REGULATORY AGENCY IDENTIFIER NUMBER(S)

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CLINICAL PROTOCOL CV019010

A Randomized, Double-Blinded, Placebo-Controlled, Study to Evaluate the Safety and Tolerability of BMS-986259 in Stabilized Patients Hospitalized for Acute Decompensated Heart Failure

Short Title:

Study of the safety of BMS-986259 post-acute decompensated heart failure

Revised Protocol Number: 01

[redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	28-Oct-2020	This amendment adds safety measures in response to the coronavirus disease 2019 (COVID-19) pandemic and addresses health authority and ethics committee requests for clarifications, as follows: • An interim analysis has been added to occur when approximately 50% of participants have completed the End of Study Visit (Day 14). • The pharmacokinetic [redacted] data collection was simplified to minimize participant burden. Minor updates to the study design schematic have also been made for clarity. • In response to the COVID-19 pandemic: o Related risks and risk mitigation measures are discussed. o A negative reverse transcription polymerase chain reaction or rapid antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is required at screening for inclusion in the study. [redacted]
Original Protocol	21-Jan-2020	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 01:

This amendment adds safety measures in response to the coronavirus disease 2019 (COVID-19) pandemic and addresses [redacted] ethics committee requests for clarifications, as follows:

- An interim analysis has been added to occur when approximately 50% of participants have completed the End of Study Visit (Day 14).
- The pharmacokinetic (PK) [redacted] data collection was simplified to minimize participant burden. Minor updates to the study design schematic have also been made for clarity.
- In response to the COVID-19 pandemic:
  - Related risks and risk mitigation measures are discussed.
  - A negative reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is required at screening for inclusion in the study.

  [redacted]
- Additional revisions, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. Minor formatting and typographical corrections have been made for accuracy and clarity throughout the document as well.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated study director/medical monitor name and contact information.	Medical monitor was changed.
Section 2: Schedule of Activities; Section 6.1: Inclusion Criteria	The following changes to Vital Signs were made: • In Table 2-1, Screening Procedural Outline (CV019010), clarified that: o Heart rate should be measured per standard of care (SOC). o Blood pressure should be measured while the participant is in a supine position (preferable). • In Table 2-2, On-Treatment and Follow-up Procedural Outline	Updated text to clarify expectations for vital signs/blood pressure measurements and to ensure alignment with the primary endpoint.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	(CV019010), added text to describe expectations for at-home blood pressure measurements. • In Section 6.1, Inclusion Criteria, added text to criterion 2) b) v) that supine position for systolic blood pressure (SBP) measurement is preferable, based on participant's condition and comfort.	
Section 2: Schedule of Activities	In Table 2-1, Screening Procedural Outline (CV019010): • Added a row for Urinalysis under Local Laboratory Assessments. • Changed footnote a to: "Screening must occur at least 24 hours post initial emergency room (ER) presentation. Randomization must occur within 8 days post initial ER presentation." In Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010): [redacted] • Removed Urine PK & Metabolite Sampling. [redacted] • Modified footnote d: "If needed, the study can be ended 1 day early, with the End of Study Visit taking place on Day 13 instead of Day 14." Added footnote d to Day 13 column title.	Updated schedule of activities for clarity and to align with protocol text.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Added footnote e to Day 14: "Evaluations performed prior to study discharge, or for participants who prematurely discontinue treatment." • Modified footnote f to: "Only performed at day of discharge (Day 6 or beyond). If study participant is not discharged on Day 6, delay assessments and sample collections until day of discharge."	
Section 2: Schedule of Activities; Section 9.4.5.2: Central Laboratory Assessments (On Treatment)	• In Table 2-2, On-Treatment and Follow-up Procedural Outline (CV019010), added footnote h to indicate that hematology, serum chemistry, and urinalysis samples should be collected predose. • In Section 9.4.5.2, before the list of central laboratory assessments, added: "The following samples should be collected predose: Hematology, Chemistry, and Urinalysis."	Updated on-treatment assessments to clarify that hematology, chemistry, and urinalysis samples are collected predose.
Section 2: Schedule of Activities	In Table 2-2, On-Treatment and Follow-Up Procedural Outline (CV019010), for 12-Lead Electrocardiogram (ECG) row, added the following note to specify timing of ECG measurements: "On Day 1, ECG will be collected pre-dose and at hours 2, 4, and 8. On Day 8 and Day 14, it will only be collected pre-dose."	Added ECG time points in order to implement more robust safety monitoring on Day 1 of the study.
Section 2: Schedule of Activities; Section 3.3.1: COVID-19-related Risks and Risk Mitigation	• In Table 2-1, Screening Procedural Outline (CV019010), SARS-CoV-2 testing (RT-PCR testing or rapid antigen test) was added.	Updates made to ensure participant and site safety and to maintain scientific integrity of the study in response to the COVID-19 pandemic.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Measures Where Applicable; Section 5.1: Overall Design; Section 6.2: Exclusion Criteria; Section 7.2: Method of Treatment Assignment; Section 8.1: Discontinuation from Study Treatment; Section 9.4.5.1: Local Laboratory Assessments for Screening	• In Table 2-2, On-Treatment and Follow-up Procedural Outline: – Footnote c was expanded to include an option for Day 8, Day 14, and Day 30 ambulatory site visits to be done at home in cases where COVID-19 local regulations prevent in-person visits. – Footnote g was added to indicate that if the Targeted PE for Day 8 and Day 14 was not performed by the site due to COVID-19 local regulations, a physical assessment will be done by the home nurse. • A new section, Section 3.3.1, COVID-19-related Risks and Risk Mitigation Measures Where Applicable, was added to address risk mitigation, including Investigational Product (IP)-related risk (Section 3.3.1.1) and general COVID-19-related risk mitigation measures (Section 3.3.1.2). • In Section 5.1, Overall Design, text was added to describe: – The requirements for SARS-CoV-2 testing (RT-PCR or rapid antigen test) at screening and a negative result in order to be randomized. – That, if the participant cannot return to the site because of COVID-19 local regulations that prevent in-person visits	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	on Day 8, Day 14, and/or Day 30, then these visits can be done at home by the home nurse in discussion with the Principal Investigator (or designee). • In Section 6.2, Exclusion Criteria, added exclusion criterion 4) vii): "Positive RT-PCR test or rapid antigen test for SARS-CoV-2 prior to randomization." • In Section 7.2, Method of Treatment Assignment, updated that study treatment will be dispensed at the Day 1 visit, instead of at study visits listed in Schedule of Activities. • In Section 8.1, Discontinuation from Study Treatment, added bullet: "Positive RT-PCR or rapid antigen test for SARS-CoV-2." • In Section 9.4.5.1, Local Laboratory Assessments for Screening, SARS-CoV-2 test (RT-PCR or rapid antigen test) was added to the list under Other Analyses.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.3: Benefit/Risk Assessment	The last sentence in the second paragraph was replaced with text describing hypotension as a risk associated with the use of BMS-986259 and the mitigation strategies implemented in the study.	To clarify risk for study participation in regards to hypotension.
Section 4: Objectives and Endpoints	Secondary endpoint was updated to include Day 1 and to expand the PK parameters of BMS-986259 to include Cmax, Tmax, and AUC(TAU) on Day 1 and Day 5, and Ctrough.	Updated secondary endpoint to characterize the PK after single dose and at steady state on Day 5.
Section 5.1: Overall Design	• Added a bullet to clarify that "ADHF must be the main reason for hospitalization, and other conditions with similar signs and symptoms must be excluded at screening." • To the second bullet, added, "Randomization must occur within a maximum of 8 days	Updated study design for clarity.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	since presentation to the ER and before hospital discharge." [redacted] • In Figure 5.1-1, the following updates were made: – Study Design was split into a Schematic portion and a Timeline portion. – Removed that participants in the Sentinel Group must have SBP < 130 mmHg. – A box was added to specify the treatment initiation window compared to initial ER presentation for both groups. – Footnote b was added to indicate that "safety review of the sentinel group requires at least 8 participants with systolic blood pressure ≥ 115 mmHg and < 130 mmHg." [redacted]	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design	Updated first sentence in penultimate paragraph to: "In addition, if systolic BP is < 85 mmHg or symptomatic hypotension occurs, the Principal Investigator (or designee; must be a medical doctor [MD]) must be contacted to make a decision as to whether an ambulatory unscheduled study visit or hospitalization is required based on overall clinical assessment. For example, asymptomatic study participants who can walk and have normal urination may not require hospitalization. BMS Study Director/Medical Monitor (or designee) must be notified."	Clarified that primary investigator makes decisions on hospitalization for hypotension based on clinical judgement.
[redacted]		
Section 5.5: Justification for Dose	Removed last paragraph and added text earlier in Section 5.5 to clarify dosing: "The observed mean exposures at steady state with repeated 3 mg QD dosing (AUC[TAU]) of 9,070 ng·h/mL remain under the mean exposure (AUC[INF]) of 38,200 ng·h/mL observed after a single 15 mg dose that was determined to be safe and well tolerated in a healthy participants study (Table 5.5-1)."	Provided further clarification on doses and exposures.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	• Inclusion criterion 3) was modified to delete the text: "The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention."	• Removed statement in criterion 3) to ensure that the protocol specifies definitive requirements for contraception.
	• Added notes (1) and (2) to inclusion criteria 3) b) ii) and 3) b) v). Note (1) in each criterion indicates that, respectively, for males who are sexually active with WOCBP and for female partners of males participating in the study, "less than highly effective methods of contraception and unacceptable methods of contraception are not permitted." Note (2) in both criteria indicates that "Hormonal contraception is also not permitted."	• Added notes to criteria 3) b) ii) and 3) b) v) to clarify contraception requirements for the study.
Section 6.1: Inclusion Criteria; Appendix 7: Country Specific Requirements/ Differences	• In Section 6.1, added notes to criteria 3) a) i) and 3) b) i) referencing Appendix 7 for maximum age limit where locally mandated. • Added Appendix 7 to provide Czech Republic specific language. For inclusion criteria 3) a) i) and 3) b) i), for females and males, respectively, added a maximum age of 75 years.	Added Czech Republic specific inclusion criteria for maximum age limits [redacted]
Section 6.2: Exclusion Criteria	• Expanded upon exclusion criterion 3) a) by listing out restrictions and prohibited treatments (phosphodiesterase type 5 [PDE5] inhibitors used for erectile dysfunction, continuous infusion of IV diuretics, inotropes and vasodilators), which are also provided in Section 7.7.	• Added details on restrictions and prohibited treatments for clarification.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Exclusion criterion 4) a) iv) was removed and deemed "Not applicable per Revised Protocol 01," and a new replacement criterion 4) a) vi) was added to modify the previous total bilirubin and liver enzyme requirements to "Liver abnormalities including total bilirubin > 1.5 × ULN or significant elevation of liver enzymes (AST or ALT > 3 × ULN)."	• Exclusion criterion was modified for clarity and to ensure appropriate level of liver enzymes is used for the study population.
Section 7.3: Blinding	Modified the last 2 paragraphs to: • Add that the Safety Review Committee is independent from the study team. • Update unblinding procedures.	Clarified role of internal Safety Review Committee and unblinding for conducting the assessment of blood pressure data in the Sentinel Group, and the planned interim analysis.
Section 7.5: Preparation/ Handling/Storage/ Accountability	Removed text: "Study medication will be prepared by an unblinded pharmacist (or appropriate designee) at time of randomization."	Clarified that unblinded pharmacist is not required, as the study will have matching placebo.
Section 7.7.1: Prohibited and/or Restricted Treatments	Revised the required window for reporting medications taken in hospital prior to study drug administration from 1 week to 8 days.	Since screening period can be up to 8 days after presentation at ER, text was updated to clarify that it needs to be ensured that all medications administered at the hospital are recorded.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.5: Pharmacokinetics; [redacted]	In Section 9.5, Pharmacokinetics: • Removed AUC(INF) from the list of PK parameters.	• Removed AUC(INF), as it cannot be calculated for steady state dosing at Day 5 for multiple dosing regimen.
	• Added text: "When multiple procedures are required at a time point, prioritize that the PK samples are collected as close to the scheduled time point as possible." • In Table 9.5-1, Pharmacokinetic [redacted] Sampling Schedule for All Participants:	• Clarified PK sample collection instruction at the time of multiple procedures.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	– Removed the following PK sampling time points: Day 1 1:00, 5:00, 7:00, 9:00, 11:00, 12:00, and 16:00 postdose, Day 4 predose, Day 5 5:00 and 15:00 postdose, and Day 7, 9, 10, 12, and 13 predose. Added the following PK sampling time points: Day 5 3:00, 6:00, 8:00, 14:00 post dose, and Day 14 predose.	• Optimized PK sampling to better characterize the PK on Day 1 and Day 5, and for participant convenience.
	[redacted]	
	– Removed urine and metabolite sample collections.	• Removed urine and metabolite sample collections because it was already shown in previous nonclinical and clinical studies that there is minimal renal excretion of BMS-986259.
	[redacted]	
	– Added footnote a: "All the PK samples should be collected as close to the scheduled time point as clinically feasible."	• Clarified PK sample collection instruction.
	– Added footnote b to clarify timing of predose sample collection in relation to the injection time and in the event of a dose delay.	• Clarified PK predose sample collection instruction.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	– Added footnote c to indicate that if End of Study Visit takes place on Day 13, indicated Day 14 PK samples should be collected on Day 13.	• Clarified End of Study Visit PK sample collection.
	– Updated footnotes d. e, f, and g to detail the timing and applicability of follow-up visits.	• Clarified follow-up timing and applicability.
	[redacted]	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3.2: Safety Analyses	The endpoint description of Adverse Events, Vital Signs, Laboratory Test Results, ECGs, and Physical Examination was moved into the Primary row. The matching statistical methods for these items were also moved into the Primary row.	Updated endpoints, safety analyses, and statistical analysis methods for accuracy to match the study objectives and endpoints.
Section 10.3.5: Interim Analyses	Replaced "Not Applicable" with a description of the planned interim analysis.	Added description for an interim analysis to formally evaluate safety during the study half-way point.
Appendix 1: Abbreviations	Definitions for new in-text abbreviations were added.	Updated for accuracy and completeness.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title:

A Randomized, Double-Blinded, Placebo-Controlled, Study to Evaluate the Safety and Tolerability of BMS-986259 in Stabilized Patients Hospitalized for Acute Decompensated Heart Failure

Short Title: Study of the safety of BMS-986259 post-acute decompensated heart failure

Study Phase: 2A

Rationale:

The main purpose of this trial is to evaluate the effect of BMS-986259 on blood pressure (BP) events defined as symptomatic hypotension or hypotension requiring study drug discontinuation, in hospitalized heart failure (HF) patients stabilized after an admission for acute decompensated HF (ADHF). The study is designed to provide data on the range of BP in which BMS-986259 is safe and well tolerated in the context of the current hospitalization for ADHF. It also aims to provide additional rationale for future development, future clinical use and to inform the design of the next Phase 2-3 studies. In addition, this study will provide initial data on the pharmacokinetics (PK) of BMS-986259 in HF participants.

Standard of care in the treatment of ADHF involves the use of intravenous (IV) loop diuretics and vasodilators, which may predispose participants to hypotension, with or without symptoms. Current guidance also recommends continuing Guidelines Directed Medical Therapy (GDMT) including angiotensin-converting enzymes (ACE), Beta-Blockers, mineralocorticoid receptor antagonists (MRA)/mineralocorticoid receptor inhibitors (MRI), and angiotensin receptor-neprilysin inhibitors (ARNI), which may also lower BP. In the Serelaxin ADHF study, RELAX-AHF, greater reductions from baseline in systolic blood pressure (SBP) were observed during IV infusion up to 48 hours in the serelaxin group (-16.5 mmHg ± 17.2) compared with placebo (-12.3 mmHg ± 17.2). Also, more participants on serelaxin than on placebo had protocol required BP-related dose reduction (29% vs 18%) or drug discontinuation (19% vs 12%). In contrast, in the chronic stable HF population of the RELAX REPEAT study, SBP in the serelaxin group did not differ from placebo. There are no data on the effect of relaxin on BP in the population of HF patients admitted for ADHF, but not yet discharged, already medically stabilized and weaned from IV vasodilators or inotropes.

Study Population:

Male and females, at least 18 years of age or local age of majority, currently hospitalized for ADHF, regardless of left ventricular ejection fraction (LVEF).

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To establish safety & tolerability of BMS-986259 when initiated in-hospital in participants stabilized after an admission for ADHF	• Incidence of clinically relevant hypotension, defined as: – Supine SBP < 85 mmHg (confirmed by repeat measurement within 30 minutes), regardless of symptoms of hypotension OR – Supine SBP < 90 mmHg (confirmed by repeat measurement within 30 minutes) AND symptoms of hypotension.
Secondary	
• To evaluate serum PK parameters in participants with HF	• PK parameters of BMS-986259: – Cmax, Tmax, and AUC(TAU) on Day 1 and Day 5 – Ctrough

Abbreviations: ADHF = acute decompensated heart failure; AUC(TAU) = area under the concentration-time curve in one dosing interval; BMS = Bristol-Myers Squibb; Cmax = maximum observed concentration; Ctrough = trough concentration; HF = heart failure; PK = pharmacokinetic; SBP = systolic blood pressure; Tmax = time of maximum observed concentration.

Overall Design:

This is a Phase 2A randomized, double-blind, placebo-controlled study of BMS-986259 in hemodynamically stabilized patients currently hospitalized for ADHF. The study is designed to establish if BMS-986259 is safe and well tolerated in this population with regards to clinically significant hypotension.

- ADHF must be the main reason for hospitalization, and other conditions with similar signs and symptoms must be excluded at screening.
- at least 24 hours after presentation to Emergency Room (ER) and no later than 8 days after presentation to ER. Time of the presentation is defined as the time of the first dose of IV diuretic in the hospital. Randomization must occur within a maximum of 8 days since presentation to ER and before hospital discharge.
- at least 12 hours since last dose change of IV loop diuretics and at least 24 hours since last dose of positive inotropes and ≥ 12 hours since the last dose of IV vasodilators.
- Prior to randomization, participants will also be tested for severe acute respiratory syndrome coronavirus 2 by reverse transcription polymerase chain reaction or rapid antigen test. Only participants with a negative test result are eligible for randomization.

Participants will be randomized 1:1 to receive BMS-986259 3 mg or placebo. Treatment will be administered subcutaneously once daily for 14 days and follow-up will last until Day 30 (± 2 days). [redacted]

[redacted]

A minimum hospital stay of 5 days from randomization/first dose of investigational product (IP) is required. If participants are discharged home before the end of active study treatment, study visits will be performed daily either as an outpatient clinic visit or by a home nurse or healthcare provider (per local regulations/requirements) who will be responsible to measure pre-dose BP, draw PK sample(s), administer the IP subcutaneously [redacted] when appropriate per study schedule.

Participants will return for up to three ambulatory visits at the site on Day 8, Day 14, Day 30 (follow-up). If the participant cannot return to the site because of coronavirus disease 2019 (COVID-19) local regulations that prevent visits in-person, these visits can be done at home by the home nurse in discussion with the Principal Investigator (or designee). In addition, at discharge, participants will receive BP measuring device and will be instructed to measure BP if symptoms consistent with hypotension occur. If systolic BP falls below 85 mmHg (on 2 repeated measurements within 30 minutes) and symptoms of hypotension persist, participants will be instructed to report to the study site or another healthcare provider if the study site cannot be reached.

Initially participants with SBP ≥ 115 mmHg will qualify to be randomized 1:1 to receive 3 mg subcutaneous BMS-986259 once daily (QD) or placebo. After approximately 8 participants with SBP ≥ 115 and < 130 mmHg have completed the treatment period, the Safety Review Committee will review the safety data from this sentinel group and ensure it is safe to proceed with the Main Group, ie., open the recruitment for participants with SBP less than 115 mmHg (but at least 100 mmHg).

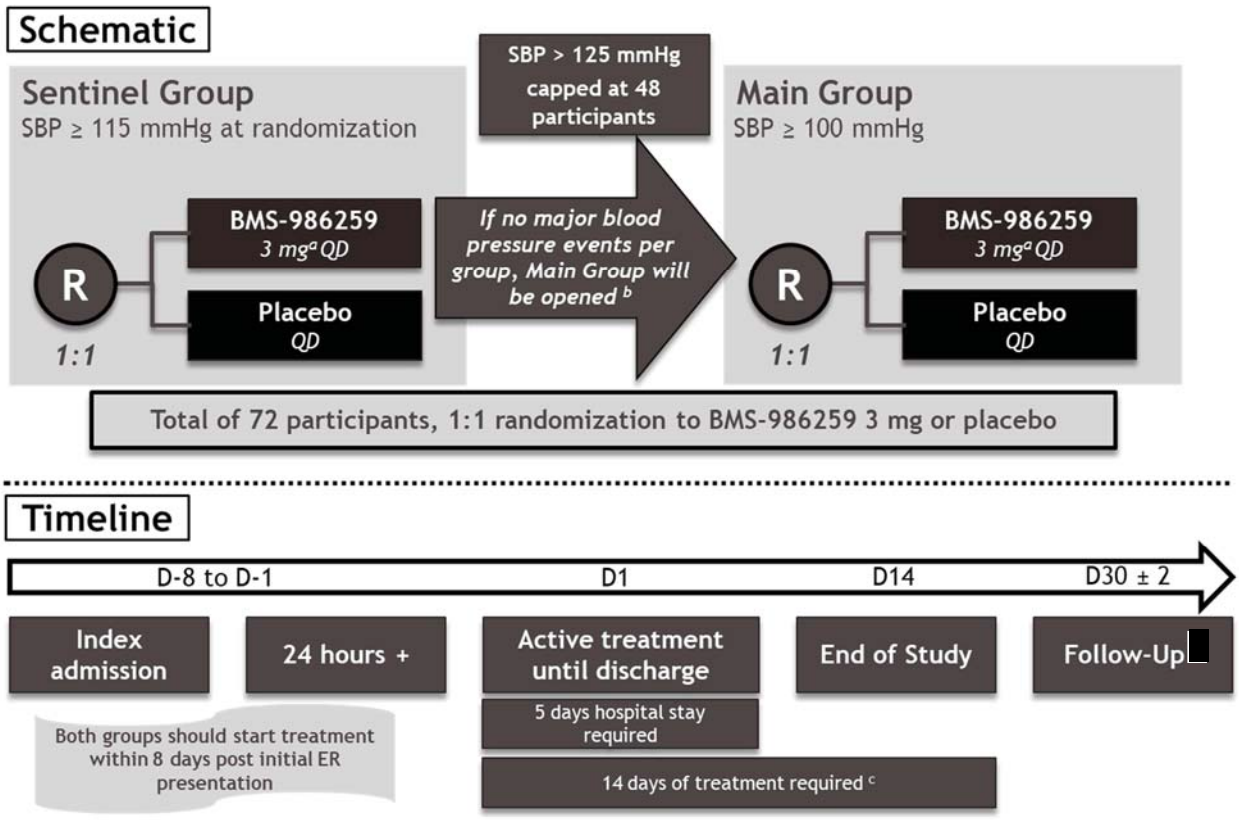
The Main Group will include participants with SBP ≥ 100 mmHg, randomized 1:1 to BMS-986259 or placebo. The proportion of participants with SBP > 125 mmHg will be capped at 48 participants.

Study drug may be down-titrated to 1 mg or discontinued according to the criteria described in dose modification.

In addition, if systolic BP is < 85 mmHg or symptomatic hypotension occurs, the Principal Investigator (or designee; must be a medical doctor [MD]) must be contacted to make a decision as to whether an ambulatory unscheduled study visit or hospitalization is required based on overall clinical assessment. For example, asymptomatic study participants who can walk and have normal urination may not require hospitalization. BMS Study Director/Medical Monitor (or designee) must be notified. A blinded clinical contact will be available 24/7 to answer questions and guide the home nurse as needed.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



Abbreviations: [redacted] D = day; ER = emergency room; [redacted] QD = once daily; R = randomization; SBP = systolic blood pressure.

[a] May be down-titrated to 1 mg or discontinued according to the dosage modification criteria described in the protocol.

[b] Safety review of the sentinel group requires at least 8 participants with blood pressure < 130 mmHg.

[c] If participant is discharged before the end of active study treatment, study visits will be performed daily either as an outpatient clinic visit or by a home nurse or healthcare provider.

[redacted]

Number of Participants:

It is estimated that a total of approximately 72 participants will be randomized with 1:1 ratio assigned to either BMS-986259 subcutaneous QD or Placebo to have at least 60 completers by the end of the study.

Treatment Arms and Duration:

Study treatment:

Study Drug for CV019010		
Medication	**Potency**	**IP/Non-IP**
BMS-986259 injection for SC administration	5 mg/vial (5 mg/mL) Dose level 3 mg and 1 mg BMS-986259 will be diluted to administer a 3 mg or 1 mg dose as a 1 mL SC injection. Details of preparation and administration are provided in the pharmacy manual	IP
Placebo injection for SC administration	N/A	IP

Abbreviations: IP = investigational product; N/A = not applicable; SC = subcutaneous.

Safety Review Committee: Yes

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CV019010)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	Note: ≥ 12 hours since the last dose change of IV loop diuretics, and ≥ 24 hours since last dose of positive inotropes and ≥ 12 hours since the last dose of IV vasodilators. See Section 6.1 and Section 6.2.
Medical History	X	Include any toxicities or allergy related to previous treatments.
Safety Assessments		
Physical Examination (PE)	X	If the Screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the Screening and pre-dose evaluation.
Physical Measurements	X	Includes height, weight, and body mass index (BMI).
Vital Signs	X	Includes body temperature, respiratory rate, blood pressure, and heart rate. Heart rate should be measured per standard of care (SOC). Blood pressure should be measured while the participant is in a supine position (preferable, based on participant's condition and comfort). Consider alternate position(s) for vital sign collection.
Assessment of Signs and Symptoms (NYHA class)	X	Refer to Appendix 6.
Concomitant Medication Use	X	See Section 7.7.
12-Lead Electrocardiogram (ECGs)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Central Laboratory Assessments		
[redacted]		

Table 2-1: Screening Procedural Outline (CV019010)

Procedure	Screening Visit[a]	Notes
Local Laboratory Assessments		Includes blood and urine samples for chemistry, CBC, hematology, and urinalysis (dipstick and full microscopic evaluation if dipstick positive). See Section 9.4.5.
SARS-CoV-2 Testing	X	RT-PCR testing or rapid antigen test must be performed prior to randomization. Potential participants found to test positive for SARS-CoV-2 will be treated according to site standard practice and in accordance with local and national regulations.
Hematology and Serum Chemistry	X	See Section 9.4.5.
Serology (Hepatitis and HIV)	X	See Section 9.4.5.
Urinalysis	X	See Section 9.4.5.
NT-proBNP or BNP	X	Local lab value for NT-proBNP or BNP can be used for eligibility.
FSH Test	X	For women < 55 years.
Monitor for Serious Adverse Events (SAEs)	X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

Abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; CBC = complete blood count; ECG = electrocardiogram; ER = emergency room; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IV = intravenous; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PE = physical examination; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SAE = serious adverse event; SOC = standard of care.

[a] Screening must occur at least 24 hours post initial emergency room (ER) presentation. Randomization must occur within 8 days post initial ER presentation.

Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010)

Procedure	Randomization D1[a]	D 2	D 3	D 4	D 5	D 6	D 7[b]	D 8 Visit[c]	D 9[b]	D 10	D 11[b]	D 12	D 13[d]	D14 End of Study Visit[c,d,e]	D30 (± 2 days) Follow-Up Visit[c]	Notes
Safety Assessments																
Targeted PE						X[f]		X[g]						X[g]		Complete before discharge.
Injection site evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X		Injection site evaluation performed daily pre-dose and in the evening. Post-discharge, a home nurse (or site personnel) will evaluate injection site prior to study drug administration.
Physical Measurements	X	X	X	X	X	X[f]		X						X		In hospital weight measurements daily until discharge. Day 1 pre-dose.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Pre-dose BP measurement on Day 1 at 0 hour; at 2, 4, 8, 12, 16, 20, 24 hours post dose.

Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010)

Procedure	Randomization D1[a]	D 2	D 3	D 4	D 5	D 6	D 7[b]	D 8 Visit[c]	D 9[b]	D 10	D 11[b]	D 12	D 13[d]	D14 End of Study Visit c,d,e	D30 (± 2 days) Follow-Up Visit[c]	Notes
																Pre-dose BP measurement on Day 2 at 0 hour, at 2, 4, 8, and 12 hours post dose. Then 4 times a day on following days until discharge, 0, 4, 8, 12 hours. Once participant is discharged home, BP to be measured pre-dose by home nurse. Participant should be in supine position (preferable, based on participant's condition and comfort) and using non-dominant arm for home measurements.
[redacted]																

Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010)

Procedure	Randomization D1[a]	D 2	D 3	D 4	D 5	D 6	D 7[b]	D 8 Visit[c]	D 9[b]	D 10	D 11[b]	D 12	D 13[d]	D14 End of Study Visit[c,d,e]	D30 (± 2 days) Follow-Up Visit[c]	Notes
[redacted]																
Assessment of Sign and Symptoms (NYHA class)	X					X[f]								X	X	
12-Lead ECG	X							X						X		ECGs should be recorded after the participant has been supine for at least 5 minutes. On Day 1, ECG will be collected pre-dose and at hours 2, 4, and 8. On Day 8 and Day 14, it will only be collected pre-dose.
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central Laboratory Assessments																

Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010)

Procedure	Randomization D1[a]	D 2	D 3	D 4	D 5	D 6	D 7[b]	D 8 Visit[c]	D 9[b]	D 10	D 11[b]	D 12	D 13[d]	D14 End of Study Visit c,d,e	D30 (± 2 days) Follow-Up Visit[c]	Notes
Hematology and Serum Chemistry[h]	X	X	X			X[f]		X						X	X	See Section 9.4.5.
Urinalysis[h]	X	X	X			X[f]		X						X	X	See Section 9.4.5.
[redacted]																

Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010)

Procedure	Randomization D1[a]	D 2	D 3	D 4	D 5	D 6	D 7[b]	D 8 Visit[c]	D 9[b]	D 10	D 11[b]	D 12	D 13[d]	D14 End of Study Visit c,d,e	D30 (± 2 days) Follow-Up Visit[c]	Notes
[redacted]																
Adverse Event Reporting																
Monitor for Non-Serious Adverse Events & Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic (PK) Assessments																
Blood PK Sampling	See Table 9.5-1 for sampling schedule															See Section 9.5.
[redacted]																

Table 2-2: On-Treatment and Follow-up Procedural Outline (CV019010)

Procedure	Randomization D1[a]	D 2	D 3	D 4	D 5	D 6	D 7[b]	D 8 Visit[c]	D 9[b]	D 10	D 11[b]	D 12	D 13[d]	D14 End of Study Visit c,d,e	D30 (± 2 days) Follow-Up Visit[c]	Notes
[redacted]																
Clinical Drug Supplies																
Randomize	X															
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X		IP is administered subcutaneously once daily.

Abbreviations: [redacted] BP = blood pressure; COVID-19 = coronavirus disease 2019; D = Day; [redacted] ECG = electrocardiogram; HF = heart failure; ICF = informed consent form; IMP = investigational medicinal product;

IP = investigational product; IV = intravenous; [redacted] NYHA = New York Heart Association; PE = physical examination; PK = pharmacokinetic[redacted].

[a] If screening and randomization are on the same day all evaluations can be performed only once.

[b] Study coordinator calls participants post-discharge to ensure investigational medicinal product (IMP) storage compliance.

[c] Participants will return to site for up to three ambulatory visits. (Day 8, Day 14, Day 30). If the participant cannot return to the site because of COVID-19 local regulations that prevent visits in-person, these visits can be done at home by the home nurse in discussion with the Principal Investigator (or designee).

[d] If needed, the study can be ended 1 day early, with the End of Study Visit taking place on Day 13 instead of Day 14.

[e] Evaluations performed prior to study discharge, or for participants who prematurely discontinue treatment.

[f] Only performed at day of discharge (Day 6 or beyond). If study participant is not discharged on Day 6, delay assessments and sample collections until day of discharge.

[g] If the physical examination was not completed by the site because of COVID-19 local regulations, a physical assessment will be done by the home nurse.

[h] These samples should be collected predose.

In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low:

- Vital signs
- Pharmacokinetic (PK) Sampling
- Safety (clinical labs)
- Safety (electrocardiogram [ECG])

[redacted]

3 INTRODUCTION

Heart failure (HF) is a clinical syndrome that results from insufficient supply of blood to maintain normal tissue function due to any structural or functional impairment of ventricular filling or ejection of blood from the heart. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance and promote fluid retention, leading to pulmonary and/or splanchnic congestion and/or peripheral edema.[1] The global burden of HF is substantial with an estimated global prevalence of 26 million. In the United States alone, an estimated 6.5 million people suffer from HF, a number that is projected to increase ~ 46% by the year 2030.[2,3] Current treatment guidelines categorize HF patients based on ejection fraction (EF): 1) heart failure with reduced ejection fraction (HFrEF) with an EF ≤ 40%, 2) heart failure with a mid-range (intermediate) ejection fraction (HFmrEF) of 41% to 49%, and 3) heart failure with preserved ejection fraction (HFpEF) with an EF ≥ 50%.[1] The pathophysiology of HF is highly complex and diverse in etiology, especially with regard to the biological pathways that lead to either HFrEF or HFpEF.[4,5,6] Although therapeutics which target the neurohormonal axis (eg, beta-blockers, angiotensin converting enzyme inhibitors and other renin angiotensin-aldosterone system (RAAS) inhibitors, as well as mineralocorticoid receptor antagonists [MRAs]) have led to a decrease in mortality rates in HFrEF patients, unmet medical need remains very high.[7] No therapy has yet been proven in a placebo-controlled clinical trial to reduce mortality rates in HFpEF patients.[7]

HF is commonly accompanied by multiple comorbidities including hypertension, diabetes mellitus, and chronic kidney disease (CKD).[5] The majority of HF patients have CKD, defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2.[8] A large meta-analyses of 80,098 hospitalized and non-hospitalized HF patients revealed that the presence of CKD is highly prognostic of worsening HF.[9] Furthermore, worsening renal function (WRF) during the 1-year period following hospital discharge for acute decompensated HF (ADHF) was a strong predictor of all-cause mortality.[10] These types of associative data combined with biological plausibility, in that renal impairment can lead to a feedback response of neurohormonal and RAAS activation, have led some investigators to suggest that CKD may play a causal role in HF.[9] However, whether or not CKD is truly on the causal pathway to worsening HF is unknown.

Human relaxin (H2-relaxin) is a peptide hormone believed to be, at least in part, responsible for the many physiological adaptations that occur during human pregnancy.[11] These changes include

an ~ 30% increase in global arterial compliance which is important to maintain efficient ventricular-arterial coupling, an ~ 30% decrease in total systemic vascular resistance (SVR), and up to an 80% and 50% increase in renal blood flow (RBF) and glomerular filtration rate (GFR), respectively.[12],[13],[14] As discussed in detail below, clinical studies in which serelaxin was administered intravenously (IV) to either normal healthy volunteers (NHV) or HF patients provided pharmacological evidence that H2-relaxin is involved, at least in part, in mediating these adaptive maternal changes. Because H2-relaxin activates both relaxin/insulin-like family peptide receptor 1 (RXFP1) and relaxin/insulin-like family peptide receptor 2 (RXFP2) it has been difficult to precisely define the individual roles of each receptor during mammalian pregnancy. However, several lines of evidence, including the noted receptor potency differential in relationship to low endogenous blood levels of H2-relaxin during human pregnancy, tissue expression patterns, and arterial compliance experiments in vessels that express RXFP1, but not RXFP2, all suggest that RXFP1 plays the larger role of the 2 receptors.[15,16] There are no reports in the literature describing loss-of-function mutations in humans for either the H2-relaxin or the RXFP1 gene. In contrast, missense mutations in either the human insulin-like peptide 3 (INSL3) or the RXFP2 gene are associated with cryptorchidism, indicating that activation of RXFP2 plays a critical role in testicular descent, which normally occurs at gestational week 24 through 34 in humans.[17] The physiological effect, if any, of RXFP2 activation in the adult human is unknown.

A short-acting recombinant form of H2-relaxin, serelaxin- (Novartis), administered IV, was demonstrated to have vasodilatory properties and to enhance both RBF and eGFR in patients with HF.[18,19,20] Serelaxin also demonstrated anti-fibrotic activity in cell-based and in preclinical models of fibrosis.[21,22] In a large Phase 3 clinical trial (RELAX-AHF-2), serelaxin, when administered as a short-term 48-hour continuous IV infusion, failed to improve long-term clinical outcomes compared with placebo in patients with ADHF.[23] Although this failure represents a setback for the advancement of novel therapeutics to treat HF, learnings from the multitude of serelaxin clinical trials, indicate that chronic administration of a therapeutic with H2-relaxin-like activity (ie, beyond 48 hours) could potentially benefit HF patients. More specifically, serelaxin was demonstrated to increase both RBF and eGFR in NHV and HF patients.[18,19,20,24,25] In a non-placebo-controlled trial, when serelaxin- was administered IV to NHV over a 5-hour period at a dose resulting in blood concentrations that closely mimicked the peak human pregnancy blood concentration of H2-relaxin (1.0 ng/mL), a 47% increase, relative to baseline, in RBF was observed, although GFR remained unchanged.[24] Changes in RBF were similar between males and females. In a separate double-blind, placebo-controlled, dose-ranging study in NHV of Japanese descent, serelaxin was given as a continuous 48-hour IV infusion at doses of 10, 30, or 100 µg/kg/day.[25] Mean blood concentrations of serelaxin at the 48-hour time point were 3.49 ng/mL, 9.82 ng/mL, and 29.2 ng/mL, respectively. Statistically significant increases in eGFR were observed for all doses of serelaxin, but not for placebo. Changes in RBF were not evaluated in this study. In a double-blind and placebo-controlled study in chronic HF patients, when compared to placebo, statistically significant increases in renal plasma flow were observed for serelaxin when given as a continuous 24-hour IV infusion at a dose of 30 µg/kg/day.[18] Changes in GFR were minimal and

not significantly different from placebo. In a separate double-blind and placebo -controlled study in which serelaxin was given to chronic HF patients as a continuous 48-hour IV infusion at the dose of 30 μg/kg/day, when compared to placebo, statistically significant increases in eGFR (difference of 4.7, 5.9 and 5.7 ml/min/1.73m^2 vs placebo, at 2, 4 and 8 weeks; $p<0.001$) were observed for serelaxin.[19] Plasma concentrations of aldosterone were decreased in the serelaxin treatment group, but not in the placebo treatment group indicating that enhancement of renal function in chronic HF patients may lead to attenuation of RAAS activation.

Hemodynamic effects of serelaxin were also studied in a double-blind, placebo-controlled trial in patients hospitalized for ADHF. When serelaxin was given as a 20-hour IV infusion at a dose of 30 μg/kg/day, hemodynamic effects were detected early (within 30 minutes), and were characterized by statistically significant reductions (versus placebo) in pulmonary capillary wedge pressure (PCWP) and pulmonary arterial pressure (PAP), with a concomitant decrease in SVR.[20] Serelaxin administration also improved renal function and decreased circulating levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker of cardiac stress.

Several investigators, through the use of subcutaneous (SC) osmotic mini-pumps which continuously deliver drug at a defined rate, demonstrated that treatment with H2-relaxin decreased fibrosis in various rodent models of cardiac, kidney, lung and liver fibrosis.[21] In a cell-based model of TGF-β-treated rat cardiac fibroblasts, serelaxin significantly decreased expression of the pro-fibrotic genes smooth muscle alpha-actin and collagen type I.[22] Changes in levels of protein phosphorylation indicated that the reduction in pro-fibrotic gene expression was the result of serelaxin-dependent suppression of activin-like kinase 5 (ALK5)/Mothers against decapentaplegic homolog 2 (SMAD2) signaling, a well-studied signaling pathway induced by TGF-β.

The ability of H2-relaxin/serelaxin to positively impact both systemic and renal hemodynamics, improve renal function, and possibly decrease cardiac fibrosis, makes H2-relaxin an attractive candidate as a chronic therapy for HF patients. However, the short-acting PK profile of H2-relaxin essentially precludes its use as a chronic therapeutic. In contrast, with a PK profile (non-clinical studies and preliminary clinical data) that supports once daily (QD) dosing and H2-relaxin-like activity, BMS-986259 represents an opportunity to provide HF patients with the therapeutic benefits anticipated for H2-relaxin when dosed chronically.

3.1 Study Rationale

The main purpose of this trial is to evaluate the effect of BMS-986259 on blood pressure (BP) events defined as symptomatic hypotension or hypotension requiring study drug discontinuation, in hospitalized HF patients stabilized after an admission for ADHF. The study is designed to provide data on the range of BP in which BMS-986259 is safe and well tolerated in the context of the current hospitalization for ADHF. It also aims to provide additional rationale for future development, future clinical use and to inform the design of the next Phase 2-3 studies. In addition, this study will provide initial data on the pharmacokinetics of BMS-986259 in HF participants.

Standard of care in the treatment of ADHF involves the use of IV loop diuretics and vasodilators, which may predispose participants to hypotension, with or without symptoms. Current guidance

also recommends continuing Guidelines Directed Medical Therapy (GDMT) including angiotensin-converting enzymes (ACE), beta-blockers, MRAs/mineralocorticoid receptor inhibitors (MRI), and angiotensin receptor-neprilysin inhibitors (ARNI), which may also lower BP. In the Serelaxin ADHF study, RELAX-AHF, greater reductions from baseline in SBP were observed during IV infusion up to 48 hours in the serelaxin group (-16.5 mmHg ± 17.2) compared with placebo (-12.3 mmHg ± 17.2). Also, more participants on serelaxin than on placebo had protocol required blood pressure-related dose reduction (29% vs 18%) or drug discontinuation (19% vs 12%).[26] In contrast, in the chronic stable HF population of the RELAX REPEAT study, SBP in the serelaxin group did not differ from placebo.[19] There are no data on the effect of relaxin on BP in the population of HF patients admitted for ADHF, but not yet discharged, already medically stabilized and weaned from IV vasodilators or inotropes.

3.2 Background

Over the last several decades, the improvements in HF treatments led to better survival and reduced hospitalization rate in patients with HFrEF. Current HF guidelines however recognize that this outcome is still not satisfactory. In the recent European data, 12-month all-cause mortality rate for hospitalized and stable ambulatory HF patients were 17% and 7%, respectively and hospitalization rates were 44% and 32%, respectively.[27] In addition, optimization of the evidence-based treatments is often limited by co-morbidities and undesired effects of treatment such as renal impairment, hyperkalemia, and low blood pressure, typical for RAAS blocking agents remaining the foundational therapy for HFrEF. In addition, no beneficial effects on outcomes were demonstrated with similar strategies in patients with HFpEF. Hence, new approaches are required to improve outcomes both in HFpEF as well as in patients with HFrEF, when optimization of therapy is particularly difficult.[28]

Several studies with recombinant human relaxin have demonstrated short-term multi-organ protection in HF patients measured as beneficial effects on biomarkers of cardiac and renal injury and improved function. The half-life of serelaxin is short after acute 48 hours infusion and long-term improvement in CV outcomes has not been seen. Short-term IV injection cannot be expected to exhibit lasting effects; therefore, to fully understand the potential long-term benefits of relaxin, one needs to develop a formulation that allows for chronic administration.

BMS-986259, is a recombinant form of H2-relaxin that contains a covalently attached fatty acid which binds to circulating albumin, extending its half-life. BMS-986259 closely mimicked the activity profile of H2-relaxin in a panel of in vitro cell-based assays, as well as in a rodent pharmacodynamic in vivo model.[29] These activity data, together with the preclinical PK and toxicology data, indicate that BMS-986259 can be safely administered subcutaneously. Preliminary data from ongoing first in human (FIH) study also support safe subcutaneous use up to 14 days. Chronic QD subcutaneous (SC) administration of BMS-986259 has the potential to benefit patients with HF. An ongoing Phase 1 study with BMS-986259 will confirm its effects on the renal function and support its potential to protect/improve renal function in HF.

The population of ADHF patients, early after admission, has the highest rate of 60 to 90 days mortality and rehospitalizations, with rates as high as 14% and 30%, respectively.[30] In the United States alone, there are more than 1 million admissions for HF as primary diagnosis per year.[31,32] This represents a high unmet need for both patients with HFrEF and HFpEF. In the ADHF population, little to no data are available about the benefits of starting chronic treatment in the hospital setting, before discharge.

3.3 Benefit/Risk Assessment

The current study is a Phase 2A, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of BMS-986259 in medically stabilized participants currently hospitalized for ADHF. Participants will continue their therapy as deemed necessary for their condition and receive any HF therapy required by HF guidelines. Participants may benefit from an ongoing assessment of their health status in the period of time immediately after discharge from the hospital. It is not known if 2 weeks of therapy with BMS-986259 can provide any symptomatic improvement and 50% of participants will receive placebo. Short -term course of BMS-986259 is not expected to translate into long-term benefit.

In the ongoing Phase 1 study in NHV (CV019-002), BMS-986259's administration was generally safe and well-tolerated. The most frequently reported adverse events (AEs) were cannula site reaction and cannula site pain related to the study procedures to measure RBF and GFR, but unrelated to the study drug. The effect on BP and heart rate (HR) in individual participants appears to be minimal. Formal statistical summaries are not available at this time as the treatment is still blinded, but no clinically significant or symptomatic hypotension has been reported. The doses evaluated thus far have been safe and well-tolerated, with no deaths, serious adverse events (SAEs), or AEs leading to discontinuation reported. In the large serelaxin development program, human recombinant relaxin was generally safe and well tolerated in participants with HF. Bristol-Myers Squibb (BMS) nonclinical and preliminary clinical data and the serelaxin clinical program suggest that the principal risk associated with the use of BMS-986259 is hypotension. Transient reductions in BP are not expected to be associated with long-term sequelae. This study is designed specifically to address this risk, and mitigation strategies are implemented, such as rigorous BP monitoring, both in-hospital and post-discharge, and a dose-modification algorithm in case of symptomatic or asymptomatic hypotension.

3.3.1 COVID-19-related Risks and Risk Mitigation Measures Where Applicable

The following risks and risk mitigating measures apply to any part of the study conducted during the coronavirus disease 2019 (COVID-19) pandemic. The study includes several features to mitigate this risk:

- The study sites have implemented standard operating procedures for risk mitigation as described in Section 3.3.1.2.
- The protocol implements severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing as shown in Table 2-1 in order to prevent randomization of participants with active COVID-19 infection and to ensure participant safety and study integrity.

3.3.1.1 Investigational Product-related Risk

At this time, BMS is tracking and accumulating data on COVID-19 and its potential effects on participants taking BMS-986259 and other investigational products (IPs). The data are analyzed on a regular basis. Based on its properties and mechanism of action, BMS-986259 is not believed to be implicated in COVID-19 infection and symptomology. The risk of COVID-19 in participants taking BMS-986259 is still unknown due to insufficient clinical data.

3.3.1.2 General COVID-19-related Risk Mitigation Measures

General risk mitigation for COVID-19 will be implemented in accordance with the sites' local prevention control procedures and relevant governmental and Institutional Review Board (IRB)-associated requirements. Such measures aim to minimize prevalence and transmission of SARS-CoV-2 among site staff and participants and include distancing, sanitization, use of personal protective equipment, and testing.

Participants found to test positive for SARS-CoV-2 after enrollment in the study will be treated according to site standard practice and in accordance with local and national regulations. In such cases, treatment with BMS-986259 will be discontinued as described in Section 8.

The risk mitigation measures are part of the protocol-specific informed consent form (ICF), and when and where applicable, will be amended based on emerging guidance.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To establish safety & tolerability of BMS-986259 when initiated in-hospital in participants stabilized after an admission for ADHF	• Incidence of clinically relevant hypotension, defined as: – Supine SBP < 85 mmHg (confirmed by repeat measurement within 30 minutes), regardless of symptoms of hypotension OR – Supine SBP < 90 mmHg (confirmed by repeat measurement within 30 minutes) AND symptoms of hypotension
Secondary • To evaluate serum PK parameters in participants with HF	• PK parameters of BMS-986259: – Cmax, Tmax, and AUC(TAU) on Day 1 and Day 5 – Ctrough

Abbreviations: [redacted] ADHF = acute decompensated heart failure; AUC(TAU) = area under the concentration-time curve in one dosing interval; BMS = Bristol-Myers Squibb; BP = blood pressure; Cmax = maximum observed concentration; Ctrough = trough concentration; [redacted] HF = heart failure; IV = intravenous; [redacted] PK = pharmacokinetic; [redacted] Tmax = time of maximum observed concentration.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2A randomized, double-blind, placebo-controlled study of BMS-986259 in hemodynamically stabilized patients currently hospitalized for ADHF. The study is designed to establish if BMS-986259 is safe and well tolerated in this population with regards to clinically significant hypotension.

- ADHF must be the main reason for hospitalization, and other conditions with similar signs and symptoms must be excluded at screening.
- at least 24 hours after presentation to Emergency Room (ER) and no later than 8 days after presentation to ER. Time of the presentation is defined as the time of the first dose of IV diuretic in the hospital. Randomization must occur within a maximum of 8 days since presentation to ER and before hospital discharge.

- at least 12 hours since last dose change of IV loop diuretics and at least 24 hours since last dose of positive inotropes and ≥12 hours since the last dose of IV vasodilators.
- Prior to randomization, participants will also be tested for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test. Only participants with a negative test result are eligible for randomization.

Participants will be randomized 1:1 to receive BMS-986259 3 mg or placebo. Treatment will be administered subcutaneously once daily for 14 days and follow-up will last until Day 30 (± 2 days).

[redacted]

A minimum hospital stay of 5 days from randomization/first dose of IP is required. If participants are discharged home before the end of active study treatment, study visits will be performed daily either as an outpatient clinic visit or by a home nurse or healthcare provider (per local regulations/requirements) who will be responsible to measure pre-dose BP, draw PK sample(s), administer the IP subcutaneously [redacted].

Participants will return for up to three ambulatory visits at the site on Day 8, Day 14, Day 30 (follow-up). If the participant cannot return to the site because of COVID-19 local regulations that prevent visits in-person, these visits can be done at home by the home nurse in discussion with the Principal Investigator (or designee). In addition, at discharge, participants will receive BP measuring device and will be instructed to measure BP if symptoms consistent with hypotension occur. If systolic BP falls below 85 mmHg (on 2 repeated measurements within 30 minutes) and symptoms of hypotension persist, participants will be instructed to report to the study site or another healthcare provider if the study site cannot be reached.

Initially participants with SBP ≥ 115 mmHg will qualify to be randomized 1:1 to receive 3 mg subcutaneous BMS-986259 QD or placebo. After approximately 8 participants with SBP ≥ 115 and < 130 mmHg have completed the treatment period, the Safety Review Committee will review the safety data from this sentinel group and ensure it is safe to proceed with the Main Group, ie., open the recruitment for participants with SBP less than 115 mmHg (but at least 100 mmHg).

The Main Group will include participants with SBP ≥ 100 mmHg, randomized 1:1 to BMS-986259 or placebo. The proportion of participants with SBP > 125 mmHg will be capped at 48 participants.

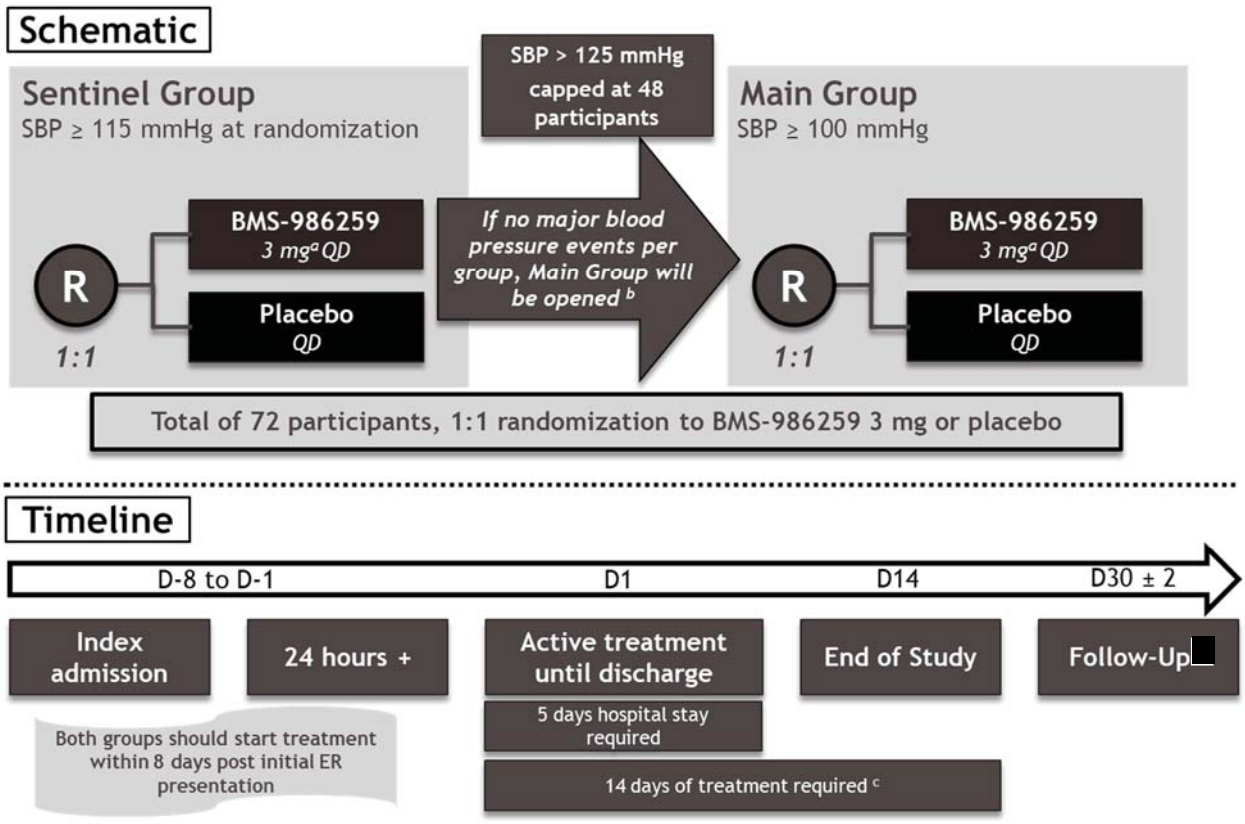
Study drug may be down-titrated to 1 mg or discontinued according to the criteria described in dose modification in Section 7.4.

In addition, if systolic BP is < 85 mmHg or symptomatic hypotension occurs, the Principal Investigator (or designee; must be a medical doctor [MD]) must be contacted to make a decision

as to whether an ambulatory unscheduled study visit or hospitalization is required based on overall clinical assessment. For example, asymptomatic study participants who can walk and have normal urination may not require hospitalization. BMS Study Director/Medical Monitor (or designee) must be notified. A blinded clinical contact will be available 24/7 to answer questions and guide the home nurse as needed.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Abbreviations: [redacted] D = day; ER = emergency room; [redacted] QD = once daily; R = randomization; SBP = systolic blood pressure.

[a] May be down-titrated to 1 mg or discontinued according to the criteria described in Section 7.4.

[b] Safety review of the sentinel group requires at least 8 participants with systolic blood pressure ≥ 115 mmHg and < 130 mmHg.

[c] If participant is discharged before the end of active study treatment, study visits will be performed daily either as an outpatient clinic visit or by a home nurse or healthcare provider.

[redacted]

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval and during follow-up. Participants will be closely monitored for AEs throughout the study.

5.1.1 Safety Review Committee

An internal Safety Review Committee will assess BP data after completion of the Sentinel Group. The Committee may request access to unblinded treatment codes for individual participants. The Committee will consist of senior clinical development individuals not directly involved in the study conduct and overseeing, including (but not limited to) senior Worldwide Patient Safety representative, a statistician, and a senior clinician.

5.2 Number of Participants

It is estimated that a total of approximately 72 participants will be randomized with 1:1 ratio assigned to either BMS-986259 subcutaneous QD or Placebo to have at least 60 completers by the end of the study.

5.3 End of Study Definition

The study treatment's duration is 14 days with an on-site follow-up visit on Day 30 (± 2 days). [redacted] The start of the trial is defined as the first visit of the first participant screened. End of trial is defined as last treatment visit and last follow-up visit of the last participant to complete the study. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

Relaxin exhibits vasodilatory effect and BMS-986259 is expected to demonstrate similar properties including potential for lowering blood pressure. Serelaxin's development program provided extensive data in patients treated for ADHF. Small difference from placebo was observed in the absolute SBP lowering, however a substantially larger proportion of patients demonstrated clinical AEs related to BP reduction. In the RELAX-AHF study, confirmed events of decreased blood pressure were reported in 18% and 29% in the placebo vs the active group, respectively.[26] In contrast, in the RELAX-REPEAT study conducted in chronic stable HF patients, there was no observed difference in blood pressure between serelaxin and placebo.[19] No data are available on the risk of clinically significant hypotension with relaxin administered to medically stabilized patients admitted for ADHF, especially in the group with SBP < 125 mmHg which was an exclusion criterion in the serelaxin program. Hypotension is one of the factors prohibiting treatment optimization with standard of care HF medications; thus, a new treatment that would be safe and well tolerated in patients with lower range of BP would be clinically valuable. This study will allow to establish safety and tolerability of BMS-986259 with regards to the risk of hypotension in such population. The population of HF patients early after admission for ADHF has the highest rates of mortality and rehospitalization, with the rates as high as 14% and 30% within 60 to 90 days, respectively.[30] This represents a high unmet need for both patients with HFrEF and HFpEF.

The duration of the study is limited by the availability of the current toxicology data (up to 2 weeks). The primary goal of the study is safety and tolerability. Fourteen days should be sufficient to establish potential for hypotension to inform further development BP margins and help to inform the design of Phase 2 / Phase 3 studies. Based on the data from the ongoing Phase 1 trial, steady state is achieved after approximately 5 days. Study duration will allow to observe participants after they achieved steady state and a minimum hospital stay of 5 days after randomization will ensure more intense monitoring while the exposures of the study drug are still increasing.

The secondary [redacted] efficacy endpoints include PK[redacted] which will provide an initial supportive data for the mechanism of action in heart failure population.

[redacted]

Finally, serum PK will be measured to validate data collected from Phase 1 in normal healthy volunteers and further inform dosing in Phase 2.

5.5 Justification for Dose

The planned dose for this study (3 mg) has been selected as a pharmacologically active and safe dose, likely to be further studied in Phase 2B, thus safety/tolerability data collected in this study will inform design of the Phase 2B study. The BMS-986259 dose selected for this study (3 mg) was associated with improvement in RBF after single and multiple doses in normal healthy participants (up to 46% increase in RBF).The 3 mg multiple doses in FIH study were also safe and well tolerated by the healthy participants.

In the FIH study (CV019002), single doses as much as 5-fold higher (15 mg) have been safely administered to healthy participants. The observed mean exposures at steady state with repeated 3 mg QD dosing (AUC[TAU]) of 9,070 ng h/mL remain under the mean exposure (AUC[INF]) of 38,200 ng h/mL observed after a single 15 mg dose that was determined to be safe and well tolerated in a healthy participants study (Table 5.5-1).

Based on preliminary results, single dose exposures (Cmax and area under the concentration-time curve [AUC]) increased in a dose-proportional manner with increasing dose. With multiple doses of 1 mg and 3 mg QD for 14 days, up to 2.5-fold (1 mg) and 2.7-fold (3 mg) accumulation of Cmax and AUC(TAU) were observed on Day 14 versus Day 1, with steady-state reached within approximately 5 days based on trough concentrations. The geometric mean Cmax and AUC values observed with a single 15 mg dose and a 3 mg QD dose are listed in Table 5.5-1.

Table 5.5-1: BMS-986259 Exposures in Healthy Participants

Dose	Cmax (ng/mL) Geometric Mean	AUC (ng·h/mL) Geometric Mean
15 mg single dose	737	38,200*
3 mg QD, Day 1	184	3,420
3 mg QD, Day 14	469	9,070

* AUC(INF)

Abbreviations: AUC = area under the curve; Cmax = maximum observed concentration; QD = once daily.

A short-acting recombinant form of human H2-relaxin, serelaxin, dosed IV, demonstrated vasodilatory properties and enhanced both RBF and eGFR in patients with HF.[18,19,20] In previous studies, serelaxin was safely administered IV for up to 48 hours in healthy participants and over 4,000 patients with HF and produced increases in RBF and GFR, as well as improvements in multiple hemodynamic parameters and biomarkers of cardiac and renal function. [18,19,20,23,24,25,26] Based on the potency ratio between serelaxin and BMS-986259, it is anticipated that the 3 mg dose of BMS-986259 is consistent with the doses found to be efficacious, safe and well tolerated in heart failure patients in the serelaxin development program.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must be willing to participate in the study and provide a written ICF.

b) Participants must be willing and able to communicate and complete all study-specific procedures and visits.

2) Type of Participant and Target Disease Characteristics

a) Patients currently hospitalized for ADHF, regardless of Left Ventricular Ejection Fraction (LVEF) ≥ 24 hours since presentation to ER defined as the time of the first dose of IV diuretic administered at the hospital, maximum of 8 days since presentation to ER and before hospital discharge.

i) ADHF is the main reason for admission and there is no other potential cause for congestive symptoms leading to index hospitalization (eg, concurrent pneumonia, acute chronic obstructive pulmonary disease [COPD] exacerbation).

ii) Dyspnea at rest or with minimal exertion upon presentation to ER, plus signs and symptoms of fluid overload that require IV therapy with loop diuretics.

iii) NT-proBNP ≥ 1400 pg/mL OR BNP ≥ 350 pg/mL upon presentation to the hospital; NT-proBNP ≥ 2000 pg/mL OR BNP ≥ 500 pg/mL if Atrial Fibrillation (AFib) present at presentation. For participants on Entresto, NT-proBNP should be used.

b) Patients must be hemodynamically stable, as assessed by the investigator, and as defined by the following criteria:

i) ≥ 12 hours since the last dose change of IV loop diuretics (ie, participants may still be on IV loop diuretics at randomization, as long as dose is stable ≥ 12 hours).

ii) ≥ 24 hours since last dose of positive inotropes.

iii) ≥ 12 hours since the last dose of IV vasodilators.

iv) Absence of symptoms of hypotension (eg, dizziness, lightheadedness, etc).

v) Supine SBP (supine position is preferable, based on participant's condition and comfort) must remain within the following range, on at least 2 routine consecutive measurements, over the 12 hours before randomization:

(1) Sentinel Group: SBP ≥ 115 mmHg.

(2) Main Group: SBP ≥100 mmHg.

3) Age and Reproductive Status

Investigators shall counsel male participants who are sexually active with women of childbearing potential (WOCBP), on the importance of pregnancy prevention, the implications of an unexpected pregnancy and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants
   i) Females, ages at least 18 or local age of majority (See Appendix 7 for maximum age limit where locally mandated).
   ii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and is not a WOCBP.
   iii) Women participants must have documented proof that they are not of childbearing potential.
   iv) Women must not be breastfeeding.

b) Male Participants
   i) Males, ages at least 18 or local age of majority (See Appendix 7 for maximum age limit where locally mandated).
   ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.
      (1) For males who are sexually active with WOCBP, less than highly effective methods of contraception and unacceptable methods of contraception are not permitted.
      (2) Hormonal contraception is also not permitted.
   iii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant or breastfeeding.
   iv) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 6 days after the last dose of study intervention.
   v) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 6 days after the last dose of study intervention in the male participant.
      (1) For female partners of males participating in the study, less than highly effective methods of contraception and unacceptable methods of contraception are not permitted.
      (2) Hormonal contraception is also not permitted.

vi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the intervention period and for at least 6 days after the last dose of study intervention.

vii) Male participants must refrain from donating sperm during the intervention period and for at least 6 days after the last dose of study intervention.

viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

6.2 Exclusion Criteria

1) Target disease exceptions

a) At randomization systolic blood pressure < 100 mmHg or > 145 mmHg.

b) At randomization HR > 120 bpm.

c) Acute cardiovascular condition other than HF decompensation either contributing to hospitalization or making participant unstable, such as acute MI/acute coronary syndrome, myocarditis, or arrhythmia with the exception of atrial fibrillation if HR within criteria limit.

d) Cardiogenic shock (defined as SBP below 90 mmHg, signs of end-organ hypoperfusion plus need for intubation, mechanical circulatory support and other life-sustaining emergency measures) at presentation to ER or at any time before randomization.

e) History of heart or any other solid organ transplant or currently on the transplant list.

f) Recipient of ventricular assist devices.

g) Use of any cardiac extracorporeal devices, within 12 weeks of study randomization. Cardiac Resynchronization Therapy Defibrillator (CRTD) and pacemakers/Implantable Cardioverter-Defibrillator (ICDs) are allowed, if implanted at least 4 weeks before randomization and no discharge within 4 weeks prior to randomization.

h) Participants with contraindications to vasodilator therapy such as restrictive or obstructive cardiomyopathy, severe mitral or aortic stenosis.

2) Medical History and Concurrent Diseases

a) Women cannot be pregnant or breastfeeding.

b) Any major surgery within 12 weeks of study randomization.

c) Suspected acute pulmonary disease such as pneumonia, exacerbation of asthma or COPD or severe chronic, pulmonary disease (eg, severe COPD , pulmonary fibrosis, patients with hypercapnia or requiring home oxygen or chronic systemic steroids)

d) Hereditary or idiopathic pulmonary hypertension.

e) History of stroke, or transient ischemic attack (TIA) within the 30 days prior to screening (according to the participants' records) or during screening.

f) Acute coronary event within 30 days prior to screening or during screening (myocardial infarction, acute coronary syndrome, or unstable angina; according to the participants' records).

g) Terminal non-cardiovascular disease such as cancer with life expectancy < 6 months.

h) Severe liver disease such as cirrhosis with evidence of portal hypertension, or acute viral hepatitis.

i) Participant is on dialysis or history of chronic or intermittent dialysis or ultrafiltration.

j) Need for mechanical ventilation any time before screening or non-invasive ventilation (CPAP, BiPAP) < 2 hrs prior to screening.

3) Prior/Concomitant Therapy:

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 Concomitant Therapy. The following are prohibited before and during the study:

   a. Phosphodiesterase type 5 (PDE5) inhibitors used for erectile dysfunction: sildenafil, tadalafil, vardenafil, etc (within 48 hours of initial study drug administration and throughout the study, up to 5 days after the last dose of study drug).

   b. Continuous infusion of IV diuretics, inotropes and vasodilators during the study.

b) Guidelines Directed Medical Therapy (GDMT) for HF is allowed, either at screening or during the study, as clinically warranted.

c) Exposure to any investigational drug or placebo, including serelaxin; within 30 days of initial study drug administration or 4 months prior to the first dose of IP, in case of exposure to long-acting biological investigational drug.

4) Laboratory Test Findings

a) Participant has key laboratory testing findings within the following ranges:

   i) Persistent electrolytes abnormalities not corrected before randomization

      (1) A sodium concentration < 130 or > 145 mEq/l.

      (2) A potassium concentration < 3.1 or > 5.5 mEq/l.

   ii) Hemoglobin < 9 g/dL, which is defined as severe anemia.

   iii) eGFR < 30 ml/min./1.73 m^2.

   iv) ***Not applicable per Revised Protocol 01***

   v) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV)-1 and -2 antibodies.

   vi) Liver abnormalities including total bilirubin > 1.5 × upper limit of normal (ULN) or significant elevation of liver enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 × ULN).

   vii) Positive RT-PCR test or rapid antigen test for SARS-CoV-2 prior to randomization.

5) Allergies and Adverse Drug Reaction

a) History of any significant drug allergy or drug-related SAE (such as anaphylaxis or hepatotoxicity).

b) History of ADAs to relaxin (eg, while in a serelaxin development program).

c) History of adverse reactions to aminoglycosides.

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been

imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

b) Employees of CRO or BMS and their first-line relatives.

c) Legal incapacity or limited legal capacity.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria. No waivers will be provided.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently **randomized** in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

In an effort to find all possible well-qualified participants, participants who have discontinued the study as a screen failure (have not been randomized) are eligible for re-screening upon presentation for a subsequent episode of ADHF, at the discretion of the investigator. If re-screened, the participant must be re-consented and a new participant number will be assigned by the IRT. Laboratory parameters and/or assessments that are included in Table 2-1 (Screening Procedural Outline) and Table 2-2 (On-treatment and Follow-up Procedural Outline), must be repeated. The participant numbers and data will be linked in the clinical database.

All screening laboratory testing will be performed locally, and tests may be repeated at the discretion of the Investigator as per site policy.

Any new result will override the previous result. The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both IP and Non-investigational Product (Non-IP) as shown in Table 7-1.

An IP, also known as investigational medicinal product (IMP) in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IPs.

Table 7-1: Study treatments for CV019010

Product Description / Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986259 injection for SC administration	5 mg/vial (5 mg/mL) Dose level 3 mg and 1 mg BMS-986259 will be diluted to administer a 3 mg or 1 mg dose as a 1 mL SC injection. Details of preparation and administration are provided in the pharmacy manual	IP	Blinded	Colorless to pale yellow liquid in vial	Refer to the label on the container and/or the pharmacy manual
Placebo injection for SC administration	N/A	IP	Blinded	Colorless to pale yellow liquid in vial	Refer to the label on the container and/or the pharmacy manual
Placebo injection to be utilized as diluent	N/A	IP	Open Label	Colorless to pale yellow liquid in vial	Refer to the label on the container and/or the pharmacy manual

Abbreviations: IP = Investigational Product; N/A = not applicable; Non-IP = Non-investigational Product; SC = subcutaneous.

BMS-986259 is not intended for participant's self-administration.

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986259	3 mg[a], 1 mg[a,b]	Daily	Subcutaneous injection
Placebo	N/A	Daily	Subcutaneous injection

[a] 5 mg/mL solution will be diluted as described in the pharmacy manual to reach the desired dosage strength

[b] 1 mg for down titration only

In the morning on Days 1 through 14 each participant will receive a subcutaneous dose of BMS-986259 or placebo, at approximately the same time.

The time of dose administration of the first dose will be called "0" hour for serum PK reporting.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

Study treatment will be dispensed at the Day 1 visit.

At the time of screening for both the Sentinel Group and Main Group, participants will be randomized to receive either BMS-986259 or placebo in a 1:1 ratio according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). Sequential numbering may restart at 00001 for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number, (eg, 0002 00001). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

During the screening visit, the investigative site will call into the enrollment option of the Interactive Response Technology (IRT) designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to randomize the participant.

7.3 Blinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the BMS Study Director / Medical Monitor (or designee), but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is via the Interactive Response Technology (IRT) system. For information on how to unblind in an emergency, consult the IRT manual.

In cases of accidental unblinding, contact the BMS Study Director / Medical Monitor (or designee) and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the BMS Study Director / Medical Monitor (or designee).

Except as noted below, members of BMS Research and Development personnel involved in the study conduct and evaluation, as well as all vendors responsible for the conduct of the trial (protocol team) will remain blinded.

A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples as PK will not be analyzed placebo samples.

An internal Safety Review Committee, independent from the study team, will assess BP data after completion of approximately 8 participants randomized with SBP ≥ 115 mmHg and < 130 mmHg in the Sentinel Group. The internal Safety Review Committee will also assess safety results, including hypotension, from the planned interim analysis (IA; Section 10.3.5).

For the assessment of BP data in the Sentinel Group and for the planned IA, an unblinded statistician and programmer(s), separate from the study team, will be performing the required safety analyses for the internal Safety Review Committee. The internal Safety Review Committee may require access to unblinded treatment codes for individual participants. Additional designated

staff of BMS Company will be provided with aggregate data from the IA for future study planning as described in the statistical analysis plan.

7.4 Dosage Modification

Any decision to decrease the dose level of study drug or discontinue study drug should be based on the investigator's assessment of the participants' clinical stability and in the overall context of the participant's condition. A dose reduction to 1 mg is allowed if certain criteria are met, as described in the section below. Study drug may be also permanently discontinued early as described in the following section.

7.4.1 Dose Down-titration

- On Days 1 through 6, if the participant experiences SBP < 85 mmHg without symptoms related to hypotension, the measurement must be repeated in 30 minutes. If the SBP remains < 85 mmHg the next day's study drug administration should be skipped and dosing should resume at 1 mg, the following day, if SBP is ≥ 85 mmHg (ie, after a 1-day drug "holiday", the treatment will resume at a reduced dose).
- On Days 1 through 6, if the participant experiences SBP < 90 mmHg and symptoms of hypotension (such as dizziness, light headedness etc), the measurement must be repeated in 30 minutes. If the SBP remains < 90 mmHg the next day's study drug administration should be skipped and dosing should resume at 1 mg, the following day, if SBP is ≥ 85 mmHg and symptoms of hypotension resolved (ie, after a 1-day drug "holiday", the treatment will resume at a reduced dose).
- On Days 1 through 6, if the participant experiences SBP fall ≥ 40 mmHg with symptoms of hypotension that in the opinion of investigator preclude further safe dosing of the participant at the initial dose level, the next day's study drug administration should be skipped and dosing should resume at 1mg the following day, if SBP is ≥ 85 mmHg and symptoms of hypotension resolved (ie, after a1-day drug "holiday", the treatment will resume at a reduced dose).
- After dose reduction, the dose cannot be increased again.

7.4.2 Permanent discontinuation of the study drug

- If the participant experiences SBP < 85 mmHg regardless of symptoms of hypotension, or symptomatic hypotension with SBP < 90 mmHg (measurements must be repeated in 30 minutes), despite dose reduction, then the study drug must be discontinued.
- On Days 7 through 14, if the participant experiences SBP < 85 mmHg regardless of symptoms of hypotension, the measurement must be repeated in 30 minutes. If the SBP remains < 85 mmHg, the study drug should be discontinued.
- On Days 7 through 14, if the participant experiences SBP < 90 mmHg and symptoms of hypotension (such as dizziness, lightheadedness, etc), the measurement must be repeated in 30 minutes. If the SBP remains < 90 mmHg, the study drug should be discontinued.

- Regardless of the day of the treatment, if the participant experiences SBP fall ≥ 40 mmHg with symptoms of hypotension, that in the opinion of investigator preclude further safe dosing of the participant, then the study drug should be discontinued.
- If the participant requires intravenous vasodilators, continuous IV diuretics or IV inotropes, the study drug should be discontinued

7.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For study drugs not provided by BMS and obtained commercially by the site, storage should in accordance with the product label.

Detailed instructions for preparing, and handling of BMS-986259 and placebo and information on dosing solution stability are provided in the Study Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications for this study are described below. Medications taken within 8 days in hospital prior to study drug administration must be recorded on the electronic case report form (eCRF).

BMS-986259 can be administered on top of Guideline Directed Medical Therapy (GDMT) for HF, as appropriate.

The following are prohibited before and during the study:

1) Exposure to any investigational drug or placebo, including serelaxin; within 30 days of initial study drug administration or 4 months prior to the first dose of IP, in case of exposure to long-acting biological investigational drug.
2) PDE5 inhibitors used for erectile dysfunction: sildenafil, tadalafil, vardenafil, etc (within 48 hours of initial study drug administration and throughout the study, up to 5 days after the last dose of study drug).
3) Continuous infusion of IV diuretics, inotropes and vasodilators during the study.

7.8 Treatment After the End of the Study

At the end of the study treatment period, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Positive RT-PCR or rapid antigen test for SARS-CoV-2
- Participants' clinical condition requires the use of continuous infusion of IV diuretics, inotropes and vasodilators
- Inability to comply with the protocol
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- BP related criteria are described in dose modification (Section 7.4)

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

[redacted]

- Blood pressure device will be provided to participants at discharge to measure BP if symptoms consistent with hypotension occur. If systolic BP falls below 85 mmHg (in 2 repeated measurements within 30 minutes) and symptoms of hypotension persist, participants will be instructed to report to the study site or another healthcare provider.

9.1 Efficacy Assessments

[redacted]

9.1.2 Investigator Assessment of Signs and Symptoms

New York Heart Association (NYHA) class will be evaluated by the investigator on Day 1, at discharge, and on Day 14 and Day 30. (See Appendix 6)

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Appendix 1 in the Investigator's Brochure (IB) represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing and if there are participants who develop ADAs, for those participants, SAEs must be collected up to 3 months.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.

- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/Independent Ethics Committee (IEC), if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious

Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 6 days after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

If any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for, 6 days after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or reduced.
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 × ULN

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECGs, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of BMS-986259 greater than the designated dose described in Section 7 will be considered an overdose. All occurrences of intentional overdose must be reported as an SAE (see Section 9.2).

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986259 can no longer be detected systemically
3) Obtain a serum sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform a physical examination.

Documentation of who performed the examination is to be recorded in source notes. A targeted physical examination may note any changes in the participant's condition (body systems) since the last assessment and does not preclude examination of any of the other body systems as clinically indicated (ie, skin). Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study.

9.4.2 Vital signs

Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Planned time points for ECGs are listed in the Schedule of Activities (Section 2). Single standard 12-lead ECGs will be recorded after the participant has been resting for at least 5 minutes in the supine position.

The Investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date the report.

The site should follow their standard practices for performing ECGs. Below is guidance to be used as a reference, if needed:

In preparation for the ECG, ensure there is minimal interference between the skin surface and the electrode. Use alcohol to prepare the skin at each electrode site. Thick chest hair should be shaved to ensure sufficient contact.

Before attaching electrodes to pick-up points, spread the electrode with electrode gel. Place the electrodes on bony areas, avoiding large muscle masses, to achieve better tracings as described below. The participant must be supine and should refrain from movement during the ECG recording.

Ensure that the participant and the electrodes (including the neutral electrode) are not exposed to conducting objects, even if grounded.

- RL: On the right leg (inside calf, midway between knee and ankle)
- LL: On the left leg (inside calf, midway between knee and ankle)
- RA: Right arm (on the inside)
- LA: Left arm (on the inside)
- V1: 4th intercostal space, at right sternal margin
- V2: 4th intercostal space, at left sternal margin

- V3: Midway between V2 and V4
- V4: 5th intercostal space at left midclavicular line
- V5: Same transverse level at V4, at anterior axillary line
- V6: Same transverse level at V4, at left midaxillary line

Keep one original ECG (print-out or electronic copy) in the medical chart and ensure a copy, assessed, initialed and dated by the Investigator, is maintained in the source documents for the study.

[redacted]

9.4.5 Clinical Safety Laboratory Assessments

Participants will have laboratory tests performed locally as necessary for treatment of ADHF following local practices. In addition, laboratory tests will be performed locally and centrally as described in the following sections.

9.4.5.1 Local Laboratory Assessments for Screening

A local laboratory will perform the following analyses and will provide reference ranges for these tests. Local Laboratory results obtained for the current episode of heart failure as part of standard of care, within 24 hours of randomization, may be used. The results of local labs will be used for eligibility determination.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus

Blood Urea Nitrogen (BUN) or Serum Urea Uric acid Glucose	Magnesium Creatine kinase eGFR
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (screening only)	
Other Analyses	
SARS-CoV-2 test (RT-PCR or rapid antigen test)	
NT-proBNP or BNP	
Follicle stimulating hormone (FSH) only required to confirm menopause in women < age 55	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro-brain natriuretic peptide; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

9.4.5.2 Central Laboratory Assessments (On Treatment)

The following laboratory tests will be performed and submitted to the Central Laboratory for analysis as per the Study Assessment and Procedures in Section 2. The following samples should be collected predose: Hematology, Chemistry, and Urinalysis.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH)	Total Protein Albumin Sodium Potassium Chloride Calcium

Creatinine Blood Urea Nitrogen (BUN) or Serum Urea Uric acid Fasting glucose	Phosphorus Magnesium Creatine kinase [redacted]
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
[redacted]	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; [redacted] LDH = lactate dehydrogenase.

The Central Laboratory and designated reference laboratories for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests.

The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory.

9.4.6 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetics

Pharmacokinetics of BMS-986259 will be derived from serum concentration versus time. The PK parameters to be assessed include:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in one dosing interval
Ctrough	Trough observed plasma concentration

Individual participant PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses. When multiple procedures are required at a time point, prioritize that the PK samples are collected as close to the scheduled time point as possible.

Table 9.5-1: Pharmacokinetic [redacted] Sampling Schedule for All Participants (CV019010)

Study Day of Sample Collection	Event	Time[a] (Relative to BMS-986259 or Placebo Dose) Hour: Min	BMS-986259/ Placebo PK Serum Sample	[redacted]
Day 1	predose[b]	00:00	X	
		3:00	X	
		6:00	X	
		8:00	X	
		10:00	X	
		14:00	X	
Day 2	predose[b]	00:00	X	
Day 3	predose[b]	00:00	X	
Day 5	predose[b]	00:00	X	
		3:00	X	
		6:00	X	
		8:00	X	
		10:00	X	
		14:00	X	
Day 6	predose[b]	00:00	X	
Day 8	predose[b]	00:00	X	

Table 9.5-1: Pharmacokinetic [redacted] Sampling Schedule for All Participants (CV019010)

Study Day of Sample Collection	Event	Time[a] (Relative to BMS-986259 or Placebo Dose) Hour: Min	BMS-986259/ Placebo PK Serum Sample	[redacted]
Day 14 End of Study Visit[c]	predose[b]	00:00	X	
Day 30 Follow-up[redacted]	Follow-up			

[redacted]

Abbreviations: [redacted] Min = minutes; [redacted] PK = pharmacokinetic.

[a] All the PK samples should be collected as close to the scheduled time point as clinically feasible.

[b] All predose samples should be taken (preferably with 30 minutes) prior to the start of subcutaneous injection. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is delayed, an additional predose sample should not be collected.

[c] If the study is ended early and the End of Study Visit takes place on Day 13 instead of Day 14, indicated Day 14 samples should be collected on Day 13.

[redacted]

The serum will be analyzed for BMS-986259 by a validated or a qualified enzyme-linked immunosorbent assay (ELISA) method assay. PK samples collected from a participant who received placebo will not be analyzed.

[redacted]

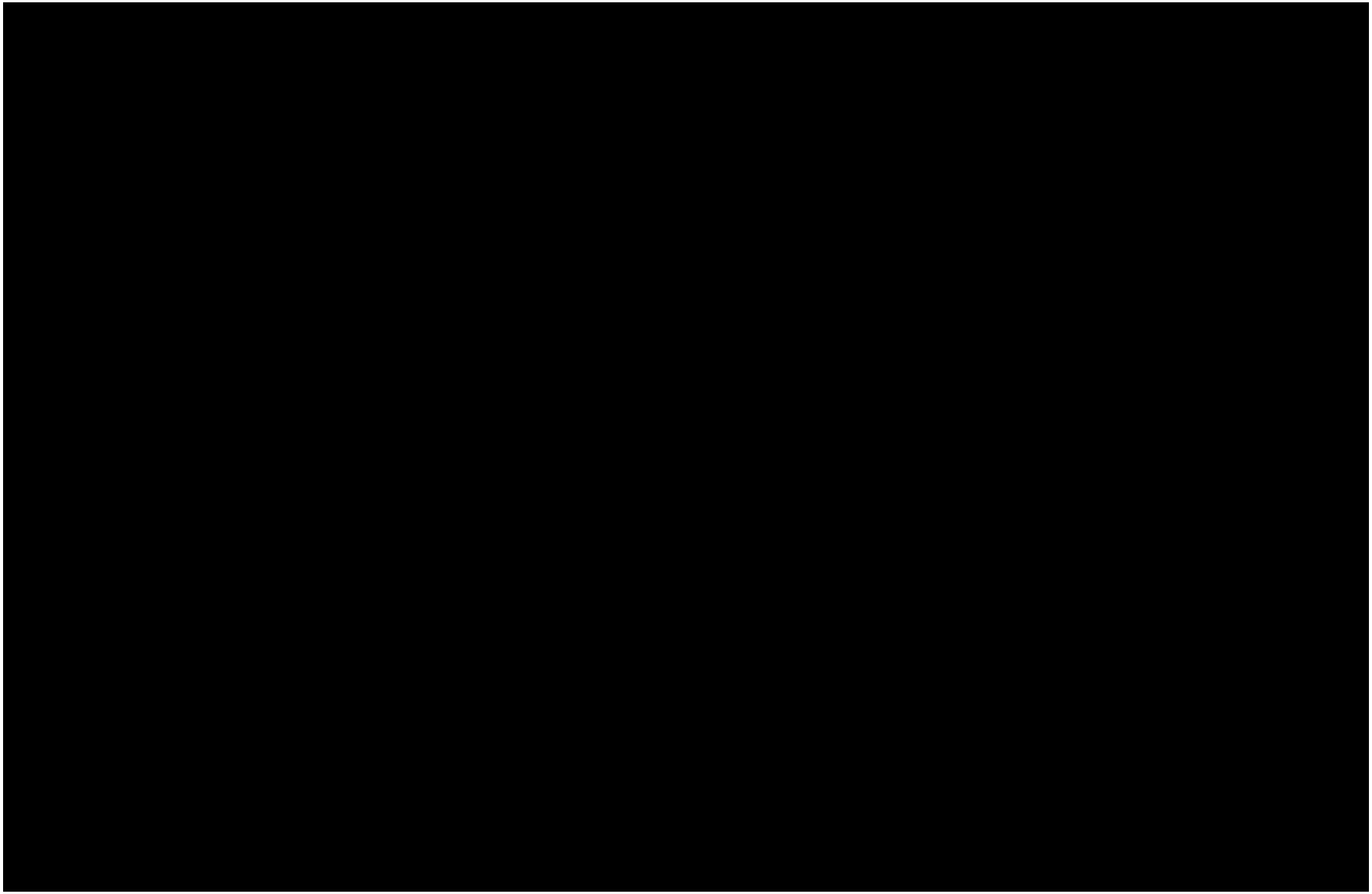
Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the investigative site and home healthcare provider in the laboratory manual.

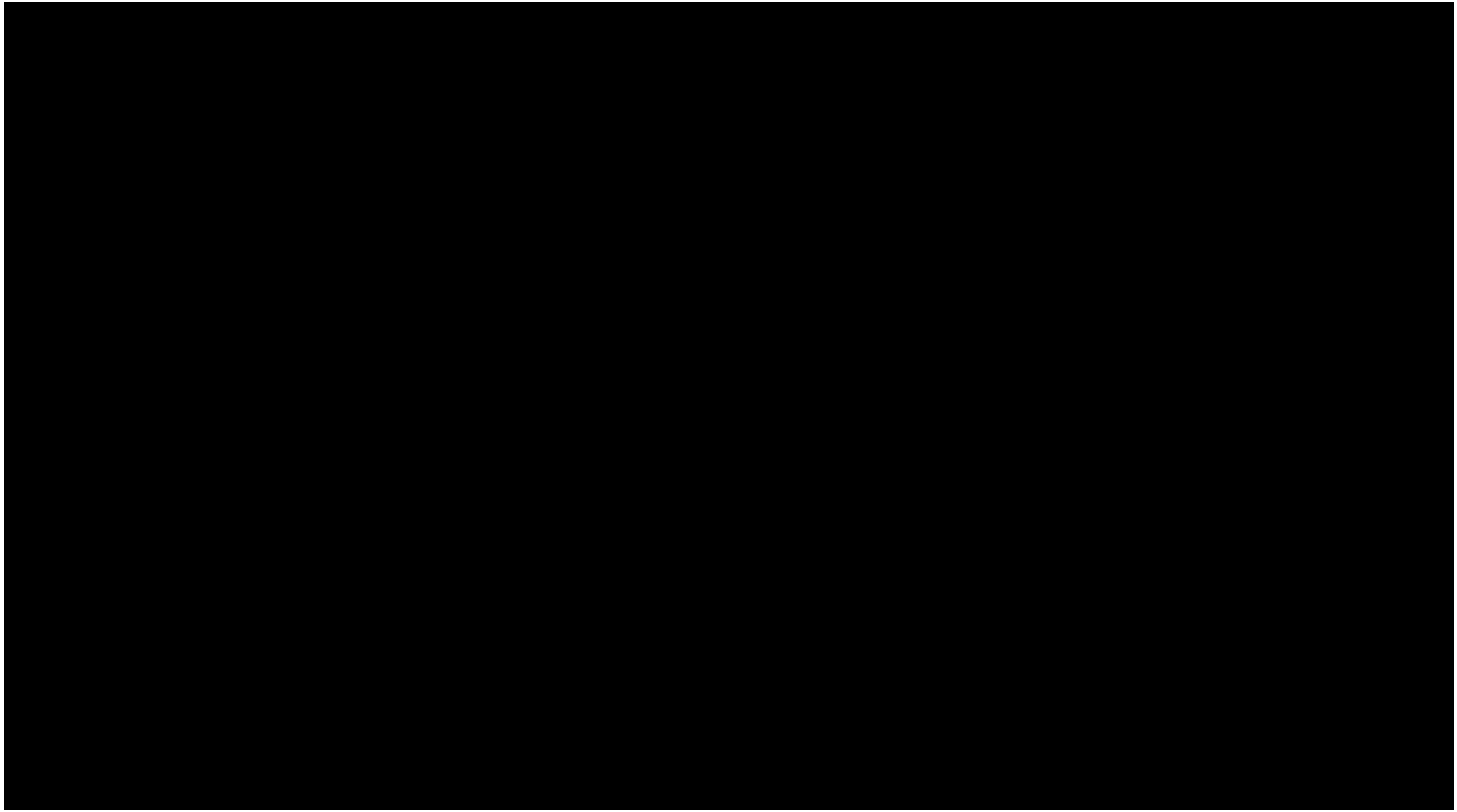
9.6 Pharmacodynamics

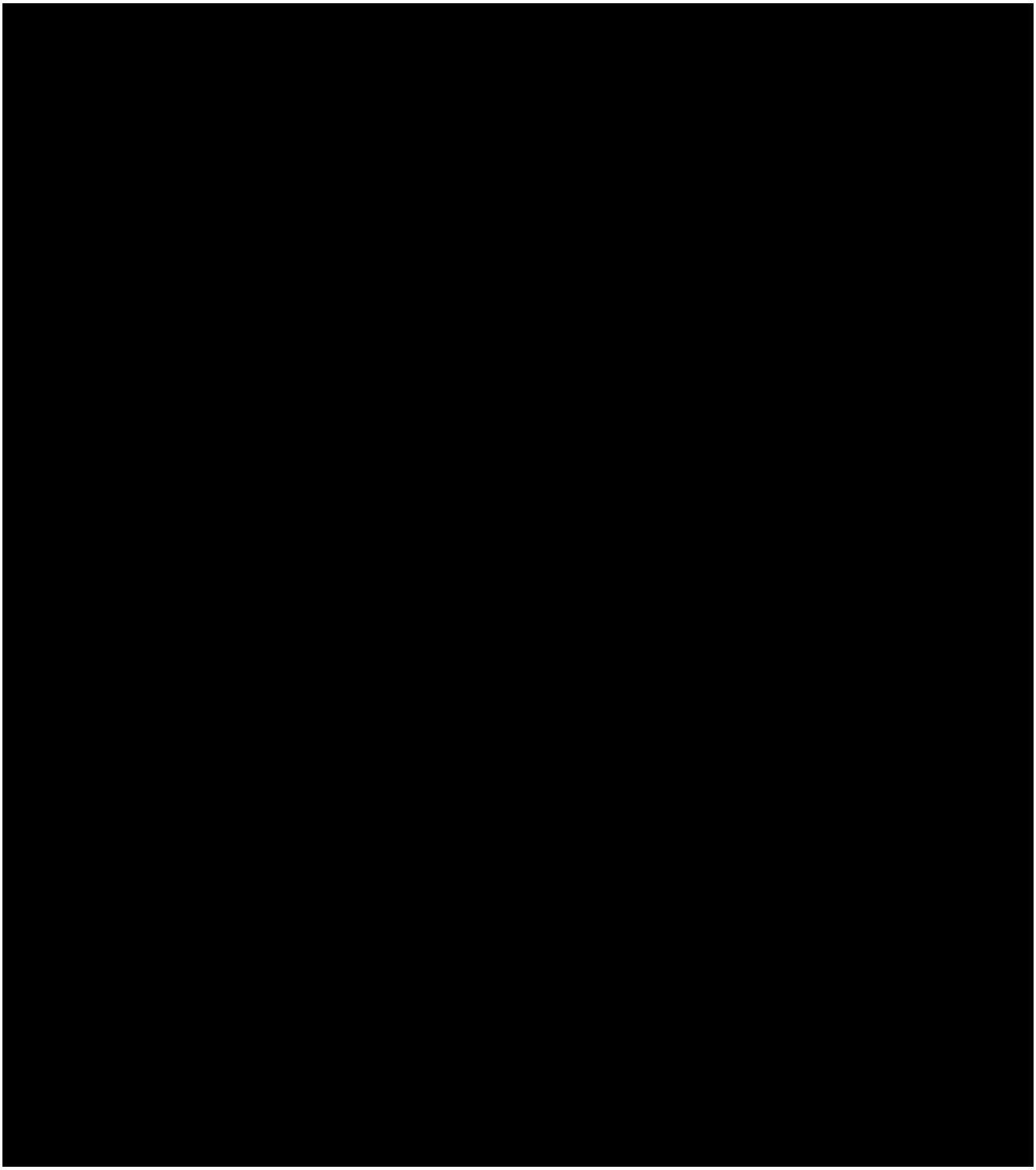
Pharmacodynamic parameters are not evaluated in this study.

[redacted]

[redacted]







9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The primary objective of the study is to evaluate safety and tolerability of BMS-986259. It is estimated there may be ~10% to 20% early treatment withdrawal. Approximately 72 participants will be randomized with 1:1 ratio to BMS-986259 subcutaneous QD and Placebo to have at least 60 completers by the end of the study. An estimation approach will be used for comparison between BMS-986259 and placebo for hypotension rate. Point estimates and associated 95% confidence intervals for event rate and relative risk ratio will be constructed to provide plausible range of values for the true comparison of interest.

The incidence of clinically relevant hypotension in the placebo group is estimated to be between ~ 5% to 15%. With N=60 and 1:1 treatment assignment ratio, the study will be able to detect a significant increase of clinical hypotension event compared to placebo ranging from 2.7 fold increase (eg, placebo rate =15%) to 5 fold increase (eg, placebo rate =5%).

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Randomized	All participants who have been randomized by IRT system Randomized population will be used for Disposition, Demographic and baseline characteristic Analyses
Safety	All randomized participants who take at least 1 dose of double blind- study treatment. Participants will be included in the treatment group they were randomized to. eg, "Data in this data set will be analyzed based on randomized treatment, except in the following cases: • If a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received. • If a participant received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment received. Safety Population will be used for all efficacy, safety [redacted] analyses
PK Population	All participants who have received at least one dose of treatment and have at least one valid PK measurement. If feasible, PK population will be used for all PK analyses

Abbreviations: IRT = Interactive Response Technology; PK = pharmacokinetic.

10.3 Statistical Analyses

A description of the participant population will be included in a statistical output report, including subgroups of age, gender and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary Not Applicable	
Secondary Not Applicable	

[redacted]

10.3.2 Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary ➢ Clinically relevant hypotension ➢ AEs ➢ Vital Signs ➢ Laboratory Test Results ➢ ECGs ➢ Physical Examination	The incidence of clinically relevant hypotension will be summarized by treatment. Point estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the risk difference and relative risk between relaxin and placebo. All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

[redacted]

Abbreviations: [redacted] AE = adverse event; CI = confidence interval; ECG = electrocardiogram; [redacted].

10.3.3 PK Analyses

Endpoint	Statistical Analysis Methods
Serum PK parameters in participants with HF	PK parameters will be listed, plotted and summarized descriptively

Abbreviations: HF = heart failure; PK = pharmacokinetic.

[redacted]

10.3.5 Interim Analyses

An IA to evaluate clinically relevant hypotension for the purpose of future study planning will be conducted when 1) approximately 30 participants complete the Day 14 End of Study Visit, and 2) approximately 15 of these have baseline SBP less than or equal to 125 mmHg. Details of the analysis conducted at the IA will be described in the statistical analysis plan.

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[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
[redacted]	[redacted]
[redacted]	[redacted]
ADHF	acute decompensated heart failure
ACE	angiotensin-converting enzymes
AE	adverse event
AFib	Atrial Fibrillation
ALK5	activin-like kinase 5
ALT	alanine aminotransferase
AR	additional research
ARNI	angiotensin receptor-neprilysin inhibitor
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BMI	body mass index
BMS	Bristol-Myers Squibb
BNP	brain natriuretic peptide
BP	Blood pressure
BUN	Blood Urea Nitrogen
CBC	complete blood count
[redacted]	[redacted]
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials

Term	Definition
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CRO	Contract Research Organization
CRTD	Cardiac Resynchronization Therapy Defibrillator
CSR	clinical study report
CTA	clinical trial agreement
Ctrough	trough concentration
D	day
[redacted]	[redacted]
DILI	drug induced liver injury
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
[redacted]	[redacted]
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
EMR	electronic medical record
ER	emergency room
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GDMT	Guidelines Directed Medical Therapy
GFR	glomerular filtration rate
H2-relaxin	human relaxin
HCG	Human chorionic gonadotropin
HF	heart failure
HIV	human immunodeficiency virus
HFmrEF	heart failure with a mid-range ejection fraction

Term	Definition
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICD	Implantable Cardioverter-Defibrillator
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
INSL3	insulin-like peptide 3
[redacted]	[redacted]
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
[redacted]	[redacted]
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MD	medical doctor
Mo	month
MOA	mechanism of action
MRA	mineralocorticoid receptor antagonist
MRI	mineralocorticoid receptor inhibitor
N/A	not applicable
[redacted]	[redacted]
NHV	normal healthy volunteers
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAP	pulmonary arterial pressure

Term	Definition
PCWP	pulmonary capillary wedge pressure
[redacted]	[redacted]
PDE5	phosphodiesterase type 5
PE	physical examination
PID	Patient identification number
PK	pharmacokinetics
QD	once daily
[redacted]	[redacted]
RAAS	renin-angiotensin-aldosterone-system
R&D	research and development
RBF	renal blood flow
RT-PCR	reverse transcription polymerase chain reaction
RXFP1	relaxin/insulin-like family peptide receptor 1
RXFP2	relaxin/insulin-like family peptide receptor 2
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	subcutaneous
SMAD2	mothers against decapentaplegic homolog 2
SOA	schedule of activities
SOC	standard of care
SOP	standard operating procedures
[redacted]	[redacted]
[redacted]	[redacted]
SUSAR	Suspected, Unexpected Serious Adverse Reaction
SVR	systemic vascular resistance
T-HALF	half-life
TIA	transient ischemic attack
Tmax	time of maximum observed concentration
ULN	upper limit of normal
WOCBP	women of childbearing potential
WRF	worsening renal function

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and

institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to

Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for

human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c] • Bilateral tubal occlusion
• Vasectomized partner Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

- Sexual abstinence

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

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
- Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

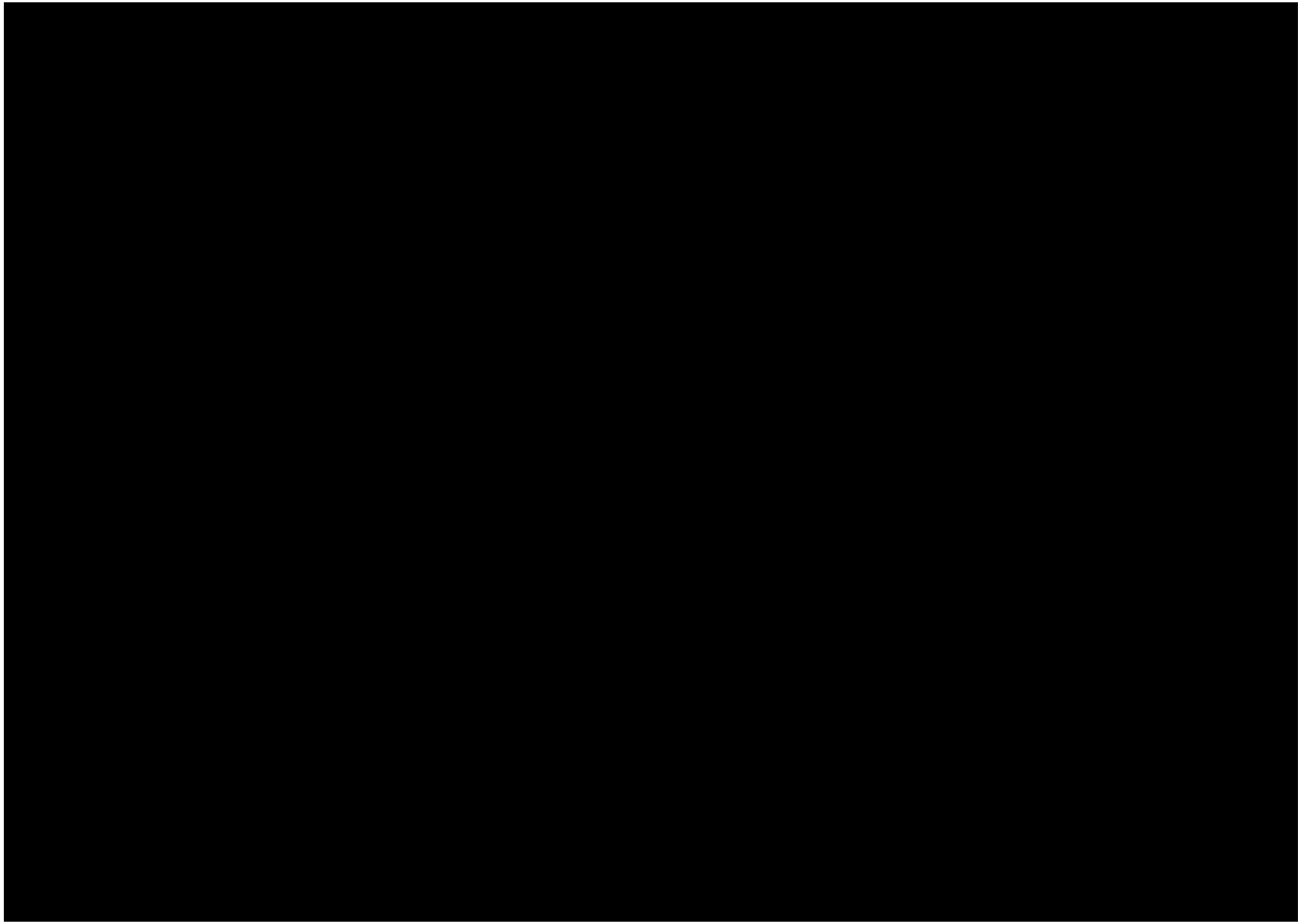
Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.



APPENDIX 6 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 7 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Original Language	Country-specific Language or Differences
Section 6.1 Inclusion criteria: Inclusion criterion 3) a) i): Females, ages at least 18 or local age of majority	Czech Republic specific language: Adding a max age of 75 years Section 6.1 Inclusion criteria. Inclusion criterion 3) a) i): Females, ages at least 18 or local age of majority and maximum 75
Section 6.1 Inclusion criteria: Inclusion criterion 3) b) i): Males, ages at least 18 or local age of majority	Czech Republic specific language: Adding a max age of 75 years Section 6.1 Inclusion criteria. Inclusion criterion 3) b) i): Males, ages at least 18 or local age of majority and maximum 75