary PD variables:

- Change in erythropoietin (mU/ml) from baseline to D14 measured by chemiluminescent enzyme-labelled immunometric assay
- Change in NT-proBNP (pg/mL) from baseline to D14 measured by standard electrochemiluminescence immunoassay

Other Exploratory PD endpoints

- Change in total body water (mL) from baseline to D14 as assessed by the indicator dilution method using deuterium oxide
- Change in uric acid (mg/dL) from baseline to 14 days as measured by standard assay
- Change in beta-hydroxybutyrate (μM) from baseline to 14 days as measured by standard enzymatic colorimetric assay
- Change in red cell mass (mL) from baseline to D14, as derived from measurements of plasma volume (assessed by the indicator dilution method using ^{131}I-labelled human albumin) and hematocrit
- Change in total blood volume (mL) from baseline to 14 days, as assessed by the indicator dilution method using ^{131}I-labelled human albumin
- Percentage of patients within 15% of ideal blood volume on study day 14
- Blood pressure (sitting, SBP and DBP) at day 14, compared to baseline

2.6.2 Primary analysis

The main pharmacodynamic variables, change from baseline to Day 14 in hemoconcentration and plasma volume, will be analyzed using an analysis of covariance (ANCOVA) model with fixed terms for treatment and stratification factor of baseline patient status (diabetic, non-diabetic, ejection fraction status (reduced-preserved), and with baseline plasma volume as covariate. An estimate for the between-group difference in treatment mean changes and corresponding 2-sided 90% confidence interval (CI) will be calculated from the model. The main treatment comparison will be between the pooled treatment (200 mg and 400 mg) group and placebo which will be made at 1-sided α=0.05 (or equivalently, 2-sided α=0.10).

No multiplicity procedures will be applied as the study is exploratory in nature.

2.6.3 Secondary analysis/analysis of secondary variables

Similar ANCOVA models as in the primary analysis will be fitted for the secondary and other pharmacodynamic variables or endpoints.

In addition, descriptive statistics for secondary and other pharmacodynamic variables in raw data and in change from baseline will be provided by treatment group (Sotagliflozin doses or placebo) for assessment from Day 1 to Day 14. Plots of the means overtime (+/-SEM) will also be presented.

2.7 ANALYSIS OF SAFETY DATA

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population.

The safety analysis will be based on the review of descriptive statistics (summary tables) and individual data for vital signs, renal function, adverse events (AEs) and other clinical laboratory values and ECG parameters.
Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and the number of patients with Treatment-Emergent Adverse Events (TEAEs) will be summarized by treatment group. Potentially clinically significant abnormalities (PCSAs) for clinical laboratory, vital sign, and ECG data and out-of-normal range values for clinical laboratory data will be flagged and summarized in frequency tables. The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review for clinical laboratory tests, vital signs and ECG parameters.

For all safety data, the observation period will be divided into three segments:

- the **pretreatment period** is defined as the time between informed consent signature and the first IMP administration;
- the **TEAE (treatment emergent AE) period** is defined as the time from the first IMP administration up to approximately 5 days after the last IMP administration (approximately 5 times the half-life of sotagliflozin);
- the **post-TEAE period** is defined as the time starting after the TEAE period up to the final study follow up telephone check.

2.7.1 Adverse events

2.7.1.1 Definitions

Adverse events will be coded to a “Preferred Term (PT)” and High Level Group Term (HLGT)”, “High Level Term (HLT)” and primary “System Organ Class (SOC)” using the Medical Dictionary for Regulatory Activities (MedDRA, version currently in use by the sponsor at the time of database lock). Their severity will be graded according NCI-CTCAE v4.03.

They will be classified into predefined standard categories according to chronological criteria:

- Pretreatment AEs: AEs that occurred, worsened or became serious during the pretreatment period.

- Treatment emergent AEs (TEAEs): AEs that occurred, worsened or became serious during the TEAE period.
- Post-TEAEs: AEs that occurred, worsened or became serious during the post-TEAE period.

TEAEs will be assigned to the treatment received at the time of the AE onset.

If the onset date (or time) of an AE (occurrence, worsening or becoming serious) is incomplete or missing, then the AE will be considered as a TEAE unless a partial date (or time) shows it as a pre- or post-treatment event

All AEs reported in the study will be listed, sorted by treatment group, subject, onset date and time.

2.7.1.2 Treatment-emergent adverse events

The following TEAEs summaries will be provided by treatment for the safety population:

- Overview of TEAEs: number and percentage of patients with any TEAE, any TEAE of special interest, any severe TEAEs, any serious TEAE, any TEAE leading to death (if any occurred), and any TEAE leading to permanent treatment discontinuation.
- Summary of TEAEs by primary SOC and PT:
  - number and percentage of patients with at least one TEAE;
  - number of occurrences of TEAEs.

Patients presenting TEAEs will be listed sorted by treatment group primary SOC and PT.

2.7.1.3 Deaths, serious, and other significant adverse events

Any deaths, serious and other significant AEs will be listed.

2.7.1.4 Adverse events leading to treatment discontinuation

Any AEs leading to permanent treatment discontinuation will be listed.

2.7.1.5 Adverse events of special interest

Adverse event of special interests (AESI) for this study are defined as follows:

- Pregnancy occurring in a female patient included in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria.
  - In the event of pregnancy in a female patient, IMP should be discontinued,
  - Follow-up of the pregnancy in a female patient or in a female partner of a male patient is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or nonserious) with IMP/non investigational medicinal product (NIMP)
  - A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and resulting in clinical symptoms and/or signs accompanied by administration of more than twice the intended daily dose within a 24-hour period. It will be recorded in the e-CRF as an AESI with immediate notification "Symptomatic OVERDOSE (accidental or intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.

    (Please note that an Asymptomatic overdose with the IMP/NIMP, accidental or intentional, defined as administration of more than twice the intended daily dose within a 24-hour period, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient, not based on accountability assessment. It will be recorded as an AE "Asymptomatic OVERDOSE, accidental or intentional.")
- ALT increased > 3X ULN

A summary of TEAEs reported as AESI (number and percentage of patients and the number of events) will be provided by AESI category and PT, sorted by decreasing incidence of PT within each AESI category.

2.7.2 Clinical laboratory evaluations

Baseline definition

The values to be used as the baselines will be the Day 1 predose assessment values. If any of the scheduled baseline tests are repeated for any subject, the last rechecked values will be considered as baselines, provided they were done before the first IMP administration.

Abnormalities analyses

For parameters with laboratory ranges and/or abnormality criteria (PCSA), analysis will be performed using all post-baseline assessments done during the TEAE period, including all unplanned and rechecked values. Counts of patients with PCSAs according to baseline status will be presented by treatment. The same type of summary tables will be provided for out-of-normal laboratory range values.

Descriptive statistics and plots

Raw data and changes from baseline will be summarized in descriptive statistics for all endpoint parameters, by treatment and scheduled time of measurement.

Additionally, graphs over time for these parameters will be presented plotting mean +/- SD by treatment.

PCSA Listings

A listing of individual data from patients with post-baseline PCSAs will be provided; values will be flagged when outside the laboratory limits and/or when reaching the PCSA criteria.

A listing of liver function data for subjects experiencing at least one of the following situations will be provided:

- ALT > 3ULN and total bilirubin > 2ULN during the study, with at least one of them being post first dose, irrespective of the definition of the TEAE period;
- Conjugated bilirubin>35% of Total bilirubin and Total bilirubin>1.5 ULN, on the same sample post first dose, irrespective of the definition for the TEAE period.

If any, a listing related to increase in ALT ≥ 2 ULN will be provided, including notably the information on drug intake, medical and surgical history, alcohol habits, and trigger factors, event details with ALT values, associated signs and symptoms.

Out-of-normal range definitions and unscheduled laboratory tests, if any, will be listed.

2.7.3 Vital signs

Heart rate (HR), systolic and diastolic blood pressures (SBP and DBP) will be analyzed as raw parameter value (for supine/sitting and standing positions), change from baseline (for supine or sitting position only) and as orthostatism parameter (standing-sitting/supine parameter values).

Body weight will be analyzed as raw parameter value and percent change from baseline and BMI will be analyzed as raw parameter value.

Baseline definition

The values to be used as baselines will be the Day 1 pre-dose assessment values. If any of the scheduled baseline tests are repeated for any subject, the last rechecked values will be considered as baselines, provided they were done before the IMP administration of the respective treatment phase, and in the same condition.

Abnormalities analyses

For all parameters, analysis will be performed using all post-baseline assessments done during the TEAE period, including all unplanned and rechecked values. Counts of patients with PCSAs will be presented by treatment, regardless of the baseline status.

Descriptive statistics and plots

For heart rate and blood pressures, raw data (supine/sitting and standing positions) and changes from baseline (supine/sitting position only) will be summarized in descriptive statistics by treatment and scheduled time of measurement.

For body weight, raw data and percent change from baseline will be summarized in descriptive statistics by treatment and scheduled time of measurement.

Additionally, graphs over time will be presented plotting mean +/- SD by treatment.

PCSA Listings

A listing of individual data from patients with post-baseline PCSAs will be provided; values will be flagged when reaching the PCSA criteria.

2.7.4 Electrocardiogram

ECG parameters (HR in bpm, QTc, QT, QRS and PR in msec) will be derived from the ECG obtained in hospital or during Visit days as per schedule of events. All parameters will be analyzed as raw data and absolute change from baseline. In addition, for the abnormalities analysis, PR and QRS will be also analyzed as percent change from baseline.

Baseline definition

The values to be used as baselines will be the Day 1 predose assessment values. If any of the scheduled baseline tests are repeated for any subject, the last rechecked values will be considered as baselines, provided they were done before the IMP administration of the respective treatment phase, and in the same condition.

Abnormalities analyses

For all parameters, analysis will be performed, using all post-baseline assessments done during the TEAE period, including all unplanned and rechecked values. Counts of patients with PCSAs will be presented by treatment, regardless of the baseline status.

Descriptive statistics and plots

ECG parameters (raw data and absolute change from baseline) will be summarized in descriptive statistics by treatment and scheduled time of measurement.

Additionally, graphs over time will be presented plotting mean +/- SD by treatment.

Listings

Following listings will be produced, using all data, including rechecked or unplanned values.

- A listing of individual data of subjects with any post-baseline PCSAs will be provided; raw data and absolute or percent change from baseline will be displayed depending on the parameter and values will be flagged when reaching the limits of the PCSA criteria;
- In addition, subjects with QTc/QTcB/QTcF >480 ms and/or change from baseline in QTc/QTcB/QTcF >60 ms will also be listed separately, using all post-dose timepoints.

- A listing of subjects with at least one abnormality in qualitative assessment (ie, abnormal 12-lead ECG) after the 1st dosing will be also provided.

2.7.5 Other related safety parameters

The HbA1c and eGFR parameters will be analysed descriptively by treatment group.

2.8 ANALYSIS OF PHARMACOKINETIC DATA

2.8.1 Pharmacokinetic parameters

No formal analysis of PK parameters will be performed. Single concentration-time-points will be subject to descriptive statistical analysis

2.9 DATA HANDLING CONVENTIONS

This section describes the rules and conventions used in the presentation and analysis of data."

In the in-text and appendices tables, the following treatment labels will be used:

- Placebo
- Sotagliflozin 200mg
- Sotagliflozin 400mg

All individual data for all included subjects will be presented in data listings, sorted by treatment group, subject number, visit and time of measurement.

For parameters with evaluations before administration and in cases of rechecked value(s) for one subject, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values.

After baseline, only observations planned in the protocol will be used in descriptive statistics.

For clinical laboratory parameters with nonnumeric values, the imputed values used for the descriptive statistics and/or the flags will be determined by considering the following rules:

- If database value is ' < X', the value used will be X/2
- If database value is ' > X', the value used will be $X + 10^{[-\text{number of digits of the considered parameter in the database}]}$

- if database value is a range (eg, 'X – Y'), the values used will be (Y + X)/2

If not otherwise stated in the statistical section of the protocol:

- Missing data other than protocol-planned baseline values will not be replaced.

- Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), minimum, maximum and median.
- Descriptive statistics for qualitative parameters will be provided using frequencies (N) and percent (%).

Handling missing data for adverse events

In case of missing or inconsistent information, an adverse event (AE will be counted as a treatment-emergent adverse event (TEAE, unless it can clearly be ruled out that it is not a TEAE (eg, by partial dates or other information).

If the start date (or time) of an AE is incomplete or missing, then the AE will be considered as a TEAE unless a partial date (or time) or comment shows it as a pre- or post-treatment event.

If relationship to study drug is missing, the AE will be assessed as unrelated if it started before administration of study medication; in all other cases it will be assumed to be related.

3 INTERIM ANALYSIS

Interim analyses will be performed following Cohort 2 and during Cohort 3 for sample size re-estimation or for the purpose of exploratory analyses. These planned interim analyses will focus on the main pharmacodynamic parameters of hemoconcentration and plasma volume. Descriptive statistics will be provided and ANCOVA analyses as described above will be performed for the interim analyses. Exploratory analyses may also be performed earlier for safety reasons, or if requested by the DMC or institutional ethics committees. In that case, the analysis will not result to any changes to the protocol.

The Statistician and Statistical Programmer will work independently to the study team on these interim analyses to ensure the blinding is preserved notably toward the Investigator. These analyses must provide only mean and variability data and exclude all individual information like minimum, maximum or median values and sample size per group. A dissemination plan of the results should be established upfront before the interim data unblinding.

The outcome of this interim analysis may lead to early termination of the trial, continuation without any changes, or continuation with changes.

4 SOFTWARE DOCUMENTATION

The analysis of clinical data will be performed, using SAS® version 9.4 or higher

5 APPENDICES

Appendix A Study flow chart

Phase	Screening	Treatment Period				Follow-up
VISIT	1	2	3	4	5 (EOT)	6 (EOS)
Day	D-21 to D-1[a]	D1	Between D3 and D6	Between D8 and D11	D14+/-1 [b]	Between D26 and D30
Informed consent[c]	X					
Discharge[c]	<------ X ------>					
IRT contact	X	X			X	X
Visit at clinical site[d]		X	X[e]	X[e]	X[e]	X
Phone check/Visit at clinical site[g]						X
Inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Prior/concomitant medications	< ---------- X ---------- >					
Randomization[h]		X				
Meal[i]		X	X	X	X	
Diary[j] (daily): IMP intake, concomitant medications, AE BP[k]		X	<---------- X ---------->			
Study treatment administration[l]						
IMP dispensing		X				
IMP administration		<---------- X ---------->				
^{131}I-albumin injection (for plasma volume assessment)		X			X	
Deuterium oxide intake (for total body water assessment)		X			X	
Safety						
Physical examination[m]	X	X			X	
Height	X					
Body weight[n]	X	X			X	
Echocardiogram[o]	X					
Vital signs[f], ECG[p]	X	X	X	X	X	
Body temperature[q]	X	X			X	
Hematology[r]	X	X[t]			X[t]	
Biochemistry[s]	X	X[t]	X	X	X[t]	

Phase	Screening	Treatment Period				Follow-up
VISIT	1	2	3	4	5 (EOT)	6 (EOS)
Day	D-21 to D-1[a]	D1	Between D3 and D6	Between D8 and D11	D14+/-1 [b]	Between D26 and D30
Liver function (AST, ALT, ALP, GGT, total and conjugated bilirubin)	X	X	X	X	X	
Urine (Lab)		X	X	X	X	
β-HCG blood test[u]	X				X	
Plasma FSH[u]	X					
Adverse event collection	< ---------- X ---------->					
Pharmacokinetics						
Sotagliflozin pharmacokinetic plasma samples[v]		X	X	X	X	
Pharmacodynamics						
Blood collection for hemoconcentration samples [w]		X			X	
Blood collection for ^{131}I-albumin		X			X	
Blood collection for deuterium oxide		X			X	
Uric acid		X			X	
Erythropoietin		X			X	
NT-proBNP		X			X	
Beta-hydroxybutyrate		X			X	

[redacted]

a The laboratory evaluation closest to D1 will be used as the screening lab in case of discrepancies with prior labs. Oral hypoglycemic drugs and long-acting insulin should not be administered the morning of D1 or D14. If appropriate (for example, for patients admitted in the early morning hours), screening procedures may also take place on D1.

b Sites should adhere to D14 whenever possible

c Occasionally, a patient might be admitted, screened and randomized on the same day. In those cases, informed consent will also be sought during that day. In other cases, randomization may take place before discharge from hospital or admitting unit. If discharge is before D1, then the patient will come back to the site at D1 (Visit 2) for Randomization and IMP dispensing. For hospitalized patients eligible for discharge on study day D1, the timing of discharge is at the discretion of the treating physician but should not be less than 6 hours following administration of study drug. Patients that are not eligible for discharge, may complete all or part of the study as inpatients (hospital or other appropriate unit).

d Those visits need not be in an oupatient setting. For example, where mobility issues might cause restrictions, or patient is in a step-down unit or rehabilitation ward, the Investigator or designee could perform the Visit and relevant assessments and collect blood or urine samples at that setting. Visit 6 is the end of study visit (EOS). All patients will have a phone check at EOS. Patients may return to the clinical site if, in the judgment of the Investigator, may require a physical examination and additional investigations. A telephone call may also be scheduled soon after the End of Treatment Visit 5.

e IMP accountability and compliance check performed at end of treatment (EOT) Visit 5 and on visits planned at clinical site (Visit 3 and Visit 4)

f Vital signs: including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting (preferably sitting) resting position. For patients returning to the day unit for D1, they should stay in the unit. Their vital signs will be assessed at baseline and every 2 hours after administration of IMP. Patients should be monitored for at least 6 hours prior to discharge from the unit.

g Phone check will be to record any adverse events that occurred after study drug discontinuation, and to record daily BP readings since EOT Visit 5. Patients may return for a further visit (Visit 6) if in the opinion of the investigator they need a follow up examination and/or investigations.

h IRT contact for screening/randomization. Randomization within 7 days of discontinuation of IV diuretic therapy.

i Meals should be taken approximately 15 min after IMP administration throughout the study. On study day Visits 2 and 5, and Visits 3 and 4, patients should fast for approximately 6 hours prior to IMP administration.

j Diary dispensed on D1 (Visit 2). The diary will be reviewed and information recorded on eCRF. If the last follow up is by phone check, all relevant information will be captured and transcribed to the eCRF. Patients who may need to remain inpatients for some or all of the visits will also receive a diary. While inpatients, relevant data such as AE and IMP intake will be entered into the diary. For inpatients, BP and concomitant medications will be recorded in the patient source documents. Those who become eligible for discharge will also receive BP monitors and continue with diary updates on a daily basis.

k Patients will be taught how to perform the automated BP readings. Automated BP readings will be performed in triplicate, between 6 AM to 10 AM on a daily basis, starting D2 and ending at the last post-study follow up.

l Study treatment ends on Day 14 (EOT).

m Physical examination includes at a minimum: heart and respiratory auscultation; peripheral arterial pulse; pupil, and abdomen examination. All physical examinations in diabetic patients, including abbreviated physical examinations, will include examination of the lower extremities to evaluate for any evidence of foot ulcers or infection should be performed as part of the general physical examination and this examination should be documented on the e-CRF.

n All body weight measurements on scale provided by site staff.

o All patients must have a documented echocardiogram, either performed during current admission or within 12 months from the index hospitalization.

p ECG at Visit 2, Visit 3 and EOT Visit 5 only.

q Oral or tympanic body temperature.

r Complete blood count / hematocrit / hemoglobin.

s Creatinine, urea, electrolytes.

t For Visits 2 (Day 1) and 5 (Day 14±1), those samples will be obtained as part of the Hemoconcentration sampling, thus no additional samples for Hematology or Biochemistry are required. It is indicated here as a reminder that baseline hematology and biochemistry is done on Visits 2 and 5. For all other Visits, Hematology and Biochemistry samples are to be obtained as indicated.

u Beta-HCG test will be for all women of child-bearing potential as defined in the inclusion/exclusion criteria, and FSH to assess menopausal status when necessary.

v Pharmacokinetic samples taken on Visit 3 and Visit 4 are pre-dose drug treatment samples.

w Hemoconcentration is determined by measurement of hematocrit, hemoglobin, albumin and total protein. Baseline biochemistry (creatinine, urea and electrolytes) and hematology (CBC) is also determined from those samples.

Appendix B Period flow chart

VISIT		VISIT 2 and VISIT 5										VISIT 3		VISIT 4	
Day		D1 and D14(+/- 1 day)[a]										Between Day 3 and Day 6		Between Day 8 – and Day 11	
Time (hour/minute)	-3H	-2.5H	-2H	-1H	0H	0.5H	1H	3H	4H	5H	6H	-2.5 H	0H	-2.5H	0 H
Indicative clock time	7 am	7:30am	8 am	9:00 am	10 am	10:30am	11 am	1 pm	2 pm	3 pm	4 pm				
Discharge[b]											X				
Concomitant medications		<- ->													
Randomization[c]	X														
IMP accountability and compliance		<- - - - - - - - - - - - - - - X - - - - - - - - - - - - - - - - ->										X		X	
Inclusion/Exclusion criteria[c]	X														
Meal[e]					X								X		X
Semi-recumbent position				<---------- X -------->											
Study treatment administration															
IMP administration					X								X		X
^{131}I-albumin injection				X											
Deuterium oxide intake[f]		X													
Safety															
Physical examination	X														
Vital signs	X					<- - - - - - - - - - - - - - - - - X[g] - - - - - - - - - - - - - - - - ->						X		X	
Body weight[o]	X														
[redacted]															
ECG	X											X			
Urine (lab)		X										X		X	
Hematology				X[h]											
Biochemistry				X[h]								X		X	
β-HCG[i]		X													
Liver function (AST,ALT, ALP, GGT, total and conjugated bilirubin)[j]			X									X		X	

VISIT		VISIT 2 and VISIT 5										VISIT 3		VISIT 4	
Day		D1 and D14(+/- 1 day)[a]										Between Day 3 and Day 6		Between Day 8 – and Day 11	
Time (hour/minute)	-3H	-2.5H	-2H	-1H	0H	0.5H	1H	3H	4H	5H	6H	-2.5 H	0H	-2.5H	0 H
Indicative clock time	7 am	7:30am	8 am	9:00 am	10 am	10:30am	11 am	1 pm	2 pm	3 pm	4 pm				
Adverse event collection	<----------X---------->														
Pharmacokinetics															
Sotagliflozin plasma samples[k]		**Day 14**: P04							**Day 1**: P00 **Day 14**: P05		**Day 1**: P01 **Day 14**: P06	P02		P03	
Pharmacodynamics															
Blood collection Hemoconcentration,[l]				X											
Blood collection for ^{131}I-albumin				X[m]											
Blood collection for deuterium oxide[n]		X					X								
Uric acid		X													
Erythropoietin		X													
NT-ProBNP		X													
Beta-hydroxybutyrate		X													
[redacted]															

a Sites should adhere to D14 whenever possible

b For hospitalized patients eligible for discharge on study day D1,,the timing of discharge from the hospital is at the discretion of the treating physician but should not be less than 6 hours following the administration of study drug. Patients that are not eligible for discharge, may complete all or part of the study as inpatients (hospital or other appropriate unit). For patients returning to the day unit for D1, they should also stay in the unit and have their vital signs assessed every 2 hours after IMP administration and discharged not sooner than 6 hours after IMP administration. Laboratory tests may be performed in the hospital or outpatient unit, depending on whether the patient remains hospitalized.

c Day 1 only. IRT contact for randomization. The time is indicative, as randomization should take place after review of inclusion/exclusion criteria

[redacted]

e Meal to be taken within 15 minutes after administration of study drug.

f Deuterium oxide intake should take place after blood collection for baseline measurements.

g Vital signs: including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting (preferably sitting) resting position. For patients returning to the day unit for D1, they should stay in the unit. Their vital signs will be assessed at baseline and every 2 hours after administration of IMP. Patients should be monitored for at least 6 hours prior to discharge from the unit.

h For Visits 2 (Day 1) and 5 (Day 14±1), those samples will be obtained as part of the Hemoconcentration sampling, thus no additional samples for Hematology or Biochemistry are required. It is indicated here as a reminder that baseline hematology and biochemistry is done on Visits 2 and 5. For all other Visits, Hematology and Biochemistry samples are to be obtained as indicated.

i β-HCG performed at screening and D14 only

j Indicative time. Those samples can be obtained at the same time as the other samples are collected, eg, biochemistry.

k Pharmacokinetic samples at T(-2.5H) collected only on Visit 3, Visit 4 and Visit 5 (D14±1).

l Hemoconcentration is determined using the following: Hematocrit, hemoglobin, total protein and albumin. Baseline biochemistry (creatinine, urea, electrolytes) and complete blood count will also be determined from those samples

m One sample will be collected just before injection of ^{131}I-albumin (-1H, PD00) and further sample collection will start 12 min following the injection. Samples will then be collected every 6 minutes starting – 0H48min: -0H48min(PD01), -0H42min(PD02), -0H36min(PD03), -0H30min(PD04), -0H24min(PD05) min. For blood collection on D14 sample notation should be: -1H (PD06), -0H48min (PD07), -0H42min (PD08), -0H36min(PD09), -0H30min(PD10), -0H24min(PD11)

n Following administration of deuterium oxide, blood collection on D1: At -2.5H (PY00), 1H (PY01), and on Day 14: At -2.5H (PY02), 1H (PY03)

o All body weight measurements on scale provided by site staff

[redacted]

Appendix C Potentially clinically significant abnormalities criteria

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
Haemoglobin		
Low	≤ 115 g/L (Male) ≤ 95 g/L (Female)	28 days/1 month to 23 months old : < 90 g/L 24 months/2 years to <16/18 years old : < 100 g/L
Decrease from baseline	≥20 g/L	≥ 20 g/L
High (adults)	≥ 185 g/L (Male) ≥ 165 g/L (Female)	
Hematocrit		
Low	≤ 0.37 v/v (Male) ≤ 0.32 v/v (Female)	28 days/1 month to 23 months old: < 0.29 v/v 24 months/2 years to <16/18 years old: < 0.32 v/v
High	≥ 0.55 v/v (Male) ≥ 0.5 v/v (Female)	28 days/1 month to 23 months old: > 0.42 v/v 24 months/2 years to <16/18 years old: > 0.47 v/v
Erythrocyte Count		
High (adults)	≥ 6 Tera/L	
Platelet Count		
Low	< 100 Giga/L	< 100 Giga/L
High	≥ 700 Giga/L	> 700 Giga/L
Leukocytes		
Low	< 3.0 Giga/L (Non-Black); < 2.0 Giga/L (Black)	Birth/0 to 23 months old : <4.0 Giga /L 24 months/2 years to <6 years old: <3.0 Giga /L 6 to <12 years old : <5.0 Giga /L 12 to 16/18 years old : <4,5 Giga /L

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
High	≥ 16.0 Giga/L	Birth/0 to 27 days old : >25.0 Giga /L 28 days/1 month to 23 months old: >20.0 Giga /L 24 months/2 years to <6 years old: >16.0 Giga /L 6 to <12 years old : >17.0 Giga /L 12 to 16/18 years old : >13.5 Giga /L
Neutrophils		
Low	< 1.5 Giga/L (Non-Black); < 1.0 Giga/L (Black)	Birth/0 to 27 days old : <4 Giga /L (1 day old) <1.5 Giga /L (2-7 days old) <1.25 Giga /L (>7 day-1 month old) 28 days/1 month to 23 months old: <1.0 Giga /L (1-3 months) <1.2 Giga /L (3-24 months) 24 months/2 years to <16/18 years old: <1.2 Giga /L
High (children)		>1 ULN
Lymphocytes		
Low (children)		Birth/0 to 27 days old : <1.2 Giga /L 28 days/1 month to 23 months old: <2.0 Giga /L 24 months/2 years to <12 years old: <1.0 Giga /L 12 to 16/18 years old : <0.6 Giga /L
High	> 4.0 Giga/L	Birth/0 to 27 days old : >17.0 Giga /L 28 days/1 month to 23 months old: >13.5 Giga /L 24 months/2 years to <6 years old: >9.5 Giga /L 6 to <12 years old : >8.0 Giga /L 12 to 16/18 years old : >6 Giga /L
Monocytes		
High (adults)	> 0.7 Giga/L	
Basophils		
High (adults)	> 0.1 Giga/L	
Eosinophils		

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
High	> 0.5 Giga/L or > ULN (if ULN ≥ 0.5 Giga/L)	> 0.5 Giga/L or > ULN (if ULN > 0.5 Giga/L)
Glucose		
Low	≤ 3.9 mmol/L and < LLN	<2.7 mmol/L
High	≥11.1 mmol/L (unfasted); ≥ 7 mmol/L (fasted)	≥10.0 mmol/L (unfasted) ≥7 mmol/L (fasted after >12 hours of fast)
Albumin		
Low (adults)	≤ 25 g/L	
Creatine Kinase		
High, all grades	> 3 ULN	≥ 3 ULN
At least grade 1 (adults)	> 3 ULN	
At least grade 2 (adults)	> 10 ULN	
Sodium		
Low	≤ 129 mmol/L	≤129 mmol/L
High	≥ 160 mmol/L	≥150 mmol/L
Potassium		
Low	< 3 mmol/L	Birth/0 to 27 days old : ≤3.0 mmol/L 28 days/1 month to 16/18 years old : ≤3.5 mmol/L
High	≥ 5.5 mmol/L	Birth/0 to 27 days old : ≥7.0 mmol/L 28 days/1 month to 23 months old : ≥6.0 mmol/L 24 months/2 years to 16/18 years old : ≥5.5 mmol/L
Creatinine		
High	≥ 150 µmol/L	Birth/0 to <6 years old : >53 µmol/L 6 years to <12 years old: >90 µmol/L 12 years to 16/18 years old: >132 µmol/L

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
Increase from baseline		
At least grade 1 (adults)	≥ 30% change from baseline	
At least grade 2 (adults)	≥ 100% change from baseline	
Creatinine Clearance		
Low, all grades	< 90 mL/min*	Birth/0 to 27 days old : < 25 ml/min/1.73m² ** 28 days/1 month to 23 months old: < 45 ml/min/1.73m² ** From 2 years old : < 60 ml/min/1.73m² **
Mild (adults)	[60 – 90[mL/min*	
Moderate (adults)	[30 – 60[mL/min*	
Severe (adults)	[15 – 30[mL/min*	
End stage (adults)	< 15 mL/min*	
*MDRD or Cokcroft-Gault equation		**GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
BUN		
High	≥ 17 mmol/L	Birth/0 to 27 days old : ≥4.3 mmol/L 28 days/1 month to 16/18 years old: ≥6.4 mmol/L
Alanine Aminotransferase		
High, at least grade 1	> 3 ULN	≥ 3 ULN
High, at least grade 2	> 5 ULN	≥ 5 ULN
High, at least grade 3	> 10 ULN	≥ 10 ULN
High, at least grade 4	> 20 ULN	≥ 20 ULN
Aspartate Aminotransferase		
High, at least grade 1	> 3 ULN	≥ 3 ULN
High, at least grade 2	> 5 ULN	≥ 5 ULN
High, at least grade 3	> 10 ULN	≥ 10 ULN
High, at least grade 4	> 20 ULN	≥ 20 ULN

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
Alkaline phosphatase		
High	> 1.5 ULN	≥ 1.5 ULN
Total Bilirubin		
High, all grades	> 1.5 ULN	≥ 1.3 ULN
At least grade 1 (adults)	> 1.5 ULN	
At least grade 2 (adults)	> 2 ULN	
Alanine Aminotransferase and tot bilirubin		
High	ALT > 3 ULN and TBILI > 2 ULN	ALT ≥ 3 ULN and TBILI ≥ 2 ULN
Direct bilirubin and total bilirubir		
High	BILDIR >35% TBILI and TBILI >1.5 ULN	BILDIR >35% TBILI and TBILI≥1.3 ULN

References:
- for adults: Criteria for Potentially Significant Abnormalities – for Phase 2/3 studies (oncology excepted) - Version 3.0 - 21-MAY-2014
- for children: Criteria for Potentially Clinically Significant Abnormalities for Studies in Children - Version 3.0 - 21-MAY-2014

ECG Parameter PCSA criteria n/N1 (%)	Adults	Children
Heart rate		
Low, at least grade 1 (adults)	<50 bpm	
Low, at least grade 2 (adults)	<40 bpm	
Low, at least grade 3 (adults)	<30 bpm	

ECG Parameter PCSA criteria n/N1 (%)	Adults	Children
Low and decrease from baseline, all grades	<50 bpm and decrease from baseline ≥20 bpm	Birth/0 to 27 days old : ≤ 90 bpm and decrease from baseline ≥20 bpm 28 days/1 month to 23 months old: ≤ 80 bpm and decrease from baseline ≥20 bpm 24 months/2 years to <6 years old: ≤ 75 bpm and decrease from baseline ≥20 bpm 6 to <12 years old : ≤ 50 bpm and decrease from baseline ≥20 bpm 12 to 16/18 years old : ≤ 50 bpm and decrease from baseline ≥20 bpm
At least grade 1 (adults)	<50 bpm and decrease from baseline ≥20 bpm	
At least grade 2 (adults)	<40 bpm and decrease from baseline ≥20 bpm	
At least grade 3 (adults)	<30 bpm and decrease from baseline ≥20 bpm	
High, at least grade 1 (adults)	>90 bpm	
High, at least grade 2 (adults)	>100 bpm	
High, at least grade 3 (adults)	>120 bpm	
High and increase from baseline, all grades	>90 bpm and increase from baseline ≥20bpm	Birth/0 to 27 days old : ≥ 190 bpm and increase from baseline ≥20 bpm 28 days/1 month to 23 months old: ≥ 175 bpm and increase from baseline ≥20 bpm 24 months/2 years to <6 years old: ≥ 140 bpm and increase from baseline ≥20 bpm 6 to <12 years old : ≥ 120 bpm and increase from baseline ≥20 bpm 12 to 16/18 years old : ≥ 120 bpm and increase from baseline ≥20 bpm
At least grade 1 (adults)	>90 bpm and increase from baseline ≥20bpm	
At least grade 2 (adults)	>100 bpm and increase from baseline ≥20bpm	
At least grade 3 (adults)	>120 bpm and increase from baseline ≥20bpm	
PR		
High, all grades	>200 ms	Birth/0 to 27 days old : ≥ 120 ms 28 days/1 month to 23 months old: ≥ 140 ms 24 months/2 years to <6 years old: ≥ 160 ms 6 to <12 years old : ≥ 170 ms 12 to 16/18 years old : ≥ 180 ms
At least grade 1 (adults)	>200 ms	

ECG Parameter PCSA criteria n/N1 (%)	Adults	Children
At least grade 2 (adults)	>220 ms	
At least grade 3 (adults)	>240 ms	
High and increase from baseline (adults)		
At least grade 1	>200 ms and increase from baseline ≥25%	
At least grade 2	>220 ms and increase from baseline ≥25%	
At least grade 3	>240 ms and increase from baseline ≥25%	
QRS		
High, all grades	>110 ms	Birth/0 to 27 days old : ≥ 85 ms 28 days/1 month to 23 months old: ≥ 85 ms 24 months/2 years to <6 years old: ≥ 95 ms 6 to <12 years old : ≥ 100 ms 12 to 16/18 years old : ≥ 110 ms
At least grade 1 (adults)	>110 ms	
At least grade 2 (adults)	>120 ms	
High and increase from baseline (adults)		
At least grade 1	>110 ms and increase from baseline ≥25%	
At least grade 2	>120 ms and increase from baseline ≥25%	
QTc Fridericia		
Increase from baseline, Grade 1	Increase from baseline]30-60] ms	All age classes: Increase from baseline (30-60] ms
Increase from baseline, Grade 2	Increase from baseline >60 ms	All age classes: Increase from baseline >60 ms

References:

- for adults: Criteria for Potentially Significant Abnormalities – for Phase 2/3 studies (oncology excepted) - Version 3.0 - 21-MAY-2014

- for children: Criteria for Potentially Clinically Significant Abnormalities for Studies in Children - Version 3.0 - 21-MAY-2014

Vital signs parameter **PCSA criteria n/N1 (%)**	**Adults**	**Children**
Systolic blood pressure supine		
Low and decrease from baseline	≤95 mmHg and decrease from baseline ≥20 mmHg	Birth/0 to 27 days old : ≤ 60 mmHg and decrease from baseline ≥20 mmHg 28 days/1 month to 23 months old: ≤ 70 mmHg and decrease from baseline ≥20 mmHg 24 months/2 years to <6 years old: ≤ 70 mmHg and decrease from baseline ≥20 mmHg 6 to <12 years old : ≤ 80 mmHg and decrease from baseline ≥20 mmHg 12 to 16/18 years old : ≤ 90 mmHg and decrease from baseline ≥20 mmHg
High and increase from baseline	≥160 mmHg and increase from baseline ≥20 mmHg	Birth/0 to 27 days old : ≥ 85 mmHg and increase from baseline ≥20 mmHg 28 days/1 month to 23 months old: ≥ 98 mmHg and increase from baseline ≥20 mmHg 24 months/2 years to <6 years old: ≥ 101 mmHg and increase from baseline ≥20 mmHg 6 to <12 years old : ≥ 108 mmHg and increase from baseline ≥20 mmHg 12 to 16/18 years old : ≥ 119 mmHg and increase from baseline ≥20 mmHg
Diastolic blood pressure supine		
Low and decrease from baseline	≤45 mmHg and decrease from baseline ≥10 mmHg	Birth/0 to <6 years old : ≤ 34 mmHg and decrease from baseline ≥10 mmHg 6 to <12 years old : ≤ 48 mmHg and decrease from baseline ≥10 mmHg 12 to 16/18 years old : ≤ 54 mmHg and decrease from baseline ≥10 mmHg
High and increase from baseline	≥110 mmHg and increase from baseline ≥10 mmHg	Birth/0 to 27 days old : ≥ 50 mmHg and increase from baseline ≥10 mmHg 28 days/1 month to 23 months old: ≥ 54 mmHg and increase from baseline ≥10 mmHg 24 months/2 years to <6 years old: ≥ 59 mmHg and increase from baseline ≥10 mmHg 6 to <12 years old : ≥ 72 mmHg and increase from baseline ≥10 mmHg 12 to 16/18 years old : ≥ 78 mmHg and increase from baseline ≥10 mmHg
Heart rate supine (adults)		
Low and decrease from baseline	≤50 bpm and decrease from baseline ≥20 bpm	
High and increase from baseline	≥120 bpm and increase from baseline ≥20 bpm	

References:
- for adults: Criteria for Potentially Significant Abnormalities – for Phase 2/3 studies (oncology excepted) - Version 3.0 - 21-MAY-2014
- for children: Criteria for Potentially Clinically Significant Abnormalities for Studies in Children - Version 3.0 - 21-MAY-2014

Appendix D Flags used in the safety PCSA and abnormality analysis

Table 2 - Flags for laboratory parameters

Flags	*Definition*
B	*Baseline value*
L	*Value < LLN*
H	*Value > ULN*
-	*Value reaching the lower PCSA limit of the list*
--	*Value reaching the second lower PCSA limit*[a]
+	*Value reaching the upper PCSA limit of the list*
++	*Value reaching the second upper PCSA limit of the list*[b]
*	*Value of ALT≥ 3 ULN and total bilirubin ≥ 2 ULN*
#	*Conjugated bilirubin > 35% total bilirubin and total bilirubin > 1.5 ULN*

[a] *applicable to creatinine clearance only for which several potential classes of PCSA are defined (moderate and severe classes are flagged in the same way "- -").*

[b] *for more than 2 upper PCSA limit, "++" flag will be used*

Table 3 - Flags for vital signs parameters

Flags	*Definition*
"B"	*Baseline value*
"-"	*Value reaching the lower PCSA limit of the list*
"+"	*Value reaching the upper PCSA limit of the list*

Table 4 - Flags for ECG

Flags	*Definition*
"B"	*Baseline value*
"-"	*Value reaching the lower PCSA limit of the list*[a]
"+"	*Value reaching the upper PCSA limit of the list*[b]
"++"	*Value reaching the second upper PCSA limit of the list*[c]

[a] *"-" is applicable to HR*

[b] *"+"is applicable to HR, PR, QRS, borderline QTc ([431-450] ms for males or [451-470] ms for females) and borderline delta QTc (delta QTc [30-60] ms).*

[c] *"++" is applicable to prolonged QTc (>450 ms for males or >470 ms for females) and prolonged delta QTc (delta QTc > 60 ms).*