REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL 1.0

Clinical Study Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of REGN5381, an NPR1 Agonist, in Heart Failure Participants with Elevated Pulmonary Capillary Wedge Pressure
Compound:	REGN5381
Protocol Number:	R5381-HF-2159
Clinical Phase:	Phase 2a
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan / 31OCT2024

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP), and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of term
ACE	Angiotensin-converting enzyme
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANP	Atrial Natriuretic Peptide (active form)
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BMI	Body mass index
BNP	Brain Natriuretic Peptide (active form)
BP	Blood Pressure
BUN	Blood urea nitrogen
CA125	Carbohydrate antigen 125ac
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
Cmax	maximum serum concentration
CO	Cardiac output
CPK	Creatine phosphokinase
CS	Clinically Significant
CVP	Central Venous Pressure
DBP	Diastolic blood pressure
DEC	Dose Escalation Committee
DIA	Diastolic Pressure (hemodynamic)
DIAPAP	Diastolic Pulmonary Artery Pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
FDA	US Food and Drug Administration
FSH	Follicle stimulating hormone

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Abbreviation	Definition of term
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IV	Intravenous
KIM-1	Kidney injury molecule-1
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLN	Lower Limit Normal
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
mPAP	Mean pulmonary artery pressure
MRA	Mineralocorticoid receptor antagonists
NCS	Not Clinically Significant
NPR1	Refers to both Natriuretic peptide receptor A protein and gene NPR1
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
PA	Protocol Amendment
PAC	Pulmonary artery catheter
PAS	Pharmacodynamic analysis set
PCSV	Potentially clinically significant values
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamics
PDE	Phosphodiesterase
PK	Pharmacokinetic
PP	Pulse Pressure
PR	Pulse rate

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Abbreviation	Definition of term
proANP	Pro-atrial natriuretic peptide
proBNP	Pro-brain natriuretic peptide
PT	Preferred term
PVR	Pulmonary vascular resistance
PWA	Pulse Wave Analysis
Q1	First quartile
Q3	Third quartile
RAP	Right atrial pressure
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RHC	Right heart catheterization
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SI	standard international
SOC	System organ class
SV	Stroke volume
SvO2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
SYS	Systolic Pressure (hemodynamic)
SYSPAP	Systolic Pulmonary Artery Pressure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHODD	The World Health Organization's Drug Dictionary
WOCBP	Women of childbearing potential

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1. OVERVIEW

The statistical analysis plan (SAP) is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol R5381-HF-2159, amendment 6 dated 09-Feb-2024.

1.1. Study Description and Objectives

This randomized, double-blind, placebo-controlled, multi-center study is designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending doses of REGN5381 in heart failure participants with symptoms of congestion.

The study is comprised of 3 groups each with different participant types (Group A, Group B and Group C). Group A is comprised of participants with heart failure with reduced ejection fraction (HFrEF) not taking sacubitril/valsartan. Group B is comprised of participants with HFrEF on sacubitril/valsartan. Group C is comprised of participants with heart failure with preserved ejection fraction (HFpEF) not taking sacubitril/valsartan.

Group B was closed to enrollment. No screening or randomization occurred in Group B before its closure. This change is reflected in Protocol Amendment 6.

All the analyses will focus on Group A and Group C separately.

1.1.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of single doses of REGN5381 in participants with heart failure with evidence of congestion.

1.1.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the effects of single doses of REGN5381 on hemodynamic parameters
- Evaluate the effects of REGN5381 on a clinical biomarker of heart failure severity
- Characterize the pharmacokinetics (PK) of single doses of REGN5381
- Assess the immunogenicity of REGN5381

1.1.3. Exploratory Objectives

The exploratory objectives of the study are to:

- Evaluate the effects of REGN5381 on downstream biomarkers of NPR1 activation
- Explore the effects of REGN5381 on oxygen delivery and extraction
- Explore the effects of REGN5381 on diuresis and renal function
- Explore the effects of REGN5381 on renal tubular injury
- Explore the effects of REGN5381 on the renin-aldosterone system

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- Explore the effects of REGN5381 on sympathetic nervous system activity
- Explore the effects of REGN5381 on biologically active ligands of the REGN5381 target (NPR1)
- Explore the effects of REGN5381 on a biomarker of atrial volume and pressure overload
- Explore the effects of REGN5381 on participant reported dyspnea
- Explore the effects of REGN5381 on hemodynamic parameters over time as measured by non-invasive pulse wave analysis
- Increase molecular understanding of heart failure and related diseases

1.2. Statistical Hypothesis

No formal statistical hypothesis will be carried out in this phase 2a study.

1.3. Interim Analysis/(es)

No formal interim analysis is planned.

1.4. Modifications from the Statistical Section in the Final Protocol

- The Pharmacodynamic Analysis Set (PAS) definition has been revised to remove the following exclusion criteria:
  - "Had any violations of inclusion/exclusion criteria": there were a series of protocol amendments that significantly altered inclusion and exclusion criteria during the study, such that applying this exclusion in the SAP could apply differently to a given participant had they been enrolled under different protocol amendments. Also, the clinical determination of whether study criteria have been violated risks introducing bias into this PD analysis.
  - "Had taken any anti-hypertensive drug during the on-treatment period": not feasible, as the protocol defines the on-treatment period as "the day from the administration of study drug to the EOS visit or last visit in the study," during which time all study participants were on anti-hypertensive drugs by protocol.

All participants in the SAF will be included regardless of their completion status. For the current definition of Pharmacodynamic Analysis Set (PAS), please refer to Section 3.2.

- Given the low number of participants in each treatment group, there are not enough degrees of freedom to analyze Pulmonary Capillary Wedge Pressure (PCWP) using a mixed-effect model with repeated measures (MMRM). Data will be presented descriptively.

1.5. Revision History for SAP Amendments

This is the original version of the SAP.

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2. INVESTIGATIONAL PLAN

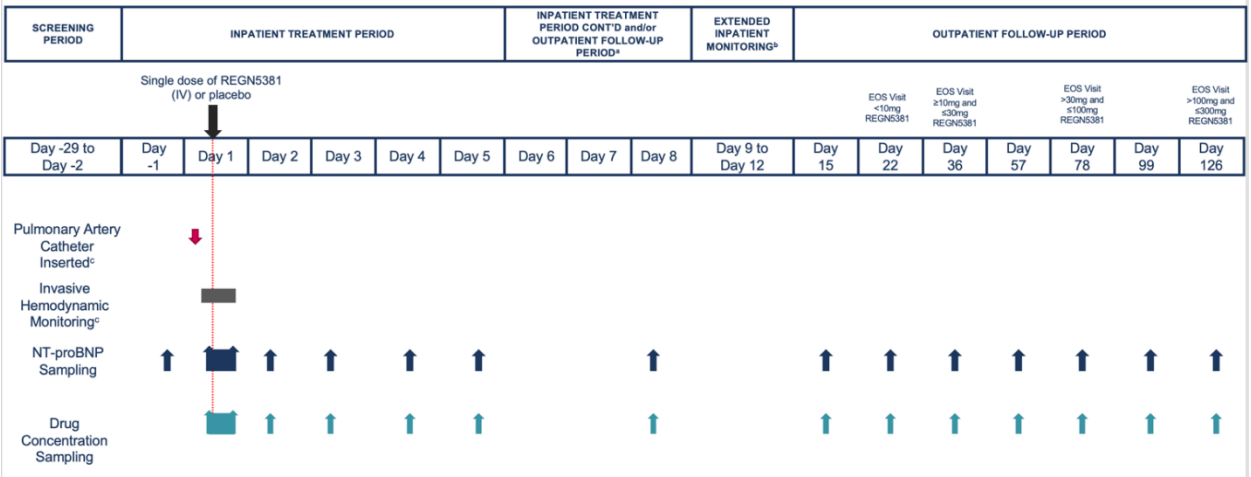
2.1. Study Design

This is a phase 2a, randomized, double-blind, placebo-controlled, multi-site study of REGN5381 in heart failure participants with symptoms of congestion. Group A is limited to participants with HFrEF not taking sacubitril/valsartan. Group B includes participants with HFrEF taking sacubitril/valsartan. Group C is limited to participants with HFpEF (not taking sacubitril/valsartan).

The study comprises a Screening Period (day -29 to day -2), an Inpatient Treatment Period (day -1 to day 5 but may extend through day 8), an Extended Inpatient Monitoring Period (day 9 to day 12), and an Outpatient Follow-up Period (beginning no earlier than day 6 and up to day 126) (Figure 1). On study day 1, participants will be randomized to receive REGN5381 or placebo. Study drug will be administered as an IV infusion.

Participants must provide informed consent in order to be eligible for randomization and enrollment in the study. In addition to the main informed consent form (ICF), separate consents may be obtained from participants who wish to provide samples for the optional pharmacogenomic sub-study.

Figure 1: Study Flow Diagram



[a] Beginning on day 5, participants may be discharged if they meet the inpatient discharge criteria. Participants may also be discharged on days 6, or 7, or remain at the facility until completion of day 8 assessments. Regardless of the study day the participant is discharged (ie, days 5, 6, 7, 8, or a later day), all safety assessments to date must be completed and all results available and reviewed by the physician, and the participant must have met discharge criteria, prior to being discharged from the inpatient unit.
[b] Participants who do not meet the inpatient discharge criteria by day 8 may remain at the study site for Extended Inpatient Monitoring until eligible to be discharged.
[c] As of PA6, right heart catheterization will only be performed for Group C.

2.1.1. Description of Study Cohorts and Dose Escalation

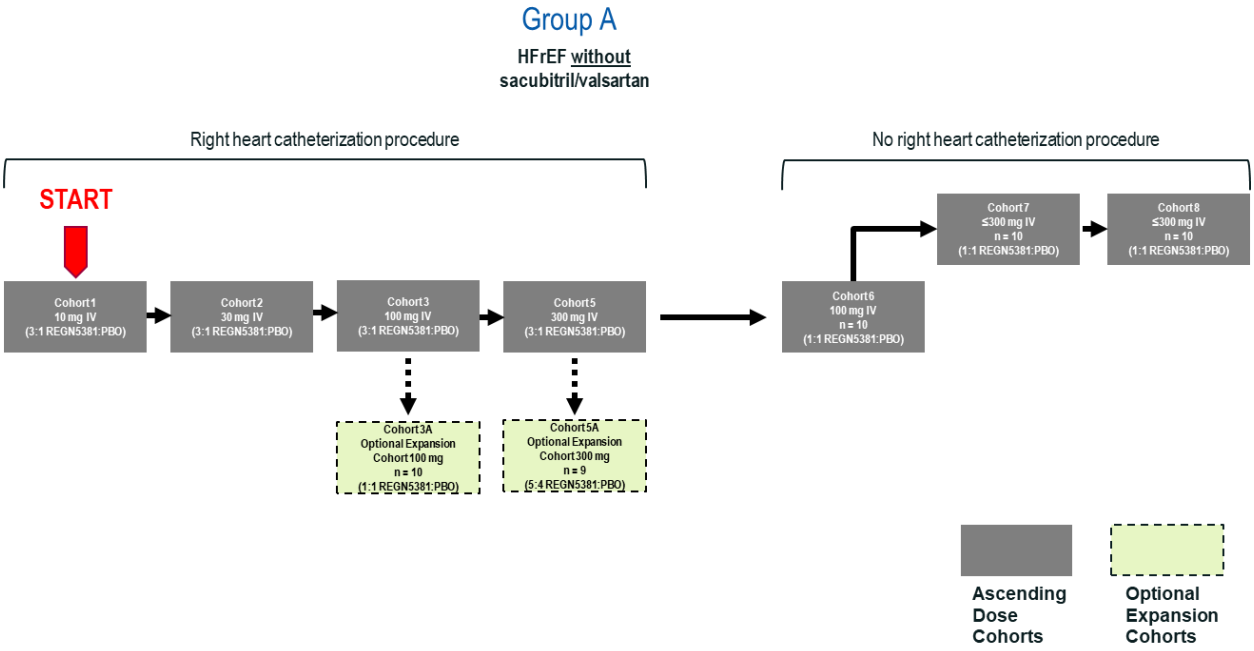
Groups A, B, and C are comprised of single ascending dose cohorts with optional expansion cohorts.

Group A: Cohort Progression and Dose Escalation

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The cohort progression and dose escalation for Group A is displayed in the below flow diagram (see Figure 2).

Figure 2: Cohort Progression and Dose Escalation Diagram (Group A)



Group A: Ascending Dose Cohorts

Participants were enrolled and randomized in 4 sequential ascending dose cohorts (Cohorts 1, 2, 3, and 5). Each dose cohort consists of 4 participants: 3 participants randomized to receive a single IV dose of REGN5381 and 1 randomized to receive placebo. PA5 added 3 additional ascending dose cohorts (Cohorts 6, 7, and 8) to evaluate single doses of 100 mg to 300 mg REGN5381 in participants not undergoing the right heart catheterization procedure. The randomization ratios for each of these cohorts are 5 participants randomized to receive a single IV dose of REGN5381 and 5 participants randomized to receive placebo.

Group A: Optional Expansion Cohorts

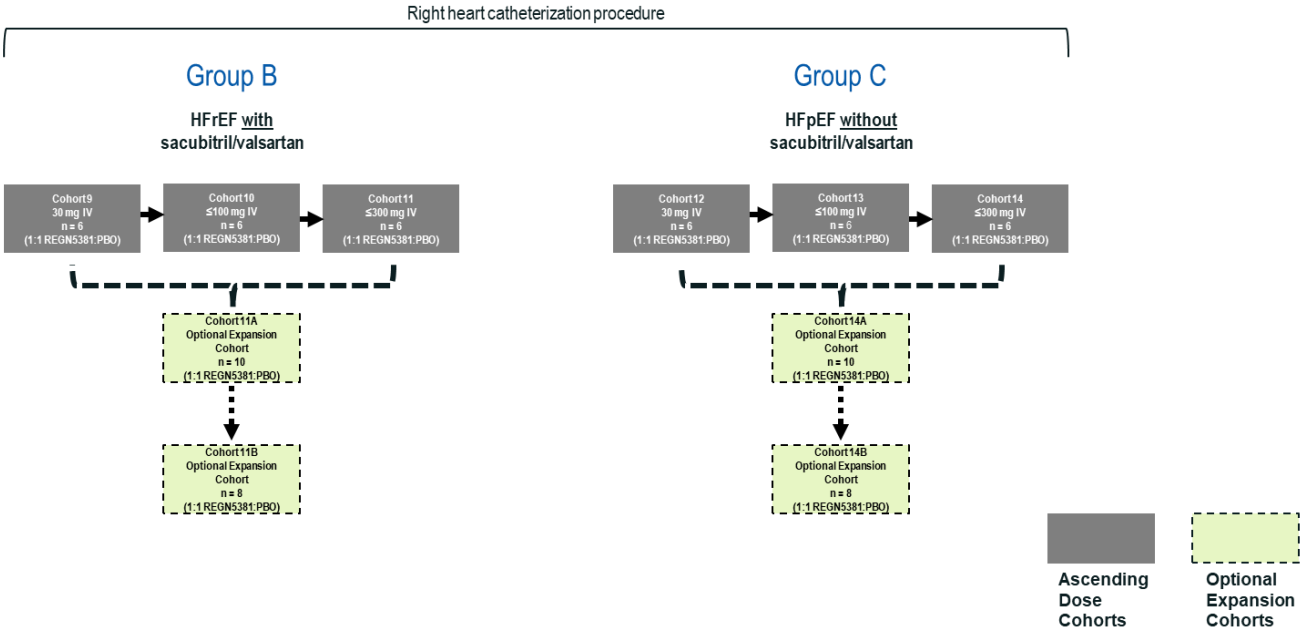
Optional expansion Cohorts 3A and 5A were partially enrolled at the 100 mg and 300 mg dose levels, respectively. The purpose of the optional expansion cohorts is to enroll at least 8 participants in a REGN5381 dose level, and at least 8 participants in a pooled placebo group. Group A enrollment was closed in both the ascending dose and optional expansion cohorts in November 2023, and this change was reflected in Protocol Amendment 6.

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2.1.2. Group B and Group C: Cohort Progression and Dose Escalation

The cohort progression and dose escalation for Group B and Group C is displayed in the below flow diagram (see Figure 3).

Figure 3: Cohort Progression and Dose Escalation Diagram (Group B and Group C)



The solid lines convey single ascending dose levels and progression through cohorts.

The dotted lines convey the Sponsor may activate the first Optional Expansion Cohort after a Dose Escalation Review meeting has occurred for a single ascending dose cohort of the same or lower dose level. The second Optional Expansion Cohort may be used at the same or lower dose level than the first Optional Expansion Cohort. Cohorts in Groups A, B, and C may occur in parallel. Group B Cohorts 9 and 10 and 11, and Group C Cohorts 12 and 13 and 14, will use sentinel dosing (1:1 REGN5381:pbo).

Group B and Group C: Ascending Dose Cohorts

Group B was closed to enrollment. No screening or randomization occurred in Group B before its closure. This change is reflected in Protocol Amendment 6.

Group C participants were enrolled and randomized in 3 sequential ascending dose cohorts: Cohorts 12, 13, 14 [30, 100, 300 mg REGN5381 or placebo, respectively]). Each dose cohort consists of 6 participants: 3 participants randomized to receive a single IV dose of REGN5381 and 3 randomized to receive placebo.

Group C: Optional Expansion Cohorts

There are 2 optional expansion cohorts in Group C (Cohorts 14A and 14B). The purpose of these optional expansion cohorts is to enroll 8 to 12 participants in a REGN5381 dose level, and 8 to 12 participants in a placebo group. These optional expansion cohorts will not exceed a dose level previously tested in the corresponding Group C ascending dose cohorts.

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2.2. Sample Size and Power Considerations

Up to 122 male and female adult participants will be randomized. In Group A, there are 4 sequential ascending cohorts and 2 optional expansion cohorts with right heart catheterization procedure (as of PA 5, there will be no further dosing of Group A participants in these optional expansion cohorts.), and 3 ascending dose cohorts without right heart catheterization procedure. In Groups B and C, there are 3 ascending dose cohorts and 2 optional expansion cohorts. The study is not powered to test any statistical hypotheses.

Based on the standard deviation (SD) from prior studies evaluating nesiritide invasive studies in participants with heart failure (Colucci, 2000), assessment of the half-width of the 90% confidence interval (CI) in pulmonary capillary wedge pressure (PCWP) after dose administration for multiple sample sizes is summarized below. The single ascending dose (SAD) cohorts and the various ratio in the optional expansion cohorts ensures at least 8 participants in a REGN5381 dose level, and at least 8 participants in a pooled placebo group, which yields a half-width of the 90% confidence interval of 5.9 mmHg in change from baseline in PCWP. With 8 to 18 participants randomized to receive REGN5381 versus 8 to 18 participants randomized to receive placebo, it would provide sufficient precision to detect a difference in PCWP between REGN5381 and the placebo group that is greater or equal to the treatment effect of nesiritide (6 mmHg within 4 to 6 hours).

Table 1: Half-Width of the 90% Confidence Interval for the Difference in Mean Change from Baseline in PCWP (mmHg)

Participants treated with REGN5381	Half-width of the 90% confidence interval
6	7.0
8	5.9
10	5.2
12	4.7
13	4.5
18	3.8

Table 1 is calculated based on the assumptions that a) The randomization ratio of REGN5381: placebo is 1:1 and b) the SD for the change from baseline in PCWP are 7.2 mmHg in the placebo group and 6.2 mmHg in the treated group respectively.

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3. ANALYSIS SETS

The following defines the analysis sets for subjects whose data will be used for statistical analysis.

3.1. Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized participants who received any study drug. Treatment administration and all clinical safety variables will be analyzed using the SAF.

3.2. Pharmacodynamic Analysis Set (PAS)

The pharmacodynamic analysis set (PAS) includes all participants in the SAF who had at least 1 non-missing post-dose PD measurement.

The PAS will be used to analyze the PD effect of REGN5381.

3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all participants who received any active study drug and who had at least 1 non-missing PK result following the dose of study drug.

3.4. Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all treated participants who received any amount of study drug (active or placebo [safety analysis set]) and had at least 1 non-missing ADA result following the dose of study drug or placebo.

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4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

In general, participants will be summarized by treatment group. Participants who received placebo will be pooled for Group A and Group C separately. Treatment groups will be defined as follows:

- Group A
    - Pooled Placebo – IV
    - REGN5381 – IV 10 mg
    - REGN5381 – IV 30 mg
    - REGN5381 – IV 100 mg
    - REGN5381 – IV 300 mg
- Group C
    - Pooled Placebo – IV
    - REGN5381 – IV 30 mg
    - REGN5381 – IV 100 mg
    - REGN5381 – IV 300 mg

Unless otherwise stated, the following conventions will be applied when presenting summary level statistics for data.

Continuous variables will be summarized within each treatment group, presenting the following summary statistics: the sample size (i.e. number of observations with an available value of the variable), average, sample standard deviation, median, minimum, maximum, 1st quartile and 3rd quartile. Categorical data will be summarized within each treatment group by frequency (i.e., total number of observations within each level of the categorical variable in a given treatment group). All levels of the categorical variable will be included. If there are observations where the level of the categorical variable is missing, a separate category titled "Missing" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with the natural ordering of the category levels.

Percentages will also be calculated for each level of the categorical variables with respect to the total sample size for the respective treatment group.

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5. PARTICIPANT DISPOSITION

The total number of screened participants who have signed the ICF, the number of screen failure and the total number of randomized participants (received a randomization number) will be summarized overall on all screened participants.

The following summaries will be provided overall and by treatment group on all randomized participants:

- The total number of participants in each analysis set (as described in Section 3)
- The total number of participants who discontinued the study, along with reasons for discontinuation
- A summary of participants by discharge status
- The number of participants who met discharge criteria on the first day they were eligible by protocol versus the number of participants who required an extended inpatient monitoring will be presented.
- Important protocol deviations

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6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics and Baseline Disease Characteristics

The following demographic variables will be summarized by treatment group and overall (by all participants combined) on the SAF:

- Age at screening (years)
- Age categories at screening (<18, ≥ 18 and < 45, ≥ 45 and < 65, ≥ 65 and < 75, ≥ 75 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino)
- Weight (kg)
- Body mass index (BMI) (kg/m2)
- Oscillometric diastolic blood pressure (DBP) (mmHg)
- Oscillometric systolic blood pressure (SBP) (mmHg)
- Orthostatic SBP difference (mmHg)
- Orthostatic DBP difference (mmHg)
- Oscillometric pulse rate (PR) (bpm)
- Pulmonary capillary wedge pressure (PCWP) (mmHg)
- NT-proBNP (pg/mL)
- eGFR (mL/min/1.73 m2)

6.2. Medical History

Medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by Primary System Organ Class (SOC) and preferred term (PT) for each treatment group (and overall) on the SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treated groups.

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7. PHARMACODYNAMIC DATA

7.1. Description of Pharmacodynamic Data

Pharmacodynamic data will be collected using invasive hemodynamic measurements obtained with right heart catheterization and non-invasive hemodynamic measurements, at the time points according to Table 2 and Table 4.

PCWP is the most relevant assessment of venous pressures and is therefore the invasive hemodynamic measure of greatest interest. This is the only invasive hemodynamic measurement collected in the eCRF. The other invasive hemodynamic measurements are collected continuously in an external data source.

All the other hemodynamic parameters not collected during the right heart catheterization are considered non-invasive. They include both data collected in the eCRF and data derived from the pulse wave analysis device, if applicable.

7.1.1. Invasive Hemodynamic Measurements

7.1.1.1. Pulmonary Capillary Wedge Pressure (PCWP)

PCWP is intermittent data at specified time points. For PCWP, a total of three sequential measurements will be collected at each time point: screening, 2 hours (+30 min), 4 hours (±30 min), and 6 hours (±30 min) post-end of infusion.

Average will be taken if multiple measurements exist for same time point and the time of collection of the last measurement will be used to identify the time point.

7.1.1.2. Other Invasive Hemodynamic Measurements

The following measurements are collected during the right heart catheterization on day 1, in addition to PCWP: Systolic Pulmonary Artery Pressure (SYSPAP, mmHg) and Diastolic Pulmonary Artery Pressure (DIAPAP, mmHg), mean pulmonary artery pressure (mPAP, in mmHg), right atrial pressure (RAP, in mmHg, assumed to be equivalent to Central Venous pressure (CVP)), cardiac output (CO, in l/min), systemic vascular resistance (SVR, in dyne-s/cm^5) and may include mixed venous oxygen saturation (SvO2) assessed using pulmonary artery oximetry when available. Other continuous hemodynamic parameters may also be collected when available (i.e. Stroke Volume (SV)).

The mPAP value recorded from the catheter will be used for the analysis. In case of missing mPAP but not missing SYSPAP (Systolic Pulmonary Artery Pressure) and DIAPAP (Diastolic Pulmonary Artery Pressure), mPAP will be calculated as follows: 1/3 * SYSPAP + 2/3 * DIAPAP.

The following parameters will be derived:

- derived systemic vascular resistance (SVR) = [(MAP-CVP)*80] / CO (in dyne-s/cm^5)
- MAP (mean arterial pressure, in mmHg) = 1/3 SBP (oscillometric systolic blood pressure collected in the eCRF) + 2/3 DBP (oscillometric diastolic blood pressure collected in the eCRF);

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- derived pulmonary vascular resistance (PVR) = [(mPAP-PCWP)*80]/ CO (in dyne-s/cm^5)

For derived PVR and derived SVR the following rules will be used for the merging of data from different sources (SBP, DBP, PCWP from eCRF and mPAP, CVP, CO from external data sources):

- use the assessment time collected in the eCRF at each time point as the reference point.

  Derived PVR calculation is based on PCWP data, therefore the time of collection of the last measurement (if multiple PCWP measurements are collected at the same time point) is used as a reference point for the PVR derivation.

  Derived SVR calculation is based on SBP and DBP data, therefore the time of collection of the measurement corresponding to the median value (if three SBP/DBP measurements are collected at the same time point) or the time of collection of the last measurement (if two SBP/DBP measurements are collected at the same time point) is used as a starting point for the SVR derivation.
- apply a ± 10 minutes window to each reference point.
- use this 20-minutes window to select all non-missing values in external pharmacodynamic data and calculate an average value. If no external pharmacodynamic data is collected during this time window, PVR and SVR will not be derived.
- merge the average values to the eCRF data and calculate PVR and SVR

7.1.2. Non-Invasive Hemodynamic Measurements

The following pharmacodynamic measurements will be collected:

- Oscillometric blood pressure (mmHg)
- Oscillometric pulse rate (bpm)

MAP (mmHg) will be calculated as described in Section 7.1.1.2.

All oscillometric BP and PR should be performed as sequential measurements taken no sooner than approximately 1 minute apart.

The median BP and PR measurement of the last three oscillometric measurements will be calculated for the analysis and the time of collection of the measurement corresponding to the median value will be used to identify the time point.

In case only two measurements are available, the median value will be calculated for the analysis and the time of collection of the last measurement will be used to identify the time point.

Pulse wave analysis device may also be used where available in select countries to collect non-invasive hemodynamic measurements: SYS (systolic blood pressure, in mmHg), DIA (diastolic blood pressure, in mmHg), PR (pulse rate, in bpm), Stroke Volume (SV, in mL/b) and Cardiac

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Output (CO) at the time points indicated in Table 2, Table 3 and Table 4. As of PA5, the duration of pulse wave analysis recording at each visit has been reduced from about 2 hours to approximately 1 hour.

7.2. Analysis of Pharmacodynamic and Exploratory Biomarkers Data

The analysis will be performed on the PAS.

7.2.1. Analysis for Invasive Hemodynamic Parameters

The observed value and change from baseline of PCWP (in cohorts undergoing right heart catheterization) will be summarized with descriptive statistics by time point. Mean values and mean changes will be plotted over time by treatment group.

The other continuous parameters of interest (CVP, CO, SYSPAP, DIAPAP, mPAP and SVR -not derived) will be analyzed with the one-hour average, which is the average of n points within the one-hour window. The time windows are calculated starting from the start of infusion time. Mean values and mean changes will be plotted over time by treatment group using the average.

7.2.2. Analysis for Non-Invasive Hemodynamic Parameters

Oscillometric measurements (SBP, DBP, PR and MAP) will be analyzed over time. Values and their change from baseline over the first 6 hours and 24 hours post-end of infusion (day 1), and through the EOS visit will be summarized with descriptive statistics by treatment group. Mean value and mean change from baseline over time will also be plotted by treatment group.

For pulse wave analysis, parameters collected from the external device (SYS, DIA, PR, SV and CO) will be analyzed over time with the one-hour average, which is the average of n points within the one-hour window. Values over time and their change from baseline will be summarized by treatment group. Mean value and mean change from baseline over time will also be plotted by treatment group using the average.

7.2.3. Exploratory Biomarkers

Each biomarker in urine (24-hour urine for cyclic guanosine monophosphate [cGMP] and sodium and spot urine for albumin, creatinine, and kidney injury molecule-1 [KIM-1]) or plasma (cGMP, N-terminal pro-brain natriuretic peptide [NT-proBNP], N-terminal pro-atrial natriuretic peptide [NT-proANP], atrial natriuretic peptide [ANP] MS, brain natriuretic peptide [BNP] ELISA and MS, norepinephrine, renin, and aldosterone) or serum carbohydrate antigen 125 (CA125) will be generated with following descriptive data: raw data at baseline, by treatment group. Change from baseline and percent change from baseline to each scheduled assessment time will be summarized with descriptive statistics. For biomarkers that are lognormally distributed, geometric means instead of arithmetic means will be reported as part of summary statistics.

In addition, the mean concentrations and mean percent change from baseline will be plotted by visit.

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8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

No formal statistical hypothesis will be carried out in this phase 2 study and multiplicity control is not applicable.

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9. SUMMARY OF EXPOSURE DATA

9.1. Investigation Study Drug Exposure and Compliance

For this single-dose study, the observation period (defined as the time between the date of study drug administration and the date of the EOS or the last visit) rather than the treatment exposure will be presented by treatment group (placebo pooled).

As study drug will be administered as a single dose in the clinic, treatment compliance is not applicable.

9.2. Duration of Follow-up

Not applicable.

9.3. Prior and Concomitant Medications

Any treatment administered will be recorded from the day of informed consent until the End of Study (EOS) visit. Medications will be coded using the latest available version of the World Health Organization's drug dictionary (WHODD). Participants will be counted once in all ATC categories linked to the medication.

Pre-treatment medications: medications taken prior to administration of the Investigational product.

Concomitant medications: medications taken following the dose of Investigational product through the EOS visit.

Number and proportion of participants taking prior/concomitant medication will be summarized by treatment group and overall and sorted by decreasing frequency of the overall group incidence of ATC Level 2 and ATC level 4 based on the SAF.

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10. ANALYSIS OF SAFETY DATA

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.1. The analysis will be performed by treatment group on the on-treatment period.

The definition for Treatment-emergent Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 14.2.

10.1. Adverse Events

All new or worsening adverse events (AEs) occurring between signing of the ICF and the end of the study will be reported using the Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized with incidence tables. Adverse event incidence tables will present the number (n) and percentage (%) of participants experiencing an AE within each treatment group. Multiple occurrences of the same event in a participant will only be counted once in the summary. For tables showing AE severity, for instances where a participant has multiple occurrences of the same PT or SOC, only the worst severity will be counted in the summary.

The AE summaries will be presented for the treatment-emergent adverse events (TEAEs), defined as those adverse events with either initial onset after study drug dose or that represents an exacerbation of a pre-existing condition after the study drug dose.

Summaries for all TEAEs by treatment group will include:

- TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by Primary SOC, PT and Maximum Severity
- TEAEs related to study drug by Primary SOC and PT
- TEAEs related to study conduct by Primary SOC and PT
- TEAEs Leading to Study Treatment Discontinuation by Primary SOC and PT
- TEAEs Leading to Study Discontinuation by Primary SOC and PT
- TEAEs Leading to Death by Primary SOC and PT
- Serious TEAEs by Primary SOC and PT
- Treatment-related TE-SAE by Soc and PT

Listings of Death and SAEs by treatment group will be provided.

10.1.1. Analysis for Adverse Events of Special Interest

Treatment-emergent AESIs will be selected for the analysis as indicated in Appendix 14.3 and summarized by treatment group

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10.2. Laboratory Parameters

Laboratory samples will be analyzed by a local laboratory.

The following parameters will be summarized by observed value and change from baseline with descriptive statistics by treatment group according to the Schedule Events in Appendix 14.1.

- Liver function tests: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase (AP), Lactate dehydrogenase (LDH), total bilirubin
- Renal function tests: creatinine, uric acid, Blood urea nitrogen (BUN)/Urea
- Electrolytes: potassium

For each parameter, mean value and mean change from baseline will be plotted at each scheduled assessment over time by treatment group.

All laboratory measurements will be evaluated by potentially clinically significant values (PCSV) criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Appendix 14.2).

Number and percentage of participants with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all participants and separately for participants in whom the PCSV criterion was normal or missing at baseline.

10.3. Vital Signs

The following vital signs parameters will be collected in the eCRF:

- Body temperature (ºC)
- Blood pressure (mmHg) (oscillometric/orthosthatic)
- Pulse rate (bpm) (oscillometric/orthosthatic)
- Respiration rate (breaths/min)

Oscillometric BP and PR will be recorded as described in Section 7.1.2.

Orthostatic BP and PR will be measured with the participant lying semi-recumbent for at least 10 minutes and after standing for at least 2 minutes. Prior to starting an assessment of orthostatic BP and PR, participants should ambulate for at least 5 minutes. Abnormal results may be repeated.

Orthostatic SBP/DBP difference at each time point will be calculated as follows: orthostatic blood pressure with standing position - Median (oscillometric blood pressure with semi-recumbent position).

Vital sign values (body temperature, oscillometric blood pressure, orthostatic parameter difference, oscillometric pulse rate, respiratory rate) and their change from baseline to all scheduled time points will be summarized with descriptive statistics by treatment group through the EOS visit on the SAF.

Vital sign measurements will be evaluated by PCSV criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Appendix 14.2).

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Number and percentage of participants with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each vital signs parameter for all participants and separately for participants in whom the PCSV criterion was normal or missing at baseline. If applicable, mean values and mean change from baseline over time will also be plotted by treatment group.

10.4. Electrocardiography (ECG)

The following standard 12-lead ECG parameters will be recorded according to the Schedule Events in Appendix 14.1 and summarized by treatment group:

- Ventricular rate (bpm)
- PR (msec)
- QRS interval (msec)
- QT (identify QTc) intervals (msec)

ECG parameters and change from baseline to all scheduled assessment times will be summarized with descriptive statistics.

ECG parameters will be evaluated by PCSV criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Appendix 14.2).

Number and percentage of participants with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for all participants and separately for participants in whom the PCSV criterion was normal or missing at baseline.

Shift tables will be constructed showing participants' transition in ECG status by treatment group from baseline to the following time points: 6 hours post-end of infusion (Day 1), Day 3, Day 4 (if applicable) and Day 5. ECG status will be categorized as: Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS) or Missing.

10.5. Other Safety Data

10.5.1. Fluid Intake Volume and Urine Output Volume Measurements

Oral fluid intake volume and urine output volume will be measured and recorded at time points listed in Table 2. Volumes for oral fluid intake and urine voids will be recorded in 6-hour intervals.

Volumes at all scheduled assessment times through the inpatient treatment period will be summarized with descriptive statistics by treatment group.

10.5.2. Dyspnea Questionnaire

The change in dyspnea status relative to the time point of admission will be summarized with descriptive statistics at each time point by treatment group, through the inpatient treatment period.

Number and proportion of participants with a markedly improved or moderately improved status (responders) will be presented at each time point.

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10.6. Immunogenicity Data

10.6.1. Immunogenicity Variables

The immunogenicity variables include ADA status and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Table 2 and Table 3. Samples positive in the REGN5381 ADA assay will be further characterized for ADA titers.

10.6.2. Analysis of Immunogenicity Data

10.6.2.1. Analysis of ADA Data

The immunogenicity variables described in Section 10.6.1 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category and maximum titer category observed in participants in the ADA analysis set. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive participant is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay.

The maximum titer category of each participant is classified as:

  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative participants
- Number (n) and percent (%) of pre-existing participants
- Number (n) and percent (%) of treatment-emergent ADA positive participants
- Number (n) and percent (%) of treatment-boosted ADA positive participants

Listing of all ADA titer levels will be provided for participants with pre-existing, treatment-emergent and treatment-boosted ADA response.

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10.6.3. Association of Immunogenicity with Exposure and Safety

10.6.3.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN5381 will be explored by treatment groups. Plots of individual REGN5381 concentration time profiles may be provided to examine the potential impact of ADA status, ADA category, maximum titer category on these profiles.

10.6.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA status
  - Treatment-emergent and treatment-boosted
  - Negative and pre-existing
- Maximum titer category
- - High
- - Moderate
- - Low

10.7. Pharmacokinetic Data

Concentrations of total REGN5381 over time will be measured. Pharmacokinetic parameters may include, but are not limited to, the following (and their-dose-normalized versions, if applicable):

- Cmax: The maximum serum concentration (Cmax)
- Clearance (CL)/F
- Vz/F
- T_{last}
- C_{last}
- t_{max}

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$$t_{1/2terminal} = \frac{\ln(2)}{\lambda z}$$

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda z}$$

- AUC_{last}– area under curve (AUC) computed from time zero to the time of the last positive concentration
- AUC_{inf}- AUC from time zero extrapolated to infinity

The concentrations of total REGN5381 over time will be measured and will be summarized by descriptive statistics for each cohort for the purpose of estimating exposures in these groups. Selected PK parameters will be analyzed using noncompartmental analysis and will be summarized using descriptive statistics which may include, but are not limited to, mean (arithmetic and/or geometric), standard deviation, standard error of the mean, coefficient of variation (%), minimum, Q1, median, Q3, and maximum.

No formal statistical hypothesis testing will be performed.

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11. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

11.1. Definition of Baseline

For oscillometric systolic blood pressure, diastolic blood pressure and pulse rate, baseline is calculated as the median of the last three measurements collected at 30 minutes prior to dose administration and the time of collection of the measurement corresponding to the median value will be used to identify the baseline time point.

In case only two measurements are collected prior to dose administration, the median value will be calculated for the analysis and the time of collection of the last measurement will be used to identify the baseline time point.

For pulmonary capillary wedge pressure, baseline is calculated as the mean of the last three measurements collected at 30 minutes prior to dose administration and the latest time point will be selected for the analysis.

For the other pharmacodynamic parameters (invasive – SYSPAP, DIAPAP, mPAP, CVP, CO - and non-invasive – SYS, DIA, PR, SV, CO-), baseline is defined as the last available average of n points over 1 hour prior to study drug administration.

Baseline weight corresponds to the screening value.

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

11.2. Data Convention

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

11.3. Data for Non-Efficacy Endpoints

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Medication missing/partial dates

No imputation of medication/procedure start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure.

Adverse event

If the severity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

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When the partial AE date/time information does not indicate that the AE started prior to study treatment or after the TEAE period, the AE will be classified as treatment-emergent.

Date of first / last injection

Since the study drug is administered at the site, the date and time of study drug administration are filled in electronic case report form (eCRF). No missing data is expected. The information is filled in eCRF.

Potentially Clinically Significant Value (PCSV)

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing, e.g., for eosinophils the PCSV is >0.5 giga/L or > upper limit of normal (ULN) if ULN ≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

When the PCSV definition involves a change from baseline value, participants must have a baseline value to be included in the summaries.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSVs.

All measurements collected during the study, including values from unscheduled visits, will be used in the PCSV analyses.

A participant who had 2 or more treatment-emergent PCSVs in each PCSV category will be counted only once in the table.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Unscheduled Assessments

The determination of baselines will be based on scheduled available assessments and unscheduled available assessments. Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the first observation will be used in summaries

11.5. Pooling of Categorical Variables for Statistical Analyses

No need to pool categorical variables for this study.

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12. TECHINCAL DETAILS PERTAINING TO INTERIM ANALYSIS/(ES)

No formal interim analysis is planned.

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13. REFERENCES

ICH E9, Statistical Principles for Clinical Trials, September 1998.

Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med 2000; 343(4):246-253.

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14. APPENDIX

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14.1. Schedule of Time and Events

Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period

	Screening Period	Inpatient Treatment Period							
Study Procedure	**Screening**	**Begin Baseline Measurements**	**Invasive Hemodynamic Monitoring, Dose Administration, Observation**	**Observation**			**Observation and Discharge (V7 is required, V8 & V9 depend on timing of participant discharge[9])**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Screening/Baseline									
Inclusion/Exclusion	X	X	X						
Informed Consent	X								
Medical History	X								
Demographics	X								
Height	X								
Laboratory Tests									
eGFR	X								
INR		X							
HIV, HBV, & HCV screen	X								
Pregnancy test (for WOCBP)[1]	X	X							
FSH (for postmenopausal women)[2]	X								
NT-proBNP (or BNP), plasma	X[3]								
Hematology panel	X	X			X		X		
Blood chemistry	X	X		X	X	X	X	X	X
Urinalysis	X				X				

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	Screening Period	Inpatient Treatment Period							
Study Procedure	**Screening**	**Begin Baseline Measurements**	**Invasive Hemodynamic Monitoring, Dose Administration, Observation**	**Observation**			**Observation and Discharge (V7 is required, V8 & V9 depend on timing of participant discharge[9])**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Inpatient Admittance and Discharge									
Clinic admission		X[4,5]							
Randomization			X[6]						
Recording of volume ins and outs (oral fluid intake volume & urine output volume)[7]			X	X					
24-hour urine collection ends[7]				X	X				
Resume home heart failure medications			X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Clinic discharge							X[9]	X[9]	X[9]
Treatment									
Administer study drug			X[10]						
Hemodynamics and Vitals									
PCWP and other invasive hemodynamic parameters			X[11, 12]						
Oscillometric BP & PR measurement[13]	X	X	X	X	X	X	X	X	X
Orthostatic BP & PR measurement[13]		X		X	X	X	X	X	X
Pulse oximetry (SpO_2)[14]		X	X	X	X	X	X	X	X

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	Screening Period	Inpatient Treatment Period							
Study Procedure	**Screening**	**Begin Baseline Measurements**	**Invasive Hemodynamic Monitoring, Dose Administration, Observation**	**Observation**			**Observation and Discharge (V7 is required, V8 & V9 depend on timing of participant discharge[9])**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Respiratory rate	X		X	X	X	X	X	X	X
Body temperature	X		X	X	X				
Patient Reported Outcomes									
Dyspnea questionnaire[15]			X	X	X	X			
Safety									
Weight[16]	X	X	X	X	X		X		
Physical examination[17]	X		X		X		X		
Telemetry (3-lead ECG)		X	X	X	X	X	X	X	X
Electrocardiogram[18]	X		X		X		X		
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X
Pharmacokinetics and Immunogenicity Samples									
Drug concentration sample[19], serum			X	X	X	X	X		
ADA sample[25], serum			X						

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	Screening Period	Inpatient Treatment Period							
Study Procedure	**Screening**	**Begin Baseline Measurements**	**Invasive Hemodynamic Monitoring, Dose Administration, Observation**	**Observation**			**Observation and Discharge (V7 is required, V8 & V9 depend on timing of participant discharge[9])**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Pharmacodynamics and Biomarker Samples									
cGMP[19], plasma		X	X	X	X				
NT-proBNP[19], plasma		X	X	X	X	X	X		
Exploratory natriuretic peptides (NT-proANP, ANP, BNP)[20], plasma			X	X	X				
Norepinephrine[20], plasma			X						
Renin and aldosterone[20], plasma			X	X	X				
CA125, serum		X			X				
Pulse wave analysis[21]			X	X	X				
cGMP & sodium 24-hour collection, urine[22]				X	X				
Spot urine (for albumin, creatinine, KIM-1)[23]		X	X	X	X				
Pharmacogenomics									
Whole blood sample for DNA isolation - optional[24]		X							

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Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period

1. Pregnancy tests will only be performed in WOCBP. An indeterminate or positive urine pregnancy test will be confirmed with a serum pregnancy test.
2. FSH will only be checked in women who have not had menses in 12 months and are assumed to be postmenopausal to confirm postmenopausal state.
3. Groups A and B: Participants need to have a NT-proBNP >1000 pg/mL or BNP >300 pg/mL (NT-proBNP >1600 pg/mL or BNP >500 pg/mL if in atrial fibrillation) within 30 days prior to randomization measured by the local laboratory. Group C: Participants need to have a NT-proBNP >300 pg/mL or BNP >100 pg/mL (NT-proBNP >900 pg/mL or BNP >300 pg/mL if in atrial fibrillation) within 30 days prior to randomization measured by the local laboratory.
4. All participants will be admitted to the clinic on the evening prior to study drug administration or at an earlier time as decided by the investigator.
5. Participants who are taking ACE inhibitors, ARBs, MRAs, nitrates, and/or diuretics will temporarily halt these medications beginning at 11:59 PM on day -1 (the night prior to the right heart catheterization). The investigator may also withhold other home medications for the participant.
6. Participants with a screening PCWP ≥15 mmHg, RAP >5 mmHg, and mPAP <40 mmHg will be randomized into the study (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively]). Participants with a screening PCWP <15 mmHg and RAP <5 mmHg will not be eligible for the study and will complete the right heart catheterization as clinically required at the discretion of the investigator. These ineligible participants will be observed for at least 4 hours after removal of the PAC. The investigator will be recommended to communicate the findings to the participant's cardiologist. Furthermore, the investigator or qualified designee will conduct a telephone check-up with the participant within 7 days following site discharge.
7. Total daily oral fluid intake and urine void total volume measurements will be recorded for 2 consecutive days (day 1 and day 2; total of 48 hours) in 6-hour intervals. For each 6-hour interval, start/stop times and volume of fluid in/out will be recorded. The first urine collection begins following study drug administration on day 1 (±2 hours) and ends on day 2. The second urine collection begins on day 2 (after completion of the first urine collection) and ends on day 3. Prior to recording and collection of urine on day 1, participants must have voided at least once on day -1 at the study site or on day 1 prior to the insertion of the PAC (urine from this void may be used for the spot urine collection, see footnote #23).
8. After removal of the catheter on day 1, participants can restart home heart failure medications under guidance provided by the sponsor but at the discretion of the investigator (Section 6.1.5 of the study protocol). It is recommended that if an investigator

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modifies a participant's discharge home heart failure medication regimen that the changes are communicated to the participant's physician. At each post-discharge outpatient visit, the investigator will re-assess and adjust participant's home heart failure medications, aiming to return the participant to their original regime where possible if clinically appropriate (Section 6.1.5 of the study protocol).

9. Participants may not be discharged earlier than day 5 and may remain under inpatient monitoring through completion of day 8 assessments. However, participants who do not meet the individual participant discharge may be kept for Extended Inpatient Monitoring after day 8. Participants will continue to be assessed until they are able to meet the discharge criteria. Participants discharged on day 5 do not need to complete day 6 or day 7 assessments. Participants discharged on day 6 do not need to complete day 7 assessments. Participants who do not meet the inpatient discharge criteria on day 8 may remain at the study site for Extended Inpatient Monitoring until eligible to be discharged. Refer to Section 6.1.6 of the study protocol for additional details. Furthermore, participants must be explicitly instructed by the investigator prior to discharge regarding how to communicate with the study site if needed (eg, in the event of an adverse event) in between study site visits during the outpatient portion of the study.
10. After right heart catheterization procedure in the catheterization laboratory, Participants are transported to the heart failure unit and then must rest for at least 30 minutes in the heart failure unit to allow baseline assessments before receiving study drug.
11. On day 1, after screening measurements, eligible participants will begin having their continuous hemodynamic data (CO, RAP, SVR, PVR, mPAP) recorded upon arrival in the inpatient monitoring unit (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively]). Continuous SvO_2 may also be collected when available. Participants must then rest for at least 30 minutes prior to measurement of the baseline PCWP and oscillometric BP & PR. The baseline PCWP and oscillometric BP & PR will be assessed no more than 30 minutes prior to start of drug administration. Additional PCWP measurements are recorded at 2 hours (+30 min), 4 hours (±30 min), and 6 hours (±30 min) post-end of infusion. The recording of continuous invasive hemodynamic data continues until completion of 6-hour post-end of infusion PCWP and oscillometric BP & PR measurements. See Table 5 of the study protocol for timing of these assessments on day 1. Whenever possible, hemodynamic parameters will be assessed before collection of PK samples and laboratory samples.
12. SvO_2 will be assessed using pulmonary artery oximetry where available.
13. Both oscillometric and orthostatic BP & PR measurements will be obtained and recorded once on the evening of clinic admission. On day 1, oscillometric BP & PR measurements will be taken pre-dose and hourly post-end of infusion for the duration of the right heart catheterization procedure (see footnote #11 and Table 5 of the study protocol). During the remaining Inpatient Treatment Period beginning on day 2, both oscillometric and orthostatic BP & PR measurements will be obtained and recorded

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approximately every 8 hours (± 1 hour) until site discharge. Additional readings beyond those specified here and including the Extended Inpatient Monitoring period may be taken at the discretion of the investigator. Whenever possible, BP and PR should be taken before collection of PK samples and laboratory samples.

14. SpO_2 will be measured continuously while the PAC is in place and the investigator should follow institutional policies for the remainder of the Inpatient Treatment Period.
15. See Table 5 of the study protocol for the timing for participants to complete a dyspnea questionnaire on day 1. On day 2 the dyspnea questionnaire should be completed 24 hours (±1 hour) post-end of infusion.
16. Participants are requested to void (empty urinary bladder) prior to being weighed each time. On day 1, participants are weighed prior to insertion of the PAC.
17. Complete physical examinations will be performed at screening. A limited physical examination, consisting of an assessment of heart, lungs, peripheral pulses, and skin will be conducted on day 1, day 3, and day 5 (see Table 5 of the study protocol for the timing of these limited physical examinations on day 1). Participants who remain onsite for the Extended Inpatient Monitoring (beginning on day 9) will receive daily limited physical examinations until site discharge (see Table 4 of the study protocol).
18. See Table 5 of the study protocol for the timing of an ECG assessment on day 1.
19. See Table 5 of the study protocol for the timing of collection of samples on day 1 to assess drug concentrations (serum), and NT-proBNP and cGMP (plasma). Samples to assess drug concentration, plasma NT-proBNP, and plasma cGMP on day 2 will be collected 24 hours (±1 hour) post-end of infusion.
20. See Table 5 of the study protocol for the timing of collection of samples on day 1 for exploratory natriuretic peptides (NT-proANP, ANP, BNP), norepinephrine, renin, and aldosterone (plasma). Samples to assess plasma exploratory natriuretic peptides, renin, and aldosterone concentrations on day 2 will be collected 24 hours (±1 hour) post-end of infusion.
21. Pulse wave analysis device may be used in the ≥100 mg dose cohorts where available in select countries to support exploratory endpoints related to non-invasive hemodynamic measurements in this study. The device will be connected for approximately 1 hour at approximately the same time of day on each occasion. On day 1 this assessment may be completed at any time prior to start of study drug infusion. Whenever possible, pulse wave analysis device activities will be conducted before collection of PK samples and laboratory samples. Further details regarding the pulse wave analysis device and assessments are provided in a study operations manual.
22. Urinary cGMP and sodium are measured in this trial as part of PD assessment. Urinary cGMP and sodium are assessed using urine samples collected over a 24-hour period (see footnote #8).

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23. Spot urine collection will occur on day -1 upon admittance to the study site or may occur on day 1 prior to PAC insertion for the right heart catheterization. The remainder of the spot urine collections needed for these assessments will be obtained from the total daily urine collections that begin on day 1 following study drug administration.
24. The pharmacogenomics sub-study ICF must be signed prior to performing this sample collection.
25. In the event of an SAE due to infusion-related reactions or hypersensitivity reactions, additional drug concentration and ADA samples may be collected at or near the onset when possible.

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Table 3: Schedule of Events for Outpatient Follow-Up Period

	Inpatient Treatment Period (Continued) and/or Outpatient Follow-Up Period			Outpatient Follow-Up Period						Unscheduled Visit[11]
Study Procedure	**Visit 10**	**Extended Inpatient Monitoring (optional)**	**Visit 11**	**Visit 12/EOS[1]**	**Visit 13/EOS[2]**	**Visit 14**	**Visit 15/EOS[3]**	**Visit 16**	**Visit 17/EOS[4]**	
Visit	**V10**		**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	
Day	**8**	**Days 9 through 12**	**15**	**22**	**36**	**57**	**78**	**99**	**126**	
Window (day)	**±1**		**±3**	**+3**	**+3**	**±3**	**+3**	**±3**	**+3**	
Vitals[5]										
Oscillometric BP & PR measurement	X	X	X	X	X	X	X	X	X	X
Orthostatic BP & PR measurement	X	X	X	X	X	X	X	X	X	X
Respiratory rate	X	X	X	X	X	X	X	X	X	
Body temperature	X		X	X	X	X	X	X	X	
Safety										
Weight	X	X	X	X	X	X	X	X	X	X
Physical examination, limited[6]		X		X[7]	X[7]		X[7]		X	X
Telemetry (3-lead ECG)	X	X								
Electrocardiogram		X		X[7]	X[7]		X[7]		X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X
Investigator assessment heart failure management[8]	X	X	X	X	X	X	X	X	X	X

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	Inpatient Treatment Period (Continued) and/or Outpatient Follow-Up Period			Outpatient Follow-Up Period						Unscheduled Visit[11]
Study Procedure	**Visit 10**	**Extended Inpatient Monitoring (optional)**	**Visit 11**	**Visit 12/EOS[1]**	**Visit 13/EOS[2]**	**Visit 14**	**Visit 15/EOS[3]**	**Visit 16**	**Visit 17/EOS[4]**	
Visit	**V10**		**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	
Day	**8**	**Days 9 through 12**	**15**	**22**	**36**	**57**	**78**	**99**	**126**	
Window (day)	**±1**		**±3**	**+3**	**+3**	**±3**	**+3**	**±3**	**+3**	
Pregnancy test (for WOCBP)[9]				X	X	X	X	X	X	X
Inpatient Discharge (if participant remains at the unit through or past day 8)										
Clinic discharge	X	X								
Laboratory Testing										
Hematology panel	X	X		X	X		X		X	X
Blood chemistry	X	X		X	X		X		X	X
Pharmacokinetics and Immunogenicity Sampling										
Drug concentration sample, serum	X		X	X	X	X	X	X	X	X
ADA sample, serum				X[7]	X[7]		X[7]		X	
Pharmacodynamics and Biomarker Samples										
NT-proBNP, plasma	X		X	X	X	X	X	X	X	X
Exploratory natriuretic peptides (NT-proANP, ANP, BNP), plasma				X	X		X		X	

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	Inpatient Treatment Period (Continued) and/or Outpatient Follow-Up Period			**Outpatient Follow-Up Period**						**Unscheduled Visit[11]**
Study Procedure	**Visit 10**	**Extended Inpatient Monitoring (optional)**	**Visit 11**	**Visit 12/EOS[1]**	**Visit 13/EOS[2]**	**Visit 14**	**Visit 15/EOS[3]**	**Visit 16**	**Visit 17/EOS[4]**	
Visit	**V10**		**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	
Day	**8**	**Days 9 through 12**	**15**	**22**	**36**	**57**	**78**	**99**	**126**	
Window (day)	**±1**		**±3**	**+3**	**+3**	**±3**	**+3**	**±3**	**+3**	
CA125, serum	X			X	X		X		X	
Pulse wave analysis[10]	X		X	X	X	X	X	X	X	X

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Footnotes for Table 3: Schedule of Events for Outpatient Follow-Up Period

1. Participants receiving <10 mg of REGN5381 will perform their EOS visit no earlier than day 22.
2. Participants receiving ≥10 mg and ≤30 mg of REGN5381 will perform their EOS visit no earlier than day 36.
3. Participants receiving >30 mg and ≤100 mg of REGN5381 will perform their EOS visits no earlier than day 78.
4. Participants receiving >100 mg and ≤300 mg of REGN5381 will perform their EOS visit no earlier than day 126.
5. ECG and SpO2 can be performed on any visit based on clinical need and judgement of the investigator.
6. The limited physical examinations will include assessment of heart, lungs, peripheral pulses, and skin.
7. These assessments will only be completed for participants undergoing the EOS visit.
8. The investigator will aim to get the participant back onto their original home heart failure medication(s) whenever possible. It is recommended if an investigator modifies a participant's home heart failure medication regimen that the changes are communicated to the participant's physician. The investigator will re-assess and adjust participant's home heart failure medications, as needed based on the investigator's clinical judgement, at each outpatient visit until the EOS visit.
9. Pregnancy tests will only be performed in WOCBP. An indeterminate or positive urine pregnancy test will be confirmed with a serum pregnancy test.
10. Pulse wave analysis device may be used in the ≥100 mg dose cohorts where available in select countries to support exploratory endpoints related to non-invasive hemodynamic measurements in this study. The device will be connected for approximately 1 hour at approximately the same time of day on each visit. Whenever possible, pulse wave analysis device activities will be conducted before collection of PK samples and laboratory samples. Further details regarding the pulse wave analysis device and assessments are provided in a study operation manual.
11. It is not required that all procedures be performed during unscheduled visits. Procedures may be conducted based on study needs and/or the investigator's clinical judgment.

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Table 4: Timing of Assessment in Relation to Study Drug Administration

Study Procedure	Day of Study Drug Administration								
	Timing Relative to Administration of Study Drug								
	Start of Infusion		Post-End of Infusion						
			0 hours	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
Window	**≤ -3 hours**	**≤ - 30 min**	**+30 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**
Start recording of continuous invasive hemodynamic parameters[1]		X (upon arrival at the inpatient monitoring unit at least 30 minutes prior to baseline PCWP measurements)							
PCWP[1]		X (baseline)			X		X		X
Oscillometric BP & PR measurement		X	X	X	X	X	X	X	X
Stop recording of continuous invasive hemodynamic parameters									X (after final PCWP measurements)
Respiratory rate	X								
Body Temperature	X								
Physical examination (limited)	X								X (within 6 hours)
Electrocardiogram	X								X (within 6 hours)
Dyspnea questionnaire	X					X			X
Drug concentration sample, serum	X		X		X		X		X
ADA sample, serum	X								

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Study Procedure	Day of Study Drug Administration								
	Timing Relative to Administration of Study Drug								
	Start of Infusion		Post-End of Infusion						
			0 hours	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
Window	**≤ -3 hours**	**≤ - 30 min**	**+30 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**
cGMP, plasma	X				X		X		X
NT-proBNP, plasma	X				X		X		X
Exploratory natriuretic peptides (NT-proANP, ANP, BNP), plasma	X								X
Norepinephrine, plasma	X		X						X
Renin and aldosterone, plasma	X								X
Pulse wave analysis	X (any time prior to start of drug infusion)								

Footnotes for Table 4: Timing of Assessment in Relation to Study Drug Administration

1. Not applicable to Group A, Cohorts 6, 7, and 8

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14.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical chemistry		
ALT*	>3 ULN and baseline ≤3 ULN* >5 ULN and baseline ≤5 ULN >10 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Each category is calculated independently.
AST*	>3 ULN and baseline ≤3 ULN* >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤1.5 ULN	
Total Bilirubin*	>1.5 ULN and baseline ≤1.5 ULN* >2 ULN and baseline ≤2.0 ULN	
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤3 ULN or TBILI ≤2ULN	
CPK*	>3 ULN and baseline ≤3 ULN* >10 ULN and baseline ≤10ULN	
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L ≥50% change from randomization value and creatinine greater than 1.02 mg/dl for female or creatinine greater than 1.18 mg/dl for male ≥100% change from baseline from randomization value and creatinine greater than 1.02 mg/dl for female or creatinine greater than 1.18 mg/dl for male	3 independent criteria

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Parameter	PCSV	Comments
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - <60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - <90 ml/min and baseline ≥90 ml/min (mild renal impairment) ≥ 25% decrease from baseline	Four independent criteria
Uric Acid Hyperuricemia: Hypouricemia:	>408 µmol/L and baseline ≤408 µmol/L <120 µmol/L and baseline ≥120 µmol/L	Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and baseline <17 mmol/L	Two independent criteria
Sodium Hyponatremia Hyponatremia	≤129 mmol/L and baseline >129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	<3 mmol/L and baseline ≥3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005 Two independent criteria
Total Cholesterol	≥7.74 mmol/L and baseline <7.74 mmol/L	Threshold for therapeutic intervention
Triglycerides	≥4.6 mmol/L and baseline <4.6 mmol/L	Threshold for therapeutic intervention
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline <11.1 mmol/L (unfasted); <7 mmol/L (fasted)	
Albumin	≤25 g/L and baseline >25 g/L	
Hematology		

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Parameter	PCSV	Comments
WBC	<3.0 Giga/L and baseline ≥3.0 Giga/L for Non-Black or <2.0 Giga/L and baseline ≥2.0 Giga/L for Black*.	
Neutrophils	<1.5 Giga/L for Non-Black or <1.0 Giga/L for Black and baseline ≥1.5 Giga/L for Non-Black or ≥1.0 Giga/L for Black*	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN≥0.5 Giga/L)	
Hemoglobin	At least 20 g/L (1.24 mmol/L) decrease versus baseline	
Hematocrit	≤0.37 v/v for male or ≤0.32 v/v and baseline >0.37 v/v for Male or >0.32 v/v for Female* ≥0.55 v/v for male or ≥0.5 v/v and baseline <0.55 v/v for Male <0.5 v/v for Female*	Two Criteria are independent.
Platelets	<100 Giga/L and baseline ≥100 Giga/L	
Vital signs		
HR	≤ 50 bpm and decrease from baseline≥20 bpm ≥ 120 bpm and increase from baseline≥20 bpm	To be applied for all positions except STANDING.

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Parameter	PCSV	Comments
SBP	≤ 95 mmHg and decrease from baseline [3] 20 mmHg ≥160 mmHg and increase from baseline ≥ 20 mmHg	To be applied for all positions except STANDING.
DBP	≤ 45 mmHg and decrease from baseline ≥10 mmHg ≥ 90 mmHg and increase from baseline ≥ 10 mmHg	To be applied for all positions except STANDING.
MAP	≤ 70 mmHg and decrease from baseline ≥10 mmHg ≥ 100 mmHg and increase from baseline ≥ 10 mmHg	
Orthostatic Hypotension	SBP St – Su ≤ -20 mmHg DBP St – Su ≤ -10 mmHg	
Weight	≥ 5 % increase versus baseline ≥ 5% decrease versus baseline	
ECG parameters		
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms and baseline <120 ms	

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Parameter	PCSV	Comments
QTc Borderline Prolonged* Additional	Absolute values (ms) Males Females Borderline 431-450 ms 451-470 ms Prolonged* > 450 ms > 470 ms QTc ≥500 ms ≥ 500 ms Increase versus baseline (Males and Females) Borderline D 30-60 ms Prolonged * D > 60 ms	To be applied to any kind of QT correction formula *QTc prolonged and DQTc > 60 ms are the PCSA to be identified in individual participants listings.

14.3. Selection criteria for AESI

AESI	Selection
Moderate to severe injection site reactions (ISRs)	Adverse Event is moderate to severe and High Level Term: Injection site reaction. Preferred term: Embolia cutis medicamentosa Injected limb mobility decreased Injection site abscess Injection site abscess sterile Injection site alopecia Injection site anaesthesia Injection site atrophy Injection site bruising Injection site calcification Injection site cellulitis Injection site coldness Injection site cyst Injection site deformation Injection site dermatitis

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	Injection site discharge Injection site discolouration Injection site discomfort Injection site dryness Injection site dysaesthesia Injection site eczema Injection site erosion Injection site erythema Injection site exfoliation Injection site extravasation Injection site fibrosis Injection site foreign body sensation in eye Injection site granuloma Injection site haematoma Injection site haemorrhage Injection site hyperaesthesia Injection site hypersensitivity Injection site hypertrichosis Injection site hypertrophy Injection site hypoaesthesia Injection site indentation Injection site induration Injection site infection Injection site inflammation Injection site injury Injection site irritation Injection site ischaemia Injection site joint discomfort Injection site joint effusion Injection site joint erythema Injection site joint infection Injection site joint inflammation Injection site joint movement impairment Injection site joint pain Injection site joint swelling Injection site joint warmth Injection site laceration Injection site lymphadenopathy Injection site macule Injection site mass

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	Injection site movement impairment Injection site muscle atrophy Injection site muscle weakness Injection site necrosis Injection site nerve damage Injection site nodule Injection site oedema Injection site pain Injection site pallor Injection site panniculitis Injection site papule Injection site paraesthesia Injection site phlebitis Injection site photosensitivity reaction Injection site plaque Injection site pruritus Injection site pustule Injection site rash Injection site reaction Injection site recall reaction Injection site scab Injection site scar Injection site streaking Injection site swelling Injection site telangiectasia Injection site thrombosis Injection site ulcer Injection site urticaria Injection site vasculitis Injection site vesicles Injection site warmth Malabsorption from injection site
Moderate to severe infusion reactions	Adverse Event is moderate to severe. Preferred Term: Angioedema Arrhythmia Asthenia Atrial fibrillation Bradycardia

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	Bronchospasm Chest discomfort Chest pain Chills Cough Dizziness Dyspnoea Fatigue Flushing Headache Hyperhidrosis Hypertension Hypotension Infusion related hypersensitivity reaction Infusion related reaction Mental status changes Myalgia Nausea Oedema peripheral Oxygen saturation decreased Presyncope Pruritus Pyrexia Rash Syncope Swelling of eyelid Swelling of face Swollen tongue Tachycardia Throat irritation Urticaria
Moderate or severe hypersensitivity reactions	Adverse Event is moderate to severe and search criteria: SMQ “Hypersensitivity” narrow. Prefered term: Acquired C1 inhibitor deficiency Acute generalised exanthematous pustulosis Administration related reaction Administration site dermatitis Administration site eczema

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	Administration site hypersensitivity Administration site rash Administration site recall reaction Administration site urticaria Administration site vasculitis AGEP-DRESS overlap Allergic bronchitis Allergic colitis Allergic cough Allergic cystitis Allergic eosinophilia Allergic gastroenteritis Allergic hepatitis Allergic keratitis Allergic lymphangitis Allergic oedema Allergic otitis externa Allergic otitis media Allergic pharyngitis Allergic reaction to excipient Allergic respiratory disease Allergic respiratory symptom Allergic sinusitis Allergic stomatitis Allergic transfusion reaction Allergy alert test positive Allergy test positive Allergy to immunoglobulin therapy Allergy to surgical sutures Allergy to vaccine Anal eczema Anaphylactic reaction Anaphylactic shock Anaphylactic transfusion reaction Anaphylactoid reaction Anaphylactoid shock Anaphylaxis treatment Angioedema Antiallergic therapy Antiendomysial antibody positive

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	Anti-neutrophil cytoplasmic antibody positive vasculitis Application site dermatitis Application site eczema Application site hypersensitivity Application site rash Application site recall reaction Application site urticaria Application site vasculitis Arthritis allergic Atopic cough Atopy Atypical Stevens-Johnson syndrome Blepharitis allergic Blood immunoglobulin E abnormal Blood immunoglobulin E increased Bone cement allergy Bromoderma Bronchospasm Bullous haemorrhagic dermatosis Catheter site dermatitis Catheter site eczema Catheter site hypersensitivity Catheter site rash Catheter site urticaria Catheter site vasculitis Chlorine sensitivity Chronic eosinophilic rhinosinusitis Chronic hyperplastic eosinophilic sinusitis Circulatory collapse Circumoral oedema Circumoral swelling Conjunctival oedema Conjunctivitis allergic Contact stomatitis Contrast media allergy Contrast media reaction Corneal oedema Cross sensitivity reaction Cutaneous vasculitis Dennie-Morgan fold

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	Dermal filler reaction Dermatitis Dermatitis acneiform Dermatitis allergic Dermatitis atopic Dermatitis bullous Dermatitis contact Dermatitis exfoliative Dermatitis exfoliative generalised Dermatitis herpetiformis Dermatitis infected Dermatitis psoriasiform Device allergy Dialysis membrane reaction Distributive shock Documented hypersensitivity to administered product Drug eruption Drug hypersensitivity Drug provocation test Drug reaction with eosinophilia and systemic symptoms Eczema Eczema infantile Eczema nummular Eczema vaccinatum Eczema vesicular Eczema weeping Encephalitis allergic Encephalopathy allergic Eosinophilic granulomatosis with polyangiitis Epidermal necrosis Epidermolysis Epidermolysis bullosa Epiglottic oedema Erythema multiforme Erythema nodosum Exfoliative rash Eye allergy Eye oedema Eye swelling Eyelid oedema

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	Face oedema Fixed eruption Generalised bullous fixed drug eruption Giant papillary conjunctivitis Gingival oedema Gingival swelling Gleich's syndrome Haemorrhagic urticaria Hand dermatitis Henoch-Schonlein purpura Henoch-Schonlein purpura nephritis Heparin-induced thrombocytopenia Hypersensitivity Hypersensitivity myocarditis Hypersensitivity pneumonitis Hypersensitivity vasculitis Idiopathic urticaria Immediate post-injection reaction Immune thrombocytopenia Immune tolerance induction Implant site dermatitis Implant site hypersensitivity Implant site rash Implant site urticaria Incision site dermatitis Incision site rash Infusion related hypersensitivity reaction Infusion related reaction Infusion site dermatitis Infusion site eczema Infusion site hypersensitivity Infusion site rash Infusion site recall reaction Infusion site urticaria Infusion site vasculitis Injection related reaction Injection site dermatitis Injection site eczema Injection site hypersensitivity Injection site rash

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	Injection site recall reaction Injection site urticaria Injection site vasculitis Instillation site hypersensitivity Instillation site rash Instillation site urticaria Interstitial granulomatous dermatitis Intestinal angioedema Iodine allergy Kounis syndrome Laryngeal oedema Laryngitis allergic Laryngospasm Laryngotracheal oedema Limbal swelling Lip oedema Lip swelling Mast cell activation syndrome Mast cell degranulation present Medical device site dermatitis Medical device site eczema Medical device site hypersensitivity Medical device site rash Medical device site recall reaction Medical device site urticaria Mouth swelling Mucocutaneous rash Multiple allergies Multiple drug hypersensitivity Nephritis allergic Nikolsky's sign positive Nodular rash NSAID exacerbated respiratory disease Nutritional supplement allergy Oculomucocutaneous syndrome Oculorespiratory syndrome Oedema mouth Oral allergy syndrome Oropharyngeal blistering Oropharyngeal oedema

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	Oropharyngeal spasm Oropharyngeal swelling Palatal oedema Palatal swelling Palisaded neutrophilic granulomatous dermatitis Palpable purpura Pathergy reaction Penile dermatitis Perioral dermatitis Periorbital dermatitis Periorbital oedema Periorbital swelling Pharyngeal oedema Pharyngeal swelling Polymers allergy Procedural shock Pruritus allergic Puncture site rash Radioallergosorbent test positive Rash Rash erythematous Rash follicular Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash neonatal Rash papular Rash papulosquamous Rash pruritic Rash pustular Rash rubelliform Rash scarlatiniform Rash vesicular Reaction to azo-dyes Reaction to colouring Reaction to excipient Reaction to flavouring Reaction to food additive Reaction to preservatives

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	Reaction to sweetener Rhinitis allergic Scleral oedema Scleritis allergic Scrotal dermatitis Scrotal oedema Serum sickness Serum sickness-like reaction Shock Shock symptom SJS-TEN overlap Skin necrosis Skin test positive Solar urticaria Solvent sensitivity Stevens-Johnson syndrome Stoma site hypersensitivity Stoma site rash Swelling face Swelling of eyelid Swollen tongue Symmetrical drug-related intertriginous and flexural exanthema Systemic contact dermatitis Tattoo associated skin reaction Tongue oedema Toxic epidermal necrolysis Toxic skin eruption Tracheal oedema Type I hypersensitivity Type II hypersensitivity Type III immune complex mediated reaction Type IV hypersensitivity reaction Urticaria Urticaria cholinergic Urticaria chronic Urticaria contact Urticaria papular Urticaria physical Urticaria pigmentosa

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	Urticaria vesiculosa Urticarial dermatitis Urticarial vasculitis Vaccination site dermatitis Vaccination site eczema Vaccination site exfoliation Vaccination site hypersensitivity Vaccination site rash Vaccination site recall reaction Vaccination site urticaria Vaccination site vasculitis Vaccination site vesicles Vaginal ulceration Vancomycin infusion reaction Vascular access site dermatitis Vascular access site eczema Vasculitic rash Vernal keratoconjunctivitis Vessel puncture site rash Vessel puncture site vesicles Vulval eczema Vulval ulceration Vulvovaginal rash Vulvovaginal ulceration Vulvovaginitis allergic
Severe hypotension (SBP <90 mm Hg)	Check based on SBP values
Elevated liver enzymes (≥3x ULN)	Check based on laboratory values

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