STATISTICAL ANALYSIS PLAN
VERSION: FINAL 2.0

Clinical Study Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of A Single Dose of REGN5381, an NPR1 Monoclonal Antibody Agonist, in Patients with Chronic Heart Failure with Reduced Ejection Fraction
Compound:	REGN5381
Protocol Number:	R5381-HF-22118
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Version 2.0 / 24 July, 2025

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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

AAS	Anti-drug antibody analysis set
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANP	Atrial natriuretic peptide
AR	Autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
AUC	Area under curve
BMI	Body mass index
BNP	Brain natriuretic peptide
CA-125	Carbohydrate antigen 125
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
C_{max}	Peak concentration
CPK	Creatine phosphokinase
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
e-CRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
FDA	Food and Drug Administration
GMR	Geometric mean ratio
HFrEF	Heart failure with reduced ejection fraction
hs-cTnT	High-sensitivity cardiac troponin-T
ICF	Informed consent form
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
KIM-1	Kidney injury molecule-1

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LDH	Lactate dehydrogenase
LLOQ	Limit of quantification
mAb	Monoclonal antibody
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed-effect model for repeated measures
NGAL	Neutrophil gelatinase-associated lipocalin
NPR1	Natriuretic peptide receptor 1
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
PDAS	Pharmacodynamic analysis set
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PRO	Patient-reported outcomes
PT	Preferred term
QTcB	QT corrected for heart using Bazett's formula
QTcF	QT corrected for heart using Fridericia's formula
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RR	Respiratory rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell

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WHO-DD	World health organization drug dictionary

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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-22118, Amendment 4 dated 27Jun2025.

1.1. Study Description and Objectives

This Phase 2, randomized, double-blind, single-dose, placebo-controlled study is designed to evaluate the safety and tolerability of a single dose of the natriuretic peptide receptor 1 (NPR1) monoclonal antibody (mAb) agonist REGN5381 in participants with heart failure with reduced ejection fraction (HFrEF), and to evaluate the early and durable pharmacodynamic (PD) effects in this participant population.

1.1.1. Primary Objective

The primary objective of the study is to evaluate the ability of REGN5381 to improve cardiopulmonary congestion.

1.1.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of REGN5381
- Evaluate the durability of effects of REGN5381 on cardiopulmonary congestion
- Evaluate the effects of REGN5381 on hemodynamics
- Characterize the drug concentration-time profile of single doses of REGN5381
- Assess the immunogenicity of REGN5381

1.1.3. Exploratory Objectives

The exploratory objectives of the study are to:

- Explore the effects of REGN5381 on heart failure clinical outcomes
- Explore the effects of REGN5381 on worsening cardiopulmonary congestion
- Explore the effects of REGN5381 on renal function
- Evaluate the effects of REGN5381 on myocardial injury
- Explore the effects of REGN5381 on biologically active ligands of the REGN5381 target (NPR1)
- Explore the effects of REGN5381 on a downstream biomarker of NPR1 activation
- Explore the effects of REGN5381 on other biomarkers of cardiopulmonary congestion
- Explore the effects of REGN5381 on patient-reported outcomes (feel and function)
- Explore health utilities and health-related quality of life outcomes

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- Explore the effects of REGN5381 on renal tubular injury
- Identify novel biomarkers that may be associated with established markers of heart failure severity
- Develop a molecular understanding of heart failure with reduced ejection fraction

1.2. Statistical Hypothesis

No formal statistical hypothesis testing will be performed.

1.3. Interim Analysis

Interim analyses may be performed for future study planning. This study will not be stopped early for success.

1.4. Modifications from the Statistical Section in the Final Protocol

This SAP is based on Protocol Amendment 4.

1.5. Revision History for SAP Amendments

This is the first amendment of SAP (Version 2.0). The major updates are listed below:

Description of Change	Brief Rationale	Section # and Name
Added cyclic GMP (change from baseline) to exploratory biomarker objectives and endpoints. Updated the study design and number of participants in Part A2 and Part B.	To align with the updates in protocol amendment 4.	Section 1.1.3 Exploratory Objectives Section 2.1 Study Design Section 2.2 Sample Size Section 15.4 Schedule of Time and Events
Added text to allow interim review safety and efficacy data.	For practical considerations of potential early review of the data.	Section 1.3 Interim Analysis
Clarified that mITT population should include participants from all three parts. Summaries will be pooled for the common dose levels.	Under the previous protocols, participants in Part A1/B and Part B were expected to be summarized separately. Protocol Amendment 4 has updated this approach to allow pooled summaries across all three parts.	Section 3.1 Efficacy Analysis Set Section 4 General Statistical Analysis Considerations Section 7.1 Description of Efficacy/Pharmacodynamic Data

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Description of Change	Brief Rationale	Section # and Name
Added descriptive summaries with geometric mean and coefficient of variation for log-normal distributed variables.	For log-normal distributed variables, the standard descriptive summaries with arithmetic mean and standard deviation can't provide the best descriptions of the data.	Section 4 General Statistical Analysis Considerations
The model of primary efficacy endpoints has been changed from ANCOVA to MMRM, with new covariate of background sacubitril-valsartan therapy, eGFR level included, and the baseline-by-treatment interaction.	Given the primary and secondary efficacy endpoints summarize the same parameter (change from baseline in NT-proBNP) across different visits, it is reasonable to apply the same model. By applying the MMRM model to both primary efficacy endpoint (change from baseline in NT-proBNP at day 8) and secondary efficacy endpoints (change from baseline in circulating NT-proBNP at weeks 2, 3, 4 and up to week 16), a more consistent and simplified analysis of this longitudinal data can be achieved.	Section 7.2 Analysis of Efficacy/Pharmacodynamic Data Section 15.1 Summary of Statistical Analyses Section 15.2 SAS Procedures
Removed details about immunogenicity analysis.	The immunogenicity analysis will be described in the clinical pharmacology report.	Section 10.6 Immunogenicity Data
Updated the Sections for Pharmacokinetic Data, and Pharmacodynamic and Other Biomarker Data	To align with the updates in protocol amendment 4.	Section 10.7. Analysis of Pharmacokinetic Data Section 10.8 Pharmacodynamic and Other Biomarker Data
Added detailed explanations for programmatically PCSV selection.	To clarify how to identify and summarize the PCSV events under different scenarios.	Section 11.3 Data for Non-Efficacy Endpoints Section 15.5 Criteria for Potentially Clinically Significant Values (PCSV)
Updated the preferred terms listing.	To align with the latest MedDRA version,	Section 15.3 Selection for AESIs

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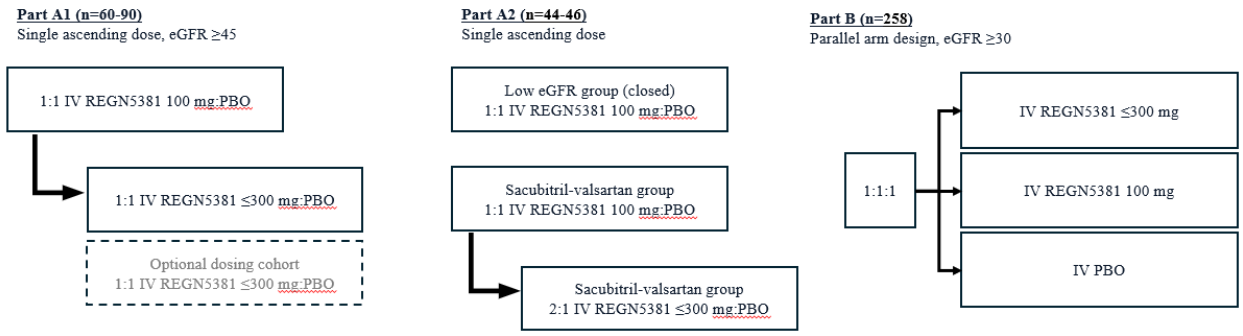
2. INVESTIGATION PLAN

2.1. Study Design

The study will be conducted in 3 parts as follows (see Figure 1):

- Part A1: a design with single ascending dose cohorts to evaluate the PD effects and safety of REGN5381 compared to placebo with a 4-day post-randomization inpatient monitoring period.
- Part A2: a design with single ascending dose cohorts to evaluate the PD effects and safety of REGN5381 compared to placebo with a 4-day post-randomization inpatient monitoring period in participants on background sacubitril-valsartan therapy, and participants with low estimated glomerular filtration rate (eGFR) (30 to 45 mL/min/1.73m^2). The low eGFR group has been closed as of Protocol Amendment 4. Participants already enrolled in this group will complete the protocol as scheduled (See Section 5.1.1.1.2 of protocol for additional details).
- Part B: a parallel arm design to evaluate PD effects and safety of REGN5381 compared to placebo in the outpatient setting.

Figure 1: Study Overview Diagram for Parts A1, A2 and B



2.1.1. Study Design: Part A1 and Part A2

In Part A1, up to 90 participants will be randomized 1:1 to receive a single intravenous (IV) dose of REGN5381 or placebo in sequential ascending dose cohorts as follows:

- 30 participants (15/arm) will receive REGN5381 100 mg IV or placebo IV
- 30 participants (15/arm) will receive REGN5381 ≤300 mg IV or placebo IV

An optional dose cohort may be enrolled as follows:

- 30 participants (15/arm) will receive REGN5381 ≤300 mg IV or placebo IV

The optional Part A1 dose cohort may evaluate a dose equal to 300 mg (eg, to obtain additional data at the 300 mg dose prior to Part B) or less than 300 mg if, for example, the 300 mg dose is not tolerated.

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In Part A2, approximately 44 to 46 participants will be randomized to receive a single IV dose of REGN5381 or placebo in sequential ascending dose cohorts with approximate numbers of participants:

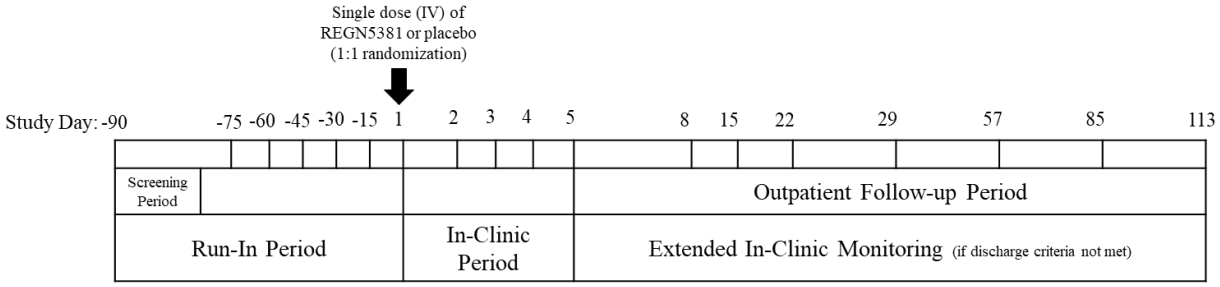
- Sacubitril-valsartan cohort: (n=42)
  - 24 participants (12/arm) will receive REGN5381 100 mg or placebo*,
  - 18 participants (12 active; 6 placebo) will receive REGN5381 ≤300 mg or placebo*.
- Low eGFR (30 to 45 mL/min/1.73 m^2) cohort (n=2-4, randomized 1:1) will receive 100 mg REGN5381 or placebo*.

*Cohorts reduced in size with Protocol Amendment 4 may have recruited more than the new target enrollment before the amendment is in effect. Additional details about the changes of Part A2 could be found in Section 5.1.1.1.1.

Screening, Run-in, Inpatient, and Outpatient Periods

Part A1 and Part A2 will include a Screening Period (day -90), a Run-in Period of 90 days (starting from initial screening visit), an Inpatient Period at least to day 5 for safety monitoring, and an Outpatient Period to study week 16 to further evaluate safety, pharmacokinetic (PK), and PD (see Figure 2).

Figure 2: Study Flow Diagram for Part A1 and Part A2



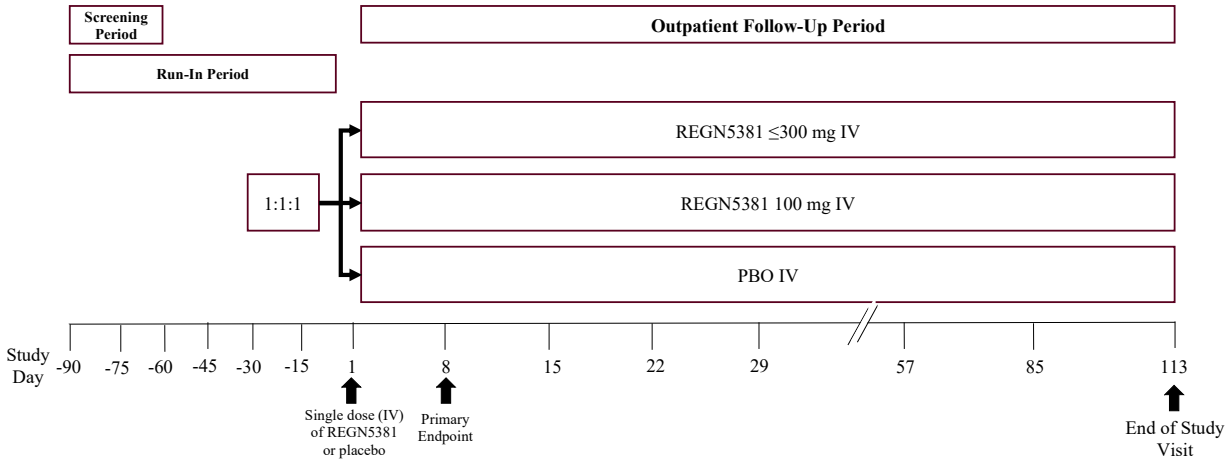
Dose escalation will occur in Part A1 and Part A2. The decision to escalate dose and the decision to initiate the sacubitril-valsartan and low eGFR cohorts in Part A2 will be made by the sponsor following review of all Part A1 vital signs, adverse events (AEs), and laboratory data after the last participant in the Part A1 100 mg cohort completes day 8 safety assessments. Additionally, data from other ongoing or completed studies of REGN5381 may inform dose escalation decisions. In lieu of dose escalation, the study may advance to Part B or be ended.

2.1.2. Study Design: Part B

Part B will be initiated following the review of safety data from each cohort in Part A1. Part B has a randomized, double-blind, placebo-controlled, parallel arm design and will evaluate the safety, PK and PD of single doses of IV REGN5381 100 mg and REGN5381 ≤300 mg in the outpatient setting (Figure 3).

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Figure 3: Study Flow Diagram for Part B



Up to approximately 258 participants will be randomized 1:1:1 to receive a single dose as follows:

- 86 participants will receive REGN5381 100 mg IV,
- 86 participants will receive REGN5381 ≤300 mg IV,
- 86 participants will receive matching placebo IV.

The maximum dose in Part B will not exceed the maximum tolerated dose from Part A1. The 300 mg dose arm may be omitted from Part B by the sponsor, or a dose level between 100 mg and 300 mg may be selected for this arm.

The duration of the screening period, run-in period, outpatient period, and assessment requirements are the same in Part B as in Part A1 and Part A2, except Part A1 and Part A2 will have an inpatient observation period to at least day 5.

2.2. Sample Size

Up to 394 participants will be randomized. The sample sizes for Part A1, Part A2 and Part B for common dose levels will be pooled and were determined using the following assumptions:

- Sample sizes in Part A1, Part A2 were based on practical considerations of safety comparisons before progressing to Part B.
- The N-terminal pro-brain natriuretic peptide (NT-proBNP) when log-transformed follows a normal distribution.
- The percent change from baseline in NT-proBNP at day 8 for placebo is assumed to be -10.0%.
- The treatment difference in terms of percent change from baseline in NT-proBNP is assumed to be -25% between the two arms (eg, REGN5381 assumed as -35.0% and placebo as -10.0%).
- The standard deviation (SD) for change from baseline in log-transformed NT-proBNP in any treatment group is assumed to be 0.7 as a conservative estimate for day 8.

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- A 10% drop out rate is expected at day 8 in both arms.

By pooling Part A1 (15 participants per active arm), Part A2 (approximately 12 participants per active arm) and Part B (86 participants per arm) for common dose levels of REGN5381, a sample size of at least 113 participants per active arm (and 133 on placebo), will allow estimation of the treatment difference in log-transformed NT-proBNP levels with a precision of ±0.1825 using 95% confidence interval. This precision corresponds to a minimum observed treatment difference of -16% reduction in the percent change from baseline in NT-proBNP levels at day 8, required to achieve statistical significance at 2-sided alpha level of 0.05.

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3. ANALYSIS SETS

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

3.1. Efficacy Analysis Set

The modified intent-to-treat (mITT) population includes all randomized participants who received study drug, from Part A1, Part A2, and Part B.

The primary analysis population for efficacy will be the mITT population. Participant data will be analyzed according to the group to which they were randomized.

3.2. Pharmacodynamic Analysis

The pharmacodynamic analysis set (PDAS) includes all randomized participants who received any study drug (active or placebo) and who had at least 1 non-missing PD measurement following study drug administration. It is based on the treatment received (as treated).

3.3. Safety Analysis Set

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. Participant data will be analyzed according to the treatment received.

3.4. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) includes all participants who received any study drug (active or placebo) and who had at least 1 non-missing result following the first dose of any study drug. The PK analysis set is based on the actual treatment received (as treated) rather than as randomized.

3.5. Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all participants who received any amount of study drug (active or placebo) and had at least 1 non-missing ADA result following the first dose of the respective study drug or placebo. The ADA analysis is based on the actual treatment received (as treated).

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4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

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

For Part A1, Part A2 and Part B, the summaries will be pooled for the common dose levels. Additional analysis may be conducted separately for participants on background sacubitril-valsartan therapy, and participants with low eGFR from Part A2 and Part B.

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. Geometric mean and coefficient of variation (CV) will be reported instead of the mean and SD for variables that are lognormally distributed.

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 arm.

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5. PARTICIPANT DISPOSITION

5.1. Screening Disposition

The number of enrolled participants (i.e. participants who signed the informed consent form) who are randomized (i.e. assigned a randomization number in the interactive voice response system [IVRS]/interactive web response system [IWRS]) will be presented. The number of participants who failed the initial screening and subsequently rescreened will be presented, categorized by the reasons for their screening failures. If applicable, the number of participants who are improperly randomized (i.e. screen-failed yet were assigned a randomization number in the IVRS/IWRS) will also be displayed. The corresponding percentages with respect to the total number of enrolled participants will also be presented.

5.2. Run-in Period Disposition

The disposition of all randomized participants during Run-in Period will be displayed by treatment group using the Randomized Set. The number of participants who complete Run-in Period will be presented. A participant is considered to have completed Run-in Period if they completed Visit 6 (day -15).

Participants who complete Run-in Period are eligible for randomization. The number of Run-in Period completers who are randomized will be reported.

Lastly, the number of participants who withdraw from the study during Run-in Period will be presented. This number will be further broken out by reason for early withdrawal from Run-in Period.

5.3. Post-Randomization Disposition

For participants who complete the Run-in Period and are randomized, the number of participants who complete Visit 8 (day 8), those who complete the study and those who withdraw after randomization will be reported. A participant is considered to have completed the study if they make it to the End-of-study (EOS) visit. The participants who withdraw from the study early will be further summarized by reason for early withdrawal from the study.

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6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized by treatment group and overall:

- Age at screening (year)
- Age categories (≥18 to <25, ≥25 to <35, ≥35 to <45, ≥45 to <55, ≥55 to <65, ≥65 years)
- Sex (Male, Female)
- Race (American Indian or Alaskan Native, Asian, Black/African American, Native Hawaiian or Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

6.2. Baseline Disease Characteristics

The following disease characteristics will be summarized by treatment group and overall:

- Time since heart failure diagnosis
- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Mean arterial pressure (MAP = 1/3×SBP + 2/3×DBP)
- Pulse rate (PR)
- Respiratory rate (RR)
- Temperature
- Renal function at baseline (eGFR) ($mL/min/1.73m^2$)

6.3. Medical History

Participant medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment arm, and overall using the mITT population.

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7. EFFICACY/PHARMACODYNAMIC DATA

7.1. Description of Efficacy/Pharmacodynamic Data

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is change from baseline in circulating NT-proBNP at day 8 for participants in Parts A1, Part A2 and B for common dose levels pooled.

7.1.2. Secondary Efficacy Endpoint

The secondary efficacy endpoints of the study are change from baseline in circulating NT-proBNP at weeks 2, 3, 4, and up to week 16 for participants in Parts A1, Part A2 and B for common dose levels pooled.

7.2. Analysis of Efficacy/Pharmacodynamic Data

NT-proBNP has been shown to be highly skewed, a natural log transformation ($\log_e$) will be applied to normalize the distribution. The treatment effect will be estimated by modeling the difference of change from baseline (ΔCFB)in log-transformed NT-proBNP at day 8 between treatment groups as:

$$\Delta CFB = CFB_{treatment} - CFB_{placebo},$$

where change from baseline = $\log_e$(post-baseline) - $\log_e$(baseline) in each treatment group.

For the analyses of the primary and secondary efficacy variables, a mixed-effect model with repeated measures (MMRM) will be used to analyze the mean change from baseline of log-scaled NT-proBNP at day 8, weeks 2, 3, 4 and up to week 16.

The MMRM model will include the following covariates as fixed effects: treatment arm (REGN5381 100 mg vs. REGN5381 ≤300 mg vs. placebo), baseline log-transformed NT-proBNP results (continuous), eGFR level (continuous), background sacubitril-valsartan therapy (Yes vs. No), visit (day 8, weeks 2, weeks 3, weeks 4, weeks 8, weeks 12 and weeks 16), treatment-by-visit interaction, baseline-by-treatment interaction and baseline-by-visit interaction.

A Kenward-Roger approximation will be used for the denominator degrees of freedom. Missing data will be implicitly handled by the model assuming a Missing At Random (MAR) mechanism. An unstructured covariance structure will be used. If the model does not converge, then the following covariance structure may be fitted, in the following order:

- compound symmetry
- autoregressive order one - AR(1)

Summary statistics including the within-treatment-group least squares (LS) mean and 95% confidence intervals (CIs) for each treatment group will be presented over time. Differences between treatment arms (REGN5381 100 mg vs. placebo and REGN5381 ≤300 mg vs. placebo) in LS means and geometric mean ratios (GMRs) at day 8, week 2, 3, 4, and up to week 16 will be calculated. Two-sided p-values (for descriptive purpose) and 95% CIs for treatment differences will be presented.

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The two-sided 95% CIs will be back-transformed into the original scale for reporting purposes. Adjusted geometric mean changes from baseline with 95% CIs will be constructed by exponentially back-transforming the LS means, and the limits of corresponding 95% CIs to percent ΔCFB (clinically relevant summary measure) as:

$$\left([e^{Lower\ Limit} - 1] \times 100\%, [e^{Upper\ Limit} - 1] \times 100\%\right)$$

An example of Statistical Analysis System (SAS) code for MMRM is presented in Section 15.2. An example of SAS code for transforming the CIs into linear scale is also presented in the same section.

7.2.1. Supplemental Analyses

NT-proBNP measurements after initiation of rescue therapy or prohibited medications will not be used for the primary efficacy analysis. A supplemental analysis with all the collected NT-proBNP measurements included may be performed to assess the robustness of the primary and secondary endpoints using same method.

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8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

No formal statistical hypothesis testing will be performed. No adjustment for multiplicity is made in this Phase 2 study.

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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).

Treatment compliance is not applicable.

9.2. Duration of Study Periods

The duration of run-in period is calculated as:

(Date of the randomization – date of the initial screening visit) +1.

For participants who are rescreened, the 'initial screening visit' refers to the visit during which they successfully pass the screening process.

The duration of observation period during the study is calculated as:

(Date of the last study visit – date of the investigational product administration) +1.

The number (%) of participants with observation periods will be presented by specific time periods. The time periods of interest are specified as: ≥75 days, ≥90 days, ≥98 days and ≥203 days.

9.3. Prior and Concomitant Medications/Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded to the Anatomical therapeutic chemical classification system (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of World Health Organization Drug Dictionary (WHO-DD). Participants will be counted once in all ATC categories linked to the medication.

The COVID-19 vaccinations are considered as concomitant medication.

Prohibited Medications

The definition of prohibited medications and procedures is described in the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

Rescue Medications

Number of participants receiving rescue therapy will be summarized by treatment group and overall.

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10. ANALYSIS OF SAFETY DATA

10.1. Adverse Events

All new or worsening AEs occurring between signing of the informed consent form (ICF) and the end of the study will be recorded and coded using the 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 arm, sorted by decreasing frequency of SOC and PT in the REGN5381 ≤300 mg IV treatment arm. 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.

Treatment-emergent AEs (TEAEs) are defined as those AEs with either initial onset after the first dose of study treatment or that worsen after the first dose of study treatment. The following summaries for TEAEs will be presented:

- TEAEs by primary SOC and PT
- TEAEs by primary SOC, PT, and maximum severity
- Treatment-related TEAEs by primary SOC and PT
- TEAEs leading to death by primary SOC and PT
- TE-Serious adverse events (SAEs) by primary SOC and PT
- Treatment-related TE-SAEs by primary SOC and PT

10.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include the following:

- Moderate to severe infusion reactions
- Moderate or severe hypersensitivity reactions
- Severe hypotension (SBP <90 mm Hg)
- Elevated liver enzymes (≥ 3× upper limit of normal [ULN] AST/ALT and <3 x upper limit of normal [ULN] AST/ALT at baseline)

Treatment-emergent AESIs will be selected for the analysis as indicated in Appendix 15.3. The following summaries for AESIs will be presented:

- TE-AESI by primary SOC and PT
- Treatment-related TE-AESIs by primary SOC and PT

10.2. Laboratory Parameters

The laboratory tests data collected in central laboratories will be summarized. If central laboratory testing is not feasible, it may be performed by a local laboratory with prior approval from the Sponsor. In such cases, the data from local laboratory tests will also be summarized. The following

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laboratory tests will be collected and summarized according to the Schedule Events in Section 15.4:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen (BUN)	Creatine kinase (CK)
Carbon dioxide/bicarbonate	Aspartate aminotransferase (AST)	eGFR
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Blood chemistry should be performed after the participants have fasted for at least approximately 8 hours at the following visits defined in the schedule of events.

Hematology

Hemoglobin	Differential:
Free Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Red blood cells (RBCs)	Monocytes
White blood cells (WBCs)	Basophils
Red cell indices	Eosinophils
Platelet count	Reticulocytes

Urinalysis

pH	Glucose	Note: If macroscopy is abnormal then reflex to microscopy.
Specific gravity	Bilirubin	
Ketones	Leukocytes	
Protein	Nitrite	

Other Laboratory Tests

Other laboratory tests include:

- C-Reactive protein
- Direct Antiglobulin Test (DAT or Coombs)

Clinical laboratory analytes will be converted to standard international (SI) units and grouped by function in summary tables. Clinical laboratory values and change from baseline in clinical laboratory values to all scheduled assessment times in will be summarized with descriptive statistics by treatment group.

Participant laboratory parameter measurements will be evaluated by potentially clinically significant value (PCSV) criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Section 15.5). Participants meeting the PCSV criteria will be summarized by participant count (and percent) for a post-baseline PCSV measurement by treatment group, regardless of baseline PCSV status. When the PCSV definition involves a change from baseline value, participants must have a baseline value to be included in

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

Shift tables will be constructed showing participants' transition in lab values from baseline to specified timepoints by treatment group. Lab values will be categorized as: Low, Normal, High or Missing.

10.3. Vital Signs

The following vital signs parameters will be recorded and summarized according to the Schedule Events in Section 15.4:

- Body temperature (ºC)
- Blood pressure (mmHg) (systolic and diastolic)
- Pulse rate (bpm)
- Respiration rate (bpm)
- Weight (kg)

Vital sign values and change from baseline in vital signs values to all scheduled assessment times will be summarized with descriptive statistics by treatment group.

Vital sign measurements will be evaluated by PCSV criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Section 15.5). Participants meeting the PCSV criteria will be summarized by participant count (and percent) for a post-baseline PCSV measurement by treatment group, regardless of baseline PCSV status.

10.4. Electrocardiography (ECG)

The following standard 12-lead ECG parameters will be recorded and analyzed summarized according to the Schedule Events in Section 15.4:

- Ventricular rate
- PR interval
- QRS interval
- RR interval
- QT corrected for heart using Fridericia's formula (QTcF) defined as:

$$QTcF(ms) = \frac{QT}{\sqrt[3]{RR}}$$

  where QT is the uncorrected QT interval measured in ms, and RR is 60/HR with HR being the heart rate in beats per minutes.

- QT corrected for heart using Bazett's formula (QTcB) defined as:

$$QTcB(ms) = \frac{QT}{\sqrt[2]{RR}}$$

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

ECG parameters will be evaluated by PCSV criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Section 8.1). Participants meeting the PCSV criteria will be summarized by participant count (and percent) for a post-baseline PCSV measurement by treatment group, regardless of baseline PCSV status.

Shift tables will be constructed showing participants' transition in ECG status from baseline to specified timepoints by treatment group. ECG status will be categorized as: Normal, Abnormal or Missing.

10.5. Clinical Outcome Data

The following clinical outcome assessments will be descriptively summarized by treatment group:

- Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score, overall summary score and clinical summary score
- EQ-5D-5L visual analog score and utility index score

10.6. Immunogenicity Data

The immunogenicity data analysis will be described in the clinical pharmacology report.

10.7. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

- Concentrations of total REGN5381 over time will be measured. The PK parameters may include, but are not limited to the following (and their-dose-normalized versions, if applicable):
  - C_{max} - peak concentration
  - T_{max} - time of peak concentration
  - T_{last} - time of the last positive (quantifiable) concentration
  - AUC_{last} - area under curve (AUC) computed from time zero to the time of the last positive concentration
- 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.
- Descriptive statistics of REGN5381 concentrations in serum at each sampling time by dose.
- Graphical presentations of median and mean (+/- SD) REGN5381 concentration in serum vs nominal time profiles. Plots of concentration vs time will be provided as both non-log and semi-log. When plotted as non-log, concentrations less than lower

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limit of quantification (LLOQ) will be set to zero (0). When plotted as semi-log, for concentrations less than LLOQ, LLOQ/2 will be imputed.

- Graphical presentations of individual REGN5381 concentration in serum vs actual sampling time profiles. When plotted as non-log, concentrations less than LLOQ will be set to zero (0). When plotted as semi-log, for concentrations less than LLOQ, LLOQ/2 will be imputed.

No formal statistical analysis will be performed.

10.8. Pharmacodynamic and Other Biomarker Data

Pharmacodynamic and biomarker variables include 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) MS, BNP ELISA, catecholamines (dopamine, epinephrine, and norepinephrine), Carbohydrate antigen 125 (CA-125), High-sensitivity cardiac troponin-T (hs-cTnT), kidney injury molecule-1 (KIM-1), KIM-1 to creatinine ratio, urine albumin creatinine ratio, and urine neutrophil gelatinase-associated lipocalin (NGAL).

The pharmacodynamic parameters will be summarized with observed value, change from baseline, and percent change from baseline at each post-baseline visit by treatment group. Change from baseline and percent change from baseline by treatment group in biomarker parameters will be plotted. For biomarkers that are log-normally distributed, geometric means will be reported as part of the summary statistics instead of arithmetic means.

The Olink proteomics data will be separately documented in a separate report.

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11. DATA CONVENTIONS

11.1. Definition of Baseline for Efficacy/Safety Variables

Definition of Baseline for Variables

Variables	Baseline Definition
Weight Height BMI	Screening visit
SBP, DBP, MAP, PR and RR ECG Temperature Blood chemistry Hematology Urinalysis Drug concentration Biomarkers	Day 1 (Visit 7) Pre-dose

For the triplicated ECG, baseline is calculated as the median of the last three ECG measurements collected prior to dose administration on day 1. In case less than three measurements are available, the median will be calculated and the latest timepoint will be selected for the analysis.

Unless otherwise specified, the baseline assessment for all measurements will be the last available measurement 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

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to randomization date, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed.

Adverse event

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If the intensity 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.

Date and Time of Study Treatment Infusion

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

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.

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 (the worst PCSV is displayed).

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables 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) may be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries.

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12. TECHCHNICAL DETAILS PERTAININING TO INTERIM ANALYSIS

No formal interim analysis is planned.

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13. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher, and R version 4.3.0 or higher.

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14. REFERENCES

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15. APPENDIX

15.1. Summary of Statistical Analyses

Efficacy/PD Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supplemental Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Change from baseline in circulating NT-proBNP at day 8	*mITT*	*Change from baseline in log-transformed NT-proBNP at day 8. NT-proBNP measurements after initiation of rescue therapy or prohibited medications will not be used.*	*MMRM: treatment, baseline log-transformed NT-proBNP results, eGFR level, background sacubitril-valsartan therapy, visit, treatment-by-visit interaction, baseline-by-treatment interaction and baseline-by-visit interaction*	*All the collected NT-proBNP measurements included, using the same MMRM model as primary analysis.*	*No*	*No*
Secondary Endpoints						
Change from baseline in circulating NT-proBNP at weeks 2, 3, 4 and up to week 16	*mITT*	*Change from baseline in log-transformed NT-proBNP at Week 2, 3, 4, 8, 12 and 16*	*MMRM: treatment, baseline log-transformed NT-proBNP results, eGFR level, background sacubitril-valsartan therapy, visit, treatment-by-visit interaction, baseline-by-treatment interaction and baseline-by-visit interaction*	*All the collected NT-proBNP measurements included, using the same MMRM model as secondary efficacy analysis.*	*No*	*No*

15.2. SAS Procedures

Below is the sample SAS code for MMRM model:

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```
PROC MIXED DATA = <data until Week 16>;
      CLASS trtpn (ref="Placebo") subjid avisitn;
      MODEL logchg = logbase trtpn sacubitril_valsartan eGFR avisitn logbase*avisitn trtpn*avisitn
logbase*trtpn;
      REPEATED avisitn / TYPE=un SUBJECT=subjid;
      LSMEANS trtpn*avisitn / pdiff cl alpha=0.05;
      ODS OUTPUT lsmeans=lsm diffs=dif;

RUN;


PROC SORT DATA = lsm;
      by avisitn trtpn;
RUN;

PROC SORT DATA = dif OUT = dif0;
      by avisitn;
      where avisitn=_avisitn;
RUN;

DATA lsm1 (keep=avisitn trtpn mean_ci gici);
      length mean_ci $40.;
      set lsm;
      by avisitn trtpn;
      mean_ci=compress(put(estimate,6.2))||' ('||compress(put(lower,6.2))||',
'||compress(put(upper,6.2))||')';
      ici='('||compress(put(lower,6.2))||', '||compress(put(upper,6.2))||')';
      gmr=put(exp(estimate)-1, 6.2);
      gml=exp(lower)-1; gmu=exp(upper)-1;
      gici= put(gmr, 6.2)||' ('||compress(put(gml,6.2))||', '||compress(put(gmu,6.2))||')';

RUN;


DATA dif1(keep=avisitn trtpn diff_ci probpair gci);
      length diff_ci $40.;
      set dif0;
      by avisitn;
      diff_ci=compress(put(estimate,6.2))||' ('||compress(put(lower,6.2))||',
'||compress(put(upper,6.2))||')';
      ci='('||compress(put(lower,6.2))||', '||compress(put(upper,6.2))||')';
      probpair=put(probt,6.4);
```


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```
      gmr=put(exp(estimate)-1, 6.2);
      gml=exp(lower)-1;
      gmu=exp(upper)-1;
      gci=put(gmr, 6.2)||' ('||compress(put(gml,6.2))||', '||compress(put(gmu,6.2))||')';

RUN;
```


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15.3. Selection for AESIs

Prior to database lock these preferred terms will be updated as necessary based on the current MedDRA version.

AESI	Selection
Moderate to severe injection site reactions	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 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

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	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 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

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	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 hypersensitivity reactions considered related to study treatment	Adverse Event is moderate to severe, treatment related 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 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

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	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 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 Blepharitis allergic Blood immunoglobulin E abnormal Blood immunoglobulin E increased Bone cement allergy Bromoderma Bronchospasm

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	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 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

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	Drug provocation test Drug reaction with eosinophilia and systemic symptoms Eczema Eczema infantile Eczema nummular Eczema vaccinatum Eczema vesicular Eczema weeping Eczematous cheilitis 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 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

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	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 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

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	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 Oropharyngeal spasm Oropharyngeal swelling Palatal oedema Palatal swelling Palisaded neutrophilic granulomatous dermatitis Palpable purpura Pathergy reaction Penile dermatitis Perioral dermatitis Periorbital dermatitis Periorbital eczema Periorbital oedema Periorbital swelling Pharyngeal oedema Pharyngeal swelling Polymers allergy Procedural shock

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	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 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

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	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 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

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	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 laboratory values
Elevated liver enzymes (≥ 3× ULN AST/ALT)	Check based on laboratory values

15.4. Schedule of Time and Events

Table 1: Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods

Study Period	**Run-In**						**Inpatient**						**Ext. Inpatient**[1]
Timing relative to study drug administration	**Screening**						**Dose Administration**		**Post-dose timepoint**				
							Pre-Dose	**Post-Dose**	**24 hours**	**48 hours**	**72 hours**	**96 hours**	
Study Day (window)	**-90 (±14 days)**	**-75 (±7 days)**	**-60 (±7 days)**	**-45 (±7 days)**	**-30 (±7 days)**	**-15 (±7 days)**	**1**	**1**	**2**	**3**	**4**	**5**	**X**
Visit Numbers	**V1**	**V2**[2]	**V3**	**V4**[2]	**V5**[3]	**V6**[2]	**V7**	**V7**	**V7**	**V7**	**V7**	**V7**	**VX**
Screening/Baseline													
Informed Consent	X												
Informed Consent (optional substudy)	X												
Inclusion/Exclusion	X		X		X		X						
Medical History	X												
Demographics	X												
Height	X												
Weight	X						X						
Echocardiogram[4]	X												
Electrocardiogram[5]	X				X		X	X[6]	X				
Hepatitis screen	X												
FSH (for post-menopausal women only)	X												
Serum pregnancy test (for WOCBP)	X												

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Study Period	**Run-In**						**Inpatient**						**Ext. Inpatient**[1]
Timing relative to study drug administration	**Screening**						**Dose Administration**		**Post-dose timepoint**				
							Pre-Dose	**Post-Dose**	**24 hours**	**48 hours**	**72 hours**	**96 hours**	
Study Day (window)	**-90 (±14 days)**	**-75 (±7 days)**	**-60 (±7 days)**	**-45 (±7 days)**	**-30 (±7 days)**	**-15 (±7 days)**	**1**	**1**	**2**	**3**	**4**	**5**	**X**
Visit Numbers	**V1**	**V2**[2]	**V3**	**V4**[2]	**V5**[3]	**V6**[2]	**V7**	**V7**	**V7**	**V7**	**V7**	**V7**	**VX**
Urine pregnancy test (for WOCBP)							X						
Inpatient Period													
Discharge												X	X
Treatment													
Randomization							X						
Administer study drug/placebo							X						
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics													
Blood sample for NT-proBNP (central)	X				X		X		X	X	X	X	
Clinical Outcome Assessments[7]													
KCCQ-23							X						
EQ-5D-5L							X						
Safety													
Temperature	X						X		X	X	X	X	
Respiratory rate	X						X	X	X	X	X	X	
Blood pressure and heart rate	X		X		X		X[8]	X[9]	X[9]	X[9]	X[9]	X[9]	X
Physical Examination	X				X								
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Review safety card												X	
Laboratory Testing													
Hematology (local)							X		X	X	X	X	X
Hematology (central)	X				X		X						
Blood Chemistry (local)							X		X	X	X	X	X
Blood Chemistry (central)	X				X		X						
Urinalysis	X												
Urine albumin: creatinine ratio	X						X						

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Study Period	Run-In						Inpatient						Ext. Inpatient[1]
Timing relative to study drug administration	Screening						Dose Administration		Post-dose timepoint				
							Pre-Dose	Post-Dose	24 hours	48 hours	72 hours	96 hours	
Study Day (window)	-90 (±14 days)	-75 (±7 days)	-60 (±7 days)	-45 (±7 days)	-30 (±7 days)	-15 (±7 days)	1	1	2	3	4	5	X
Visit Numbers	V1	V2[2]	V3	V4[2]	V5[3]	V6[2]	V7	V7	V7	V7	V7	V7	VX
Pharmacokinetics and Immunogenicity[10]													
Drug conc. sample							X	X[11]	X	X	X	X	
ADA sample							X						
Biomarkers													
Blood sample for Olink proteomics							X						
Blood sample for high sensitivity troponin T							X			X			
Blood sample for ANP/BNP MS							X			X			
Blood sample for BNP ELISA							X		X	X			
Blood sample for NT-proANP							X		X	X			
Blood sample for CA-125							X						
Urine sample for KIM-1/creatinine ratio							X						
Urine NGAL							X						
Urine sample for exploratory research							X						
Blood sample for exploratory research (plasma and serum)							X						
Blood sample for future research (serum and plasma) optional							X						
Blood sample for DNA isolation (optional)							X						

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15.4.1. Footnotes for Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods

1. Extended inpatient visit(s) will occur every day from day 6 onwards for participants that do not meet the discharge criteria. Assessments at planned visits in Table 1 will be done instead of assessments at extended inpatient visits if they occur on the same day.
2. The visit will be conducted by telephone.
3. Participants may repeat visit 5 once if background medications for heart failure are adjusted within 30 days prior to randomization or if randomization is delayed for non-safety reasons.
4. No echocardiogram required if report is available from an echocardiogram performed within 3 months prior to screening. Echocardiogram may be performed during initial screening period or run-in period, prior to visit 5.
5. ECG can be performed on any visit based on clinical need and judgement of the investigator. Scheduled ECGs in Part A1 and A2 should be performed in triplicate from Visit 7 Pre-Dose through Visit 11. Triplicates are not required at Visit 1 or Visit 5.
6. ECG should be completed in triplicate within approximately 30 minutes after the end of infusion.
7. All patient-reported outcomes (PRO) assessments must be completed prior to any clinical assessments, where possible.
8. Pre-dose blood pressure and heart rate should be checked as close as possible to time of dose administration.
9. Blood pressure and heart rate will be checked approximately 1, 2, 4 and 8 hours after the end of study drug infusion then approximately every 8 hours.
10. 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.
11. Drug concentration sample should be collected within approximately 30 minutes after end of infusion.

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Table 2: Part B Screening, Run-in, and Day 1 Administration Schedule of Events

Study Period	Run-In						Dosing	Dosing
	Screening							
Timing relative to study drug administration							Pre-Dose	Post-Dose
Study Day (window)	-90 (±14 days)	-75 (±7 days)	-60 (±7 days)	-45 (±7 days)	-30 (±14 days)	-15 (±7 days)	Study Day 1	Study Day 1
Visit Numbers	V1	V2[1]	V3	V4[1]	V5[2]	V6[1]	V7	V7
Screening/Baseline								
Informed Consent	X							
Informed Consent (optional substudy)	X							
Inclusion/Exclusion	X		X		X		X	
Medical History	X							
Demographics	X							
Height	X							
Weight	X						X	
Echocardiogram[3]	X							
Electrocardiogram[4]	X						X	X[5]
Hepatitis screen	X							
FSH (for post-menopausal women only)	X							
Serum pregnancy test (for WOCBP)	X							
Urine pregnancy test (for WOCBP)							X	
Treatment								
Randomization							X	
Administer study drug/placebo							X	
Concomitant medications and procedures	X	X	X	X	X	X	X	X
Pharmacodynamics								
Blood sample for NT-proBNP (central)	X				X		X	
Clinical Outcome Assessments[6]								
KCCQ-23							X	
EQ-5D-5L							X	
Safety								
Temperature	X						X	
Respiratory rate	X						X	X
Blood pressure and heart rate	X				X		X[7]	X
Physical Examination	X				X			
Adverse Events	X	X	X	X	X	X	X	
Review safety card								X
Laboratory Testing								
Hematology (central)	X				X		X	
Blood Chemistry (central)	X				X		X	
Urinalysis	X							

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Study Period	Run-In						Dosing	Dosing
	Screening							
Timing relative to study drug administration							Pre-Dose	Post-Dose
Study Day (window)	-90 (±14 days)	-75 (±7 days)	-60 (±7 days)	-45 (±7 days)	-30 (±14 days)	-15 (±7 days)	Study Day 1	Study Day 1
Visit Numbers	V1	V2[1]	V3	V4[1]	V5[2]	V6[1]	V7	V7
Urine albumin: creatinine ratio	X						X	
Pharmacokinetics and Immunogenicity[8]								
Drug conc. sample							X	X[9]
ADA sample							X	
Biomarkers								
Blood sample for Olink proteomics							X	
Blood sample for high sensitivity troponin T							X	
Blood sample for cGMP							X	
Blood sample for ANP/BNP MS							X	
Blood sample for BNP ELISA							X	
Blood sample for NT-proANP							X	
Blood sample for CA-125							X	
Urine sample for KIM-1/creatinine ratio							X	
Urine NGAL							X	
Urine sample for exploratory research							X	
Blood sample for exploratory research (plasma and serum)							X	
Blood sample for future research (serum and plasma) optional							X	
Blood sample for DNA isolation (optional)							X	

15.4.2. Footnotes for Part B Day 1 Administration Schedule of Events

1. The visit will be conducted by telephone.
2. Participants may repeat visit 5 once if background medications for heart failure are adjusted within 30 days prior to randomization or if randomization is delayed for non-safety reasons.
3. Only required if no echocardiogram report is available performed within 3 months prior to screening.
4. ECG can be performed on any visit based on clinical need and judgement of the investigator.
5. ECG should be completed within approximately 30 minutes after the end of infusion.

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6. All PROs assessments must be completed prior to any clinical assessments, where possible.
7. Pre-dose blood pressure and heart rate should be checked as close as possible to time of dose administration.
8. 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.
9. Drug concentration sample should be collected within approximately 30 minutes after end of infusion.

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Table 3: Parts A1, A2, and B Outpatient Period Schedule of Events

Study Period	Outpatient							
Study Day (Week)	**Day 8 (Wk 1)[5]**	**Day 15 (Wk 2)**	**Day 22 (Wk 3)**	**Day 29 (Wk 4)**	**Day 57 (Wk 8)**	**Day 85 (Wk 12)**	**Day 113/EOS (Wk 16)**	**Early Termination (ET)**
Window (Days)	**±1**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	
Visit	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	
Treatment								
Concomitant medications and procedures	X	X	X	X	X	X	X	X
Pharmacodynamics								
Blood sample for NT-proBNP (central)	X	X	X	X	X	X	X	X
Clinical Outcome Assessments[1]								
KCCQ-23		X		X	X	X	X	X
EQ-5D-5L				X	X	X	X	X
Safety								
Blood pressure and heart rate	X[5]	X	X	X	X	X	X	X
Adverse Events	X[5]	X	X	X	X	X	X	X
Review safety card	X	X	X	X	X	X		
Pregnancy test for WOCBP[2]				X	X	X	X	X
Electrocardiogram[3]	X			X				
Laboratory Testing								
Hematology panel (central) [4]	X			X			X	X
Blood chemistry (central)	X[5]	X	X	X	X	X	X	X
Urine albumin: creatinine ratio	X			X	X	X	X	X
Pharmacokinetics and Immunogenicity								
Drug conc. sample	X	X	X	X	X	X	X	X
ADA sample					X		X	X
Biomarkers								
Blood sample for Olink proteomics	X			X			X	X
Blood sample for high sensitivity troponin T	X	X	X	X			X	X
Blood sample for cGMP	X	X	X	X				
Blood sample for ANP/BNP MS	X			X			X	X
Blood sample for BNP ELISA	X	X	X	X	X	X	X	X
Blood sample for NT-proANP	X	X	X	X	X	X	X	X
Blood sample for CA-125	X			X			X	X
Urine sample for KIM-1/creatinine ratio	X			X			X	X
Urine NGAL	X			X			X	X
Urine sample for exploratory research	X			X			X	X
Blood sample for Exploratory research (plasma and serum)	X			X			X	X
Blood sample for future research (serum and plasma) (optional)	X			X			X	X

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15.4.3. Footnotes for Parts A1, A2, and B Outpatient Period Schedule of Events

1. All PRO assessments must be completed prior to any clinical assessments, where possible
2. The investigator must ensure that negative pregnancy tests are reported by participants at the specified visits and report any positive test at any time to the sponsor (see Section 9.1.3 in protocol).
3. ECG can be performed on any visit based on clinical need and judgement of the investigator.
4. Hematology may be performed by local laboratory at all scheduled timepoints if central hematology testing is not feasible and with prior approval from the sponsor.
5. Participants with eGFR 30 to 45 mL/min/1.73 m^2 in Part B will have an outpatient visit on study day 4±1 day (2 to 4 days after study drug infusion) for evaluation for adverse events, blood pressure and heart rate, and lab chemistry. Central lab chemistry (or if available and preferred by investigator, local lab chemistry) result will be reviewed by the investigator as soon as available, before or as a part of visit 8, study day 8.

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15.5. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV For Studies in healthy subjects only	Comments
Clinical chemistry		
ALT	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Each category is calculated independently. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, >5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided
AST	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Each category is calculated independently. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤1.5 ULN	
Total Bilirubin	>1.5 and ≤2 ULN and baseline ≤1.5 ULN >2 ULN and baseline ≤2.0 ULN	If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤3 ULN or TBILI ≤2ULN	
Creatine phosphokinase (CPK)	>3 and ≤10 ULN and baseline ≤3 ULN >10 ULN and baseline ≤10ULN	If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided

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Parameter	PCSV For Studies in healthy subjects only	Comments
Creatinine	≥150 umol/L (Adults) and baseline < 150 umol/L ≥50% change from randomization value and creatinine greater than 90.19 umol/L (1.02 mg/dl) for female or creatinine greater than 104.34 umol/L (1.18 mg/dl) for male ≥100% change from randomization value and creatinine greater than 90.19 umol/L (1.02 mg/dl) for female or creatinine greater than 104.34 umol/L (1.18 mg/dl) for male	3 independent criteria
Urine albumin creatinine ratio	>300 mg/g and baseline ≤300 mg/g	
eGFR	≥ 25% fall from baseline	
Creatinine Clearance (CKD-EPI 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)	Four independent criteria, will provide additional shift table if needed
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
Chloride Hypochloremia: Hyperchloremia:	 <80 mmol/L and baseline ≥80 mmol/L >115 mmol/L and baseline ≤115 mmol/L	Two independent criteria

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Parameter	PCSV For Studies in healthy subjects only	Comments
Sodium Hyponatremia: Hypernatremia:	 ≤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	Two independent criteria
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	
Troponin	>22 ng/L for male or >14 ng/L for female >2URL >5 URL >10 URL	
Hematology		
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. ≥16.0 Giga/L and baseline <16 Giga/L	
Lymphocytes	>4.0 Giga/L and baseline ≤4.0 Giga/L	
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	

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Parameter	PCSV For Studies in healthy subjects only	Comments
Monocytes	>0.7 Giga/L and baseline ≤0.7 Giga/L	
Basophils	>0.1 Giga/L and baseline ≤0.1 Giga/L	
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	≤115 g/L for male or ≤95 g/L for female and baseline >115 g/L for male or >95 g/L for Female ≥185 g/L for male or ≥165 g/L for female and baseline <185 g/L for male or <165 g/L for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
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.
RBC	≥6 Tera/L and baseline <6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.
Platelets	<100 Giga/L and baseline ≥100 Giga/L ≥700 Giga/L and baseline <700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and baseline >4.6 ≥8 and baseline <8	Two independent criteria
Vital signs		

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Parameter	PCSV For Studies in healthy subjects only	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	
MAP	≤70 mmHg and decrease from baseline ≥10 mmHg ≥100 mmHg and increase from baseline ≥10 mmHg	
ECG		Ref.: CPMP 1997 guideline.
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 For Studies in healthy subjects only	Comments
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: >430 to ≤450ms for male or >450 to ≤470ms and baseline ≤430 ms for Male or ≤450 ms for Female Prolonged: >450 ms for male or >470 ms for female and baseline ≤450 ms for Male or ≤470 ms for Female ≥500 ms and baseline <500 ms Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSV to be identified in individual subjects/patients listings. 5 independent criteria

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