Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE ASCENDING DOSES OF REGN5381, AN NPR1 AGONIST, IN HEART FAILURE PATIENTS WITH ELEVATED PULMONARY CAPILLARY WEDGE PRESSURE

Compound:	REGN5381
Clinical Phase:	2a
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AMENDMENT HISTORY

Amendment 6

The main purpose of this amendment is to implement changes to align with the latest EU-CTR guidelines and incorporate Health Authority recommendations.

Description of Change	Brief Rationale	Section # and Name
Updated the below for compliance with the new EU Clinical Trial Regulation (CTR) • Added a row for short title (Synopsis). • EU CTR guidance - added Recruitment strategy and data protection, and updated end of study definition, retention of records and clinical study data transparency.	The EU-CTR 536/2014 will standardize and harmonize the conduct and management of interventional clinical trials across the EU with legally binding rules on requirements and increased transparency.	Clinical Study Protocol Synopsis – Short Title (new), End of Study Definition Section 6.1.9 End of Study Definition Section 12.4.3 Recruitment Strategy (new) Section 12.4.4 Data Protection (new) Section 13.5 Clinical Study Data Transparency
Additional AEs were added to the list of Selected Adverse Events of Special Interest	[redacted]	Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Criteria for Rescue therapy permitted during the treatment period was updated	[redacted]	Section 8.2.1 Rescue therapy (new)
Consolidated language about Ischemic Hepatitis has been added.	[redacted]	Section 8.2.2 Specific Complications of Cardiac Failure or Reversible Severe Hypotension to Consider in Differential Diagnosis (new)
Addition of enhanced cardiac monitoring	[redacted]	Section 8.2.2 Specific Complications of Cardiac Failure or Reversible Severe Hypotension to Consider in Differential Diagnosis (new)
Bilirubin and Coagulation parameters for participants with increased AST/ALT levels (3 x ULN)	[redacted]	Section 8.2.2 Specific Complications of Cardiac Failure or Reversible Severe Hypotension to Consider in Differential Diagnosis (new) Section 9.2.4.11 Laboratory Testing – Other Laboratory Tests

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Close enrollment to Group A (HFrEF patients not taking sacubitril/valsartan) and Group B (HFrEF patients taking sacubitril/valsartan)	As HFrEF patients will be the focus of a forthcoming Phase 2 clinical trial, enrollment of these patients in this study is expected to become duplicative. Accordingly, Groups A and B in this study will be closed to enrollment. Any patients already enrolled in the study should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.	Throughout the document
Added Telemetry to the 'Extended Inpatient Monitoring (optional)' column in the Schedule of Events	The telemetry row was erroneously excluded from Table 4 during the extension of the Extended Monitoring period in protocol amendment 5	Section 6.1.2 Extended Inpatient Monitoring Period Section 9.2.4.8 Telemetry (3-lead Electrocardiogram) Table 4 Schedule of Events for Outpatient Follow-Up Period
Edited the estimated study duration in the Clinical Study Protocol Synopsis.	This update was made to accurately describe the study duration in the Clinical Study Protocol Synopsis	Clinical Study Protocol Synopsis: Study Duration
Made administrative revisions and addressed minor editorial and typographical errors.	These updates were incorporated to ensure overall accuracy and consistency	Throughout the document.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Amendment 5

The main purpose of this amendment is to implement additional safety measures and incorporate additional study eligibility requirements to help mitigate potential risks. At the time of this amendment, 20 patients have been dosed with REGN5381 or placebo in this study, of which 2 patients experienced an SAE. One of these patients experienced a fatal SAE. Both of these patients have been dosed with 300mg REGN5381 or placebo. The key changes include extension of the inpatient observation period and exclusion of patients with eGFR≤45 mL/min, systolic BP≤110mmHg or mean pulmonary pressure ≥40 mmHg.

Description of Change	Brief Rationale	Section # and Name
Safety data has been updated with current information from the 3 clinical studies with REGN5381	At the time of this amendment, Cohorts 1, 2, 3, and 5 (10, 30, 100, and 300 mg REGN5381 or placebo, respectively) of Group A (HFrEF patients not taking sacubitril/valsartan) have been completed. In addition, optional expansion Cohorts 3A (100 mg REGN5381 or placebo) and 5A (300 mg REGN5381 or placebo) have each enrolled 2 patients. Of the 20 patients that have been dosed, 2 patients experienced an SAE. Both of these patients were in the 300mg dose cohorts (Cohorts 5 and 5A). One of these patients experienced a fatal SAE. Although the patients' heart failure and pulmonary hypertension were the primary basis for these events, it is the sponsor's assessment that the hemodynamic (venodilatory) effects of REGN5381 may have been contributory and therefore that both of these events were possibly related to study drug. As a result the study was paused, and an urgent safety notification for study halt was sent to all health authorities and investigators. Due to the occurrence of these 2 SAEs, protocol amendment 5 has incorporated additional study eligibility requirements and safety design elements to mitigate potential risks to trial participants by excluding patients considered	Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 3.3.1 Risk Benefit for REGN5381 Section 6.1.7.2 Group A: Ascending Dose Cohorts

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
	at risk for these events and allow further dosing.	
The inclusion criterion for systolic blood pressure levels at screening and day -1 will be increased from >100 mmHg to ≥110 mmHg	This will provide a greater safety margin given possible blood pressure lowering effects of REGN5381.	Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria: Criterion # 10
The inclusion criterion for heart failure with reduced ejection fraction (HFrEF) patients now requires an LVEF ≥20% and <50% (for HFrEF patients not taking sacubitril/valsartan [Group A] and HFrEF patients on sacubitril/valsartan [Group B])	Patients with LVEF <20% have lower hemodynamic reserve and may be more clinically unstable. Excluding these patients provides an additional safety mitigation.	Section 3.2.1 Rationale for Study Design Section 7.2.1 Inclusion Criteria: Criterion # 5
The inclusion criterion for NT-proBNP levels at screening for patients with heart failure with preserved ejection fraction (HFpEF) (Group C) will be decreased from >1000 pg/mL to >300 pg/mL.	Patients with HFpEF have significantly lower NT-proBNP levels than those with HFrEF. Therefore, the NT-proBNP thresholds for study inclusion in Group C will be decreased to appropriately reflect the intended population to be enrolled in this study. An NT-proBNP level >300 has a specificity of approximately 77-85% and a sensitivity of approximately 46-59% for diagnosis of congestion in HFpEF. In addition inclusion criteria of PCWP≥15mmHg will ensure that patients have congestion.	Clinical Study Protocol Synopsis: Study Design Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria: Criterion #8 (new) Section 9.1.1 Footnotes for Table 3: Schedule of Events for Screening Period and Inpatient Treatment Period: Footnote #3
The exclusion criterion has been revised from severe pulmonary hypertension to a medical history, at any time, of more than moderate pulmonary hypertension (ie, moderate-to-severe, or severe pulmonary hypertension are excluded). It has also been worded to clearly state that any patient with prior documentation of moderate-to-	This is intended to provide a greater safety margin as it further restricts the patient population from severe pulmonary hypertension to those with moderate-to-severe or severe pulmonary hypertension. Both patients that had the SAEs in question had a history of severe pulmonary hypertension. It is believed that this condition likely	Section 3.2.1 Rationale for Study Design Section 7.2.2 Exclusion Criteria: Criterion #12

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
severe or severe pulmonary hypertension is excluded, regardless of mean pulmonary artery pressure (mPAP) results at screening.	contributed to their course following REGN5381 administration. This change is intended to provide a greater safety margin given that patients with very high pulmonary pressures may be more prone to hypotension due to the venodilatory actions of REGN5381.	
Inclusion criteria now require an echocardiogram to have been performed within 90 days of screening instead of within 6 months	This will provide a more up to date measurement of ejection fraction, valvular function and pulmonary pressures (for assessment of pulmonary hypertension) since these may change over the course of 6 months. This will ensure patients with a left ventricular ejection fraction < 20% and patients with moderate-to-severe pulmonary hypetension are excluded (new exclusion criteria in this amendment).	Section 7.2.1 Inclusion Criteria: Criteria #5 and #6
The exclusion criterion for pulmonary hypertension has been revised to exclude a mean pulmonary artery pressure ≥40 mmHg at screening instead of ≥45 mmHg	This is intended to provide a greater safety margin given that patients with very high pulmonary pressures may be more prone to hypotension due to the venodilatory actions of REGN5381.	Section 3.2.1 Rationale for Study Design Section 7.2.2 Exclusion Criteria: Criterion #12 Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period: Footnote #6
The exclusion criterion for eGFR has been revised to exclude an eGFR ≤45 mL/min/1.73 m^2 at the screening visit instead of ≤30 mL/min/1.73 m^2	This is intended to provide a greater safety margin as patients with severe renal impairment may be more sensitive to hypotension due to the venodilatory actions of REGN5381.	Section 3.2.1 Rationale for Study Design Section 7.2.2 Exclusion Criteria: Criterion #25

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
The exclusion criterion for valvular regurgitation has been revised to state more clearly that the exclusion of 'more than moderate valvular regurgitation' means that moderate-to-severe or severe valvular regurgitation is excluded	Patients with moderately severe or severe pulmonary hypertension are more likely to have tricuspid regurgitation. This clarification is intended to decrease the likelihood that patients with moderately severe or severe valvular regurgitation (and concomitant pulmonary hypertension) will be inadvertently enrolled in the study.	Section 7.2.2 Exclusion Criteria: Criterion #4
The exclusion criterion for ventricular tachycardia has been revised to exclude any medical history, at any time, of sustained ventricular tachycardia	Patients with history of sustained ventricular tachycardia are at greater risk of future ventricular arrhythmias and may be more clinically unstable. Excluding these patients is intended to provide an additional safety mitigation.	Section 7.2.2 Exclusion Criteria: Criterion #13 (new)
The length of required post-dose inpatient monitoring has been extended from 3 days to at least 5 days	In the two patients that had SAEs, significant clinical and/or laboratory abnormalities occurred after day 3, but by day 5. Extending the length of post-dose inpatient monitoring will provide a greater duration of safety monitoring and is intended to ensure that any adverse hemodynamic or laboratory effects are promptly detected and managed.	Section 3.2.1 Rationale for Study Design Section 6.1 Study Design and Duration Figure 1 Study Flow Diagram Section 6.1.1 Inpatient Treatment Period Section 6.1.2 Extended Inpatient Monitoring Period Section 6.1.6 Inpatient Discharge Criteria Table 3 Schedule of Events for Screening Period and Inpatient Treatment Period Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period: Footnote #9, 17 Table 4 Schedule of Events for Outpatient Follow-Up Period

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Blood pressure thresholds for restarting home heart failure medications have been increased by 10 mmHg (ie, from 90 mmHg to 100 mmHg and from 100 mmHg to 110 mmHg).	This is intended to provide a greater safety margin given the possible blood pressure lowering effects of REGN5381.	Section 6.1.5 Restarting Home Heart Failure Medications Table 2 Restarting Home Heart Failure Medications Section 6.1.6 Inpatient Discharge Criteria Section 7.2.2 Exclusion Criteria: Criterion #21
The inpatient discharge criteria have been revised to state more clearly that all inpatient local labs and all safety data must be reviewed through the day of discharge by the investigator prior to discharge. Previous versions of this protocol did not require lab data be reviewed prior to discharge.	This change is intended to provide additional safety monitoring to ensure that any adverse hemodynamic or laboratory effects are detected prior to discharge.	Section 3.2.1 Rationale for Study Design Section 6.1.1 Inpatient Treatment Period Section 6.1.6 Inpatient Discharge Criteria
The cohort and dose progression criteria have been revised for cohorts utilizing dose levels >100 mg. Dosing of the first 2 patients (randomized 1:1 REGN5381:placebo) will occur in parallel for ascending dose cohorts in Groups A, B, and C. Both sentinel patients must complete safety assessments through day 8, the safety data through day 8 is reviewed, and a decision to continue study drug dosing in the cohort is documented by the investigator and the Sponsor, prior to dosing of the remaining patients in the cohort. For all groups, the 100 mg dose level cohort must be fully dosed, each patient completed follow-up visits through day 22, and the safety data reviewed internally with senior leaders and at a DEC meeting, prior to dose escalation greater than 100 mg	This will provide additional safety monitoring to ensure that any adverse hemodynamic or laboratory effects are detected prior to dosing of the next patient.	3.2.2 Rationale for Dose Selection Section 6.1.7 Description of Study Cohorts and Dose Escalation Figure 2 Cohort Progression and Dose Escalation Diagram (Group A) Figure 3 Cohort Progression and Dose Escalation Diagram (Group B and Group C) Section 6.1.7.2 Group A: Ascending Dose Cohorts Section 6.1.7.3 Optional Expansion Cohorts Section 6.1.7.4 Group B and Group C: Ascending Dose Cohorts Section 6.1.7.5 Group B and Group C: Optional Expansion Cohorts Section 6.1.7.6 Dose Escalation and Cohort Progression Section 7.2.1 Inclusion Criteria: Criterion #4

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
Starting dose for patients with HFrEF on sacubitril/valsartan (Group B) will be 30 mg and starting dose for patients with HFpEF (Group C) will be 30 mg	Potential risks will be mitigated by requiring the initial dose level to be 30 mg which is half-log less than the maximum tolerated dose level in HFrEF patients not taking sacubitril/valsartan (Group A) at this time, which was 100 mg.	Clinical Study Protocol Synopsis: Study Design Section 3.2.1 Rationale for Study Design Section 6.1.7.1 Study Groups
The randomization ratios in all future cohorts will be balanced (ie, 1:1)	Balanced randomization allows for optimal analysis of safety signals. This adjustment in the randomization ratio is intended to provide a more robust understanding of the safety and tolerability profile of REGN5381 in a setting where adverse events in the intended population are expected to be relatively high, even in the absence of active treatment.	Figure 2 Cohort Progression and Dose Escalation Diagram (Group A) Figure 3 Cohort Progression and Dose Escalation Diagram (Group B and Group C) Section 6.1.7.4 Group B and Group C: Ascending Dose Cohorts
An additional ascending dosing cohort has been added to Groups B and C (HFrEF patients on sacubitril/valsartan and HFpEF patients not taking sacubitril/valsartan, respectively).	This is to allow testing of doses from 30 mg to ≤300 mg without incremental dose increases of more than half log.	Figure 3 Cohort Progression and Dose Escalation Diagram (Group B and Group C) Section 6.1.7.4 Group B and Group C: Ascending Dose Cohorts Section 6.1.7.5 Group B and Group C: Optional Expansion Cohorts
Enrollment in Group A (HFrEF patients not taking sacubitril/valsartan) will be continued, but without right heart catheterization.	Review of available hemodynamic data at the time of this amendment suggest that there are adequate pulmonary capillary wedge pressure data at the 100 mg and 300 mg dose levels in this HFrEF patient population (not taking sacubitril/valsartan). Thus, the objective of assessing invasive hemodynamic effects of REGN5381 in Group A has been met and there is not a need for additional invasive assessments in this population at these doses. Going forward the primary aim in this group is to continue safety and tolerability assessments, which do not require right heart catheterization.	Clinical Study Protocol Synopsis: Study Design Section 3.2.1 Rationale for Study Design Section 9.2.8.1 Right Heart Catheterization and Invasive Hemodynamic Measurements Section 6.1 Study Description and Duration Section 6.1.1 Inpatient Treatment Period Section 6.1.7.1 Study Groups Section 6.1.7.2 Group A: Ascending Dose Cohorts

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
		Section 9.1.3 Footnotes for Table 5: Timing of Assessment in Relation to Study Drug (new)
The duration of pulse wave analysis recording at each visit has been reduced from about 2 hours to approximately 1 hour	Collection of these data over approximately 1 hour is considered sufficient to meet the exploratory objectives of the study. Furthermore, this will also allow more time for performance of the many other study related activities that occur on day 1 after the pulse wave analysis such as invasive hemodynamic monitoring.	Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period: Footnote #21 Section 9.1.2 Footnotes for Table 3: Schedule of Events for Outpatient Period Follow-Up Period: Footnote #9
The number of planned patients has been decreased from up to 149 to up to 122	This is to account for changes to study design and planned cohorts	Clinical Study Protocol Synopsis: Population, Statistical Plan Section 7.1 Number of Patients Planned Section 8.5 Method of Treatment Assignment Section 11.2 Justification of Sample Size
Minor editorial and typographical errors have been addressed and administrative revisions made	These updates were incorporated to ensure overall accuracy and consistency	Throughout the document

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Amendment 4

The purpose of this amendment is to modify the inclusion and exclusion criteria. The revisions have previously been communicated via an Urgent Safety Measure (USM).

Description of Change	Brief Rationale	Section # and Name
Additional inclusion and exclusion criteria have been added: Exclusion criterion: Medical history of severe pulmonary hypertension or a mean pulmonary artery pressure ≥45 mmHg at screening. Exclusion criterion: Medical history of liver cirrhosis. Inclusion criterion: Taking a stable approved dose of an Angiotensin Converting Enzyme (ACE) inhibitor, Angiotensin Receptor Blocker (ARB), hydralazine, or nitrates for at least 30 days prior to the screening visit (only for Group A).	These changes are being made following the issuance of a USM triggered by a serious adverse event (SAE) in the 300 mg dose cohort. The additional inclusion and exclusion criteria are intended to ensure the safety of patients participating in the study. Patients with severe pulmonary hypertension and liver cirrhosis are now excluded as they are at increased risk of developing acute organ injury in the setting of reduced blood pressure, an expected drug effect of REGN5381. The protocol now requires that HFrEF patients in Group A are on a stable dose of a vasodilator. This will increase the likelihood that, after discontinuing their previous vasodilator, they will better tolerate the vasodilatory actions of REGN5381.	Section 7.2.1 Inclusion Criteria: #16 Section 7.2.2 Exclusion Criteria: #12 and #27 Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period: #6
Minor editorial change	Corrected a typo	7.2.2 Exclusion Criteria: #21

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Amendment 3

The main purpose of this amendment is to incorporate additional separate cohorts to include patients with left ventricular ejection fraction ≥50%, to include patients currently taking sacubitril/valsartan, and to test a dose of ≤300 mg REGN5381.

Description of Change	Brief Rationale	Section # and Name
R5381-HF-2159 Protocol Amendment 2 (PA2) only included patients in single ascending dose cohorts with heart failure and reduced ejection fraction (HFrEF) not receiving sacubitril/valsartan (**Group A**). In this protocol amendment, an additional group (**Group B**) is being added to enroll HFrEF patients receiving sacubitril/valsartan in the study. Group B patients will be enrolled in a single dose cohort (Cohort 8) with the first 2 patients enrolled as a sentinel group. An optional dose cohort (Cohort 8B) will allow exploration of an additional dose level with the first 2 patients enrolled as a sentinel group. Optional expansion cohorts (Cohorts 8C and 9) may be enrolled to study additional patients at a dose level studied previously in Cohorts 8 or 8B. The dose selected for Cohort 8 will be no greater than 1/3 of the highest dose level previously tested in Group A that is deemed sufficiently well-tolerated. The dose selected for Cohort 8B will be no more than 3 times greater than that tested in Cohort 8 and deemed to be sufficiently well-tolerated. The dose selected for Cohorts 8C and 9 will be no greater than any dose level previously tested in Cohorts 8 or 8B.	The addition of Group B will allow the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of REGN5381 to be assessed in patients receiving sacubitril/valsartan. Sacubitril/valsartan is now guideline recommended standard of care for patients with HFrEF. Therefore, it is important to understand the effects of REGN5381 when added to this therapy. PA2 excluded patients on sacubitril/valsartan to avoid any potential additive pharmacology given the possible overlapping mechanisms of action. Potential risks of combination pharmacology will be mitigated by requiring the initial dose level to be no more than 1/3 of the highest dose level previously evaluated in patients not on sacubitril/valsartan (Group A) and deemed sufficiently well-tolerated. It is unclear whether sacubitril/valsartan acts through the NPR1 pathway, and direct measurement of cardiac pressures and related hemodynamics are likely to be the most effective way of assessing additivity of effects.	Clinical Study Protocol Synopsis: Study Design, Population, Statistical Plan Section 3.2.1 Rationale for Study Design Section 3.3.1 Risk Benefit for REGN5381 Section 6.1 Study Description and Duration Section 6.1.7 Description of Study Cohorts and Dose Escalation Figure 2 Cohort Progression and Dose Escalation Diagram (Group A) Section 6.1.7.1 Study Groups (New Section) Section 6.1.7.2 Group A: Ascending Dose Cohorts Section 6.1.7.3 Group A: Sentinel Dosing for Ascending Dose Cohorts Section 6.1.7.4 Group: A: Optional Dose Level Cohorts Section 6.1.7.3 Optional Expansion Cohorts Section 6.1.7.6 Group A: Dose Escalation and Cohort Progression Figure 3 Cohort Progression and Dose Escalation Diagram (Group B and Group C) Section 6.1.7.7 Group B and Group C: Sentinel Dosing (New Section) Section 6.1.7.8 Group B and Group C: Optional Dose Level Cohorts (New Section)

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
		Section 6.1.7.9 Group B and Group C: Optional Expansion Cohorts (New Section) Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria: #5 and 15 Section 7.2.2 Exclusion Criteria: #2 Section 8.5 Method of Treatment Assignment Section 8.9.1 Prohibited Medications Section 11.2 Justification of Sample Size
An additional group (**Group C**) is being added to enroll patients with heart failure and preserved ejection fraction (HFpEF). Similar to Group B, Group C patients will be enrolled in a single dose cohort (Cohort 10) with the first 2 patients enrolled as a sentinel group. An optional dose cohort (Cohort 10B) will allow exploration of an additional dose level with the first 2 patients enrolled as a sentinel group. Optional expansion cohorts (Cohorts 10C and 11) may be enrolled to study additional patients at a dose level studied previously in cohorts 10 or 10B. The dose selected for Cohort 10 will be no greater than 1/3 of the highest dose level previously tested in Group A that is deemed sufficiently well-tolerated. The dose selected for Cohort 10B will be no more than 3 times greater than that tested in Cohort 10 and deemed to be sufficiently well-tolerated. Optional Cohorts 10C and 11 may use any dose up to what	The addition of Group C will allow the safety, tolerability, and PK/PD of REGN5381 to be investigated in HFpEF. HFpEF is a large subpopulation of heart failure with a limited number of available therapies and a large unmet need. It is reasonable to hypothesize that reduction in cardiac pressures, which are expected with NPR1 agonism, may translate to benefit in these patients since congestion is also present in HFpEF. Since hemodynamic responses to vasodilators may differ between patients with HFrEF and HFpEF, direct measurement of heart pressures through catheterization is needed to evaluate this.	Title Page Clinical Study Protocol Synopsis: Title, Objectives, Study Design, Population, Statistical Plan Section 2.1 Primary Objective Section 3.1 Hypothesis Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 6.1.7.1 Study Groups (New Section) Section 6.1.7.7 Group B and Group C: Sentinel Dosing (New Section) Section 6.1.7.8 Group B and Group C: Optional Dose Level Cohorts (New Section) Section 6.1.7.9 Group B and Group C: Optional Expansion Cohorts (New Section) Figure 3 Cohort Progression and Dose Escalation Diagram (Group B and Group C) Section 7.1 Number of Patients Planned

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
was previously tested in Cohorts 10 or 10B.		Section 7.2 Study Population Section 7.2.1 Inclusion Criteria: #6 and 15 Section 7.2.2 Exclusion Criteria: #2 Section 8.5 Method of Treatment Assignment Section 8.9.1 Prohibited Medications Section 11.2 Justification of Sample Size Signature of Sponsor's Responsible Officers: Study Title
Additional cohorts for ≤300 mg intravenous [IV] REGN5381 (Cohort 5 and Cohort 7) are being added to the single ascending dose scheme in Group A, should safety and tolerability and hemodynamic data from lower dose cohorts support dose escalation. Cohort 5 is an additional sequential ascending dose cohort for ≤300 mg. Cohort 7 is an optional cohort should dose escalations smaller than 300 mg occur. Optional expansion cohorts (Cohort 5A and Cohort 7A) were also added to allow enrollment of additional patients at the dose level studied in Cohort 5 and Cohort 7. The end of study (EOS) visit for patients in cohorts with dose levels >100 mg to ≤300 mg will occur no earlier than study day 126.	Previously, in healthy normotensive and mildly hypertensive individuals, IV doses of REGN5381 up to 100 mg have been shown to be sufficiently safe and well tolerated to warrant continued clinical investigation in the phase 1 healthy volunteer study, R5381-HV-1987. Evaluation of REGN5381 at the ≤300 mg dose level in this study will enable the safety, tolerability, PK, and PD of the higher dose to be explored in heart failure patients. In the FIH study (R5381-HV-1987), flattening of the hemodynamic dose-response relationship was not observed up to 100 mg IV. Therefore, doses >100 mg may be necessary in order to fully explore the hemodynamic response in the patient population. The maximum nominal dose level 300 mg IV may only be pursued if hemodynamic responses have not clearly reached E_{max} and should the observed safety and tolerability at lower dose levels permit.	Clinical Study Protocol Synopsis: Study Design, Treatments Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Figure 2 Cohort Progression and Dose Escalation Diagram (Group A) Table 4 Schedule of Events for Outpatient Follow-Up Period Section 9.1.2 Footnotes for Table 3: Schedule of Events for Outpatient Follow-Up Period; footnote #4 Section 11.2 Justification of Sample Size

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
The inclusion criterion for NT-proBNP levels at screening was increased from >300 pg/mL to >1000 pg/mL.	This will allow for inclusion of more congested patients and will reduce the screen fail rate at right heart catheterization. An NT-proBNP cutoff greater than 1000 pg/mL will increase the specificity for congestion to more than 85% with a sensitivity of approximately 90%. It is reasonable to hypothesize that reduction in cardiac pressures, which are expected with NPR1 agonism, are most likely to benefit patients with more congestion.	Clinical Study Protocol Synopsis; Study Design Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, criterion #7 Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period, footnote #3
An additional inclusion criterion has been added that patients must also have a Right Atrial Pressure (RAP) >5 mmHg on screening right heart catheterization. Inclusion criterion #3 was also expanded for further clarification.	This will allow inclusion of patients with right sided congestion since a normal RAP is ≤5mmHg. PA2 only contained inclusion criteria for left sided congestion (PCWP≥15mmHg). A small minority of patients have elevated PCWP without elevation of RAP, ie, left sided congestion without right sided congestion. Given that the preclinical data suggests that REGN5381 is a systemic venodilator this inclusion criteria will provide additional assurance that all participants have elevated systemic venous pressures. For inclusion criterion #3 additional examples of signs and symptoms of congestive heart failure were provided for clarification.	Clinical Study Protocol Synopsis; Study Design Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 6.1.1 Inpatient Treatment Period Section 7.2.1 Inclusion Criteria, criterion #3 and #9 Section 7.2.2 Exclusion Criteria, criterion #20 Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period; footnote #6
Additional oscillometric BP & PR measurements were added on day 1 during the RHC procedure.	To more closely monitor systemic blood pressure and pulse rate changes and to better understand if any relationships exist with continuous hemodynamic parameters following drug administration	Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period, footnote #13 Table 5 Timing of Assessment in Relation to Study Drug Administration

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Description of Change	Brief Rationale	Section # and Name
An additional exploratory objective has been added to measure hemodynamic parameters non-invasively using pulse wave analysis.	To allow assessment of the durability of some hemodynamic effects beyond day 1 (the right heart catheterization is conducted only on the day of dosing).	Clinical Study Protocol Synopsis: Objectives Section 2.3 Exploratory Objectives Section 4.1.3 Exploratory Endpoints Section 5.6 Pharmacodynamic and Other Biomarker Variables Table 3 Schedule of Events for Screening Period and Inpatient Treatment Period Section 9.1.1 Footnotes for Table 2: Schedule of Events for Screening Period and Inpatient Treatment Period, footnote #21 Table 4 Schedule of Events for Outpatient Follow-Up Period Section 9.1.2 Footnotes for Table 3: Schedule of Events for Outpatient Period Follow-Up Period, footnote #9 Table 5 Timing of Assessment in Relation to Study Drug Administration Section 9.2.8.13 Non-Invasive Hemodynamic Parameters Derived from Pulse Wave Analysis
An additional exploratory endpoint has been added to measure carbohydrate antigen 125 (CA125), a biomarker of heart failure.	To better understand the mechanism of action of REGN5381 by measuring its effects on a marker of the severity of congestion and prognosis	Section 4.1.3 Exploratory Endpoints Section 5.6 Pharmacodynamic and Other Biomarker Variables Section 6.1.1 Inpatient Treatment Period Table 3 Schedule of Events for Screening Period and Inpatient Treatment Period Table 4 Schedule of Events for Outpatient Follow-Up Period Section 9.2.8.6 CA125 Levels (New Section)

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Description of Change	Brief Rationale	Section # and Name
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 6.1.4 Provision of Sacubitril/Valsartan to Study Participants After Trial Completion (New Section)
Minor edits for clarifications, corrections, general editorial modifications, and minor changes	Edits were made to ensure that the protocol is clear and consistent	Throughout the protocol

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Amendment 2

The main purpose of this amendment is to modify the protocol following feedback from various Health Authorities.

Description of Change	Brief Rationale	Section # and Name
Included additional pregnancy testing to the Outpatient Follow-Up period of the study	Additional pregnancy testing will increase the frequency of monitoring for pregnancy over the total expected exposure of the study drug	Section 6.1.3 Outpatient Follow-Up Period Table 4 Schedule of Events for Outpatient Follow-Up Period Section 9.1.2 Footnotes for Table 3: Schedule of Events for Outpatient Follow-Up Period, #7
Added rows to the Schedule of Events to account for measuring estimated glomerular filtration rate and international normalized ratio	These rows were erroneously not included in the schedule of events	Table 3 Schedule of Events for Screening Period and Inpatient Treatment Period Section 7.2.2 Exclusion Criteria #25 Section 9.2.4.11 Laboratory Testing, other laboratory tests
Edits were made to two exclusion criteria	These exclusion criteria were revised for clarification	Section 7.2.2 Exclusion Criteria #28 and #30
Language regarding COVID-19 vaccine and boosters has been added to the protocol	This additional language was added to provide guidance on the choices subjects have with regard to receiving a COVID-19 vaccination	Section 3.3 Risk-Benefit Section 7.2.2 Exclusion Criteria #33 Section 8.9 Concomitant Medications
Revised the exclusion criterion for women of childbearing potential	Minor clarifications were made to align with the updated study protocol template	Section 7.2.2 Exclusion Criteria #32
Added '/procedures' to the 'concomitant medication' row of the schedule of events and updated the blood chemistry language Replaced ENTRESTO (trade name) with sacubitril/valsartan (international nonproprietary name [INN])	Administrative changes	Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 7.2.2 Exclusion Criteria, #2 Section 8.9.1 Prohibited Medications Table 3 Schedule of Events for Screening Period and Inpatient Treatment Period Table 4 Schedule of Events for Outpatient Follow-up Period Section 9.2.4.11 Laboratory Testing

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Amendment 1

The purpose of this amendment is to change references of this being a phase 1b study to phase 2a.

Description of Change	Brief Rationale	Section # and Name
All mentions of this being a phase 1b study have been changed to phase 2a.	The objectives of this study are consistent with a phase 2a trial as per the ICH guidelines. This change was made to align with the clinical trial requirements in the countries where the study is being conducted.	Title page Clinical Study Protocol Synopsis: Title, Study Design, Statistical Plan Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 11.1 Statistical Hypothesis Section 20 Investigator's Agreement

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of term
ACE	Angiotensin-converting enzyme
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANP	Atrial Natriuretic Peptide (active form)
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
AUC	Area under the curve
BNP	Brain Natriuretic Peptide (active form)
BP	Blood Pressure
BUN	Blood urea nitrogen
CA125	Carbohydrate antigen 125
cGMP	Cyclic guanosine monophosphate
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CTFG	Clinical Trial Facilitation Group
CVP	Central venous pressure
DBP	Diastolic blood pressure
DEC	Dose Escalation Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of study
FDA	US Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Abbreviation	Definition of term
eGFR	Estimated glomerular filtration rate
GPS	Global Patient Safety
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B virus surface antigen
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HPS	Hepatopulmonary syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
KIM-1	Kidney injury molecule-1
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease
mPAP	Mean pulmonary artery pressure
MRA	Mineralocorticoid receptor antagonists
NHP	Nonhuman primates
NPR1	Refers to both Natriuretic peptide receptor A protein and gene NPR1
NPR-A	Natriuretic peptide receptor A
NPR-C	Natriuretic peptide clearance receptor (encoded by the gene NPR3)
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAC	Pulmonary artery catheter
PA	Protocol Amendment
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamics

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Abbreviation	Definition of term
PK	Pharmacokinetic
proANP	Pro-atrial natriuretic peptide
proBNP	Pro-brain natriuretic peptide
PR	Pulse rate
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RBC	Red blood cell
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
RHC	Right heart catheterization
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SV	Stroke volume
SvO2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WOCBP	Women of childbearing potential

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

TABLE OF CONTENTS

AMENDMENT HISTORY 2
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 20
1. INTRODUCTION 35
2. STUDY OBJECTIVES 39
2.1. Primary Objective 39
2.2. Secondary Objectives 39
2.3. Exploratory Objectives 39
3. HYPOTHESIS AND RATIONALE 40
3.1. Hypothesis 40
3.2. Rationale 40
3.2.1. Rationale for Study Design 40
3.2.2. Rationale for Dose Selection 45
3.3. Risk-Benefit 46
3.3.1. Risk Benefit for REGN5381 46
4. ENDPOINTS 47
4.1. Primary and Secondary Endpoints 47
4.1.1. Primary Endpoint 47
4.1.2. Secondary Endpoints 47
4.1.3. Exploratory Endpoints 47
5. STUDY VARIABLES 49
5.1. Demographic and Baseline Characteristics 49
5.2. Safety Variables 49
5.3. Patient Reported Outcomes 49
5.4. Pharmacokinetic Variables 49
5.5. Immunogenicity Variables 49
5.6. Pharmacodynamic and Other Biomarker Variables 49
6. STUDY DESIGN 50
6.1. Study Description and Duration 50
6.1.1. Inpatient Treatment Period 51
6.1.2. Extended Inpatient Monitoring Period 53
6.1.3. Outpatient Follow-Up Period 53

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

6.1.4. Provision of Sacubitril/Valsartan to Study Participants After Trial Completion 53
6.1.5. Restarting Home Heart Failure Medications 53
6.1.6. Inpatient Discharge Criteria 54
6.1.7. Description of Study Cohorts and Dose Escalation 55
6.1.7.1. Study Groups 56
6.1.7.2. Group A: Ascending Dose Cohorts 57
6.1.7.3. Group A: Optional Expansion Cohorts 57
6.1.7.4. Group B and Group C: Ascending Dose Cohorts 58
6.1.7.5. Group B and Group C: Optional Expansion Cohorts 59
6.1.7.6. Dose Escalation and Cohort Progression 59
6.1.8. Study Stopping Rules 60
6.1.8.1. Individual Participant Stopping Rules 60
6.1.8.2. Study Stopping Criteria 60
6.1.9. End of Study Definition 60
6.2. Planned Interim Analysis 60
7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS 61
7.1. Number of Participants Planned 61
7.2. Study Population 61
7.2.1. Inclusion Criteria 61
7.2.2. Exclusion Criteria 62
7.3. Premature Withdrawal from the Study 66
7.4. Replacement of Participants 66
7.5. Re-Screening of Participants 66
8. STUDY TREATMENTS 67
8.1. Investigational and Reference Treatments 67
8.2. Rescue Treatments 67
8.2.1. Rescue Therapy 67
8.2.2. Specific Complications of Cardiac Failure or Reversible Severe Hypotension to Consider in Differential Diagnosis 68
8.3. Dose Modification and Study Treatment Discontinuation Rules 68
8.3.1. Dose Modification 68

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

8.3.2. Study Drug Discontinuation 68
8.4. Management of Acute Reactions 69
8.4.1. Acute Intravenous Infusion Reactions 69
8.4.1.1. Interruption of the Intravenous Infusion 69
8.4.1.2. Termination of the Intravenous Infusion 69
8.5. Method of Treatment Assignment 70
8.6. Blinding 70
8.7. Emergency Unblinding 71
8.8. Treatment Logistics and Accountability 71
8.8.1. Packaging, Labeling, and Storage 71
8.8.2. Supply and Disposition of Treatments 71
8.8.3. Treatment Accountability 72
8.8.4. Treatment Compliance 72
8.9. Concomitant Medications 72
8.9.1. Prohibited Medications 72
8.9.2. Permitted Medications 72
9. STUDY SCHEDULE OF EVENTS AND PROCEDURES 74
9.1. Schedule of Events 74
9.1.1. Footnotes for Table 3: Schedule of Events for Screening Period and Inpatient Treatment Period 78
9.1.2. Footnotes for Table 4: Schedule of Events for Outpatient Period Follow-Up Period 84
9.1.3. Footnotes for Table 5: Timing of Assessment in Relation to Study Drug Administration 86
9.1.4. Early Termination Visit 87
9.1.5. Unscheduled Visits 87
9.2. Study Procedures 87
9.2.1. Procedures Performed Only at the Screening/Baseline Visit 87
9.2.1.1. Height 87
9.2.1.2. Clinic Admission for Baseline Measurements and Randomization 87
9.2.2. Procedures Related to Study Drug Administration 88
9.2.3. Efficacy Procedures 88
9.2.4. Safety Procedures 88

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9.2.4.1. Body Weight 88
9.2.4.2. Oscillometric Blood Pressure and Pulse Rate Measurement 88
9.2.4.3. Orthostatic Blood Pressure and Pulse Rate Measurement 88
9.2.4.4. Pulse Oximetry 88
9.2.4.5. Respiratory Rate Measurement 88
9.2.4.6. Body Temperature Measurement 88
9.2.4.7. Physical Examination 89
9.2.4.8. Telemetry (3-lead Electrocardiogram) 89
9.2.4.9. Electrocardiogram 89
9.2.4.10. Oral Fluid Intake Volume and Urine Output Volume Measurements 89
9.2.4.11. Laboratory Testing 89
9.2.5. Drug Concentration and Measurements 91
9.2.6. Immunogenicity Measurements and Samples 91
9.2.7. Patient-Reported Outcomes 91
9.2.7.1. Dyspnea Questionnaire 91
9.2.8. Pharmacodynamic and Exploratory Biomarker Procedures 91
9.2.8.1. Right Heart Catheterization and Invasive Hemodynamic Measurements 92
9.2.8.2. cGMP Levels 92
9.2.8.3. NT-proBNP 92
9.2.8.4. NT-proANP 92
9.2.8.5. ANP and BNP Levels 92
9.2.8.6. CA125 Levels 93
9.2.8.7. Norepinephrine Levels 93
9.2.8.8. Renin Levels 93
9.2.8.9. Aldosterone Levels 93
9.2.8.10. Urine Sodium Levels 93
9.2.8.11. Kidney Injury Molecule-1 (KIM-1) 93
9.2.8.12. Urinary Albumin Creatinine Ratio 94
9.2.8.13. Non-Invasive Hemodynamic Parameters Derived from Pulse Wave Analysis 94
9.2.9. Pharmacogenomic Analysis (Optional) 94
10. SAFETY EVALUATION AND REPORTING 95
10.1. Recording and Reporting Adverse Events 95
10.1.1. General Guidelines 95

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

10.1.2. Reporting Procedure 96
10.1.3. Events that Require Expedited Reporting to Sponsor 96
10.2. Definitions 97
10.2.1. Adverse Event 97
10.2.2. Serious Adverse Event 97
10.2.3. Adverse Events of Special Interest 97
10.2.4. Infusion Reactions 98
10.2.5. Severity 98
10.2.6. Causality 98
10.3. Safety Monitoring 100
10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators 100
11. STATISTICAL PLAN 101
11.1. Statistical Hypothesis 101
11.2. Justification of Sample Size 101
11.3. Analysis Sets 102
11.3.1. Safety Analysis Set 102
11.3.2. Pharmacodynamic Analysis Set (PAS) 102
11.3.3. Pharmacokinetic Analysis Set 102
11.3.4. Immunogenicity Analysis Set 102
11.4. Statistical Methods 102
11.4.1. Participant Disposition 103
11.4.2. Demography and Baseline Characteristics 103
11.4.3. Efficacy/Pharmacodynamic Endpoint Analyses 103
11.4.4. Control of Multiplicity 103
11.4.5. Safety Analysis 104
11.4.5.1. Adverse Events 104
11.4.5.2. Other Safety 104
11.4.5.3. Treatment Exposure 105
11.4.5.4. Treatment Compliance 105
11.4.6. Pharmacokinetics 105
11.4.6.1. Analysis of Drug Concentration Data 105
11.4.7. Analysis of Immunogenicity Data 105

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

11.5. Statistical Considerations Surrounding the Premature Termination of a Study 106
12. QUALITY CONTROL AND QUALITY ASSURANCE 107
12.1. Data Management and Electronic Systems 107
12.1.1. Data Management 107
12.1.2. Electronic Systems 107
12.2. Study Monitoring 107
12.2.1. Monitoring of Study Sites 107
12.2.2. Source Document Requirements 108
12.2.3. Case Report Form Requirements 108
12.3. Audits and Inspections 108
12.4. Study Documentation 109
12.4.1. Certification of Accuracy of Data 109
12.4.2. Retention of Records 109
12.4.3. Recruitment Strategy 109
12.4.4. Data Protection 109
13. ETHICAL AND REGULATORY CONSIDERATIONS 111
13.1. Good Clinical Practice Statement 111
13.2. Informed Consent 111
13.3. Participants Confidentiality and Data Protection 111
13.4. Institutional Review Board/Ethics Committee 112
13.5. Clinical Study Data Transparency 112
14. PROTOCOL AMENDMENTS 113
15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE 114
15.1. Premature Termination of the Study 114
15.2. Close-out of a Site 114
16. CONFIDENTIALITY 114
17. FINANCING AND INSURANCE 114
18. PUBLICATION POLICY 114
19. REFERENCES 115
20. INVESTIGATOR'S AGREEMENT 119
SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS 120

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

LIST OF TABLES

Table 1: Study Groups and Cohorts....37
Table 2: Restarting Home Heart Failure Medications....54
Table 3: Schedule of Events for Screening Period and Inpatient Treatment Period....75
Table 4: Schedule of Events for Outpatient Follow-Up Period....82
Table 5: Timing of Assessment in Relation to Study Drug Administration....85
Table 6: Half- Width of the 90% Confidence Interval for the Difference in Mean Change from Baseline in PCWP (mmHg)....101

LIST OF FIGURES

Figure 1: Study Flow Diagram....51
Figure 2: Cohort Progression and Dose Escalation Diagram (Group A)....56
Figure 3: Cohort Progression and Dose Escalation Diagram (Group B and Group C)....58

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of REGN5381, an NPR1 Agonist, in Heart Failure Patients with Elevated Pulmonary Capillary Wedge Pressure
Short Title	REGN5381 in heart failure patients with elevated pulmonary capillary wedge pressure
Site Locations	Approximately 10 to 12 sites are expected globally
Objectives	**Primary Objective** The primary objective of the study is to evaluate the safety and tolerability of single doses of REGN5381 in patients with heart failure with evidence of congestion. **Secondary Objectives** The secondary objectives of the study are to: • Evaluate the effects of single doses of REGN5381 on hemodynamic parameters • Evaluate the effects of REGN5381 on a clinical biomarker of heart failure severity • Characterize the pharmacokinetics of single doses of REGN5381 • Assess the immunogenicity of REGN5381 **Exploratory Objectives** The exploratory objectives of the study are to: • Evaluate the effects of REGN5381 on downstream biomarkers of NPR1 activation • Explore the effects of REGN5381 on oxygen delivery and extraction • Explore the effects of REGN5381 on diuresis and renal function • Explore the effects of REGN5381 on renal tubular injury • Explore the effects of REGN5381 on the renin-aldosterone system • Explore the effects of REGN5381 on sympathetic nervous system activity • Explore the effects of REGN5381 on biologically active ligands of the REGN5381 target (NPR1) • Explore the effects of REGN5381 on a biomarker of atrial volume and pressure overload • Explore the effects of REGN5381 on patient reported dyspnea • Explore the effects of REGN5381 on hemodynamic parameters over time as measured by non-invasive pulse wave analysis • Increase molecular understanding of heart failure and related diseases

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Study Design	This is a phase 2a, randomized, double-blind, placebo-controlled, multi-site study of REGN5381 in heart failure patients with symptoms of congestion. The study is comprised of 3 patient study groups. Group A is comprised of patients with heart failure with reduced ejection fraction (HFrEF) not on sacubitril/valsartan. Group B is comprised of patients with HFrEF on sacubitril/valsartan. Group C is comprised of patients with heart failure with preserved ejection fraction (HFpEF) not on sacubitril/valsartan. Group A used a single ascending dose design (dose levels are 10 mg to ≤300 mg) with optional dose level cohorts (not to exceed 300 mg) to further explore the dose range, or optional expansion cohorts to evaluate more patients at a specific dose level. As of PA5, invasive right heart catheterization will no longer be performed in Group A patients. Groups B and C use single dose cohorts with the option to further expand to evaluate the dose further in these patient populations (at an initial dose level 30 mg). An optional dose level cohort will allow exploration of an additional dose level in Groups B and C (with a maximum dose of ≤300 mg). Study drug will be administered as an IV infusion. Note: Groups A and B enrollment has been closed as of PA6. However, patients already enrolled in these groups will complete their follow-up accordingly. Study patients are ambulatory heart failure patients with New York Heart Association (New York Heart Association (NYHA) Classification, 2018) class II or III symptoms who have objective evidence of congestion including N-terminal pro-brain natriuretic peptide (NT-proBNP) >1000 pg/mL in Group B or >300 pg/mL in Group C. Patients will be admitted to a hospital one day prior to the right heart catheterization (RHC) and those with a pulmonary capillary wedge pressure (PCWP) ≥15 mmHg and right atrial pressure (RAP) >5 mmHg will be eligible and randomized to study drug vs placebo. Heart failure medications other than beta-blockers will be withheld for the duration of the RHC (sacubitril/valsartan will not be held in Group B). Invasive hemodynamic measures including PCWP, right atrial pressure (RAP) and cardiac output (CO) will be monitored for a period of at least 6 hours. After removal of the pulmonary artery catheter, patients will remain in hospital for observation and re-starting of their home heart failure medications for a total of at least 5 nights. Patients will return to the study site for outpatient safety assessments and additional biomarker assessments. Note: Groups A and B enrollment has been closed as of PA6. However, patients already enrolled in these groups will complete their follow-up accordingly.
Study Duration	Depending on the dose cohort, the duration of the study for a participant is approximately 51 to 155 days which includes the screening period (up to 4 weeks).
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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Population

Sample Size:	Up to a total of 122 adult patients will be randomized in this study. In Group A, 20 patients have been randomized and dosed in ascending dose cohorts and optional expansion cohorts with the right heart catheterization procedure. Up to an additional 30 patients may be randomized across 3 ascending dose cohorts in Group A without the right heart catheterization procedure. No further dosing of cohorts undergoing the right heart catheterization procedure will occur in Group A. Right heart catheterization will only occur in Groups B and C cohorts. In Group B, up to 36 patients may be randomized across 3 ascending dose cohorts and 2 optional expansion cohorts. In Group C, up to 36 patients may also be randomized across 3 ascending dose cohorts and 2 optional expansion cohorts. Note: Groups A and B enrollment has been closed as of PA6. However, patients already enrolled in these groups will complete their follow-up accordingly.
Target Population:	Eligible patients for this study are ambulatory males and females with NYHA class II/III heart failure that in the opinion of the investigator have a clinical indication for right heart catheterization.

Treatments

Study Drug **Dose/Route/Schedule:**	REGN5381 drug product is supplied as a lyophilized powder in a sterile single-use vial. Patients will receive either REGN5381(≤300 mg) or matching placebo as a single IV infusion.
Placebo **Route/Schedule:**	Placebo to match REGN5381, is supplied as a lyophilized powder in a sterile single-use vial.

Endpoints

Primary:	The incidence and severity of treatment-emergent adverse events (TEAEs) through the end-of-study (EOS) visit.
Secondary:	The secondary endpoints are: • Change from baseline in PCWP, RAP, CO, systemic vascular resistance (SVR), mean pulmonary artery pressure (mPAP), and pulmonary vascular resistance (PVR) over 6 hours post-dose administration (in cohorts undergoing right heart catheterization) • Change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse rate (PR) over the first 6 hours and 24 hours post-dose administration (day 1), and through the EOS visit • Change from baseline in NT-proBNP to 6 hours and 24 hours post-dose administration (day 1), and through the EOS visit • Concentrations of REGN5381 in serum through the EOS visit • Incidence and titer of anti-drug antibodies (ADA) over time

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Procedures and Assessments	Safety assessments will include monitoring of body weight, vital signs (oscillometric and orthostatic blood pressure (BP) and PR, temperature, and respiratory rate), physical examination, pulse oximetry, telemetry, electrocardiogram (ECG), laboratory testing, and the monitoring and reporting of adverse events (AEs). Pharmacodynamic (PD) measurements will include invasive hemodynamic measurements obtained at right heart catheterization. Samples will also be collected for drug concentration, ADA and biomarker measurements (including but not limited to NT-proBNP, cyclic guanosine monophosphate (cGMP), international normalized ratio (INR), estimated glomerular filtration rate (eGFR), renin, and aldosterone).
Statistical Plan	**Statistical Hypothesis**: There is no formal statistical hypothesis in this phase 2 study. Analysis of efficacy/PD variables will be descriptive. The focus of the study is to evaluate the safety, tolerability and hemodynamic effects of REGN5381 in heart failure patients. The comparison groups for the hemodynamic endpoints are patients who receive REGN5381 versus patients who receive placebo. **Justification of Sample Size**: Up to 122 adult patients will be randomized in: • 4 sequential single ascending dose cohorts for HFrEF patients not taking sacubitril/valsartan with right heart catheterization procedure (N=16 - Cohort 1, 2, 3, 5 [10, 30, 100, 300 mg REGN5381 or placebo, respectively] (randomized 3:1)) • 3 ascending cohorts for HFrEF patients not taking sacubitril/valsartan without right heart catheterization procedure (N=30 - Cohort 6, 7, 8 [100, ≤300, ≤300 mg REGN5381 or placebo, respectively]) • 3 ascending cohorts for HFrEF patients with sacubitril/valsartan (N=18 - Cohort 9, 10, 11 [30, ≤100, ≤300 mg REGN5381 or placebo, respectively]), and 3 ascending cohorts for HFpEF patients without sacubitril/valsartan (N=18 - Cohort 12, 13, 14 [30, ≤100, ≤300 mg REGN5381 or placebo, respectively]) • In addition, there are 6 optional expansion cohorts (N=40 - Cohorts 3A, 5A, 11A, 11B, 14A, 14B). This will allow enrollment of at least 8 and up to 18 patients at a specific dose and at least 8 and up to 18 patients in a placebo group Based on the standard deviation (SD) from prior studies evaluating nesiritide in heart failure, 8 patients in each group will provide enough precision with the half-width of 90% confidence interval as 5.9 mmHg (which is within the expected effect size of 6 mmHg to 11 mmHg observed with nesiritide). **Analysis of Endpoints**: Safety and tolerability will be assessed by clinical review of all relevant parameters including BP, PR, pulse oximetry, telemetry, temperature, respiratory rate, physical examination, ECGs, urine output, laboratory evaluations (hematology, chemistry, urinalysis), and AEs. For the PCWP in expansion active treatment cohort versus pooled placebo, summary statistics and nominal p-value will be provided by treatment group, using mixed-effect model with repeated measures. Nominal p-values will be provided as a measure of the strength of evidence.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

	The continuously collected PD parameters will be analyzed with moving average. Summary statistics including the mean change from baseline over the 6 hours post-dosing and standard error (SE) will be provided by treatment groups.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 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).

NPR1 is a Therapeutic Target in Heart Failure

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 receptor that mediates the functions of ANP and BNP is known as natriuretic peptide receptor A (NPR-A), which is encoded by the gene *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). It has been suggested that 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-00336967-1.0 Approved - 09 Feb 2024 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 (O'Connor, 2011) (Packer, 2017) (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 Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved for this indication (McMurray, 2014) (Entresto (sacubitril and valsartan) [Prescribing Information], 2021). 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 results in only modest elevations of natriuretic peptides (Myhre, 2019), 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 Preclinical Development

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.

In vivo studies have demonstrated that 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, preclinical models are limited in defining and predicting the exact hemodynamic effects of REGN5381 in humans, and of particular importance, in patients with congestive heart failure. More detailed information is provided in the Investigator's Brochure (IB), Section 4.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

REGN5381 Clinical Development

REGN5381 has been or is currently being evaluated in 3 clinical studies: R5381-HV-1987, R9035-HV-2125, and this study R5381-HF-2159. Refer to the Investigator's Brochure for detailed information from these studies.

This study, R5381-HF-2159, is a randomized, double-blind, placebo-controlled, multi-site study of REGN5381 in heart failure patients with symptoms of congestion. Preliminarily, as of 15 May 2023, a total of 20 patients have received a single dose of REGN5381 or placebo in this study, and all patients were in Group A (HFrEF not on sacubitril/valsartan). The following cohorts were completed, and patients in each cohort were dosed in a 3:1 REGN5381:placebo randomization ratio: 4 patients in Cohort 1 at the 10 mg dose level, 4 patients in Cohort 2 at the 30 mg dose level, 4 patients in Cohort 3 at the 100 mg dose level, and 4 patients in Cohort 5 at the 300 mg dose level. Two cohorts were also initiated but not completed: 2 patients in Cohort 3A (optional expansion cohort) at the 100 mg dose level (randomization 1:1 REGN5381:placebo), and 2 patients in Cohort 5A (optional expansion cohort) at the 300 mg dose level (randomization 5:4 REGN5381:placebo) (see Table 1).

Table 1: Study Groups and Cohorts

Group	Cohort	Dose	Randomization (REGN5381:PBO)
Group A: HFrEF patients not taking sacubitril/valsartan	Cohort 1	10 mg IV	3:1
	Cohort 2	30 mg IV	3:1
	Cohort 3	100 mg IV	3:1
	Cohort 3A	100 mg IV	1:1
	Cohort 5	300 mg IV	3:1
	Cohort 5A	300 mg IV	5:4
	Cohort 6	100 mg IV	1:1
	Cohort 7	≤300 mg IV	1:1
	Cohort 8	≤300 mg IV	1:1
Group B: HFrEF patients on sacubitril/valsartan	Cohort 9	30 mg IV	1:1
	Cohort 10	≤100 mg IV	1:1
	Cohort 11	≤300 mg IV	1:1
	Cohort 11A	≤Dose level tested in Cohort 11	1:1
	Cohort 11B	≤Dose level tested in Cohort 11	1:1
Group C: HFpEF patients not taking sacubitril/valsartan	Cohort 12	30 mg IV	1:1
	Cohort 13	≤100 mg IV	1:1
	Cohort 14	≤300 mg IV	1:1
	Cohort 14A	≤Dose level tested in Cohort 14	1:1
	Cohort 14B	≤Dose level tested in Cohort 14	1:1

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

To date, a total of 12 TEAEs have been reported across all 20 patients. Two of these TEAEs were serious adverse events (SAEs). Each SAE occurred in a patient in a 300 mg dose level cohort (one patient in Cohort 5 and one patient in Cohort 5A). One patient with a history of severe pulmonary hypertension and liver cirrhosis experienced Ischemic hepatitis possibly precipitated from hypoperfusion. The patient experienced a transient episode of hypotension with tachycardia and anxiety. A second patient with a history of severe pulmonary hypertension, renal insufficiency and ventricular arrhythmias, presented with worsening heart failure and experienced fatal cardiac failure in which symptomatic hypotension contributed. The hemodynamic (venodilatory) effects of REGN5381 in the setting of severe pulmonary hypertension and other co-morbidities may have contributed to the course in these patients. Refer to the Investigator's Brochure for detailed information regarding these 2 SAEs in the R5381-HF-2159 study. In addition, review of available hemodynamic data at the time of this amendment suggests the expected hemodynamic effects, with reductions in pulmonary capillary wedge pressure (PCWP) apparent at the 100 mg and 300 mg dose levels in this HFrEF patient population not on sacubitril/valsartan.

These data, along with clinical experience with recombinant ANP and BNP (Saito, 1987), suggest 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. Healthy participants have normal (low) CVPs, and when these pressures are lowered to below normal levels by NPR1 agonists, this reduces venous filling during the cardiac cycle and thus reduces SV. In contrast, congestive heart failure patients have elevated CVPs. Stroke volume was shown to improve when congestive heart failure patients receive treatment with the NPR1 agonist nesiritide (Saito, 1987). In fact, lowering of venous pressures is the therapeutic goal in congested patients and is the mechanism by which they are "decongested" resulting in dyspnea relief. This is because lowering of venous pressures from an abnormally high pressure back to a normal level improves the Frank-Starling relationship. It is hypothesized that REGN5381 will reduce venous pressures in this population and improve hemodynamics, including SV.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

The secondary objectives of the study are to:

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

2.3. Exploratory Objectives

The exploratory objectives of the study are to:

- Evaluate the effects of REGN5381 on downstream biomarkers of NPR1 activation
- Explore the effects of REGN5381 on oxygen delivery and extraction
- Explore the effects of REGN5381 on diuresis and renal function
- Explore the effects of REGN5381 on renal tubular injury
- Explore the effects of REGN5381 on the renin-aldosterone system
- Explore the effects of REGN5381 on sympathetic nervous system activity
- Explore the effects of REGN5381 on biologically active ligands of the REGN5381 target (NPR1)
- Explore the effects of REGN5381 on a biomarker of atrial volume and pressure overload
- Explore the effects of REGN5381 on patient reported dyspnea
- Explore the effects of REGN5381 on hemodynamic parameters over time as measured by non-invasive pulse wave analysis
- Increase molecular understanding of heart failure and related diseases

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

REGN5381 is sufficiently safe and well tolerated in heart failure patients with congestion to permit continued clinical investigation.

3.2. Rationale

3.2.1. Rationale for Study Design

Note: Groups A and B enrollment has been closed as of PA6. However, patients already enrolled in these groups will complete their follow-up accordingly.

This is a phase 2a, randomized, double-blind, placebo-controlled, multi-site study of REGN5381 in heart failure patients with congestion. The study is designed to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of single ascending doses of the NPR1 agonist mAb REGN5381 in ambulatory heart failure patients with congestion. This study uses a single ascending dose (SAD) design in addition to optional expansion cohorts, further described below.

The study population is comprised of ambulatory heart failure patients with congestion. HFrEF patients on sacubitril/valsartan (Group B) and HFpEF patients not taking sacubitril/valsartan (Group C) will be undergoing a right heart catheterization as part of this study. Right heart catheterization is a commonly performed procedure in patients with heart failure and is used by clinicians to better understand patients' fluid status, intracardiac pressures, and hemodynamics (particularly when these are uncertain from clinical assessment) in order to optimize treatment. Right heart catheterization is the most accurate way to measure intracardiac pressures, and elevated intracardiac pressures are the primary cause of symptoms in heart failure (Lindenfeld, 2010) (Yancy, 2013). Evaluating the effects of REGN5381 on intracardiac pressures will improve understanding of its hemodynamic effects, and therefore its therapeutic potential for future applications. In addition, a clear understanding of hemodynamic changes caused by REGN5381 (eg, effects on systemic vascular resistance, venous pressures, and cardiac output) will allow better evaluation and treatment of any potential hemodynamic AEs or safety signals. As of PA5, invasive right heart catheterization will no longer be performed in HFrEF patients not taking sacubitril/valsartan (Group A) as a review of currently available hemodynamic data suggests reductions in PCWP at the 100 mg and 300 mg dose levels in this HFrEF patient population not on sacubitril/valsartan. Thus, the objective of assessing the right heart hemodynamic effects of REGN5381 in Group A has been met and there is not a need to do further invasive testing. Going forward the primary aim in Group A is to continue safety and tolerability assessments.

Several protocol elements have been instituted to ensure the safety of trial participants. The study will be conducted at sites that have physicians and nursing staff familiar with performing right heart catheterization in heart failure patients, the appropriate monitoring (eg, telemetry and pulse oximetry), and institutional policies for management of catheters including those aimed at ensuring sterile technique to minimize infection risk. The site must have standard emergency equipment available in addition to vasopressors and IV fluid therapy for use in patients with symptomatic hypotension (Section 8.2). Additionally, the length of the invasive monitoring is of limited duration and no longer than needed to accomplish the study goals and to ensure patient safety, in order to limit risks to the patient (this is discussed more in detail below). However, if the

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

investigator deems it necessary to continue invasive hemodynamic monitoring for longer than the period required in the protocol for purposes of safely guiding medical management of the patient, the protocol allows for that discretion. Other elements to ensure patient safety and minimize study risk include a sequential single ascending dose design, a Dose Escalation Committee (DEC), protocol-specified rules regarding management of concomitant heart failure medications, strict inpatient discharge criteria, and an Extended Inpatient Monitoring period available for patients who are deemed not ready for discharge (Section 6.1).

The trial population is comprised of New York Heart Association (New York Heart Association (NYHA) Classification, 2018) class II or class III heart failure patients with signs and/or symptoms of congestion. Groups B and C patients must have a clinical indication for right heart catheterization in the opinion of the investigator, as was the requirement for Group A patients randomized and dosed in cohorts involving the RHC procedure. NYHA class I patients are those with no functional limitations during normal physical activity and usually do not require right heart catheterization in the context of their clinical care. NYHA class IV patients are clinically unstable and not suitable for participation in a first-in-patient heart failure study. NYHA class II and III patients typically have mild to moderate symptoms of heart failure with some physical activity restrictions however are often managed in the outpatient setting (Ponikowski, 2016) (New York Heart Association (NYHA) Classification, 2018).

Group A will enroll heart failure patients with reduced LVEF <50% and ≥20% (HFrEF), as this population has a relatively well-understood pathophysiology and well-characterized hemodynamic responses to venous and arterial vasodilators. As of PA5, a total of 20 patients have received a single dose of REGN5381 or placebo in this study, and all patients were in Group A (HFrEF not on sacubitril/valsartan). As per PA5, patients in Group A cohorts will be dosed without undergoing right heart catheterization. Dose levels of 100 mg to ≤300 mg in Group A will continue to be tested in an ascending dose manner in order to obtain further safety, tolerability, PK, and non-invasive hemodynamic PD data. Due to the occurrence of the 2 SAEs in Group A (as discussed in Section 1 with additional details available in the IB), PA5 has incorporated additional study eligibility requirements and safety design elements.

The SBP inclusion criterion has been increased from 100 mmHg to 110 mmHg which is intended to provide a greater safety margin given possible BP lowering effects of REGN5381. Each patient must complete study day 8, and all day 8 safety assessments including vitals and local labs reviewed prior to dosing of the next patient in the same cohort. This will provide additional safety monitoring to ensure that any adverse hemodynamic or laboratory effects are detected prior to dosing of the next patient. Patients with more than moderate (ie, moderately-severe or severe) valvular heart disease or known infiltrative or hypertrophic cardiomyopathy are excluded to avoid confounding from multiple underlying pathophysiological mechanisms, and for safety purposes. Patients with a medical history at any time of more than moderate pulmonary hypertension (ie, moderate to severe or severe pulmonary hypertension) are excluded. Patients with a mPAP ≥40 mmHg during screening are also excluded as these patients may be more prone to hypotension due to the venodilatory actions of REGN5381. Patients with more than mild-moderately reduced renal function (eGFR ≤45) are excluded as these patients may be more sensitive to hypotension and worsening renal function due to the vasodilatory actions of REGN5381. Groups A and B patients must also have an LVEF <50% and ≥20% as patients with LVEF <20% have lower hemodynamic reserve and may be more clinically unstable. Excluding these patients is intended to provide an additional safety mitigation. Patients on heart failure medications that are

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

hypothesized to act in part via NPR1 (sacubitril/valsartan) or through cGMP, a downstream PD effect of NPR1 agonism (vericiguat, sildenafil), are excluded from Groups A and C to avoid potential overlap in mechanism of action of REGN5381.

Group B plans to enroll patients with LVEF <50% and ≥20% that are on a stable regimen of sacubitril/valsartan to understand the safety and tolerability and hemodynamics of REGN5381 when added on top of sacubitril/valsartan (a fixed dose combination of sacubitril, a neprilysin inhibitor, which inhibits the degradation of the natriuretic peptides ANP and BNP and valsartan, an angiotensin receptor blocker). Sacubitril/valsartan is now guideline recommended standard of care for patients with HFrEF. Therefore, it is important to understand the effects of REGN5381 when added to this therapy, both from a safety and tolerability perspective, but also an additive efficacy one. Up until PA2, patients on sacubitril/valsartan were excluded to avoid any potential additive pharmacology given the possible overlapping mechanisms of action (NPR1 activation) and to ensure that assessment of the hemodynamic effects of REGN5381 was not confounded by use of medication also impacting the NPR1 pathway. It is unclear whether sacubitril/valsartan acts through the NPR1 pathway, and invasive hemodynamic data are the most direct measure of determining the presence of combination pharmacology. Potential risks of combination pharmacology will be mitigated by an initial dose of 30 mg, which is a dose level previously tested in Group A and deemed sufficiently well-tolerated, with no more than half-log (approximately 3-fold) dose escalations.

To better understand the safety, tolerability and hemodynamic effects of REGN5381 in heart failure patients with preserved ejection fractions (HFpEF), Group C of this study will selectively enroll patients with LVEF ≥50%. HFpEF is a large subpopulation of heart failure with a limited number of available therapies and a large unmet need. NPR1 agonism by REGN5381 is postulated to reduce central venous blood pressure which may lead to benefits in heart failure patients with normal ejection fraction since they also suffer from venous congestion. Since it is unclear whether hemodynamic data from patients with reduced ejection fraction can be extrapolated to those with preserved ejection fraction, potential risks will be mitigated by an initial dose of 30 mg, which is a dose level previously tested in Group A and deemed sufficiently well-tolerated, with no more than half-log (approximately 3-fold) dose escalations. Assessment by right heart catheterization will be used to better understand hemodynamics in the HFpEF population.

For cohorts with right heart catheterization, patients must have a PCWP ≥15 mmHg and a RAP >5 mmHg on right heart catheterization in order to be eligible for randomization. A normal PCWP is 4 mmHg to 12 mmHg (Zipes, 2005). A PCWP ≥15 mmHg is an objective measure of left sided congestion. A normal RAP is 1 mmHg to 5 mmHg (Zipes, 2005). A RAP >5 mmHg is an objective measure of right sided congestion. Presence of PCWP ≥15 mmHg and RAP >5 mmHg ensures that appropriate patients with combined left and right sided congestion are selected for this study. Ensuring that patients have congestion may permit a more thorough exploration of exposure-response relationships than might be possible in a healthy participant population with normal venous pressures.

Patients in Groups A and B are required to have an NT-proBNP >1000 pg/mL (or >1600 pg/mL if in atrial fibrillation) plasma level within 30 days prior to randomization, which has a specificity of more than approximately 85% and a sensitivity of approximately 90% for diagnosis of congestion (Ponikowski, 2016) (Panagopoulou, 2013) (Januzzi, 2005). Alternatively, in the event that NT-proBNP testing is not used locally, a BNP >300 pg/mL (or >500 pg/mL if in atrial

fibrillation) is allowed. Elevated NT-proBNP or BNP is a sign of elevated venous pressures, providing additional assurance that patients undergoing right heart catheterization in this study are congested. Patients in Group C are required to have an NT-proBNP >300 pg/mL (or >900 pg/mL if in atrial fibrillation) within 30 days prior to randomization, which has a specificity of approximately 77-85% and a sensitivity of approximately 46-59% for diagnosis of congestion in HFpEF (Reddy, 2018). In the event that NT-proBNP testing is not used locally, a BNP >100 pg/mL (or >300 pg/mL if in atrial fibrillation) is allowed.

While REGN5381 binds and activates NPR1 in the presence or absence of the endogenous ligands (ANP and BNP), it is possible that the PD or PK of REGN5381 might differ in patients with elevated levels of natriuretic peptides (ie, elevated NT-proBNP) as opposed to healthy subjects. For instance, in heart failure patients NPR1 levels may differ (Lanfear, 2010) which could impact the REGN5381 clearance rate, elevated ANP and BNP levels may be less biologically active (truncated forms), and/or there may be down-regulation of NPR1 signaling (Section 1). Understanding that the PD or PK of REGN5381 may differ in heart failure patients, the sponsor selected 10 mg as the initial, conservative starting dose since this was the lowest dose showing minimal but clear hemodynamic effects in the ongoing FIH study (R5381-HV-1987). Dose levels up to a maximum dose of 300 mg, with strict dose escalation criteria, were evaluated in Group A. As discussed previously, there is uncertainty regarding whether heart failure patients have elevated levels of active natriuretic peptides. Active ANP and BNP levels will also be measured in this study (if assay is available) which will permit exploratory analyses as to whether PD or PK of REGN5381 differs in patients based on levels of active endogenous ligands.

Home heart failure medications, except for beta-blockers, will be withheld during the right heart catheterization and the invasive hemodynamic assessment period. The primary purpose of this is to minimize the potential for risk of excessive BP lowering following REGN5381 administration, as REGN5381 lowers BP in preclinical models and the ongoing FIH study (R5381-HV-1987). Beta-blockers will not be held, because they have minimal BP lowering effects in most heart failure patients and additionally have beneficial anti-arrhythmic effects. As noted above, it is anticipated that REGN5381 might have less impact on systemic arterial BP in heart failure patients in comparison to the effect in healthy participants, as was the case with other NPR1 agonists such as ANP (Saito, 1987). This is because a component of the BP effects of NPR1 agonists in healthy subjects relates to excessive venous pressure lowering and impact on SV, an effect that is not expected in congested heart failure patients with elevated venous pressures where the aim is to normalize venous pressures rather than reduce them below normal. Nonetheless, holding other heart failure agents with hemodynamic effects through completion of 6-hour hemodynamic monitoring poses little risk to the patient and provides an additional layer of safety in the design. Furthermore, administration of heart failure medications could also affect and confound hemodynamic assessments during the right heart catheterization. Patients unable to safely hold these medications will be excluded from the study.

In Group B, sacubitril/valsartan will not be held since the study specifically aims to understand the safety and tolerability of REGN5381 on top of sacubitril/valsartan. Thus in Group B, home heart failure medications, except for sacubitril/valsartan and beta-blockers, will be withheld during the right heart catheterization and the invasive hemodynamic assessment period.

It is anticipated that REGN5381 might impact the ability to restart home heart failure medications due to its effect on systemic BP. In order to optimize patient safety, the protocol specifies the

manner by which heart failure medications can be restarted after the invasive hemodynamic monitoring period. This provides a framework for the investigator to act within, and to avoid addition of medications in circumstances that could pose a safety risk (ie, addition of BP lowering agents like angiotensin-converting enzyme [ACE] inhibitors in patients with hypotension). However, heart failure medical management is best left to the treating physician, and therefore the protocol allows some investigator discretion as to when and how to restart medications. The goal will be for patients to get back on their home heart failure medications wherever possible. Patients cannot be discharged without tolerating their home medications unless the investigator feels that medications can be restarted or titrated as an outpatient. Even in that instance, the protocol still requires that patients are on a beta-blocker prior to discharge (if they were taking this medication at home).

The 6-hour period of invasive hemodynamic assessments immediately after drug administration was chosen in order to capture the effects of REGN5381 on invasive hemodynamic measures during the anticipated time of maximum REGN5381 concentration in plasma. Many institutions limit the duration of invasive hemodynamic monitoring, given that risks to a pulmonary artery catheter (eg, infection) increase over time. Invasive hemodynamic monitoring of patients for only 6 hours after study drug administration will accomplish the study goals while limiting the total duration of catheter exposure to well below institutional limits, even allowing for required patient care (eg, sterile dressing placement, monitoring activities such as telemetry, transport time) that uses significant time. Preclinical studies as well as the FIH study (30 mg dose cohort; SV effects) demonstrated that hemodynamic responses to REGN5381 occur quickly, within an hour of administration. Furthermore, the length of 6 hours for hemodynamic measurements will allow comparison to reported studies evaluating the effects of human and recombinant BNP on PCWP (Abraham, 1998) (Colucci, 2000).

PCWP is the most relevant assessment of venous pressures and is therefore the invasive hemodynamic measure of greatest interest. Prior invasive hemodynamic studies in heart failure have demonstrated standard deviations for PCWP of between 3 mmHg to 8 mmHg with a coefficient of variation between 0.11 to 0.29 over 6-hours (Colucci, 2000). Based on this, a minimum of 8 patients and up to 12 patients receiving REGN5381 at a specific dose level and a minimum of 8 patients and up to 12 patients in the placebo group provide enough precision to detect a difference of 5.9 mmHg (which is within the expected effect size of 6 mmHg to 11 mmHg observed with nesiritide) (Abraham, 1998) (Colucci, 2000). However, it is possible that the treatment effect of REGN5381 is greater than that of nesiritide, and as noted previously, there are theoretical possibilities that dose-dependent effects in heart failure patients might differ as compared to effects in healthy participants. For these reasons, the study is designed with a smaller initial cohort size (3:1, REGN5381:placebo) and additional optional expansion cohorts for each dose level which ensures the possibility of dosing up to 12 patients per dose level, only if needed to achieve the study objectives. This design element limits patient exposure and allows for efficient dose-finding in this first-in-patient study.

The length of the inpatient treatment period was chosen to provide sufficient time to conduct PK/PD sampling and to allow for monitoring of adverse events (AEs). PA5 increases the minimum length of the inpatient treatment period to at least day 5 and may be extended beyond that time at the investigator's discretion. This is because in the two patients that had SAEs, significant clinical and/or laboratory abnormalities occurred after day 3, but by day 5. Extending the length of post-dose inpatient monitoring will provide a greater duration of safety monitoring to ensure that

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

any adverse hemodynamic or laboratory effects are promptly detected and managed. Patients will also be assessed for dyspnea using a standardized questionnaire. The protocol requires that patients have stable hemodynamics, resolution of any AEs, and tolerance of home heart failure medications prior to discharge (see Section 6.1.6). In addition, PA5 makes clear that the investigator review of all safety assessments (including chemistry, hematology, urinalysis, vitals, and ECG) through day of discharge is required prior to discharge. Patients who are not suitable for discharge will remain inpatient until they can be discharged safety. Importantly, the number of patients requiring extended inpatient monitoring will be reviewed by the dose escalation committee, providing data to guide dose escalations in a safe manner (Section 6.1.7).

The length of the Outpatient Follow-Up Period is designed to follow patients until REGN5381 concentrations in plasma are below the lower limit of quantification (LLOQ), which is approximately 100-fold lower than the minimum REGN5381 concentration at which PD effects have been observed in the first-in-human study (R5381-HV-1987).

3.2.2. Rationale for Dose Selection

A starting dose of 10 mg IV is supported by the safety, tolerability, and PD data from the FIH study (R5381-HV-1987). A dose of 300 mg IV was supported by the safety, tolerability, and PD data from the R9035-HV-2125 study, a phase 1, randomized, double-blind, placebo-controlled, 2-part FIH study evaluating the safety and tolerability of single IV doses of REGN9035 and REGN5381, alone and when administered sequentially. In these studies, doses of 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg REGN5381 administered IV were sufficiently safe and well-tolerated in normal healthy participants to support further exploration. The observed PD effects in healthy volunteers in the FIH study support further exploration in heart failure patients. Specifically, a 5 mmHg to 10 mmHg reduction in SBP was observed within 24 hours post-dose that was well tolerated in healthy volunteers. This was associated with a 20% reduction in SV index that persisted through the end of the inpatient monitoring period of 72 hours. These PD effects suggest that NPR1 agonism reduces venous pressures, thus resulting in a modest reduction in BP and SV in healthy volunteers. This study will directly measure venous pressure using right heart catheterization.

Selection of the nominal maximum 300 mg IV dose level was supported by the predicted PK model in humans, whereby C_{max} of REGN5381 is predicted to be around 102 mg/L after a single 300 mg IV dose, yielding a predicted exposure multiple of 4-fold against C_{max} of 408 mg/L at the no-observed-adverse effect level (NOAEL) dose of 5 mg/kg IV in NHP.

Single IV doses of up to 300 mg were previously administered in this study to participants with heart failure with reduced ejection fraction, and a potential safety signal was observed in 2 patients with potentially contributing comorbidities. Therefore, this study will resume with a 100 mg dose which was well tolerated and is predicted to achieve active levels for 7 days or longer. If 100 mg is well tolerated, the dose will be escalated to 300 mg. Based on the PK data observed from all the studies to date, the highest doses (100 and 300 mg) selected for IV administration in this study are characterized by a brief distribution phase, followed by a linear elimination phase when concentrations were sufficient to saturate the target mediated pathway, and a terminal non-linear target mediated elimination phase when the concentrations are insufficient to saturate the target mediated pathway. The doses are expected to saturate the NPR1 receptor in the study population for about > 4 weeks. This will ultimately facilitate dose and regimen selection.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Predicted area under the curve (AUC_{inf}) in healthy volunteers for the 100 mg administered is approximately 30.8-fold higher and the 300 mg dose is approximately 6.7-fold higher than the AUC_{tau} at the NOAEL of 12800 µg day/L estimated from a PK model derived from 5-week toxicology study in cynomolgus monkeys.

Dose escalation for each cohort in this study will proceed following review of the PD and safety/toleration data, provided that the previous doses of REGN5381 are sufficiently safe and well tolerated to allow for continued investigation (see Section 6.1.7).

3.3. Risk-Benefit

Patients in this study will not directly benefit from treatment during participation. The data generated will be used to guide dosing regimens for future studies of REGN5381. Participants in this study will be required to withhold home heart failure medications (excluding beta-blockers) for a brief period which poses minimal risks.

More detailed information about the known and expected benefits and risks may be found in the Investigator's Brochure and Informed Consent documents.

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

For information regarding the permitted timing of COVID-19 vaccinations, see Section 7.2.2 Exclusion Criteria, criterion #33 and Section 8.9 Concomitant Medications.

3.3.1. Risk Benefit for REGN5381

Important potential risks for REGN5381 include those associated with mAbs including hypersensitivity reactions, immunogenicity, and embryo-fetal toxicity, as well as mechanism-specific risks including transient symptomatic hypotension, symptomatic tachycardia in normotensive participants, and worsening renal function in participants with heart failure.

The current study in heart failure participants will monitor participants after a single dose administration (REGN5381 or placebo) within the inpatient setting for at least 5 days with close hemodynamic monitoring. Strict criteria must be met for individual patient release to the outpatient follow-up period. Finally, protocol-defined rescue therapies will be made available to the study site including supplemental IV fluids and short-acting alpha-1-agonists (Section 8.2). Further, for each dosing cohort, careful review of medical monitoring safety data will be performed (Section 8.2) and strict criteria for dose escalation (Section 6.1.7) employed. These measures in conjunction with individual and study stopping rules (Section 6.1.8) will enable exploration of the hemodynamics and safety of this novel therapeutic agent in this difficult to treat population. More detailed information about the known and expected benefits and risks of REGN5381 may be found in the Investigator's Brochure and Informed Consent documents.

Heart failure remains an area of unmet need and NPR1 agonism by REGN5381 is postulated to reduce central venous blood pressure which may lead to benefits in patients with HFrEF and HFpEF since they both suffer from venous congestion.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The incidence and severity of TEAEs through the end-of-study (EOS) visit.

4.1.2. Secondary Endpoints

The secondary endpoints are:

- Change from baseline in PCWP, right atrial pressure (RAP), CO, SVR, mean pulmonary artery pressure (mPAP), and pulmonary vascular resistance (PVR) over 6 hours post-dose administration (in cohorts undergoing right heart catheterization)
- Change from baseline in SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse rate (PR) over the first 6 hours and 24 hours post-dose administration (day 1), and through the EOS visit
- Change from baseline in NT-proBNP to 6 hours and 24 hours post-dose administration (day 1), and through the EOS visit
- Concentrations of REGN5381 in serum through the EOS visit
- Immunogenicity, as measured by anti-drug antibodies (ADA) to REGN5381, through the EOS visit

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Change in plasma and urine cGMP through the inpatient treatment period
- Change from baseline in mixed venous oxygen saturation (SvO_2) over 6 hours post-dose administration
- Total daily urine output through the inpatient treatment period
- Change from baseline in estimated glomerular filtration rate (eGFR) through the EOS visit
- Change from baseline in urinary albumin to creatinine ratio through the inpatient treatment period
- Total sodium excretion in urine through the inpatient treatment period
- Change from baseline in urinary kidney injury molecule-1 (KIM-1) to creatinine ratio through the inpatient treatment period
- Change from baseline in plasma aldosterone levels, plasma renin levels, and renin-aldosterone ratio through the inpatient treatment period
- Change from baseline in norepinephrine concentration in plasma through the inpatient treatment period

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

- Change from baseline in ANP and BNP over time
- Change from baseline in NT-proANP over time
- Change from baseline in carbohydrate antigen 125 (CA125) over time
- Change from baseline in participant reported dyspnea on 7-point Likert scale through the inpatient treatment period
- Change from baseline in hemodynamic parameters measured by non-invasive pulse wave analysis

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

5. STUDY VARIABLES

5.1. 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.

5.2. Safety Variables

The safety variables include oscillometric and orthostatic BP and PR, pulse oximetry, telemetry, other vital signs (eg, temperature and respiratory rate), physical examination, electrocardiograms (ECGs), oral fluid intake volume and urine output volume, laboratory evaluations (hematology, chemistry, and urinalysis), and AEs.

5.3. Patient Reported Outcomes

The participant reported outcome variable is derived from a 7-point dyspnea questionnaire.

5.4. Pharmacokinetic Variables

The PK variable is the concentration of total REGN5381 and time. These sampling time points are specified in Table 3, Table 4, and Table 5.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 3, Table 4, and Table 5.

5.6. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic variables are derived from the right heart catheterization on day 1 and include PCWP, RAP, SVR, PVR, mPAP, CO, and may include SvO_2 when available. Additional pharmacodynamic data may be derived from the pulse wave analysis device if available (BP, PR, and SV).

Biomarker variables are the concentrations of each biomarker in urine (24-hour urine for cGMP and sodium and spot urine for albumin, creatinine, and KIM-1) or plasma (cGMP, NT-proBNP NT-proANP, ANP, BNP, norepinephrine, renin, and aldosterone) or serum (CA125) and time (Table 3, Table 4, and Table 5).

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 2a, randomized, double-blind, placebo-controlled, multi-site study of REGN5381 in heart failure participants with symptoms of congestion. Group A is limited to participants with HFrEF not taking sacubitril/valsartan. Group B will be limited to participants with HFrEF taking sacubitril/valsartan. Group C will be limited to participants with HFpEF (not taking sacubitril/valsartan). The primary objective of this study is to evaluate the safety and tolerability of single IV doses of REGN5381, a NPR1 agonist, in ambulatory participants with heart failure and congestion. Key secondary objectives are to assess the effects of REGN5381 on hemodynamic parameters and a clinical biomarker of heart failure severity. For Group A, this study uses a single ascending dose design (dose levels are 10 mg to ≤300 mg) with optional expansion cohorts to evaluate more participants at a specific dose level (as described in Section 6.1.7). As of PA6, 23 participants have had a right heart catheterization in Group A. The invasive right heart catheterization will no longer be performed in future Group A participants. Groups B and C will use single dose cohorts with optional expansion cohorts to evaluate more participants at a specific dose level (as described in Section 6.1.7). Right heart catheterizations will occur only in Groups B and C cohorts. The initial dose level is 30 mg for Group B and 30 mg for Group C. Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

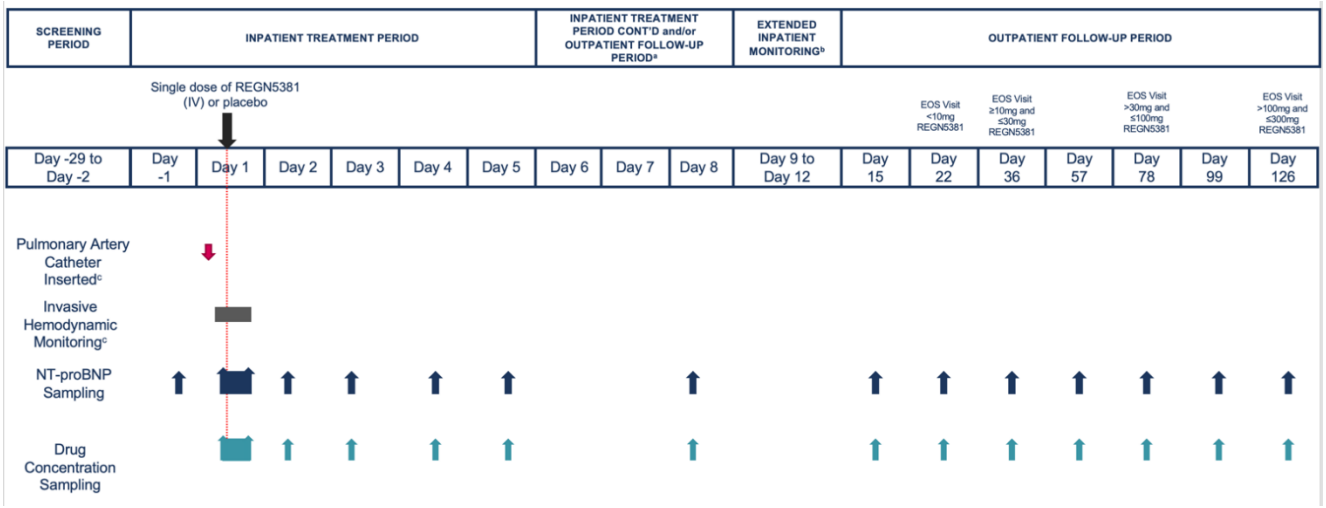
Study Design Description

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

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Figure 1: Study Flow Diagram



[a] Beginning on day 5, participants may be discharged if they meet the inpatient discharge criteria. Participants may also be discharged on days 6, or 7, or remain at the facility until completion of day 8 assessments. Regardless of the study day the participant is discharged (ie, days 5, 6, 7, 8, or a later day), all safety assessments to date must be completed and all results available and reviewed by the physician, and the participant must have met discharge criteria, prior to being discharged from the inpatient unit.

[b] Participants who do not meet the inpatient discharge criteria by day 8 may remain at the study site for Extended Inpatient Monitoring until eligible to be discharged.

[c] As of PA6, right heart catheterization will only be performed for Group C.

Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly. Study participants are ambulatory participants with NYHA class II or III heart failure and symptoms and/or signs of congestion. Notable inclusion criteria include NT-proBNP levels >1000 pg/mL (for Groups A and B), or NT-proBNP levels > 300 pg/mL (for Group C), and SBP ≥110 mmHg at the screening visit and pre-dose (day -1) visit. Women of childbearing potential (WOCBP) are included in this study but must follow appropriate contraceptive measures as described in the Inclusion/Exclusion criteria (Section 7.2.1, Section 7.2.2). Participants taking sacubitril/valsartan, are excluded from Group A and Group C of this study. However, participants in Group B will be on sacubitril/valsartan. For Groups B and C, participants with a PCWP ≥15 mmHg and a RAP >5 mmHg during the clinically indicated right heart catheterization are eligible.

6.1.1. Inpatient Treatment Period

Eligible participants will be admitted to an inpatient unit on day -1, the day prior to the right heart catheterization (Table 3) to allow for collection of laboratory assessments and baseline measures.

Blood pressure (BP) will be assessed using an oscillometric upper arm cuff. The oscillometric measurements are used to assess BP for inclusion/exclusion and as a safety measure through the study at each visit.

Standard safety assessments, including assessment of treatment emergent adverse events (TEAEs), vital signs, labs, and ECGs and telemetry (3-lead ECG) will be performed throughout the inpatient period.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Beginning at 11:59 PM on day -1 (the night prior to the planned right heart catheterization), all participants taking ACE inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), nitrates, and/or diuretics will temporarily halt these medications. The investigator may also withhold any other home medications at their discretion. Participants will follow local institutional policy regarding fluid and dietary restrictions prior to the RHC procedure.

As of PA6, only participants in Group C will undergo right heart catheterization. On the morning of day 1, participants will present to the catheterization laboratory to undergo right heart catheterization with placement of a pulmonary artery catheter (PAC) for a screening PCWP and RAP measurements to determine eligibility.

- **Participants with a screening PCWP ≥15 mmHg and RAP >5 mmHg are eligible for the study** and will be randomized if they meet the other eligibility criteria. The PAC will remain in place following the screening PCWP measurement using sterile techniques and secured according to institutional policies.
- Participants with a screening PCWP <15 mmHg or a RAP ≤5 mmHg will not be eligible for the study, and these participants will complete the right heart catheterization as clinically required and resume their home heart failure medications at the discretion of the investigator. The participants will be observed for at least 4 hours after removal of the PAC. The investigator will be recommended to communicate the findings to the participant's cardiologist. Furthermore, the investigator or qualified designee will conduct a telephone check-up with the participant within 7 days following site discharge.

Eligible randomized participants will be transported to an inpatient monitoring unit equipped with trained staff, continuous telemetry, and hemodynamic monitoring capabilities. Participants must rest for at least 30 minutes after transport to the monitored unit prior to measurement of baseline PCWP (Table 3). Details of monitoring, assessments, and procedures required during the invasive hemodynamic monitoring period of the study are described in a study operations manual.

Study drug (REGN5381 or placebo) will be administered after measurement of baseline hemodynamic parameters.

The PAC will remain in place for a total of 6 hours after study drug administration but may remain in place for a longer duration of time per investigator discretion if additional hemodynamic monitoring is required. The PAC may be removed earlier if it poses a safety risk in the opinion of the investigator. Other safety monitoring, including telemetry, will continue for the duration of the Inpatient Treatment Period.

Participants will remain in the hospital at least through day 5. Urine volumes and fluid intake will be recorded for 48 hours (day 1 to day 2), and biospecimens (blood and urine) will be collected for measurement of cyclic guanosine monophosphate (cGMP), NT-proBNP, NT-proANP, ANP, BNP, CA125, norepinephrine, renin, and aldosterone (Table 3 and Table 5). A limited physical examination and dyspnea questionnaire will be completed several times during the inpatient period. No earlier than after completion and review of day 5 safety assessments may participants be assessed for discharge using specific safety criteria (Section 6.1.6).

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Participants may resume their previously held medications after the 6-hour invasive hemodynamic monitoring period, as outlined by the sponsor and guided by the investigator (Section 6.1.5).

6.1.2. Extended Inpatient Monitoring Period

If there is a safety concern or if participants are unable to meet discharge criteria following completion and review of day 8 safety assessments, they may remain at the study site for Extended Inpatient Monitoring until eligible to be discharged (Section 6.1.6). Participants will remain at the study site for standard safety assessments, including assessment of TEAEs, vital signs, laboratory testing, dyspnea questionnaire, a limited physical examination, telemetry and ECG (Table 3).

6.1.3. Outpatient Follow-Up Period

Participants will return to the study site for standard safety assessments, including assessment of TEAEs, vital signs, laboratory testing, a limited physical examination, pregnancy testing, and ECG. Samples will also be collected for measurement of PK, ADA, and natriuretic peptides (Table 4). The timing of the EOS visit for each cohort is based on the predicted time for REGN5381 concentrations to decline below LLOQ (see REGN5381 IB for additional details).

6.1.4. 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. Implementation of this provision requires ethics committee and health authority approval from all participating countries. 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 local regulations. To be eligible, participants must complete the study and must commence treatment within 3 months of the end of study 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.

6.1.5. Restarting Home Heart Failure Medications

The goal prior to discharge is for participants to resume previously held home heart failure medications (and any other home medications that were held), with guidance from the sponsor at the direction of the investigator (Table 2). After the 6-hour hemodynamic monitoring period on day 1, participants who have a SBP ≥110 mmHg can restart all their home heart failure medications at the discretion of the investigator. Those who have a SBP ≥100 but <110 mmHg can restart their home diuretic, but all other home heart failure medications (except beta-blockers) will continue to be held at the discretion of the investigator. Participants who have a SBP <100 mmHg must continue to hold their home heart failure medications (except beta-blockers) on day 1. If at any time point the participant meets criteria to restart home medications but the investigator chooses to continue holding home medications, the investigator must document and communicate the reason to the sponsor within 24 hours.

Beginning on day 2, participants who have a SBP ≥110 mmHg can restart all of their home heart failure medications at the discretion of the investigator. Those who have a SBP ≥100 but <110 mmHg can restart their diuretic or, if the diuretic is already resumed, can restart one of their other held home heart failure medications, at the discretion of the investigator. Participants who

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

have a SBP <100 mmHg will continue to hold their home heart failure medications. Home heart failure medications may be restarted or started at lower doses at the discretion of the investigator.

Participants who were unable to resume their home heart failure medications initially will continue to be evaluated on day 2 onwards in order to resume the necessary home heart failure medications. The investigator will aim to titrate and/or restart each participant's home heart failure medications at each outpatient visit to achieve the same drug regimen as prior to the study or as recommended by heart failure guidelines. It is recommended that if the investigator makes any changes to a participant's home heart failure regimen that the changes are communicated to the participant's physician.

Table 2: Restarting Home Heart Failure Medications

Day 1: After Pulmonary Artery Catheter is Removed Or 6-hours Post-end of Infusion for Group A Cohorts 6, 7, 8		Beginning on Day 2 + Onward	
SBP ≥110 mmHg	⇨ May restart home heart failure (HF) medications	SBP ≥110 mmHg	⇨ May restart home HF medications
SBP ≥100 mmHg and <110 mmHg	⇨ May restart home diuretic Do not restart other home HF medications	SBP ≥100 mmHg and <110 mmHg	⇨ May restart one home HF medication
SBP <100 mmHg	⇨ Do not restart any additional home HF medications	SBP <100 mmHg	⇨ Do not restart any additional home heart failure medications

Note: Sponsor provided guidance for participants to resume held home heart failure medications (ACE inhibitors, ARBs, MRAs, nitrates, and diuretics). Please note that beta-blockers are not held for this study. Investigator discretion should be utilized at each step. Participants who are ineligible to resume home medications after the catheter has been removed on day 1 will thereafter be continually assessed to see if home heart failure medications can be re-started by the investigator. The investigator will reassess home heart failure medications during the Outpatient Follow-Up Period with the aim of getting participants back to their original home medication regime. It is recommended that if the investigator makes any changes to a participant's outpatient heart failure regimen that the changes are communicated to the participant's physician.

6.1.6. Inpatient Discharge Criteria

Participants will be monitored as inpatients at least until day 5 (and up to day 8). Once discharge day safety assessments have been completed and results reviewed, participants may be discharged if they meet all the following criteria:

- SBP ≥100 mmHg (for at least 2 hours after starting home heart failure medications if restarting these drugs on day 3 or later)
- Pulse rate ≤100 bpm
- All safety assessments (including chemistry, hematology, urinalysis, vitals, ECG) through day of discharge, inclusive of the day of discharge, have been reviewed by the

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

physician prior to participant discharge (participants will be monitored as inpatients at least until day 5).

- Resume previously held home heart failure medications*
- No unresolved AEs that warrant continued inpatient monitoring [δ]

  * The investigator may deem the participant fit for discharge if the first 2 criteria are met, and in their opinion the restarting or up-titration of home heart failure medications can be safely and appropriately performed in an outpatient setting. However, a participant cannot be discharged without a beta-blocker (unless the participant was not on a beta-blocker when entering the study).

- [δ] Note that if the participant has unresolved AEs on day 5, the investigator may deem the participant fit for discharge if the first 3 criteria are met and the AEs can be monitored and managed in the outpatient setting.

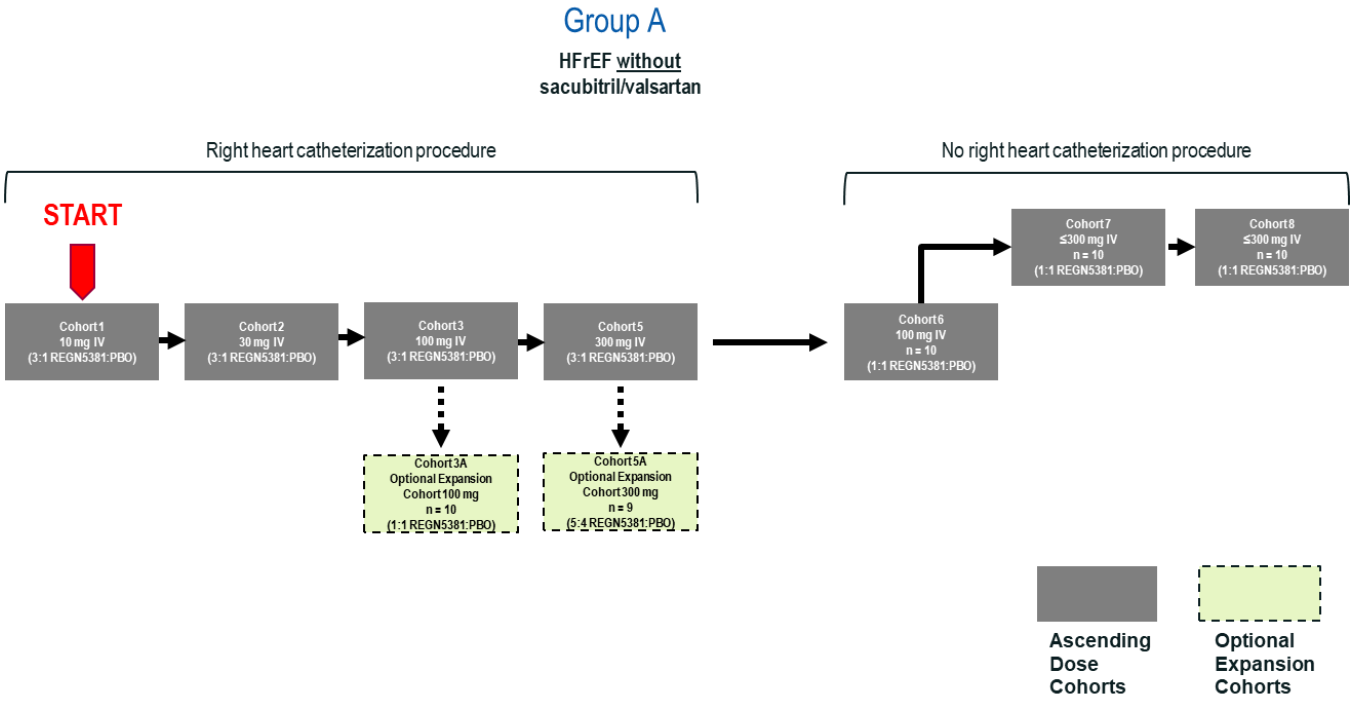
Participants may not be discharged earlier than day 5 and may remain under inpatient monitoring through completion of day 8 assessments. However, participants who do not meet the individual participant discharge may be kept for Extended Inpatient Monitoring after day 8. Participants will continue to be assessed until they are able to meet the discharge criteria. The investigator will also continually re-assess participants' home heart failure regimens during the Outpatient Follow-Up Period.

6.1.7. Description of Study Cohorts and Dose Escalation

The study is comprised of 3 groups each with different participant types (Group A, Group B, and Group C). Group A is comprised of HFrEF participants not taking sacubitril/valsartan. Group B is comprised of HFrEF participants on sacubitril/valsartan. Group C is comprised of HFpEF participants not taking sacubitril/valsartan. All groups have a single ascending dose design. Optional expansion cohorts allow enrollment of additional participants at a given dose (details below). Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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



The solid arrows convey single ascending dose levels and progression through cohorts.
The dotted arrows convey the Sponsor may activate the Optional Expansion Cohort at any time point after a Dose Escalation Review meeting has occurred for the initial 3:1 (REGN5381:PBO) cohort of the same dose level.
As of PA5, there will be no further dosing of Group A participants undergoing a right heart catheterization.
Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

As of PA5, additional cohorts will test previously tested dose levels (≤300 mg) in cohorts without invasive hemodynamic measurements (Cohorts 6, 7, and 8).

6.1.7.1. Study Groups

Groups A, B, and C are comprised of single ascending dose cohorts with optional expansion cohorts. As of PA5, Group A is comprised of additional single ascending dose cohorts to continue evaluating dose levels of 100 mg to ≤300 mg without the right heart catheterization procedure. Groups A, B, and C may all enroll in parallel. The initial dose level for both Group B and Group C will be 30 mg. These initial dose levels selected for Groups B and C were determined after review of all safety and hemodynamic data from completed Group A cohorts at the time of PA5. This included review of safety and tolerability data, including vital signs, labs, ECGs, and adverse events (AEs). Data review of hemodynamic and biomarker data and antibody concentrations over time may also inform dosing decisions. Given the multi-site nature of this study, the Sponsor has processes in place for safety events to be communicated to sites as soon as the Sponsor is aware, and dosing of individual participants will occur according to relevant study plans for sentinel dosing as described below.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

6.1.7.2. Group A: Ascending Dose Cohorts

Participants were enrolled and randomized in 4 sequential ascending dose cohorts (Cohorts 1, 2, 3, and 5 [10, 30, 100, and 300 mg REGN5381 or placebo, respectively]). Each dose cohort consisted of 4 participants: 3 participants randomized to receive a single IV dose of REGN5381 and 1 randomized to receive placebo. As of PA5, Cohorts 1, 2, 3, and 5 were completed.

PA5 added 3 additional ascending dose cohorts (Cohorts 6, 7, and 8) to evaluate single doses of 100 mg to ≤300 mg REGN5381 in participants not undergoing the right heart catheterization procedure. The randomization ratios for each of these cohorts are 5 participants randomized to receive a single IV dose of REGN5381 and 5 participants randomized to receive placebo.

Cohort 6 (100 mg dose level) will not require sentinel dosing. Cohort 7 (≤300 mg dose level) will require sentinel dosing if the dose level selected is >100 mg. Cohort 8 (≤300 mg dose level) will not require sentinel dosing if that dose level or higher has been sufficiently well tolerated in Cohort 7.

The two sentinel participants in Cohort 7 (and Cohort 8 if the dose level selected in Cohort 8 is greater than the dose level selected for Cohort 7) may be dosed in parallel: 1 participant randomized to REGN5381 and 1 participant randomized to placebo. These sentinel participants each must complete safety assessments through day 8 (Visit 10), the safety data through day 8 are reviewed, and a decision to continue study drug dosing in the cohort is documented by the investigator and the sponsor, prior to dosing of the remaining participants in the cohort. Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

6.1.7.3. Group A: Optional Expansion Cohorts

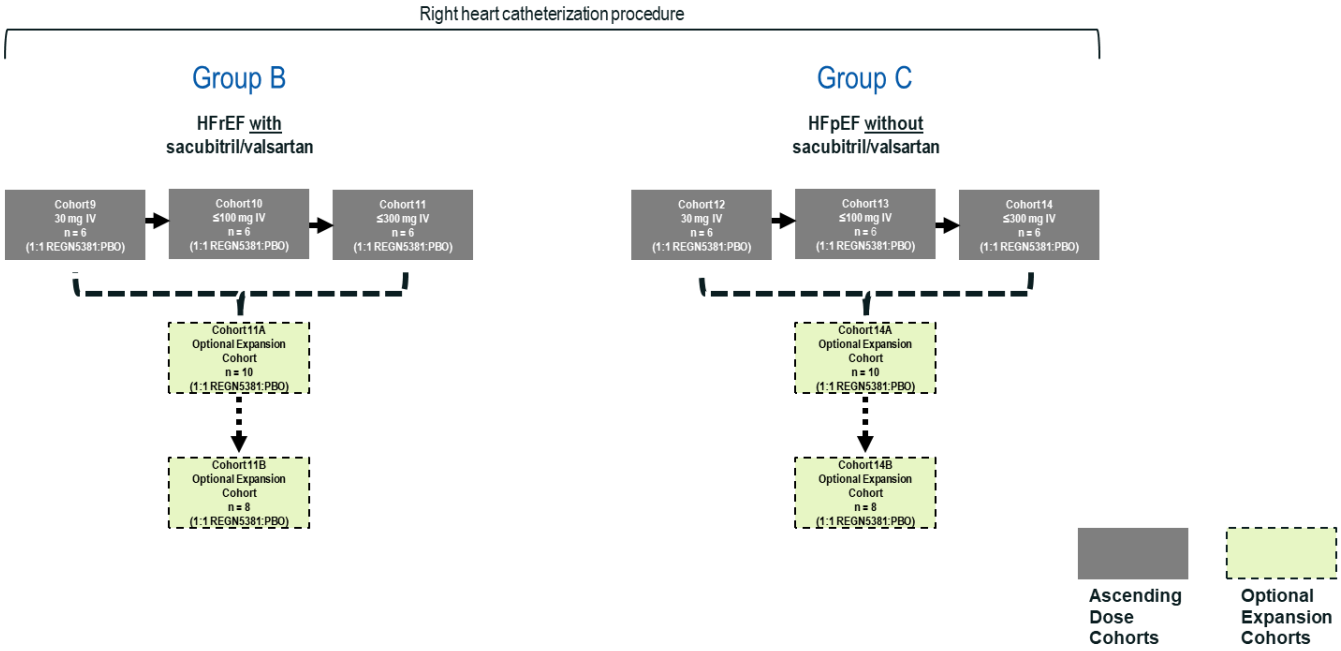
Group A enrollment has been closed as of PA6. However, participants already enrolled in the group will complete their follow-up accordingly.

As of PA5, there will be no further dosing of Group A participants in these optional expansion cohorts.

Optional expansion Cohorts 3A and 5A were partially enrolled at the 100 mg and 300 mg dose levels, respectively. The purpose of the optional expansion cohorts was to enroll at least 8 participants in a REGN5381 dose level, and at least 8 participants in a pooled placebo group.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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



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

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

6.1.7.4. Group B and Group C: Ascending Dose Cohorts

Group B enrollment has been closed as of PA6.

Participants will be enrolled and randomized in up to 3 sequential ascending dose cohorts in each group (Group B [HFrEF participants on sacubitril/valsartan] Cohorts 9, 10, 11 [30, ≤100, ≤300 mg REGN5381 or placebo, respectively], and Group C [HFpEF participants not taking sacubitril/valsartan] Cohorts 12, 13, 14 [30, ≤100, ≤300 mg REGN5381 or placebo, respectively]). Each dose cohort consists of 6 participants: 3 participants randomized to receive a single IV dose of REGN5381 and 3 randomized to receive placebo.

These ascending dose cohorts will require sentinel dosing. Two sentinel participants may be dosed in parallel: 1 participant randomized to REGN5381 and 1 participant randomized to placebo. These sentinel participants each must complete safety assessments through day 8 (Visit 10), the safety data through day 8 are reviewed, and a decision to continue study drug dosing in the cohort is documented by the investigator and the Sponsor, prior to dosing of the remaining participants in the cohort. Sentinel dosing is not required if the selected dose level is the same or lower than the prior cohort within the same group.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

6.1.7.5. Group B and Group C: Optional Expansion Cohorts

Group B enrollment has been closed as of PA6. However, participants already enrolled in this group will complete their follow-up accordingly.

There are 2 optional expansion cohorts in Group B (HFrEF participants on sacubitril/valsartan) (Cohorts 11A and 11B) and 2 optional expansion cohorts in Group C (HFpEF participants not taking sacubitril/valsartan) (Cohorts 14A and 14B). The purpose of these optional expansion cohorts is to enroll 8 to 12 participants in a REGN5381 dose level, and 8 to 12 participants in a placebo group. These optional expansion cohorts will not exceed a dose level previously tested in the corresponding Group B and Group C ascending dose cohorts.

Based on previous studies assessing the PD of the natriuretic peptide receptor agonist nesiritide in heart failure patients (Colucci, 2000), 8 to 12 participants randomized to receive REGN5381 versus 8 to 12 participants randomized to receive placebo would provide sufficient precision to detect a difference in PCWP between REGN5381 and the placebo group that is greater or equal to the treatment effect of nesiritide (6 mmHg within 4 to 6 hours) (see Section 11.2).

Participants in Group B Cohorts 11A and 11B and Group C Cohorts 14A and 14B do not need to undergo sentinel dosing as the selected dose level will not have exceeded a previously tested dose level. Cohorts in Groups A, B, and C may occur in parallel.

6.1.7.6. Dose Escalation and Cohort Progression

Applicable for Groups A, B, and C: the 100 mg dose level cohort must be fully dosed, each participant completed follow-up visits through day 22 (Visit 12), and the safety data reviewed internally with senior leaders and at a DEC meeting, prior to dose escalation greater than 100 mg (although screening for the next dose cohort may begin prior to confirmation that the current dose is safe). The following cohort progressions have this day 22 requirement:

- Group A (HFrEF participants not taking sacubitril/valsartan): Cohort 6 (100 mg dose level) to Cohort 7 (≤300 mg dose level) OR Cohort 7 (≤300 mg dose level) to Cohort 8 (≤300 mg dose level) if the selected dose level for Cohort 7 is not 300 mg
- Group B (HFrEF participants on sacubitril/valsartan): Cohort 10 (≤100 mg dose level) to Cohort 11 (≤300 mg dose level)
- Group C (HFpEF participants not taking sacubitril/valsartan): Cohort 13 (≤100 mg dose level) to Cohort 14 (≤300 mg dose level)

Furthermore, HFrEF participants taking sacubitril/valsartan will not be dosed at the 300 mg dose level until a cohort of HFrEF participants not on sacubitril/valsartan have been dosed and the dose level was found to be sufficiently well tolerated.

For all other ascending dose cohorts, dosing in the next dose cohort may occur once all participants enrolled in the previous cohort have been observed for at least 7 days post-study drug administration, have completed day 8 (visit 10) safety assessments, and the data has been reviewed at a DEC meeting (although screening for the next dose cohort may begin prior to confirmation that the current dose is safe).

The DEC meetings will be led by a designated member of the Regeneron clinical team (generally either the Medical Director/Study Director or the clinical trial manager) and at a minimum will be

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

attended by the Regeneron Medical Director and the GPS lead; Investigators will be invited to attend the DEC meetings, and other individuals may be included as needed. The outcome of the DEC meeting will be documented and filed appropriately.

Decisions on whether to escalate to the next dose level, de-escalate the dose level, or enroll an optional expansion cohort will be based upon an analysis of safety and tolerability data, including vital signs, labs, ECGs, and adverse events (AEs). Data review of hemodynamic and biomarker data and antibody concentrations over time may also inform dose escalation decisions.

6.1.8. Study Stopping Rules

6.1.8.1. Individual Participant Stopping Rules

Participants may terminate the study early if the investigator determines that additional study visits pose a risk to the participant. The investigator must then notify the sponsor within 24 hours of the event. All serious adverse events (SAEs), regardless of the presumed relationship to study drug, must be reported to the Sponsor within 24 hours. If a participant terminates the study early, the investigator may make a reasonable attempt to continue following the participant through site and/or telephone visits.

6.1.8.2. Study Stopping Criteria

If 1 fatal/life-threatening 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 evaluates whether the study stopping criterion has been met. 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 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, and the Sponsor will inform 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.

6.1.9. 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.

6.2. Planned Interim Analysis

No formal interim analysis is planned.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

7.1. Number of Participants Planned

Up to a total of 122 adult participants will be randomized in this study. In HFrEF participants not taking sacubitril/valsartan (Group A), as of PA6, 20 participants have been randomized and dosed in ascending dose cohorts and optional expansion cohorts with the right heart catheterization procedure, and 3 participants have been randomized across 3 ascending dose cohorts without the right heart catheterization procedure. No further enrollment is planned in Group A. In HFrEF participants on sacubitril/valsartan (Group B), up to 36 participants were planned to be randomized across 3 ascending dose cohorts and 2 optional expansion cohorts. However, Group B has not enrolled and as of PA6 will be closed for enrollment. In HFpEF participants not taking sacubitril/valsartan (Group C), up to 36 participants may also be randomized across 3 ascending dose cohorts and 2 optional expansion cohorts.

7.2. Study Population

Eligible participants for this study are ambulatory males and females with NYHA class II/III heart failure that in the opinion of the investigator have a clinical indication for right heart catheterization.

7.2.1. Inclusion Criteria

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

Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

1. Male or female participants between 18 to 75 years of age (inclusive) at the screening visit
2. Body mass index (Duong, 2008)between 18 and 35 kg/m^2, inclusive, rounded to the nearest whole number
3. Ambulatory participants with New York Heart Association class II/III heart failure and at least 1 sign and/or symptom of congestion (eg, dyspnea on exertion, worsening edema, orthopnea, etc.)
4. Participants who, in the opinion of the investigator, require a right heart catheterization (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively]). Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.
5. Left ventricular ejection fraction ≥20 % and <50% on echocardiogram (ie, HFrEF participants) within 90 days prior to randomization (only for HFrEF participants [Group A and Group B]). Note: Group A has stopped enrolling and Group B will not enroll participants.
6. Left ventricular ejection fraction ≥50% on echocardiogram (ie, HFpEF participants) within 90 days prior to randomization (only for HFpEF participants [Group C])

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

7. NT-proBNP >1000 pg/mL or BNP >300 pg/mL (NT-proBNP >1600 pg/mL or BNP >500 pg/mL if in atrial fibrillation) within 30 days prior to randomization measured by the local laboratory (only for HFrEF participants [Group A and Group B]). Note: Group A has stopped enrolling and Group B will not enroll participants.
8. NT-proBNP >300 pg/mL or BNP >100 pg/mL (NT-proBNP >900 pg/mL or BNP >300 pg/mL if in atrial fibrillation) within 30 days prior to randomization measured by the local laboratory (only for HFpEF participants [Group C])
9. Pulmonary capillary wedge pressure (PCWP) ≥15 mmHg and Right Atrial Pressure >5 mmHg on right heart catheterization the morning of anticipated study drug dose administration (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively]). Note: Group A has stopped enrolling and Group B will not enroll participants.
10. Systolic blood pressure ≥110 mmHg at the screening visit and on day -1
11. Hematocrit >30% at the screening visit and day -1
12. Willing and able to comply with clinic visits and study-related procedures
13. Provide informed consent signed by study participant or legally acceptable representative
14. Able to understand and complete study-related questionnaires
15. Taking a stable dose of sacubitril/valsartan for 3 months prior to randomization (only for HFrEF participants on sacubitril/valsartan [Group B]). Note: Group A has stopped enrolling and Group B will not enroll participants.
16. Taking a stable approved dose of an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, hydralazine, or nitrates for at least 30 days prior to the screening visit (only for HFrEF participants not taking sacubitril/valsartan [Group A]). Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

7.2.2. Exclusion Criteria

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

Note: Groups A and B enrollment has been closed as of PA6. However, participants already enrolled in these groups will complete their follow-up accordingly.

1. Currently taking IV vasodilators and/or inotropes
2. Taking sacubitril/valsartan (only for HFrEF and HFpEF participants not taking sacubitril/valsartan [Group A and Group C, respectively])
3. Taking a phosphodiesterase (PDE) inhibitor (eg, sildenafil), or a soluble guanylate cyclase stimulator (SGCS; ie, vericiguat) within 2 weeks of the screening visit or planning on taking sacubitril/valsartan, a PDE inhibitor, or a SGCS at any point during the study.
4. More than moderate valvular regurgitation/stenosis (ie, moderate-to-severe or severe) on echocardiogram within 90 days prior to randomization

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

5. Known infiltrative or hypertrophic cardiomyopathy
6. Acute coronary syndrome within prior 6 months of randomization
7. History of cardiac arrest
8. Cardiac surgery within 3 months of randomization
9. Pacemaker or defibrillator placement within prior 30 days of randomization
10. Severe chronic obstructive pulmonary disease (COPD) (defined as Forced Expiratory Volume in 1st second [FEV1] <50% of predicted or Global Initiative for Chronic Obstructive Lung Disease [GOLD] 3 or 4)
11. Pulmonary arterial hypertension (WHO Group 1)
12. Any medical history at any time of more than moderate pulmonary hypertension (ie, moderate-to-severe, or severe pulmonary hypertension are excluded). In addition, participants with a mPAP ≥40 mmHg during the right heart catheterization procedure at screening are also excluded.
13. Any medical history at any time of sustained ventricular tachycardia
14. Congenital heart disease (repaired or unrepaired)
15. Inability to lie flat for cardiac catheterization
16. Participants awaiting heart transplant, united network for organ sharing (UNOS) status 1-5 or equivalent
17. Participants who have received iodinated contrast within 7 days prior to randomization
18. Any condition or finding on right heart catheterization where the investigator feels that participant's safety may be compromised by study participation (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively])
19. Bleeding diathesis that in the opinion of the investigator would not allow safe performance of right heart catheterization (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively]). Participants with an international normalized ratio (INR) >2.5 or <75,000 platelets/liter on day -1 will be excluded.
20. Inability to measure PCWP or Right Atrial Pressure (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively])
21. Unable to safely hold dose(s) of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, nitrates, and/or diuretics beginning at 11:59 PM on day -1 (the night prior to the scheduled right heart catheterization) until completion of the right heart catheterization (for an anticipated duration of ~12 hours)

    Note: Once SBP ≥110 mmHg after completion of the right heart catheterization, participants may resume all of their previously held medications

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

22. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor
23. Presents any concern to the study investigator that might confound the results of the study or poses an additional risk to the participant by their participation in the study
24. Was hospitalized (ie, >24 hours) for any reason within 30 days of the screening visit
25. Using the Modification of Diet in Renal Disease (MDRD) equation, has an eGFR of ≤45 mL/min/1.73 m^2 at the screening visit

    Note: If participant has an eGFR ≤45 mL/min/1.73 m2, one repeat test is allowed. Participant may be enrolled if repeat demonstrates eGFR of >45 mL/min/1.73 m2.
26. History of alcohol abuse within the last 1 year prior to dosing
27. Medical history of liver cirrhosis
28. Is positive for human immunodeficiency virus (HIV) or has an active hepatitis B infection at the screening visit
29. Is positive for hepatitis C virus (HCV) antibody and subsequently positive for qualitative (ie, detected or not detected) HCV RNA test at the screening visit
30. Any malignancy, except for 1) non-melanoma skin cancer or 2) cervical/anus in-situ or 3) those that have been resected with no evidence of metastatic disease for 3 years prior to the screening visit
31. Has a history of significant multiple and/or severe allergies (eg, latex gloves), or has had an anaphylactic reaction to prescription or non-prescription drugs or food
32. 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) of an investigational biologic drug, or at least 4 weeks for other investigational drug, prior to the screening visit
33. Has received a COVID-19 vaccination within 1 week of planned start of study medication or for which the planned COVID-19 vaccinations would not be completed 1 week prior to start of study drug
34. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period 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 the last study drug administration.
35. Pregnant or breastfeeding women

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

36. 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 4 months after the last study drug administration. 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;
    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, 2020) 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 not acceptable methods of contraception. Female condom and male condom should not be used together.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

7.3. 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.

Participant who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.4.

7.4. Replacement of Participants

Participants prematurely withdrawn from the study 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 first dose 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.

7.5. Re-Screening of Participants

Participants considered screen failures may be rescreened once following a discussion between the investigator and sponsor.

Participants who were screened, determined to be eligible, and reserved for enrollment in a particular cohort may be rescreened for a later cohort if they subsequently fall outside of their original screening window.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Study treatment is REGN5381 drug product, lyophilized, glass vial and matching placebo.

Final presentations will be outlined in the pharmacy manual.

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

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Rescue Treatments

Rescue treatments are indicated for symptomatic hypotension (SBP <90 mmHg associated with loss of consciousness or lightheadedness/dizziness).

Participants experiencing symptomatic hypotension will be treated by site investigators as informed by clinical assessment including extended inpatient stay if required. Investigators will have invasive hemodynamic data to help guide management and may continue invasive hemodynamic monitoring for longer than required in the protocol if in their opinion, continued invasive hemodynamic monitoring will be useful in participant management. Sites will have access to vasopressors (including adrenergic receptor agonists) and IV fluids. The investigator may modify or hold participant's home heart failure medications at their discretion.

8.2.1. Rescue Therapy

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

- 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)
- Difficulties in 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
- Other relevant medical emergency, at the discretion of the investigator

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, but are not limited to loop diuretics, thiazide diuretics, oral vasodilators, beta blockers, mineralocorticoid receptor antagonists, SGLT2 and SGLT1/2 inhibitors, IV vasodilators, inotropes, intravenous fluids, vasopressors, non-invasive positive airway pressure (eg, CPAP or bilevel PAP), mechanical ventilation, extracorporeal life support, and ventricular assist devices.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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).

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

Investigators are reminded that ischemic hepatitis is a 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 ECG and pulse oximetry to aid diagnosis of HPS along with extra monitoring of serum bilirubin and coagulation parameters if needed.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual participant is not allowed.

8.3.2. Study Drug Discontinuation

Participants who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Participants who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.4.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

8.4. Management of Acute Reactions

8.4.1. 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 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

8.4.1.1. 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.

8.4.1.2. 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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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

8.5. Method of Treatment Assignment

Up to 122 participants will be randomized. In HFrEF participants not taking sacubitril/valsartan (Group A): 4 sequential ascending cohorts and 2 optional expansion cohorts. In HFrEF participants on sacubitril/valsartan (Group B): 3 ascending dose cohorts and 2 optional expansion cohorts. In HFpEF participants not taking sacubitril/valsartan (Group C): 3 ascending dose cohorts and 2 optional expansion cohorts.

The randomization ratios of participants receiving either REGN5381 or placebo are 3:1 (Cohort 1 to Cohort 3, Cohort 5), 1:1 (Cohort 9 to Cohort 14), 1:1 (Cohort 11B, Cohort 14B), 5:4 (Cohort 5A), and 1:1 (Cohort 3A, Cohort 6 to Cohort 8, Cohort 11A, Cohort 14A) (see Table 1, Figure 2, and Figure 3).

Participants will be randomized 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).

8.6. 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 EOS visit per cohort but will not be blinded to any other study data. Aggregated summary data by treatment groups will be reviewed during the study in an ongoing basis.

Other Regeneron personnel who are not in regular contact with the study site may be unblinded to all study data as needed, such as for dose escalation, safety review, or other data review. The Study Statistician and Statistical Programmer will be unblinded to participant randomization assignments and all study data for ongoing data review.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

8.7. 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.

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

8.8. Treatment Logistics and Accountability

8.8.1. 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.

8.8.2. 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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

8.8.3. 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 and/or other records of documentation (including reports from validated systems, ie, EMR or IRT) must be provided to the sponsor at the conclusion of the study.

8.8.4. Treatment Compliance

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

8.9. Concomitant Medications

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

If a subject 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.

8.9.1. Prohibited Medications

Use of the following medications are prohibited through the end of study: valsartan/sacubitril (in Group A and Group C only), phosphodiesterase (PDE) inhibitors (eg, sildenafil), and soluble guanylate cyclase stimulators (SGCS; eg, vericiguat).

Use of the following medications are prohibited through the end of study unless required at the discretion of the investigator or treating physicians: intravenously administered vasodilators or inotropes.

8.9.2. Permitted Medications

All medications are permitted except those listed in Section 8.9.1.

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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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 1 week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. 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 3 and Table 4.

The timing of certain study procedures relative to study drug infusion is presented in Table 5.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Table 3: Schedule of Events for Screening Period and Inpatient Treatment Period

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

	Screening Period	Inpatient Treatment Period							
Study Procedure	**Screening**	**Begin Baseline Measurements**	**Invasive Hemodynamic Monitoring, Dose Administration, Observation**	**Observation**			**Observation and Discharge (V7 is required, V8 & V9 depend on timing of participant discharge[9])**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
24-hour urine collection ends[7]				X	X				
Resume home heart failure medications			X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Clinic discharge							X[9]	X[9]	X[9]
Treatment									
Administer study drug			X[10]						
Hemodynamics and Vitals									
PCWP and other invasive hemodynamic parameters			X[11, 12]						
Oscillometric BP & PR measurement[13]	X	X	X	X	X	X	X	X	X
Orthostatic BP & PR measurement[13]		X		X	X	X	X	X	X
Pulse oximetry (SpO_2)[14]		X	X	X	X	X	X	X	X
Respiratory rate	X		X	X	X	X	X	X	X
Body temperature	X		X	X	X				
Patient Reported Outcomes									
Dyspnea questionnaire[15]			X	X	X	X			
Safety									
Weight[16]	X	X	X	X	X		X		
Physical examination[17]	X		X		X		X		
Telemetry (3-lead ECG)		X	X	X	X	X	X	X	X
Electrocardiogram[18]	X		X		X		X		
Adverse events	X	X	X	X	X	X	X	X	X

	Screening Period	Inpatient Treatment Period							
Study Procedure	**Screening**	**Begin Baseline Measurements**	**Invasive Hemodynamic Monitoring, Dose Administration, Observation**	**Observation**			**Observation and Discharge (V7 is required, V8 & V9 depend on timing of participant discharge[9])**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X
Pharmacokinetics and Immunogenicity Samples									
Drug concentration sample[19], serum			X	X	X	X	X		
ADA sample[25], serum			X						
Pharmacodynamics and Biomarker Samples									
cGMP[19], plasma		X	X	X	X				
NT-proBNP[19], plasma		X	X	X	X	X	X		
Exploratory natriuretic peptides (NT-proANP, ANP, BNP)[20], plasma			X	X	X				
Norepinephrine[20], plasma			X						
Renin and aldosterone[20], plasma			X	X	X				
CA125, serum		X			X				
Pulse wave analysis[21]			X	X	X				
cGMP & sodium 24-hour collection, urine[22]				X	X				
Spot urine (for albumin, creatinine, KIM-1)[23]		X	X	X	X				
Pharmacogenomics									
Whole blood sample for DNA isolation - optional[24]		X							

9.1.1. Footnotes for Table 3: Schedule of Events for Screening Period and Inpatient Treatment Period

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

8. After removal of the catheter on day 1, participants can restart home heart failure medications under guidance provided by the sponsor but at the discretion of the investigator (Section 6.1.5). It is recommended that if an investigator modifies a participant's discharge home heart failure medication regimen that the changes are communicated to the participant's physician. At each post-discharge outpatient visit, the investigator will re-assess and adjust patient's home heart failure medications, aiming to return the patient to their original regime where possible if clinically appropriate (Section 6.1.5).
9. Participants may not be discharged earlier than day 5 and may remain under inpatient monitoring through completion of day 8 assessments. However, participants who do not meet the individual participant discharge may be kept for Extended Inpatient Monitoring after day 8. Participants will continue to be assessed until they are able to meet the discharge criteria. Participants discharged on day 5 do not need to complete day 6 or day 7 assessments. Participants discharged on day 6 do not need to complete day 7 assessments. Participants who do not meet the inpatient discharge criteria on day 8 may remain at the study site for Extended Inpatient Monitoring until eligible to be discharged. Refer to Section 6.1.6 for additional details. Furthermore, participants must be explicitly instructed by the investigator prior to discharge regarding how to communicate with the study site if needed (eg, in the event of an adverse event) in between study site visits during the outpatient portion of the study.
10. After right heart catheterization procedure in the catheterization laboratory, participants are transported to the heart failure unit and then must rest for at least 30 minutes in the heart failure unit to allow baseline assessments before receiving study drug.
11. On day 1, after screening measurements, eligible participants will begin having their continuous hemodynamic data (CO, RAP, SVR, PVR, mPAP) recorded upon arrival in the inpatient monitoring unit (not applicable for HFrEF participants not taking sacubitril/valsartan [Group A] Cohorts 6, 7, and 8 [100 mg, ≤300 mg, and ≤300 mg REGN5381 or placebo, respectively]). Continuous SvO_2 may also be collected when available. Participants must then rest for at least 30 minutes prior to measurement of the baseline PCWP and oscillometric BP & PR. The baseline PCWP and oscillometric BP & PR will be assessed no more than 30 minutes prior to start of drug administration. Additional PCWP measurements are recorded at 2 hours (+30 min), 4 hours (±30 min), and 6 hours (±30 min) post-end of infusion. The recording of continuous invasive hemodynamic data continues until completion of 6-hour post-end of infusion PCWP and oscillometric BP & PR measurements. See Table 5 for timing of these assessments on day 1. Whenever possible, hemodynamic parameters will be assessed before collection of PK samples and laboratory samples.
12. SvO_2 will be assessed using pulmonary artery oximetry where available.
13. Both oscillometric and orthostatic BP & PR measurements will be obtained and recorded once on the evening of clinic admission. On day 1, oscillometric BP & PR measurements will be taken pre-dose and hourly post-end of infusion for the duration of the right heart catheterization procedure (see footnote #11 and Table 5). During the remaining Inpatient Treatment Period beginning on day 2, both oscillometric and orthostatic BP & PR measurements will be obtained and recorded approximately every 8 hours (± 1 hour) until site discharge. Additional readings beyond those specified here and including the Extended

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Inpatient Monitoring period may be taken at the discretion of the investigator. Whenever possible, BP and PR should be taken before collection of PK samples and laboratory samples.

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

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Table 4: Schedule of Events for Outpatient Follow-Up Period

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

	Inpatient Treatment Period (Continued) and/or Outpatient Follow-Up Period			Outpatient Follow-Up Period						Unscheduled Visit[11]
Study Procedure	**Visit 10**	**Extended Inpatient Monitoring (optional)**	**Visit 11**	**Visit 12/EOS[1]**	**Visit 13/EOS[2]**	**Visit 14**	**Visit 15/EOS[3]**	**Visit 16**	**Visit 17/EOS[4]**	
Visit	**V10**		**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	
Day	**8**	**Days 9 through 12**	**15**	**22**	**36**	**57**	**78**	**99**	**126**	
Window (day)	**±1**		**±3**	**+3**	**+3**	**±3**	**+3**	**±3**	**+3**	
Inpatient Discharge (if patient remains at the unit through or past day 8)										
Clinic discharge	X	X								
Laboratory Testing										
Hematology panel	X	X		X	X		X		X	X
Blood chemistry	X	X		X	X		X		X	X
Pharmacokinetics and Immunogenicity Sampling										
Drug concentration sample, serum	X		X	X	X	X	X	X	X	X
ADA sample, serum				X[7]	X[7]		X[7]		X	
Pharmacodynamics and Biomarker Samples										
NT-proBNP, plasma	X		X	X	X	X	X	X	X	X
Exploratory natriuretic peptides (NT-proANP, ANP, BNP), plasma				X	X		X		X	
CA125, serum	X			X	X		X		X	
Pulse wave analysis[10]	X		X	X	X	X	X	X	X	X

9.1.2. Footnotes for Table 4: Schedule of Events for Outpatient Period Follow-Up Period

1. Participants receiving <10 mg of REGN5381 will perform their EOS visit no earlier than day 22.
2. Participants receiving ≥10 mg and ≤30 mg of REGN5381 will perform their EOS visit no earlier than day 36.
3. Participants receiving >30 mg and ≤100 mg of REGN5381 will perform their EOS visits no earlier than day 78.
4. Participants receiving >100 mg and ≤300 mg of REGN5381 will perform their EOS visit no earlier than day 126.
5. ECG and SpO_2 can be performed on any visit based on clinical need and judgement of the investigator.
6. The limited physical examinations will include assessment of heart, lungs, peripheral pulses, and skin.
7. These assessments will only be completed for participants undergoing the EOS visit.
8. The investigator will aim to get the participant back onto their original home heart failure medication(s) whenever possible. It is recommended if an investigator modifies a participant's home heart failure medication regimen that the changes are communicated to the participant's physician. The investigator will re-assess and adjust participant's home heart failure medications, as needed based on the investigator's clinical judgement, at each outpatient visit until the EOS visit.
9. Pregnancy tests will only be performed in WOCBP. An indeterminate or positive urine pregnancy test will be confirmed with a serum pregnancy test.
10. Pulse wave analysis device may be used in the ≥100 mg dose cohorts where available in select countries to support exploratory endpoints related to non-invasive hemodynamic measurements in this study. The device will be connected for approximately 1 hour at approximately the same time of day on each visit. Whenever possible, pulse wave analysis device activities will be conducted before collection of PK samples and laboratory samples. Further details regarding the pulse wave analysis device and assessments are provided in a study operations manual.
11. It is not required that all procedures be performed during unscheduled visits. Procedures may be conducted based on study needs and/or the investigator's clinical judgment.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Table 5: Timing of Assessment in Relation to Study Drug Administration

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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

9.1.3. Footnotes for Table 5: Timing of Assessment in Relation to Study Drug Administration

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9.1.4. Early Termination Visit

Participants who are withdrawn from the study before the planned end-of-study visit will be asked to return to the clinic: once for an early termination visit consisting of the end of study assessments described in Table 4.

9.1.5. 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.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

At the initial screening visit, participants will sign the ICFs 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 (Table 3):

- 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 HIV, HBV, and HCV screens measured by a local laboratory (Section 9.2.4.11)
- Perform a FSH screen measured by a local laboratory (Section 9.2.4.11)
- Provide results from NT-proBNP or BNP test within 30 days prior to randomization or have the test conducted at a local laboratory (Section 9.2.4.11)

Additional screening visits may be scheduled within the screening window as needed.

9.2.1.1. Height

Participants should not be wearing shoes during height assessment. Height will be recorded to the nearest 1 cm (Table 3).

9.2.1.2. Clinic Admission for Baseline Measurements and Randomization

All participants will be admitted to the clinic on the evening prior to study drug administration or at an earlier time as decided by the investigator.

Participants who are taking ACE inhibitors, ARBs, MRAs, nitrates, and/or diuretics will temporarily halt these medications beginning at 11:59 PM on day -1 (the night prior to the right heart catheterization). The investigator may also withhold other home medications for the participant. Participants will follow local institutional policy regarding fluid and dietary restrictions prior to the right heart catheterization procedure.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9.2.2. Procedures Related to Study Drug Administration

Study drug will be administered at the time point indicated in Table 3. Emergency equipment and medications for the treatment of infusion reactions must be available (Section 8.4.1). Participants will be monitored for up to 4 hours post-dose for any adverse reactions.

9.2.3. Efficacy Procedures

Pharmacodynamic procedures will be performed (Section 9.2.8).

9.2.4. Safety Procedures

9.2.4.1. Body Weight

Body weight will be assessed using calibrated scales at the specified visits in Table 3 and Table 4. Participants should void (empty bladder) prior to weight assessment. Participants should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg. At the screening visit, weight will also be used to calculate BMI for the purpose of collecting baseline demographics.

9.2.4.2. Oscillometric Blood Pressure and Pulse Rate Measurement

Oscillometric BP and PR will be recorded using an automated, inflatable cuff placed on the participant's upper arm at time points indicated in Table 3, Table 4, and Table 5. All oscillometric BP and PR measurements referred to in this study should be performed as 4 sequential measurements taken no sooner than approximately 1 minute apart. The median BP and PR measurement of the last 3 measurements should be used as the value for that time point. The participant's arm (left versus right) used for each assessment should be recorded.

9.2.4.3. Orthostatic Blood Pressure and Pulse Rate Measurement

Orthostatic BP and PR will be measured at the specified visits indicated in Table 3 and Table 4. Orthostatic BP and PR are measured with the participant lying semi-recumbent for at least 10 minutes and after standing for at least 2 minutes. Prior to starting an assessment of orthostatic BP and PR, participants should ambulate for at least 5 minutes. The participant's arm (left versus right) used for each assessment should be recorded. Abnormal results may be repeated.

9.2.4.4. Pulse Oximetry

Oxygen saturation on pulse oximetry (SpO_2) will be measured continuously while PAC is in place (Table 3). The investigator should follow institutional policies for the remainder of the Inpatient Treatment Period.

9.2.4.5. Respiratory Rate Measurement

Respiratory rate will be measured at time points according to Table 3, Table 4, and Table 5.

9.2.4.6. Body Temperature Measurement

Body temperature will be measured at time points according to Table 3, Table 4, and Table 5.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9.2.4.7. Physical Examination

A thorough and complete physical examination will be performed at the screening visit (Table 3). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the participant's medical history.

A limited physical examination, consisting of an assessment of heart, lungs, peripheral pulses, and skin will be conducted at time points according to Table 4 and Table 5. Participants who remain onsite for the extended inpatient monitoring will receive daily limited physical examinations until site discharge.

9.2.4.8. Telemetry (3-lead Electrocardiogram)

Three-lead ECG telemetry will be performed continuously at time points according to Table 3 and Table 4.

9.2.4.9. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 3, Table 4, and Table 5. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTc) intervals will be recorded. The ECG reports will be retained with the source.

9.2.4.10. Oral Fluid Intake Volume and Urine Output Volume Measurements

Oral fluid intake volume and urine output volume will be measured and recorded at visits listed in Table 3. Volumes for oral fluid intake and urine voids will be recorded in 6-hour intervals. Prior to the start of the first 24-hour urine collection beginning on day 1, participants will be asked to empty their bladder. The start of urine collection should match the start of study drug administration on day 1 (± 2 hours). For each interval, start/stop times will be recorded, and volume fluid in and volume fluid out will be recorded.

9.2.4.11. Laboratory Testing

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

Samples for laboratory testing will be collected at visits according to Table 3 and Table 4. Tests will include:

Blood Chemistry

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

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Hematology

Hemoglobin
Hematocrit
Red blood cells (RBCs)
White blood cells (WBCs)
Red cell indices
Platelet count

Differential:
- Neutrophils
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

Urinalysis

Dipstick:

Bilirubin	Urobilinogen
pH	Nitrite
Specific gravity	RBC heme
Ketones	Glucose
Protein	

Microscopic:
- RBC count
- WBC count
- Urine formed elements

Other Laboratory Tests

Human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) screen

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

Follicle-stimulating hormone (FSH) test in women to confirm postmenopausal status

NT-proBNP or BNP test at a local laboratory for study eligibility

International normalized ratio (INR)

Estimated glomerular filtration rate (eGFR)

Bilirubin and coagulation parameters for participants with increased AST/ALT levels (≥3x ULN) will be performed at investigator's discretion

If local laboratory is unable to complete on 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 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 10.1.1.

9.2.5. Drug Concentration and Measurements

Samples for drug concentration measurement will be collected at visits listed in Table 3 and Table 4 and at the time points during visits as listed in Table 5.

9.2.6. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3, Table 4, and Table 5.

9.2.7. Patient-Reported Outcomes

9.2.7.1. Dyspnea Questionnaire

Participants will be asked about their experience of dyspnea as outlined in Table 3 and Table 5. The 7-point Likert scale is a validated scale to evaluate dyspnea status. Participants are asked to evaluate their dyspnea status compared to the status when they were admitted. Status score ranges from 1 (markedly worse) to 4 (no change) to 7 (markedly better). Higher scores reflect improved dyspnea status (West, 2010).

9.2.8. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore how REGN5381 may modify the natriuretic peptide pathway underlying the disease process in participants with heart failure. In particular, the potential role of NPR1 and the effect of REGN5381 on NPR1 and the biomarkers/PD will be explored.

Pharmacodynamic measurements will be conducted using right heart catheterization and invasive hemodynamic measurements at the time points according to Table 3 and Table 5.

Biomarker samples will be collected at time points according to Table 3, Table 4, and Table 5. PD marker/Biomarker measurements will be performed to determine effects on biomarkers of heart failure or relevant physiological and pathogenic processes. The biomarkers studied are believed to be relevant to the pathophysiology of indication, target engagement, mechanism of action of the REGN5831 as a direct agonist of NPR1 and possible toxicities. Additional and/or residual samples collected for other purposes (ie, PK, ADA and biomarker samples) will be banked for exploratory research directly related to drug, disease, target pathway. The samples will be stored for up to

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations).

9.2.8.1. Right Heart Catheterization and Invasive Hemodynamic Measurements

Right heart catheterization will be performed on day 1 and the following parameters will be measured and/or calculated as indicated in Table 3 and Table 5: CO, PCWP, RAP, SVR, PVR, and mPAP (not applicable for Group A Cohorts 6, 7, and 8). SvO_2 may be collected when available. Other continuous hemodynamic parameters such as pulse rate may also be collected when available. In contrast to the other hemodynamic parameters, PCWP is intermittent data at specified time points. For PCWP, a total of 3 sequential measurements will be collected at each time point beginning with the screening hemodynamic measurements. These are measures of congestion and circulatory hemodynamics. Measurement of these parameters at baseline and modulation over time is a secondary endpoint in this study. Details regarding the procedures during the right heart catheterization are described in a study operations manual. Results from these analyses will be reported in the CSR.

9.2.8.2. cGMP Levels

Plasma and urine samples will be collected to measure cGMP levels at the time points indicated in Table 3 and Table 5. cGMP is a measure of NPR1 activity in response to engagement by REGN NPR1 agonists REGN5381. Modulation of cGMP is an exploratory measure in this study. Results from these analyses will be reported in the CSR.

9.2.8.3. NT-proBNP

Plasma samples will be collected to measure NT-proBNP levels at the time points indicated in Table 3, Table 4, and Table 5. NT-proBNP is a clinical biomarker of heart failure. Measurement of NT-proBNP at baseline and modulation over time is a secondary biomarker in this study. Results from these analyses will be reported in the CSR.

9.2.8.4. NT-proANP

Plasma samples will be collected to measure NT-proANP levels at the time points indicated in Table 3, Table 4, and Table 5. NT-proANP is a clinical biomarker of atrial volume and pressure overload. Measurement of NT-proANP at baseline and modulation over time is an exploratory measure in this study. Results from these analyses may be reported in the CSR.

9.2.8.5. ANP and BNP Levels

Plasma samples will be collected to measure ANP and BNP levels at the time points indicated in Table 3, Table 4, and Table 5. ANP and BNP are biomarkers that enable study of the impact of REGN5381 agonism of NPR1 on one of its measurable endogenous agonists. Measurement of ANP and BNP at baseline and modulation over time are exploratory measures in this study (if the assay is available). Results from these analyses may be reported in the CSR.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9.2.8.6. CA125 Levels

Blood samples will be collected to measure Carbohydrate antigen 125 (CA125) levels at the time points indicated in Table 3 and Table 4. While CA125 was traditionally used as a marker for ovarian cancer, it has more recently been found to be a biomarker of congestion in heart failure. CA125 has shown a positive association with clinical congestion and adverse clinical outcomes (Núñez, 2020) (Núñez, 2017). Measurement of CA125 at baseline and modulation over time are exploratory measures in this study. Results from these analyses may be reported in the CSR.

9.2.8.7. Norepinephrine Levels

Plasma samples will be collected to measure norepinephrine levels at the time points indicated in Table 3 and Table 5. Norepinephrine is a biomarker on sympathetic nervous system activity. Measurement of norepinephrine at baseline and modulation of norepinephrine over time are exploratory measures in this study. Results from these analyses may be reported in the CSR.

9.2.8.8. Renin Levels

Plasma samples will be collected to measure renin levels at the time points indicated in Table 3 and Table 5. Renin is a biomarker that might inform mechanism of action of REGN5381. These assessments will provide valuable information regarding the downstream effects of NPR1 agonism. Measurement of renin at baseline and modulation of renin over time are exploratory measures in this study. Results from these analyses may be reported in the CSR.

9.2.8.9. Aldosterone Levels

Plasma samples will be collected to measure aldosterone levels at the time points indicated in Table 3 and Table 5. Aldosterone is a biomarker that might inform mechanism of action of REGN5381. These assessments will provide valuable information regarding the downstream effects of NPR1 agonism. Measurement of aldosterone at baseline and modulation of aldosterone over time are exploratory measures in this study. Results from these analyses may be reported in the CSR.

9.2.8.10. Urine Sodium Levels

Urine sodium measures the excretion of sodium by the kidneys. Increases in natriuresis (or excretion of sodium in the urine) have been observed with engagement of NPR1. Modulation of urine sodium by REGN5381 is an exploratory measure in this study. Samples will be collected as indicated in Table 3. Results from these analyses may be reported in the CSR.

9.2.8.11. Kidney Injury Molecule-1 (KIM-1)

Urine samples will be collected to measure KIM-1 levels at the time points indicated in Table 3. KIM-1 to creatinine ratio is a measure of renal tubular injury. Measurement of KIM-1 to creatinine ratio at baseline and modulation over time are exploratory measures in this study. Results from these analyses may be reported in the CSR.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

9.2.8.12. Urinary Albumin Creatinine Ratio

Urine samples will be collected to measure urinary albumin to creatinine ratio at the time points indicated in Table 3. Urinary albumin to creatinine ratio is a measure of urinary albumin excretion. Measurement of urinary albumin to creatinine ratio at baseline and modulation over time are exploratory measures in this study. Results from these analyses may be reported in the CSR.

9.2.8.13. Non-Invasive Hemodynamic Parameters Derived from Pulse Wave Analysis

Pulse wave analysis device may be used in the ≥100 mg dose cohorts where available in select countries to measure BP, PR, and SV at the time points indicated in Table 3, Table 4, and Table 5. The finger cuff system collects these parameters using a combination of photoplethysmography and a volume clamp method to continuously capture pulse wave data for non-invasive hemodynamic monitoring. Measurement of non-invasive hemodynamic measures at baseline and modulation over time are exploratory measures in this study.

9.2.9. 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 but can be collected at a later study visit (Table 3). 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 NPR1 pathway, heart failure and/or chronic kidney disease. These samples will be single-coded as defined by the International Council for Harmonisation (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 other 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 and 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-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of on-treatment period (see Section 11.4.5.1). 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 also 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 10.2. 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 SAE (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 10.2 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 10.1.3.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

10.1.2. 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.

10.1.3. 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 injection site reactions
  - Moderate to severe infusion reactions
  - Moderate or severe hypersensitivity reactions
  - Severe hypotension (SBP <90 mm Hg)
  - Elevated liver enzymes (≥3x ULN)
- **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 study participant or female partner of a male study participant, 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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

10.2. Definitions

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

10.2.2. 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.

10.2.3. 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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

10.2.4. Infusion Reactions

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

10.2.5. 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 participant'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.

10.2.6. 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.

Include the following when applicable] For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

- Concomitant medications /procedures
- 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
- 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/procedures), 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/procedures) 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/procedures), 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/procedures) or other external factors.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

10.3. 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.

10.4. 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 Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (REGN5381) is assessed against the Reference Safety Information section of the Investigator's Brochure 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 Clinical Study Report to health authorities and IECs/IRB as appropriate.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

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

11.2. Justification of Sample Size

Up to 122 male and female adult participants will be randomized. In HFrEF participants not taking sacubitril/valsartan (Group A): 4 sequential ascending cohorts and 2 optional expansion cohorts with right heart catheterization procedure (as of PA5, there will be no further dosing of Group A participants in these optional expansion cohorts.), and 3 ascending dose cohorts without right heart catheterization procedure. In HFrEF participants on sacubitril/valsartan (Group B): 3 ascending dose cohorts and 2 optional expansion cohorts. In HFpEF participants not taking sacubitril/valsartan (Group C): 3 ascending dose cohorts and 2 optional expansion cohorts. The group population, randomization ratio and the dose levels for cohorts are defined in Section 6.1.7. The study is not powered to test any statistical hypotheses.

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

Table 6: Half- Width of the 90% Confidence Interval for the Difference in Mean Change from Baseline in PCWP (mmHg)

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

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

11.3. Analysis Sets

11.3.1. Safety Analysis Set

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

11.3.2. Pharmacodynamic Analysis Set (PAS)

The pharmacodynamic analysis set (PAS) includes all participants in the SAF except for those who are excluded for the reasons listed in below, which may potentially confound with the PD analyses; it is based on the treatment received (as treated).

Exclusions:

- Had not completed study treatment
- Had any violations of inclusion/exclusion criteria
- Had taken any anti-hypertensive drug during the on-treatment period

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

11.3.3. Pharmacokinetic Analysis Set

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

11.3.4. Immunogenicity Analysis Set

The ADA analysis set includes all participants who received study drug and had at least 1 non-missing ADA result following the first study drug dose.

11.4. Statistical Methods

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

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

Unless otherwise specified, participants receiving placebo will be pooled across cohorts.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

11.4.1. Participant Disposition

The following will be provided:

- The total number of screened participants who have signed the ICF
- The total number of randomized participants: received a randomization number
- The total number of participants who discontinued the study, and the reasons for discontinuation
- The total number of participants who discontinued from study treatment, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all participants combined.

11.4.3. Efficacy/Pharmacodynamic Endpoint Analyses

The secondary endpoints to evaluate the hemodynamic effects of REGN5381 are:

- Change from baseline in PCWP, RAP, CO, SVR, mPAP, and PVR over 6 hours post-dose administration
- Change from baseline in SBP, DBP, MAP, and PR over the first 6 hours and 24 hours post-dose administration (day 1), and through the EOS visit

The comparison groups for the above endpoints are participants who receive REGN5381 versus participants who receive placebo.

PCWP will be assessed every 2 hours post-end of study drug infusion. The other invasive hemodynamic parameters (RAP, CO, SVR, mPAP, PVR) will be assessed via descriptive statistics. The baseline for these parameters is defined as the measurements and data collected prior to dosing.

For the expansion active treatment cohort versus pooled placebo, summary statistics including the mean change from baseline over the 6 hours post-dosing, standard error (SE), corresponding 90% confidence interval, and nominal p-value will be provided for PCWP for REGN5381 vs placebo group, using mixed-effect model with repeated measures (MMRM). Nominal p-values will be provided as a measure of the strength of evidence. The MMRM model will include treatment, time point, baseline-by-time point interaction and treatment-by-time point interaction, as well as the continuous fixed covariate of baseline value. If the MMRM model does not converge, analysis of the PCWP will be conducted using analysis of covariance at each time point.

The continuous collected PD parameters will be analyzed with moving average. Mean changes (±SE) will be plotted over time by the treatment group using the moving average. Summary statistics including the mean change from baseline over the 6 hours post-dosing and standard error (SE) will be provided by treatment groups.

11.4.4. Control of Multiplicity

Not applicable.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from the administration of study drug to the EOS visit or last visit in the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of participants with at least 1 TEAE by system organ class (SOC) and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- Treatment related TEAEs presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (body temperature, PR, BP, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

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

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

11.4.5.3. 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).

11.4.5.4. Treatment Compliance

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

11.4.6. Pharmacokinetics

11.4.6.1. 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):

- AUC_{last} – area under curve (AUC) computed from time zero to the time of the last positive concentration
- AUC_{inf} - AUC from time zero extrapolated to infinity
- C_{max} – peak concentration
- T_{max} - time of peak concentration
- T_{last} - time of the last positive (quantifiable) concentration
- CL – clearance
- V_{ss} - volume of distribution at steady state

The concentrations of total REGN5381 over time and selected PK parameters will be summarized by descriptive statistics for each cohort for the purpose of estimating exposures in these groups. Selected PK parameters will be calculated using non-compartmental analysis and will be summarized using descriptive statistics which may include, but are not limited to, mean (arithmetic and/or geometric), standard deviation, standard error of the mean, coefficient of variation (%), minimum, Q1, median, Q3, and maximum. This descriptive statistical assessment will include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by participant, time point, and dose cohort/group will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of participants (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

11.5. 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 15.1.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

12. 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.

12.1. Data Management and Electronic Systems

12.1.1. 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).

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

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

12.1.2. Electronic Systems

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

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

12.2. Study Monitoring

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

12.2.2. 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.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic case report forms (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.

12.3. 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, 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.

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

12.4. Study Documentation

12.4.1. 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 participant final eCRF that will be provided to the sponsor.

12.4.2. 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.

12.4.3. 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.

12.4.4. 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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

- 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.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. 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.

13.2. 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 EC. A copy of the 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.

13.3. 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-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted 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 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 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 EC approval letter with a current list of the 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 EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. For data integrity, scientific, and statistical reasons, published results from all participants will be disclosed following End of Study (Section 6.1.9).

Treatment codes will be disseminated to each investigation site thereafter.

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

14. PROTOCOL AMENDMENTS

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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

15.1. 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.

15.2. 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 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.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of REGN5381, an NPR1 Agonist, in Heart Failure Patients with Elevated Pulmonary Capillary Wedge Pressure, 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 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)

VV-RIM-00336967-1.0 Approved - 09 Feb 2024 GMT-5:00

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 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of REGN5381, an NPR1 Agonist, in Heart Failure Patients with Elevated Pulmonary Capillary Wedge Pressure

Protocol Number: R5381-HF-2159

Protocol Version: R5381-HF-2159 Amendment 6

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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