NOVARTIS

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

CLCZ696BUS13

A 52 week, open label evaluation of the effects of sacubitril/valsartan (LCZ696) therapy on biomarkers, myocardial remodeling and patient-reported outcomes in heart failure with reduced left ventricular ejection fraction: (PROVE-HF)

Statistical Analysis Plan (SAP)

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22-Feb-2019	Prior to DB Lock	Creation of Amendment 1	1. Updated to align with protocol version 03 (amended protocol) dated 27-Feb-2018: removal of interim analysis 2. Updated list of abbreviations 3. Clarified MedDRA version 4. Clarified WHO Drug version 5. Specified that geometric means and confidence intervals will be presented for biomarker data 6. Updated baseline definitions for biomarkers and echo variables 7. Added subgroups for the analysis of the primary objective 8. Specified addional biomarkers for the summary of baseline characteristics 9. Updated table of BB standardization factors 10. Clarified LOCF method for supportive analysis of primary objective 11. Added two supportive analyses of the primary objective based on alternative baseline definitions for echocardiographic variables 12. Removed optional sensitivity analysis of KCCQ-23 clincial summary score change from baseline at one year using propensity score stratification	1. Section 1.1 Study design; Section 2.14 Interim analysis 2. List of abbreviations table 3. Section 2.3.3 Demographics and other baseline characteristics; Section 2.8.1.1 Coding of AEs; Section 2.8.2 Deaths; Section 5.2 AE coding/grading 4. Section 2.4.2 Prior, concomitant and post therapies 5. Section 2.1 Data analysis general information 6. Section 2.1.1 7. Section 2.2.1 Subgroup of interest 8. Section 2.3.3 Demographics and other baseline characteristics 9. Section 2.4.2 Prior, concomitant and post therapies 10. Section 2.5.4 Supportive analyses 11. Section 2.5.4 Supportive analyses 12. Section 2.7.2 Statistical hypothesis, model, and method of analysis 13. Section 2.8.1.3 AE summaries

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			13. Added AE summaries: non-serious AEs ≥5%, SAEs ≥0.5%, SAEs by seriousness criteria, AE overview 14. Specified conversion factors for lab values indicated as <*x* or >*x* 15. Specified repeated measures analysis of change from baseline for echocardiographic variables, biomarkers, and KCCQ-23 domains/scores 16. Added summary of patients with hypotension based on SBP criteria 17. Added summary of patients with hyperkalemia based on central lab data 18. Added summary of patients with worsening renal function based on central lab data 19. Added summary of positively adjudicated angioedema 20. Added subgroup analyses of KCCQ-23 clinical summary score change from baseline at one year 21. For biomarkers specified that values <LOD will be converted to (0.5)(LOD); and samples from patients who withdrew consent will not be analyzed by the central laboratory 22. Specified that results for the exploratory labile biomarker ANP will be reported separately from the other biomarkers 23. Added analysis of new exploratory endpoint defined as total CV deaths and heart failure hospitalizations	14. Section 2.8.3 Laboratory data 15. Section 2.8.4 Echocardiographic data; Section 2.11.1 Kansas City Cardiomyopathy Questionnaire; Section 2.12 Biomarkers 16. Section 2.8.5.1 Vital signs 17. Section 2.8.5.3 Hyperkalemia 18. Section 2.8.5..4 Creatinine 19. Section 2.8.5.7 Angioedema 20. Section 2.11.1 Kansas City Cardiomyopathy Questionnaire 21. Section 2.12 Biomarkers 22. Section 2.12 Biomarkers 23. Section 2.13 Other exploratory analyses 24. Section 2.13 Other exploratory analyses 25. Section 2.13 Other exploratory analyses 26. Section 2.13 Other exploratory analyses 27. Section 5.1.4 Heart failure diagnosis date imputation 28. Section 5.6 Rule of exclusion criteria of analysis sets 29. Section 2.4.2 Prior, concomitant and post therapies

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			24. Added summary of number of events at 3 months, at 6 months, and at one year 25. Modified analysis of the association between number of events and biomarkers and echocardiographic variables to present Spearman (instead of Pearson) correlation coefficients 26. Added summary of change from baseline and change from last-to-present at each visit for the subset of patients who have change from baseline or change from last-to-present values, respectively, for all 3 BNP assays at the given visit 27. Added imputation rules for partial HF diagnosis dates 28. Updated tables 1 and 2 for rules of exclusion criteria of analysis sets 29. Added separate summaries of prior and concomitant CV, HF, ACEi, and ARB medications 30. Clarified that subgroup defined by NT-proBNP concentration ≤1000 pg/mL at Month 12 is determined in patients with baseline NT-proBNP >1000 pg/mL 31. Added new subgroup defined by NT-proBNP concentration ≤1000 pg/mL at Month 12 for patients with baseline NT-proBNP >1000 pg/mL, or >30% reduction from baseline in NT-proBNP at Month 12 32. Added summary of total number of CV deaths and heart failure hospitalizations for	30. Section 2.2.1 Subgroup of interest 31. Section 2.2.1 Subgroup of interest 32. Section 2.13 Other exploratory analyses

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			patients with baseline NT-proBNP value >1000 pg/mL who achieve an NT-proBNP value ≤1000 pg/mL, or who have >30% reduction from baseline in NT-proBNP	

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List of abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
ALT	Alanine Aminotransferase
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate Aminotransferase
BB	β-Blocker, β-Blocking agent
BID	bis in diem/twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BSS	Biomarker sub-study set
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
cGMP	Cyclic guanosine monophosphate
CHF	Chronic heart failure
CFR	US Code of Federal Regulations
CRF/eCRF	(electronic) Case Report/Record Form
CRO	Contract Research Organization
CRT-D	Cardiac resynchronization therapy defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
CSR	Clinical study report
CV	Cardiovascular
DBP	Diastolic blood pressure
DCT	Data collection tool
DM	Diabetes mellitus
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
Echo	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
GCP	Good Clinical Practice
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
hs-Troponin	High sensitivity troponin
HTN	Hypertension
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology

KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrial
LAVi	Left atrial volume index
LVEF	Left ventricular ejection fraction
LVEDVi	Left ventricular end diastolic volume index
LVESVi	Left ventricular end systolic volume index
LV	Left ventricular
mmHg	Millimeter mercury
MOA	Mechanism of action
MRI	Magnetic resonance imaging
NEP	Neutral endopeptidase
NP	Natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
pg/mL	Picogram per milliliter
RAAS	Renin angiotensin aldosterone system
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SS	Safety set
sST2	Soluble ST2
SUSAR	Suspected Unexpected Serious Adverse Reactions
TIA	Transient ischemic attack
TS	Treatment set
UBC	United BioSource Corporation
ULN	Upper limit of normal
USPI	United States prescribing information/package insert
VAD	Ventricular assistance device
WHF	Worsening heart failure
WoC	Withdrawal of Consent

1 Introduction

The statistical analysis plan (SAP) will outline in detail the analyses planned in the protocol. The analyses will be used to generate the Clinical Study Report (CSR). The SAP is based on protocol version 03 (amended protocol) dated 27-Feb-2018 and the data collection tool (DCT) version 10.0 dated 27-Nov-2018.

1.1 Study design

This study will use a multicenter, open-label, single-arm design in a population of outpatients with heart failure and reduced ejection fraction (HFrEF) ≤40%. The study duration is a maximum of 52 weeks (365 days). A study cohort of approximately 830 patients will be enrolled in approximately 100 centers in the United States. At the time of enrollment, patients will be considered eligible if they are identified as clinically appropriate HFrEF patients and who are candidates to receive sacubitril/valsartan per the United States Prescribing Information (USPI) prescribing information. As this is a single-arm open-label design, all patients will be treated with sacubitril/valsartan and no randomization will be done.

Patients will enter a 4-week screening epoch to confirm that they meet all study inclusion criteria and none of the exclusion criteria. Patients that have been treated with an angiotensin converting enzyme inhibitor (ACEi) before the study will require a 36-hour wash out period before starting sacubitril/valsartan treatment.

Sacubitril/valsartan will be dispensed to eligible patients on Study Day 1. The initial dose will be determined by the investigator and per the approved indication described in the USPI. The three doses available are: 24/26 mg bis in diem/twice a day (BID) (Dose Level 1), 49/51 mg BID (Dose Level 2), and 97/103 mg BID (Dose Level 3). Open-label treatment will be provided through the duration of the trial. Adjustment of the sacubitril/valsartan dose levels may be increased on an every 2-4 week basis per USPI to the desired target maintenance dose of 97/103 mg BID or increased within a 1-2 week time period based on clinical need and/or investigator judgment.

The primary analysis time point will be 12 months.

1.2 Study objectives and endpoints

The primary objective of this study is to examine the association between change in concentration of N-terminal pro b-type natriuretic peptide (NT-proBNP) and change in structural cardiac measurements (left ventricular end systolic and diastolic volume indices [LVESi, LVEDi], left ventricular ejection fraction [LVEF], and left atrial volume index [LAVi]) from baseline to one year.

The secondary objectives are:

1. To examine the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LVESi, LVEDi, LVEF, and LAVi) from baseline to 6 months overall and in subgroups of interest. Subgroups for this analysis are listed in Section 2.2.1.

2. To examine the association between the change in NT-proBNP concentrations and patient-reported outcomes from the Kansas City Cardiomyopathy Questionnaire (KCCQ)-23 during a year of follow up.

The exploratory objectives are:

1. To examine change in concentration of other efficacy, heart failure (HF) prognosis, or mechanism of action (MOA) biomarkers collected in the full patient population from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic parameters.
2. To examine the association between cardiovascular(CV) events following sacubitril/valsartan initiation and up-titration, during the follow-up period of 12 months, with change in "efficacy" biomarkers and echocardiographic remodeling indices. The CV events include:
    a. Worsening heart failure (WHF)
    b. Heart failure hospitalization
    c. CV death
3. In a subset of patients (N = up to 300) with carefully collected and processed labile MOA biomarkers:
    a. To examine effects of sacubitril/valsartan on concentrations of B-type natriuretic peptide (BNP), as determined by several different assays used in clinical practice.
    b. To examine change in concentration of MOA biomarkers from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables.

2 Statistical methods

2.1 Data analysis general information

United BioSource Corporation (UBC), a Novartis-designated Contract Research Organization (CRO) will be performing all analyses outlined in this SAP. SAS® version 9.3 (or higher) will be used for all analyses.

Data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Unless otherwise specified, for continuous data, the mean, standard deviation, median, first and third quartiles, interquartile range, and minimum and maximum values will be presented. Geometric means and 95% confidence intervals will also be presented for biomarker data. For categorical data, frequencies and percentages will be presented. All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

All data will be provided in listings in addition to summaries described below.

2.1.1 General definitions

Study treatment

All eligible patients will receive open-label sacubitril/valsartan through the duration of the trial.

Baseline

For echocardiographic variables baseline is defined as the last non-missing assessment performed ≤1 week from the date of first administration of study treatment.

For biomarkers baseline is defined as the last non-missing assessment collected ≤6 hours from the time of first administration of study treatment. If the assessment was collected on the date of first administration of study treatment, but the timing relative to first administration of study treatment cannot be determined, the assessment will be excluded from the determination of baseline.

For all other assessments baseline is defined as the last non-missing assessment prior to or on the date of first administration of study treatment.

Unscheduled assessments will be excluded from the determination of baseline.

Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date a dose of sacubitril/valsartan is administered and recorded on the Dosage Administration Record - At Visit (Visit 2) electronic case report form (eCRF).

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date a dose of sacubitril/valsartan is administered and recorded on the Study Completion eCRF. In the event this date is not available from the Study Completion eCRF, it will be obtained from the Dosage Administration Record - Summary eCRF.

Study day

The study day describes the day of the assessment relative to the date of first administration of study treatment at Visit 2 (Day 1/Baseline).

The study day will be calculated as the difference between the date of assessment and the date of first administration of study treatment, plus 1. If the date of assessment is prior to the date of first administration of study treatment, the study day will be negative and will be calculated as the difference between the date of the assessment and the date of first administration of study treatment.

Last contact

The date of last contact will be the last visit date for each patient and will be derived by examining all visit data collected in the eCRFs.

Year, month and week

For reporting purposes, the rules below will be followed to convert a year, month, and week to days.

1 year = 365.25 days

1 month = 30.3475 days

1 week = 7 days

1 day = 24 hours

2.2 Analysis sets

The following subject sets will be used for the statistical reporting and analyses:

The Treatment Set (TS) will consist of all patients enrolled at Visit 2.

The Full Analysis Set (FAS) will consist of all patients enrolled at Visit 2 with the exception for those patients who have not been qualified for study treatment and have not received study drug, but have been inadvertently entered into the study. Efficacy variables will be analyzed based on the FAS as the primary set.

The Biomarker Sub-study Set (BSS) will consist of all patients in the FAS with one or more collected and processed samples for labile blood biomarkers and BNP.

The Safety Set (SS) will consist of all patients who received at least one dose of study treatment. The SS will be used for the analyses of safety variables.

2.2.1 Subgroup of interest

The following subgroups will be analyzed for the primary objective:

1. New onset HF or naïve to ACEi/angiotensin receptor blocker (ARB) therapy (No, Yes)
2. Baseline NT-proBNP (<600 pg/mL, or <400 pg/mL if hospitalized for HF within 1 year) (No, Yes)
3. Target dose of sacubitril/valsartan (dose level 3) achieved by Month 12 (No, Yes)
4. NT-proBNP concentration ≤1000 pg/mL at Month 12 for patients with baseline NT-proBNP >1000 pg/mL (No, Yes)
5. NT-proBNP concentration ≤1000 pg/mL at Month 12 for patients with baseline NT-proBNP >1000 pg/mL, or >30% reduction from baseline in NT-proBNP at Month 12 (No, Yes)
6. Groups defined by quintiles of response time (defined for patients with baseline NT-proBNP >1000 pg/mL as the time from baseline to date when NT-proBNP ≤1000 pg/mL) through Month 12
7. Groups defined by quintiles of time spent with NT-proBNP ≤1000 pg/mL across study visits through Month 12
8. Age (<75 years, ≥75 years)
9. Baseline New York Heart Association (NYHA) class (I and II, III and IV)
10. Prior atrial fibrillation (AF) (No, Yes)

11. Baseline body mass index (BMI) (<30 kg/m^2, ≥30 kg/m^2)
12. Baseline NT-proBNP <125 pg/mL (No, Yes)
13. Groups defined by quartiles of baseline estimated glomerular filtration rate (eGFR)
14. Prior diabetes (No, Yes)
15. Prior ACEi/ARB (No [naïve], Yes)

The following subgroups will be analyzed for the secondary objective of the calculation of Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values:

1. New onset HF or naïve to ACEi/ARB therapy (No, Yes)
2. Baseline NT-proBNP (<600 pg/mL, or <400 pg/mL if hospitalized for HF within 1 year) (No, Yes)
3. Target dose of sacubitril/valsartan (dose level 3) achieved by Month 12 (No, Yes)
4. NT-proBNP concentration ≤1000 pg/mL at Month 12 for patients with baseline NT-proBNP >1000 pg/mL (No, Yes)
5. NT-proBNP concentration ≤1000 pg/mL at Month 12 for patients with baseline NT-proBNP >1000 pg/mL, or >30% reduction from baseline in NT-proBNP at Month 12 (No, Yes)
6. Groups defined by quintiles of response time (defined for patients with baseline NT-proBNP >1000 pg/mL as the time from baseline to date when NT-proBNP ≤1000 pg/mL) through Month 12
7. Groups defined by quintiles of time spent with NT-proBNP ≤1000 pg/mL across study visits though Month 12

The following subgroups will be analyzed for the exploratory objective of the analysis at each study visit for each BNP assay of the change in concentration of BNP:

1. New onset HF or naïve to ACEi/ARB therapy (No, Yes)
2. Baseline BNP (<150 pg/mL, or <100 pg/mL if hospitalized for HF within 1 year) (No, Yes)
3. Target dose of sacubitril/valsartan (dose level 3) achieved by Mnoth 12 (No, Yes)

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

All patients will be used for the summary of patient disposition. The following categories will be summarized:

- Number of patients who were screened
- Screening phase disposition

  - Completed
  - Adverse event
  - Death
  - Pregnancy
  - Screen failure
  - Study terminated by sponsor
  - Technical problems
  - Lost to follow-up
  - Physician decision
  - Subject/Guardian decision
- Number and percentage of patients who continued into the open-label treatment phase
- Number and percentage of patients who were treated
- Number and percentage of patients who completed study treatment
- Number and percentage of patients who achieved dose level 3
- Number and percentage of patients who did not achieve dose level 3
  - Reason for not achieving dose level 3
    i. Hyperkalemia
    ii. Symptomatic hypotension
    iii. Renal dysfunction
    iv. Angioedema
    v. Other adverse event
    vi. Unrelated to study treatment tolerability
- Number and percentage of patients who prematurely discontinued study treatment
- Patient status at study completion
  - Completed
  - Adverse event
  - Death
  - Pregnancy
  - Protocol deviation
  - Study terminated by sponsor
  - Technical problems
  - Lost to follow-up

- Physician decision
- Subject/guardian decision

- Study duration in months [*(date of last contact/death – date of first administration of study treatment +1)/30.3475*]

Additionally, listings of inclusion/exclusion criteria, screening disposition, and study treatment disposition will be provided.

2.3.2 Protocol deviations

The number and percentage of patients with protocol deviations by category will be summarized. Additionally, a listing of protocol deviations during the study will also be presented. The TS will be used.

2.3.3 Demographics and other baseline characteristics

Demographics, baseline characteristics and disease history are collected at the screening visit. Descriptive summaries and/or listings will be provided. The number and percentage (categorical variables) and descriptive statistics (continuous data) for the information below will be summarized.

The FAS and BSS will be used.

Demographics and baseline characteristics

Demographic variables include:

- Age (years)
  - Age group (<65 years, ≥65 years; <75 years, ≥75 years)
- Sex (Male, Female)
  - Child bearing status (Able to bear children, Post-menopausal, Sterile - of child bearing age)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Other, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Source of patient referral:
  - Physician's own practice
  - Physician referral
  - Television advertisement
  - Radio advertisement
  - Print advertisement
  - Internet

- Newsletter/Educational material
- Advocacy group
- ER or hospital
- Friend/family member
- Patient database
- Unknown
- Other

General baseline characteristic variables include:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2) [*weight (kg)/height (m^2)*]
  - BMI categories (<20, 20 - <25, 25 - 30, >30 kg/m^2)
- eGFR (ml/min/1.73 m^2)
  - eGFR categories (<45, 45 - <60, ≥60 mL/min/1.73 m^2)

Biomarker baseline characteristic variables include:

- NT-proBNP (pg/mL)
  - NT-proBNP categories (<300, 300 - <1000, 1000 - <1600, 1600 - <3000, ≥3000 pg/mL; <1000, ≥1000 pg/mL)
- BNP#1 (Alere) (pg/mL), BNP#2 (Abbott) (pg/mL), and BNP#3 (Siemens) (pg/mL)
  - BNP#1 - BNP#3 categories (<100, 100 - <225, 225 - <400, 400 - <800, ≥800 pg/mL)
- hs-Troponin T (ng/L)
- sST2 (ng/mL)
- UcGMP (nmol/L)
- UcGMP to Urinary Creatinine ratio (nmol/mmol)
- Mid-regional pro-adrenomedullin (nmol/L)

Key structural cardiac baseline characteristic variables include:

- Left ventricular end systolic volume index, LVESVi (mL/m^2)
- Left ventricular end diastolic volume index, LVEDVi (mL/m^2)
- Left ventricular ejection fraction, LVEF (%)

- Left atrial volume index, LAVi (mL/m^2)
- Diastolic function (E/E')

Disease history

Disease history variables, as collected on the Heart Failure History eCRF at screening, include:

- Time since diagnosis (months)
- New onset heart failure (No, Yes)
- NYHA classification [best value during the month prior to screening visit] (I, II, III, IV)
- Primary heart failure etiology (Ischemic, Non-ischemic)
    - Non-ischemic etiology (Hypertensive [No, Yes], Diabetic [No, Yes], Alcoholic [No, Yes], Myocarditis [No, Yes], Peripartum [No, Yes], Drug induced [non-chemotherapy] [No, Yes], Chemotherapy [No, Yes], Idiopathic Other [No, Yes], Valvular heart disease [No, Yes], Other [No, Yes])
- Myocardial infarction (No, Yes)
- Coronary revascularization (No, Yes)
    - Coronary revascularization type (Percutaneous coronary intervention [PCI], Coronary Artery Bypass Graft [CABG])
- Prior heart failure hospitalization (No, Yes)
    - Number of heart failure hospitalizations in the last 12 months
- Most recent ejection fraction (%)
    - Ejection fraction categories (<25%, 25% - <35%, ≥35%)
    - Method used (Magnetic Resonance Imaging [MRI], Echocardiography, Nuclear [SPECT/PET/MUGA], Ventriculogram, Other)
- Known history of diabetes mellitus (No, Yes)

Cardiovascular history

Cardiovascular history will be summarized. The following disease information will be collected:

- Hypertension (No, Yes, Unknown)
- Transient Ischemic Attack (TIA) (No, Yes, Unknown)
- Stroke (No, Yes, Unknown)
- Peripheral vascular disease (No, Yes, Unknown)
- Chronic Kidney Disease (CKD) stage (CKD stage 1 [eGFR ≥90], CKD stage 2 [eGFR 60 - 89], CKD stage 3 [eGFR 30 - 59], CKD stage 4 [eGFR 15 - 29], CKD stage 5 [eGFR <15 or dialysis], No CKD)
- Arrhythmia (No, Yes, Unknown)

- Arrhythmia type (Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular tachycardia)

- Pacemaker/Implantable Cardioverter Defibrillator (ICD) (No, Yes, Unknown)
  - Device type (Pacemaker, Cardiac resynchronization therapy - no ICD [CRT-P], Cardiac resynchronization therapy - with ICD [CRT-D], ICD only [single/dual chamber], Unknown)
- Moderate to severe valvular heart disease (No, Yes, Unknown)
  - Valvular heart disease type (Mitral regurgitation, Aortic regurgitation, Aortic stenosis, Tricuspid regurgitation, Other)
- Prior valvular surgery (No, Yes, Unknown)
  - Valvular surgery type (Mitral, Aortic, Tricuspid, Pulmonic)

Non-cardiovascular medical history

Non-cardiovascular medical history will be summarized and listed. The summary will be presented by primary system organ class (SOC) and preferred term (PT). Non-cardiovascular medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v21.0 or higher).

Surgeries and Medical Procedures

Surgeries and medical procedures will be listed. Surgeries and medical procedures will be coded using MedDRA terminology (v21.0 or higher).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SS will be used for all analyses associated with study treatment and medications, unless otherwise specified.

2.4.1 Study treatment / compliance

The duration of study treatment is defined as:

Duration (days) = (date of last study treatment – date of first study treatment) +1

The dates of first and last study treatment are defined in Section 2.1.1.

Summary statistics will be displayed for the duration of study treatment.

The duration of study treatment will also be categorized into 90-day time intervals (<90, 90 - <180, 180 - <270, ≥270 days.). The number and percentage of patients in each category will be presented.

Total patient-days of exposure will also be summarized.

In addition, the number and percentage of patients at each dose level dispensed by visit will be summarized. The number and percentage of the maximum dose level dispensed will also be presented. Similarly, the up-titrated doses, down-titrated doses and unchanged doses will be summarized by visit.

All information on dose administration will be listed.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Reference List (v2017 Mar or later). Prior and concomitant medications are mutually exclusive, as defined below:

- A prior medication is defined as any medication with an end date prior to the first dose of study treatment.
- A concomitant medication is defined as any medication taken on or after the start of study treatment. A prior medication that is 'ongoing' at the time of the first study treatment or whose end date is after first study treatment will be considered a concomitant medication.

The number and percentage of patients with prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term (PT). Separate summaries of prior CV, HF, ACEi, and ARB medications will also be produced. Concomitant medications will be summarized in a similar fashion. All medications will be listed.

The number and percentage of patients will be summarized by ACEi/ARB status (ACEi/ARB naïve [never exposed], previously on ACEi/ARB but not currently taking [previously exposed], and currently taking) at screening.

In addition, among patients with concomitant use of beta-blocking agents (based on ATC class C07) the total daily dose achieved at one year will be calculated. The total daily beta blocker (BB) dose will be converted to an equivalent total daily dose of metoprolol succinate extended release (Gaggin 2014) as described below. The total daily dose in equivalent mg of metoprolol succinate extended release will be calculated for each BB by multiplying the BB total daily dose (mg) by the standardization factor in the table below. For patients without concomitant use of beta-blocking agents at one year, the total daily dose in equivalent mg of metoprolol succinate extended release will be set to 0 for purposes of analysis.

Beta Blocker	**Standardization Factor**
atenolol	2
bisoprolol, bisopropol fumarate	20
carvedilol, carvedilol phosphate hemihydrate	4
labetalol	0.25
metoprolol tartrate immediate release, metoprolol tartrate, metoprolol, metoprolol succinate	1.0
nadolol	0.833
propranolol	0.833
sotalol	0.833
nebivolol hydrochloride	10

The resulting standardized BB dose (metoprolol succinate extended release equivalent dose) will be summarized with descriptive statistics and categorized into dose groups in two ways:

- As five discrete dose groups (Fiuzat, 2016) having total daily dose = 0, 1 to 13, 14 to 25, 26 to 50, and 51 to 200 mg
- As three discrete dose groups, having total daily dose = 0, 1 to 24, and ≥25 mg.

The number and percentage of patients in each category will be presented.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoints are the change in concentration of NT-proBNP from baseline to one year, and the changes in structural cardiac measurements LVESVi, LVEDVi, LVEF, LAVi, and diastolic function (E/E') from baseline to one year. The analysis of the primary endpoints will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed NT-proBNP and each structural cardiac measurement (LVESVi, LVEDVi, LVEF, LAVi, and E/E') from baseline to one year.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

2.5.4 Supportive analyses

Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed NT-proBNP and each structural cardiac measurement from baseline to one year using the last observation carried forward (LOCF) method used to impute missing data at one year. In particular, if the NT-proBNP value or the structural cardiac measurement value is missing at one year, then the NT-proBNP and structural cardiac measurement values at 6 months, if both available, will be carried forward.

Spearman correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed NT-proBNP and each structural cardiac measurement from baseline to one year.

Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed NT-proBNP and each structural cardiac measurement from baseline to one year where baseline for the structural cardiac measurements will be defined as:

- The last non-missing assessment prior to or on the date of first administration of study treatment.

- The nominal Visit 2 (Baseline) assessment, regardless of when it occurred relative to the date of first administration of study treatment.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary objectives

2.7.1 Secondary endpoints

Secondary endpoints include the following:

1. Change in concentration of NT-proBNP from baseline to 6 months
2. Change in LVESVi, LVEDVi, LVEF, LAVi, and E/E' from baseline to 6 months
3. Change in KCCQ-23 clinical summary score from baseline to 12 months

2.7.2 Statistical hypothesis, model, and method of analysis

Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed NT-proBNP and LVESVi, LVEDVi, LVEF, LAVi, and E/E' from baseline to 6 months.

An analysis of variance will be performed to compare the mean change in the KCCQ-23 clinical summary score between the groups of patients with NT-proBNP<1000 pg/mL and ≥1000 pg/mL at one year (i.e., NT-proBNP status). It is likely that groups defined in this way will be different with respect to characteristics that are also associated with the KCCQ-23 clinical summary score.

In order to assess the relative imbalance between NT-proBNP status groups with respect to characteristics that may be associated with the KCCQ-23 clinical summary score, key characteristics of interest will be summarized descriptively. These characteristics include baseline KCCQ-23 clinical summary score, age (<75, ≥75 years), baseline LVEF (≤median, >median) from echo, baseline eGFR (≤median, >median), primary HF etiology (ischemic, non-ischemic), prior AF, and standardized BB dose achieved at one year (0, 1 to 24, ≥25 mg).

Multivariable regression will be used to compare the mean change in KCCQ-23 clinical summary score between the NT-proBNP status group, accounting for these characteristics by including them as covariates in the model.

2.7.3 Handling of missing values

For the analysis of secondary endpoints, if a patient has no post-baseline value at the given time point (6 months or one year), the missing value will not be imputed and the patient will be removed from the analysis.

2.8 Safety analyses

Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data.

2.8.1 Adverse events (AEs)

2.8.1.1 Coding of AEs

Adverse events (AEs) will be coded using MedDRA terminology (v21.0 or later).

2.8.1.2 General rules for AE reporting

AE summaries will include all treatment-emergent AEs (TEAEs). TEAEs are defined as AEs starting on or after the first day of study treatment. All AEs will be listed. AEs starting prior to the first day of study treatment (non-TEAEs) will be flagged in the listings.

All TEAEs will be summarized.

TEAEs will be summarized by presenting the number and percentage of patients having at least one TEAE, having at least one TEAE in each primary SOC, and for each PT using MedDRA terminology. A patient with multiple occurrences of a TEAE will be counted only once in the AE category.

Separate summaries will be presented by SOC, PT, and severity. A patient with multiple severities for an AE will be summarized under the worse severity recorded for the event.

Any information collected will be listed as appropriate.

2.8.1.3 AE summaries

The following summary tables will be provided:

- AEs, regardless of study treatment relationship, by primary SOC, PT, and worst severity
- Most frequent (≥5%) AEs, regardless of study treatment relationship, by PT
- Most frequent (≥5%) non-serious AEs, regardless of study treatment relationship, by PT
- AEs, suspected to be related to study treatment, by primary SOC and PT
- Serious adverse events (SAEs), regardless of study treatment relationship, by primary SOC and PT
- SAEs, suspected to be related to study treatment, by primary SOC and PT
- SAEs occurring with a frequency of ≥0.5%, regardless of study treatment relationship, by PT
- SAEs, regardless of study treatment relationship, by primary SOC, PT, and seriousness criteria
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT

- Death resulting from AEs, regardless of study treatment relationship, by primary SOC and PT

In addition, an overview of TEAEs presenting the number and percentage of patients having at least one TEAE for each of the above categories will be provided.

2.8.2 Deaths

Patient deaths will be summarized by primary SOC and PT, as well as by primary cause of death, type of cardiovascular death, type of non-cardiovascular death, and whether an autopsy was performed. A patient listing of all deaths with primary and contributing reasons for death will be provided. All patients in FAS will be included for the above analysis. Deaths will be coded using MedDRA terminology (v21.0 or later).

In addition, occurrences of resuscitated sudden death will be summarized based on the SS. The number and percentage of patients actively resuscitated will be presented.

2.8.3 Laboratory data

Laboratory values will be summarized using shift tables (from baseline to most extreme post-baseline value) for each laboratory parameter. The number and percentage of patients will be presented by baseline and worst post-baseline lab value, with lab values classified as low, normal, high, and low/high using the upper and lower limit of normal values to define categories. Unscheduled assessments will be considered.

In addition, laboratory values and the change from baseline for each parameter by visit will be summarized. In the event there are multiple laboratory values within a visit, the worst value will be summarized.

A separate summary table will be presented with the number and percentage of patients having notable lab abnormalities based on percent change from baseline (see Section 5.3 for a list of notable laboratory abnormalities). Unscheduled assessments will be considered.

Listings of all laboratory values will be provided. A separate listing for pregnancy tests will be provided. Any notable laboratory abnormalities will be flagged in the listings.

Laboratory values indicated as $<x$ will be converted to $(0.5)(x)$ for purposes of analysis. Laboratory values indicated as $>x$ will be converted to the values specified in the below table for purposes of analysis.

Laboratory Test	Unconverted Value	Converted Value for Analysis
Erythrocytes	>7.00	7.1
HDL Cholesterol	>135	135.1
Hemoglobin A1C	>15.5	15.51
Potassium	>7.0	7.1
Urine Erythrocytes	>182	182.1
Urine Leukocytes	>182	182.1

2.8.4 Echocardiographic data

Echocardiographic parameters (LVESVi, LVEDVi, LVEF, LAVi, and E/E') will be summarized by visit. Values and the change from baseline for each parameter by visit will be summarized. Change from baseline at visits will be analyzed using a repeated measures ANCOVA model with visit as a fixed-effect factor and the baseline value as a covariate. An unstructured covariance structure will be initially considered. The change from baseline estimates, corresponding two-sided 95% confidence intervals, and p-values will be provided at each post-baseline visit.

2.8.5 Other safety data

2.8.5.1 Vital signs

All vital signs (systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiration rate [breaths per minute], weight [kg], height [cm], and BMI [kg/m^2]) will be descriptively summarized at each visit. Change from baseline will also be presented. Note that height is only collected at Visit 1.

A separate summary table will be presented with the number and percentage of patients having notable vital signs based on changes relative to baseline values (see Section 5.4 for a list of notable vital signs). In addition, the number and percentage of patients with hypotension (SBP <90 mmHg) will be presented. Unscheduled assessments will be considered.

2.8.5.2 Symptomatic Hypotension

The number and percentage of patients experiencing significant and/or non-resolving symptoms of lightheadedness, dizziness, feeling faint, blurred vision, auditory disturbances, emesis, or syncope will be presented by visit. The following characteristics will be summarized for patients experiencing one or more of these symptoms:

- Whether symptoms occur only with standing
- Treatment or medication change as a result of episode
- Lowest documented systolic blood pressure with this episode
- Systolic blood pressure position (Supine, Seated, Standing)
- Lowest documented diastolic blood pressure with this episode
- Diastolic blood pressure position (Supine, Seated, Standing)

2.8.5.3 Hyperkalemia

The number and percentage of patients reporting a hyperkalemia episode as an AE or SAE will be presented by visit. The highest potassium value for each event will be summarized. This will be based on data collected from the Hyperkalemia Labs eCRF.

The number and percentage of patients with hyperkalemia during the study will be determined from the central laboratory data as potassium >5.3 mEq/L. Unscheduled assessments will be considered.

2.8.5.4 Creatinine

The number and percentage of patients reporting an elevated creatinine event as an AE or SAE will be presented by visit. The highest creatinine recorded for each event will be summarized. This will be based on data collected from the Creatinine Labs eCRF.

The number and percentage of patients with worsening renal function during the study will be determined from the central laboratory data as a worsening (decrease) in eGFR of ≥35% from baseline, or an increase in creatinine of ≥0.5 mg/dL from baseline and a worsening (decrease) in eGFR of ≥25% from baseline. Unscheduled assessments will be considered.

2.8.5.5 Pregnancy

Among patients able to bear children, the number and percentage of patients assessed with a urine pregnancy test will be presented. Pregnancy test results (Negative, Positive, Unknown) will be summarized.

2.8.5.6 Heart Failure (HF) Signs and Symptoms

The number and percentage of patients in the following heart failure signs and symptoms categories will be summarized by visit:

- NYHA classification (Class I, Class II, Class III, Class IV)
- Paroxysmal nocturnal dyspnea (Absent, Present)
- Dyspnea at rest (Absent, Present)
- Dyspnea upon effort (Absent, Present)
    - Dyspnea category (Mild, Moderate, Severe)
- Fatigue (Absent, Present)
- Orthopnea (Absent, Present)
    - Orthopnea category (1 pillow [10 cm elevation], 2 pillows [20 cm elevation], >2 pillows [>20 cm elevation])
- Jugular venous distention (Absent, Present, Not Available)
    - Jugular venous distension category (<6 , 6 to 10, >10 cm)
- Edema (Absent, Trace, Feet and Ankles, Lower Legs or Thighs, Sacrum)
    - Edema category (Trace, 1+, 2+, 3+)
    - Feet and ankles (No, Yes)
    - Lower legs or thighs (No, Yes)
    - Sacrum (No, Yes)
- Rales (Absent, Present)
    - Rales category (<1/3, 1/3 to 2/3, >2/3)
- Presence of a third heart sound (Absent, Present, Not Available)

2.8.5.7 Angioedema

Data collected from the angioedema assessment and questionnaire will be summarized. Separate summaries will be produced for suspected angioedema and positively adjudicated angioedema. The number and percentage of patients for categorical variables and summary statistics for continuous variables for the following angioedema assessment data will be presented.

- Outcome (Not recovered/Not resolved, Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Fatal, Unknown)
    - Duration of angioedema in days [*end date – start date + 1*]
- Timing of event (After first dose, after multiple doses, dose not given) [not asked for events that occurred during Screening study phase]
    - Study medication discontinued due to event (No, Yes)
    - Event occurred within 1 day of dosing (Within 1 day of dose but less than or equal to 1 hour, within 1 day of dose but greater than 1 hour, After 1 day of dosing, Unknown)
- History of prior angioedema or angioedema like event (No, Yes, Unknown)
    - If yes, medications taken at time of previous event:
        - ACE inhibitor
        - ARB
        - Renin inhibitor
        - Other medications
- Presence of hereditary angioedema (No, Yes, Unknown)
- Any family members with history of angioedema-like events (No, Yes, Unknown)
- Signs and symptoms for current event
    - Shortness of breath/dyspnea
    - Difficulty swallowing/dysphagia
    - Difficulty speaking/dysarthria
    - Pain on swallowing/odynophagia
    - Stridor
    - Abdominal pain
    - Other
- Edema present (No, Yes)
    - Periorbital edema
    - Head edema

  - Neck edema
  - Lip edema
  - Tongue edema
  - Throat edema
  - Submandibular edema
  - Genitalia edema
  - Extremities edema
  - Other
- Previous edematous episodes (No, Yes, Unknown)
  - Number of previous edematous episodes
- ACEi taken in the past (before screening) (No, Yes, Unknown)
- ACEi taken (other than study medication) during trial participation after screening (No, Yes, Unknown)
  - Dose changed within 2 days of event (No, Yes, Unknown)
- ARB taken in the past (before screening) (No, Yes, Unknown)
- ARB taken (other than study medication) during trial participation after screening (No, Yes, Unknown)
  - Dose changed within 2 days of event (No, Yes, Unknown)
- Patient suffering from influenza, common cold or upper respiratory tract infection? (No, Yes, Unknown)
- Medication allergies (No, Yes, Unknown)
- Food allergies (No, Yes, Unknown)
- Potential causes of angioedema-like event
  - Food
  - Insect bite
  - Animal exposure
  - Medication
  - Dental work
  - Pollen
  - Dust
  - Concomitant disease
  - Idiopathic

- Other

- Medical intervention (No, Yes)
  - Administration of H-1 blocker
  - Administration of H-2 blocker
  - Administration of steroids
  - Administration of epinephrine
  - Admission to hospital
  - Admission to ER
  - Endotracheal intubation
  - Tracheostomy
  - Discontinuation of ACE inhibitor (other than study medication)
  - Discontinuation of ARB (other than study medication)
  - Other

All angioedema assessment data will be listed. Additionally, the adjudicated assessment of the event will be listed separately.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

Not applicable

2.11 Patient-reported outcomes (PRO)

All analyses will be performed on the FAS.

2.11.1 Kansas City Cardiomyopathy Questionnaire

The KCCQ-23 is a self-administered questionnaire consisting of 23 items (Green et al 2000), each with different Likert scaling, that quantifies disease-specific health status for patients with congestive heart failure. The KCCQ-23 is scored within the domains of physical limitation, symptom frequency, symptom severity, symptom stability, self-efficacy and knowledge, social limitation, and quality of life (QoL). Scores from each domain are transformed to a 0-100 scale. The clinical summary score is calculated by combining the physical limitation, symptom frequency, symptom severity, social limitation, and QoL domains.

Missing values within each domain will be imputed using the average of the answered items within the same domain. Scale scores will be transformed into values of 0 to 100 by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100. Further details on calculation of the transformed scores are available in the programming

specifications section of the SAP Tables, Figures, and Listings (TFL) Shells document. All analysis will be based on the transformed score.

Values and the change from baseline in the composite score for each domain, clinical summary score, and an overall summary score will be summarized by visit. Change from baseline at visits will be analyzed using a repeated measures ANCOVA model with visit as a fixed-effect factor and the baseline value as a covariate. An unstructured covariance structure will be initially considered. The change from baseline estimates, corresponding two-sided 95% confidence intervals, and p-values will be provided at each post-baseline visit.

The above analysis will be performed for the clinical summary score within the subgroups defined for the secondary objective in Section 2.2.1.

For patients who die, a worst score (score of 0) will be imputed for the domain scores and clinical and overall summary scores at all subsequent scheduled visits after the date of death where these scores would have been assessed.

Additional KCCQ-23 analyses are described in Section 2.7.

2.12 Biomarkers

The standard or more stable MOA biomarkers, assessed in the full patient population, include NT-proBNP, hs-Troponin T, sST2, UcGMP, and UcGMP to Urinary Creatinine ratio. Values and the change from baseline for each biomarker will be summarized by visit. Analyses will be based on the FAS.

Labile MOA biomarkers, collected only in the subset (N = up to 300) of patients in the biomarker sub-study, include BNP#1 (Alere), BNP#2 (Abbott), and BNP#3 (Siemens) (i.e., BNP assessed with three different assays) and Mid-regional pro-adrenomedullin. Values and the change from baseline for each biomarker will be summarized by visit. Analyses will be based on the BSS.

Change from baseline in biomarkers at visits will be analyzed using a repeated measures ANCOVA model with visit as a fixed-effect factor and the baseline value as a covariate. An unstructured covariance structure will be initially considered. The change from baseline estimates, corresponding two-sided 95% confidence intervals, and p-values will be provided at each post-baseline visit.

Biomarker values will be based on clinical laboratory samples processed and assessed by the central laboratory. Values below the limit of detection (LOD) (i.e., indicated as <LOD) will be converted to (0.5)(LOD) for purposes of analysis.

Biomarker samples from patients who withdrew consent will not be analyzed by the central laboratory.

Any other biomarkers collected but not specifically mentioned in these sections will be analyzed in the same manner.

Due to the timing of receipt of data for ANP, results for this exploratory labile biomarker will be reported separately from the biomarkers metioned above.

2.13 Other Exploratory analyses

All analyses will be based on the FAS unless otherwise specified.

Exploratory variables (changes from baseline, unless otherwise indicated) include the following:

1. Concentration of other standard efficacy, HF prognosis, or MOA biomarkers collected in the full patient population (i.e., hs-Troponin T, sST2, UcGMP, and UcGMP to Urinary Creatinine ratio) at 3 months, 6 months, and 1 year; and concentration of NT-proBNP at 3 months.
2. Echocardiographic variables at 3 months, 6 months, and 1 year, including LVESVi, LVEDVi, LVEF, LAVi, and E/E.
3. Total CV events during the follow up period of one year. The CV events include:
   a. Worsening heart failure (WHF)
   b. Heart failure hospitalization
   c. CV death
4. Total CV deaths and heart failure hospitalizations during the follow up period of one year.
5. Concentration of labile biomarkers, value and change from baseline in the subset of patients (N = up to 300) with collected and processed samples.
6. Time to an NT-proBNP value of ≤1000 pg/mL (time to response).
7. Time spent with an NT-proBNP value ≤1000 pg/mL (time in response) during one year of follow up.

Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed concentration of the more stable biomarkers (exploratory variables 1) and echocardiographic variables (exploratory variables 2) from baseline to 3 months, 6 months, and one year.

Spearman correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between total number of events (CV events – exploratory variable 3; CV deaths and heart failure hospitalizations – exploratory variable 4) and the change in log-transformed biomarkers (exploratory variables 1) from baseline to one year.

Spearman correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between the total number of events (CV events – exploratory variable 3; CV deaths and heart failure hospitalizations – exploratory variable 4) and the change in echocardiographic variables (exploratory variables 2) from baseline to one year.

The total number of events (CV events – exploratory variable 3; CV deaths and heart failure hospitalizations – exploratory variable 4) during the follow up period of one year will be summarized for patients with a baseline NT-proBNP value >1000 pg/mL who achieve an NT-proBNP value ≤1000 pg/mL at any point during the following time periods (separately):

baseline to 3 months, baseline to 6 months, and baseline to one year. The total number of events will also be summarized for patients with a baseline NT-proBNP value >1000 pg/mL who achieve an NT-proBNP value ≤1000 pg/mL at 3 months, at 6 months, and at one year, separately. The total number of CV deaths and heart failure hospitalizations (exploratory variable 4) will be summarized in a similar fashion for patients with a baseline NT-proBNP value >1000 pg/mL who achieve an NT-proBNP value ≤1000 pg/mL, or who have >30% reduction from baseline in NT-proBNP. Unscheduled NT-proBNP assessments will not be considered.

The time to an NT-proBNP value of ≤1000 pg/mL ("time to response" – exploratory variable 6) for patients with a baseline NT-proBNP value >1000 pg/mL, as well as the time spent with an NT-proBNP value ≤1000 pg/mL ("time in response" – exploratory variable 7), during one year of follow up, will be calculated for patients with and without an event (CV events – exploratory variable 3; CV deaths and heart failure hospitalizations – exploratory variable 4). Unscheduled NT-proBNP assessments will not be considered.

Time in response will be estimated using NT-proBNP values assessed during follow up by assuming either no change in value between assessments (i.e., assuming a piecewise-constant concentration profile) or by employing linear interpolation between assessments to estimate values and response status. Unscheduled NT-proBNP assessments will not be considered.

In the subset of patients (N = up to 300) with collected and processed samples for labile MOA biomarkers (the BSS):

- Concentration of BNP#1, BNP#2, BNP#3 (exploratory variables 5) – value and change from baseline at each visit will be summarized (also see Section 2.12). The value and change from baseline at each visit will also be summarized for the subset of patients who have change from baseline values for all 3 BNP assays at the given visit.
- Concentration of other labile MOA biomarker Mid-regional pro-adrenomedullin (exploratory variables 5) – value and change from baseline at each visit will be summarized (also see Section 2.12).
- Change in concentration of each BNP assay (exploratory variables 5) from last-to-present interim visit will be summarized at each visit. The value and change from last-to-present at each visit will also be summarized for the subset of patients who have change from last-to-present values for all 3 BNP assays at the given visit.
- Pearson correlation coefficients and the corresponding two-sided 95% confidence intervals and p-values will be calculated to examine the association between change in log-transformed concentration of labile MOA biomarkers (exploratory variables5) and echocardiographic variables (exploratory variables 2) from baseline to 3 months, 6 months, and one year.

2.14 Interim analysis

Not applicable.

3 Sample size calculation

The objective of this study is to estimate the correlation coefficient between change in log NT-proBNP and each structural cardiac measurement overall and in each subgroup of interest. We would like to estimate the correlation coefficient with a precision (half-width of the confidence interval (CI)) of at least 0.15 for a 2-sided 95% CI in the intended subgroups of interest. The subgroups of interest are: (1) patients with HFrEF and "low" NT-proBNP (<600 if not hospitalized or <400 if hospitalized) or "low" BNP (<150 if not hospitalized, <100 if hospitalized) at baseline (Ambrosy, 2012), (2) patients with new onset HF and/or RAAS naïve (Fonarow, 2010), and (3) patients who are not receiving the target sacubitril/valsartan dose (McMurray, 2014). It is estimated that these subgroups will represent approximately 25%, 20% and 30% of the study population, respectively. Assuming, the population correlation coefficient of -0.35 (Weiner, 2013) for the overall study sample and within each subgroup, the smallest sample size that would yield a precision of at least 0.15 for the estimated correlation coefficient would be n=133. Accounting for assumed 20% drop-out rate, 166 patients would be required. If the n=166 was the smallest subgroup of interest (20% of the overall study population), an overall sample size of 830 would be required to enroll in this study. For any other subgroup with more than 166 patients will yield precision smaller than 0.15 for the estimated correlation coefficient. For the overall sample size of N=830 patients the precision of the estimate of correlation coefficient would be 0.07 (PASS 2008).

4 Change to protocol specified analyses

As of finalization of initial version of SAP dated 09-May-2017

The following changes to protocol specified analyses (relative to protocol version 01 [amended protocol] dated 23-Sep-2016) were made:

- Diastolic function, E/E', is included in the primary endpoint for analyses, in addition to the other echocardiographic measures specified in the protocol.
- The analysis of CV events and echocardiographic parameters is not included in the analyses specified in the protocol.
- The following subgroups for the primary analysis were not included in the protocol.
    - Age group (<75 years, ≥75 years)
    - NYHA class at baseline (I and II, III and IV)
    - AF at baseline (No, Yes)
    - Baseline BMI (<30 kg/m^2, ≥30 kg/m^2)
- The analysis of Pearson's correlation coefficient to examine the association between both concentration value and change from baseline in concentration of the more stable biomarkers (exploratory variables 1) and echocardiographic variables and LVEF (exploratory variables 2) at three months is now included with other exploratory analyses in Section 2.13.

As of finalization of SAP amendment 1 dated 22-Feb-2019

The following changes to protocol specified analyses (relative to protocol version 03 [amended protocol] dated 27-Feb-2018) were made:

- Modified baseline definitions for biomarkers and echocardiographic variables to account for assessments performed post first dose of study treatment
- Added the following subgroups for the analysis of the primary objective:
    - Baseline NT-proBNP <125 pg/mL (No, Yes)
    - Groups defined by quartiles of baseline estimated glomerular filtration rate (eGFR)
    - Prior diabetes (No, Yes)
    - Prior ACEi/ARB (No [naïve], Yes)
- Added two supportive analyses of the primary objective based on the following alternative baseline definitions for echocardiographic variables:
    - The last non-missing assessment prior to or on the date of first administration of study treatment
    - The nominal Visit 2 (Baseline) assessment, regardless of when it occurred relative to the date of first administration of study treatment
- Removed optional sensitivity analysis of KCCQ-23 clincial summary score change from baseline at one year using propensity score stratification
- Specified repeated measures analysis of change from baseline for echocardiographic variables, biomarkers, and KCCQ-23 domains/scores
- Added descriptive summary of patients with hypotension
- Added separate descriptive summaries of patients with hyperkalemia or worsening renal function, based on central laboratory data
- Added subgroup analyses of KCCQ-23 clinical summary score change from baseline at one year
- Clarified that, due to the timing of receipt of data from ANP, results for this exploratory labile biomarker will be reported separately from the other biomarkers
- Added analysis of new exploratory endpoint defined as total CV deaths and heart failure hospitalizations
- Added summary of number of events at 3 months, at 6 months, and at one year
- Modified analysis of the association between number of events and biomarkers and echocardiographic variables to present Spearman (instead of Pearson) correlation coefficients
- Added summary of change from baseline and change from last-to-present at each visit for the subset of patients who have change from baseline or change from last-to-present values, respectively, for all 3 BNP assays at the given visit

- Added summary of positively adjudicated angioedema
- Clarified that subgroup defined by NT-proBNP concentration ≤1000 pg/mL at Month 12 is determined in patients with baseline NT-proBNP >1000 pg/mL
- Added new subgroup defined by NT-proBNP concentration ≤1000 pg/mL at Month 12 for patients with baseline NT-proBNP >1000 pg/mL, or >30% reduction from baseline in NT-proBNP at Month 12
- Added summary of total number of CV deaths and heart failure hospitalizations for patients with baseline NT-proBNP value >1000 pg/mL who achieve an NT-proBNP value ≤1000 pg/mL, or who have >30% reduction from baseline in NT-proBNP

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Full dates for study treatment collected on the eCRF are required; therefore, no imputations will be made.

5.1.2 AE date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

Missing day and month

- If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.

- If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.

- If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.

Missing month only

- Treat day as missing and replace both month and day according to the above procedure.

Missing day only

- If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.

- If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.

- If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

Missing year

- Date left missing.

Missing month

- Impute ‘December’.

Missing day

- Impute ‘last date of that month’.

5.1.3 Concomitant medication date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

Missing day and month

- If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.

- If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.

- If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.

Missing month only

- Treat day as missing and replace both month and day according to the above procedure.

Missing day only

- If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.

- If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.

- If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

Missing year

- Date left missing. Consider the medication to have been received at all periods after that period determined by the start date.

Missing month

- Impute 'December'.

Missing day

- Impute 'last date of that month'.

5.1.4 Heart failure diagnosis date imputation

The following algorithm should be used to estimate the heart failure diagnosis date for which only partial information is known:

Missing day and month

- January 1 will be assigned to the missing fields.

Missing month only

- Treat day as missing and replace both month and day according to the above procedure.

Missing day only

- Assign first of the month to the missing day.

5.2 AEs coding/grading

The UBC coding team will code the AE terms using MedDRA v21.0 or later. If any terms are not coded, the data management team will issue queries to sites to update the AE term appropriately.

5.3 Laboratory parameters derivations

5.3.1 Laboratory grading

The collected laboratory values will be summarized by severity (low/normal/high) and not converted to Common Terminology Criteria for Adverse Events (CTCAE) grades.

5.3.2 Notable laboratory values

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase

AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease

5.4 Vital signs

5.4.1 Notable vital sign values

Systolic blood pressure	<90 mmHg and decrease of >20 mmHg from baseline
	>180 mmHg and increase of >20 mmHg from baseline
Diastolic blood pressure	<50 mmHg and decrease of >15 mmHg from baseline
	>105 mmHg and increase of >15 mmHg from baseline
Pulse	<50 bpm and decrease of > 15 bpm from baseline
	>120 bpm and increase of >15 bpm from baseline
Weight	>7% decrease; >7% increase

5.5 Statistical models

5.5.1 Primary analysis

The Pearson product-moment correlation, ρ_{xy}, between variables X and Y for a population is defined by

$$\rho_{xy} = \frac{\mathrm{Cov}(x,y)}{\sqrt{\mathrm{V}(x)\mathrm{V}(y)}} = \frac{\mathrm{E}(\,(x-\mathrm{E}(x))(y-\mathrm{E}(y))\,)}{\sqrt{\mathrm{E}(x-\mathrm{E}(x))^2\,\mathrm{E}(y-\mathrm{E}(y))^2}}$$

The sample correlation is expressed in terms of the sample means of x and y as

$$r_{xy} = \frac{\sum_i (\,(x_i-\bar{x})(y_i-\bar{y})\,)}{\sqrt{\sum_i (x_i-\bar{x})^2\,\sum_i (y_i-\bar{y})^2}}$$

The Spearman rank-order correlation is expressed in terms of the ranks, R_i and S_i (and their respective means) of x_i and y_i , as

$$\theta = \frac{\sum_i (\,(R_i-\bar{R})(S_i-\bar{S})\,)}{\sqrt{\sum_i (R_i-\bar{R})^2\,\sum (S_i-\bar{S})^2}}$$

The SAS CORR procedure will be used to estimate Pearson and Spearman correlation coefficients, and their two-sided 95% CIs (refer to the TFL Shells document for additional details).

5.6 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause patients to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
NA	NA	NA

Table 2 Patient Classification

Analysis Set	Protocol Deviation ID that cause patients to be excluded	*Non-PD criteria that cause* patients to be excluded
TS	NA	Not enrolled at Visit 2
FAS	NA	Not in TS
SS	NA	No study treatment received

6 Reference

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