Salubris Biotherapeutics, Inc.
Protocol #: JK07.1.01 Amendment 3

A Randomized, Double-Blind, Placebo-controlled, Single-ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of JK07 in Subjects with Heart Failure with Reduced Ejection Fraction (HFrEF)

Statistical Analysis Plan

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Prepared for:
Sam Murphy
Chief Executive Officer

Salubris Biotherapeutics, Inc
45 West Watkins Mill Road, Suite E
Gaithersburg, MD 20878

Prepared by:
Ninon Francois
Associate Biostatistician

IQVIA Biotech
2400 Ellis Road, Pod A, Level 4
Durham, NC 27703

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CONTENTS

List of Abbreviations 5

I.Introduction 7

A. Background 7
B. Purpose of the Statistical Analysis Plan 7

II.Protocol Objectives 7

A. Primary 8
B. Secondary 8
C. Exploratory 8

III.Study Endpoints 8

A. Primary 8
B. Secondary 9
C. Exploratory 9

IV.Study Design 10

A. Design Overview 10
B. Study Population 12
C. Sample Size 13
D. Treatment Randomization 13

V.General Analytical Considerations 14

A. Data Sources 14
B. Definition of Baseline 14
C. Study Day 14
D. Missing Data 14
E. Multiple Study Centers 16
F. Covariate Adjustment in Primary Analysis 16
G. Sample Size Reassessment 16
H. Interim Analyses 16
I. Test Sizes 16
J. Multiple Comparisons 16
K. Analysis Populations 16
L. Subgroups of Analysis Populations 17
M. Data Display Characteristics 17

VI.Subject Accountability 19

A. Demographics and Baseline Characteristics 19
B. Disposition 20
C. Protocol Deviations 21

VII.Safety Analyses 21

A. Exposure 21
B. Adverse Events 22
C. Clinical Laboratory Results 24

D. Vital Signs 24
E. Medical History 25
F. Surgical History 25
G. Electrocardiograms (Digital 12-Lead Triplicate ECGs) 25
H. Incidence of Emergent Rhythm Abnormality (Arrhythmias) 26
I. Prior Medications or Concomitant Medications 27

VIII. Pharmacokinetic Analyses 27

A. PK Data Handling 27
B. Calculation of PK Parameters 28
C. Statistical Analysis of PK Concentration Data 29
D. Statistical Analyses of PK Parameters 30

IX. Exploratory Pharmacodynamic Analysis 31

A. Analysis of 2-dimensional Transthoracic Echocardiography (2D-TTE) and Biomarkers 31
B. Potential Effect of JK07 on QTc Prolongation[2] 31

X. Exploratory Biomarkers 35

XI. Immunogenicity Assessments 35

XII. Changes from Protocol 36

XIII. References 36

List of Abbreviations

2D-TTE	2-Dimensional Transthoracic Echocardiography
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time from time zero extrapolated to infinity
$AUC_{(0\text{-}last)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
BLQ	Lower Limit of Quantitation
BMI	Body Mass Index
CFBL	Change from Baseline
CL	Systemic clearance
C_{max}	Maximum Concentration Observed
CO	Cardiac Output
CTCAE	Common Terminology Criteria for Analysis Events
DLAEs	Dose-limiting Adverse Events
DRC	Data Review committee
ECG	12-lead Electrocardiogram
eCRF	Electronic Case Report Form
E/e'	Derived left ventricular filling pressure
HCSD	Highest Confirmed Safe Dose
HF	Heart Failure
IP	Investigational Product
λ_z	Elimination rate constant
IVC	Inferior Vena Cava
IVRS/IWRS	Interactive Voice/Web Response System
LVEDV	End Diastolic Left Ventricular Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	End Systolic Left Ventricular Volume
MedDRA	Medical Dictionary for Regulatory Activities

NCA	Standard Non-compartmental Analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SV	Stroke Volume
SVR	Systemic Vascular Resistance
TEAE	Treatment-emergent Adverse Event
TLF	Tables, Listing, and Figure
$t_{1/2}$	Terminal half-life
t_{max}	Time to C_{max}
V_z	Volume of distribution

I. Introduction

A. Background

JK07 is a recombinant fusion protein consisting of a human neuregulin-1 (NRG-1) active domain and an anti-human epidermal growth factor receptor 3 (HER3) monoclonal antibody, thus limiting HER3-mediated gastrointestinal toxicity and oncogenic potential while preserving/activating the HER4-mediated cardiovascular potential.

The main purpose of the study is to evaluate the safety, tolerability, immunogenicity, and pharmacokinetics (PK) of JK07, administered intravenously to subjects with heart failure (HF) with reduced ejection fraction (HFrEF ≤ 40%). Change in left ventricular ejection fraction (LVEF), potential predictive biomarkers of response to JK07, and changes in QT interval will also be explored.

The protocol for Study JK07.1.01 describes the general approach to analysis of data from the study. This analysis plan describes additional details needed to complete such an analysis.

B. Purpose of the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is based on the JK07.1.01 study Protocol Amendment 3.0, providing additional details concerning the statistical analyses outlined in the protocol and reflecting any changes to the protocol.

This SAP will govern the analysis of data from this study. This plan contains definitions of analysis populations, derived variables, data handling rules, format of data presentation and statistical methods for the safety, pharmacokinetic (PK), and pharmacodynamic (PD) analyses. The plan may be modified until the time of database lock. The database will be locked after medical/scientific review of the data has been completed, protocol deviations have been identified, and the data have been declared clean. The purpose of the SAP is to ensure the credibility of the study findings by pre-specified statistical approaches to the study data prior to the database lock. This plan will not repeat all the definitions given in the protocol but will provide further details of summaries and analyses planned therein. Any deviations from the analysis plan, including any after the time of database lock, will be documented as such in the study report. Table, Listing, and Figure (TLF) shells are provided in a separate, accompanying document. The SAP will take precedence over the protocol.

II. Protocol Objectives

A. Primary

To assess the safety and tolerability profile, including immunogenicity, of JK07, administered intravenously according to protocol-defined dosing regimen.

B. Secondary

To determine the pharmacokinetic (PK) characteristics of JK07 administered intravenously according to protocol-defined dosing regimen.

C. Exploratory

- Explore left ventricular and systemic vascular resistance (SVR) performance indices measured by 2-dimensional transthoracic echocardiography (2D-TTE) of JK07, as change from baseline compared with placebo.
- Explore potential predictive biomarkers of response to JK07 in this dosing regimen.
- Explore relationship between JK07 plasma concentrations, if any, and changes in QT intervals during dosing.

III. Study Endpoints

A. Primary

- Incidence and severity of treatment-emergent adverse events (TEAEs) and their relationship to the investigational product (IP).
- 12-lead electrocardiogram (ECG) parameters (heart rate, PR, QRS, QT, QTcF) change from baseline derived as mean from triplicate ECG recording as well as QT and QTcF outlier analyses.
- Change from Baseline in the incidence of rhythm abnormalities (retrieved from telemetry readings for 48 hours postdose).
- Change from Baseline in Laboratory parameters (hematology, chemistry, coagulation, and lipid panels)
- Immunogenicity:
  - Incidence of early and delayed-type hypersensitivity responses
  - Presence of serum anti-JK07 antibodies (confirmed positive antibody response, titer, neutralizing antibodies)
- Change from Baseline in Vital Signs (Blood Pressure, Temperature, Heart Rate, Respiratory Rate)

- Relationship between Vital Signs (Blood Pressure, Temperature, Heart Rate, Respiratory Rate) and JK07, comparing with relationship between Vital Signs and Placebo

B. Secondary

Pharmacokinetic parameters of intact JK 07 including, but not limited to:

- Maximum Concentration Observed (C_{max})
- Time to C_{max} (t_{max})
- Area under the concentration-time curve to the last quantifiable concentration and extrapolated to infinity [$AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$]
- Half-life ($t_{1/2}$)
- Elimination rate constant (λ_z)
- Systemic clearance (CL)
- Volume of distribution (V_z)

Surrogate measurement of intact JK07 will be carried out through detection of both the JK07 antibody domain and the JK07 NRG-1 peptide fragment in the evaluation of pharmacokinetic parameters.

C. Exploratory

Microbubble contrast-enhanced 2-dimentional transthoracic echocardiography (2D-TTE) results:

- Ejection fraction (LVEF)
- Multiple 2 and 4-chamber left (LV) and right ventricular (RV) dimensions, including:
    - end systolic left ventricular volume (LVESV)
    - end diastolic left ventricular volume (LVEDV)
    - left atrial area and volume
    - valvular insufficiency and/or gradients

Multiple calculated monitoring parameters using velocity and flow measurements entered by sites, including:

- Stroke volume (SV)
- Cardiac output (CO)
- Derived left ventricular filling pressure (E/e')

- LV Circumferential Shortening (CS)

Biomarker concentrations:

- Observed value and change from baseline in the following
  - Additional biomarkers: hsCRP, troponin-I and/or hs-troponin T, CPK, CPK-MB, and lactate dehydrogenase.
  - Exploratory biomarkers: NT-proBNP, total BNP

Plasma concentrations:

- Concentration-QT correlation performed on baseline-corrected QTcF time matched with PK.

IV. Study Design

A. Design Overview

This is a phase 1, randomized, double blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, immunogenicity, and pharmacokinetics (PK) of JK07 in subjects 18 to 80 years of age of chronic heart failure (HF) with reduced ejection fraction (HFrEF) ≤ 40%.

Initially 5 cohorts are planned with the option to expand the study to a total of 7 cohorts. The size of the cohorts will range from 5 to 9 subjects. Each cohort will include a single active unblinded sentinel subject receiving a single introversive dose of JK07 prior to randomizing JK07 or placebo administration in the remaining of the cohort.

Approximately 8 investigators and study centers are expected to participate in this study. A maximum of 63 subjects will be enrolled into dose escalation cohorts. Five dose escalation cohorts are planned. Two additional cohorts may be added per the Data Review Committee (DRC) decision (total up to 7 cohorts). The details of the treatment design are in the protocol Amendment 2, section 4.1. In summary:

- For each dose level, the DRC will evaluate the sentinel subject's safety data for clinical effects and dose limiting adverse events (DLAEs) and decide whether to randomize and apply treatment to other subjects in this cohort at JK07: placebo = 3:1.
- When a clinical effect observed in a subject (sentinel subject or randomized subject), the DRC will decide whether to proceed with the trial in the cohort as planned, expand the cohort (up to a maximum of 9 subjects in total, i.e. 1 open-label JK07 sentinel subject, and 6:2 [JK07: placebo] randomized, double-blind subjects), stop the trial, or reduce the dose level.

- The DRC evaluates the safety data of all subjects in the evaluation period (at least 15 days and up to 180 days following the administration of the IP) and decides whether to proceed dose escalation.

The study schema is presented in Figure 1.

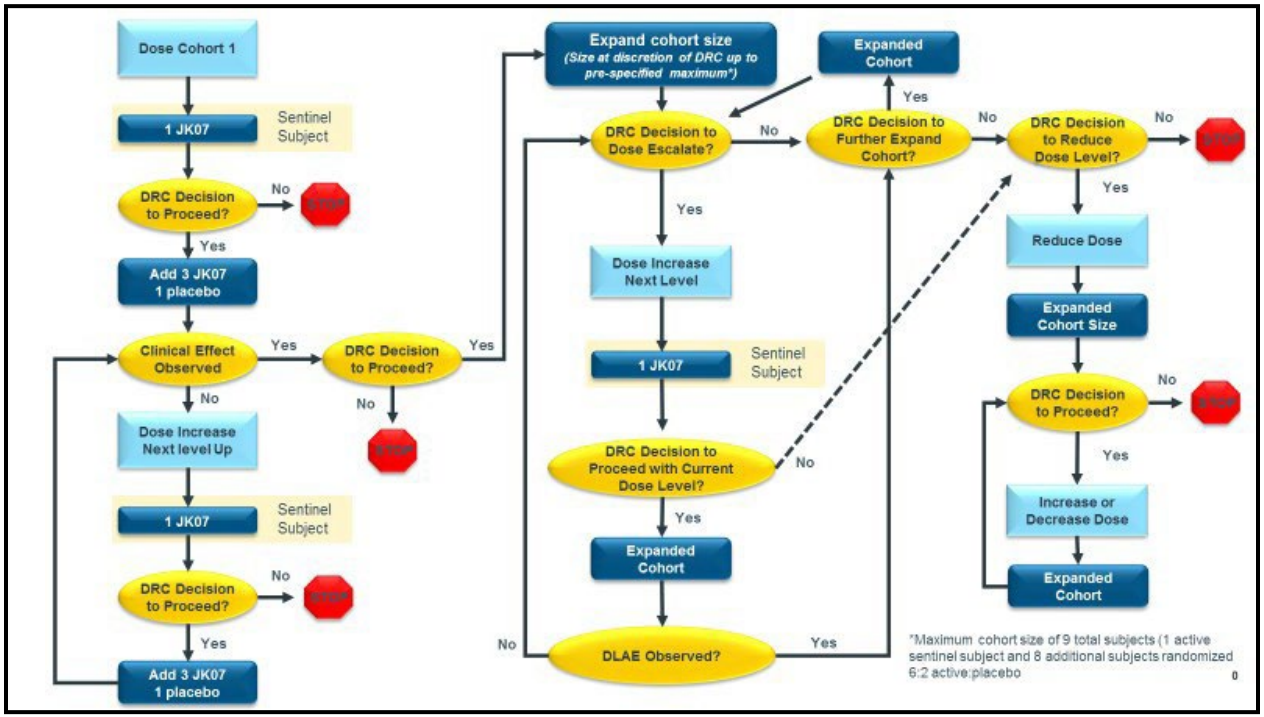

Figure 1 Study Schema

The JK07 dose level of which are shown in Table 1. The process above will proceed until the highest planned dose level (1.08 mg/kg) is reached or the DRC decides not to escalate dose further. Two additional higher cohorts may be added as per the DRC recommendation (total up to 7 cohorts with the highest JK07 dose administered not to exceed 2.5 mg/kg without further amending the protocol. DRC may decide to reduce the amount of dose in cohort 6 and cohort 7 based on the results of the previous cohorts. They may also decide to proceed with a cohort of decreased dose level (which may be pre-assigned dose level or not). Following a dose reduction, the DRC may

subsequently proceed with another cohort with reduced or increased dose level. A sentinel subject is required only if the selected dose level is above the previous Highest Confirmed Safe Dose (HCSD).

Table 1 Dose Levels

Cohort	Dose level of JK07
Cohort 1	0.03 mg/kg
Cohort 2	0.09 mg/kg
Cohort 3	0.27 mg/kg
Cohort 4	0.54 mg/kg
Cohort 5	1.08 mg/kg

Subjects' safety/tolerability data in at least the first 15 days of the study will be used for DRC's decision in whether to escalate to the next dose level. Preliminary PK results, and/or PD/biomarker results will also be taken into consideration if available and applicable. The DRC determines whether an AE observed after JK07 administration is DLAE and monitors DLAEs throughout the study. After Day 30, only SAEs deemed at least possibly related to the IP or study procedures will be captured and may be taken into consideration for dose escalation where applicable. In addition, subjects withdrawn due to an adverse event (AE) prior to the IP administration will be replaced.

B. Study Population

Individuals eligible to participate in this study must meet the criteria listed in Sections 5.1 and 5.2 of the Protocol.

All relevant medical and non-medical conditions will be taken into consideration when the decision is made upon whether this Protocol is suitable for a subject. Eligibility criteria may not be waived.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

C. Sample Size

Approximately 8 investigators and study centers are expected to participate in this study. A maximum of 63 subjects will be enrolled in the dose escalation cohorts. Five dose cohorts are planned. Two additional cohorts may be added as per the Data Review Committee (DRC) recommendation (total up to 7 cohorts) to receive IP.

For this study, no prospective calculations of statistical power have been made. The sample size is not based on statistical considerations but is typical for studies of this nature and is considered adequate to characterize the distribution of the planned endpoints. Any statistical testing will be considered exploratory and descriptive.

D. Treatment Randomization

Double blind randomization with placebo control is employed in this study to minimize bias. All subjects other than sentinel subjects will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each study center. Study treatment will be administered by the site.

For those subjects other than sentinel subjects, prior to randomization each subject will be assigned a unique number (randomization number) in ascending numerical order at each study center. The randomization number encodes the subject's assignment to either JK07 or placebo, according to the randomization schedule generated prior to the study by the Randomization Biostatistician at IQVIA Biotech. Each subject will be dispensed blinded study treatment, labeled with his/her unique randomization number on Day 1 of the study.

The details of randomization and unblinding plan and randomization schedule are documented separately.

Subjects will be randomized to study treatment at cohort level. After a sentinel patient is enrolled, each cohort will randomize 4 subjects in a 3:1 ratio to JK07 vs. Placebo. Subject stratification is not required.

V. General Analytical Considerations

A. Data Sources

Data are recorded on electronic Case Report Forms (eCRF), entered into the study's electronic data capture system (EDC), unless it is data that is being transmitted to the Sponsor or designee electronically. Laboratory Data will be transmitted to the Sponsor by Q^2 Solutions.

Statistical analysis will be performed following IQVIA Biotech standard operating procedures and on the IQVIA Biotech computer network. All statistical analyses will be performed using SAS Version 9.4 with program code prepared specifically for the project by qualified IQVIA Biotech statisticians and SAS programmers.

B. Definition of Baseline

This is a single-dose study. Unless otherwise specified, baseline is defined as the last non-missing measurement prior to study IP administration. Change from baseline will be calculated as post-baseline values minus baseline values.

C. Study Day

Day 1 is defined as the date of treatment. Study day is calculated relative to the date of Day 1. The day before Day 1 is Day -1.

- If an event occurs after Day 1, Study Day = Event Date – Date of Day 1 +1;
- If an event occurs prior to Day 1, Study Day = Event date – Date of Day 1.

D. Missing Data

Unless stated below, no imputation will be performed on missing safety and efficacy data, Missing data are simply noted as missing or "-" in tables and listings. If a baseline value is missing, change from baseline will not be calculated.

Missing or Partial Heart Failure Diagnosis Date. Partial heart failure diagnosis dates will be imputed in order to calculate the disease duration.

- A completely missing diagnosis date will not be imputed.

- A heart failure diagnosis date missing the month and day will be imputed as Jan 1st of the year.
- A heart failure diagnosis date missing the day will be imputed as the 1st of the month.

Missing Dates in Adverse Events form and Concomitant Medications form. Every effort will be made to avoid missing/partial dates in on-study data including AE and medication start and stop dates. Dates from these forms will be reported in listings as collected.

AEs that cannot be definitely determined as occurring prior to study IP administration will be counted as treatment-emergent adverse events (TEAEs) unless either the partial start date or a partial or complete end date documents the AE as occurring prior to treatment. Partial dates of AEs will be imputed as follows:

- Completely missing start date will not be imputed, and the event will be considered treatment-emergent unless the answer to "Did the event occur during or after study drug infusion?" is "No, event is not treatment emergent" on the Adverse Events CRF form.
- Start date missing both the month and day will be imputed as:
    - The IP administration date if the year of the start date is the same as that of the IP administration date.
    - Otherwise, Jan 1st of the year of the start date will be used.
- Start date missing the day will be imputed as:
    - The IP administration date if the year and month of the start date are the same as that of the IP administration date.
    - Otherwise, the 1st day of the month of the start date will be used.
- Partial or missing AE stop dates will not be imputed.

If the answer to "Did the event occur during or after study drug infusion?" is "Yes, event is treatment emergent" on the Adverse Events CRF form, the event will be considered treatment-emergent.

Partial dates entered on the Concomitant Medications (CM) form will be imputed as follows, for the purposes of determining whether the record is a prior or concomitant medication:

- Completely missing stop date will not be imputed. Medications will be considered as concomitant.
- Stop date missing both the month and day will be imputed as Dec 31st of the year of the stop date.
- Stop date missing the day will be imputed as the last date of the month of the stop date.

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead. If there is no date of death in the EDC for a subject and the planned imputed date is later than the End of Study date, then the End of Study date will be used for the stop date.

E. Multiple Study Centers

No adjustment for study center is planned. Data from all investigational sites will be pooled in the analyses.

F. Covariate Adjustment in Primary Analysis

No covariate adjustments are planned.

G. Sample Size Reassessment

Not Applicable.

H. Interim Analyses

No formal interim analyses are planned. Handling of the safety results and the data reports for DRC are described in the DRC Charter. Pharmacokinetic parameters will be calculated using available JK07 concentrations and scheduled sampling times.

I. Test Sizes

Not Applicable.

J. Multiple Comparisons

Not Applicable.

K. Analysis Populations

Five (5) analysis populations will be defined for use with various analyses:

- Safety Evaluation Population: subjects who are randomized and have a dose of IP (either JK07 or placebo) administered. Subjects will be analyzed according to the treatment they received.

- Dose-Limiting Adverse Event (DLAE) Evaluation Population: all subjects in the safety population who have a dose of IP (either JK07 or placebo) administered and have completed the 15-day DLAE follow-up period (Day 1 to Day 15). Subjects will be analyzed according to the treatment they received.

- PK Evaluation Population: subjects who have a dose of IP (either JK07 or placebo) administered and have at least one quantifiable IP plasma concentration collected after dose IP administration, with no major protocol deviations which are considered to affect the PK results. This population will be used for the PK concentration data summaries and listings.

- PK Parameter Population: subjects from PK Evaluation Population who had at least 1 PK parameter of JK07 available. Subjects will be excluded from the PK analysis if they have too few serum concentration data points to allow accurate assessment of PK parameters. This population will be used for the PK parameter data summaries and listings.

- Exploratory PD/biomarker Evaluation Population: The PD population will include all randomized subjects who have a dose of IP (either JK07 or placebo) administered and have at least one post-baseline exploratory PD endpoint collected post-dose without any major protocol deviations which are considered to affect the PD results. The PD population will be used for the analyses/summaries of PD/biomarker endpoints. Subjects will be analyzed according to the treatment they received.

Criteria for major protocol deviations excluding subjects from the PK or PD evaluation population will be determined based on a blinded review of the data prior to the unblinding of the study, as defined in the Clinical Monitoring Plan. Subjects with protocol deviations affecting PK or PD results will be determined prior to the database lock.

L. Subgroups of Analysis Populations

No subgroup analyses are planned.

M. Data Display Characteristics

Data displays produced for this study will include three types – summary tables, data listings, and figures. Summary tables and figures will be produced as specified in the following section. Data listings will list the data recorded on the electronic case report form (eCRF) as defined in Study Data Tabulation Model (SDTM) or derived for each subject. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Unless otherwise specified, listings will be ordered by treatment, cohort, subject number, and date/time of assessment. Data listings will not display subject initials.

Subjects who received placebo will be combined into one treatment group for purposes of analysis. Therefore, the treatment groups will be the following (as applicable depending on the open cohorts):

- JK07 0.03 mg/kg
- JK07 0.09 mg/kg
- JK07 0.27 mg/kg
- JK07 0.54 mg/kg
- JK07 1.08 mg/kg
- Placebo (corresponding to the pooled group of subjects receiving the placebo)

The PK and exploratory PD analyses will be performed at CR Medicon, and the other analyses will be performed by qualified IQVIA Biotech statisticians and SAS programmers. SAS 9.4 or higher (SAS Institute, Inc., Cary, North Carolina) will be employed for all the statistical analyses.

Pharmacokinetic parameters will be derived using standard non-compartmental analysis (NCA) methods with Phoenix WinNonlin® Version 8.0 (Certara, L.P. Princeton, New Jersey, United States of America [USA]) at Nanjing CR Medicon Pharmaceutical Technology Co., Ltd.

Summary tables will display descriptive summary statistics calculated for each of the treatment groups, unless described otherwise in following sections. Results will be summarized by treatment and overall, where appropriate.

The following descriptive statistics will be used when applicable to summarize the data unless otherwise specified:

- Continuous variables: number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min) and maximum (max)
- PK concentrations and parameters: coefficient of variation (%CV), geometric mean (geom. Mean) and geometric %CV (geom. %CV), except t_{max} which will only be presented with min, median, and max.
- Categorical variables: Categorical data will be summarized with the number of non-missing values and the frequency of each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise. Percentages will be presented to one decimal place, except 100% which will be displayed without any decimal places, or stated otherwise.

- The mean value will be presented one decimal place more than raw. The standard deviation will be presented two decimal places more than raw data, except %CV and geom. %CV will be presented with one decimal place. The minimum, maximum, and median values will be presented to the same precision as the raw data. A maximum of four decimal places will be presented.
- Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.
- The NCA parameters will not be reported to any greater precision than that of the observed concentration data. Default reporting in text and tables is 3 significant figures except for time related parameters. Time related parameters will be reported to two decimal places.

Subjects with protocol deviations/violations affecting PK/PD results will be determined prior to the database lock.

VI. Subject Accountability

A. Demographics and Baseline Characteristics

Data collected on the following characteristics at Screening or Baseline will be summarized in a table presented in a listing by actual treatment group for all randomized subjects:

- Age (Age will be calculated as the number of years elapsed between birth date and the date of the screening visit, adjusted for whether the birthday has passed as of the final day of the screening visit).
- Age categories (<65 vs. >=65) and (<75 vs. >=75)
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight at baseline (kg)
- Body Mass Index (BMI) at baseline: Calculated as the individual's body mass (kg) divided by the square of their height (m) with the unit of kg/m^2
- Time from NYHA Diagnosis to Informed Consent (months): calculated as (NYHA Diagnosis Date – Informed Consent Date) / 30.417
- NYHA Class of HF Diagnosis at baseline

Demographic and baseline characteristic data will also be presented in a by-subject listing.

B. Disposition

The summary table of subject disposition will include all screened subjects and display the following by treatment (if applicable):

- Number of subjects who screened
- Number and percentage of subjects who failed screening with the failed inclusion/exclusion criteria as the reason of screen failure
- Number of randomized subjects
- Number and percentage of randomization failures, using the number of randomized subjects as denominator for the percentages. Randomization failure subjects are those that passed initial screening assessments and were randomized into the trial but failed out on Day 1 due to any Day 1 labs/assessments making them ineligible (e.g., they had become pregnant, lab values were unacceptable per exclusion criteria, any morning test results were exclusionary).

  Subjects who discontinued the study with discontinuation reason = "Randomization Failure" on the Study Discontinuation Form will be counted as randomization failures in the summary.
- Number and percentage of subjects in each analysis population, using the number of randomized subjects as denominator.
- Number and subjects discharged later than Day 3.
- Study completion status (completed or permanently discontinued). List the number and percentage of subjects for each reason of discontinuation, using the number of randomized subjects as denominator for the percentages.
- Number of days in the study among the randomized subjects, calculated as: End of Study Date (completion or discontinuation) – IP administration date + 1.

The following termination reasons as recorded on the End of Study form will be considered:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Study terminated by sponsor
- Subject non-compliance/protocol violation
- Withdrawal of consent

A listing will present subject enrollment, with the protocol version for which subject was enrolled, and the inclusion in each analysis population.

A separate listing by subject will display the details of screen failure reason of each subject.

A by-subject listing will display subject disposition. All randomized subjects will be included.

C. Protocol Deviations

Protocol Deviations will be summarized with number (and percentage) of subjects in each protocol deviation category in a table by treatment and cohort. Minor and major deviations will be displayed separately. In addition, a listing will be presented for subjects with protocol deviations, with the date of screening, sentinel or randomized, date of randomization (if applicable), cohort, treatment received (if applicable), and details of protocol deviation.

VII. Safety Analyses

All safety analyses will be performed on the Safety Evaluation Population. Analyses specific to DLAEs will use the DLAE Evaluation Population. The subjects given placebo are also included specifically to compare against JK07 such that the background disease from the treatment effects in the study population may be assessed and better discerned. All safety data will be evaluated based on Common Terminology Criteria for Analysis Events (CTCAE) Version 5.0, and listed by cohort, subject, and visit. Categorical data will be summarized in count and percentage by cohort and category.

For laboratory test results, vital signs, ECG results, weight, and body mass index (BMI), observed values and change from baseline (CFBL) will be summarized by cohort and visit using descriptive statistics.

A. Exposure

Exposure to study treatment (JK07 or Placebo) will be listed by subject and will present the planned dose and actual dose (including units), and the date and time of infusion, and interruption and the reason for interruption (if applicable).

B. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the study IP. A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened in severity on or after the date of the IP administration (Day 1). All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 and will be summarized by System Organ Class (SOC) and Preferred Term (PT).

All adverse events will be graded using the Common Terminology Criteria for Analysis Events (CTCAE) Version 5.0, ranging from 1 to 5: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life threatening or disabling), or Grade 5 (Death). If the grade is missing for a TEAE, the event will be counted as grade 3 in the summary tables.

Subjects will be observed for possible allergic reactions following the treatment and will be monitored for DLAEs throughout the study. All AEs, including SAEs, will be collected from the time of enrollment until 30 days after the treatment. Following the first 30 days, only SAEs that are at least possibly related to the treatment or study procedures will be collected.

An overall summary for subjects with AEs will be summarized by cohort (each dose level of JK07 and the placebo group pooled across all the treatment groups) including the following subsets. The number of events and subjects will be included.

- **AEs**
- **TEAEs**
- TEAEs related to study drug. This subset includes TEAEs with a drug relationship of "possibly related" and "definitely related", or a missing drug relationship.
- Serious TEAEs
- Serious TEAEs related to study drug. This subset includes Serious TEAEs with a drug relationship of "possibly related" and "definitely related", or a missing drug relationship.
- TEAEs leading to study drug permanent discontinuation
- TEAEs leading to study drug infusion interruption. This subset includes TEAEs with an answer "Yes" to the question "Was infusion interrupted?" on the Infusion Drug Administration form.
- Treatment-emergent infusion site reactions. This subset includes TEAEs with an answer "Yes" to the question "Was this an infusion site reaction?" on the AE form
- TEAES by maximum grade. Only present the number of subjects for this subset.

- **DLAEs**
- DLAEs related to study drug. This subset includes DLAEs with a drug relationship of "possibly related" and "definitely related", or a missing drug relationship.
- Serious DLAEs
- Serious DLAEs related to study drug. This subset includes Serious DLAEs with a drug relationship of "possibly related" and "definitely related", or a missing drug relationship.
- DLAEs leading to study drug permanent discontinuation
- DLAEs leading to study drug infusion interruption. This subset includes DLAEs with an answer "Yes" to the question "Was infusion interrupted?" on the Infusion Drug Administration form.
- DLAEs with infusion site reactions. This subset includes DLAEs with an answer "Yes" to the question "Was this an infusion site reaction?" on the AE form
- **SAEs**

In addition, summary tables will present the number and percentage of subjects and events by treatment group and overall, ordered by System Organ Class (SOC), Preferred Term (PT), and by the following classes, using the Safety Evaluation Population:

- SAEs
- SAEs having Infusion Site Reaction
- TEAEs
- TEAEs leading to study drug infusion interruption
- TEAEs leading to study drug permanent discontinuation
- TEAEs related to study drug
- TEAEs having Infusion Site Reaction
- DLAEs
- TEAEs by maximum severity (i.e. by CTCAE grading)
- TEAEs by maximum relationship to study drug

The DLAEs will be summarized by SOC and PT for the DLAE Evaluation Population.

At each level of summary of subject, a subject will be counted once if he/she reported one or more events. Specifically:

- For summary of TEAEs by severity, a subject will be classified according to the most severe event.
- For summary of TEAEs by relationship to study drug, a subject will be classified according to the closest relationship.

- For summary of SAEs by outcome, a subject will be classified according to the worst outcome.

For summary of TEAEs by action taken with study drug, a subject will be classified as "Drug Permanently Discontinued," "Dose Interrupted," "Other Action," or "Dose Not changed."

All AEs will be presented in a by-subject listing, detailing in the verbatim term given by the investigator, PT, SOC, start date, end date or ongoing, severity, seriousness, outcome, relationship to the study drug, and action taken. Treatment-emergent infusion site reactions, TEAEs leading to drug permanently discontinuation, and TEAEs related to study drug, DLAEs, SAEs, and deaths will be presented in separate listings respectively.

C. Clinical Laboratory Results

Laboratory test results include hematology; chemistry (including serum glucose on the Fingerstick Glucose Multi - Local form in the CRF); coagulation, urinalysis, analyzed by the local labs and collected in the EDC system. The severity of laboratory abnormalities will be graded using the CTCAE whenever possible.

Summaries of actual values and changes from baseline will be summarized descriptively by treatment group and overall for each scheduled visit and each timepoint where applicable.

For all laboratory tests, shift tables summarizing the Principal Investigator's assessment of abnormality – i.e. Normal, Abnormal Clinically Significant (CS), Abnormal Non-Clinically Significant (NCS) – will be displayed. The counts and percentages of subjects who were normal at baseline and became abnormal subsequently, or the opposite, will be presented.

All laboratory test results will be presented in by-subject listings, with collection date, result and unit, normality and clinical significance, change from baseline, and the CTCAE grading wherever possible, at each visit and timepoint (where applicable). Abnormal results will be presented in a separate listing.

D. Vital Signs

Vital sign parameters, including the weight, body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure, will be summarized using descriptive statistics by cohort at each visit, by treatment group (and placebo) and overall. Absolute values and changes from baseline will be presented.

Vital signs will also be presented in a by-subject listing, detailed in result, unit, CFBL.

E. Medical History

Medical History will be coded using MedDRA version 22.1, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety Evaluation Population by treatment group and overall.

Medical History will also be presented in a by-subject listing, detailed in SOC, preferred term start date, and end date (or ongoing). For each subject, the subject number will be displayed only once.

F. Surgical History

A listing will be generated for subjects with surgical history, detailed in location, description, start date and end date.

G. Electrocardiograms (Digital 12-Lead Triplicate ECGs)

Each subject will receive triplicate, twelve-lead ECG evaluations including HR, PR, QRS, QT (uncorrected), QTcF (corrected), and an overall evaluation of normality and clinical significance during screening and starting on Day 1 following admission to the hospital. ECG data will be collected, reviewed and analyzed by a Central Reader and the Principal Investigator. Findings identified by the Central Reader will be listed only for the concerned subjects.

The triplicate measurements of each subject at each timepoint will be averaged before summary. The observed values and mean CFBL of these ECG measurements will be summarized by cohort at each timepoint using descriptive statistics including 90% confidence interval of the mean. The overall ECG evaluation results, alone with shift from baseline (from abnormal to normal, or from normal to abnormal) will be summarized in a separate table by each treatment cohort and aggregated placebo at each visit. Results collected by the Central Reader and the Principal Investigator will be displayed separately.

Categories of QT and QTcF intervals (431-450 ms and >450 ms for males, and 451-470 and >470 ms for females) and CFBL in QT and QTcF intervals (30-60 ms, and >60 ms) will be summarized using counts and percentages by cohort and sampling time. Additional corrections to QT may be analyzed in a similar way. Results collected by the Central Reader and the Principal Investigator will be displayed separately.

A significant proportion of HFrEF patients with pre-existing implanted functional atrio-ventricular (A-V sequential) pacemakers and cardiac resynchronization devices (CRT), may be unevaluable with respect to QT/QTc analysis due to the inherently prolonged and fixed QRS configuration. The presence of these devices, which include defibrillators, is not considered an increased safety risk.

The electrocardiogram analysis will be conducted by cohort in the following two groups and presented separately:

- All subjects
- Subjects not having pacemakers identified by the contents of ECG overall evaluation. If none of the ECG evaluations have the word "pace" or "paced" or "pacemaker" or "electronic" or "electronically" or "resynchronization" or "CRT" for a subject, the subject is considered not to have a pacemaker or CRT (cardiac resynchronization therapy).

A by-subject listing will be presented with observed ECG evaluations and CFBL at each visit, detailed in observation date, timepoint, value of each measurement, whether the subject had an implantable pacing device, and the overall assessment. The abnormal ECG results will be listed separately. In addition, categories of QT and QTcF records will be presented in a separate listing. An additional listing presenting Central Reader's findings will be produced, only for subjects presenting findings.

H. Incidence of Emergent Rhythm Abnormality (Arrhythmias)

Based on the primary endpoint of rhythm abnormalities and available data, incidence of emergent rhythm abnormalities will be analyzed.

Subjects will be supplied with an e-Patch to monitor heart rhythm for continuous 14 days during the screening period. Clinically significant rhythm abnormalities during the screening period will result in exclusion from randomization on the basis of exclusion criteria 12 (page 37 of Protocol Amendment 3). Continuous telemetry monitoring will start as soon as practicable after hospital admission on Day 1 and prior to the treatment. It will continue until 48 hours after the end of study drug infusion on Day 3.

The percentage of emergent clinically significant arrhythmias detected by telemetry will be compared, both overall and on a per day basis following the administration (i.e. 0-24 hours and 24-48 hours), between each treatment group and placebo and will be presented in a summary table.

A listing will be generated for all subjects with incidence of rhythm abnormality.

I. Prior Medications or Concomitant Medications

Any medication, vaccine, or therapy (including over-the-counter or prescription medicines, vitamins, and/or [herbal] supplements) that a subject receives within 30 days before informed consent, or receives during the study, must be recorded in the eCRF along with the reason for use, the dates of administration including start and end dates, and the dosage information including dose and frequency.

Prior Medications (PMs) are defined as any medication that starts and stops before Day 1 (IP administration day).

Concomitant Medications (CMs) are defined as any medication that:

- Starts prior to Day 1 and continues after Day 1
- Starts between Day 1 and early termination visit or end of study visit

Medications will be coded using the Sep 2019 version of WHO Drug. Prior medications and Concomitant Medications will be summarized separately by treatment group and overall, and organized to display the Anatomical Therapeutic Chemical (ATC) Class of each coded medication and, within that, the Preferred Term (PT) of the coded medication. The summary tables will display counts and percentages of subjects who reported at least one prior or concomitant medication in each represented PT. Prior medications that ended more than 30 days before the informed consent date will not be included in the summary table.

A by-subject listing will be presented with verbatim term given by the investigator, PT, ATC, indication (for adverse event, medical history, or prophylaxis), dose and units, frequency, route of administration, and whether it is prior medication or concomitant medication. For prior medications, the number of days between the medication's end date and the informed consent date will be displayed, and medications that ended more than 30 days before informed consent will be flagged. Within each subject, medications will be sorted by descending frequency of ATC and Preferred Term.

VIII. Pharmacokinetic Analyses

The analyses described in this section will be performed at CR Medicon.

A. PK Data Handling

The following data handling conventions apply to computations of PK concentration descriptive statistics:

- Observed concentrations that are below the lower limit of quantitation (BLQ) will be set to 0. The calculated mean concentrations are used in overlaid mean (± SD) concentration time profiles.
- If the calculated mean concentration is BLQ, the mean value shall be reported in the outputs as 0, SD and CV% shall be reported as ND (not determined). Min, median, and max may be reported. If any of these values are BLQ, it shall be reported as less than the lower limit of quantitation (< LLOQ) value.

The following data handling conventions apply to PK parameter calculation and individual serum concentration-time profiles.:

- Observed concentrations that are BLQ will be assigned a value of zero if they are prior to C_{max}. Observed concentrations of BLQ that occurs after C_{max} will be set to missing.
- The PK parameters for JK07 will be listed and included in the parameter summaries and statistical analyses if the predose concentration value of serum JK07 is not greater than 5% of C_{max} in the profile. If the predose concentration value of serum JK07 is greater than 5% of C_{max} in the profile, the profile will be reviewed in conjunction with JK07 serum concentrations measured at other timepoints prior to dosing on a case-by-case basis to evaluate if exclusion of data is warranted.
- The predose (within 30 minutes prior to start of infusion) value will serve as concentration at time 0 hour.
- Missing postdose values will be treated as missing and evaluated for potential impacts on PK (e.g., around C_{max}) and exclusions may be warranted for affected parameters prior to data analysis.

B. Calculation of PK Parameters

PK parameters for serum JK07 will be estimated by NCA methods using actual elapsed time from start of the IV infusion. A minimum of 4 quantifiable after dose concentrations will be required for all calculations.

If appropriate and feasible, the PK parameters listed in Table 2 will be calculated but not limited to for serum JK07 concentrations obtained from PK Evaluation Population:

Table 2: Parameters for Pharmacokinetic Analysis

PK Parameters	Definition
C_{max}	Maximum concentration obtained directly from the observed concentration versus time data.

PK Parameters	Definition
t_{max}	Time to C_{max}.
$AUC_{(0\text{-inf})}$	Area under the serum concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation. If the percentage of AUC obtained by extrapolation is greater than 20%, $AUC_{(0\text{-inf})}$ and related parameters (CL and V_z) will be listed but not included in any summaries or inferential analyses.
$AUC_{(0\text{-last})}$	Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
CL	Systemic clearance.
V_z	Volume of distribution.
$t_{½}$	Terminal half-life; a minimum of 3 points will be used for estimation.
λ_z	Terminal rate constant; if Rsq (adj) is <0.800, then λ_z, $t_{½}$, and related parameters will be listed but not included in any summaries or inferential analyses

In addition to the PK parameters presented above, dose normalized exposure parameters C_{max} and $AUC_{(0\text{-inf})}$ (or $AUC_{(0\text{-last})}$ if $AUC_{(0\text{-inf})}$ is not calculable in most subjects) will also be calculated. The lower and upper limits on time (λ_{z_lower} / λ_{z_upper}) for the data used in the calculation of λ_z, the numbers of points (No_points_λ_z) used in the calculation of λ_z and the Rsq (adj) will also be listed.

Calculated individual PK parameters of JK07 will be listed and descriptively summarized by active treatment and cohort for the PK evaluation population.

C. Statistical Analysis of PK Concentration Data

Individual observed serum concentration-time data for JK07 will be listed. Serum concentration of JK07 will be summarized using descriptive statistics by active treatment and cohort at scheduled time point for the PK evaluation population. Summary statistics including the number of observations (n), mean, SD, %CV, min, median, max, number of values below the lower limit of quantitation (n_BLQ), Geom. Mean and Geom. %CV will be calculated for all nominal concentration time points. All individual BLQ concentration values will be presented as 'BLQ' in the concentration tables and footnoted accordingly.

JK07 serum concentration-time profiles will be graphically displayed by active treatment and cohort on linear and semilogarithmic scales, as appropriate. Plots of individual values versus actual time grouped by active treatment and cohort (one plot for each cohort)

will be presented. Plots of overlaid mean (± SD) concentration versus nominal time grouped by active treatment and cohort will also be presented.

D. Statistical Analyses of PK Parameters

PK parameters for each subject in the PK parameter population will be listed and summarized using descriptive statistics by active treatment and cohort. Summary statistics including n, mean, SD, %CV, min, median, max, Geom. Mean and Geom. %CV will be calculated for serum JK07 PK parameters (except for t_{max} which will only be presented as min, median and max).

Scatter plots of individual values and Geom. Mean of PK parameters, $AUC_{(0\text{-inf})}$ (or $AUC_{(0\text{-last})}$ if $AUC_{(0\text{-inf})}$ is not calculable in most subjects) and C_{max} as well as dose-normalized exposure parameters versus dose will be presented.

The proportionality of the PK parameters such as C_{max} and $AUC_{(0\text{-inf})}$ (or $AUC_{(0\text{-last})}$ if $AUC_{(0\text{-inf})}$ is not calculable in most subjects) over the administered dose range may also be explored graphically using a power model by confidence interval criteria. This approach will be based on a linear relationship between the natural log-transformed PK parameter and log-transformed dose:

$$\ln(\text{parameter}) = \beta 0 + \beta 1 \cdot \ln(\text{dose})$$

Where, β0 is the intercept and β1 is the slope of the line.

The assessment involves a test of whether a 90% confidence interval of β1 fits within a pre-specified critical interval, normalized for the dose range, i.e. whether

$$1 + \frac{\ln(\theta_L)}{\ln(r)} < \beta 1 < 1 + \frac{\ln(\theta_H)}{\ln(r)}$$

where θ_L is the lower bound of the critical interval, r is the ratio of the highest dose to the lowest dose, and θ_H is the upper bound of the critical interval. For this analysis θ_L and θ_H will be chosen as 0.5 and 2.0[1], respectively, to reflect a practical assessment of approximate dose-proportionality. 90% confidence interval of β1 will be summarized.

In the case that dose-proportionality is not confirmed over the entire dose-range, linearity over a smaller dose range will be assessed.

A sample of SAS implementation code for analyzing dose proportionality is shown below:

```
* Assess the dose proportionality by using a power model
  with applying natural log transformation on parameters
  (AUC and Cmax) and dose;
proc mixed data=pk_dataset;
      class usubjid;
      model logpkval=logdose / ddfm=kr;
* logpkval and logdose correspond to the log transformed
  value of the PK parameter and dose, respectively;
      random usubjid;
* apply subject as random effect;
      estimate 'mean slope of logdose' logdose 1 /cl alpha=0.1;
* calculate 90% Confidence Interval for mean slope of logdose;
    ods output estimates=estimate;
run;
```

IX. Exploratory Pharmacodynamic Analysis

The analyses described in this section will be performed at CR Medicon.

A. Analysis of 2-dimensional Transthoracic Echocardiography (2D-TTE) and Biomarkers

Same as the non-PK/PD analysis, the subjects who received placebo will be combined into one treatment group for purposes of analysis. The baseline measure will be defined as the last non-missing measure prior to initiation of IP. Change from baseline will be calculated as post baseline value subtracted by value at baseline. Exploratory inferential comparisons to placebo may also be performed.

Results of the 2D-TTE and biomarkers and their change from baseline values (as applicable) will be listed and descriptively summarized by treatment at scheduled time point (details are in the Protocol JK07.1.01 – Amendment 3 Section 1.3, Schedule of Activities) Summary statistics including n, min, max, mean, SD and median will be calculated.

Values outside of the laboratory's reference range (i.e., those with low or high values) will be flagged in the listings if applicable.

B. Potential Effect of JK07 on QTc Prolongation[2]

For the analysis of a serum concentration to QT (C-QT) relationship, ECG values will be combined with the subject-specific, time-matched JK07 concentration assessments.

1. Baseline

The baseline value will be derived as mean from triplicate ECG recordings measured prior to initiation of IP. The baseline QTc should be included in the C-QTc model as a covariate.

2. Correction Formulae

Fridericia corrected QT interval (QTcF) = $QT/RR^{1/3}$, RR refers to a normalized heart rate of 60 bpm.

ΔQTcF refers to the predose baseline-corrected QTcF interval and ΔΔQTcF refers to the ΔQTcF interval corrected for placebo.

3. Exploratory Plots of Model

Subjects who received placebo will be combined into 1 treatment group for purposes of analysis. Basic assumptions can efficiently be evaluated using simple graphics to show that:

- No Effect of JK07 on change of HR

Plot of mean change from baseline in heart rate (ΔHR) and 2-sided 90% CIs vs. time by treatment.

Plot of mean change from baseline placebo-adjusted heart rate (ΔΔHR) and 2-sided 90% CIs vs. time by treatment.

- QTcF interval is independent of HR

Scatterplot of QTcF and RR intervals by treatment with linear regression line and 90% confidence interval.

- No time delay between drug concentrations and ΔQTcF

Plots of mean ΔΔQTcF and drug concentration and 2-sided 90% CIs vs. time by treatment.

Plot of mean ΔΔQTcF and 2-sided 90% CIs vs. concentration connected in temporal order by treatment.

A delay of mean ΔQTcF with respect to the C_{max} of the JK07 of > 1.5 hours is considered an indication of hysteresis unless all values of ΔQTcF are <5 msec.

- Linear C-QTcF relationship

Scatter plot of paired ΔQTcF vs. concentration data with smooth line and 90%confidence intervals and linear regression line.

4. QTcF-Concentration Model Analysis

If the exploratory plots indicate the modeling assumptions are met, an exploratory evaluation of C-QT relationship will be conducted using a linear mixed effects model, with the drug-free-corrected (i.e., predose-corrected) change from baseline in QTcF as the response variable. Independent variables will include the fixed effects time-matched JK07 serum concentration, treatment indicator (treatment = 1 for subjects receiving JK07, and 0 otherwise), time point as a categorical variable, influence of baseline on intercept and random effects for subject and time matched JK07 serum concentration.

$$\Delta QTc_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 TIME_k + \theta_4 (QTc_{ij0} - \overline{QTc_0})$$

$$\Delta QTc_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 TIME_k + \theta_4 (QTc_{ij0} - \overline{QTc_0})$$

Where:

$\Delta QTc_{ijk}\Delta QTc_{ijk}$ is the change from baseline in QTc for subject i in treatment j at time k.

θ_0 is the population mean intercept in the absence of a treatment effect.

$\eta_{0,i}$ is the random effect associated with the intercept term θ_0.

θ_1 is the fixed effect associated with treatment TRT_j (0 = placebo, 1 = active drug).

θ_2 is the population mean slope of the assumed linear association between concentration and $\Delta QTc_{ijk}\Delta QTc_{ijk}$.

$\eta_{2,i}$ is the random effect associated with the slope θ_2.

C_{ijk} is the concentration for subject i in treatment j and time k.

θ_3 is the fixed effect associated with time.

θ_4 is the fixed effect associated with baseline QTc_{ij0}.

$\overline{QTc_0 QTc_0}$ is overall mean of QTc_{ij0}, i.e., the mean of all the baseline (= time 0) QTc values. It is assumed the random effects are normally distributed with mean [0,0] and an unstructured covariance matrix G, whereas the residuals are normally distributed with mean 0 and variance R.

Estimation of model-derived $\Delta\Delta QTc\Delta\Delta QTc$ at concentrations of interest

Estimated mean $\Delta\Delta QTc(C) = \hat{\theta}_1 + C\hat{\theta}_2 \Delta\Delta QTc(C) = \hat{\theta}_1 + C\hat{\theta}_2$

Estimated SE = $\sqrt{var(\widehat{??}_1) + C^2 var(\widehat{??}_2) + 2C\ cov(\widehat{??}_1, \widehat{??}_2)}$

90% CI = Estimated mean $\Delta\Delta QTc(C) \pm t(0.95, df)$ $\times \Delta\Delta QTc(C) \pm t(0.95, df)$ ×Estimated SE

The upper bound of the 2-sided 90% CI will be compared with the regulatory threshold of 10 ms.

SAS code used for linear mixed effects model as below:

```
PROC MIXED DATA=dataset;
  CLASS time subjid trt;
        /* trt=1 for active and trt=0 for placebo */
  MODEL dQTc = trt conc time predoseQTc/DDFM=KR;
              /* conc=Concentration*/
  RANDOM intercept conc/SUBJECT=subjid type=UN;
RUN;
```

5. Model Evaluation

To assess the appropriateness of a priori choice of linear model between ΔQTcF and serum concentration, the following goodness of fit plot will be assessed:

- Quantiles of concentrations and ΔQTcF overlaid with slope of final model.

Model parameters are to be presented in tabular format showing the estimate, standard error of the estimate, *p* value and 90% confidence interval.

6. Model development for adapted C-QTc models

If the exploratory plots indicate the modeling assumptions are not met, additional modeling steps are recommended to determine objectively the appropriate C-QT model. When apparent differences in the time course and/or distribution of HR between on- and off-drug conditions are observed in exploratory plots, other approaches to evaluate QT/QT should be considered. In this case, one stand-alone modeling analysis plan (MAP) needs to be generated.

X. Exploratory Biomarkers

The analyses described in this section will be performed at CR Medicon.

The analysis of exploratory biomarkers will be performed using the exploratory PD/biomarker evaluation population. Descriptive summary statistics will be reported for the actual observed and change from baseline for the following biomarkers (hsCRP, troponin-I or hs-troponin T, CPK, CPK-MB, lactate dehydrogenase, NT-proBNP and total BNP) by treatment groups and visits (Day 1 pre-infusion, Day 2, 7, 15, 30, 60, 90, 135, 180 (or end of study visit)). Baseline values are those obtained at pre-infusion on Day 1.

Separate summaries will be produced for results collected by Local labs (in the EDC system) and by Central labs (by Q^2 vendor).

Exploratory biomarker results will be listed.

XI. Immunogenicity Assessments

The analyses described in this section will be performed at CR Medicon.

Subjects who received placebo will be combined into 1 treatment group for purposes of analysis.

Serum samples for the antibody assays will be collected at Day 1, 4, 7, 15, 30, 90 and EOS/180. Additionally, subjects who do not complete all required visits or withdraw from the study early are required to complete End-of Study/Early-Termination assessments. The serum samples for antibodies will be assayed for neutralizing antibodies.

Immunogenicity will be evaluated using descriptive statistics. The number and percentage of subjects for ADA and neutralizing antibodies results will be summarized by treatment at scheduled time point as well as all post-baseline visits. Percentages for the neutralizing antibody result are based on the number of positive ADA results at that visit. ADanalysisA titers of subjects who becomes antibody positive will be summarized by treatment and cohort as received along with nominal collection time. Summary statistics including n, min, max, mean and median will be calculated. In addition, incidence of early and delayed-type hypersensitivity responses will be summarized by ADA results (positive or negative) and by treatment.

Antibody information of subjects will be presented in the form of data listings.

XII. Changes from Protocol

Per Protocol section 9.4.3 Safety Analyses, the incidence of treatment-emergent abnormal vital signs should be summarized using descriptive statistics. However, no abnormality flag for vital signs was collected, therefore no specific table or listing for abnormal vital signs will be produced.

Note that abnormal and clinically significant vital signs will be registered as adverse events, as mentioned in the Protocol section 8.3.7: “Any emergent laboratory abnormality (e.g., clinical chemistry or hematology) or other abnormal assessment findings (e.g., ECG or vital signs) that meets any of the following criteria should be recorded as an AE or SAE”.

XIII. References

1. Hummel J, McKendrick S, Brindley C, et al. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. Pharmaceutical Statistics 2009; 8(1): 38-49.

2. Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. Journal of Pharmacokinetics and Pharmacodynamics 2018; 45: 383–97.