Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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
Study Name:	NATRIX-BNP
Clinical Phase:	2
Protocol Number:	R5381-HF-22118
Protocol Version:	R5381-HF-22118 Amendment 4
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AMENDMENT HISTORY

Amendment 4

The primary purpose of this amendment is to broaden the participant population to be enrolled in Part B to better reflect the current standard of care by including participants receiving sacubitril-valsartan as background therapy, and to more effectively obtain data in a participant population with high unmet need by including participants with low estimated glomerular filtration rate (eGFR), defined as 30 to 45 mL/min/1.73 m^2. The inclusion of these participants in Part B will enhance the scientific value of the study's primary objective, which is to assess the effect of REGN5381 on cardiopulmonary congestion, by targeting a more relevant participant demographic while maintaining adequate provisions for participant safety.

Protocol Amendment 4 introduces the following key changes:

Participants on Sacubitril-Valsartan

- The number of participants in the **Part A2 sacubitril-valsartan cohort** has been reduced from 50 to 42, while Part B has been expanded to maintain overall study enrollment.
- In **Part B**, participants receiving sacubitril-valsartan as background therapy will be allowed to enroll following a sponsor review of cumulative safety data from the Part A2 sacubitril-valsartan cohort, after all participants have completed day 8 safety assessments.

Participants with Low eGFR

- Enrollment for the **Part A2 low eGFR cohort** has been closed to further enrollment, and Part B has been increased in size by approximately the same number of participants to maintain overall study enrollment.
- Participants with low eGFR and receiving sacubitril-valsartan as background therapy will be allowed to enroll in the **Part A2 sacubitril-valsartan cohort** with 4-day inpatient monitoring.
- In **Part B**, participants with low eGFR will be allowed to enroll, with stricter safety monitoring through an additional safety follow-up visit (day 4±1 day post treatment). There will be an early safety data assessment by the sponsor, for the first 6 participants in the low eGFR group completing day 29 post treatment. Furthermore, study stopping criteria specific to participants with low eGFR have been implemented.

These changes are supported by accumulating clinical safety experience with REGN5381, which includes a total of 95 participants with heart failure (HF) across 2 ongoing studies (R5381-HF-2159 and R5381-HF-22118) who received single IV doses of REGN5381 up to 300 mg or placebo as of the safety data cutoff date of Addendum 1 to Investigator's Brochure (IB) Edition 5 (01Apr 2025). Overall, REGN5381 has a reasonable safety and tolerability profile, and the benefit-risk profile for continued investigation remains favorable to date.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Inclusion of participants receiving sacubitril-valsartan in Part B		
The number of participants in Part A2 sacubitril-valsartan single escalating dose cohort has been reduced from a total of 50 to 42. Overall, Part B has been increased in size by approximately the same number of participants as the reduction in the number of participants in Part A2.	Based on the accumulating safety profile of REGN5381 and the expanding use of sacubitril-valsartan, the A2 sacubitril-valsartan cohorts are being modestly reduced in size to allow sacubitril-valsartan in Part B earlier. Part B population will better reflect the global standard of care, and because Part B has a larger site footprint, this will allow a greater number of sacubitril-valsartan participants to be dosed.	Clinical Study Protocol Synopsis: Study Design, Population Section 3.2.3 Rationale for Study Design Changes in Protocol Amendment 4 (*new section*) Section 5.1.1 Study Design: Part A1 and Part A2 Section 6.1 Number of Participants Planned
Participants receiving sacubitril-valsartan as background therapy will be allowed to enroll in Part B of the study. Study eligibility criteria and concomitant medication requirements have been modified accordingly.	To better reflect the current standard of care in heart failure with reduced ejection fraction (HFrEF) by allowing enrollment of participants on sacubitril-valsartan in Part B while maintaining adequate provisions for participant safety.	Clinical Study Protocol Synopsis: Study Design; Population Section 3.2.1 Rationale for Study Design Section 6.2.1 Inclusion Criteria; criterion #9 and #10 Section 6.2.2 Exclusion Criteria, criterion #3, and #20, #21, and #22 Section 3.3.1.6 Background Therapy, Prohibited, and Permitted Medications Section 7.10.1 Prohibited Medications Section 7.10.2 Permitted Medications
The decision to randomize participants on sacubitril-valsartan in Part B will be made if REGN5381 is found to be sufficiently safe and tolerated in participants on sacubitril-valsartan based on a following a Sponsor review of cumulative safety data from all Part	While REGN5381 and sacubitril-valsartan have demonstrated additive pharmacodynamic effects in preclinical animal models, this is the first study to evaluate the combination in humans. Inpatient monitoring and cumulative safety	Section 5.1.3.7 Decision to Initiate Inclusion of Participants on Background Sacubitril-Valsartan in Part B

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
A2 participants on sacubitril-valsartan, after all participants have completed day 8 safety assessments.	review of these initial cohorts will be performed before proceeding to the outpatient-monitored Part B.	
Part B randomization will be stratified by sacubitril-valsartan background therapy (yes/no).	Sacubitril-valsartan acts in part through NPR1 signaling. The effect of baseline activation of this signaling pathway on the treatment effect of REGN5381 is unknown. Thus, balancing treatment assignment of participants on background sacubitril-valsartan is indicated.	Clinical Study Protocol Synopsis: Statistical Plan Section 5.1.2.1 Changes to Part B in Protocol Amendment 4 (*new section*) Section 7.6 Method of Treatment Assignment Section 10.4.3 Efficacy Analyses
Inclusion of participants with low eGFR in Part A2 Sacubitril-Valsartan Cohort and Part B		
Part A2 low eGFR cohort has been closed to further enrollment. Overall, Part B has been increased in size by approximately the same number of participants as the reduction in the number of participants in Part A2. Participants with low eGFR (defined as 30 to 45 mL/min/1.73 m^2) will be allowed to enroll in Part B of the study in addition to the Part A2 sacubitril-valsartan cohort. Study eligibility criteria have been modified accordingly.	Participants with low eGFR and HF are a population of greater unmet need and may benefit more from NPR1 activation. Part B has a larger site footprint, facilitating more extensive study of this small but important subpopulation that has not enrolled sufficiently in the smaller site footprint of Part A. Safety data to date in this and other studies with REGN5381 do not suggest an adverse effect on renal function and demonstrate that inclusion/exclusion criteria in place (including pulmonary hypertension exclusion, SBP >110 mm Hg requirement) minimize the risk of hypotension and hypotension-related renal injury.	Clinical Study Protocol Synopsis: Study Design; Population Section 3.2.1 Rationale for Study Design Section 3.2.3 Rationale for Study Design Changes in Protocol Amendment 4 (*new section*) Section 5.1 Study Description and Duration Section 5.1.1.1 Changes to Part A2 in Protocol Amendment 4 *(new section)* Section 5.1.1.1.2 Low eGFR Cohorts in Part A2 *(new section)* Section 5.1.1.5 Low eGFR Cohorts in Part A2 Section 5.1.3.5 Part B *(new section)*

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
		Section 6.1 Number of Participants Planned Section 6.2.1 Inclusion Criteria, criterion #10 Section 6.2.2 Exclusion Criteria, criterion #3
Participants with low eGFR to be enrolled in Part B will have an additional outpatient visit on day 4 (±1 day) for evaluation for adverse events, blood pressure, heart rate, and serum chemistry. The chemistry results will be made available for Investigator's review before the day 8 study visit.	Activation of the NPR1 pathway has been shown to benefit patients with HF and reduced eGFR. However, concern remains that patients with low eGFR are at risk of acute kidney injury (AKI) in response to vasoactive agents. Should AKI occur, evidence of it is typically apparent 24-72 hours following the hemodynamic insult. Thus, an additional visit 2-4 days after the date of infusion is appropriate for early detection of AKI.	Section 3.2.3 Rationale for Study Design Changes in Protocol Amendment 4 (*new section*) Section 3.3.1.4 Low eGFR *(new section)* Table 3 Parts A1, A2, and B Outpatient Period Schedule of Events Section 8.1.3 Footnotes for Parts A1, A2, and B Outpatient Period Schedule of Events, footnote #5 Section 8.2.3.2 Vital Signs
In addition to the continuous safety monitoring of participants in the trial, the sponsor will perform a formal early assessment of safety for participants with low eGFR entering Part B. This assessment of the first 6 participants with low eGFR will occur when the sixth participant completes the day 29 visit. Until this review is completed, no more than 3 additional participants may be randomized; after the review, enrollment of participants with low eGFR in Part B will continue if supported by the safety data.	To augment patient safety measures in participants with low eGFR.	Section 3.3.1.4 Low eGFR Section 5.1.2.1.2 Participants with Low eGFR in Part B (*new section*)
Participants with low eGFR in Part B will be randomized to REGN5381 100 mg, REGN5381 300 mg, or placebo at	To ensure equal treatment arm allocation of the low eGFR population, which is expected to be small in number, and to ensure representation of the treatment arms	Section 7.6 Method of Treatment Assignment

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
a ratio of 1:1:1 (first 6 participants at 2:2:2).	in the six participant safety data group to be reviewed by the Sponsor before continuing with enrollment of participants with low eGFR in Part B	
The following stopping criterion has been added: For participants in the low eGFR group (30 to 45 mL/min/1.73 m^2) in Part A2 or Part B, severe hypotension, any other serious AE and/or acute kidney injury will prompt an immediate safety review. If such event is assessed as related to the study drug by the investigator and the sponsor, further enrollment of low eGFR participants will be paused immediately. Further inclusion of low eGFR participants will only resume after IDMC consultation.	To augment participant safety measures in participants with low eGFR.	Section 3.3.1.4 Low eGFR (*new section*) Section 5.1.5.1 Specific Rules for Participants with a Low eGFR
Primary Efficacy Analysis Changes Related to Broadening Part B Population		
The sample size per REGN5381 arm has been increased from 82 to 113 by pooling the common dose levels of REGN5381 across Parts A1, A2, and B. With this increased size of 113 per active arm, the minimum observed treatment difference between REGN5381 and placebo required to achieve statistical significance changes from -18% to -16%. The overall study sample size remains unchanged at approximately 394 in total; the increased sample size in REGN5381 arm reflects the pooling and reallocation of A2 participants (previously excluded from primary analysis) with Part B.	To better detect a potentially smaller treatment effect if background sacubitril-valsartan decreases the magnitude of treatment effect of REGN5381 relative to placebo.	Clinical Study Protocol Synopsis: Statistical Analysis – Justification of Sample Size Section 5.1.3 Description of Study Cohorts and Dose Escalation Section 10.2 Justification of Sample Size
The model of primary efficacy endpoints has been changed from ANCOVA to MMRM, with a new covariate of background sacubitril-valsartan therapy 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	Clinical Study Protocol Synopsis: Statistical Analysis – Efficacy Analysis Section 10.4.3 Efficacy Analyses

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
	(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.	
Other Changes		
Added flexibility to specified sequence of obtaining vital signs relative to blood sampling when withdrawn from an indwelling IV catheter and not by venipuncture.	To reduce procedural complexity of assessments without compromising accuracy of vital sign measurements.	Section 8.2.3.2 Vital Signs
Removed 2.5 hour fasting requirement from baseline ECG assessment for participants in Part B.	QTc analysis is being performed in Part A1 and A2 only, and the fasting requirement is for this analysis. Thus, the fasting is not needed in Part B. This simplifies the timing of day 1 and reduces participant burden.	Section 8.2.3.5 Electrocardiogram
Added [redacted] to exploratory biomarker objectives and endpoints	This is a proximal molecular marker of NPR1 activation. This will be used to better understand target engagement and durability of effect of REGN5381.	Section 2 Study Objectives and Endpoints Section 4.5 Pharmacodynamic and Other Biomarker Variables Section 8.2.7.12 cGMP (*new section*)
Added [redacted]	This exploratory endpoint was described in the study procedures but baseline testing omitted in error from the tabulated SOE.	Table 2 Part B Screening, Run-in, and Day 1 Administration Schedule of Events
Updated the immunogenicity sections to reflect the sponsor's current language and analysis plans.	To align with the sponsor's current protocol template, operations, and analysis plans.	Section 2 Study Objectives and Endpoints Section 4.4 Immunogenicity Variables Section 10.4.7 Analysis of Immunogenicity Data
Updated the section related to analysis of pharmacodynamics and exploratory biomarker data and analysis of drug concentration data to reflect the sponsor's current analysis plan.	To align with the sponsor's current protocol template, operations, and analysis plans	Section 10.4.8 Analysis of Pharmacodynamic and Exploratory Biomarker Data

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
		Section 10.4.6.1 Analysis of Drug Concentration Data
Exclusion of participants with any history of requiring positive inotropic support was highlighted as a study design element ensuring participant safety measure.	To align prohibited medication section with exclusion criteria, and highlight a safety measure already in place to exclude participants who are at a higher risk of low output heart failure and hemodynamic instability.	Section 3.3.1.1 Participant Selection Section 3.3.1.6 Background Therapy, Prohibited, and Permitted Medications
Discussion of prior clinical data in the Risk-Benefit section has been streamlined. Out-of-date descriptions of available clinical data were replaced with reference to the current IB.	To reference a data source that is reliably updated.	Section 1 Introduction Section 3.3 Benefit-Risk
National requirements and local regulations have been included in the clause about post-trial sacubitril-valsartan provision.	Per Health Authority request, to provide additional clarity	Section 5.1.4 Provision of Sacubitril/Valsartan to Study Participants After Trial Completion
Expanded the schedule of events footnote that allows for visit 5 repeat due to medication changes, to also apply to participants who have experienced a delay in randomization for non-safety reasons During the Run-In Period, visit 5 (day -30) may be repeated once if randomization (on visit 7 (day 1) is delayed for non-safety reasons. This is in addition to the currently allowed visit 5 repeat if needed due to medication changes.	To prevent unnecessary patient burden potentially caused by requiring the repeat of the entire Run-In Period in cases where randomization is delayed for non-safety reasons (eg, scheduling)	Section 8.1.1 Footnotes for Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods, footnote #3 Section 8.1.2 Footnotes for Part B Day 1 Administration Schedule of Events , footnote #2
Minor administrative revisions and minor typographical errors were addressed.	To ensure overall accuracy and consistency	Throughout the document

Amendment 3

The primary purpose of this amendment is to decrease the level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) required for study inclusion to improve study enrollment.

Description of Change	Brief Rationale	Section # and Name
The inclusion criterion for plasma NT-proBNP levels was decreased to **≥800 pg/mL** (or ≥**1000 pg/mL** in atrial	To revise the NT-proBNP level required for study inclusion in line with that observed in the targeted	Section 5.1.1 Study Design: Part A1 and Part A2

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
fibrillation) at initial screening (day -90) and ≥600 pg/mL (≥800 pg/mL in atrial fibrillation) at visit 5 (day -30). Previously, the cutoffs in this inclusion criterion were plasma NT-proBNP levels of **≥900 pg/mL** (or **≥1200 pg/mL** if in atrial fibrillation).	patient population (stable, chronic heart failure with congestion)	Section 6.2.1 Inclusion Criteria; criterion #5, and #11 Section 3.3.1.1 Participant Selection
Statement regarding sacubitril-valsartan provision after trial completion was revised, to remove language that required health authority and ethics committee approvals from all participating countries before implementation of the provision.	Not applicable for this study as standard of care (sacubitril-valsartan) will be provided when approved on a per-country basis.	Section 5.1.4 Provision of Sacubitril/Valsartan to Study Participants After Trial Completion
Central laboratory testing for hematology may be performed by local laboratory if central testing is not feasible, and with prior approval from the Sponsor.	For operational flexibility	Section 8.1.1 Footnotes for Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods; Footnote #12 Section 8.1.2 Footnotes for Part B day 1 Administration Schedule of Events; Footnote #10 Section 8.1.3 Footnotes for Parts A1, A2, and B Outpatient Period Schedule of Events; Footnote #4 Section 8.2.3.8 Laboratory Testing
Minor administrative revisions and minor typographical errors were addressed.	These updates were incorporated to ensure overall accuracy and consistency	Throughout the document

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Amendment 2

The primary purposes of this amendment are to add additional safety controls and reporting as recommended by the Independent Data Monitoring Committee (IDMC), implement Health Authority feedback, add additional option to offer standard of care as part of the compensation post-trial, and to further define the statistical methods.

Description of Change	Brief Rationale	Section # and Name
IDMC-Recommended Changes		
Monthly safety summary including serious adverse event (SAE) listings will be provided to the Independent Data Monitoring Committee (IDMC), in addition to the 2 planned safety review meetings at 30% and 60% of anticipated enrollment.	To augment IDMC oversight in the interest of patient safety measures. This change is a specific recommendation of the IDMC and is included in the IDMC charter.	Section 5.3.1 Independent Data Monitoring Committee
Participants with any history of requiring positive inotropic support will be excluded.	New exclusion criterion to augment patient safety, as any history of prior requirement of positive inotropic circulatory support predicts propensity to low output cardiac failure and/or hypotension. This change is a specific recommendation of the IDMC.	Section 6.2.2 Exclusion Criterion #11
Health Authority Request		
Participants with hemoglobin <9.0 g/dL at screening will be excluded.	Health Authority request intended to exclude patients with conditions that exhibit symptoms similar to heart failure	Section 6.2.2 Exclusion Criterion #32
Patient Eligibility Criteria		
Body mass index (BMI)-based inclusion criterion was expanded to include up to 45 kg/m^2.	No safety or pharmacology concerns have been identified that would preclude the inclusion of participants up to 45 kg/m^2, the previous limit was 40 kg/m^2. This would improve study enrollment and provide additional data on how the doses perform in a higher weight population.	Section 6.2.1 Inclusion Criterion #2
Anti-HBc test-based exclusion criterion has been updated to specify anti-HBc IgM assay.	Clear specification of the anti-HBc IgM assay excludes only those with active HBV infection, as is appropriate for this study. Previous exclusion criterion (without isotype specification) typically defaults to a total antibody assay (IgG + IgM),	Section 6.2.2 Exclusion Criterion #23

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
	which unnecessarily excludes participants with clinically insignificant resolved HBV infection history (IgG+).	
Other changes were made for consistency, accuracy, and clarity: • Removed statement that estimated glomerular filtration rate (eGFR)-based exclusion criterion may be modified in Part B of the study • Edited exclusion criterion describing prohibited concomitant medications to exclude IV nitrates and IV vasodilators throughout run-in period • Removed inaccurate statement that participants on sacubitril-valsartan may be considered for inclusion in Part B • Removed redundant exclusion criterion around substance use disorders	To address inconsistent or ambiguous criteria and improve study conduct: • Participants with eGFR 30-45 mL/min/1.73 m^2 will be studied exclusively in Part A2 of the study for optimal safety monitoring in this subpopulation • Simplifies concomitant medication exclusion in response to HA request to reduce risk of overlapping mechanism of action. • Participants on sacubitril-valsartan will be studied exclusively in Part A2 for optimal safety monitoring in this subpopulation • Substance use disorders is covered by exclusion criterion #10 that precludes participants with psychiatric disease that may confer unreasonable risk to the patient's participation in the study per the Investigator's judgement	Section 6.2.2 Exclusion Criterion #3, #19, #20, #21
Statistical Plan		
Justification of sample size updated	Some details are removed as they were found not relevant in a study where there is no formal hypothesis testing. Also added flexibility to pooling plan in the event Part A and B doses are nonidentical.	Section Clinical Study Protocol Synopsis: Population Section 10.2 Justification of Sample Size
Analysis sets (PADS, SAF, PK, ADA) changed from "as randomized" to "as treated"	Would be more accurate analysis in rare case that participant does not receive the treatment to which they were randomized.	Section 10.3.2 Pharmacodynamic Analysis Set Section 10.3.3 Safety Analysis Set Section 10.3.4 Pharmacokinetic Analysis Set Section 10.3.5 Immunogenicity Analysis Set

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Definition of pharmacodynamic analysis set updated	Minor edits, streamlined to currently approved REGN template language.	Section 10.3.2 Pharmacodynamic Analysis Set
Secondary efficacy analyses updated to include MMRM for secondary endpoints	Using MMRM instead of ANCOVA to evaluate the secondary efficacy endpoints at multiple timepoints.	Section 10.4.3.2 Secondary Efficacy Analyses
Reworded the details on study data blinding.	Clarified the access and roles of study personnel to blinded data.	Section 7.7 Blinding
Schedule of Events		
Single ECGs will be required at screening visits instead of triplicate ECGs. Triplicate ECGs will continue being required at timepoints corresponding to pharmacokinetics (PK) sample collection.	Triplicate ECGs only required to enable QT effect analysis; single ECGs sufficient for safety assessment at screening visits	Section 8.1.1 Footnotes for Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods. Footnote #5 Section 8.2.3.5 Electrocardiogram
Discharge criteria reassessment was added to Part A Extended Inpatient Stay visit.	Allows addition of EDC element track discharge criteria during extended inpatient days to understand trends in causes for extended monitoring.	Section 5.1.1 Study Design
Other Changes		
A statement allowing for the provision of 1 year of sacubitril/valsartan to trial participants, following successful completion of the EOS visit, was added to the protocol. Implementation of this provision requires ethics committee and health authority approval from all participating countries.	To further enhance the likelihood of clinical trial participation by providing incentive to participants in the form of standard of care medication after completion of the EOS visit, to eligible trial participants and subject to local regulations and at the discretion of the investigator.	Section 5.1.4 Provision of Sacubitril/Valsartan to Study Participants after Trial Completion (New Section)
Added description of the primary endpoint to specify NT-proBNP as a biomarker of cardiopulmonary congestion	To provide a direct description of the relationship between the primary endpoint and associated objective	Section Clinical Study Protocol Synopsis Objectives and Endpoints Section 2 Study Objectives and Endpoints
Removed inaccurate statement that participants on sacubitril-valsartan may be considered for inclusion in Part B	Participants on sacubitril-valsartan will be studied exclusively in Part A2 for optimal safety monitoring in this subpopulation	Section 5.1.2 Study Design: Part B Section 7.10.1 Prohibited Medications
• Updated description of the planned number of participants to be enrolled to streamline	• For clarity of enrollment plans • For accuracy	Section 6.1 Number of Participants Planned

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
• Removed mention of matched placebo		
Removed irrelevant footer lipoprotein from table listing Blood Chemistry tests	For accuracy as no lipid testing is required in study	Section 8.2.3.8 Laboratory Testing
Addressed minor administrative updates and typographical error	To ensure overall accuracy and consistency	Throughout the document

Amendment 1

The main purpose of this amendment is to modify the protocol in response to Health Authority feedback.

Description of Change	Brief Rationale	Section # and Name
Exclusion criterion was added to prevent enrollment of participants with a history of syncope and/or autonomic dysfunction	Health Authority recommendation to align study participant eligibility criteria with the REGN5381 'Guidance for the Investigators' in the Investigator's Brochure	Section 7.2.2 Exclusion Criteria; Criterion #5 and #6
Predose Urine Pregnancy Test on study day 1 was added to Schedule of Events (SOE) for Part A1 and Part A2, additional contraception requirements have been added to the exclusion criteria, and footnote was added to clarify the monthly pregnancy tests requirement during the Outpatient Schedule of Events.	Health Authority recommendation to ensure negative pregnancy test result no earlier than within 72 hours before drug administration and that hormonal contraception in women of childbearing potential is supplemented with a barrier method (preferably male condom)	Table 1 Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods Section 7.2.2 Exclusion Criteria; criterion #30 Section 9.1.3 Footnotes for Parts A1, A2, and B Outpatient Period Schedule of Events; Footnote #2
Blood chemistry and hematology (central lab) sample collection on study day -30 was added to the SOE for Part B.	In the initial protocol, these procedures were described in the study procedures but omitted in error from the tabulated SOE	Table 2 Part B Screening, Run-in, and day 1 Administration Schedule of Events
Minor administrative revisions and minor typographical errors were addressed.	These updates were incorporated to ensure overall accuracy and consistency	Throughout the document

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
ACEi	Angiotensin-converting enzyme inhibitors
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blockers
ARNI	Angiotensin receptor/neprilysin inhibitor
AST	Aspartate aminotransferase
AUC	Area under curve
BNP	Brain natriuretic peptide
BP	Blood pressure
CA-125	Carbohydrate antigen 125
CFB	Change from baseline
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
C_{max}	Peak concentration
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CSR	Clinical study report
CVP	Central venous pressure
DBP	Diastolic blood pressure
DSM-5 TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E_{max}	Maximum effect
EOS	End of study
FBR	Future biomedical research
FDA	Food and Drug Administration

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GDMT	Guideline-directed medical therapy
GPS	Global Patient Safety
HCV	Hepatitis C virus
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HBsAg	Hepatitis B surface antigen
hs-cTnT	High-sensitivity cardiac troponin-T
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committees
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
KIM-1	Kidney injury molecule-1
LAM	Lactational amenorrhea method
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAP	Mean arterial pressure
mITT	Modified intent-to-treat
MRA	Mineralocorticoid receptor antagonist
NGAL	Neutrophil gelatinase-associated lipocalin
NHP	Nonhuman primates
NPR1	Natriuretic peptide receptor 1
NPR-A	Natriuretic peptide receptor A
NPR-C	Natriuretic peptide clearance receptor
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

PA4	Protocol Amendment 4
PDAS	Pharmacodynamic analysis set
PCSV	Potentially clinically significant value
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient-reported outcomes
PT	Preferred term
RBC	Red blood cell
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid
RVSP	Right ventricular systolic pressure
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SV	Stroke volume
SVR	Systemic vascular resistance
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

TABLE OF CONTENTS

AMENDMENT HISTORY 3
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 15
CLINICAL STUDY PROTOCOL SYNOPSIS 25
1. INTRODUCTION 31
2. STUDY OBJECTIVES AND ENDPOINTS 33
3. HYPOTHESIS AND RATIONALE 35
3.1. Hypotheses 35
3.2. Rationale 35
3.2.1. Rationale for Study Design 35
3.2.1.1. Endpoints 35
3.2.2. Rationale for Dose Selection 37
3.2.3. Rationale for Study Design Changes in Protocol Amendment 4 38
3.3. Risk-Benefit 39
3.3.1. Design Elements to Ensure Participant Safety 40
3.3.1.1. Participant Selection 41
3.3.1.2. Run-in Period 42
3.3.1.3. Inpatient Monitoring 42
3.3.1.4. Low eGFR 42
3.3.1.5. Dose Escalation and Cohort Progression 43
3.3.1.6. Background Therapy, Prohibited, and Permitted Medications 43
4. STUDY VARIABLES 45
4.1. Demographic and Baseline Characteristics 45
4.2. Safety Variables 45
4.3. Pharmacokinetic Variables 45
4.4. Immunogenicity Variables 45
4.5. Pharmacodynamic and Other Biomarker Variables 45
5. STUDY DESIGN 46
5.1. Study Description and Duration 46
5.1.1. Study Design: Part A1 and Part A2 46
5.1.1.1. Changes to Part A2 in Protocol Amendment 4 47
5.1.1.2. Screening, Run-in, Inpatient, and Outpatient Periods 47

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

5.1.1.3. Optional ≤300mg Dosing Cohort in Part A1 49
5.1.1.4. Sacubitril-Valsartan Cohorts in Part A2 50
5.1.1.5. Low eGFR Cohorts in Part A2 50
5.1.2. Study Design: Part B 50
5.1.2.1. Changes to Part B in Protocol Amendment 4 51
5.1.3. Description of Study Cohorts and Dose Escalation 52
5.1.3.1. Study Cohorts Part A 52
5.1.3.2. Dose Escalation 52
5.1.3.3. Decision to Initiate Sacubitril-Valsartan Cohorts in Part A2 52
5.1.3.4. Decision to Initiate Low eGFR Cohorts in Part A2 52
5.1.3.5. Part B 53
5.1.3.6. Decision to Initiate Part B 53
5.1.3.7. Decision to Initiate Inclusion of Participants on Background Sacubitril-Valsartan in Part B 53
5.1.4. Provision of Sacubitril/Valsartan to Study Participants After Trial Completion 53
5.1.5. Study Stopping Rules 53
5.1.5.1. Specific Rules for Participants with a Low eGFR 54
5.1.6. End of Study Definition 54
5.2. Planned Interim Analysis 54
5.3. Study Committees 54
5.3.1. Independent Data Monitoring Committee 54
6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS 56
6.1. Number of Participants Planned 56
6.2. Study Population 56
6.2.1. Inclusion Criteria 57
6.2.2. Exclusion Criteria 58
6.3. Premature Withdrawal from the Study 61
6.4. Replacement of Participants 61
7. STUDY TREATMENTS 62
7.1. Investigational and Reference Treatments 62
7.2. Background Treatments 62

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

7.3. Rescue Treatments 62
7.3.1. Rescue Therapy 62
7.3.2. Specific Complications of Cardiac Failure or Reversible Severe Hypotension to Consider in Differential Diagnosis 63
7.4. Dose Modification and Study Treatment Discontinuation Rules 63
7.4.1. Dose Modification 63
7.4.2. Study Drug Discontinuation 63
7.5. Management of Acute Reactions 63
7.5.1. Acute Intravenous Infusion Reactions 63
7.5.1.1. Interruption of the Intravenous Infusion 64
7.5.1.2. Termination of the Intravenous Infusion 64
7.6. Method of Treatment Assignment 65
7.7. Blinding 65
7.8. Emergency Unblinding 65
7.9. Treatment Logistics and Accountability 66
7.9.1. Packaging, Labeling, and Storage 66
7.9.2. Supply and Disposition of Treatments 66
7.9.3. Treatment Accountability 66
7.9.4. Treatment Compliance 66
7.10. Concomitant Medications 67
7.10.1. Prohibited Medications 67
7.10.2. Permitted Medications 67
8. STUDY SCHEDULE OF EVENTS AND PROCEDURES 68
8.1. Schedule of Events 68
8.1.1. Footnotes for Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods 72
8.1.2. Footnotes for Part B Day 1 Administration Schedule of Events 75
8.1.3. Footnotes for Parts A1, A2, and B Outpatient Period Schedule of Events 78
8.1.4. Early Termination Visit 78
8.1.5. Unscheduled Visits 78
8.2. Study Procedures 78
8.2.1. Procedures Performed Only at the Screening/Baseline Visit 78
8.2.2. Efficacy Procedures 79

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.2.3. Safety Procedures 79
8.2.3.1. Body Weight 79
8.2.3.2. Vital Signs 79
8.2.3.3. Blood Pressure 79
8.2.3.4. Physical Examination 79
8.2.3.5. Electrocardiogram 79
8.2.3.6. Echocardiogram 79
8.2.3.7. Safety Card 80
8.2.3.8. Laboratory Testing 80
8.2.4. Drug Concentration and Measurements 82
8.2.5. Immunogenicity Measurements and Samples 82
8.2.6. Clinical Outcome Assessments 82
8.2.6.1. Kansas City Cardiomyopathy Questionnaire (KCCQ) 82
8.2.6.2. EQ-5D-5L 82
8.2.7. Pharmacodynamic and Exploratory Biomarker Procedures 82
8.2.7.1. NT-proBNP 83
8.2.7.2. Olink Proteomics 83
8.2.7.3. High-sensitivity Troponin T 83
8.2.7.4. ANP and BNP MS Levels 83
8.2.7.5. BNP Enzyme-Linked Immunosorbent Assay (ELISA) 83
8.2.7.6. NT-proANP 83
8.2.7.7. CA-125 83
8.2.7.8. Urine Kidney Injury Molecule-1 (KIM-1) 84
8.2.7.9. Urine Albumin Creatinine Ratio 84
8.2.7.10. Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) 84
8.2.7.11. Exploratory Biomarker Research 84
8.2.7.12. cGMP 84
8.2.8. Future Biomedical Research (Optional) 84
8.2.9. Pharmacogenomic Analysis (Optional) 85
9. SAFETY EVALUATION AND REPORTING 86
9.1. Recording and Reporting Adverse Events 86
9.1.1. General Guidelines 86
9.1.2. Reporting Procedure 87

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

9.1.3. Events that Require Expedited Reporting to Sponsor 87
9.2. Definitions 87
9.2.1. Adverse Event 87
9.2.2. Serious Adverse Event 88
9.2.3. Adverse Events of Special Interest 88
9.2.4. Infusion Reactions 88
9.2.5. Severity 89
9.2.6. Causality 89
9.3. Safety Monitoring 90
9.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators 91
10. STATISTICAL PLAN 92
10.1. Statistical Hypothesis 92
10.2. Justification of Sample Size 92
10.3. Analysis Sets 93
10.3.1. Efficacy Analysis Sets 93
10.3.2. Pharmacodynamic Analysis Set 93
10.3.3. Safety Analysis Set 93
10.3.4. Pharmacokinetic Analysis Sets 93
10.3.5. Immunogenicity Analysis Sets 93
10.4. Statistical Methods 93
10.4.1. Participant Disposition 93
10.4.2. Demography and Baseline Characteristics 93
10.4.3. Efficacy Analyses 94
10.4.4. Control of Multiplicity 94
10.4.5. Safety Analysis 94
10.4.5.1. Adverse Events 94
10.4.5.2. Other Safety 95
10.4.5.3. Treatment Exposure 95
10.4.5.4. Treatment Compliance 95
10.4.6. Pharmacokinetics 95
10.4.6.1. Analysis of Drug Concentration Data 95
10.4.7. Analysis of Immunogenicity Data 96

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

10.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data....96
10.5. Statistical Considerations Surrounding the Premature Termination of a Study....96
11. QUALITY CONTROL AND QUALITY ASSURANCE....97
11.1. Data Management and Electronic Systems....97
11.1.1. Data Management....97
11.1.2. Electronic Systems....97
11.2. Study Monitoring....97
11.2.1. Monitoring of Study Sites....97
11.2.2. Source Document Requirements....98
11.2.3. Case Report Form Requirements....98
11.3. Audits and Inspections....98
11.4. Study Documentation....99
11.4.1. Certification of Accuracy of Data....99
11.4.2. Retention of Records....99
11.4.3. Recruitment Strategy....99
11.4.4. Data Protection....99
12. ETHICAL AND REGULATORY CONSIDERATIONS....101
12.1. Good Clinical Practice Statement....101
12.2. Informed Consent....101
12.3. Participants Confidentiality and Data Protection....101
12.4. Institutional Review Board/Ethics Committee....102
12.5. Clinical Study Data Transparency....102
13. PROTOCOL AMENDMENTS....103
14. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE....104
14.1. Premature Termination of the Study....104
14.2. Close-out of a Site....104
15. CONFIDENTIALITY....104
16. FINANCING AND INSURANCE....104
17. PUBLICATION POLICY....104
18. REFERENCES....105
19. INVESTIGATOR'S AGREEMENT....111
SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS....112

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

LIST OF TABLES

Table 1: Part A1 and Part A2 Schedule of Events: Screening, Run-In, Inpatient Dosing Periods....69

Table 2: Part B Screening, Run-in, and Day 1 Administration Schedule of Events....73

Table 3: Parts A1, A2, and B Outpatient Period Schedule of Events....76

LIST OF FIGURES

Figure 1: Study Overview Diagram for Parts A1, A2 and B....46

Figure 2: Study Flow Diagram for Part A1 and Part A2....48

Figure 3: Study Flow Diagram for Part B....50

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

CLINICAL STUDY PROTOCOL SYNOPSIS

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
Short Title	REGN5381 in participants with heart failure with reduced ejection fraction
Site Locations	This study will be conducted at multiple sites, globally.
Principal Investigator	[TBD]
Objectives and Endpoints	**Primary Objective:** The primary objective of the study is to evaluate the ability of REGN5381 to improve cardiopulmonary congestion. **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 **Exploratory Objectives:** The exploratory objectives of the study are to: [redacted]

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Primary Endpoint:

The primary endpoint of the study is the change from baseline in circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of cardiopulmonary congestion, at day 8.

Secondary Endpoints:

The secondary endpoints are:

- Occurrence and severity of treatment emergent adverse events (TEAEs) through the end of study (EOS) visit (week 16)
- Change from baseline in circulating NT-proBNP at weeks 2, 3, 4 and up to week 16
- Change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate at each visit through week 16
- Concentrations of REGN5381 in serum through the EOS visit
- Incidence and magnitude of anti-drug antibodies (ADA) to REGN5381 through the EOS visit

Study Design

The study will be conducted in 3 parts as follows:

- **Part A1**: single ascending dose cohorts to evaluate the pharmacodynamic effects and safety of REGN5381 compared to placebo with a 4-day post-randomization inpatient monitoring period,
- **Part A2**: single ascending dose cohorts to evaluate the pharmacodynamic 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 eGFR (30 to 45 mL/min/1.73m^2). The low eGFR group has been closed as of PA4. Participants already enrolled in this group will complete the protocol visits as scheduled.
- **Part B**: parallel arm design study to evaluate pharmacodynamic effects and safety of REGN5381 compared to placebo in the outpatient setting.

Part A1 and Part A2 have a randomized, double-blind, placebo-controlled, single ascending dose escalation design and will evaluate the safety, pharmacokinetic (PK) and pharmacodynamic (PD) of a single dose of intravenous (IV) REGN5381 versus placebo with a 4-day post-randomization inpatient monitoring period.

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

- REGN5381 100 mg IV or placebo IV (n=30; 15/arm)
- REGN5381 ≤300 mg IV or placebo IV (n=30; 15/arm)
- Optional Part A1 cohort: REGN5381 ≤300 mg IV or placebo IV (n=30; 15/arm)

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.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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

- Sacubitril-valsartan cohort (N=42)
  - 24 participants (12/arm) will receive 100 mg REGN5381 or placebo,
  - 18 participants (12 active: 6 placebo) will receive ≤300 mg REGN5381 or placebo
- Low eGFR (30 to 45 mL/min/1.73 m^2) cohort (N=2-4)
  - 2 to 4 participants (0 to 4/arm) will receive 100 mg REGN5381 or placebo,

    (The low eGFR group has been closed as of PA4. Participants already enrolled in this group will complete the protocol visits as scheduled.)

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, PK, and PD.

Part B will be initiated following the review of safety data from each cohort in Part A. 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.

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

- REGN5381 100 mg IV
- REGN5381 ≤300 mg IV
- Placebo IV

Part B will exclude participants on background sacubitril-valsartan until a safety evaluation following the completion of study day 8 of the last participant in the A2 sacubitril-valsartan group (≤300 mg cohort). If the safety profile of REGN5381 on background sacubitril-valsartan is acceptable in Part A2, the sponsor may open Part B to include participants on background sacubitril-valsartan.

The maximum dose in Part B will not exceed the maximum tolerated dose from Part A1. A dose level lower than 300 mg may be selected in place of 300 mg following evaluation of this dose level in the optional cohort in Part A1.

The duration of the screening period, run-in 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.

Study Duration

The duration of the study for a participant is approximately 203 days, including the 90-day Run-in period.

End of Study Definition

The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator). Unscheduled

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

	visits may occur after the planned end of study visit if additional follow follow-up of a participant (eg, safety follow-up) is warranted.
Population	
Sample Size:	Approximately up to 394 participants will be enrolled in the study with approximate numbers of participants as follows: **Part A1** (N=60 to 90), – 30 participants (15/arm) will receive 100 mg REGN5381 or placebo, – 30 participants (15/arm) will receive ≤300 mg REGN5381 or placebo, – Optional cohort: 30 participants (15/arm) will receive ≤300 mg REGN5381 or placebo, **Part A2** (N=44 to 46)***,** • Sacubitril-valsartan cohort: (N=42)*, – 24 participants (12/arm) will receive 100 mg REGN5381 or placebo*, – 18 participants (12 active: 6 placebo) will receive REGN5381 ≤300 mg IV*. • Low eGFR (30 to 45 mL/min/1.73 m^2) cohort – 2-4 participants (randomized 1:1) will receive 100 mg REGN5381 or placebo*. **Part B** (N=258), – 86 participants will receive REGN5381 100 mg IV, – 86 participants will receive REGN5381 ≤300 mg IV, – 86 participants will receive placebo IV. *Cohorts reduced in size with PA4 may have recruited more than the new target enrollment before the amendment is in effect.
Target Population:	The study population includes adults with HFrEF with elevated NT-proBNP receiving stable background therapy for heart failure.
Treatments	
Study Drug **Dose/Route/Schedule:**	REGN5381 drug product is supplied as a lyophilized powder in a sterile single-use vial. Participants will receive REGN5381 as a single IV infusion.
Placebo **Route/Schedule:**	Placebo to match REGN5381, is supplied as a lyophilized powder in a sterile single-use vial. Participants will receive placebo as a single IV infusion.
Procedures and Assessments	Safety assessments will include monitoring of vital signs (temperature, pulse, blood pressure, heart rate, and respiration rate), physical examination,

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

	electrocardiogram (ECG), laboratory testing, and the monitoring and reporting of adverse events (AEs). PD assessment will be determined by measurements of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Samples will also be collected for drug concentration, ADA and biomarker measurements (including, but not limited to cGMP, ANP, BNP, catecholamines, carbohydrate antigen 125 (CA-125), cardiac troponin (hsTnT), KIM-1, and Olink proteomics). Clinical outcome assessments will be assessed through the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D-5L.
Statistical Plan	**Justification of Sample Size** Based on the assumed -25% difference in means of percent change from baseline in NT-proBNP at day 8 (REGN5381 assumed as -35.0% and placebo as -10.0%) , and a pooled standard deviation (SD) of 0.7, a sample size of at least 113 participants per active arm (15 from Part A1, 12 from Part A2, and 86 from Part B), 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. **Efficacy Analyses** The modified intent-to-treat (mITT) population includes all randomized participants who received study drug. The primary endpoint of the study is the change from baseline in NT-proBNP at day 8. The secondary efficacy endpoints include changes from baseline in circulating NT-proBNP at weeks 2, 3, 4 and up to week 16. Efficacy analyses are conducted on the mITT population for participants with common dose levels, aggregated across Parts A1, A2, and B. 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 changes 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, baseline log-transformed NT-proBNP results (continuous), background sacubitril-valsartan therapy (Yes/No), eGFR level (30 to 45 mL/min/1.73 m^2 vs. >45 mL/min/1.73 m^2), visit, treatment-by-visit interaction, baseline-by-treatment interaction and baseline-by-visit interaction. Summary statistics including the least squares (LS) mean, standard error (SE), 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 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. Any NT-proBNP measurements after initiation of rescue therapy or prohibited medications will not be used for either primary or secondary efficacy analyses. **Safety Analyses**

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

	The safety analysis set (SAF) includes all randomized participants who received any study drug. It is based on the treatment as received. Overview of treatment emergent adverse events (TEAEs), TEAEs by primary System Organ Class (SOC) and Preferred Term (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-SAEs by primary SOC and PT, Treatment-related TE-SAEs by primary SOC and PT, TE-AESI (adverse event of special interest) by primary SOC, and PT, Treatment-related TE-AESIs by primary SOC and PT will be summarized by treatment group.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

1. INTRODUCTION

Heart failure is a common worldwide cause of disability, hospitalization, and death (Butrous, 2016). It affects 26 million people globally with a prevalence of about 2% to 3% in the general population, rising to approximately 10% to 20% for those aged >65 years (Ceia, 2002) (Ponikowski, 2016) (Savarese, 2017) Heart failure is the leading cause of hospitalization for those over 65 and its incidence is expected to increase with an aging population (Mozaffarian, 2016) (Azad, 2014) (Butrous, 2016). Heart failure is associated with activation of several compensatory neurohormonal systems that have beneficial as well as maladaptive effects. This includes the sympathetic nervous system, the renin-aldosterone angiotensin system, and the natriuretic peptide system (Hartupee, 2017).

The most common symptoms of heart failure, shortness of breath and exertional fatigue, are primarily due to venous congestion and elevated intracardiac filling pressures (Ponikowski, 2016). In response to elevated intracardiac pressures, atrial and ventricular cardiomyocytes produce and secrete hormones known as natriuretic peptides (Baba, 2019) (Daniels, 2007). The natriuretic peptides Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) are increased in heart failure patients and have significant clinical value in both diagnosis and prognosis (Baba, 2019) (Ponikowski, 2016). Natriuretic peptides have been reported to have diuretic, natriuretic, BP lowering effects, and to inhibit the renin-angiotensin-aldosterone system as well as sympathetic activation (Kerkelä, 2015) (Mangiafico, 2013) (Volpe, 2016).

The pro-peptide NT-proBNP is secreted by cardiomyocytes in response to myocardial pressure and stretch, and reflects the pressure and volume status of the heart (Brandstrup, 2020) (Cwikiel, 2022), two important parameters that determine the clinical status of HF patients. NT-proBNP is increasingly used as a proof of concept and dose selection biomarker for clinical development programs for new heart failure therapies (Butler, 2017) (Filippatos, 2016) (Gheorghiade, 2015) (Pieske, 2017) (Voors, 2019) (Solomon, 2012).

The receptor that mediates the functions of ANP and BNP is known as natriuretic peptide receptor A (NPR-A), which is encoded by the gene natriuretic peptide receptor 1 (NPR1) (note: for simplicity, the sponsor uses NPR1 to refer to both the gene and protein). NPR1 is a membrane-bound guanylate cyclase that mediates the intracellular conversion of guanosine triphosphate to cGMP (Lugnier, 2019). NPR1 is widely expressed, including in the kidneys, vasculature, adrenal glands, and brain (Lugnier, 2019) (The Human Protein Atlas: NPR1, 2005). Clearance of ANP and BNP from the circulation occurs primarily through degradation by matrix metalloproteinases including neprilysin, and via the natriuretic peptide clearance receptor, NPR-C (encoded by the gene NPR3) (Lugnier, 2019) (Mangiafico, 2013).

Data suggest that the high levels of natriuretic peptides observed in heart failure patients may not equate to high levels of NPR1 activation (Lee, 2016). Natriuretic peptides are produced as pro-peptides (proBNP and proANP) that are cleaved, resulting in a 1:1 ratio of NT-proBNP or N-terminal pro-atrial natriuretic peptide (NT-proANP) (inactive) and BNP or ANP, the active ligands for NPR1. These active ligands have short half-lives, and have many truncated forms which have made them challenging to accurately quantify (Lugnier, 2019) (Semenov, 2018). Heart failure patients have increased rates of ANP and BNP degradation (resulting in higher levels of truncated forms of less biologically active ANP and BNP), and additionally may have down-regulation of NPR1 signaling (Baerts, 2012) (Singh, 2006).

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Given the effects of the natriuretic peptides on fluid homeostasis and hemodynamics, the NPR1 pathway has long been a therapeutic target in heart failure. A variety of synthesized natriuretic peptides including nesiritide, ularitide and carperitide have been developed, and their hemodynamic effects are well-characterized in heart failure patients (Ichiki, 2019) (Meems, 2016). Nesiritide, a recombinant human BNP, reduced pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) through its arterial and vasodilatory effects in patients with acutely decompensated heart failure, with consequent significant improvements in dyspnea (Colucci, 2000). Nesiritide is a non-specific (arterial and venous) vasodilator. These peptide NPR1 agonists have limited utility for chronic heart failure management, as they are short-lived molecules that require continuous infusion in a hospitalized setting. Carperitide is approved in Japan for management of acute decompensated heart failure; however, no natriuretic peptides are currently approved by other health authorities.

More recently, sacubitril-valsartan, a combination neprilysin inhibitor and angiotensin II receptor blocker, was shown to improve outcomes in heart failure and was approved for this indication by global health authorities including Food and Drug Administration (FDA) and European Medicines Agency (EMA) (McMurray, 2014) (Entresto (sacubitril and valsartan) [Prescribing Information], 2021). Sacubitril-valsartan is recommended as part of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) (Heidenreich, 2022a) (Maddox, 2024) (McDonagh, 2021), with increasing uptake worldwide. Patients receiving sacubitril-valsartan have lower rates of cardiovascular events and hospitalization as well as better renal outcomes (Myhre, 2019), representing a stable HFrEF population on optimal GDMT. The effects of sacubitril-valsartan are thought to be at least partly mediated through NPR1 receptor activation, as sacubitril inhibits neprilysin-mediated degradation of natriuretic peptides (Entresto (sacubitril and valsartan) [Prescribing Information], 2021). However, sacubitril-valsartan showed only modest elevations of natriuretic peptides in patients with heart failure (Solomon, 2012), and two recent phase 3 studies of sacubitril-valsartan with alternative comparator arms have raised questions regarding the contribution of sacubitril to the observed outcomes in the initial pivotal study (Pfeffer, 2021) (Solomon, 2012) (Solomon, 2019).

The natriuretic peptide pathway remains a promising therapeutic strategy for improving symptoms and clinical outcomes in patients with congested heart failure, and there is a need for better therapies for sustained agonism of NPR1.

REGN5381 is a human immunoglobulin G4-based monoclonal antibody (mAb) that binds and activates NPR1 in both the presence and absence of the endogenous ligands ANP and BNP. REGN5381 is a direct agonist of NPR1 whose long duration of effect may provide sustained hemodynamic control and cardiac unloading compared with current therapies.

REGN5381 induced predictable and persistent reductions of systemic BP in euvolemic normotensive telemetered male cynomolgus monkeys (nonhuman primates [NHP]). Studies in anesthetized canines with invasive hemodynamic monitoring demonstrated that REGN5381 induced acute reductions in systemic BP and central venous pressure (CVP). These data suggest a contribution of venous pressure lowering to the systemic BP effects of REGN5381, perhaps through decreased cardiac filling and consequent decreased stroke volume (SV). However, nonclinical models are limited in defining and predicting the exact hemodynamic effects of REGN5381 in humans, and of particular importance, in participants with congestive heart failure. More nonclinical data are provided in the Investigator's Brochure (IB).

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Evaluate the ability of REGN5381 to improve cardiopulmonary congestion	• Change from baseline in circulating NT-proBNP, a biomarker of cardiopulmonary congestion, at day 8
Secondary	
• Evaluate the safety and tolerability of REGN5381	• Occurrence and severity of TEAEs through the EOS visit (week 16)
• Evaluate the durability of effects of REGN5381 on cardiopulmonary congestion	• Change from baseline in circulating NT-proBNP at weeks 2, 3, 4 and up to week 16
• Evaluate the effects of REGN5381 on hemodynamics	• Change from baseline in SBP, DBP, MAP, and HR at each visit through week 16
• Characterize the drug concentration-time profile of single doses of REGN5381	• Concentrations of REGN5381 in serum through the EOS visit
• Assess the immunogenicity of REGN5381	• Incidence and magnitude of ADAs to REGN5381 through the EOS visit
Exploratory	
[redacted]	

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Objectives	Endpoints
[redacted]	

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

A single dose of REGN5381 decreases circulating NT-proBNP levels in participants with chronic heart failure with reduced ejection fraction (HFrEF) and is sufficiently safe and well tolerated to permit continued clinical investigation.

3.2. Rationale

3.2.1. Rationale for Study Design

The goals of this study are to evaluate the safety and tolerability of a single dose of the NPR1 monoclonal antibody agonist REGN5381 in participants with HFrEF, and to evaluate the early and durable PD effects in this participant population. The study is designed in 2 parts to achieve these goals: Part A1 and Part A2 will evaluate the safety and tolerability of a single IV dose of REGN5381 in sequential ascending dose cohorts with inpatient monitoring to at least day 5 prior to expanding into the larger Part B which occurs in the outpatient setting. The study is designed to detect clinically significant reductions in NT-proBNP, a biomarker of cardiopulmonary congestion. In addition, following the first Part A1 100 mg cohort, the safety of REGN5381 will be evaluated in two additional Part A2 cohorts in participants receiving sacubitril-valsartan at baseline and participants with eGFR 30 to 45 mL/min/1.73 m^2 to acquire safety data in these subgroups in an inpatient monitored setting.

As of Protocol Amendment 4 (PA4), participants on sacubitril-valsartan and participants with low eGFR will be allowed to enroll in Part B (Section 5.1.2.1) while maintaining adequate provisions for participant safety (Section 5.1.3.7).

The Part A2 low eGFR cohort has been closed as of PA4 (Section 5.1.1.1). Participants already enrolled in this group will complete the protocol as scheduled. In addition to Part B, the Part A2 sacubitril-valsartan cohort will require eGFR ≥30 mL/min/1.73 m^2.

Rationale for study design changes in PA4 is described in Section 3.2.3.

3.2.1.1. Endpoints

NT-proBNP as measure of cardiopulmonary congestion (primary and secondary endpoint): The primary objective of the study is to determine whether REGN5381 improves cardiopulmonary congestion, which will be assessed by reductions in plasma concentrations of NT-proBNP, a clinically validated biomarker of cardiopulmonary congestion. Prior NP agonists, such as nesiritide, were recombinant infusions with short duration of activity (half-lives less than an hour), whereas our early data with the antibody agonist REGN5381 predicts achievement of NPR1 saturating levels for at least 3-4 weeks after single dose administration of 100 mg or 300 mg. NT-proBNP will be assessed at timepoints through the end of the study to evaluate the durability of REGN5381 effects on congestion.

Change from baseline in NT-proBNP was selected as a proof-of-concept endpoint because it has several desirable features. NT-proBNP has a half-life around two hours, providing temporal resolution to show acute changes in these cardiac parameters in response to therapy (Weber, 2006). Therapies that work through natriuretic peptides (sacubitril-valsartan) and through cGMP

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

(vericiguat and sacubitril-valsartan) have demonstrated therapeutic decreases in NT-proBNP (Armstrong, 2022) (Velazquez, 2019). NT-proBNP levels predict long term cardiovascular outcomes including death and hospitalization (Goetze, 2020) (McDonagh, 2022).

The treatment difference in terms of percent change from baseline in NT-proBNP is assumed to be -25% between the two arms (eg, REGN5381 is -35.0% and placebo is -10.0%) based on sacubitril-valsartan's effect compared to control in PIONEER-HF (Velazquez, 2019) (-25.7%, treatment difference in percent change from baseline from a time-weighted average of weeks 4 and 8) and in PARAMOUNT (Solomon, 2012) (-19.6%, treatment difference in percent change from baseline at week 12).

NT-proBNP variability and treatment effect assumptions were derived from recent trial of empagliflozin (Januzzi, 2021) in participants with HFrEF and elevated NT-proBNP. In this study, the SD of log (CFB) at week 4 was 0.58 and at week 12 was 0.72 in the control arm, and the control arm percent change from baseline (CFB) was 7% (95% confidence interval [CI] 5-10%) decline in NT-proBNP at week 4. These are taken as estimates for variability for our day 8 primary endpoint, as changes to background therapy, which may impact NT-proBNP levels, are expected to be smaller over 1 week compared to 4-12 weeks reported in similar populations, and the run-in period is designed to reduce endpoint variability.

The time period for evaluating the primary endpoint, baseline through day 8, was chosen because the 100 mg dose level is predicted to maintain concentrations of REGN5381 that saturate the NPR1 receptor and result in maximal PD effects for at least that time period. The 300 mg dose level is predicted to maintain saturating concentrations of REGN5381 to 4 weeks. NT-proBNP levels will also be measured at 2, 3, 4, 8, 12, and 16 weeks to provide an estimate of the durability of REGN5381-induced effects on the NPR1 receptor.

Systolic and diastolic blood pressure as a measure of the hemodynamic effects of REGN5381 (secondary endpoint): Clinical data to date indicates a dose dependent reduction in blood pressure in healthy and mildly hypertensive volunteers. Heart failure participants with cardiopulmonary congestion may have a different response to the expected venodilatory effect of REGN5381, but some participants may experience a decrease in blood pressure. Systolic and diastolic blood pressure will be measured before and after study drug administration and all subsequent study visits.

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VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

[redacted]

3.2.2. Rationale for Dose Selection

REGN5381 doses have been selected based on safety, tolerability, PD and PK from a single ascending dose FIH study in healthy and mildly hypertensive participants (R5381-HV-1987), a single ascending dose study in healthy participants that administers REGN5381 alone and with a reversal agent (R9035-HV-2125), and a single dose study in heart failure participants being hospitalized for clinically indicated right ventricular catheterization (R5381-HF-2159).

Preclinically, the pharmacologic effect of REGN5381 in reducing blood pressures has been studied in multiples studies in non-human primates (NHP) with a dose range covering 0.008 to 25 mg/kg. The lowest dose illustrating a statistically significant SBP reduction (assessed as 24-hour average post dose) was identified at 0.031 mg/kg; the associated C_{max} of 0.8 mg/L (estimated by simulation) was considered as the minimal efficacious concentration. In the study where the highest dose level of 25 mg/kg IV and SC was tested, no additional or excessive reduction in blood pressure was observed when compared to the next lower dose level (5 mg/kg), while the hypotensive effect sustained for the entire 8-week study duration, which indicated that E_{max} was achieved and durable.

In the ongoing R5381-HF-2159 study, an expected dose-dependent immediate reduction in pulmonary capillary wedge pressure (and other hemodynamic parameters) has been observed after administration of the 100- and 300-mg doses in HFrEF participants.

Single IV doses of up to 300 mg were found to be tolerable in healthy volunteers. Single IV doses of up to 300 mg were administered to participants with heart failure with reduced ejection fraction, and 2 potentially related SAEs (one Grade 4 and one Grade 5) were observed in two participants with potentially contributing comorbidities (see Section 3.3). Therefore, this study will begin with single IV dose of 100 mg which was well tolerated in all participants, including those with HFrEF, and is predicted to achieve active levels for at least 2 weeks. In addition, this study will focus on a more stable population that is predicted to be able to tolerate venodilation. If 100 mg is well tolerated, the dose will be escalated up to 300 mg (see Figure 1).

Based on PK data from all the studies conducted to date (R5381-HV-1987, R9035-HV-2125, and R5381-HF-2159) saturation of the TMC pathway was evident at concentrations in serum exceeding ~1-5 mg/L depending on the population. As such, single doses of 100 mg and 300 mg IV have been selected are predicted to saturate the NPR1 receptor in this study population for > 2 weeks.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

REGN5381 was well-tolerated in healthy and mildly hypertensive participants when administered as single doses from 0.3 mg to 300 mg IV and 30 and 100 mg SC. In addition, the exposure (cumulative AUC) achieved at the NOAEL of 15 mg/kg SC in a 26-week GLP compliant toxicology study in NHPs was approximately 130-fold greater than the predicted AUC following a single dose of 300 mg (highest proposed dose) in the clinic; the corresponding C_{max} comparison resulted in approximately 9.6-fold margins. Therefore, considering both maximal concentration and total exposure following, the proposed 300 mg IV dose is not expected to exceed exposures experienced in the program already.

Results from this study will ultimately facilitate dose and regimen selection for future studies.

3.2.3. Rationale for Study Design Changes in Protocol Amendment 4

Participants on Sacubitril-Valsartan

- **Reduction in Size of Sacubitril-Valsartan A2 Cohort**

  Based on the accumulating safety profile of REGN5381 and the expanding use of sacubitril-valsartan, the A2 sacubitril-valsartan cohorts are being modestly reduced in size to allow sacubitril-valsartan in Part B earlier. Because Part B has a larger site footprint, this will allow a greater number of study participants on sacubitril-valsartan to be dosed, and the Part B population will better reflect the global standard of care.

- **Inclusion of Sacubitril-Valsartan in Part B**

  Recognizing the increasing role of sacubitril-valsartan in the standard of care for chronic HFrEF, participants receiving background sacubitril-valsartan therapy will be included in Part B of the study following the evaluation of safety data from the sacubitril-valsartan group in Part A2. By tolerating a stable dose of background sacubitril-valsartan therapy and with systolic blood pressure meeting study inclusion criteria, these participants demonstrate tolerance of a vasodilator in general, and more specifically, activation of the NPR1 pathway via the effects of sacubitril.

Participants with Low eGFR

- **Low eGFR A2 Cohort Closed to Further Enrollment**

  Participants with low eGFR and HF represent a population of greater unmet need and may benefit more from NPR1 activation. Part B has a larger site footprint, facilitating more extensive study of this small but important subpopulation that has not enrolled sufficiently in the smaller site footprint of Part A.

- Inclusion of Low eGFR in Sacubitril-Valsartan A2 Cohort

  Participants with low eGFR and receiving sacubitril-valsartan as background therapy will be allowed to enroll in the Part A2 sacubitril-valsartan cohort. Participants receiving sacubitril-valsartan have lower rates of cardiovascular events and hospitalization as well as better renal outcomes, and participants who have both HF and CKD have been identified as potentially having greater benefit from this therapy. With increasing effort in achieving GDMT in this subpopulation, inclusion of low eGFR participants in the sacubitril-valsartan cohort makes the study population more representative of the HF population.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

- **Inclusion of Low eGFR in Part B**

  Participants with low eGFR (defined as 30–45 mL/min/1.73 m^2) will be allowed to enroll in Part B of the study. This decision is based on safety data to date in this and other studies with REGN5381, which do not suggest an adverse effect on renal function. Furthermore, the inclusion/exclusion criteria in place (including pulmonary hypertension exclusion, SBP >110 mm Hg requirement) minimize the risk of hypotension and hypotension-related renal injury.

  For participants in Part B with eGFR 30 to 45 mL/min/1.73 m^2, there will be an additional visit 48 to 96 hours after study drug administration (3 days post dose, ±1 day). Activation of the NPR1 pathway has been shown to benefit participants with HF and reduced eGFR. However, concern remains that participants with low eGFR are at risk of acute kidney injury (AKI) in response to vasoactive agents. Should AKI occur, evidence of it is typically apparent 24 to 72 hours following the hemodynamic insult. Thus, an additional visit 2 to 4 days after the date of infusion is appropriate for early detection of AKI.

3.3. Risk-Benefit

Heart failure affects 26 million people globally (Ceia, 2002) (Ponikowski, 2016) (Savarese, 2017) and is a leading cause of disability, hospitalization and death (Butrous, 2016). Heart failure is the leading cause of hospitalization for those over 65 and its incidence is expected to increase with an aging population (Mozaffarian, 2016) (Azad, 2014) (Butrous, 2016). Heart failure symptoms include dyspnea, fatigue, edema and exacerbations of these symptoms are often the result of increased venous congestion and elevated intracardiac filling pressures (Ponikowski, 2016). Despite guidelines recommending the “four pillars” of heart failure therapy that includes beta blockers; ACEi, ARBs, or ARNIs; MRAs; and SGLT2 inhibitors; unmet need continues (McMurray, 2019). Furthermore, compliance to HF therapy has been a challenge and becomes even more limited in patients with CKD who may not tolerate medications that inhibit the renin-angiotensin-aldosterone system (Patel, 2021). Therefore, there is an unmet need for therapies that have a sustained favorable action on HF pathophysiology that lack some of the limiting factors such as hyperkalemia seen with ACEi, ARBs, ARNIs, and MRAs.

Based on the literature, the NPR1 pathway is thought to play a critical role in fluid homeostasis, sodium balance, and vasodilation. Agonism of this pathway is thought to be beneficial to patients suffering from heart failure, kidney disease, and hypertension. Recombinant natriuretic peptides have been developed and have demonstrated reductions in pulmonary capillary wedge pressure, systemic vascular resistance, and dyspnea (Colucci, 2000) an d show no effect on serum potassium levels (Elkayam, 2002). However, due to the short half-lives of natriuretic peptides, short-term infusion of nesiritide for 1-7 days was shown not to decrease the rate of death or rehospitalization in patients with acute heart failure (O'Connor, 2011). It is hypothesized that a long acting NPR1 agonist like REGN5381 could have sustained beneficial effects on cardiac hemodynamics and patient symptoms while lacking any effect of serum potassium concentrations. A long-acting therapy with the potential for infrequent dosing could also improve compliance in HF patients.

Preclinical studies to date have demonstrated that REGN5381 binds to the NPR1 receptor and causes a sustained but predictable reduction in blood pressure. This may benefit patients with congestive heart failure or chronic kidney disease by reducing venous congestion.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Based on the mechanism of action, potential risks for REGN5381 include symptomatic hypotension, symptomatic tachycardia, worsening renal function in patients with heart failure, systemic hypersensitivity reactions, embryofetal toxicity, and immunogenicity (anti-REGN5381 antibody formation).

Clinical experience with recombinant ANP and BNP in patients with congestive heart failure (Saito, 1987), suggests that administration of an NPR1 agonist leads to lowering of CVP concurrent with changes in SV (reflecting low venous pressures and diminished cardiac filling) without an obvious change in systemic BP. Congestive heart failure patients have elevated CVPs and SV was shown to improve when congestive heart failure patients receive treatment with the NPR1 agonist nesiritide (Saito, 1987). In fact, the lowering of venous pressures is the therapeutic goal in congested patients and is the mechanism by which they are decongested resulting in dyspnea relief.

Low dose nesiritide decreased plasma creatinine and blood urea nitrogen in patients with decompensated heart failure, suggesting that NPR1 agonism may have renal protective effects (Riter, 2006). Nonclinical data in two animal models of chronic kidney disease suggest REGN5381 may have renal protective effects, slowing the glomerular filtration rate decline and improving mortality (see IB for details). By improving cardiopulmonary congestion in patients with decompensated heart failure, REGN5381 may reduce escalating diuretic doses and prolonged courses that increase acute kidney injury risk. Conversely, blood pressure lowering effects from the vasodilatory action of REGN5381 could have an adverse effect on renal function.

Dose levels up to 300 mg of REGN5381 have been well-tolerated in two healthy volunteer studies (R5381-HV-1987 and R9035-HV-2125) to date. Hemodynamic data from these studies show dose-dependent reductions in SBP and an increase in heart rate.

An ongoing study (R5381-HF-2159) in participants with HF and a clinical indication for right heart catheterization has been assessing REGN5381 in dose levels up to 300 mg IV. Available safety data so far from this study, found REGN5381 to have a reasonable safety and tolerability profile in HF participants both with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Blinded aggregate analysis of hemodynamic data from participants with HFrEF receiving single IV doses of REGN5381 or placebo in this study shows reductions in PCWP apparent in a cohort receiving 100 mg or placebo, and in a cohort receiving 300 mg or placebo. In the current study (R5381-HF-22118), 36 participants have been dosed with REGN5381 or placebo (data cutoff 01 Apr 2025).
Available data from completed and ongoing clinical studies as well as nonclinical data demonstrate potentially beneficial hemodynamic effects of REGN5381 that include reductions in systemic BP in healthy normotensive and mildly hypertensive participants and reductions in PCWP in participants with HF, effects which are consistent with its mechanism of action. Please refer to the IB for further details.

3.3.1. Design Elements to Ensure Participant Safety

The current study has several design elements aimed at ensuring participant safety, informed by the safety experience to date in participants with heart failure, including (1) careful participant selection, (2) 90-day run-in period, (3) inpatient monitoring in Part A, (4) Part A with single ascending dose design, (5) careful consideration of safety data by the sponsor before dose escalation (6) IDMC oversight:

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

3.3.1.1. Participant Selection

- BP exclusion criteria: REGN5381 has the potential to lower BP in participants with HFrEF. Therefore, BP evaluations during screening and prior to randomization will be performed to ensure that trial participants have sufficient systemic BP to tolerate any BP lowering by REGN5381. For 30 days before randomization, the SBP must be 110 to 160 mm Hg. This excludes low SBP to provide a safety margin for hypotension.
- Enrollment of participants with cardiopulmonary congestion: The inclusion criteria were designed to select participants with sufficient venous hypertension and cardiopulmonary congestion who will best tolerate venous vasodilation by REGN5381. Participants with cardiopulmonary congestion will be identified through the presence of elevated NT-proBNP. The NT-proBNP thresholds used to select participants for enrollment in this study have >80% specificity for cardiopulmonary congestion in participants in emergency departments (Januzzi, 2005) (Panagopoulou, 2013) and are similar to thresholds used in previous studies of investigational agents in the ambulatory chronic heart failure population. Based on previous clinical trials of nesiritide and sacubitril-valsartan (Fitzgerald, 2005) (Velazquez, 2019), these inclusion criteria are chosen to enroll a population that is likely to be responsive to NPR1 agonism.
- Exclusion of participants with recent HF hospitalization: The period following a HF hospitalization is a period of time when participants are at highest risk for death and rehospitalization. Heart failure readmission and mortality remains elevated after discharge, with readmission rates declining by half approximately 5 weeks post discharge and mortality declining by half approximately 2 weeks post discharge (Dharmarajan, 2017). With the goal of avoiding this high-risk time period, this study will exclude participants less than 6 months after hospital discharge at the time of randomization.
- Optimization of background HF therapy: Participants on optimal guideline-directed therapy for heart failure have lower rates of adverse events including hospitalization and death. This study will include a run-in period that will allow optimization and stabilization of background therapy.
- Exclusion of severe pulmonary hypertension: Participants with greater than moderate pulmonary hypertension are excluded by medical history or recent (<3 months) echocardiography. REGN5381 is a vasodilator with preferential effects on venous vasculature, and it is possible that participants with more than moderate pulmonary hypertension may be predisposed to hypotension and/or end-organ dysfunction in response to venodilation.
- Exclusion of chronic liver disease: Participants with liver disease might have lower systemic vascular resistance and increased sensitivity to vasodilators. Therefore, participants with chronic liver disease are excluded in case these participants are more sensitive to REGN5381 pharmacologic effects.
- Exclusion of low eGFR (<30 mL/min/1.73 m^2): Transient hypotension, intravascular volume depletion, and medication-induced acute kidney injuries are potential

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

precipitants of worsening renal function in participants with heart failure. Participants with severe renal disease (eGFR <30 mL/min/1.73 m^2) will be excluded to provide a margin of safety for acute renal injury that may result from changes in hemodynamics and to minimize disease-related AEs of acute kidney injury.

- Exclusion of participants with severely reduced LVEF (<20%): Participants with a severely reduced EF are at greater risk of hypotension. Participants will be required to have a recent echocardiogram within the last 3 months to confirm they have an LVEF ≥20%.
- Exclusion of participants with more than moderate valvular disease: Participants with HF and severe valvular disease may be at higher risk of hypotension secondary to vasodilation. Participants will be required to have a recent echocardiogram within the last 3 months to confirm they do not have more than moderate valvular disease.
- Exclusion of participants with any history of requiring positive inotropic support: Participants with a history of management with positive inotropic agents such as dobutamine are at higher risk of low output heart failure and hemodynamic instability.

3.3.1.2. Run-in Period

The 90-day run-in period establishes clinical stability over time prior to the study drug administration, allowing the exclusion of participants on a markedly deteriorating trajectory, such as participants who experience acute decompensated heart failure. The run-in period will also allow participants to have their background heart failure medication adjusted if necessary to achieve stability of medical regimen by the time of randomization, reducing the need for titration during the study treatment period. Further, optimization of guideline-directed medical therapy reduces adverse clinical events in heart failure participants. The requirement of stable diuretic and vasodilator therapy during the final 30 days of the run-in also reduces NT-proBNP variability leading into the treatment period.

3.3.1.3. Inpatient Monitoring

The hospital setting facilitates assessment of the safety of administration of REGN5381 by allowing frequent blood pressure and safety lab assessments as well as allowing rapid treatment of any AEs. The duration of inpatient safety monitoring in Part A1 and A2 is 4 days after the day of study drug administration (to study day 5), which permits safety monitoring in the hospital setting that extends beyond the time of expected peak hemodynamic effects. In the inpatient setting, such events can be identified and managed rapidly. Data from the first-in-human study (R5381-HV-1987) demonstrated that peak hemodynamic effects of REGN5381 were observed within 24 hours of the IV infusion. The two SAEs in heart failure participants electively admitted for right heart catheterization (R5381-HF-2159) became evident clinically or by abnormal laboratory values between 24- and 72-hours post-dose.

3.3.1.4. Low eGFR

As described in Section 5.1.2.1, an early safety review will be performed by the Sponsor in the first 6 participants who enter Part B with eGFR 30 to 45 mL/min/1.73 m^2 after the sixth participant has completed the day 29 visit. While this early assessment of safety is being performed, no more than 3 additional participants with an eGFR of 30 to 45 mL/min/1.73 m^2 may be randomized until

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

the safety review is completed. Enrollment of participants with low eGFR will continue only if supported by safety data.

Low eGFR participants in Part B will have an additional visit 48 to 96 hours after the study drug administration (day 4±1 day). Serum chemistry from this visit will be reviewed by the investigator at or before the day 8 visit to evaluate renal function.

In addition to these safety measures, specific stopping criteria for enrollment of participants with low eGFR are described in Section 5.1.5.1.

3.3.1.5. Dose Escalation and Cohort Progression

Part A1 will evaluate the 100 mg and ≤300 mg dose levels sequentially in small cohorts to ensure sufficient safety and tolerability at these dose levels prior to expanding to a larger Part B in which participants will be randomized to 100 mg, ≤300 mg or placebo. Part A1 will be performed at a limited number of sites that are selected for the ability to have extensive communication with the sponsor, and that employs a dose escalation design to obtain additional safety experience prior to proceeding with a higher dose level. After evaluating safety through the ascending dose design of Part A1, Part B will open additional sites and enroll up to three parallel arms to facilitate the completion of the proof-of-concept study. The Part A2 cohort with participants on background sacubitril-valsartan therapy may begin after safety data is obtained and tolerability through day 8 is established in the first 100 mg cohort in Part A1, due to the overlapping mechanism of action of REGN5381 that may increase blood pressure effects. The Part A2 cohort with low eGFR may begin only after safety data is obtained and dose tolerability is established in the first 100 mg cohort in Part A1, due to sensitivity to blood pressure changes and concerns for acute worsening of kidney function in this subpopulation.

3.3.1.6. Background Therapy, Prohibited, and Permitted Medications

Participants must remain on a stable background therapy regimen for heart failure for at least 30 days prior to randomization until the end of study visit to (1) ensure that baseline plasma NT-proBNP concentrations reflect a clinically stable state of the participant, and (2) to permit evaluation of the PD effects of REGN5381 without confounding effects of changes to background therapy. A period of stable background therapy for outpatients with HFrEF is consistent with standard of care practices when a new investigational therapy is initiated. Exceptions to a stable background therapy regimen during this time period are made for adjustment of medical therapy as needed and for safety reasons (eg, management of hypotension and laboratory abnormalities).

Other than sacubitril-valsartan, heart failure medications that act via NPR1 (carperitide) or act through cGMP, a downstream PD effect of NPR1 agonism (vericiguat, sildenafil), are excluded from the study to avoid any potential overlap with the mechanism of action of REGN5381.

Participants with any history of requiring positive inotropic medications will be excluded, as they are at higher risk of low output heart failure, hemodynamic instability, and hypotension. However, positive inotropic medications will not be prohibited during the inpatient period after study drug administration as they may be required if the participant's clinical status were to worsen.

The evaluation of participants with HFrEF receiving background sacubitril-valsartan combination therapy is planned in a separate cohort and subsequently in Part B, since (1) sacubitril-valsartan combination therapy is increasingly used for HFrEF worldwide, and (2) preclinical data suggest

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

that REGN5381 has additional PD effects in the presence of sacubitril-valsartan. Recognizing the increasing role of sacubitril-valsartan in the standard of care for chronic HFrEF, participants receiving background sacubitril-valsartan therapy will be included in Part B of the study following the evaluation of safety data from the sacubitril-valsartan group in Part A2. By tolerating a stable dose of background sacubitril-valsartan therapy and with systolic blood pressure meeting study inclusion criteria, these participants demonstrate tolerance of a vasodilator in general, and more specifically, activation of the NPR1 pathway via the effects of sacubitril.

Recognizing that an event of unforeseen circumstances, eg, COVID-19 restrictions/national/international emergencies may have an impact on the conduct of clinical trials, the sponsor does not intend to screen any participants in this study until the impact of the emergency is deemed manageable and no longer interfering with the conduct of studies at individual sites, and participants can safely participate in this study.

The continuity of clinical study conduct dictated by the schedule of events and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Any study data collected using an alternative mechanism will be documented.

More detailed information about the known and expected benefits and risks of REGN5381 may be found in the IB.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics, medical history, and medication history for each participant.

4.2. Safety Variables

The safety variables include blood pressure, heart rate, other vital signs (eg, temperature and respiratory rate), physical examination, electrocardiograms (ECGs), laboratory evaluations (hematology, chemistry, and urinalysis), and monitoring AEs.

4.3. Pharmacokinetic Variables

The PK variables include the concentrations of total REGN5381 and time. The sampling timepoints are specified in Table 1, Table 2, Table 3.

4.4. Immunogenicity Variables

The immunogenicity variables include ADA status (positive or negative), magnitude, and nominal time-point/visit.

The sampling timepoints are specified in Table 1, Table 2, and Table 3.

4.5. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and biomarker variables include cGMP, NT-proBNP, NT-proANP, ANP, BNP, catecholamines, CA-125, cardiac troponin (hsTnT), KIM-1, and Olink proteomics.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

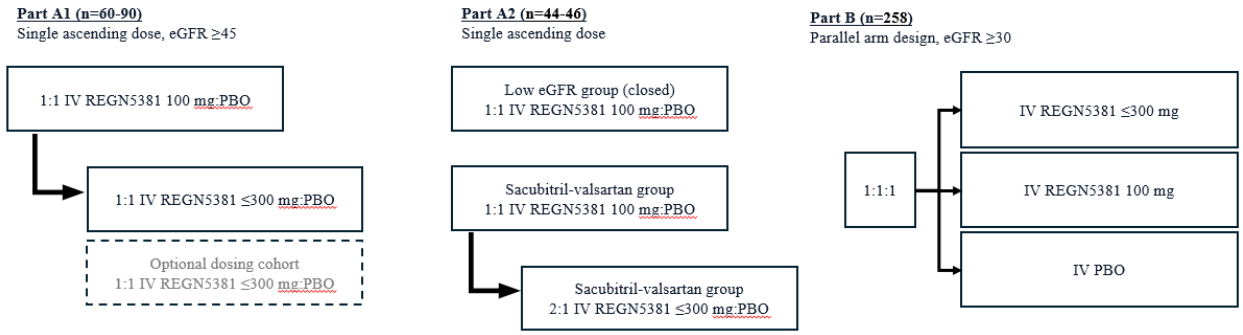
5. STUDY DESIGN

5.1. Study Description and Duration

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 eGFR (30 to 45 mL/min/1.73m^2). The low eGFR group has been closed as of PA4. Participants already enrolled in this group will complete the protocol as scheduled (See Section 5.1.1.1.2 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



5.1.1. Study Design: Part A1 and Part A2

Part A1 and Part A2 have a randomized, double-blind, placebo-controlled, single ascending dose escalation design and will evaluate the safety, PK and PD of a single dose of IV REGN5381 versus placebo with a 4-day post-randomization inpatient monitoring period.

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

- REGN5381 100 mg IV or placebo IV (n=30; 15/arm)
- REGN5381 ≤300 mg IV or placebo IV (n=30; 15/arm)
- Optional Part A1 Cohort: REGN5381 ≤300 mg IV or placebo IV (n=30; 15/arm)

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.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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

- Sacubitril-valsartan cohort: (n=42)
  - 24 participants (12/arm) will receive 100 mg REGN5381 or placebo*,
  - 18 participants (12 active; 6 placebo) will receive ≤300 mg REGN5381 IV*.
- 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 PA4 may have recruited more than the new target enrollment before the amendment is in effect.

Initiation of subsequent dosing cohorts with higher doses in Part A1 and Part A2 will only occur after evaluation of safety of REGN5381 in prior cohorts by the sponsor (see Section 5.1.3.2). The sacubitril-valsartan cohort and low eGFR cohort in Part A2 may run parallel to the higher dose cohorts that follow the 100 mg cohort in Part A1.

5.1.1.1. Changes to Part A2 in Protocol Amendment 4

5.1.1.1.1. Sacubitril-Valsartan Cohort in Part A2

The number of participants in the Part A2 sacubitril-valsartan cohort has been reduced, while Part B has been expanded by approximately the same number of participants to maintain overall study enrollment.

The Part A2 sacubitril-valsartan cohort will require eGFR ≥30 mL/min/1.73 m^2.

5.1.1.1.2. Low eGFR Cohort in Part A2

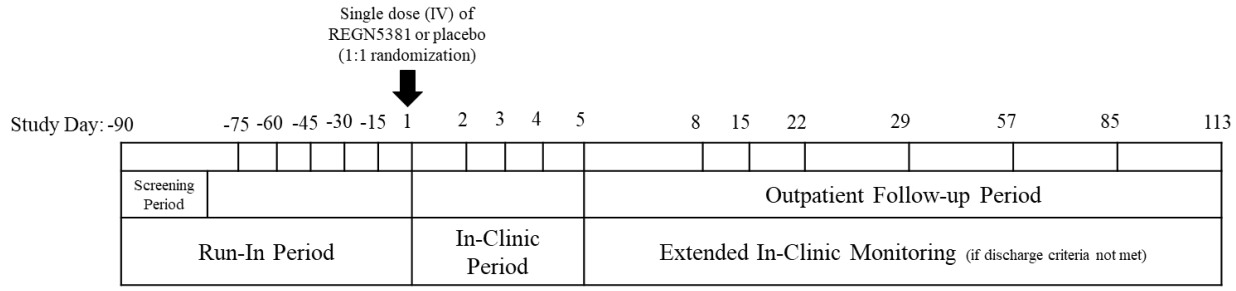
Enrollment for the Part A2 low eGFR cohort has been closed to further enrollment, and Part B has been increased in size by approximately the same number of participants to maintain overall study enrollment. Participants already enrolled in this group will complete the protocol as scheduled. The participant population (with exception of the eGFR cutoff) and schedule of events will be identical to the other cohorts in Part A1.

5.1.1.2. 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, PK, and PD (see Figure 2).

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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



Screening Period

Participants will be screened for eligibility in the initial screening visit (day -90). Participants must provide informed consent to be eligible for randomization and enrollment in the study. Procedures during the Screening Period can be performed over several days, if needed. Participants are required to have an NT-proBNP ≥800 pg/mL (≥1000 pg/mL if in atrial fibrillation) during the Screening Period (visit 1) and NT-proBNP ≥600 pg/mL (≥800 pg/mL if in atrial fibrillation) at visit 5, around 30 days prior to randomization.

Rescreening is allowed for participants who failed screening at an earlier time point. Participants who fail screening may be screened one additional time. Some procedures may not need to be repeated if they were previously completed within 28 days (±7 days) prior to first dose. Participants that fail screening due to sacubitril-valsartan or eGFR inclusion criteria during run-in do not need to repeat the run-in period to be enrolled in a different cohort for which they meet criteria.

Run-in Period

After initial screening visit, participants will enter a 90-day run-in period consisting of two in-person visits (visits 3 and 5) and three telephone visits (visits 2, 4, and 6). Eligibility will be assessed in both in-person visits during the Run-in Period. NT-proBNP will be assessed for eligibility in the second visit during the Run-in Period (visit 5). Background therapy may be adjusted by the investigator according to local guidelines up through day -30. The dose and regimen of background heart failure therapies should remain stable for 30 days prior to the study drug administration. If a participant has background medication(s) for heart failure adjusted within 30 days prior to randomization, visit 5 may be repeated once to recheck NT-proBNP approximately 30 days prior to randomization. At a minimum, this regimen should include a beta-blocker (unless contraindicated or previously not tolerated) and at least one of the following: an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or hydralazine. This regimen may also include stable doses and regimens of loop and/or thiazide diuretics, mineralocorticoid receptor antagonists, SGLT2 inhibitors, and/or other standard of care therapies other than the prohibited therapies listed in the protocol.

Refer to Section 7.10 for complete detail on management of concurrent medications including rescue therapies. There will be no restrictions to dietary intake during the study.

No study drug will be administered during the run-in period. At visit 5, participants will be reevaluated for inclusion into the study including sample collection of NT-proBNP.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Inpatient Period

After completion of the Run-In Period, participants will be admitted to an inpatient facility on day 1 for study drug administration and safety monitoring through day 5. Assessments for eligibility prior to randomization include blood pressure, heart rate, and ECG. Baseline assessments, including blood draws for central laboratory testing (NT-proBNP, serum chemistry, urine creatinine, and hematology) and questionnaires for patient-reported outcomes (PROs), will also be performed prior to study drug administration.

All participants will receive a single dose of REGN5381 IV or placebo IV on the day 1 visit. After study drug administration, participants will have blood pressure and heart rate checked approximately 1, 2, 4, and 8 hours after the end of study drug administration then approximately every 8 hours. ECGs will be performed multiple times after study drug administration. Participants will have continued monitoring during the Inpatient Period with assessment of vital signs, serum chemistry, and hematology.

Participants are eligible to be discharged on day 5 if the following criteria are met in Part A1 and Part A2:

- Participant has completed day 5 safety assessments (see Table 1),
- Absence of symptomatic hypotension (defined as SBP <100 mm Hg with associated symptoms, eg, lightheadedness, dizziness),
- No clinically significant changes in local safety labs drawn on the day of discharge (according to local lab results), in the opinion of the investigator,
- Absence of a TEAE that, in the opinion of the investigator, requires ongoing in-hospital monitoring.

If one or more of the Discharge Criteria are not met on day 5, discharge may occur at any point after day 5 per the clinical judgment of the investigator in consultation with the sponsor. Discharge Criteria should be evaluated during the extended inpatient visit(s).

Complete assessments and procedures during the inpatient period are outlined in Table 1 and Table 2.

Outpatient Period

Participants will be monitored for 16 weeks after the study drug administration. Safety assessments throughout the study will include vital signs, laboratory tests (hematology and chemistry), physical examination, and monitoring for AEs (see Table 3). At the discretion of the investigator and in consultation with the sponsor, participants may continue to receive additional monitoring for ongoing unresolved AEs after week 16.

5.1.1.3. Optional ≤300mg Dosing Cohort in Part A1

Approximately 30 participants may be randomized 1:1 to receive a single dose of REGN5381 ≤300 mg or placebo in each cohort. This optional cohort may be initiated at an intermediate dose (a dose between 100 mg and 300 mg) if REGN5381 is not well-tolerated at the 300 mg dose level, to obtain additional PK data at an intermediate dose, or may be initiated at 100 mg or 300 mg dose level for additional data for these doses with Part A1 monitoring to inform Part B. They will follow

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

the Part A1 and Part A2 schedule of assessments, including a requirement to remain under inpatient observation up to day 5 and follow the same guidelines for the management of heart failure medical therapy and Discharge Criteria.

5.1.1.4. Sacubitril-Valsartan Cohorts in Part A2

These cohorts may be initiated after the last participant in the initial 100 mg cohort in Part A1 completes day 8 safety assessments and this data has been reviewed. After all participants in the 100 mg cohort on background sacubitril-valsartan completes day 8 safety assessments and this data is reviewed, the ≤300 mg cohort may be initiated. Available efficacy and safety data from other completed or ongoing clinical studies may also inform initiation of this cohort. The participant population (with exception of sacubitril-valsartan use) and schedule of events will be identical to the other cohorts in Part A1. These cohorts may run parallel to the higher dose cohorts that follow the 100 mg cohort in Part A1.

5.1.1.5. Low eGFR Cohorts in Part A2

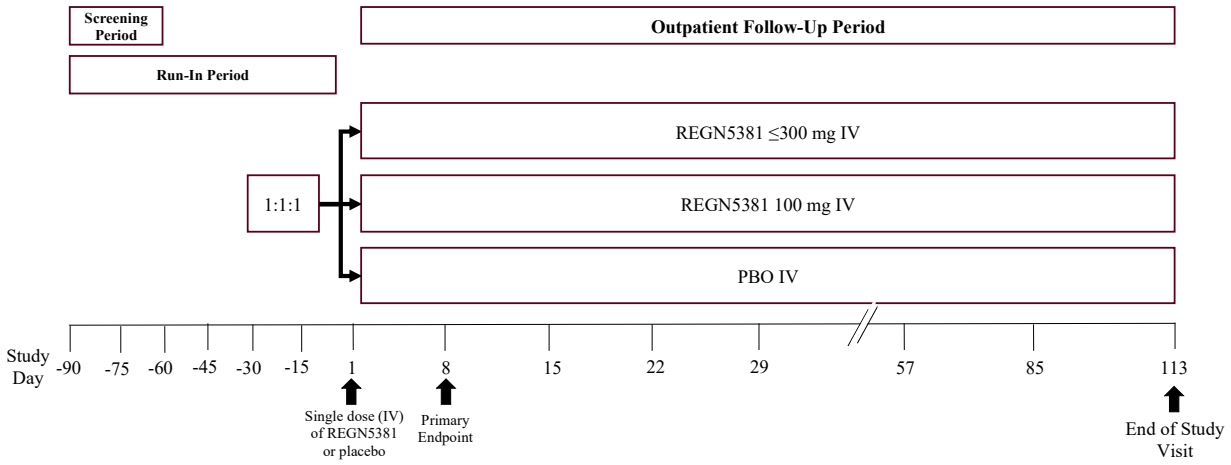
The A2 low eGFR cohort has been closed as of PA4 (see Section 5.1.1.1.2 for additional details).

These cohorts may be initiated after the last participant in the initial 100 mg cohort in Part A1 completes day 8 safety assessments and this data has been reviewed. Available efficacy and safety data from other completed or ongoing clinical studies may also inform initiation of this cohort. The participant population (with exception of the eGFR cutoff) and schedule of events will be identical to the other cohorts in Part A1. These cohorts may run parallel to the higher dose cohorts that follow the 100 mg cohort in Part A.

5.1.2. 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).

Figure 3: Study Flow Diagram for Part B



VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

The decision to initiate Part B is described in Section 5.1.3.6. .

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

- REGN5381 100 mg IV
- REGN5381 ≤300 mg IV
- 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 (see Figure 3 and Table 2).

After study drug administration, participants will be monitored in the clinic for a minimum of 2 hours after completion of study drug infusion. Safety assessments after study drug administration will include assessment of blood pressure, heart rate, and respiratory rate. Participants will return to the clinic for follow-up assessments described in Table 3.

5.1.2.1. **Changes to Part B in Protocol Amendment 4**

5.1.2.1.1. Participants on Sacubitril-Valsartan in Part B

Participants receiving sacubitril-valsartan as background therapy will be allowed to enroll in Part B of the study. Refer to Section 5.1.3.7 for additional details.

5.1.2.1.2. Participants with Low eGFR in Part B

Participants with low eGFR (defined as 30 to 45 mL/min/1.73 m^2) will be allowed to enroll in Part B of the study. The first 6 participants with eGFR 30 to 45 mL/min/1.73m^2 in Part B will be randomized to REGN5381 100 mg, 300 mg, or placebo at 2:2:2. As described in Section 3.3.1.4 an early safety review will be performed in the first 6 participants who enter Part B with eGFR 30 to 45 mL/min/1.73 m^2 after the sixth participant has completed their day 29 visit. While this early assessment of safety is being performed, no more than 3 additional participants with an eGFR of 30 to 45 mL/min/1.73 m^2 may be randomized to study drug until the safety review is completed. Screening may be paused, if necessary, to avoid exceeding the additional 3 participants randomized.

For participants in Part B with an eGFR of 30 to 45 mL/min/1.73 m^2 based on the most recent result obtained prior to visit 7 (typically at visit 5, unless testing is repeated), an additional safety visit is required. The visit will occur 2 to 4 days after study drug administration (3 days post dose, ±1 day). Serum chemistry results from this visit will be reviewed by the investigator as soon as available, at or before the study day 8 visit to evaluate renal function. This chemistry lab test may be performed utilizing the local or central laboratory at the investigator's discretion.

In addition to these safety measures, specific stopping criteria for enrollment of participants with low eGFR are described in Section 5.1.5.1.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

5.1.3. Description of Study Cohorts and Dose Escalation

5.1.3.1. Study Cohorts Part A

In Part A1, up to approximately 60 participants will be enrolled into single ascending dose cohorts (30/cohort) (or up to 90 participants if the optional dose cohort is enrolled). In Part A2, up to approximately 46 participants will be enrolled into the sacubitril-valsartan and low eGFR cohorts. Participants will be randomized to receive a single IV dose of REGN5381 or placebo with approximate numbers of participants as follows:

- Part A1:
  - REGN5381 100 mg or placebo (n=30; 15/arm)
  - REGN5381 ≤300 mg or placebo (n=30; 15/arm)
  - Optional ≤300 mg cohort: REGN5381 ≤300 mg IV or placebo (n=30; 15/arm)
- Part A2:
  - Sacubitril-valsartan cohort (n=42)*:
    - REGN5381 100 mg IV or placebo* (n=24; 12/arm),
    - REGN5381 ≤300 mg IV or placebo* (n=18, 12 active; 6 placebo)
  - Low eGFR (30 to 45 mL/min/1.73 m^2) cohort (n=2-4, randomized 1:1)*: REGN5381 100 mg IV or placebo. The low eGFR group has been closed as of PA4. Participants already enrolled in this group will complete the protocol as scheduled.

*Cohorts reduced in size with PA4 may have recruited more than the new target enrollment before the amendment is in effect.

5.1.3.2. Dose Escalation

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, 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.

5.1.3.3. Decision to Initiate Sacubitril-Valsartan Cohorts in Part A2

The decision to initiate the sacubitril-valsartan cohorts will be made following a review of safety data from the 100 mg dose cohort in Part A1 by the sponsor after the last participant in that cohort completes day 8 safety assessments. Available safety data beyond day 8 will be included for those participants that have progressed further in the study.

5.1.3.4. Decision to Initiate Low eGFR Cohorts in Part A2

The decision to initiate the low eGFR cohorts will be made following a review of safety data from the 100 mg dose cohort in Part A1 by the sponsor after the last participant in that cohort completes day 8 safety assessments. Available safety data beyond day 8 will be included for those participants

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

that have progressed further in the study.

5.1.3.5. Part B

In Part B, up to approximately 258 participants will be enrolled into 3 arms (86/arm). Participants will be randomized to receive a single IV dose of REGN5381 or placebo with approximate numbers of participants as follows:

Part B (N=258)

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

5.1.3.6. Decision to Initiate Part B

The decision to initiate Part B will be made following a review of safety data from Part A1 by the sponsor after the last participant in the Part A1 ≤300 mg dose cohort (or optional ≤300 mg dose cohort) completes day 8 safety assessments. Available safety data beyond day 8 will be included for those participants that have progressed further in the study. Additional safety measures may be implemented following review of the safety data in Part A1 in consultation with the IDMC.

5.1.3.7. Decision to Initiate Inclusion of Participants on Background Sacubitril-Valsartan in Part B

The decision to include participants on background sacubitril-valsartan in Part B will be made following a review of safety data from Part A2 by the sponsor after the last participant in the Part A2 sacubitril-valsartan cohort ≤300 mg dose cohort completes day 8 safety assessments. Available safety data beyond day 8 will be included for those participants that have progressed further in the study. Randomization of participants on sacubitril-valsartan therapy in Part B will begin only after the evaluation of the Part A2 sacubitril-valsartan safety data.

5.1.4. Provision of Sacubitril/Valsartan to Study Participants After Trial Completion

After completion of the EOS visit, participants may be offered sacubitril/valsartan if they meet the local treatment guidelines and at the Principal Investigator's discretion. The Sponsor will provide funding for the site(s) to pay for sacubitril/valsartan for up to 1 year for each eligible participant, subject to national requirements and local regulations. To be eligible, participants must complete the study and must commence treatment within 3 months of the EOS visit. Administration of sacubitril/valsartan is solely at the discretion of the investigator, is not considered to be a part of this clinical trial, is the responsibility of the investigator and treating physicians. No data will be collected by the Sponsor.

5.1.5. Study Stopping Rules

If 1 fatal event related to study drug were to occur during this study, then the study will be paused; no other participant will be dosed until further notice, including the cohort currently being dosed (ie, dosing of study drug in all study participants will be paused) while the sponsor, in consultation with the IDMC, evaluates whether the study stopping criterion has been met. If a life-threatening event related to study drug were to occur during this study, the Sponsor, in consultation with the

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

IDMC, will evaluate whether criteria have been met to pause or stop the study, or issue an urgent safety memo to investigators. Occurrence of such events will trigger an aggregate data review by the Regeneron Safety Oversight Committee, which will include senior clinical, regulatory, and pharmacovigilance leaders at Regeneron. Regeneron personnel involved in any unblinded senior level cross-functional review will not be directly involved in the conduct of the clinical study. If the Regeneron Safety Oversight Committee, in consultation with the IDMC, determines that the stopping criterion has not been met, the sponsor will continue the study. If the sponsor determines that the stopping criterion have been met, the study will be stopped or modified, and the sponsor will inform (or, in the case of modification, seek agreement from) the regulatory/Ethics Committees in accordance with local regulatory requirements. If after stopping the study, the sponsor later determines it is appropriate to restart the study, dosing of study drug will be resumed only after agreement with the investigator and regulatory procedures have been completed.

An IDMC will actively monitor interim data to review the ongoing safety of participants and may recommend halting enrollment or pausing the study, or implementing changes in study conduct as deemed necessary (see Section 5.3.1).

Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

5.1.5.1. Specific Rules for Participants with a Low eGFR

For participants in the low eGFR group (30 to 45 mL/min/1.73 m^2) in Part A2 or Part B, severe hypotension (defined as SBP <90 mm Hg) and/or acute kidney injury (defined as an increase in serum creatinine of ≥2x baseline or decrease in eGFR of ≥50% from baseline) will prompt an immediate review of the safety data for the affected participant and other low eGFR group participants by the sponsor. If such event is assessed as related to the study drug by the investigator and the sponsor, further randomization of low eGFR participants will be paused immediately. Further randomization of low eGFR participants will only resume after IDMC consultation.

5.1.6. End of Study Definition

The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator). Unscheduled visits may still occur after the planned EOS visit if additional follow-up of a participant (eg, safety follow-up) is warranted.

5.2. Planned Interim Analysis

No formal interim analysis is planned.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

This study will have an external IDMC which will review the safety data at 30% and 60% of anticipated enrollment, reviewing all safety data for participants through study day 8, as well as all available data for those participants who are beyond study day 8.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

The IDMC will monitor unblinded data to assess the safety and efficacy profile of REGN5381. If at any time the IDMC has significant concerns regarding a meaningful imbalance in TEAEs, treatment-emergent SAEs, or treatment-emergent AESIs, the IDMC may make a recommendation to the sponsor to pause or halt the study or make other changes in the study conduct (such as change enrollment criteria, drop a dose arm, or reduce the dose within an arm). This will prompt a review by the sponsor who will decide to implement, modify, or reject the recommendation. Any decisions related to a change in study conduct, temporary halt, study termination, or study restart will adhere to applicable regulatory procedures as required by local laws. There will be monthly reviews of AE data and 2 comprehensive reviews of all data.

Details of the IDMC will be provided in a separate charter.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

6.1. Number of Participants Planned

Approximately up to 394 participants will be enrolled in the study with approximate numbers of participants per group as follows:

Part A1 (N=60-90),

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

- An optional dose cohort may be enrolled as follows:
  - 30 participants (15/arm) will receive ≤300 mg REGN5381 or placebo.

Part A2 (N=44-46)*,

- Sacubitril-valsartan cohort (N=42)*,
  - 24 participants (12/arm) will receive 100 mg REGN5381 or placebo*,
  - 18 participants (12 active: 6 placebo) will receive ≤300 mg REGN5381 or placebo*.
- Low eGFR (30 to 45 mL/min/1.73 m^2) cohort (N=2-4)*,
  - 2-4 participants (0-4/arm) will receive 100 mg REGN5381 or placebo*,

    (The low eGFR group has been closed as of PA4. Participants already enrolled in this group will complete the protocol as scheduled.)

Part B (N=258),

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

*Cohorts reduced in size with PA4 may have recruited more than the new target enrollment before the amendment is in effect.

6.2. Study Population

The study population includes adults with HFrEF with elevated NT-proBNP receiving stable background therapy for heart failure.

It is a general objective that clinical trials should reflect the global diversity of populations most likely to use the drug if approved (EMA, 2021) (FDA, 2022). This supports ethical, scientific, and clinical purposes.

Diversity considerations are a component of site selection criteria. Black and Hispanic individuals bear a disproportionate burden of morbidity and mortality in the United States (Miller, 2021), and

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

underrepresentation in clinical trials is well-documented (Aldrighetti, 2021) (Caston, 2022). English language is not a requirement for study enrollment.

6.2.1. Inclusion Criteria

A participant must meet the following criteria to be eligible for inclusion in the study:

1. ≥18 years of age, or local age of adulthood, at screening,
2. Body mass index (BMI) between 18 and 45 kg/m^2, inclusive, at initial screening visit,
3. Diagnosis of chronic heart failure,
4. Left ventricular ejection fraction 20-49% by echocardiogram performed within 3 months of screening,
5. Criterion was replaced by criterion #11 in protocol amendment 3.
6. Receiving optimized standard of care therapy for heart failure, as determined by the investigator, at baseline (day 1) with no change in the dose or frequency of administration for at least 30 days prior to randomization. At a minimum, this should include a beta blocker (unless contraindicated or previously not tolerated), and at least one of the following: an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or hydralazine,
7. Able and willing to perform all planned study procedures and questionnaires safely and successfully in the opinion of the investigator,
8. Provide informed consent signed by study participant,
9. **Sacubitril-valsartan treatment**

   Protocol Amendment 4: treatment with sacubitril-valsartan at screening and at baseline permitted in Part A2 sacubitril-valsartan cohort and in Part B if supported by safety data from the Part A2 sacubitril-valsartan cohort.

   Protocol Amendment ≤3: Sacubitril-valsartan cohort only: treatment with sacubitril-valsartan at screening and at baseline.

10. **eGFR levels**

    Protocol Amendment 4: Estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2 according to locally used formula (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] preferred), at screening (visit 1) or approximately 30 days prior to randomization (visit 5). eGFR of 30 to 45 mL/min/1.73 m^2 is permitted in Part B and A2 sacubitril-valsartan cohort, with the most recent result obtained prior to visit 7 (typically at visit 5, unless testing is repeated) used to determine if the participant is considered to be low eGFR,

    Protocol Amendment ≤3: Low eGFR cohort only: eGFR of 30 to 45 mL/min/1.73 m^2 at screening and within approximately 30 days of randomization. Low eGFR cohort closed as of PA4.

    Note: If participant has an eGFR out of range at any time during screening up to the time of first administration of study drug, one repeat test is allowed. Participant may be enrolled

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

if repeat and all subsequent measurements up to the time of first dose demonstrate eGFR in range.

11. Plasma NT-proBNP ≥800 pg/mL (or ≥1000 pg/mL if in atrial fibrillation) at screening (visit 1) and NT-proBNP ≥600 pg/mL (or ≥800 pg/mL if in atrial fibrillation) approximately 30 days prior to randomization (visit 5).

6.2.2. Exclusion Criteria

A participant who meets any of the following criteria will be excluded from the study:

1. Hospital discharge within 180 days of anticipated randomization,
2. Resting SBP that remains out of range after two repeated measurements prior to randomization at any time during the last 30 days of run-in (day -30) to day 1: <110 mm Hg or >160 mm Hg,
3. Criterion was replaced by inclusion criterion #10 in protocol amendment 4.
4. Current or recent diagnosis of acute coronary syndrome or myocardial infarction (symptoms of ischemia or new ischemic ECG changes in combination with an increase in cardiac enzymes) <6 months prior to initial screening or during the Run-in period,
5. History of symptomatic autonomic dysfunction as evidenced by orthostatic hypotension and/or syncope,
6. Unexplained syncope <12 months prior to initial screening or during the Run-in period,
7. Current diagnosis of moderate or severe pericardial effusion, or evidence of cardiac tamponade on most recent echocardiogram,
8. Current diagnosis of acute myocarditis or pericarditis,
9. Current diagnosis of high-grade atrioventricular block, including second-degree type II AV block and third-degree AV block (complete heart block) unless adequately managed by a permanent pacemaker, as determined by the investigator. Participants with any current indication or plan for pacemaker implantation (including but not limited to heart block, sinus node dysfunction, or tachy-brady syndrome), at screening or before dose administration on day 1 are also excluded. (second-degree type I AV block is not excluded)
10. History of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurological disease, as assessed by the investigator that may confer unreasonable risk to the participant's participation in the study,
11. Any history or current diagnosis of any of the following:
    a. Any prior diagnosis of severe pulmonary hypertension (regardless of current findings),
    b. Echocardiographic evidence of more than moderate pulmonary hypertension, defined as an estimated right ventricular systolic pressure ≥55 mm Hg on the most recent echocardiogram prior to or at screening, severe right ventricular dilation/hypertrophy or flattening of the interventricular septum consistent with severe pulmonary hypertension, or a mean pulmonary artery pressure >40 mm Hg by right heart catheterization within the past year if available,
    c. Cardiac sarcoidosis or cardiac amyloidosis,

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

d. Hypertrophic obstructive cardiomyopathy,
e. Restrictive or constrictive cardiomyopathy,
f. Any history of sustained ventricular tachyarrhythmias, eg documented sustained ventricular tachycardia, appropriate defibrillator shocks, confirmed ventricular arrhythmia causing syncope, and/or sudden cardiac death (with successful resuscitation),
g. Any history of requiring positive inotropic support,
h. Heart transplantation.

12. Uncorrected congenital heart disease,
13. Currently uncorrected moderate-to-severe or severe stenotic or regurgitant cardiac valve disease,
14. Cardiac surgery (ie, coronary artery bypass grafting, valvular surgery, or any other open intracardiac surgery) within 6 months prior to screening or any planned surgery during the study,
15. Percutaneous coronary revascularization in the prior 30 days, or planned during the study,
16. Implantation of a cardiac resynchronization therapy device in the prior 90 days, or planned during the study, or planned device optimization 30 days prior to randomization or during the study,
17. Current chronic lung disease requiring long-term oxygen therapy,
18. Any malignancy, except for non-melanoma skin cancer or cervical/anus in-situ, that have been resected with no evidence of metastatic disease for 3 years prior to screening,
19. Receiving a medication during screening or run-in period that is not permitted during the study (see Section 7.10.1), including IV nitrates and vasodilators, phosphodiesterase-5 inhibitors (eg, vardenafil, sildenafil, tadalafil), carperitide, or vericiguat,
20. Criterion was replaced by inclusion criterion #9 in protocol amendment 4.
21. [Criterion Removed]
22. Medical history of liver cirrhosis, or current Child-Pugh B or C hepatobiliary disease, or AST or ALT ≥3x ULN,
23. Is positive for HBsAg or hepatitis B core antigen IgM antibody (anti-HBc IgM) at screening,
24. Is positive for hepatitis C antibody and positive for qualitative (ie, detected or not detected) HCV RNA test at screening,
25. Known allergy to REGN5381 or its excipients,
26. Participated in any clinical research study evaluating another investigational drug including biologics or therapy, including specific immunotherapy, within 90 days or at least 5 half-lives (whichever is longer) for an investigational biologic drug, or at least 4 weeks for small molecules or other investigational drugs, prior to screening,
27. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor,

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

28. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study and for 4 months after the last study drug administration: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited for 4 months after study drug administration,
29. Pregnant or breastfeeding women,
30. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include:
    a. Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening, supplemented with a barrier method, preferably male condom;
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
    c. bilateral tubal occlusion/ligation;
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
    e. sexual abstinence†, ‡.

    Note: Pregnancy testing and contraception are required for WOCBP.*
    Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile*.*

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance.

    †Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

    ‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

not acceptable methods of contraception. Female condom and male condom should not be used together.

31. Is committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
32. Hemoglobin <9.0 g/dL at screening

6.3. Premature Withdrawal from the Study

A participant has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a participant from the study if it is no longer in the interest of the participant to continue in the study, or if the participant's continuation in the study places the scientific outcome of the study at risk (eg, if a participant does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

Participants who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 8.1.4.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.4.2.

6.4. Replacement of Participants

Participants prematurely withdrawn from the study during the Run-in period can be replaced, if needed, to ensure an adequate number of evaluable participants. The Medical/Study Director, in cooperation with the Study Biostatistician, will decide whether or not to replace a withdrawn participant.

Participants enrolled and withdrawn from study any time prior to the beginning of administration of study drug will not be considered evaluable for assessment and will be replaced with another participant. All participants who have received a dose of study drug will be included in an as treated analysis.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

REGN5381 Drug Product, Lyophilized, 265 mg per vial and matching placebo.

Participants will receive either REGN5381 or matching placebo as a single dose administered via IV infusion.

Final presentations and instructions on dose preparation will be provided in the pharmacy manual.

7.2. Background Treatments

Background therapy may be adjusted at the discretion of the treating physician during the first 60 days of the run-in period according to local guidelines as determined by the investigator. Participants must remain on a stable background therapy regimen for heart failure for at least 30 days prior to randomization until the end of study. At a minimum, this regimen must include, unless contraindicated or previously not tolerated, a beta-blocker and least one of the following: an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or hydralazine.

7.3. Rescue Treatments

7.3.1. Rescue Therapy

Rescue therapy is permitted during the treatment period if one or more of the following criteria are met as determined by the investigator:

- New or increasing clinical signs or symptoms of cardiopulmonary congestion and/or low output state due to heart failure (including but not limited to worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or clinical evidence of organ hypoperfusion)
- Persistent worsened control of blood pressure
- Symptomatic hypotension (SBP <90 mm Hg associated with loss of consciousness or lightheadedness/dizziness) at the discretion of the investigator.
  - Participants experiencing symptomatic hypotension will be treated by site investigators as informed by clinical assessment including extended inpatient stay if required.

Rescue therapy includes any escalation of the heart failure regimen, including initiation of one or more new therapies for heart failure or an increase to the dose or frequency of administration of any current concomitant medication for heart failure. Permitted rescue therapies include loop diuretics, thiazide diuretics, oral vasodilators, beta blockers, mineralocorticoid receptor antagonists, SGLT2 and SGLT1/2 inhibitors, IV vasodilators, inotropes, vasopressors, non-invasive positive airway pressure (eg, CPAP or bilevel PAP), mechanical ventilation, extracorporeal life support, and ventricular assist devices.

Background therapy may be temporarily or permanently withheld, or doses may be down titrated to manage an adverse event (eg, hypotension or laboratory abnormality requiring a change in therapy).

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

7.3.2. Specific Complications of Cardiac Failure or Reversible Severe Hypotension to Consider in Differential Diagnosis

Investigators are reminded that ischemic hepatitis is not an uncommon complication of cardiac failure or reversible severe hypotension, but is one of multiple etiologies of increases in AST and ALT, therefore:

- in participants presenting with jaundice, vomiting, abdominal pain and/or oliguria after an episode of significant/severe hypotension, ischemic hepatitis should be considered and evaluated along with other common causes of increased AST and ALT including, but not limited to, viral hepatitis, drug-induced hepatitis, and alcohol-induced hepatitis,
- similarly, in participants with unexplained elevated transaminases (AST/ALT), early rise in lactic dehydrogenase (LDH) and renal failure, ischemic hepatitis should also be considered in the differential diagnosis while evaluating these participants.
- hepatopulmonary syndrome (HPS) which is defined as the triad of liver disorder, arterial deoxygenation abnormalities, and widespread pulmonary vasodilatation causing right-to-left shunt leading to hypoxemia. Intrapulmonary vasodilatation indicating HPS can also frequently occur in participants with hypoxic hepatitis. It is usually reversible after normalization of the hepatic dysfunction.
  - clinicians should consider intrapulmonary vasodilatation and HPS in participants with hypoxic hepatitis and/or with elevated levels of transaminases and should perform pulse oximetry to aid diagnosis of HPS and extra monitoring of serum bilirubin and coagulation parameters

7.4. Dose Modification and Study Treatment Discontinuation Rules

7.4.1. Dose Modification

Dose modification for an individual participant is not allowed.

7.4.2. Study Drug Discontinuation

Study drug discontinuation is not applicable in this single-dose study. See Section 7.5.1.1 and Section 7.5.1.2 if there is interruption during the single intravenous infusion.

Participants who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.4.

7.5. Management of Acute Reactions

7.5.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.2.4) and graded using the grading scales as instructed in Section 9.2.5.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

7.5.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Sustained/severe cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

7.5.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

7.6. Method of Treatment Assignment

Up to approximately 136 eligible participants in Part A1 and Part A2 and up to approximately 258 eligible participants in Part B will be randomized to one of the treatment groups as described in Section 5.1.1 and Section 5.1.2.

Randomization in Part B will be stratified by background sacubitril-valsartan therapy (defined as being on sacubitril-valsartan at both visit 5 and randomization) and eGFR 30 to 45 mL/min/1.73 m^2 based on last result before visit 7 as follows:

- Sacubitril-valsartan, or Non-sacubitril-valsartan
- eGFR 30 to 45 mL/min/1.73 m2, or eGFR >45 mL/min/1.73 m2

The first 6 participants with eGFR 30 to 45 mL/min/1.73 m^2 in Part B will be randomized to REGN5381 100 mg, 300 mg, or placebo at 2:2:2. After these initial 6 participants, the randomization will continue to be stratified by low eGFR yes/no to ensure balanced randomization of this small subgroup.

Randomization will be implemented according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

7.7. Blinding

Participants, the investigator(s), and site personnel are blinded to treatment assignment to maintain objectivity of study assessments. The study site investigational pharmacist(s) or qualified designee(s) is unblinded to treatment assignment for the purposes of preparing investigational study drug. The sponsor, Medical Director/Study Director and any other Regeneron personnel and/or individuals representing the sponsor who are in regular contact with the study site will remain blinded to individual participant randomization assignments through the final database lock. These individuals representing the sponsor may have access to all other study data for monitoring purposes.

Other Regeneron personnel who are not in regular contact with the study site may be unblinded to study data as needed, including a Statistician and Statistical Programmer who will be unblinded to participant randomization assignments and study data.

7.8. Emergency Unblinding

Unblinding of treatment assignment for a participant may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the participant's treatment assignment. Study drug will be discontinued for participants whose treatment has been unblinded/unmasked (Section 7.4.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

- Only the affected participants will be unblinded.
- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind/unmask the participant. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the participant

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the participant's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.9. Treatment Logistics and Accountability

7.9.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

7.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed / returned to the sponsor or designee.

7.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each participant
- returned from each participant (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

7.10. Concomitant Medications

Any treatment administered from the time of informed consent to end of follow-up period will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

If a participant intends to receive a COVID-19 vaccine (initial series or booster), before the start of study drug administration, day 1 of the study and the events associated with day 1, should not occur until at least 1 week after any COVID-19 vaccination dosing.

During the treatment period, it is recommended to delay COVID-19 vaccination, either as an initial series or as a booster dose, until participants are receiving and tolerating a steady dose of study drug.

COVID-19 vaccination, either as an initial series or as a booster dose, received during the study, will be treated as a concomitant medication. As noted, administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product (at least 72 hours, ideally by at least one week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

7.10.1. Prohibited Medications

The following medications are prohibited:

- Carperitide, vericiguat, and phosphodiesterase 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil, and avanafil) are prohibited from screening through study week 16.

7.10.2. Permitted Medications

The following concomitant medications for the management of heart failure are permitted as part of the background therapy regimen:

- Oral vasodilators (ie, ACE inhibitor, angiotensin receptor blocker, oral nitrates, hydralazine)
- Beta blockers
- Mineralocorticoid receptor antagonists
- Digoxin
- SGLT2 and SGLT1/2 inhibitors
- Ivabradine
- Loop diuretics
- Thiazide diuretics
- Sacubitril-valsartan
  - (for Part A2, only in specified cohort)
  - (for Part B, following safety review of the Part A2 sacubitril-valsartan cohort as described in Section 5.1.3.7)

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 1.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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												
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]													

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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**
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)[12]	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						
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						

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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 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						

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.1.1. 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 3 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 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.
12. 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.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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)[10]	X				X		X	
Blood Chemistry (central)	X				X		X	
Urinalysis	X							

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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	

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.1.2. 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.
6. All PRO 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.
10. 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.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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**	
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

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.1.3. 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).
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.

8.1.4. Early Termination Visit

Participants who are withdrawn from the study before the primary endpoint visit (day 8) will be asked to return to the clinic: once for an early termination visit consisting of the end of study assessments described in Table 3 and again at selected visits (eg, the primary endpoint visit [day 8/visit 2] and key secondary endpoint visit(s), as applicable).

8.1.5. Unscheduled Visits

All attempts should be made to keep participants on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. Unscheduled visits may occur after the end of study visit for the purposes of additional safety follow-up, if required.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

At the initial screening visit, subjects will sign the informed consent forms to indicate their willingness to participate in the clinical trial. The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Assessment of study eligibility for study participation based on inclusion/exclusion criteria; review of specific criteria may also be performed at pre-dose/day 1
- Collection of medical history information
- Collection of demographics information
- Perform HBV and HCV screens
- Perform a FSH screen
- NT-proBNP

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

- Arrangements for echocardiography, if needed

8.2.2. Efficacy Procedures

Pharmacodynamic procedures will be performed (Section 8.2.7).

8.2.3. Safety Procedures

8.2.3.1. Body Weight

Body weight will be assessed using calibrated scales at the specified visits in Table 1 and Table 2. Subjects should void (empty bladder) prior to weight assessment. Subjects should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

8.2.3.2. Vital Signs

Vital signs, including temperature, heart rate, pulse and respiration, will be collected at time points according to Table 1 and Table 2. Heart rate and blood pressure should be performed before venipuncture (sequence not essential if blood sampling via an indwelling IV catheter).

8.2.3.3. Blood Pressure

Blood pressure will be assessed during the Screening Period and within approximately 1 hour prior to study drug administration on day 1; participants will be excluded if SBP is <110 mm Hg or >160 mm Hg at any time during the 30 days prior to study drug administration.

8.2.3.4. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1 and Table 2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the participant's medical history.

8.2.3.5. Electrocardiogram

A standard 12-lead ECG will be performed in at time points according to Table 1, Table 2, and Table 3. In Parts A1 and A2, scheduled ECGs from visit 7 Pre-Dose through visit 11 will be performed in triplicate and stored for future analysis. Single ECGs are sufficient for ECGs scheduled in Part A1 and A2 visit 1 and visit 5, and for all ECGs scheduled in Part B. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source. All ECGs should be performed after ≥10 minutes of rest and before vital signs and venipuncture. Participants in Parts A1 and A2 should fast for 2.5 hours prior to the baseline and post-dose ECGs performed on study day 1.

8.2.3.6. Echocardiogram

A historical echocardiogram report performed within 3 months prior to screening may be used to fulfill eligibility criteria. If multiple echocardiograms are available, the echocardiogram performed closest to the time of screening should be used. If a historical echocardiogram is not available, an echocardiogram should be performed during the screening period or run in period prior to visit 5

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

(30 days prior to randomization). The report must include quantification of left ventricular ejection fraction, exclude any valvular disease more than moderate in severity, and include an estimate of RVSP, or state that tricuspid regurgitant jet is inadequate for estimating RVSP. If tricuspid regurgitant jet is inadequate for the estimation of RVSP, severe right ventricular hypertrophy, severe right ventricular dilation, and flattening of the interventricular septum suggestive of severe pulmonary hypertension must be excluded.

8.2.3.7. Safety Card

Participants will be provided with a Safety Card. This card will provide information required in an emergency situation, including the study number, the name of the study drug (REGN5381), sponsor name and emergency contact details for investigator. This card will be reviewed at the time points according to Table 1, Table 2, and Table 3.

8.2.3.8. Laboratory Testing

Hematology, chemistry, urinalysis, albumin:creatinine ratio, and pregnancy testing samples will be analyzed by local and central laboratories. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

Samples for laboratory testing will be collected at visits according to Table 1, Table 2, and Table 3. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen /Urea	Creatine phosphokinase (CPK)
Carbon dioxide/Bicarbonate	Aspartate aminotransferase (AST)	
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology*

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

*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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Pregnancy test for WOCBP; urine or serum samples, as indicated.

FSH test in women to confirm postmenopausal status.

Bilirubin and coagulation parameters for participants with increased AST/ALT levels (≥3x ULN)

If local laboratory is unable to complete one of these laboratory tests, a central laboratory may be consulted.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.1.1.

8.2.4. Drug Concentration and Measurements

Samples for drug concentration measurement will be collected at visits listed in Table 1, Table 2, and Table 3. Actual time of collection must be recorded. Any unused samples may be used for exploratory research, biomarker research (Section 8.2.7), and/or future biomedical research (Section 8.2.8).

8.2.5. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected in serum at the visits listed in Table 1, Table 2, and Table 3. Any unused samples may be used for exploratory research, biomarker research (Section 8.2.7), and/or future biomedical research (Section 8.2.8).

8.2.6. Clinical Outcome Assessments

8.2.6.1. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item self-administered questionnaire developed to independently measure the participant's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life within a 2-week recall period (Green, 2000).

8.2.6.2. EQ-5D-5L

The EQ-5D-5L assesses participant quality of life on five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is assessed through a single question using a 5-point Likert scale and one visual analog scale (0-100) using a recall period of "today"; expected time of completion is approximately 3.5-5 minutes.

8.2.7. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore [redacted]

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.2.7.1. NT-proBNP

Serum samples will be collected to measure NT-proBNP levels at the time points indicated in Table 2, and Table 3. NT-proBNP is a clinical biomarker of heart failure. Measurement of NT-proBNP at baseline and modulation over time is a primary endpoint in this study. Results from these analyses will be reported in the CSR.

8.2.7.2. Olink Proteomics

Plasma samples will be collected for Olink proteomics at the time points indicated in Table 1, Table 2 and Table 3. Olink proteomics is a high-throughput protein biomarker discovery platform. Measuring the changes in potentially thousands of proteins in response to drug treatment may provide circulating biomarkers responses. Results from the analysis may be reported in the CSR.

8.2.7.3. High-sensitivity Troponin T

[redacted] are exploratory measures in this study. Results from these analyses may be reported in the CSR.

8.2.7.4. ANP and BNP MS Levels

[redacted] are exploratory measures in this study (if the assay is available). Results from these analyses may be reported in the CSR.

8.2.7.5. BNP Enzyme-Linked Immunosorbent Assay (ELISA)

[redacted] are exploratory measures in this study (if the assay is available). Results from these analyses may be reported in the CSR.

8.2.7.6. NT-proANP

[redacted] exploratory measure in this study. Results from these analyses may be reported in the CSR.

8.2.7.7. CA-125

[redacted] are exploratory measures in this study. Results from these analyses may be reported in the CSR.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.2.7.8. Urine Kidney Injury Molecule-1 (KIM-1)

[redacted] are exploratory measures in this study. Results from these analyses may be reported in the CSR.

8.2.7.9. Urine Albumin Creatinine Ratio

[redacted] are exploratory measures in this study. Results from these analyses may be reported in the CSR.

8.2.7.10. Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL)

[redacted] are exploratory measures in this study. Results from these analyses may be reported in the CSR.

8.2.7.11. Exploratory Biomarker Research

Additional and/or residual blood and urine samples collected for other purposes (ie, PK, ADA, and biomarker samples) will be banked for exploratory research directly related to the drug, REGN5381 and to the disease, heart failure and/or chronic kidney disease and related diseases. The samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations).

8.2.7.12. cGMP

[redacted] an exploratory measure in this study. Results from these analyses may be reported in the CSR.

8.2.8. Future Biomedical Research (Optional)

Where applicable by law, participants who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional samples will be collected for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

8.2.9. Pharmacogenomic Analysis (Optional)

Participants who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of heart failure and/or chronic kidney disease and related diseases. These samples will be single-coded as defined by the ICH guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN5381, heart failure and/or chronic kidney disease or other related clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of heart failure and/or chronic kidney disease or other related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or heart failure and/or chronic kidney disease and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

9. SAFETY EVALUATION AND REPORTING

9.1. Recording and Reporting Adverse Events

9.1.1. General Guidelines

The investigator must promptly record all adverse events occurring during the study data collection per the schedule of events (see Section 8.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the participant. Adverse events may be directly observed, reported spontaneously by the participant, or by questioning the participant at each study visit. Participants should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.2. The investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 9.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 9.1.3.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

9.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

9.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Selected Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest 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 (≥3x ULN AST/ALT)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 4 months of the last dose of study drug. Any complication of pregnancy affecting a female study participant or female partner of a male study participant, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

9.2. Definitions

9.2.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH, 1994).

For studies with patient-reported outcomes (PRO), the PRO data are generally not reportable as individual AEs and thus will not be reported or reconciled as such.

9.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a participant is a passenger).
- Is **life-threatening** – in the view of the investigator, the participant is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires inpatient **hospitalization** or **prolongation of existing hospitalization**. Inpatient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

9.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

9.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 24 hours after the infusion is completed.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

9.2.5. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the participant normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the participant.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or participant hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

Mild: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

Severe: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

9.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

- Participant's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, participant's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, participant's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

9.3. Safety Monitoring

The investigator will monitor the safety of study participant at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, GPS; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

9.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the contract research organization (CRO) will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN5381) as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (REGN5381) is assessed against the Reference Safety Information section of the IB that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and IECs/IRB as appropriate.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

10. STATISTICAL PLAN

10.1. Statistical Hypothesis

No formal statistical hypothesis testing will be performed. The treatment difference between REGN5381 groups and placebo group in the change from baseline at day 8 in NT-proBNP will be estimated in this phase 2 study.

10.2. Justification of Sample Size

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

- Sample sizes in Part A1 and Part A2 were based on practical considerations of safety comparisons before progressing to Part B.
- The 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% based on EMPEROR-Reduced study, in which the percent change from baseline in NT-proBNP was -7% (95% CI, -5 to -10%) at 4 weeks. (The EMPEROR-Reduced study had a timepoint closest to the primary endpoint in a similar patient population).
- The treatment difference in terms of percent change from baseline in NT-proBNP is assumed to be -25% between the 2 arms (eg, REGN5381 assumed as -35.0% and placebo as -10.0%) based on sacubitril-valsartan's effect compared to control in PIONEER-HF (-25.7%, treatment difference in percent change from baseline from a time-weighted average of weeks 4 and 8) and in PARAMOUNT (-19.6%, treatment difference in percent change from baseline at week 12), which is equivalent to a -0.3254 (REGN5381 minus placebo) difference of means for log-transformed change from baseline of NT-proBNP.
- The 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. Other outpatient studies have SDs ranging from 0.5 to 0.8.
- A 10% drop out rate is expected at day 8 in both arms based on RELAX-AHF and PIONEER-HF (Metra, 2013) (Velazquez, 2019) where dropout rates varied from 5% to 15%.

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.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The modified intent-to-treat (mITT) population includes all randomized participants who have 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.

10.3.2. Pharmacodynamic Analysis Set

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).

10.3.3. Safety Analysis Set

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

10.3.4. Pharmacokinetic Analysis Sets

The PK analysis set 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).

10.3.5. Immunogenicity Analysis Sets

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).

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of participants reflected in the calculation (n), mean, SD, first quartile (Q1), median, third quartile (Q3), minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Participant Disposition

The number and percentage of participants screened, randomized, and the primary reasons for screening failure and discontinuation will be summarized.

10.4.2. Demography and Baseline Characteristics

Demographic variables (eg, age, race, and gender), baseline characteristics, medical history, and prior and concomitant mediations and therapies will be summarized by treatment group and by all

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

participants combined in the mITT population. See Section 4.1 for a full list of demographic and baseline variables. No statistical hypothesis testing will be performed on demographic or baseline characteristics.

10.4.3. Efficacy Analyses

The primary endpoint of the study is the change from baseline in NT-proBNP at day 8. The secondary efficacy endpoints include changes from baseline in circulating NT-proBNP at weeks 2, 3, 4 and up to week 16. Efficacy analyses are conducted on the mITT population for participants with common dose levels, aggregated across Parts A1, A2, and B.

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 changes 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, baseline log-transformed NT-proBNP results (continuous), background sacubitril-valsartan therapy (Yes/No), eGFR level (30 to 45 mL/min/1.73 m^2 vs >45 mL/min/1.73 m^2), visit, treatment-by-visit interaction, baseline-by-treatment interaction and baseline-by-visit interaction.

Summary statistics including the least squares (LS) mean, standard error (SE), 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 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.

Any NT-proBNP measurements after initiation of rescue therapy or prohibited medications will not be used for either primary or secondary efficacy analyses.

10.4.4. Control of Multiplicity

No adjustment for multiplicity is made in this Phase 2 study.

10.4.5. Safety Analysis

10.4.5.1. Adverse Events

Definitions

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.

Analysis

The number (n) and percentage (%) of participants who reported any of the following will be summarized by treatment group:

- Overview of TEAEs
- TEAEs by primary SOC and PT
- TEAEs by primary SOC, PT, and maximum severity
- Treatment-related TEAEs by primary SOC and PT

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

- TEAEs leading to death by primary SOC and PT
- TE-SAEs by primary SOC and PT
- Treatment-related TE-SAEs by primary SOC and PT
- TE-AESI by primary SOC, and PT
- Treatment-related TE-AESIs by primary SOC and PT

Additional details of safety analysis will be provided in the SAP.

10.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized.

Laboratory Tests

Laboratory test results will be summarized.

Number and percentage of participants with a potentially clinically significant value (PCSV) will be tabulated.

10.4.5.3. Treatment Exposure

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).

10.4.5.4. Treatment Compliance

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

10.4.6. Pharmacokinetics

10.4.6.1. Analysis of Drug Concentration Data

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

The concentrations of total REGN5381 over time and selected pharmacokinetic parameters will be summarized by descriptive statistics for each of the treatment groups.

No formal statistical hypothesis testing will be performed.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

10.4.7. Analysis of Immunogenicity Data

The incidence of positive ADA response for study drug will be assessed as absolute occurrence (n) and percent of participants (%), presented by treatment groups. Listing of ADA magnitude will be provided for participants positive in the ADA assay.

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

10.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Descriptive statistics of biomarkers by study visit and by treatment group will be generated. Summary statistics of biomarkers including mean and medians will be evaluated for change from baseline through the end of the study.

10.5. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 14.1.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

11. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

11.1. Data Management and Electronic Systems

11.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

Adverse events and medical history will be coded using MedDRA. A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC), Medidata Rave.

11.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

11.2. Study Monitoring

11.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate participant records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every participant enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each participant, the investigator must provide an electronic signature. A copy of each participant CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

11.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor’s participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

In all instances, the confidentiality of the data must be respected.

11.4. Study Documentation

11.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of participants final eCRF that will be provided to the sponsor.

11.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

11.4.3. Recruitment Strategy

Potential study participants may be identified by the investigator through a variety of means, such as publicizing the study or using existing participant lists. Recruitment resources may include, but are not limited to, recruitment flyers, brochures, social media ads, newspaper ads, radio ads, etc. A third-party vendor may assist in recruitment efforts, such as the development of recruitment materials. All participant-facing recruitment material, including media advertising and receptionist scripts, will be reviewed and approved by the appropriate IRB/EC/authority prior to use. Resources may be in paper or electronic form. Regeneron will not access any participant identifiable information as part of recruitment efforts.

11.4.4. Data Protection

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

- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

12.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each participant prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the participant in language that he/she can understand. The ICF should be signed and dated by the participant and by the investigator or authorized designee who reviewed the ICF with the participant.

- Participants who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Participants who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the participant's study record, and a copy of the signed ICF must be given to the participant.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study participants must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the participant's study record and a copy must be given to the participant.

12.3. Participants Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study participant will be maintained. Participants should be identified by a participant identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The participant's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

12.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the participants (eg, advertising) before any participant may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the participant, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of participants or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

12.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

13. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

14. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

14.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

14.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any participant within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of participants required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the participants' interests.

15. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

16. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

17. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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VV-RIM-00418905-1.0 Approved - 27 Jun 2025 GMT-5:00

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19. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: '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' and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study 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

Protocol Number: R5381-HF-22118

Protocol Version: R5381-HF-22118 Amendment 4

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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