TITLE PAGE

Protocol Title:

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)

Protocol Number: JK07.1.01 Amendment 3

Product: JK07 (recombinant fusion protein consisting of a fully human anti-human epidermal growth factor receptor 3 [HER3] immunoglobin G1 [IgG1] and an active polypeptide fragment from human neuregulin-1 [NRG-1])

Short Title: Phase 1 Study of JK07 in Subjects with Heart Failure with Reduced Ejection Fraction (HFrEF)

Study Phase: Phase 1

Sponsor Name: Salubris Biotherapeutics, Inc.

Legal Registered Address: 45 West Watkins Mill Rd, Suite E, Gaithersburg, MD 20878

Regulatory Agency Identifying Number(s): IND 142367

Version	**Date**
Original	21 November 2019
Amendment 1	19 February 2020
Amendment 2	03 March 2020
Amendment 3	09 April 2021

SPONSOR SIGNATORY:

I have read this protocol in its entirety and agree to conduct the study accordingly:

DocuSigned by Samuel L Murphy
Samuel L Murphy | I approve this document 20-Apr-2021 | 13:42:20 PDT
80848BA47CF74988AFF76708E4094C73

20-Apr-2021 | 13:42:27 PDT

Sam Murphy, PhD — **Date**

Chief Executive Officer

Salubris Biotherapeutics

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20-Apr-2021 | 13:58:05 PDT

Neal Salomon, MD — **Date**

Consulting Chief Medical Officer and Medical Monitor

Salubris Biotherapeutics

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SUMMARY OF CHANGES

Summary of changes for prior amendments may be found in Section 11.0 Appendix 7.

Amendment 3: 09 APR 2021

Rationale for the amendment:

- Revision of descriptions of study procedures for clarification
- Update to Sponsor signatory
- Revision and updates to eligibility criteria to allow for improved documentation and investigator interpretation/discretion
- Updates to the document for consistency including deletion of repetitive and unnecessary templated language
- Minor editorial and grammatical corrections were made throughout the document.

Where applicable added text is ***bolded and italicized***. Deleted text has ~~strikethrough.~~

Section	Change	Reason
Sponsor Signatory	~~John Li CEO~~ ***Sam Murphy, PhD, Chief Executive Officer*** ***Neal Salomon, MD, Chief Consulting Medical Officer and Medical Monitor***	Administrative
Section 1.0: Protocol Summary, **Section 3.0:** Objectives and Endpoints and **Section 11, Appendix 5:** 2-D TTE Parameters	Primary: Deletion of thyroid panel from list of laboratory parameters for assessment of change from baseline Exploratory: revision of 2D-TTE to be performed: • Microbubble contrast-enhanced 2-dimensional transthoracic echocardiography (2D-TTE) results~~:~~ ~~ejection fraction~~, ***including, but not limited to: 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; ~~right ventricular size and function, right ventricular global longitudinal strain, tricuspid valve regurgitation velocity, and mitral valve regurgitation grade (quantitative); as well as ,~~ ***valvular insufficiency and/or gradients,*** ~~(IVC) size and collapsibility ratios;~~ and multiple calculated monitoring parameters using velocity and flow measurements, including stroke volume (SV), cardiac output (CO), derived left ventricular filling pressure (E/e'). ~~) and systemic vascular resistance (SVR) calculations~~.	Administrative Clarification of assessment parameters
Section 1.0: Protocol Synopsis, Treatment Groups and Duration, **Section 4.1:** Overall Design **Section 4.6.2:** Criteria for Stopping Dose Escalation	Revision of language	Clarification of directions regarding dose escalation procedures by the DRC

Section	Change	Reason
Section 1.3: Table 1 - Schedule of Activities, Table 2 - Schedule of Digital ECG Assessments, Specimen Collection, and ECHO Assessments (Day 1 through 3); **Section 5.3.1:** Meals and Dietary Restrictions; **Section 8.2.5**: Electrocardiograms; **Section 8.5.1:** **(**Pharmacokinetics) Collection of Samples;	Table 1 SoA revisions are listed below and are applicable to other tables and sections listed. Addition: ***Subjects must be fasted for 10 hours before each on-site visit*** Screening Visit; extension of screening period from Day -35 to ***Day -45*** Footnotes: Vital signs; change in requirement for the need for to be performed at the same time as ECGs rather than immediately following. Footnote "a" In-patient stay addition: requirement for patients to receive a ***light*** breakfast/***snack*** prior to IP administration. Footnote "c" Physical examination addition: requirement ***subjects must verify they have no prior history of malignancy and/or have undergone cancer screening.*** Footnote "g" Serum chemistry, liver, kidney, and coagulation assessments addition: ***coagulation panel will not be performed on Day 60, Day 90, or Day 135. Drugs of abuse to be performed as per local practices at Screening only***. Footnote "i" Lipid Panel clarification: ~~(fasting at screening and on Day 90)~~ ***and should be performed as part of clinical chemistry at all timepoints indicated for clinical chemistry (see Table 14).*** Footnote "o" ECG clarification: following IP infusion, 0.5, 1, 2, 4, and 8 hours from the end of the IP infusion, 24- and 48-hours ~~after the start~~ ***clock-time matched within ± 30 minutes*** **of** ~~the IP infusion~~ ***pre-dose Day 1 ECG assessment, prior to a light breakfast/snack.*** Footnote "q" clarification: PK Blood Samples: at 0.5, 1, 2, 4, 8, 12, 24 hours (Day 2), and 48 hours (Day 3) ~~from the end of the infusion~~ ***timed to no more than 10 minutes following completion of ECG assessment.*** Addition of a ***+1 day window for sampling Day 7.*** Footnote "r" clarification: ***HbA1c to be performed at the Screening visit only.*** Footnote "u" Randomization update**:** ***Randomization will occur approximately one to two weeks prior to scheduled date of IP infusion, at the time of scheduling the inpatient admission, and will trigger shipment of IP and administration kit to site. See Section 6.3 for description of randomization procedures.*** Footnote "v": Study Day 11 and 20 addition: ***Study visits on Day 11 and Day 22 may be conducted remotely at the discretion of the Principal Investigator based on their local risk assessment, in which case, the requirement for vital signs, ECGs, physical examination, and PK blood draws will be waived. The procedures will be performed as per the SoA if the visit take place at the clinical site.***	Update to and clarification of study procedures
Section 4.6.1 Study Stopping Criteria	• Any ***emergent*** symptomatic or asymptomatic cardiac arrhythmia requiring at least urgent medical intervention. • ~~Any ≥ moderate (corresponding to Common Terminology Criteria for Adverse Events [CTCAE version 5 (v5)] Grade 2) hematologic, non-hematologic, hepato-cellular, renal toxicity ≥7 days~~. ***Any emergent Grade 3 or greater (>/=) toxicity except untreated nausea, diarrhea,***	Clarification of criteria.

Section	Change	Reason
	vomiting, constipation, abdominal pain. Any of these will be considered DLTs if persisting >72 hours despite appropriate treatment. Any ***emergent*** ≥ severe (corresponding to CTCAE v5 Grade 3) hematologic, non-hematologic, hepato-cellular, renal toxicity	
Section 5.1: Inclusion Criteria	Criterion 2: Stable HF defined as no hospitalizations for cardiac-related issues within the previous ***2*** ~~3~~ months prior to the screening visit or between screening and randomization, ***other than for routine percutaneous procedures such as device, battery, generator changes or pacemaker lead insertion/replacement***. Criterion 4: Subjects must be taking clinician-directed appropriate pharmacological therapy for HF as per the 2017 ACC/AHA/HFSA treatment guidelines (Yancy et al, 2017) ***and at investigator determined discretion*** at stable doses (except for diuretics) for at least ~~3~~***2*** months prior to ~~screening~~***informed consent***. Criterion 5: ***Subjects without implantable cardioverter-defibrillators (ICDs) are eligible.*** Subjects with implantable ICDs ~~if the devices are not "pacing~~ ***are allowed at the discretion of the investigator, but only if both the following criteria are met: (a) paced beats cannot exceed 15% of beats as quantified by screening e-Patch, and (b) if a non-paced baseline ECG can be obtained on Day 1 prior to study drug administration.*** Criterion 6: Body mass index ≥18 kg/m^2 and ***≤45***~~40~~ ***kg/m^2***	Revision and clarification of criteria to allow for improved documentation and investigator interpretation/discretion.
Section 5.2: Exclusion Criteria	Criterion 4: Diagnosed with ***medically documented*** acute coronary syndrome within 3 months of screening or a ***medically documented*** acute myocardial infarction within 6 months of screening. Criterion 8: Sustained systolic ***BP <90*** ~~<100~~ mm Hg and/or diastolic BP <50 mm Hg (confirmed by a duplicate seated reading) on at least 3 consecutive readings (~~self monitored or~~ office) ….. Criterion 9: Resting HR >100 beats per minute (bpm) at Screening (Visit 1) or prior to randomization which is sustained for >15 minutes in two episodes separated by one hour of observation ***except in sustained atrial fibrillation when HR of up to 110 bpm is acceptable.*** Criterion 10: Cerebrovascular accident or hospitalizations for CV (cardiovascular) causes other than routine ***percutaneous procedures such as device, battery, generator changes or pacemaker lead insertion/replacement or*** device generator changes, including HF, chest pain, stroke, transient ischemic attack, or arrhythmias within ~~3~~***2*** months prior to screening. Criterion 11: Subjects at screening have an abnormal or clinically significant 12-lead ECG abnormality, ~~(e.g. QRS >120 msec, PR >210 msec, heart rate (HR) <45 bpm, sustained HR >100 bpm)~~ that, in the opinion of the Investigator, would affect efficacy or safety evaluation or place the subject at risk. Criterion 15: For subjects on warfarin or other anticoagulants, an INR (or PT/~~PTT~~) considered by the Principal Investigator as therapeutically appropriate will be allowed.	Revision and clarification of criteria to allow for improved documentation and investigator interpretation/discretion.

Section	Change	Reason
	Criterion 18: Concurrent treatment with Class I**a** or III antiarrhythmic drugs (~~unless~~ the medication ~~was~~***must have been*** discontinued more than ~~3~~***2*** months before ~~enrollment~~***informed consent***). Criterion 20: Known history of or active alcohol abuse (no more than 14 units/week for males or 7 units/week for females) or use of illicit drugs within 1 year prior to randomization ~~other than~~***(excluding*** recreational use of marijuana or ~~cannabis~~ ***cannabidiol [CBD]***-based products). Criterion 22: history of ***pathologically confirmed*** malignancy of any type or any ***pathologically confirmed*** pre-malignant condition (e.g., ductal carcinoma in situ, colonic polyp ***with premalignant diagnosis***, or cervical atypia).	
Section 6.0: Study Treatment	New language added: ***This is a double-blind study. The investigational treatment and placebo infusions will be identical in physical appearance. Other than in the case of sentinel subjects, the treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor, study vendors, or DRC. The treatment codes will be held by a third-party clinical research services vendor designated by the Sponsor.*** ***Where possible, and as applicable, hospital admission and IP administration should take place on Monday or Tuesday to allow for Day 7 follow-up visits to take place on the following Monday.*** ***With the exception of IP infusion administered to the sentinel subject in each cohort, all study staff will be blinded to IP identification.*** ***The total infusion time, inclusive of saline flush should be 60 minutes*** and should not exceed 75 minutes.	Addition of new language and revision of existing language to clarify study procedures.
Section 6.2: Preparation, Handling, and Storage	Revision to allow for pharmacy staff to document preparation of IP according to local standards of practice and to mandate that all records be available for inspection.	Simplification of procedures
Section 6.3: Randomization and Blinding	Deletion of unnecessary templated language and insertion of language describing the IWRS procedures.	Clarification of procedures
Section 6.4.1: Treatment Strategy and **Section 6.4.2:** Warnings and Precautions	Sections deleted.	Deletion of unnecessary language.
Section 6.5: Concomitant Medications	Substitution of 'time of informed consent" and deletion of "time of enrollment" as the starting timepoint for collection of data	Clarification of study procedures.
Section 6.6: Dose Modification	Deletion of language. Addition of: ***As this is a single-dose study, dose modification within an individual subject is not applicable.***	Deletion of unnecessary template language and clarification of study procedure.
Section 7.2: Subject Discontinuation	Addition: Subjects withdrawing due to an AE ~~should be followed up according to the follow-up visit~~ ***at any time should be followed up until resolution, stabilization, the event is otherwise explained, the subject is lost to follow-up (Section 8.3.8) or until the end of their participation in the***	Clarification of study procedure

Section	Change	Reason
	study. Subjects should be encouraged to complete the End of Study visit activities.	
Section 8.2: Safety Assessments	Addition: ***Subjects will be observed for injection site reactions until Day 4 following IP administration, for DLAEs until Day 15 following IP administration, and for AEs and SAEs from the time of informed consent until 30 days after the IP administration. Following Day 30, only SAEs deemed at least possibly related to the study drug or study procedures will be collected until the End of Study visit (Day 180).***	Clarification of timelines for safety reporting.
Section 8.2.5: Electrocardiograms	Addition: ***During Screening and beginning no more than 45 days before Day 1, all subjects will be supplied with, and instructed how to use a e-Patch for continuous 14-day heart rhythm monitoring as outlined in the Table 1 SoA. A 14-continuous day heart rhythm monitoring assessment will be collected using the e-Patch with monitoring completed no later than Day -10 unless confirmed with the sponsor. Where applicable, the screening ECG and Day 1 baseline ECG must be obtained without evidence of pacing.***	Addition of description of ePatch procedures
Section 8.3.8: Follow-up of AEs and SAEs.	Revision: All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3) ***or until the end of their participation in the study. Subjects should be encouraged to complete the End of Study visit activities.***	Clarification of duration of follow-up for SAEs.
Section 8.4: Treatment of Overdose	Revision: Obtain blood sample for PK analysis ~~within 30 days from~~ ***as specified in Table 1 SoA***.~~the date of the last dose of study intervention if requested by the medical monitor (determined on a case by case basis).~~	Revision of study procedure
Section 8.8: Biomarkers	Addition of lactate dehydrogenase	Revision of study procedures
Section 9.4.3: Safety Analyses	For 12-lead ECG parameters: ***If relevant, analysis excluding ECGs capturing paced beats will be performed.***	Clarification of procedures
Section 9.6: Data Review Committee	Addition of description of procedures outlined in the synopsis.	Clarification of procedures.
Section 11: Regulatory, Ethical, and Study Oversight, **Appendix 2:** Study and Study Procedures	Addition of language describing procedures for changes to the protocol.	Update of study procedures

LIST OF ABBREVIATIONS

Abbreviation	Definition
2D-TTE	2-dimensional transthoracic echocardiography
ACC/AHA/HFSA	American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America
ACS	American Cancer Society
ADA	anti-drug-antibody
AE	adverse event
ANC	absolute neutrophil count
$AUC_{(0\text{-inf})}$	area under the plasma concentration-time curve 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
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
BNP	brain natriuretic peptide
CBD	cannabidiol
CL	systemic clearance
C_{max}	maximum concentration
CO	cardiac output
CPK	creatine phosphokinase
CPK-MB	creatine phosphokinase – muscle/brain
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTnI	cardiac troponin I
CV	cardiovascular
DD2	diastolic dysfunction Grade 2
DLAE	dose-limiting adverse events
DRC	Data Review Committee
DRE	disease-related events
ECG	electrocardiogram
ECRF	case report form
eCRF	electronic case report form
E	early diastole
E/e’	derived left ventricular filling pressure
EGF	epidermal growth factor
FIH	first-in-human
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCSD	highest confirmed safe dose
HED	human equivalent dose
HER3	human epidermal growth factor receptor 3
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
hsCRP	high-sensitivity C-reactive protein
hs-troponin	high-sensitivity troponin

Abbreviation	Definition
ICD	implantable cardioverter-defibrillators
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IP	investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	intravenous
IVC	inferior vena cava
IVRS/IWRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
$+LVdp/dt_{max}$	maximum rate of rise of left ventricular pressure
LVEDV	end diastolic left ventricular volume
LVEF	left ventricular ejection fraction
LVESV	end systolic left ventricular volume
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
NHP	non-human primates
NOAEL	no observed adverse effect level
NRG-1	neuregulin-1
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PBS	phosphate buffered saline
PD	pharmacodynamic
PK	pharmacokinetic
PT	prothrombin time
PTT	partial thromboplastin time
QTca	heart-rate corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RC_{max}	ratio of C_{max}
$RAUC_{(0\text{-}inf)}$	ratio of $AUC_{(0\text{-}inf)}$
$RAUC_{(0\text{-}last)}$	ratio of $AUC_{(0\text{-}last)}$
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	systemic vascular resistance
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximal concentration
ULN	upper limit of normal
WOCBP	women of child-bearing potential
λ_z	terminal rate constant

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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)

Rationale: 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 (GI) 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 (IV) to subjects with heart failure 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 be also explored.

Objectives and Endpoints:

Objectives	Endpoints
Primary	

• Assess the safety and tolerability profile, including immunogenicity, of JK07, administered intravenously according to protocol-defined dosing regimen.	• 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 recordings 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).
	• Laboratory parameters – change from baseline each assessment time point per Table 1 Schedule of Assessments (SoA) postdose: hematology, chemistry, coagulation, and lipid panels.
	• Immunogenicity
	  o Incidence of early and delayed-type hypersensitivity responses.
	  o Presence of serum anti-JK07 antibodies (confirmed positive antibody response, titer, neutralizing antibodies).
	• Vital signs – change from baseline in vital signs and the relationship to JK07 compared with placebo, including:
	  o Blood pressure (BP)
	  o Temperature
	  o Heart rate (HR)
	  o Respiratory rate (RR).

Secondary	
• To determine the PK characteristics of JK07 administered intravenously according to protocol-defined dosing regimen.	• Pharmacokinetic parameters of intact JK07 including, but not limited to, maximum concentration (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), and volume of distribution (V_z). Surrogate measurement of intact JK07 to be carried out through detection of both the JK07 antibody domain and the JK07 NRG-1 peptide fragment in the evaluation of pharmacokinetic parameters.
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.	• Microbubble contrast-enhanced 2-dimensional transthoracic echocardiography (2D-TTE) results, including, but not limited to: 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, and multiple calculated monitoring parameters using velocity and flow measurements, including stroke volume (SV), cardiac output (CO), derived left ventricular filling pressure (E/e'). • Observed biomarker concentrations and corresponding changes from baseline. • Concentration-QT correlation performed on baseline-corrected QTcF time matched with PK.

Overall Design:

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

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 one single active unblinded sentinel subject receiving a single IV dose of JK07 prior to randomized JK07 or placebo administration in the remainder of the cohort.

A Data Review Committee (DRC) will be established to review emerging data, to monitor safety aspects of the study, to select the JK07 dose during dose escalation, and to adapt the randomization scheme. The DRC will evaluate the emerging clinical, laboratory and cardiac safety data, inclusive from the first 48 hours after dosing of the sentinel subject, and prior to randomized blinded IP administration in the remainder of the cohort.

Number of Investigators and Study Centers:

Approximately 8 Investigators and study centers are expected to participate in this study.

Number of Subjects:

A maximum of 63 subjects will be randomized into dose escalation cohorts. Five dose escalation cohorts are planned. Two additional cohorts may be added as per the DRC recommendation (total up to 7 cohorts).

Treatment Groups and Duration:

In Cohort 1, if no clinical effect is observed in the sentinel subject, the DRC will decide whether to proceed with the randomization of 4 additional subjects (3:1, JK07: placebo) to receive blinded IP. Once the last subject in Cohort 1 completes the evaluation period, the DRC will decide whether to proceed to Cohort 2. The evaluation period for dose escalation to the next cohort will be at a minimum, the available safety data through Day 15 following the administration of the IP on Day 1 for all subjects in the current dose cohort. Safety data will continue to be collected

up to 180 days following the administration of the IP and may additionally be taken into consideration for dose escalation when available. Cohort 2 and subsequent cohorts will proceed as Cohort 1 until either of the following occur: a sentinel subject exhibits, in the opinion of the DRC, a clinical effect (efficacy or safety observation), or a cohort exhibits, in the opinion of the DRC, a clinical effect.

Once a clinical effect is observed, the DRC may, at its discretion, expand the size of that cohort in which a clinical effect is first observed, and subsequent cohorts, up to a maximum of 9 subjects (1 open-label JK07 sentinel subject, and 6:2 [JK07: placebo] randomized, double-blind subjects).

Following observation of a clinical effect and a decision to expand the size of the cohort at which the clinical effect was observed, the DRC will decide whether to dose escalate after the last subject in the expansion cohort completes the evaluation period. If the DRC decides to escalate the dose, a single unblinded sentinel subject will receive JK07 at the next dose level. If following the completion of the evaluation period of that sentinel subject the DRC decides to proceed, the remainder of the subjects in the expanded cohort size will receive JK07 or placebo according to the direction of the DRC, and this sequence will repeat until the highest planned dose level is reached or until the DRC determines not to dose escalate further.

Cohort dose levels of JK07 are as follows: the starting dose has been selected at 1/30 of the human equivalent dose (HED) at the no-observed adverse effect level (NOAEL) in the cynomolgus monkey (3 mg/kg/week). A conservative approach of body surface area scaling was employed for this conversion (HED) at the monkey NOAEL = 0.97 mg/kg/week). The subsequent provisional doses have been set at a 3-fold increase from the prior dose for the first 2 dose escalations (Cohort 2 through Cohort 3). The subsequent dose escalations (Cohort 4 through Cohort 5) have been set at a 2-fold increase from the prior dose; based on emerging safety and/or PK results of the previous cohorts, the DRC can allow a 3-fold increase. Additionally, the DRC may also reduce the incremental dose escalations based on the results of the previous cohorts.

Dose Level	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

Note: Initially 5 cohorts are planned. Two additional higher cohorts may be added as per the DRC recommendation (total up to 7 cohorts). The highest JK07 dose administered not to exceed 2.5 mg/kg without further amending the protocol.

Subjects will be observed for injection site reactions until Day 4 following study treatment and will be monitored for signs of dose-limiting adverse events (DLAE) until Day 15 following study treatment.

Beginning on Day 1 and prior to study drug administration, subjects will be observed on continuous telemetry for the duration of the hospital stay. During this period blood will be collected for PK, biomarkers and safety laboratory assessments, vital sign and ECG assessments will be performed, and 2D-TTE will be performed pre-dose, and at 6- and 30-hours post-dose, to observe for possible clinical activity.

The DRC will evaluate each sentinel subject as well as active treatment subjects in each dose cohort for DLAEs. To support dose escalation decisions by the DRC, safety, and tolerability results for all subjects in each cohort through at least Day 15 will be included in this review. During the review of the safety and tolerability results the DRC may make the determination to escalate to the next dose level or expand the size of the current cohort further, if not already at the maximum size, following which further dose escalation could proceed. Alternatively, the DRC may determine to decrease to a lower dose level which may be an additional cohort at an intermediary dose or a pre-assigned cohort. In the case that an intermediary dose is selected, a single sentinel subject will receive JK07 prior to randomization of the remaining subjects in the cohort. Following a dose reduction, the DRC may subsequently decide to further reduce the dose level in a subsequent cohort or increase the dose in a subsequent cohort. A sentinel subject is required only if the selected de-escalated dose is above the previously Highest Confirmed Safe Dose (HCSD).

At the time of the DRC safety review of the entire cohort, PK results if available for that cohort, will be evaluated (along with results of prior cohorts, as available).

Statistical Methods:

Sample size calculation: The sample size for this study 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.

Analysis sets:

- Safety Evaluation Population: All subjects randomly assigned to the IP and who take 1 dose of IP. Subjects will be analyzed according to the treatment they received.
- DLAE Evaluation Population: All subjects who received 1 dose of IP and completed the 15-day DLAE follow-up period.
- PK Evaluation Population: All subjects who received at least 1 dose of JK07 and have at least 1 quantifiable JK07 plasma concentration collected postdose without important protocol deviations/violations or events thought to significantly affect the PK results.
- Exploratory PD/biomarker Evaluation Population: All subjects who take 1 dose of IP and have at least 1 exploratory PD variable or biomarker endpoint collected postdose without important protocol deviations/violations or events thought to significantly affect the PD results.

Safety Analyses: All data will be provided in data listings sorted by treatment group, subject number, and visit. Summary data will be presented in a tabular format by treatment group, by scheduled time point, visit, and overall (as appropriate). Categorical data will be summarized by the number and percentage of subjects in each category. Continuous data will be summarized by descriptive statistics including at a minimum sample size (n), mean, standard deviation, median, minimum, and maximum. Change from baseline will be calculated as value postdose subtracted by value at baseline. The baseline measure will be defined as the last non-missing measure prior to initiation of the IP. Outliers for QT and QTc defined under outcome measures will be summarized using cumulative counts and percentages by treatment and sampling time, if appropriate. Abnormal findings on 12-lead ECG will be summarized by treatment using descriptive statistics.

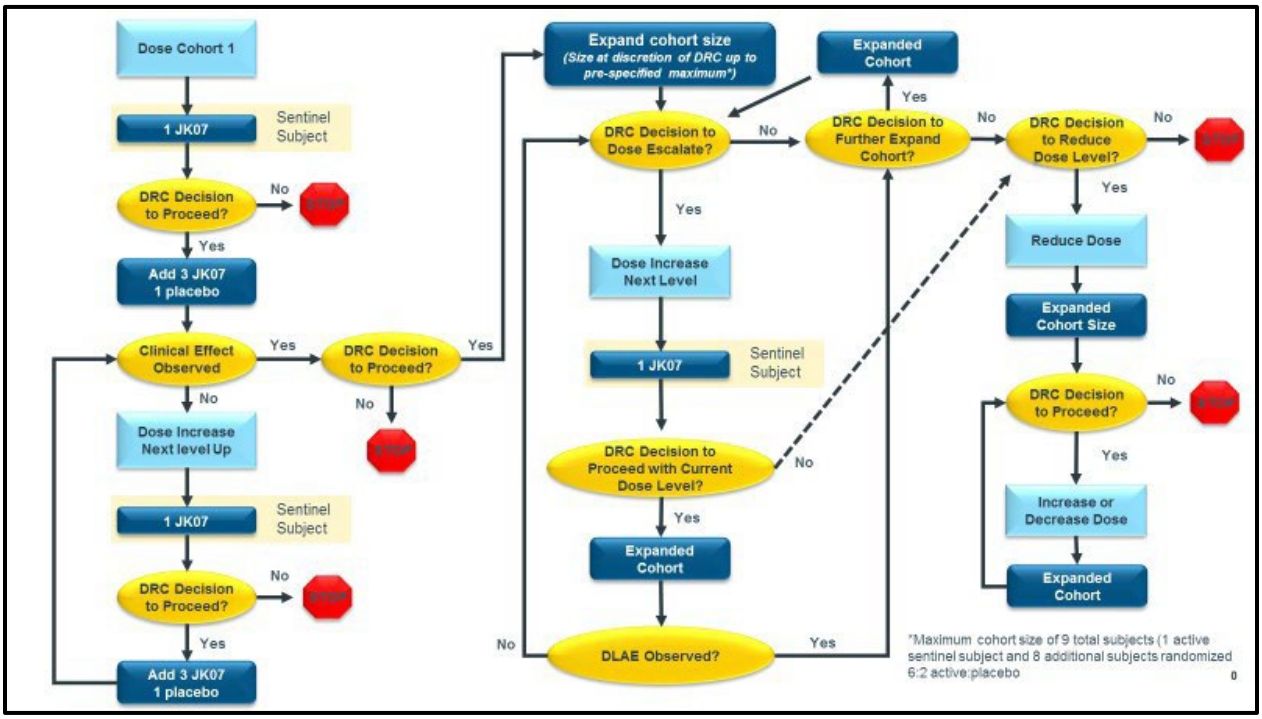
PK Analyses: Intact JK07 concentrations, determined through detection of both the antibody domain and NRG-1 peptide, and calculated parameters will be listed and descriptively summarized by active treatment for the PK Evaluation population. Dose proportionality will be explored graphically, and, if applicable, using a power model.

Exploratory PD Analyses: Results of the exploratory endpoints (2D-TTE results and biomarkers) and their change from baseline values (as applicable) will be listed and descriptively summarized by treatment. Exploratory inferential comparisons with placebo may also be performed, if appropriate. An exploratory evaluation of a plasma concentration to QT (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 plasma concentration obtained on Day 1, treatment indicator (treatment = 1 for subjects receiving JK07, and 0 otherwise), time point as a categorical variable, and random effects subject and time-matched JK07 plasma concentration obtained on Day 1.

Data Monitoring Committee: Yes

1.2 Schema

Figure 1 Study Schema



Abbreviations: DLAE, dose-limiting adverse events; DRC, Data Review Committee.

1.3 Schedule of Activities

Table 1 Schedule of Assessments

(note that X denotes activity on a given day, but may denote a single or multiple instances of the indicated activity)

	Screening	**In Hospital**		**Follow-up**										**EOS/ 180[t]**
		Subjects must be fasted for 10 hours before each on-site visit												
Study Day	**-45 to 0**	**1[a]**	**2**	**3**	**4**	**7**	**11[v]**	**15**	**22[v]**	**30**	**60**	**90**	**135**	
Window						**+1**	**-1**	**+/-2**	**+/-2**	**+/-2**	**+/-5**	**+/-5**	**+/-7**	**+/-10**
In-patient stay[a]		X	X	**X**										
Hospital discharge[b]				X										
Informed consent	X													
Demographics	X													
Past medical history	X													
Height *(at screening only)* and Weight	X	X		X		X	X	X		X	X	X	X	X
Vital signs *(at same time point as ECGs)*	X	X	X	X	X	X	X[v]	X		X	X	X	X	X
Physical examination[c]	X	X	X	X	X	X	X[v]	X	X[v]	X	X	X	X	X
Blood-based pregnancy test[d]	X													
Urine pregnancy test[d]		X								X	X	X	X	X
IP administration		X												
Check for injection site reaction[e]		X	X	X	X									
Adverse events[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry and liver, kidney, and coagulation panels[g]	X	X	X			X		X		X	X[g]	X[g]	X[g]	X
Complete blood count[h]	X	X	X	X		X		X		X	X	X	X	X

	Screening	In Hospital		Follow-up										EOS/ 180[t]
		Subjects must be fasted for 10 hours before each on-site visit												
Study Day	**-45 to 0**	**1[a]**	**2**	**3**	**4**	**7**	**11[v]**	**15**	**22[v]**	**30**	**60**	**90**	**135**	
Window						**+1**	**-1**	**+/-2**	**+/-2**	**+/-2**	**+/-5**	**+/-5**	**+/-7**	**+/-10**
Lipid panel[i]	X	X	X			X		X		X	X	X	X	X
Urinalysis[j]	X	X	X			X		X						
Muscle and inflammatory biomarkers[k]		X	X			X		X		X	X	X	X	X
Additional biomarkers: Cardiac troponins, CPK-MB, CPK, and hsCRP assessment[l]	X	X	X	X		X		X		X	X	X	X	X
Immunogenicity Assessment[m]		X			X	X		X		X		X		X
Telemetry[n]		X	X	X										
Digital 12-lead ECG[o]	X	X	X	X	X	X	X[v]	X		X	X	X	X	X
2D-TTE[p]	X	X	X			X		X		X	X	X	X	X
PK sample collection[q]		X	X	X	X	X	X[v]	X	X[v]	X	X			
Fingerstick glucose[r]		X	X	X	X									
ECG patch recording[s]	X													
Thyroid panel	X													
Viral serology	X													
Randomization[u]	X													

Abbreviations: 2D-TTE, 2-dimensional transthoracic echocardiography; β-hCG, beta-human chorionic gonadotrophin; CPK-MB, creatine kinase – muscle/brain; CPK, creatine phosphokinase; ECG, electrocardiogram; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillators; IP, investigational product; LDH, lactate dehydrogenase; LDL, low density lipoprotein; PK, pharmacokinetic.

[a] Subjects should be admitted in the hospital study unit by 7:00 AM, or as early as practicable, on Day 1. The subject should arrive fasted (at least 10-hour fast). All baseline clinical and laboratory assessments should be conducted prior to light breakfast/snack being provided to the subject. Subjects will be scheduled for discharge on the morning of Day 3.

[b] Subjects will be scheduled for hospital discharge on Day 3, after completion of all planned in-patient safety, PK, and exploratory PD/biomarker assessments. However, subjects may be asked to remain in the hospital study unit for more than 48 hours after the IP administration at the Investigator's discretion.

[c] A full physical examination will be performed at screening. An abbreviated physical examination will be conducted at all other visits. See Section 8.2.1. During screening all subjects must verify they have no prior history of malignancy and/or have undergone cancer screening or undergo cancer screening according to American Cancer Society Guidelines (Appendix 1 Cancer Screening Guidelines).

[d] Women of childbearing potential only. β-hCG blood test at screening, urine dipstick test upon admission on Day 1 prior to IP administration to confirm absence of pregnancy, and urine specimens at all time points thereafter.

[e] See Section 8.2.2 for assessment times and parameters.

[f] All AEs, including SAEs will be collected from the time of study enrollment and until 30 days after the IP administration. Following the first 30 days, only SAEs deemed at least possibly related to the study drug or study procedures should be collected. Refer to Table 9 for additional details.

[g] See Appendix 3 Clinical Laboratory Tests for a complete list of analytes and schedule of collections and analysis. Coagulation panel **will not be performed** on Day 60, Day 90, or Day 135. Drugs of abuse to be performed as per local practices at Screening only.

[h] See Appendix 3 Clinical Laboratory Tests for parameters included in the complete blood count.

[i] Lipid profile includes total cholesterol, HDL, LDL, and triglycerides, and should be performed as part of clinical chemistry at all timepoints indicated for clinical chemistry (see Table 14).

[j] See Table 13 for a complete list of urinalysis parameters.

[k] See Section 8.8 for a complete list of muscle and inflammatory biomarkers.

[l] On Day 1 multiple blood samples for safety evaluation will be collected as follows: troponin I and/or hs troponin T, CPK, CPK-MB, and hsCRP prior to infusion and at 4, 8, and 12 hours from end of infusion.

[m] Refer to Section 8.2.8 for immunogenicity assessments.

[n] Continuous telemetry monitoring will be started as soon as practicable after hospital admission on Day 1 and prior to IP infusion, and will be continued until 48 hours after the end of the IP infusion on Day 3. In the case of any abnormal finding, the Investigator will determine whether the finding constitutes an abnormal event and whether an unscheduled ECG should be conducted.

[o] Triplicate 12-lead digital ECGs will be performed during screening and starting on Day 1 following admission to the hospital. ECG assessment will be performed at each specified time point after the subject has been supine for ≥5 minutes. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be performed as closely as possible in succession but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes with no more than 2 min between them. Vital signs are scheduled at the same time points and will be collected prior to completion of the ECG assessment, and the ECG assessment will be prior to PK sample collections at simultaneously scheduled time points.

- The post-screening times for the ECGs will be as follows: prior to the IP infusion, immediately following IP infusion, 0.5, 1, 2, 4, and 8 hours from the end of the IP infusion, 24- and 48-hours clock-time matched within ± 30 minutes of pre-dose Day 1 ECG assessment, prior to a light breakfast/snack (see Table 2 for additional details).
- These ECGs will be read by the Investigator to ensure subject safety. These ECGs must be taken immediately before PK sampling.

[p] On Day 1, 2D-TTE measurements will be performed pre-dose and at 6 ± 0.5 hours post-dose. On Day 2, the assessment is scheduled for 30 ± 0.5 hours post-dose. See Section 8.2.9 for a description of exploratory 2D-TTE assessments.

[q] The PK blood samples will be collected as follows: Prior to the IP administration, at the end of the infusion, at 0.5, 1, 2, 4, 8, and 12 hours, at 24 hours (Day 2) and 48 hours (Day 3) timed to no more than 10 minutes following completion of ECG assessment, at 72 hours (Day 4), 144 hours (Day 7), 240 hours (Day 11), 336 hours (Day 15), and 504 hours (Day 22) from the end of the infusion, and on Day 30 and Day 60 (see Table 2). Note that sample collection times may be modified based on emerging PK results and 1 additional blood sample may be collected if deemed appropriate (up to 18 samples). Windows for the first 48 hours of PK collections are identified in Table 2; a ±8-hour window is permitted for PK collections on Day 4 and a +1 day is permitted on Day 7. Windows for subsequent PK sample collections are indicated in the SoA above.

[r] Blood glucose samples will be collected by fingerprick test and read using standard glucometer at the same timepoint as the PK samples through 96h (Day 4) postdose. HbA1c to be performed at the Screening visit only.

[s] During the screening period and no more than 45 days before Day 1, all subjects will be supplied with, and instructed how to use a e-Patch for continuous 14-day heart rhythm monitoring. Subjects must then perform 14 continuous days of heart rhythm monitoring using the e-Patch. Unless otherwise approved by the sponsor, monitoring should be completed no later than Day -10 to allow for processing of data by the manufacturer and evaluation of baseline ECG parameters and arrhythmia incidents by the site.

[t] Subjects who do not complete all required visits or withdraw from the study early are required to complete End-of Study/Early-Termination assessments (Day 180) as described in Section 7.2.

[u] Randomization will occur approximately one to two weeks prior to scheduled date of IP infusion, at the time of scheduling the inpatient admission, and will trigger shipment of IP and administration kit to site. See Section 6.3 for description of randomization procedures.

[v] Study visits on Day 11 and Day 22 may be conducted remotely at the discretion of the Principal Investigator based on their local risk assessment, in which case, the requirement for vital signs, ECGs, physical examination, and PK blood draws will be waived. The procedures will be performed as per the SoA if the visit takes place at the clinical site.

NOTE: See Appendix 3 Clinical Laboratory Tests, Table 13 for a complete list of protocol-required laboratory assessments that will be performed; see Table 14 for a list of safety laboratory assessments (and assessment timepoints) that will be performed by the local laboratory; see Table 15 for a list of safety and exploratory biomarker assessments that will be performed by a central laboratory.

Table 2 Schedule of Digital ECG Assessments, Specimen Collection, and ECHO Assessments (Day 1 through 3)

Schedule of Assessments (Day 1 – Day 3)			
(Order of activities to be completed left to right, top to bottom)			
	Day 1		
Time relative to dose[a]	**12-lead ECG[b]**	**Specimen Collection (Labs)**	**2D-TTE**
No food consumption for 10 hours before predose ECG assessment, specimen collection and ECHO			
Predose (prior to start of infusion)	X[c]		
		Safety (local) Biomarkers (central) PK (central) Glucose (fingerstick) Urinalysis (local) Urine β-hCG (local)	
			X
Light Breakfast/ Snack	XXXX		
Drug Infusion	XXXX		
End of infusion (**no later than** 5 minutes from end-of-infusion)	X[d]		
		PK (central) Glucose (fingerstick)	
0.5 hour from end-of-infusion	X		
		PK (central) Glucose (fingerstick)	
1 hour from end-of-infusion	X		
		PK (central) Glucose (fingerstick)	
2 hours from end-of-infusion	X		
		PK (central) Glucose (fingerstick)	
4 hours from end-of-infusion	X		
		Safety (local) PK (central) Glucose (fingerstick)	

Schedule of Assessments (Day 1 – Day 3)			
(Order of activities to be completed left to right, top to bottom)			
	Day 1		
Time relative to dose[a]	**12-lead ECG[b]**	**Specimen Collection (Labs)**	**2D-TTE**
6 hours from end-of-infusion			X
8 hours from end-of-infusion	X		
		Safety (local) PK (central) Glucose (fingerstick)	
12 hours from end-of-infusion		Safety (local) PK (central) Glucose (fingerstick)	
	Day 2		
	12-lead ECG[b]	**Blood Collection (Labs)**	**ECHO**
24 hours[e] from end-of-infusion	X		
		Safety (local) Biomarkers (central) PK (central) Glucose (fingerstick) Urinalysis (local)	
30 hours from end-of-infusion			X
	Day 3		
	12-lead ECG[b]	**Blood Collection (Labs)**	**ECHO**
48 hours[f] from end-of-infusion	X		
		Safety (local) PK (central) Glucose (fingerstick)	

Abbreviations: 2D-TTE, 2-dimensional transthoracic echocardiography; β-hCG, beta human chorionic gonadotrophin; ECHO, ECG, electrocardiogram; PK, pharmacokinetics

[a] ±5-minute window will be allowed for PK samples taken up to 1-hour postdose; a ±15-minute window will be allowed for samples taken at 2 to 12 hours postdose, samples taken at 24- and 48-hours postdose must be taken within 10 minutes after the 24- and 48-hour ECG assessments.

[b] At the time of ECGs, subject should have rested in a supine position for at least 5 minutes.

[c] 12-lead digital ECG must be performed **prior** to the PK sample collection and should be collected as close to the scheduled times as possible. For 12-lead digital ECG assessments scheduled for up to and including 4 hours, the ECG assessments should be within 10 minutes prior to the PK sample collection; for subsequent ECG assessment, a window of 30 minutes prior to PK collection (or less) is desired.

[d] All required ECG leads will be secured to the patient and attached to an ECG machine prior to administration of the IP to facilitate immediate post-infusion recording.

[e] For the 24-hour time point on Day 2, the ECG assessment should be clock time-matched within ±30 minutes of the pre-dose Day 1 ECG assessment, prior to light breakfast/snack, and the PK sample should be clock time-matched to no more than 10 minutes following completion of the ECG assessment.

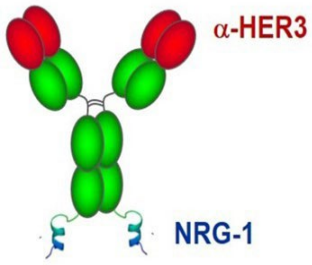
[f] For the 48-hour time point on Day 3, the ECG assessment should be clock time matched within ±30 minutes of the pre-dose Day 1 ECG assessment, prior to light breakfast/ snack, and the PK sample should be clock time matched to no more than 10 minutes following completion of the ECG assessment.

2.0 INTRODUCTION

2.1 Study Rationale

Salubris Biotherapeutics, Inc. (hereafter referred to as SalubrisBio, or "the Sponsor") is developing a therapeutic protein, JK07, for the treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF) (New York Heart Association [NYHA] Class II-III). JK07 is a recombinant fusion protein consisting of a fully human monoclonal antibody that antagonizes human epidermal growth factor (EGF) receptor 3 (HER3) and an active polypeptide fragment of human growth factor neuregulin-1 (NRG-1). The EGF-like domain of NRG-1β2α is fused to the C-terminus of the antibody heavy chain via a linker in a homodimeric configuration (Figure 2).

Figure 2 Schematic Structure of JK07



Neuregulin-1 is a member of the EGF family. All isoforms of NRG-1 share a common EGF-like domain essential for its biological activity (Parodi and Kuhn, 2014). Neureglin-1 is known to be the ligand for HER3 and HER4 (Parodi and Kuhn, 2014). Binding of NRG-1 to either HER3 or HER4 enables heterodimerization of the bound receptor with HER2 and subsequent tyrosine protein kinase activation, which transduces intracellular signaling cascades. Human HER4, but not HER3, is expressed in adult myocardium (Sundaresan et al., 1998; Zhao et al., 1998; Rohrback et al., 1999). Upon engagement of HER4 receptor, NRG-1 can induce cardiomyocyte differentiation, promote cardiac function, and protect cardiomyocytes from apoptosis (Sundaresan et al., 1998).

Numerous animal studies have demonstrated that NRG-1 has an ameliorative effect in HF (Odiete et al., 2012), including ischemic HF, dilated cardiomyopathy, chemotherapy-induced HF, and viral myocarditis. Several clinical studies in patients with HF have also shown that both full length NRG-1 (cimaglermin) and a recombinant NRG-1 protein fragment containing the EGF-like domain (recombinant human NRG-1 [Neucardin®]) can have acute and sustained positive hemodynamic effects (Lenihan et al., 2016; Gao et al., 2010; Jabbour et al., 2011).

Three key factors, however, limit the clinical applications and utility of recombinant human NRG-1. Firstly, signaling of NRG-1 through HER3 may promote cancer development and/or progression, raising serious concerns for any application requiring chronic administration or without grave cardiovascular (CV) risk factors. Secondly, HER3 is normally expressed on the gastrointestinal (GI) tract and over-activation of HER3 by NRG-1 may disrupt GI epithelial integrity and homeostasis, leading to severe GI toxicity and thus, loss of a therapeutic window for NRG-1. In fact, several clinical studies testing recombinant NRG-1 have reported that the most commonly observed treatment-related adverse events were GI in nature (Lenihan et al., 2016; Gao et al., 2010; Jabbour et al., 2011). Thirdly, both clinically tested recombinant human NRG-1 molecules (Neucardin and cimaglermin) have shown a short half-life, indicating that burdensome dosing and administration schedules may be required to achieve the desired therapeutic levels of exposure. Hence, there exists a need to provide an NRG-1-based therapeutic that retains clinically significant therapeutic potential across a variety of CV indications including HF but with a lower risk of

oncogenesis or promotion of cancer progression, better GI tolerability, and a more favorable pharmacokinetic (PK) profile. To that end, SalubrisBio has developed JK07, a recombinant protein in which a sequence corresponding to the EGF-like domain of NRG-1 is fused to the C-terminus of the HER3-specific antagonistic antibody heavy chain, to limit the HER3 activation in response to NRG-1 stimulation without compromising the activity of NRG-1 in inducing HER4 activation, and at the same time the antibody backbone format confers a molecular half-life of a typical monoclonal antibody, enabling more convenient dosing and administration, and a potentially favorable PK profile from the standpoint of efficacy and safety.

This first-in-human (FIH), randomized, double-blind, placebo-controlled, single-ascending dose study for JK07 is intended to support development to reduce the risk of CV death and hospitalization for HF in patients with chronic HF (NYHA Class II-III) and reduced ejection fraction when administered in conjunction with other HF therapies. The nonclinical pharmacology program for JK07 exhibits its pharmacodynamic (PD) actions and efficacy in vitro and in non-human primate models of HFrEF and HFpEF, and a rodent model of HFrEF. The safety and toxicokinetic profile of JK07 for investigation in human clinical trials has been further established in single-dose and repeated-dose toxicology studies conducted in cynomolgus macaques and Sprague-Dawley rats.

2.2 Background

Heart failure is a potentially fatal disease that affects more than 6.5 million people in the United States. Within 5 years of diagnosis, the mortality rate of diseased individuals is 50 % (Shah et al, 2017). Due to an aging population, the condition has continued to increase over the past several decades, and among Americans aged 40 and older, there is a 20 % lifetime risk of developing the disease (Chavey et al, 2017).

JK07 consists of a fully human monoclonal antagonistic antibody specific for HER3 and an active polypeptide fragment of the cardioprotective growth factor NRG-1 (Figure 2). It is designed to stimulate cardioprotective signaling mediated by NRG-1 through HER4 while at the same time mitigating NRG-1 stimulation of HER3 signaling, a pathway that is thought to cause side effects and toxicity without contributing to the therapeutic potential.

In vitro studies have demonstrated that JK07 induced HER2:HER4 dimerization with potency similar to NRG-1; whereas its ability to induce HER2:HER3 dimerization was significantly reduced in comparison to NRG-1. In vivo, JK07 has demonstrated pharmacodynamic activity in rodent and non-human primate (NHP) models of heart failure.

Briefly, in rodents, histopathological analysis of myocardial tissues performed at 4 weeks post-treatment showed that JK07 partially alleviated the pathological changes in the myocardial infarction zone, including significant reduction of necrotic cells, narrowed interstitial spaces between myocardial cells, and recovery of myocardial fiber arrangement towards normal structure. JK07 significantly improved cardiac contractility, increased ejection fraction and $+LVdp/dt_{max}$, partially reversed left ventricular enlargement, reduced left ventricular preload, reduced pulmonary edema and paw edema, lowered the plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptic (BNP), and alleviated myocardial pathological damage.

Compared to other animal models, NHPs have a relatively longer life span and are more susceptible to diseases that are the high-risk factors for heart failure, such as hypertension, abnormal lipid metabolism, type 2 diabetes mellitus and other metabolic diseases (Gong et al., 2013), making them more prone to the development of spontaneous heart failure. NHPs with spontaneous heart failure are highly similar to humans in terms of etiology, pathogenesis, and progression of the disease. Therefore, NHP with spontaneous heart failure is a uniquely clinically relevant model for studying the pathogenesis of heart failure in humans, as well as for the pre-clinical evaluation of drugs treating heart failure.

Based on the systolic/diastolic functions of the left ventricle, heart failure is categorized into two types: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). JK07 was examined in a study of 26 middle/old-aged rhesus monkeys with spontaneous chronic heart failure with either HFpEF with diastolic dysfunctional characteristics of e'<8, E/e'>8 and grade II diastolic dysfunction (DD2) (13 monkeys), or HFrEF with systolic dysfunctional characteristics of left ventricular ejection fraction (LVEF) at 30-51 % and cardiac remodeling (13 monkeys). Enrolled animals were assigned into 3 groups and received weekly IV injection of JK07 1 mg/kg for a total of two injections (5 animals each with HFrEF and HFpEF), Entresto® (sacubitril/valsartan) at the human-equivalent dose (HED) (6.6 mg/kg/day) for a total of 49 days (7 weeks) (5 animals each with HFrEF and HFpEF), and placebo IV injection of phosphate buffered saline (PBS) (3 for each with HFrEF and HFpEF) for a total of two injections.

JK07 significantly improved the systolic function in rhesus monkeys with HFrEF. Specifically, 3/5 animals in the JK07 group showed a statistically significant increase in LVEF from their corresponding baseline at 3 weeks post-treatment, accompanied by significant improvement in cardiac remodeling. At 7 weeks post-treatment (6 weeks after the last dosing of JK07) LVEF remained significantly increased over baseline in 2/5 animals. In contrast, none of the animals in the placebo group showed significant changes in LVEF throughout the study. In the sacubitril/valsartan group, 1/5 animal at 3 weeks post-treatment and 3/5 animals at 7 weeks post-treatment demonstrated statistically significant increases in LVEF from baseline.

JK07 resulted in significant increases in peak velocity of mitral annulus at early diastole (e') and significant decreases in ratio of peak velocity of mitral blood flow at early diastole to peak velocity of mitral annulus at early diastole (E/e') from baselines in 3/5 animals with HFpEF at both 3- and 7- weeks post-treatment. The grade of diastolic dysfunction was improved by at least one grade in these 3/5 animals receiving JK07, according to the clinical criteria used for the diagnosis of diastolic dysfunction. In the sacubitril/valsartan group, only 1/5 animal demonstrated mild improvement in diastolic function after 7 weeks of continuous dosing. Animals receiving placebo showed no improvement from their baselines in diastolic function throughout the study.

No incidences of AEs were observed during the study, except that mild elevations of some of the liver function indexes were detected in animals receiving JK07. Specifically, mild elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or gamma glutamyl transferase (GGT) were detected from Day 10 to Day 11 in 2/10 animals receiving JK07 (1 mg/kg). Animals were each given 0.3 g/day of glutathione through intramuscular injection for 3 days, and most liver function indexes were returned to baseline on Day 15.

Overall, JK07 not only improved LVEF and alleviated cardiac remodeling in rhesus monkeys with spontaneous HFrEF, but also significantly improved the diastolic function in monkeys with HFpEF. Moreover, these improvements in systolic/diastolic function were sustained even after the treatment had been stopped for 6 weeks. No severe AEs were observed during the study, except for the abnormality in liver function which may arise in animals receiving repeat-dose of JK07.

JK07 has also been tested in a comprehensive toxicology program. Single dose IV studies have been performed in monkey with a 2-week follow-up. Weekly Good Laboratory Practice (GLP) compliant repeat-dose IV studies for durations of up to 2 weeks in the rat, with a 2-week recovery period, and up to 4 weeks in the monkey with a 4- week recovery period, have also been completed. Tissue cross-reactivity of JK07 with human tissues in vitro has been conducted.

From the repeat-dose GLP toxicology study in the more relevant monkey species, the no-observed adverse effect level (NOAEL) was defined as 3 mg/kg which is equivalent to a dose of 0.96 mg/kg in humans. The lowest effective dose was 1 mg/kg in the monkey PD study, in which two doses were administered, and this dose level is equivalent to 0.32 mg/kg in humans (FDA 2005). Overall, single IV administration of JK07 support the proposed IV clinical route of administration. These studies demonstrate that an IV infusion of JK07 at an HED of 0.32 mg/kg has potential cardiac benefit in the absence of toxicity in

monkeys. The FIH starting dose is 0.03 mg/kg as a single 60-minute IV administration and is 32 x lower than the estimated NOAEL in humans derived from a repeat-dose toxicity study in monkeys and 10 x lower than the effective HED derived from the PD studies in monkeys with HFrEF.

A detailed description of the chemistry, nonclinical pharmacology, pharmacological, and safety results of JK07 is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

JK07 is a FIH study and has, therefore, not been previously evaluated in human subjects with HFrEF; however, clinical safety reported with recombinant human NRG-1 therapies include most commonly GI disorders (e.g., nausea, diarrhea, vomiting, poor appetite) and reports of headache, dizziness, and fatigue (Lenihan et al., 2016; Gao et al., 2010; Jabbour et al., 2011). Gastrointestinal AEs were most often observed at the higher doses. Serious treatment-emergent AEs (TEAEs) were uncommon with both agents.

While these initial studies showed that recombinant human NRG-1-based therapies were generally well tolerated in patients, the observance of long-term cardiac effects makes clinical evaluation in healthy volunteers unethical. It is the sponsor's opinion that given the potential for an extended duration of CV effects, the FIH study should be conducted in subjects with HFrEF (LVEF ≤40 %).

Additionally, consistent with findings in studies conducted and published with NRG-1 in humans (Lenihan et al., 2016; Jabbour et al. 2011), JK07 showed sustained ameliorative effects following an acute dosing period in rat and rhesus monkey models of HF, further reinforcing the rationale for a FIH study in patients.

JK07 has been tested in a comprehensive toxicology program. A single dose IV study has been performed in monkeys with a 2-week follow-up. Repeat-dose IV studies for durations of up to 2 weeks in the rat, with twice-weekly administrations and a 2-week recovery period, and up to 4 weeks in the monkey, with weekly administrations and a 4-week recovery period, have also been completed. Tissue cross-reactivity of JK07 with human tissues in vitro has been conducted.

In the more relevant monkey species, two toxicology studies were conducted. In a single-dose non-GLP toxicology study, reflective of the single-dose study design proposed for the FIH clinical study, the NOAEL was 30 mg/kg, or 320 x the proposed starting HED of 0.03 mg/kg. Target organ effects were observed in heart and/or kidney in males and female animals given ≥10 mg/kg in this study, which is 107 x higher than the proposed starting HED. In a repeat-dose pivotal GLP toxicology study in monkeys, the NOAEL was 3 mg/kg, or 32 x the proposed starting HED.

Overall, IV administration in non-clinical studies of JK07 supports the proposed IV clinical route of administration. These studies demonstrate that an IV bolus infusion of JK07 at HEDs of 0.16 to 0.32 mg/kg/dose has potential cardiac benefit in the absence of toxicity in rats and NHP, respectively.

In the GLP-compliant 4-week repeated-dose toxicity study in cynomolgus monkeys, minimal and transient JK07-related prolongation in heart rate corrected QT (QTca) intervals were observed. The maximum increase recorded was approximately 23 msec; a QTca dose response was not evident. The minimal and transient QTca prolongation observed in this study did not result in any cardiac electrical instability. No JK07-related abnormalities in rhythm or waveform morphology were found at any dose level based on comparison of predose and postdose electrocardiographic recordings. There were no JK07-related changes in ECG parameters and all ECGs evaluated in this study were qualitatively considered normal for cynomolgus monkeys. Nevertheless, an inpatient stay will be required in this FIH study in order to monitor subjects by ECG and telemetry during the first 48 hours after IP administration, with additional follow-up monitoring at later time points as detailed in Table 1 (SoA).

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study. This study will be performed in compliance with the

protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements. Aspects of the study concerned with the investigational product(s) (IPs) will meet the requirements of Good Manufacturing Practice (GMP).

3.0 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are described in Table 3.

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• Assess the safety and tolerability profile, including immunogenicity, of JK07, administered IV according to protocol-defined dosing regimen.	• Incidence and severity of TEAEs and their relationship to the IP. • 12-lead ECG parameters (heart rate, PR, QRS, QT, QTcF) change from baseline derived as mean from triplicate ECG recordings 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). • Laboratory parameters – change from baseline each assessment time point per Table 1 SoA postdose: hematology, chemistry, coagulation, and lipid panels. • Immunogenicity o Incidence of early and delayed-type hypersensitivity responses. o Presence of serum anti-JK07 antibodies (confirmed positive antibody response, titer, neutralizing antibodies). • Vital signs – change from baseline in vital signs and the relationship to JK07 compared with placebo, including: o Blood pressure (BP) o Temperature o Heart rate (HR) o Respiratory rate (HR)
Secondary	
• To determine the PK characteristics of JK07 administered IV according to protocol-defined dosing regimen.	• PK parameters of intact JK07 including, but not limited to, maximum concentration (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), and volume of distribution (V_z). Surrogate measurement of intact JK07 to be carried out through detection of both the JK07 antibody domain and the JK07 NRG-1 peptide fragment in the evaluation of PK parameters.
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.	• Microbubble contrast-enhanced (2D-TTE) results, including, but not limited to: 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, and multiple calculated monitoring parameters using velocity and flow measurements, including stroke volume (SV), cardiac output (CO), derived left ventricular filling pressure (E/e'). • Observed biomarker concentrations and corresponding changes from baseline. • Concentration-QT correlation performed on the QTcF time matched with PK.

4.0 STUDY DESIGN

4.1 Overall Design

This is a phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study to assess the safety, tolerability, immunogenicity, and PK of JK07 in HF subjects 18 to 80 years of age with LVEF ≤40 %.

To be eligible for this trial, subjects must have been maintained on an optimal HF medical regimen for at least 2 months prior to informed consent and remain on the same treatment regimen throughout the course of the study, per the 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines/Heart Failure Society of America (ACC/AHA/HFSA) treatment guidelines (Yancy et al, 2017).

Subjects will give informed consent prior to initiation of screening procedures. During screening, all subjects will undergo 2D-TTE to measure the following parameters: left ventricular chamber dimensions, including LVESV and left ventricular end diastolic volume (LVEDV), LVEF, and multiple calculated monitoring parameters using velocity and flow measurements (i.e., stroke volume [SV], cardiac output [CO], derived left ventricular filling pressure (E/e') according to the American Society of Echocardiography guidelines (full set of measurements provided in Section 11.0, Appendix 5). Subjects will also undergo a physical examination, 12-lead ECG assessment, blood sampling for laboratory parameters, and urine testing. Safety assessments at screening will include hematology, biochemistry, coagulation, liver, and thyroid function. There will be additional blood sample collection prior to IP administration for baseline myocardial biomarkers, PK, and immunogenicity assessment (Table 1).

A Data Review Committee (DRC) will be established to review emerging data, to monitor safety aspects of the study, to select the JK07 dose during dose escalation, and to adapt the randomization scheme. The DRC will evaluate the emerging clinical, laboratory and cardiac safety data, from the first three days postdose for the sentinel subject, prior to randomized blinded IP administration in the remainder of the cohort.

Initially 5 dose escalation cohorts are planned with the option at the discretion of the DRC to expand the study to a total of 7 dose escalation cohorts. The size of the cohorts will range from 5 to 9 subjects. A maximum of 63 subjects will be enrolled into dose escalation cohorts. Each dose escalation cohort will include one single active unblinded sentinel subject receiving a single IV dose of JK07 prior to randomized JK07 or placebo administration in the remainder of the cohort.

Subjects will be observed in the hospital on continuous telemetry from as soon as practicable following admission and prior to IP administration, and until shortly before discharge on Day 3. During this time, they will additionally have safety labs, vital signs, PK, and biomarker samples collected, and ECGs and 2D-TTEs performed. Hospital evaluation is performed for safety reasons. 12-lead ECG values will be extracted within 10 minutes prior to the time-matched PK sample collections. Subjects will be observed for injection site reactions until Day 4 following IP administration, for dose-limiting adverse events (DLAEs) until Day 15 following IP administration, and for SAEs from the time of enrollment until 30 days after the IP administration. Following the Day 30, only SAEs deemed at least possibly related to the study drug or study procedures should be collected.

4.2 Scientific Rationale for Study Design

Compared with an open-label design, double-blind trials are an especially stringent way of conducting a trial that attempts to eliminate subjective, unrecognized biases carried out by experimental subjects (usually human bias) and conductors. In most cases, double-blind studies are regarded to achieve a higher standard of scientific rigor than single-blind or unblinded studies.

Evaluating JK07 using a rigorous double-blind trial in a patient population with HF provides more reliable data to assess the safety and exploratory efficacy of the product in patients affected by HF. Furthermore, since subjects enrolled in this trial must have been maintained on an optimal HF medical regimen (Yancy et al, 2017) for at least 2 months prior to informed consent and remain on the same treatment regimen throughout the course of the study, there is no detriment to the blinding, either to placebo group or the active treatment group. Specifically, subjects will remain on their standard clinician-directed appropriate pharmacological therapy, meaning there is no added risk related to medication changes for subjects enrolled in the trial. Moreover, initial confinement of subjects at the clinic and overall extensive safety assessments will permit careful monitoring of study effects under blinded conditions, and analysis by categorical and continuous descriptive statistics.

Key inclusion criteria of this proposed phase 1 study are "subjects between ≥18 and ≤80 years of age with stable NYHA Class II or III HF diagnosis, LVEF ≤40 %, and on stable doses of HF therapy (except for diuretics) as per the 2017 ACC/AHA/HFSA treatment guidelines (Yancy et al, 2017) for at least 2 months prior to informed consent" (Section 5.1). This population is appropriate for the primary safety evaluation of JK07 in this FIH study and includes patients who may benefit from this treatment. In order not to confound the initial safety results with tenuous subjects, subjects with NYHA Class IV will not be included. Analogous recombinant human NRG-1 therapies were generally well-tolerated in NYHA Class II and III subjects (Lenihan et al., 2016; Gao et al., 2010; Jabbour et al., 2011). The cimaglermin phase 1 study enrolled adult patients with NYHA Class II and III HF with reduced ejection fraction (LVEF ≤40 %) (Lenihan et al., 2016). Similarly, patients with NYHA Class II and III HF with LVEF <40 % were enrolled in both published Neucardin phase 2 studies (Gao et al., 2010; Jabbour et al., 2011). All 3 studies enrolled patients on stable standard therapy.

Generation of initial phase 1 data in this moderately affected HF population will provide support for the evaluation of safety and efficacy in future studies that may include more severe patients, including NYHA Class IV HF. While the sponsor expects more severe HF patients could benefit from treatment with JK07, inclusion of NYHA Class II patients showing mild symptoms and impairment due to HF is important, as these patients may have more of an opportunity to benefit from cardiac regeneration due to JK07 treatment earlier during disease, to slow, stabilize, or reverse disease progression. Moreover, although the primary objective of the study is to assess the safety of JK07, the recruitment of HFrEF patients rather than healthy volunteers may increase the ability of this study to detect signals of efficacy.

The study will also include a sentinel subject (1 active treated subject) in each dosing cohort to protect the population involved in the study by potentially identifying any serious AE in a single subject prior to exposing an entire cohort to the treatment, thereby increasing the level of safety in this JK07 phase 1 trial. The low(er) dose cohorts are sized at 5 subjects (1 active lead-in followed by a randomized active: placebo [3:1] main cohort) to effectively escalate through dose levels not anticipated to exert any effects. Dose escalation will not occur until at least 14 days of safety data (i.e., through Day 15) have been evaluated by the DRC and the dose has been established as safe and well tolerated. Following observation of a clinical effect, the DRC has the option to expand the size of the cohort at which the clinical effect was observed and subsequent cohorts to a total of 9 subjects (1 active lead-in followed by a randomized active:placebo [6:2] main cohort). The expanded cohort size will allow a more robust evaluation of JK07 doses with clinical activity. All cohorts shall proceed per the treatment algorithm, with continuous monitoring of emerging safety data, including clinical signs, laboratory values, and cardiac safety monitoring. Although it is appreciated that some adverse effects could take longer to manifest, it is believed that the time frame between the dosing of the sentinel subject and the subsequent cohort of approximately 5x the anticipated half-life ($t_{1/2}$) of the JK07 is enough to minimize this risk.

A GLP-compliant 4-week repeated-dose toxicity study in cynomolgus monkeys showed minimal and transient JK07-related prolongation in QTca intervals (the maximum increase recorded was approximately 23 msec; a QTca dose response was not evident). The current phase 1 study requires subjects to be confined in the hospital on continuous 12-lead Holter/telemetry combination prior to dose administration and for

48 hours following dose administration. Baseline-corrected (clock-time matched) QT and QT interval corrected for heart rate using Fridericia's correction formula (QTcF) intervals will be evaluated for potential effects by JK07. If effects are evident, a concentration-response relationship between time-matched JK07 concentrations and change in QTcF interval will be explored.

In the same study dose-independent minimal to moderate myocardial degeneration was observed during autopsy. The current phase 1 study requires 2D-TTE monitoring at screening, during the hospital stay and at multiple follow-up visits to check for improvement or worsening of indexes of myocardium contractility.

In the same study, there were also a dose-independent minimal JK07-related increases in cardiac troponin I (cTnI) at 10 and 30 mg/kg on Day 8 and at 30 mg/kg on Day 28, with recovery by Day 56. Although the highest cTnI values occurred in a control animal at multiple time points (Animal No. 1504, Days -7 through 28), the increased frequency of values at 10 and 30 mg/kg suggested a possible JK07-related effect. Since the increases in cTnI could potentially be correlated with microscopic findings of myocardial degeneration, this phase 1 study will monitor a wide panel of safety and efficacy biomarkers which are useful to carefully detect any effect of JK07 on myocardium (NT-proBNP, total BNP, high-sensitivity C-reactive protein [hsCRP (], troponin-I, high-sensitivity [hs]-troponin T, creatine phosphokinase [CPK], creatine kinase-muscle/brain [CPK-MB]). It should be noted that NRG-1 directly activates NT-proBNP expression which complicates the normal relationship between the levels of that biomarker and cardiomyocyte damage. Changes in this biomarker, therefore, need to be interpreted with caution and in the context of the totality of the data.

Systemic exposure of JK07 will be measured by utilizing an immunoassay targeting two different domains of JK07. The capture antibody will be specific for the NRG-1 sequence of JK07, and the detection antibody will be specific for the antibody domain, using a biotinylated anti-idiotype antibody binding to the variable sequence of JK07 antibody domain. Use of the two antibodies together will provide exposure data specifically for the intact JK07 molecule over time across JK07 dose levels. NRG-1 peptide cleaved from JK07, with or without the linker, is expected to have a very short half-life in circulation and to be below detectable levels in circulation.

As JK07 is a monoclonal antibody, anti-drug antibody (ADA) response for JK07 will be evaluated periodically throughout the study with blood samples collected as early as 3 days after dose administration.

4.3 Justification for Dose

Cohort dose levels of JK07 are as follows: the clinical starting dose of a single 0.03 mg/kg IV infusion has been selected at 1/32 of the HED at the NOAEL in the cynomolgus monkey (3 mg/kg/week). A conservative approach of body surface area scaling was employed for this conversion of HED at the monkey NOAEL (0.97 mg/kg/week). The subsequent provisional doses have been set at a 3-fold increase from the prior dose for the first 2 dose escalations (Cohort 2 through Cohort 3). The subsequent dose escalations (Cohort 4 through Cohort 5) have been set at a 2-fold increase from the prior dose; based on emerging safety and/or PK results of the previous cohorts; the DRC can allow a 3-fold increase. Additionally, the DRC may also reduce the incremental dose escalations based on the results of the previous cohorts (Table 4).

The sponsor and the FDA agreed that, as a conservative approach, a starting dose should be chosen which is unlikely to exhibit any clinical effect. On a molar equivalent basis, the starting dose is equivalent to the cimaglermin dose of 0.015 mg/kg, which is at the low end of the three pooled dose levels which did not show clinical efficacy with cimaglermin (0.007 mg/kg, 0.021 mg/kg, and 0.063 mg/kg), and 100 x below the dose level at which a DLAE was observed for cimaglermin.

Table 4 Dose Escalation Per Cohort

Dose Level	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

Note: Initially 5 cohorts are planned. Two additional higher cohorts may be added as per the DRC recommendation (total up to 7 cohorts). The highest JK07 dose administered not to exceed 2.5 mg/kg without further amending the protocol.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in Table 1 SoA.

4.5 Dose Escalation Criteria

The DRC will evaluate each sentinel, as well as active and placebo subjects in each dose cohort for DLAEs. To support dose escalation, safety, and tolerability results for all subjects within a cohort through at least Day 15 will be included in this review. At the time of the DRC safety review of the entire cohort, PK results, if available for that cohort, will be evaluated (along with results of prior cohorts, as applicable).

At any time during the trial, the Sponsor has the right to discontinue the trial. Any consented subject who is withdrawn due to an AE or screen failure prior to the IP administration will be replaced.

If recommended by the DRC, up to 2 additional higher dose cohorts, at incremental dose levels to be determined by the DRC, may be enrolled to further evaluate the safety and tolerability, PK parameters, and exploratory PD/biomarker endpoints of JK07 at doses greater than 1.08 mg/kg without a protocol amendment. The highest JK07 dose administered will not exceed 2.5 mg/kg without further amending the protocol. After due consideration, the DRC may recommend a modification to the Table 1 SoA based on emerging safety or PK results. Scheduled times of assessments may be modified without an amendment if the length of the study duration (end-of-study visit) is not extended, and the changes do not result in more than 1 additional visit. Furthermore, collection of blood for 1 additional set of laboratory evaluations, 1 PK sample, and/or 1 biomarker sample may also be added without a protocol amendment. Should the DRC make recommendations for more extensive changes to the study, the Sponsor may choose to amend the protocol to allow for these changes.

Also see Section 4.1, Overall Design

Note: Should a safety concern arise other than the DLAE, the DRC might recommend that the trial stop after discussion with the Sponsor. The dataset may be unblinded for each cohort but no less than 30 days after the DRC has made the decision to proceed to the next cohort.

4.6 Study Stopping Criteria

Intravenous administration for any individual subject will be stopped if the subject experiences a serious adverse event (SAE) or a clinically significant, drug-related AE during the infusion, which in the opinion of the study physician, Principal Investigator, or Sponsor's medical representative, warrants discontinuation of the study for that subject's well-being. The definitions of an AE and an SAE can be found in Section 8.3.

The final determination of whether any AE observed following JK07 administration is considered dose-limiting will be at the discretion of the DRC. Guidance provided to the DRC will be to view as a possible DLAE any AE at least possibly related to IP that results in any new finding of the following if observed within the first 15 days of treatment (DLAE assessment period):

- Any febrile neutropenia [absolute neutrophil count (ANC)] <1000/mm^3, temperature >38.3 °C (101 °F)] for >1 hour.
- Any signs and/or symptoms of myocardial ischemia/myocardial infarction (diagnosis to be based on Thygesen et al. 2018), and any asymptomatic/symptomatic significant (> 2 mm for > 2 minutes) new ST segment deviation (elevation or depression), as defined in Hicks et al. 2018.
- Any emergent symptomatic or asymptomatic cardiac arrhythmia requiring at least urgent medical intervention.
- Any ≥ QTc(F) prolongation of >500 msec or >60 msec above baseline (based on an average QTcF value of triplicate ECGs).
- Any emergent ≥ severe (corresponding to CTCAE v5 Grade 3) hematologic, non-hematologic, hepato-cellular, or renal toxicity except for untreated nausea, diarrhea, vomiting, constipation, abdominal pain. Any of these will be considered DLTs if persisting >72 hours despite appropriate treatment.
- Any at least moderate CD4 lymphocyte count ≤400 mm^3.
- Any at least moderate infusion-related reaction or inability to deliver a complete dose due to possible treatment-related toxicity.
- An AE or SAE that, in the opinion of the DRC, is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk. In addition, the DRC may identify as a DLAE, any AE that impairs daily function, or abnormality occurring in subjects treated with JK07 at any time during the trial.

Each DLAE must be recorded in the eCRF.

4.6.1 Stopping Criteria for Individual Subjects

The infusion for any individual subject will be stopped if the subject experiences a SAE or a clinically significant possibly drug-related related AE during the infusion, which in the opinion of the study physician, Principal Investigator, or Sponsor's medical representative, warrants discontinuation of the infusion for that subject's well-being.

4.6.2 Criteria for Stopping Dose Escalation

The decision to stop dose escalation will be at the discretion of the DRC and all the criteria leading to this decision will be documented in the meeting minutes.

If the DRC decides not to dose escalate, the current cohort may be expanded, if not already at the maximum size, following which further dose escalation could proceed. If the decision is to de-escalate to the prior cohort, up to 8 subjects randomized (6:2, JK07:placebo), without an additional unblinded sentinel subject may be added to the cohort, after which, safety and tolerability will be reassessed. If the decision is to de-escalate to an intermediate dose between the prior cohort and the cohort at which dose escalation was halted, the cohort will comprise a single sentinel subject receiving JK07 followed by randomization of a minimum of 4 subjects (3:1, JK07:placebo) in the cohort. See Section 9.6 for details regarding the number of subjects to be enrolled in de-escalated or intermediate de-escalated cohorts.

4.6.3 Criteria for Stopping the Study

Criteria for stopping the study will be at the discretion of the DRC and all decisions taken will be clearly documented in the meeting minutes. This decision will be based on the cumulative evaluation of the study results and include not only DLAE but also safety concerns other than DLAEs which may arise.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. 18 to 80 years of age, with stable NYHA Class II or III HF diagnosis, evident at least 6 months prior to enrollment as confirmed by medical history.
2. Stable HF defined as no hospitalizations for cardiac-related issues within the previous 2 months prior to the screening visit or between screening and randomization, other than for routine percutaneous procedures such as device, battery, generator changes or pacemaker lead insertion/replacement.
3. Subjects with clearly interpretable ECHO images and with a screening LVEF ≤40 % in the absence of ≥Grade 3 valvular disease on 2D-TTE.
4. Subjects must be taking clinician-directed appropriate pharmacological therapy for HF as per the 2017 ACC/AHA/HFSA treatment guidelines (Yancy et al, 2017) and at investigator determined discretion at stable doses (except for diuretics) for at least 2 months prior to informed consent.
5. Subjects without implantable cardioverter-defibrillators (ICDs) are eligible. Subjects with ICDs are allowed at the discretion of the investigator, but only if both of the following criteria are met: (a) paced beats cannot exceed 15% of beats as quantified by screening e-Patch, and (b) if a non-paced baseline ECG can be obtained on Day 1 prior to study drug administration.
6. Body mass index ≥18 kg/m^2 and ≤45 kg/m^2
7. Screening hemoglobin ≥9.0 g/dL, platelets ≥100x10^9 /mL, ANC ≥1500/mL.
8. Sexually mature male subjects must agree to use a medically accepted method of contraception throughout the study and be willing and able to continue contraception until the end of the study (6-month time point).
9. Females of childbearing potential must present with a negative blood pregnancy test, must not be lactating, and must agree to employ adequate birth control measures for the duration of the study and be willing and able to continue contraception until the end of the study (6-month time point).
10. Subject is capable of giving signed informed consent as described in Section 11.0 Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
11. Subject is willing and able to comply with the requirements of the protocol.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Participating in any other study and have received any other investigational drug within 30 days prior to screening or 5-half-lives, whichever is longer, or any other investigational implanted device within 30 days prior to screening, or are taking part in a nonmedication study which, in the opinion of the Investigator, would interfere with study compliance or outcome assessments.
2. Any past participation in a study that has investigated the NRG-1 pathway (e.g., Neucardin, cimaglermin).

3. Heart failure due to hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia (ARVD), stress-induced ("Takotsubo") cardiomyopathy, chemotherapy-induced cardiomyopathy, peripartum cardiomyopathy, infiltrative or inflammatory cardiomyopathies, and primary valvular disease.
4. Diagnosed with medically documented acute coronary syndrome within 3 months of screening or a medically documented acute myocardial infarction within 6 months of screening.
5. Cardiac surgery, coronary artery revascularization, percutaneous coronary intervention, or valvuloplasty within 3 months prior to screening.
6. Any subject who has received an indication for coronary revascularization within 3 months prior to screening.
7. Any major surgical procedure within 1 month prior to screening or planned surgical procedure during the study period.
8. Sustained systolic BP <90 mm Hg and/or diastolic BP <50 mm Hg (confirmed by a duplicate seated reading) on at least 3 consecutive readings (office) following informed consent and prior to randomization, or overt symptomatic hypotension defined as a decrease in systolic BP of 20 mm Hg or a decrease in diastolic BP of 10 mm Hg within three minutes of standing when compared with BP from the sitting or supine position or accompanied by dizziness, syncope, blurry vision.
9. Resting HR >100 beats per minute (bpm) at Screening (Visit 1) or prior to randomization which is sustained for >15 minutes in two episodes separated by one hour of observation except in sustained atrial fibrillation when HR of up to 110 bpm is acceptable.
10. Cerebrovascular accident or hospitalizations for CV (cardiovascular) causes other than routine percutaneous procedures such as device, battery, generator changes or pacemaker lead insertion/replacement, including HF, chest pain, stroke, transient ischemic attack, or arrhythmias within 2 months prior to screening.
11. Subjects at screening have an abnormal or clinically significant 12-lead ECG abnormality, that, in the opinion of the Investigator, would affect efficacy or safety evaluation or place the subject at risk.
12. History or evidence of clinically significant arrhythmias uncontrolled by drug therapy or use of an implantable defibrillator, long QT syndrome, or evidence of QT prolongation with QTcF >450 ms for males or QTcF >470 ms for females during screening and/or prior to randomization.
13. Clinically significant renal dysfunction as measured by the estimated glomerular filtration rate of <45 mL/min/1.73m^2 as calculated by local laboratory standards (Cockcroft-Gault equation for estimation of creatinine clearance [CrCl] [Cockcroft and Gault. 1976]) at screening, or a clinically significant change in renal function between screening and baseline.
14. Clinically significant liver dysfunction as measured by: ALT >2.0 × the upper limit of normal (ULN), alkaline phosphatase > 2.0 × ULN, AST >2.0 × ULN, or GGT >2.0 × ULN or serum bilirubin ≥ 1.2 × ULN at screening, or a clinically significant change in liver function between screening and baseline.
15. Subjects with alteration of the coagulation panel (international normalized ratio [INR]) and/or prothrombin time (PT) ≥1.5 × the ULN; activated partial thromboplastin time (aPTT) ≥1.5 × ULN, or serum albumin ≤3 gm/dL. For subjects on warfarin or other anticoagulants, an INR (or PT) considered by the Principal Investigator as therapeutically appropriate will be allowed.
16. Subjects with values of total CPK and/or CK-MB >2.5x ULN per institutional standards at screening.

17. Any subject who by Investigator's judgement, has a significant hematuria or proteinuria at screening.
18. Concurrent treatment with Class Ia or III antiarrhythmic drugs (the medication must have been discontinued more than 2 months before informed consent).
19. Positive screening for human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C virus antibodies.
20. Known history of or active alcohol abuse (no more than 14 units/week for males or 7 units/week for females) or use of illicit drugs within 1 year prior to randomization (excluding recreational use of marijuana or cannabidiol [CBD]-based products).
21. Other medical or psychiatric condition that, in the opinion of the Investigator, would preclude obtaining voluntary consent/assent or would confound the secondary objectives of study.
22. A history of pathologically confirmed malignancy of any type or any pathologically confirmed pre-malignant condition (e.g., ductal carcinoma in situ, colonic polyp with premalignant diagnosis, or cervical atypia). All subjects are to undergo cancer screening following study enrollment in accordance with American Cancer Society Guidelines (See Section 11.0 Appendix 1).
23. Pregnant or lactating at screening.
24. Subjects with clinically significant or poorly controlled disease including, but not limited to, endocrine (including diabetes and thyroid) disease, neurological or psychiatric (even mild), GI, hematological, urological, immunological, or ophthalmic diseases as determined by the Investigator.
25. Subjects who are not non-smokers or light smokers (no more than 5 cigarettes per day) and who cannot abstain from smoking from 2 weeks prior to the administration of IP through the end of the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects are required to fast for at least 10 hours prior to each visit, including the Day 1 hospital admission.

On Day 1, pre-dose assessments will be performed after a minimum 10 hour fast. A light breakfast/snack will be provided after completion of all scheduled pre-dose assessments. Subjects will receive a typical institutional lunch and dinner for a HF patient. A snack may be allowed in the evening of Day 1. The snack must be consumed to allow for a minimum 10-hour fast so that the 24-hour Day 2 procedures are clock-time matched to the extent possible to predose of Day 1 (See Table 2). Subjects should receive the same lunch, the same dinner, and the same evening snack, at as close to the same times as possible, on Day 2. Subjects must again be fasted for at least 10 hours prior to the 48-hour Day 3 study procedures.

5.3.2 Caffeine, Alcohol, and Tobacco

Subjects with a known history of alcohol abuse will be excluded from this study. From Day 1 until completion of the 12-lead ECG and related study procedures on Day 3, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate). Subject will have to abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) starting 24 hours before any subsequent visit.

From Day -3 until completion of the 12-lead ECG and related study procedures on Day 3 subjects will abstain from alcohol intake and will have to abstain from alcohol intake starting 24 hours before all subsequent visits.

Subjects who use tobacco or e-cigarette products, or CBD products, will be instructed that use of nicotine-containing products (including nicotine patches) or CBD products will not be permitted from two weeks prior to IP administration until after the final follow-up visit.

5.3.3 Activity

Subjects will remain in the hospital for Day 1 and the initial 48 hours of the postdose period for safety evaluations: vital sign assessments, physical exams, blood, and urine collections for PK (blood only), biomarkers, and safety laboratory assessments, and telemetry/ECG evaluation. During the full course of the study any contact or vigorous competitive sporting activity must be avoided.

5.4 Screen Failures

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.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened without consent of medical monitor.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol (Table 5).

This is a double-blind study. The investigational treatment and placebo infusions will be identical in physical appearance. Other than in the case of sentinel subjects, the treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor, study vendors, or DRC. The treatment codes will be held by a third-party clinical research services vendor designated by the Sponsor.

Where possible, and as applicable, hospital admission and IP administration should take place on Monday or Tuesday to allow for Day 7 follow-up visits to take place on the following Monday.

6.1 Study Treatment(s) Administered

Table 5 Study Treatment Details

Study Treatment[a] Name:	JK07 (recombinant fusion protein consisting of a fully human immunoglobulin G1 monoclonal antibody and an active polypeptide fragment of the human growth factor NRG-1)	JK07 matching placebo
Dosage Formulation:	Sterile solution	Sterile solution
Unit Dose Strength(s)/Dosage Level(s):	20 mg/mL JK07 in 2 mL of formulation buffer containing 25 mM histidine/histidine-HCl, 205 mM sucrose, 0.04 % (w/v) polysorbate 80, pH 6.0.	Formulation buffer (25 mM histidine/histidine-HCl, 205 mM sucrose, 0.04 % polysorbate-80, pH 6.0).
Route of Administration:	Intravenous (IV) infusion over 60 minutes using a syringe pump or infusion pump	IV infusion over 60 minutes using a syringe pump or infusion pump
Dosing Instructions:	Single dose per protocol treatment regimen	Single dose per protocol treatment regimen
Packaging and Labeling:	Study treatment will be provided in a single-use vial or vials. Each vial will be labeled as required per country requirement. JK07 will be provided with the appropriate infusion kits as part of the Clinical Trial Supplies.	JK07-matching placebo will be provided in the appropriate infusion kits as part of the Clinical Trial Supplies.
Manufacturer:	Emergent Camden	Emergent Camden
Prepared Solution Expiration:	JK07 infusions will be prepared at the study center for administration within 4 hours following the dose preparation.	Placebo infusions will be prepared at the study center for administration within 4 hours after dose preparation.

[a] With the exception of IP infusion administered to the sentinel subject in each cohort, all study staff will be blinded to IP identification

The infusion will be managed through a syringe pump or infusion pump. A needle or catheter between 16G and 21G is required by this protocol (choice as per Site procedures); needles narrower than 21G are NOT allowed. The total infusion time, inclusive of saline flush should be 60 minutes and should not exceed 75 minutes, and reasons to exceed this time must be reported. The infusion time should not be less than 60 minutes under any circumstance. The date/time of start and time of stop of the infusion, infusion rate, volume infused, any interruption, and stop/restart will be documented in the eCRF.

A detailed description of the shipment, storage, and preparation of IP is provided in the Pharmacy Manual.

In the event of a presumed acute infusion reaction, institutional standard of care treatment should be undertaken. If the infusion must be stopped in the opinion of the investigator due to an AE, the infusion may NOT be restarted (Section 4.6.1). The AE must be documented in the eCRF.

6.2 Preparation/Handling/Storage/Accountability

1. All investigational drug supplies in the study will be stored at 2-8 °C in a secure place under the responsibility of the Investigator or other authorized individual.
2. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
3. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. Designated pharmacy staff will prepare the study drug. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff. Preparation of study drug will be documented in accordance with local site standard of practice.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). All records must be available for inspection.
5. Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual and Clinical Monitoring Plan.

6.3 Randomization and Blinding

All subjects other than sentinel subjects will be centrally assigned to randomized study treatment using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each study center.

Subjects will be randomized to study treatment via stratified randomization. Separate randomization schedules will be used within each cohort (randomly permuted blocks within strata).

Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Trial Management Associate and Sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. Under no circumstances should there be any delay in emergency treatment of a subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (eCRF), as applicable.
Blinded FIH which may require unblinding subject/cohort	After each dose group, the DRC will determine the dosing regimen(s) for the next cohort. This decision will generally be made without breaking the randomization code. If judged necessary by the DRC, an individual or the complete cohort may be unblinded during evaluation of the study data. Before unblinding, a decision should be made about the action to be taken based on the revealed treatment allocation. The rationale for unblinding, etc., will be documented in meeting minutes.

Sentinel Subject	Each cohort at a new dose level higher than those previously tested shall have a single unblinded sentinel subject who will receive active treatment.
Unblinding by cohort	Thirty days following the decision by the DRC to dose escalate to a new dose level, unblinding of the previous cohort is permitted.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs. All dose administrations will be performed in the study center, in resting conditions under the supervision of appropriately trained staff.

6.5 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or [herbal] supplements) that the subject is receiving at the time of informed consent (within 30 days before informed consent) or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

All medications and concomitant treatment administered from screening through the final study visit (Early Termination or End of Treatment) will be recorded. Documentation will include the name of treatment, indication, dose (including units), and date(s) of administration.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. A list of excluded medications/therapy is provided in Section 11.0, Appendix 4. Initiation of any new medications after enrollment must be discussed with the CRO and Sponsor Medical Monitor prior to initiation.

Other than in the event of an infusion reaction, acetaminophen use is prohibited for the period beginning 7 days pre-dose and ending 15 days postdose, and outside of this time should be used only occasionally and at doses approved for the age of the subject. Occasional use of ibuprofen or naproxen sodium for pain relief, at doses approved for the age of the subject, is permitted. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.

6.5.1 Rescue Medicine

Not applicable.

6.6 Dose Modification

As this is a single-dose study, dose modification within an individual subject is not applicable. Dose escalation and de-escalation criteria within a cohort may be found in Section 4.5.

6.7 Treatment after the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for subjects with HFrEF, so these subjects will continue with the optimal therapy for HFrEF as established by the 2017 ACC/AHA/HFSA treatment guidelines (Yancy et al, 2017).

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects are free to withdraw consent and discontinue participation in the study at any time, without prejudice. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator, as further described in the protocol.

The process for dose escalation and the stopping criteria for the study are described in Section 4.0.

If a subject, who does not meet enrollment criteria, is inadvertently enrolled, and the failure to meet enrollment criteria is discovered prior to IP administration, the subject should be discontinued from the study and Sponsor or Sponsor designee must be contacted. If a subject, who does not meet enrollment criteria, is inadvertently enrolled in the study, and has already received IP administration, the subject should be allowed to continue with the study given that following the single IP administration there are no additional treatments or invasive tests other than standard blood draws.

Any consented subject who is withdrawn prior to the IP administration will be replaced.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

The following actions must be taken if a subject discontinues or withdraws from the study:

- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See Table 1 SoA, End of Study visit (Day 180) for data to be collected at the time of study discontinuation. Should a subject request or decide to withdraw from the study prior to the End of Study visit, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Subjects withdrawing due to an AE at any time should be followed up until resolution, stabilization, the event is otherwise explained, the subject is lost to follow-up (Section 8.3.8) or until the end of their participation in the study. Subjects should be encouraged to complete the End of Study visit activities.
- Subjects who voluntarily withdraw will be termed dropouts. Dropouts and subjects withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the study center for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific study centers or of the study are handled as part of Section 11.0 Appendix 2.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Table 1, Table 2, and Appendix 3, Table 13 and Table 14.

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor as soon as practicable upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Table 1 SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Table 1 SoA.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, is expected not to exceed 420 mL. The planned blood collections over the first month of the study are not expected to exceed 270 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Demographic information, including date of birth, gender, ethnicity, race, height, and weight, will be recorded at the Screening Visit.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in Table 1, and Table 2, and Appendix 3, Table 13 and Table 14.

Subjects will be observed for injection site reactions until Day 4 following IP administration, for DLAEs until Day 15 following IP administration, and for AEs and SAEs from the time of informed consent until 30 days after the IP administration. Following Day 30, only SAEs deemed at least possibly related to the study drug or study procedures will be collected until the End of Study visit (Day 180).

The safety of JK07 in patients with heart failure with reduced ejection fraction will be evaluated based on criteria described by the CTCAE Version 5.0.

The investigator will monitor the occurrence of all AEs during the first 30 days after administration of the study drug. All AEs must be recorded in the source documents and on the appropriate page(s) of the case report form. All SAEs including any deaths, which occur up to and including 30 days after administration of the study drug, must be reported to the Medical Monitor within one working day, whether or not considered causally related to the study drug. Following the first 30 days, only SAEs deemed at least possibly related to the study drug or study procedures should be collected and reported as such. All AEs and SAEs will be followed until resolution, stabilization, until the event is otherwise explained, until the end of their participation in the study, or until the subject is lost to follow-up.

8.2.1 Physical Examinations

A complete physical examination will be performed at screening and include, at a minimum, assessments of the CV, respiratory, GI, and neurological systems. Height (i.e., at screening only) and weight will also be measured and recorded.

A brief physical examination will be conducted at all other visits and include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Injection Site Assessment

The site of infusion of the study drug will be assessed for local reactions at the times shown in the SoA (Table 1). Any findings (or lack thereof) will be documented in the subject's eCRF. During Day 1 (1 early assessment and 1 late assessment/end of the day), the Investigator may choose to evaluate the infusion site as deemed appropriate.

Infusion site evaluations will be made by clinical staff as described below; if an injection site reaction greater than that typically expected for the insertion of an IV line is observed, a physician will characterize and document the reaction as an AE. The infusion site will continue to be reviewed at the time points indicated in the SoA (Table 1), or until the AE is resolved.

Infusion sites will be monitored for pain, tenderness, erythema and swelling. Each infusion site reaction will be categorized using the intensity grading scheme presented in Table 6; the intensity of each resulting AE will be categorized as described in (e.g., at least moderate intensity injection site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgement).

Table 6 Injection Site Reaction Grading Scheme

Intensity Grading					
Reaction	**Absent (0)**	**Mild [a] (1)**	**Moderate [a] (2)**	**Severe [a] (3)**	**Potentially Life-threatening (4)**
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever or prevents daily activity	Any use of narcotic pain reliver or prevents daily activity	Hospital visit (A and E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	A and E visit or hospitalization
Erythema/redness	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	>10.0 cm	Necrosis or exfoliative dermatitis
Induration/swelling	Absent	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	>10.0 cm or prevents daily activity	Necrosis
Other[b]	Absent		Present		

Abbreviation: A and E; adverse event.
[a] Measurements refer to the reaction at the greatest single diameter.
[b] Any other reactions such as bruising, itching, or ulceration will be recorded as absent or graded as to severity.

8.2.3 Pregnancy Test

Subjects of childbearing potential will have a blood-based β-hCG pregnancy test performed at screening, a hospital-based qualitative immuno-assay for hCG in urine performed on Day 1 and confirmed negative prior to IP administration, and urine pregnancy tests performed at Days 30, 60, 90, 135, and 180. The screening and Day 1 results must be available and must be negative before the subject is administered the dose of the IP. A positive pregnancy test at screening or on Day 1 will disqualify the subject from the participation in the study.

8.2.4 Medical History

A complete evaluation of past medical history will be performed at screening and will include details of subjects with a stable NYHA Class II or III HF diagnosis at least 6 months prior to screening and at the time of enrolment.

8.2.5 Electrocardiograms

During Screening and beginning no more than 45 days before Day 1, all subjects will be supplied with, and instructed how to use a e-Patch for continuous 14-day heart rhythm monitoring as outlined in the Table 1 SoA. A 14-continuous day heart rhythm monitoring assessment will be collected using the e-Patch with monitoring completed no later than Day -10 unless confirmed with the sponsor.

Triplicate 12-lead ECGs will be performed prior to PK sample collection as outlined in Table 1 and Table 2. Local site will calculate heart rate and measure HR, PR, QRS, QT, and QTcF intervals for the first 48 hours. Where applicable, the screening ECG and Day 1 baseline ECG must be obtained without evidence of pacing.

All required ECG leads will be secured to the patient and attached to an ECG machine prior to administration of the IP to facilitate immediate post-infusion recording.

Subject should be supine for ≥5 minutes prior to each ECG performed.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be performed as closely as possible in succession but no more than 2 minutes apart. The full set of triplicates should be completed in <5 minutes with no more than 2 min between them.

All ECGs must be collected prior to simultaneously scheduled blood sample collections (PK, biomarker, and/or laboratory assessments).

In the first 48-hours hours post-infusion, ECGs and PK samples must be performed in close proximity (within 10 minutes up to 4 hours postdose and after the 24- and 48-hour ECGs clock-time matched to the baseline ECG; within 30 minutes prior at other times greater than 4 hours postdose).

For safety reasons triplicate 12-lead ECGs will be printed and evaluated onsite.

8.2.6 Vital Signs

- Temperature, RR, HR, and BP measurements will be assessed.
- BP and HR measurements will be assessed in resting position, with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP should be measured using the arm not used for the IP administration.
- BP and HR measurements should be preceded by at least 5 minutes of resting position for the subject in a quiet setting without distractions (e.g., television, cell phones).

- Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded in the eCRF.
- Vital signs will be collected at the same timepoint as scheduled ECG collections and prior to collection of blood for PK, biomarker and/or safety laboratory assessments.

8.2.7 Clinical Safety Laboratory Assessments

- See Appendix 3 Table 13 for the list of clinical laboratory tests to be performed and to the Table 1 SoA for the timing and frequency. See Appendix 3 Table 13 and Table 14, respectively for local and central laboratory assessments.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not related to HFrEF or any other pre-existing condition at the time of enrollment, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal, relative to baseline values, within 30 days after the dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the Table 1 SoA.
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.8 Immunogenicity Assessments

Antibodies to JK07 will be evaluated in serum samples collected from all subjects according to the Table 1 SoA. Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to JK07. Samples which show a positive response in the screening assay will be evaluated using a confirmatory ADA assay, and the confirmed positive samples will be reported and their potential for neutralizing activity will be explored. Other analyses will be performed to verify the stability of JK07 and to further characterize the immunogenicity of JK07.

The detection and characterization of antibodies to JK07 will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s). Samples may be stored for a maximum of 10 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to JK07.

8.2.9 Two-dimensional Transthoracic Echocardiography

Left ventricular and hemodynamic performance indices measured by 2D-TTE will be explored. Potential effects of JK07 will be evaluated as change from baseline and will be compared with changes from baseline in subjects receiving placebo.

On Day 1, 2D-TTE will be performed locally following American Society of Echocardiography guidelines and recommendations, pre-dose and at 6 hours ± 30 minutes, and on Day 2 at 30 hours ± 30 minutes following completion of the dosing infusion, and at subsequent times described in the Table 1 SoA.

The full examination will be evaluated locally for safety and will be digitally transferred to the Central Laboratory for centralized evaluation and centralized calculation of the measurements. Measurements taken by the Central Laboratory will include but are not limited to: ejection fraction, multiple LV chamber dimensions, including LVESV, LVEDV, as well as multiple calculated monitoring parameters using velocity and flow measurements including SV, CO, and E/e' calculations (Please see Appendix 5 for detailed listing).

8.3 Safety Monitoring and Reporting

8.3.1 Adverse Events

In accordance with the ICH E2A guideline, and 21 Code of Federal Regulations (CFR) §312.32, an 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 this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

This includes the following:

- Any abnormal laboratory test results relative to baseline values (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

8.3.2 Serious Adverse Events

An SAE is defined as an event that, at any dose, meets any of the criteria in Table 7.

Table 7 Definitions of Serious Adverse Events

Criteria	Description
Fatal:	The AE resulted in death
Life-threatening:	The AE placed the subject at immediate risk of death. (This classification does not apply to an AE that hypothetically might have caused death if it had been more severe)
Hospitalization/prolongation of hospitalization:	The AE resulted in hospitalization or prolongation of hospitalization
Disability/incapacity:	The AE resulted in a disability, significant incapacity, or substantial disruption of the subjects' ability to conduct normal life functions
Congenital anomaly/birth defect:	The AE was an adverse outcome in a child or fetus of a subject exposed to the study treatment regimen before conception or during pregnancy
Medically important	The AE was a medically important event that did not meet any of the above criteria, but may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above (examples include allergic bronchospasm that required treatment in an emergency room, seizures that do not result in hospitalization, or blood dyscrasias)

This SAE classification does not apply for the following hospitalizations:

- Admissions for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits) in the absence of any clinical AE
- Admissions at the discretion of the Investigator
- Admissions for elective or pre-planned treatment or procedure for a pre-existing condition that is unrelated to the condition under study and has not worsened since providing informed consent
- Admissions for routine treatment (e.g., platelet transfusion, IV diuresis) or monitoring of the condition under study not associated with any deterioration in condition
- Admissions for routine procedures (e.g., bone marrow aspiration, thoracentesis) associated with the disease under study
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above

Note: Complications and/or prolonged admissions for routine treatment or procedure do require SAE reporting.

8.3.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs will be collected from the time of enrollment and until 30 days after the IP administration. Following the first 30 days, only SAEs deemed at least possibly related to the study drug or study procedures should be collected.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

Investigators are not obligated to actively seek AEs or SAEs for subjects after their study participation ends. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

All SAEs will be recorded on an SAE report form and reported to the Sponsor designee within 24 hours of the investigator's awareness of the event. The Investigator will submit any updated SAE data to the Sponsor

designee within 24 hours of the investigator's awareness of any follow-up information associated with the event.

SAE reports will be submitted to IQVIA Biotech Safety Management Department via one of the following methods:

Safety email in-box: Safety-Inbox.Biotech@IQVIA.com

Safety Fax: +1 919.313.1412 (US Toll-free: 1-866-761-1274)

For initial SAE reports, the following minimum criteria must be reported on the SAE form:

- Subject Number
- Date of event onset
- Description of event
- Study treatment
- Relationship to study treatment

8.3.4 Method of Detecting AEs and SAEs

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to JK07 or study procedures, or that caused the patient to discontinue JK07 or the study (see Section 7.0).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.5 Grading and Intensity of Adverse Events

Adverse events will be graded using CTCAE v5 as shown in Table 8. The reported verbatim term should be the most descriptive medical diagnosis and does not have to be found in CTCAE v5. Regardless of severity, some events may also meet regulatory serious criteria (See Section 8.3.2).

The terms "severe" and "serious" are not synonymous. Note the distinction between the severity and the seriousness of an AE. Severity refers to the intensity of an AE. A severe event is not necessarily an SAE. For example, headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed in Section 8.3.2. "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

Table 8 Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE v5 grading criteria)	Transient or mild discomfort (<48 hours); no interference with the subject's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE v5 grading criteria)	Mild to moderate interference with the subject's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE v5 grading criteria)	Considerable interference with the subject's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE v5 grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to adverse event	

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0
a. Use the alternative descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE v5 listing.

8.3.6 Relationship to Study Drug

The investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. Some considerations are presented in Table 9.

Table 9 Relatedness of Adverse Events to Investigational Product

NOT RELATED:	This category is applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and/or the clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of the study drug and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLY, or DEFINITELY RELATED.
UNLIKELY RELATED:	This category is applicable to those AEs that could easily be explained by the patient's clinical status or other factors and/or there is a poor temporal relationship with the administration of the study drug.
POSSIBLY RELATED:	This category applies to those AEs that, are judged to be perhaps related to the study drug administration. An AE may be considered POSSIBLY RELATED when it meets at least one of the following criteria: 1. It follows a reasonable temporal sequence from administration of the study drug. 2. It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It follows a known or expected response pattern to the study drug.
DEFINITELY RELATED:	This category applies to those AEs that are incontrovertibly related to study drug administration. An AE may be assigned to this category if it meets at least the first three of the following criteria: 1. It follows a reasonable temporal sequence from administration of the study drug. 2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., depression, fixed drug eruptions, tardive dyskinesia, etc.). 4. It follows a known or expected response pattern to the study drug. 5. It reappears or worsens when the study drug is re-administered.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.3.7 Recording AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.

It is not acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested. In this case, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records before provided.

Each AE is to be evaluated for:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity (including grade changes as per the CRF completion guidelines
- Causal relationship with study drug or protocol-mandated procedures
- Seriousness
- Action taken
- Outcome

Whenever possible, a unifying diagnosis should be reported as opposed to a listing of individual symptoms. However, symptoms should be grouped into a diagnosis only if each sign or symptom is a medically confirmed component of that diagnosis as evidenced by current standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE.

A preexisting medical condition is one that is present during the screening period for this study. Such conditions should be recorded as General Medical History and Baseline Conditions. A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study.

For hospitalizations or surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

When reporting an SAE of progression of the disease under investigation, specific manifestations of the progression (e.g., acute coronary syndrome, acute pulmonary edema) should be reported, rather than the general term "disease progression."

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:

- Associated with clinical signs and/or symptoms
- Requires medical or surgical intervention
- May require a change in current therapy, and leads to study treatment discontinuation, delay, or interruption
- Otherwise clinically significant as determined by the Investigator

Whenever possible, the clinical diagnosis, rather than the laboratory result, should be reported by the Investigator (e.g., anemia versus low hematocrit).

Emergent and clinically significant abnormal laboratory values occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

Laboratory abnormalities that are not deemed clinically significant by the Investigator should not be reported as AEs.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be recorded on an eCRF and SAE report form, and expeditiously reported to the Sponsor. This includes death attributed to progression of disease.

- When recording a death on an eCRF or SAE Report Form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept.
- Death is an outcome of an event. The event that resulted in death (e.g., sepsis, stroke, myocardial infarction, etc.) should be recorded in the eCRF and reported on the SAE report form.
- If the death is attributed to progression of disease, record "disease progression" as the SAE term on the SAE Report Form.
- The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later on (e.g., after autopsy).

8.3.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3) or until the end of their participation in the study. Subjects should be encouraged to complete the End of Study visit activities.

8.3.9 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and maintain it in the site's regulatory binder along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.10 Pregnancy

Notify the sponsor or its designee regarding a pregnancy that occurs in either a study patient or occurs in the female partner of a male patient during his participation in this study within 24 hours.

If a female subject becomes pregnant after consent and during the screening process but prior to IP administration, the subject should be withdrawn immediately, and should not receive IP. If a female subject becomes pregnant after treatment, the subject should be allowed to continue with the study given that following the single IP administration there are no additional treatments and no invasive tests or procedures. Counseling should be provided to the subject in order to inform their decisions on study continuation and on the pregnancy.

While pregnancy itself is not considered an AE, any pregnancy complication should be reported to the sponsor or its designee. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth,

congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported to the sponsor or its designee as soon as the Investigator or his/her staff learns of the event. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive JK07. Details of all pregnancies in female partners of male patients will be collected after the start of JK07 and until 28 days after IP administration.

If a male subject has a female partner who becomes pregnant during the study, the subject must be unblinded in order to inform whether appropriate counseling of the female partner is necessary. In this circumstance, the unblinded male subject can remain on study and continue with follow-up visits as scheduled.

After obtaining the necessary signed ICF from the pregnant partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor designee within 24 hours of learning of the partner's pregnancy, in the same fashion as an SAE, as noted in Section 8.3.3.

The pregnant partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

8.3.11 Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study.

8.3.12 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The DRC will carefully evaluate all AEs as to whether they are considered a TEAE or DLAE.

8.4 Treatment of Overdose

The JK07 dose administered in this study should not exceed 2.5 mg/kg without further amending the protocol (See dose escalation in Table 4). An overdose is any dose above the assigned dose level for a given cohort that is administered over the pre-specified 60-minute period.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically or through the EOS visit (180 days; whichever is longer).
3. Obtain blood samples for PK analysis as specified in the Table 1 SoA.
4. Document the quantity of the excess dose as well as the duration of the infusion in the eCRF.
5. Overdose is reportable to Safety only when associated with an SAE.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

8.5.1 Collection of Samples

Venous blood samples of approximately 5 mL will be collected for measurement of serum concentrations of JK07 at times as specified in the Table 1 SoA and Table 2. Instructions for the collection and handling

of biological samples will be provided by the Sponsor in a separate Laboratory Manual. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. The actual date and time (24-hour clock time) of each sample will be recorded. The start date/time and stop date/time of the infusion and other pertinent information (See Section 6.1) will also be recorded. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Predose samples may be collected within 30 minutes prior to start of infusion. The end-of-infusion sample must be taken no later than 5 minutes from end-of-infusion. A 5-minute window will be allowed for samples taken up to 1-hour postdose; a 15-minute window will be allowed for samples taken at 2 to 12 hours postdose, a 10-minute window from the completion of ECG assessments at 24- and 48-hours postdose; a ±8-hour window is permitted for PK collections on Day 4, and a +1 day window for Day 7. For all subsequent days, the PK sample should be collected within the Table 1 SoA specified windows.

8.5.2 Determination of Drug Concentration

Samples for the determination of JK07 serum concentration will be analyzed on behalf of the Sponsor using appropriate validated bioanalytical methods. JK07 concentrations are to be determined from an immunoassay targeting both the antibody domain and the NRG-1 peptide fragment. Full details of the bioanalytical methods will be described in the separate Bioanalytical Report(s).

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Remaining serum samples may be subjected to further analysis by the Sponsor or designee for the development of additional bioanalytical assays and/or for further investigation of JK07 stability/degradation. Samples collected for analyses of JK07 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5.3 Calculation of Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.0 or higher (Certara, L.P. Princeton, New Jersey, United States of America [USA]) and/or SAS® EG 7.23 or higher (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from dosing will be used for the final serum PK parameter calculations. Nominal time from dosing will be used for any interim PK parameter calculations.

The PK parameters in Table 10 will be determined for serum JK07 concentrations obtained from both assays, when possible. A minimum of 4 quantifiable postdose concentrations will be required for all calculations.

Table 10 Plasma/Serum/Whole Blood Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Maximum concentration obtained directly from the observed concentration versus time data.
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 30%, $AUC_{(0\text{-inf})}$ 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

Dose normalized exposure parameters will also be calculated.

Additional serum parameters may be calculated if deemed appropriate. Further details with respect to the PK analysis will be provided in the Statistical Analysis Plan (SAP).

Drug concentration information that may unblind a given cohort will not be reported to study centers or blinded personnel until that cohort has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and study center study files but will not constitute a protocol amendment.

8.6 Pharmacodynamics

Pharmacodynamics will not be evaluated in this study. The exploratory 2D-TTE assessments are described in Section 8.2.9. Exploratory biomarker assessment details are outlined in Section 8.8.

8.7 Genetics

Genetics will not be evaluated in this study.

8.8 Biomarkers

- Collection of samples for biomarker research is a component of the safety monitoring for this study and also an exploratory part of this study. Samples will be tested for predictive muscle and inflammatory biomarkers to evaluate their association with the observed clinical responses to JK07. The following samples for the safety and exploratory muscle and inflammatory biomarkers will be collected from all subjects in this study as specified in the SoA:
  - Additional biomarkers: hsCRP, troponin-I and/or hs-troponin T, CPK, CPK-MB, and lactate dehydrogenase.
  - Exploratory biomarkers: NT-proBNP, total BNP
- Venous blood samples of approximately 10 mL will be collected at several time points as per the SoA (Table 1) and Appendix 3, Table 15, for measurement of exploratory biomarkers. Instructions

for the collection and handling of biological samples will be provided by the Sponsor in a separate Laboratory Manual.

- Serum biomarker samples will be analyzed by the Sponsor designated clinical laboratory (Q^2 Solutions).

8.9 Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Formal statistical hypothesis testing is not planned for this study. All analyses will be considered exploratory and descriptive.

9.2 Sample Size Determination

The study will enroll up to a maximum of 63 subjects who will be randomized into dose escalation cohorts. 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.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 11.

Table 11 Analysis Sets

Analysis Set	Description
Safety Evaluation Population	All subjects randomly assigned to the IP and who take at least 1 dose of IP. Subjects will be analyzed according to the treatment they received.
Dose-limiting Adverse Event (DLAE) Evaluation Population	All subjects who received at least 1 dose of IP and completed the 15-day DLAE follow-up period.
Pharmacokinetic (PK) Evaluation Population	All subjects who received at least 1 dose of IP and have at least 1 quantifiable IP plasma concentration collected postdose without important protocol deviations/violations or events thought to significantly affect the PK results.
Exploratory Pharmacodynamic (PD)/Biomarker Evaluation Population	All subjects who take at least 1 dose of IP and have at least 1 exploratory PD variable or biomarker endpoint collected postdose without important protocol deviations/violations or events thought to significantly affect the PD results.

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section focusses on the summary of the planned statistical analyses of the primary and secondary endpoints.

All analyses, summaries, and listings will be performed using SAS® software (EG 7.23 or higher). Results will be summarized by treatment and overall, where appropriate. Subjects who received placebo will be combined into 1 treatment group for purposes of analysis. Change from baseline will be calculated as value postdose subtracted by value at baseline. The baseline measure will be defined as the last non-missing measure prior to initiation of IP.

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

- Continuous variables: sample size (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).
- Summaries for JK07 concentrations will include the coefficient of variation and PK parameter summaries will also include the geometric mean (except for t_{max} which will only be presented as min, median, max).
- Categorical variables: frequencies and percentages.

Individual subject data will be presented in listings.

9.4.1 Efficacy Analyses

See Section 9.4.4 for assessment of exploratory efficacy analyses.

9.4.2 Pharmacokinetic/Pharmacodynamic Analyses

PK Analysis:

JK07 concentrations derived from the validated assay, concentration ratios, and calculated parameters will be listed and descriptively summarized by active treatment for the PK population (subjects who have received JK07 and do not have any protocol deviations/events which may affect the PK results). JK07 serum concentration-time profiles will be graphically displayed by treatment on linear and semilogarithmic scale for each assay, as appropriate. Scatter plots of individual values and geometric means of PK parameters, area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{(0\text{-}inf)}$ [or area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration ($AUC_{(0\text{-}last)}$) if $AUC_{(0\text{-}inf)}$ is not calculable in most subjects]), C_{max} as well as dose-normalized exposure parameters versus dose will be presented.

Dose proportionality of 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 using a power model.

Further details will be presented in the SAP.

Exploratory Exposure-Response Analysis:

An exploratory evaluation of a plasma concentration to QT (C-QT) relationship will be conducted using a linear mixed effects model, with the drug-free-corrected (Day -1-corrected) change from baseline in QTcF as the response variable, denoted as ΔQTcF. Independent variables will include the fixed effects time-matched JK07 plasma concentration obtained on Day 1, treatment indicator (treatment = 1 for subjects receiving JK07, and 0 otherwise), time point as a categorical variable, and random effects subject and time-matched JK07 plasma concentration obtained on Day 1. The analysis will be performed for the exploratory PD/biomarker population. Figures for mean time-matched change from baseline QTcF values versus JK07 mean concentrations (time-matched with QTcF) on Days 1 will also be generated. Hysteresis will be examined via by-subject hysteresis plots. Departures from a linear relationship will be examined graphically, and additional C-QT relationships other than the linear relationship may be explored if supported by data. A detailed plan of this analysis will be presented as part of the statistical analysis plan. The results for the C-QT analysis will be included in the CSR for this study. Further details will be presented in the SAP.

Exposure-response relationships may also be explored for safety and/or biomarker endpoint. Details regarding these analyses will be provided in the SAP.

Pharmacokinetic data from this study may be pooled with data from other future study(ies) and analyzed using population modeling approaches or used to explore exposure-response relationships. If performed, separate analysis plan(s) will be prepared; results from these analyses will not be part of the clinical study report.

9.4.3 Safety Analyses

All safety analyses will be performed on the Safety Population.

All safety data will be listed according to treatment group, subject number, and visit.

The AEs are defined in Section 8.3.1. The DLAE are defined in Section 4.6.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22. The number of AEs and incidence rates will be tabulated by preferred term and system organ class.

The AEs will be coded by maximum severity, relationship to study treatment, as SAEs or DLTs as needed, and will be categorized and tabulated for each treatment group (cohort).

DLAEs will be presented in the same manner as the AEs.

Incidence of injection site reactions will be summarized by treatment group, and if appropriate by assessment time.

All laboratory test results, vital signs measurements, ECG results, weight, and body mass index will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign, and ECG values will also be summarized using descriptive statistics.

For 12-lead ECG parameters (HR, PR, QRS, QT, QTcF), the 90 % confidence interval will also be presented for each parameter mean and change from baseline values. Outliers for QT and QTcF defined under outcome measures will be summarized using counts and percentages by treatment and sampling time, if appropriate and using subject-level maximum over time by treatment. The following categories will be presented by treatment and overall, for JK07:

- outlier QT and QTcF intervals (450-480 ms, 480-500 ms and >500 ms)
- change from baseline in QT and QTcF intervals (30-60 ms and >60 ms)

Additional corrections to QT may also be similarly analyzed. If relevant, analysis excluding ECGs capturing paced beats will be performed.

Abnormal findings on 12-lead ECG will be summarized by treatment using descriptive statistics.

All recorded ECGs will be interpreted on site and subsequently collected, digitized, and sent for central laboratory standardized measurements. The incidence (number of subjects and percent) of a confirmed positive ADA response will be summarized by treatment. The incidence of neutralizing anti-drug antibody response will also be summarized, if appropriate.

All data will be provided in data listings sorted by treatment group, subject number, and visit.

9.4.4 Other Analyses

Results of the exploratory endpoints (2D-TTE and biomarkers) and the change from baseline values (as applicable) will be listed and descriptively summarized by treatment and scheduled time point. Exploratory inferential comparisons to placebo may also be performed, if appropriate.

9.4.5 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of all outcomes.

Missing data will be excluded from the analyses. No imputation will be performed, unless specified.

9.5 Interim Analyses

No formal interim analyses are planned. Pharmacokinetic parameters will be calculated using available JK07 concentrations and scheduled sampling times to support JK07 dose escalation decisions, as applicable. Handling of the safety results obtained up to Day 15 after dose administrations will be described in the DRC Charter which will be prepared separately from the protocol.

9.6 Data Review Committee

A DRC consisting of members who are independent from the Sponsor will be established. The DRC will be composed of a minimum of 3 qualified cardiologists (independent voting members), and 3 non-voting members (including a biostatistician and Sponsor's medical monitor). When needed, ad hoc members or subject matter experts can be invited to participate as nonvoting participants. The DRC will have a separate charter from the protocol.

The DRC is responsible for reviewing and evaluating unblinded safety data for sentinel subjects, and blinded safety data (and safety data unblinded only on an as-needed basis) collected for at least 14 days and subsequently cumulatively at regularly scheduled meetings as defined in a separate DRC charter (minimum prior to each planned dose escalation). The DRC may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. The DRC will be responsible for making recommendations as to whether it is scientifically and ethically appropriate to continue enrollment, discontinue treatment groups, or stop the study. Additional responsibilities for the DRC include initiation of enrollment at the next dose level. The DRC meetings will be documented in written meeting minutes.

In the first cohort, if no clinical effect is observed in the sentinel subject, the DRC will decide whether to proceed with the randomization of four additional subjects (3:1, JK07: placebo) to receive blinded IP. Once the last subject in the first cohort completes the evaluation period, which includes assessments through Day 15, the DRC will decide whether to proceed to the second cohort. The second cohort and subsequent cohorts will proceed as the first cohort until either of the following occur: a sentinel subject exhibits in the opinion of the DRC, a clinical effect (efficacy or safety observation), or a cohort exhibits, in the opinion of the DRC, a clinical effect.

Once a clinical effect is observed, the DRC may, at its discretion, expand the size of that cohort in which a clinical effect is first observed, and subsequent cohorts, up to a maximum of nine subjects (1 open-label JK07 sentinel subject, and 6:2 [JK07:placebo] randomized, double-blind subjects).

Following observation of a clinical effect and a decision to expand the size of the first cohort at which the clinical effect was observed, the DRC will decide whether to dose escalate after the last subject in the expansion cohort completes the evaluation period. If the DRC establishes to escalate the dose, a single unblinded sentinel subject will receive JK07 at the next dose level. If following the completion of the evaluation period of that sentinel subject the DRC decides to proceed, the remainder of the subjects in the expanded cohort size will receive JK07 or placebo according to the direction of the DRC, and this sequence will repeat until the highest planned dose level is reached or until the DRC determines not to dose escalate further.

During the review of the safety/tolerability results the DRC may make the determination to expand the size of the current cohort further, if not already at the maximum size, following which further dose escalation could proceed. Alternatively, the DRC may determine to decrease to a lower dose level with an additional cohort, which may be an intermediary dose or a pre-assigned cohort, which would include up to eight subjects randomized 6:2 [JK07: placebo], ~~with or~~ without an additional unblinded active sentinel subject. If the decision is to de-escalate to an intermediate dose between the prior cohort and the cohort at which dose escalation was halted, the cohort will comprise a single sentinel subject receiving JK07 followed by randomization of a minimum of 4 subjects (3:1, JK07: placebo) in the cohort. For any dose reduction to a dose below the highest established safe dose (i.e., below a dose for which the DRC approved expansion from a sentinel subject to enrollment of a full cohort), no sentinel subject will be required. Following a dose reduction, the DRC may subsequently decide to further reduce the dose level in a subsequent cohort of similar size or increase the dose in a subsequent cohort with or without the inclusion of a sentinel subject at the discretion of the DRC.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Cancer Screening Guidelines

AMERICAN CANCER SOCIETY GUIDELINES FOR THE EARLY DETECTION OF CANCER

Screening tests are used to find cancer before a person has any symptoms. Here are the American Cancer Society's recommendations to help guide you when you talk to your doctor about screening for certain cancers.

Breast cancer

- **Women ages 40 to 44** should have the choice to start annual breast cancer screening with mammograms (x-rays of the breast) if they wish to do so.
- **Women age 45 to 54** should get mammograms every year.
- **Women 55 and older** should switch to mammograms every 2 years or can continue yearly screening.
- Screening should continue as long as a woman is in good health and is expected to live 10 more years or longer.
- **All women** should be familiar with the known benefits, limitations, and potential harms linked to breast cancer screening.

Women should also know how their breasts normally look and feel and report any breast changes to a health care provider right away.

Some women – because of their family history, a genetic tendency, or certain other factors – should be screened with magnetic resonance imaging (MRIs) along with mammograms (the number of women who fall into this category is very small.) Talk with a health care provider about your risk for breast cancer and the best screening plan for you.

Colon and rectal cancer and polyps

For people at average risk for colorectal cancer, the American Cancer Society recommends starting regular screening at **age 45**. This can be done either with a sensitive test that looks for signs of cancer in a person's stool (a stool-based test), or with an exam that looks at the colon and rectum (a visual exam). Talk to your health care provider about which tests might be good options for you, and to your insurance provider about your coverage. No matter which test you choose, the most important thing is to get screened.

If you're in good health, you should continue regular screening through **age 75**.

For people **ages 76 through 85**, talk with your health care provider about whether continuing to get screened is right for you. When deciding, take into account your own preferences, overall health, and past screening history.

People **over 85** should no longer get colorectal cancer screening.

If you choose to be screened with a test other than colonoscopy, any abnormal test result needs to be followed up with a colonoscopy.

Cervical cancer

- **Cervical cancer testing should start at age 21.** Women under age 21 should not be tested.

- **Women between the ages of 21 and 29** should have a Pap test done every 3 years. HPV testing should not be used in this age group unless it's needed after an abnormal Pap test result.
- **Women between the ages of 30 and 65** should have a Pap test plus an HPV test (called "co-testing") done every 5 years. This is the preferred approach, but it's OK to have a Pap test alone every 3 years.
- **Women over age 65** who have had regular cervical cancer testing in the past 10 years with normal results should not be tested for cervical cancer. Once testing is stopped, it should not be started again. Women with a history of a serious cervical pre-cancer should continue to be tested for at least 20 years after that diagnosis, even if testing goes past age 65.
- **A woman who has had her uterus and cervix removed (a total hysterectomy)** for reasons not related to cervical cancer and who has no history of cervical cancer or serious pre-cancer should not be tested.
- **All women who have been vaccinated against HPV** should still follow the screening recommendations for their age groups.

Some women – because of their health history (HIV infection, organ transplant, DES exposure, etc.) – may need a different screening schedule for cervical cancer. Talk to a health care provider about your history.

Endometrial cancer

The American Cancer Society recommends that at the time of menopause, all women should be told about the risks and symptoms of endometrial cancer. Women should report any unexpected vaginal bleeding or spotting to their doctors.

Some women – because of their history – may need to consider having a yearly endometrial biopsy. Please talk with a health care provider about your history.

Lung cancer

The American Cancer Society recommends yearly lung cancer screening with a low-dose CT scan (LDCT) for certain people at higher risk for lung cancer who meet the following conditions:

- Are aged 55 to 74 years and in fairly good health
  and
- Currently smoke or have quit smoking in the past 15 years
  and
- Have at least a 30 pack-year smoking history. (A pack-year is 1 pack of cigarettes per day per year. One pack per day for 30 years or 2 packs per day for 15 years would both be 30 pack-years.)

Before getting screened, you should talk to your health care provider about:

- Your risk for lung cancer
- How you can quit smoking, if you still smoke
- The possible benefits, limits, and harms of lung cancer screening
- Where you can get screened

You should also talk with your insurance provider about your coverage.

Prostate cancer

The American Cancer Society recommends that men make an informed decision with a health care provider about whether to be tested for prostate cancer. Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment. We believe that men should not be tested without first learning about what we know and don't know about the risks and possible benefits of testing and treatment.

Starting at age 50, men should talk to a health care provider about the pros and cons of testing so they can decide if testing is the right choice for them.

If you are African American or have a father or brother who had prostate cancer before age 65, you should have this talk with a health care provider starting at age 45.

If you decide to be tested, you should get a PSA blood test with or without a rectal exam. How often you're tested will depend on your PSA level.

Source: https://www.cancer.org/healthy/find-cancer-early/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html Accessed March 30, 2021

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki of World Medical Association and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, Administrative Letters, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 8 Signature of Investigator). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study related duties and functions, the Investigator/institution should ensure this individual, or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Administrative Structure

In addition to safety monitoring by the investigators, safety will be monitored by the DRC as described in Section 9.6. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, e.g., PK scientists, statisticians, clinical specialists etc. The administrative structure of the study is described in Table 12.

Table 12 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring	CRO (IQVIA Biotech) Neal Salomon, MD - Consulting Chief Medical Officer and Medical Monitor
Study Master File	CRO (IQVIA Biotech)
Randomization Code	CRO (IQVIA Biotech)
Data Management	CRO (IQVIA Biotech)
Clinical Supply Management	3rd Party
Biostatistics Medical Writing	CRO (IQVIA Biotech)/ IQVIA
Laboratory Assessments	3rd Party
Electrocardiogram Collection, Review, and Analysis	3rd Party
Pharmacokinetic Sample Testing	3rd Party
Management of Event Adjudication	CRO (IQVIA Biotech)
Adjudication Committee	CRO (IQVIA Biotech)
Steering Committee	N/A
Safety Monitoring Committee (see Section 9.6)	CRO (IQVIA Biotech)

Medical Monitor

Neal Salomon, MD

Consulting Chief Medical Officer and Medical Monitor, SalubrisBio

Phone: 410-419-8501 (cell)

Fax: 410-560-1562

Email: neal.salomon@salubrisbio.com

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All subject data relating to the study will be recorded either as printed source documents from the subject's medical record, or will be recorded on printed eCRF's, it will then be entered into the study's electronic data capture system (EDC), unless it is data that is being transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

Changes to the Protocol

This protocol is to be followed exactly. Amendments must receive IRB/IEC approval prior to implementation. As appropriate, protocol amendments will be submitted to regulatory authorities on a timely basis.

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments and administrative change directives will be distributed to all protocol recipients with appropriate instructions.

The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor may make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

- Blood will be collected for local laboratory assessments at times when the central laboratory results are not expected to be available in time for either study treatment administration and/or response evaluation. The local laboratory results must be entered into the eCRF. Table 14 identifies local laboratory assessments scheduled for this study (and the specific timepoints for assessment) but may not be fully comprehensive in cases where additional safety follow-up deemed appropriate by the Investigator. Table 15 identifies blood draw requirements for central lab assessment.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- All results must be recorded in the eCRF.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**	
Hematology	Platelet Count	WBC Count with Differential:
	RBC Count	Neutrophils
	Hb	Lymphocytes
	Hct	Monocytes
	RBC Indices:	Eosinophils
	MCV	Basophils
	MCH	
	MCHC	
	%Reticulocytes	
Clinical Chemistry	ALT/ SGPT	
	Albumin	Phosphate
	ALP	Potassium
	AST/ SGOT	Total bilirubin (conjugated and unconjugated if clinically indicated)
	BUN	Direct bilirubin
	Calcium	Total Cholesterol
	Carbon dioxide (bicarbonate)	Total Protein
	Chloride	Triglycerides
	Creatinine	Uric acid
	Fasting Glucose	
	GGT	
	HDL Cholesterol	
	LDL Cholesterol	
Coagulation	INR	aPTT
	Prothrombin time (PT)	Fibrinogen
Additional biomarkers	CPK[a]	hs CRP
	CPK-MB[a]	Troponin I [b]
	hs Troponin T [b]	LDH
Urinalysis	Leucocytes	RBCs
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	Myoglobin
Viral serology	HIV I and II	HCV
	HBsAg	HBV PCR
Drugs of abuse and alcohol[c]		
Thyroid profile	TSH Total T4 T3	T4 Total T3
Glycosylated hemoglobin	HbA1c	
Other screening tests	Urine β-hCG pregnancy test (as needed for subjects of childbearing potential) Study-required laboratory assessments will be performed by local and central laboratories. Table 14 shows the Safety Laboratory Assessments Performed by Local Laboratories. Table 15 lists the protocol required local laboratory collections for Central Laboratory Analysis.	

Laboratory Assessments	Parameters
	The results of each test must be entered in the eCRF.

Abbreviations: ALP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; β-hCG, beta human chorionic gonadotrophin; BUN, blood urea nitrogen; CPK, creatine phosphokinase; CPK-MB, creatinine phosphokinase – muscle brain fraction; GGT, gamma glutamyl transferase; Hb, hemoglobin; HBV, Hepatitis B Virus; HCT, hematocrit; HCV, Hepatitis C Virus; HDL, high-density lipoprotein; HIV, Human Immunodeficiency Virus; hs-CRP, high sensitivity C-reactive protein; INR, International Normalized Ratio; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PCR, polymerase chain reaction; PT, prothrombin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transferase; SGPT, serum glutamic-pyruvic transaminase; T3, free triiodothyronine; T4, free thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cell

[a] For safety laboratory assessments performed by the local laboratory, if CPK and CPK-MB are not included together on a single panel, then CPK-MB alone can be measured. If CPK and CPK-MB are not included together on a single panel and there is no local test available for CPK-MB, then CPK alone may be measured.

[b] For local laboratory safety assessments, only one of either Troponin I or hs Troponin T must be included, and the second biomarker may be optionally included.

[c] Performed as per local standard of practice/guidelines at Screening visit only

Table 14 Schedule of Protocol-required Safety Laboratory Assessments Performed by the Local Laboratory

Day	Time (hours)	Panel	Comment
Screening	No more than 45 days prior to IP administration	Chemistry[a]	
		Hematology	
		Coagulation	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP, LDH
		HIV/HBV/HCV	
		β-hCG (blood sample)	
		Urinalysis	
		Thyroid profile	
Day 1 prior to IP administration	Upon admission	Chemistry[a]	
		Hematology	
		Coagulation	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Glucose	Fingerstick
		Urinalysis	Including urine-based pregnancy dipstick for pre-menopausal women
Day 1 postdose	End of infusion	Glucose	Fingerstick
	4	Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Glucose	Fingerstick
	8 hours postdose	Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Glucose	Fingerstick
	12 hours postdose	Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Glucose	Fingerstick
2	24 hours postdose	Chemistry[a]	
		Hematology	
		Coagulation	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Glucose	Fingerstick
		Urinalysis	
3	48 hours postdose	Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Hematology	
		Glucose	Fingerstick
4	72 hours postdose	Glucose	Fingerstick
7		Chemistry[a]	
		Hematology	
		Coagulation	

Day	Time (hours)	Panel	Comment
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Urinalysis	
15		Chemistry[a]	
		Hematology	
		Coagulation	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I and/or hs Troponin T, hsCRP[c], LDH
		Urinalysis	
30		Chemistry[a]	
		Hematology	
		Coagulation	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I [c] and/or hs Troponin T [c], hsCRP[c], LDH
60		Chemistry[a]	
		Hematology	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I [c] and/or hs Troponin T [c], hsCRP[c], LDH
90		Chemistry[a]	
		Hematology	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I [c] and/or hs Troponin T [c], hsCRP, LDH
135		Chemistry[a]	
		Hematology	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I [c] and/or hs Troponin T [c], hsCRP[c], LDH
180		Chemistry[a]	
		Hematology	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I [c] and/or hs Troponin T [c], hsCRP[c], LDH
End-of-study (prior to Day 180 due to patient or investigator-initiated withdrawal)		Chemistry[a]	
		Hematology	
		Coagulation	
		Additional biomarkers	CPK [b], CPK-MB [b], Troponin I [c] and/or hs Troponin T [c], hsCRP

Abbreviations: β-hCG, beta human chorionic gonadotrophin; CPK, creatine phosphokinase; CPK-MB, creatinine phosphokinase – muscle brain fraction; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase

[a] All clinical chemistries are to be drawn FASTING >10hours.

[b] For safety laboratory assessments performed by the local laboratory, if CPK and CPK-MB are not included together on a single panel, then CPK-MB alone can be measured. If CPK and CPK-MB are not included together on a single panel and there is no local test available for CPK-MB, then the test may be omitted.

[c] For local laboratory safety assessments, only one of either Troponin I or hs Troponin T must be included, and the second biomarker may be optionally included.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind any blinded cohort will not be reported to study centers or other blinded personnel until the cohort has been unblinded.

Table 15 Schedule of Protocol-required Blood Collections to be Obtained by the Local Laboratory for Central Laboratory Analysis

Day	Sample to be Collected for Central Lab Analysis by the Local Laboratory
Day 1 (Pre-infusion)	Exploratory biomarkers[a] / PK / Immunogenicity
Day 1 (End of infusion [EoI])	PK
Day 1 (0.5 hour from EoI)	PK
Day 1 (1 hour from EoI)	PK
Day 1 (2 hours from EoI)	PK
Day 1 (4 hours from EoI)	PK
Day 1 (8 hours from EoI)	PK
Day 1 (12 hours from EoI)	PK
Day 2 (24 hours from EoI)	Exploratory biomarkers[a] / PK
Day 3 (48 hours from EoI)	PK
Day 4 (72 hours from EoI)	PK / Immunogenicity
Day 7	Exploratory biomarkers[a] / PK / Immunogenicity
Day 11	PK
Day 15	Exploratory biomarkers[a] / PK / Immunogenicity
Day 22	PK
Day 30	Exploratory biomarkers[a] / PK / Immunogenicity
Day 60	Exploratory biomarkers[a] / PK
Day 90	Exploratory biomarkers[a] / Immunogenicity
Day 135	Exploratory biomarkers[a]
Day 180 / End of Study Visit	Exploratory biomarkers[a] / Immunogenicity

Abbreviations: EOI, end of infusion; PK, pharmacokinetics

[a] BNP, hsCRP, NT-proBNP, Troponin I, hs Troponin T

Appendix 4 Excluded Medications/Therapy

Excluded medications/therapy is listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

- Any recombinant neuregulin apart from JK07
  - Neucardin and cimaglermin
- Class 1a (including procainamide, quinidine, disopyramide) and Class 3 (including amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmics
- Acetaminophen for the period beginning 7 days pre-dose and ending 15 days postdose
- Drugs that are known to prolong QT:
  - Fluoroquinolones: ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin
  - Macrolides: erythromycin, azithromycin, clarithromycin
  - Antifungal agents: ketoconazole, itraconazole, pentamidine
  - Antipsychotics: thioridazine, haloperidol, droperidol, atypical antipsychotic, (e.g., ziprasidone)
  - Antidepressants: citalopram, escitalopram
  - Antiemetics: dolasetron, droperidol, ondansetron, granisetron
  - Others: propofol, chloroquine

For a complete listing of all prohibited medications, please consider the listed drugs in the following website as “known” to prolong QT:

https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf

Appendix 5 2-D TTE Parameters

- LVIDs (mm)
- LVIDd (mm)
- LVIDd diameter/BSA (mm/m^2)
- LVIDd diameter/height (mm/m^2)
- Septal thickness (cm)
- Posterior Wall thickness (cm)
- Biplane MOD
- LVEDV (mls/m^2)
- LVESV (mls/m^2)
- LVSV (mls/m^2)
- LVEF (%)
- Circumferential Shortening (CS) + EDC-ESC/EDC
- Cardiac Output/Cardiac Index & Stroke Volume (LVOT VTI pulsed wave Doppler method)
- Diastolic Function Grade (E/A ratio, E/E′ ratio)
- Mitral Valve Regurgitation Grade (Quantitative)
- Left Atrial Area and Volume
- Right Ventricular Size and Function
- Tricuspid Valve Regurgitation Velocity
- Peak Mitral Valve Regurgitant Velocity
- Left Ventricular Outflow Tract Doppler Time Velocity Integral

Abbreviations: BSA, body surface area; CS, circumferential shortening; E/A ratio, ratio of early (E) to late (A) ventricular filling velocity; EDC, end diastolic circumference; ESV, end systolic circumference; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal end-diastolic diameter; LVIDs, left ventricular internal end-systolic diameter; LVOT left ventricular outflow tract; MOD, method of disks; SVR, systemic vascular resistance; VTI, ventricular time integral

Appendix 6 Contraceptive Guidance

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.

   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on hormone therapy and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their hormone therapy during the study. Otherwise, they must discontinue hormone therapy to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 5.1]:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for no less than 90 days after the administration of study treatment.
  - Agree to use a male condom and have their partner use of a contraceptive method with a failure rate of <1 % per year as described in Table 16 when having penile- vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, subjects must refrain from donating sperm for the duration of the study and for no less than 90 days after the administration of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Table 16 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1 % per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] Oral. Intravaginal. Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation Oral. Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] Intrauterine device (IUD). Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 90 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential after the last dose of study treatment.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Additional pregnancy testing should be performed at times specified in the schedule of assessments during the treatment period and at timepoints corresponding to protocol-defined time frame in Section 5.1 after the dose of study treatment and as required locally.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

- Pregnancy testing, with a sensitivity of 10 mIU/mL will be performed in a certified laboratory and in accordance with instructions provided in its package insert.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.10. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Appendix 7 Summary of Changes

Amendment 1: 19February2020

Rationale for the amendment:

The main purpose of this amendment is to:

- Update the Schedule of Activities
- Revision and update of the Background and Benefit/Risk sections
- Clarification of blood sampling and volumes for biomarkers, PK, and immunogenicity
- Update of PK assessment methods and variables
- Correction of justification for dose
- Clarification of eligibility criteria and study procedures including discontinuation criteria and adverse event relatedness to study drug
- Update the medical monitor
- Updates to the document for consistency
- Minor editorial and grammatical changes

Where applicable added text is ***bolded and italicized***. Deleted text has ~~strikethrough~~.

Section	Change	Reason
Title Page	JK07 (recombinant fusion protein consisting of a fully human anti-human epidermal growth factor receptor 3 [HER3] immunoglobin G1 [IgG1] ~~monoclonal antibody~~ and an active polypeptide fragment from human neuregulin-1 [NRG-1])	Administrative update
Synopsis and Section 3.0: Objectives and Endpoints	Pharmacokinetic parameters of ***intact*** JK07 including, but not limited to, maximum concentration (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), and volume of distribution (V_z). Surrogate ~~assessment~~ ***measurement of intact*** JK07 ~~stability~~ to be ~~evaluated~~ ***carried out*** through ~~parallel~~ assays to detect ***both*** the JK07 antibody domain and the JK07 NRG-1 peptide fragment ***in the evaluation of pharmacokinetic parameters***.	Clarification of PK assessment
Table 1: SoA, new footnote "e"	***All AEs, including SAEs will be collected from the time of study enrollment and until 30 days after the IP administration. Following the first 30 days, only SAEs deemed at least possibly related to the study drug or study procedures should be collected. Refer to Table 9 for additional details.***	Clarification of AE assessment timing
Section 2.2: Background		Revision of text and reference format
Section 2.3: Benefit/Risk Assessment		Revision of text and reference format
Table 1: SoA and **Section 4.1:** Study Design	Day 1: Addition of blood sample collection prior to IP administration of baseline myocardial biomarkers, PK and immunogenicity assessment.	Clarification of blood sampling
Section 4.2: Scientific Rationale and **Section 8.8**: Biomarkers	Deletion of monitoring of MCP-1 (monocyte chemoattractant protein), IL-6 (interleukin-6), aldosterone, pro-collagen 5, aldolase, and myoglobin. Clarification of the immunoassays to be used for assessment of JK07 exposure.	Clarification of biomarkers

Section	Change	Reason
Section 4.3: Justification of Dose	Cohort dose levels of JK07 are as follows: the clinical starting dose of a single 0.03 mg/kg IV infusion has been selected at 1/~~30~~***32*** of the human equivalent dose at the NOAEL in the cynomolgus monkey (3 mg/kg/week).	Correction
Section 5.2: Exclusion Criterion 8	Sustained systolic blood pressure <100 mm Hg and/or diastolic blood pressure <50 mm Hg (confirmed by a duplicate seated reading) on at least 3 consecutive readings (self-monitored or office) following informed consent and prior to randomization, or overt symptomatic hypotension ***defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position or accompanied by dizziness, syncope, blurry vision.***	Clarification
Section 5.2: Exclusion Criterion 9	~~Sustained~~ Resting ~~–~~heart rate >100 beats per minute (bpm) at Screening (Visit 1) or prior to randomization ***which is sustained for >15 minutes in two episodes separated by one hour of observation.***	Clarification
Section 5.3: Lifestyle Considerations	Subjects should be in a fasted state (at least 10 hours) at assigned or designated times as per the study team for all other visits.	Addition of fasting prior to all visits
Section 5.3.2: Caffeine, Alcohol, and Tobacco	CBD products will not be permitted from two weeks prior to IP administration until after the final follow-up visit.	Addition of restriction on use of CBD products.
Section 7.1: Discontinuation of Study Treatment	If a subject, who does not meet enrollment criteria, is inadvertently enrolled, ~~that subject must~~ ***and the failure to meet enrollment criteria is discovered prior to IP administration***, the subject should be discontinued from the study ~~treatment~~ and the Sponsor or Sponsor designee must be contacted. ~~An exception may~~***If a subject, who does not meet enrollment criteria, is inadvertently enrolled in the study and has already received IP administration,*** the subject should be ~~granted in rare circumstances for which there is a compelling safety reason to allow the subject~~ ***allowed*** to continue~~. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the subject to continue in the study~~ ***with the study given that following the single IP administration there are no additional treatments and no invasive tests.***	Clarification of discontinuation criteria
Section 8.3.6: Relationship to Study Drug; Table 9 Relatedness	Revision of table and definitions	Clarification of definition of degrees of relatedness
Section 8.5.3: Calculation of Derivation of Pharmacokinetic Variables; Table 10	Deletion of $RC_{max,}$ $RAUC_{(0\text{-inf}),\text{ and }}RAUC_{(0\text{-last})}$	Update to PK assessment
Section 8.8: Biomarkers	Venous blood samples of approximately ~~1~~410 mL will be collected at several time points	Clarification of blood volume
Section 11: Appendix 1	Insertion of complete American Cancer Society Guidelines for Screening	Addition

Section	Change	Reason
Section 11: Appendix 2	Deletion of Mark Tulchinskiy, MD as medical monitor Addition of Neal Salomon, MD as medical monitor	Administrative update

Amendment 2: 03March2020

Rationale for the amendment:

The main purpose of this amendment is to:

- Update the Schedule of Activities to reflect Day 3 activities and Holter/telemetry monitoring
- Compliance with regulatory requests regarding inclusion/exclusion criteria and Investigational Product expiration
- Updates to the document for consistency
- Minor editorial and grammatical changes

Where applicable added text is ***bolded and italicized***. Deleted text has ~~strikethrough~~.

Section	Change	Reason
Section1.3: SoA, footnote "a"	Day 3 marked for in-patient hospital stay and telemetry in the Schedule of Activities. ***Subjects will be scheduled for discharge on the morning of Day 3.***	Telemetry monitoring will continue until 48 hours after completion of IP which extends into Day 3.
Section 1.3: SoA, footnote "m"	Continuous telemetry monitoring will be started as soon as practicable after hospital admission on Day1 and prior to IP infusion, and will be continued until 48 hours after the end of the IP infusion ***on Day 3***.	Administrative update
Section 4.2: Scientific Rationale for Study Design	Holter/telemetry combination ***prior to dose administration*** and for 48 hours following dose administration.	Consistency
Section 5.1: Inclusion Criterion 1	Male or female adult subjects between 18 and 80 years of age, with stable NYHA Class II or III HF diagnosis ~~(ischemic or nonischemic confirmed by medical history)~~ at least 6 months prior to enrollment.	Compliance with FDA request to make inclusion/ exclusion criteria mutually exclusive with respect to non-ischemic cardiomyopathy.
Section 5.2: Exclusion Criterion 3	Heart failure due to ***hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia (ARVD), stress-induced ("Takotsubo") cardiomyopathy, chemotherapy-induced cardiomyopathy, peripartum cardiomyopathy, infiltrative or inflammatory cardiomyopathies, and primary valvular disease***, ~~in the opinion of their treating cardiologist, to etiologies other than ischemic or nonischemic. Examples of exclusionary HF etiologies include primary valvular disease, infiltrative or inflammatory cardiomyopathies~~	Compliance with FDA request to make inclusion/ exclusion criteria mutually exclusive with respect to non-ischemic cardiomyopathy
Section 6.1: Table 5	JK07 infusions will be prepared at the study center for administration within ***4*** ~~6~~ hours following the dose preparation. Placebo infusions will be prepared at the study center for administration within ***4*** ~~6~~ hours following the dose preparation. Intravenous (IV) infusion over 60 minutes using a syringe pump ***or infusion pump.***	Compliance with FDA request to reduce IP hold time from six hours to four hours. Administrative change: To provide greater flexibility to

Section	Change	Reason
		sites in delivering the specified infusion volume in the allotted time.
Section 6.2: Preparation/ Handling/ Storage	All investigational drug supplies in the study will be stored at ***2-8 °C*** ~~4ºC~~ in a secure place under the responsibility of the Investigator or other authorized individual.	Administrative change: The storage temperature was incorrectly listed as -4°C, which does not allow for standard temperature variance under refrigeration.
Table 13: Safety Laboratory Assessments	***Myoglobin*** added to the list of analytes for urinalysis	Administrative update
Table 14: Schedule of Protocol-required Safety Laboratory Assessments Performed by the Local Laboratory	***LDH*** added to the list of additional biomarkers at Screening, Day 1 prior to IP administration, Day 1 at 4, 8, & 12 hours post dose, Day 2 at 24 hours post dose, Day 3 at 48 hours post dose, and on Days 7, 15, 30, 60, 90, 135, and 180.	Administrative update

Appendix 8 Signature of Investigator

PROTOCOL TITLE: 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)

PROTOCOL NO: JK07.1.01

VERSION: Amendment 3

This protocol is a confidential communication of Salubris Biotherapeutics, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Salubris Biotherapeutics, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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