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Trial Design

Rationale and design of the comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial

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ABSTRACT

Objective: The objective is to assess the safety, tolerability, and efficacy of sacubitril/valsartan compared with enalapril in patients with heart failure (HF) with a reduced ejection fraction (EF) stabilized during hospitalization for acute decompensated HF.

Background: Sacubitril/valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor, improves survival among ambulatory HF patients with a reduced EF. However, there is very limited experience with the in-hospital initiation of sacubitril/valsartan in patients who have been stabilized following hospitalization for acute decompensated HF.

Methods: PIONEER-HF is a 12-week, prospective, multicenter, double-blind, randomized controlled trial enrolling a planned 882 patients at more than 100 participating sites in the United States. Medically stable patients ≥18 years of age with an EF ≤40% and an amino terminal-pro b-type natriuretic peptide ≥1600 pg/mL or b-type natriuretic peptide ≥400 pg/mL are eligible for participation no earlier than 24 hours and up to 10 days from initial presentation while still hospitalized. Patients are randomly assigned 1:1 to in-hospital initiation of sacubitril/valsartan titrated to 97/103 mg by mouth twice daily versus enalapril titrated to 10 mg by mouth twice daily for 8 weeks. All patients receive open-label treatment with sacubitril/valsartan for the remaining 4 weeks of

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Registration of randomized clinical trial

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the study. The primary efficacy end point is the time-averaged proportional change in amino terminal-pro b-type natriuretic peptide from baseline through weeks 4 and 8. Secondary and exploratory end points include serum and urinary biomarkers as well as clinical outcomes. Safety end points include the incidence of angioedema, hypotension, renal insufficiency, and hyperkalemia.

Conclusion: The PIONEER-HF trial will inform clinical practice by providing evidence on the safety, tolerability, and efficacy of in-hospital initiation of sacubitril/valsartan among patients who have been stabilized following an admission for acute decompensated HF with a reduced EF.

Heart failure (HF) is a global pandemic with an estimated worldwide prevalence of 38 million patients.[1,2] In the United States alone, there are more than 1 million admissions for HF as a primary diagnosis per year, representing 1%-2% of all hospitalizations.[3,4] In addition, the early postdischarge mortality and readmission rates have remained unchanged and may be as high, respectively, as 15% and 30% within 60-90 days.[5] Despite numerous promising clinical development programs, there have been relatively few major breakthroughs in the management of HF in the acute setting, and the cornerstone of therapy remains intravenous (IV) diuretics, vasodilators, and less commonly inotropes.[6]

The **P**rospective comparison of an **AR**Ni with an **A**cei to **D**etermine the **I**mpact on **G**lobal **M**ortality and morbidity in **H**eart **F**ailure (PARADIGM-HF) trial showed that compared with enalapril, sacubitril/valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor (ARNi),[7] led to a robust 20% relative risk reduction in cardiovascular (CV) mortality and hospitalization for worsening HF among ambulatory HF patients with an ejection fraction (EF) ≤40% (ie, changed to ≤35% by an amendment to the protocol midtrial) and New York Heart Association functional class II-IV symptoms.[8,9] In response, the American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines were updated in 2016 to recommend as follows: In patients with chronic symptomatic HF with reduced EF, New York Heart Association class II or III, who tolerate an angiotensin converting-enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), replacement by an ARNi is recommended to further reduce morbidity and mortality.[10]

Despite the impressive results seen in the PARADIGM-HF trial, there is a more limited experience with sacubitril/valsartan in patients hospitalized for acute decompensated HF and patients with severe signs and symptoms of HF.[8,9] Approximately 40% of study participants had no prior history of hospitalization for HF, and only 15% of patients were admitted for a primary diagnosis of HF over the entire duration of the study. In addition, less than 1% of patients (n = 60) enrolled in the PARADIGM-HF trial reported New York Heart Association functional class IV symptoms at baseline. Thus, the goal of the com**P**ar**I**son **O**f sacubitril/valsarta**N** versus **E**nalapril on **E**ffect on nt-p**R**o-bnp in patients stabilized from an acute **H**eart **F**ailure episode (PIONEER-HF) trial is to generate new evidence for in-hospital initiation of sacubitril/valsartan and evaluate the safety and potential role of this new therapy in medically stable patients hospitalized for acute decompensated HF with a reduced EF.

Methods

Overview

PIONEER-HF is a prospective, multicenter, double-blind, randomized controlled trial designed to assess the safety, tolerability, and efficacy of in-hospital initiation of sacubitril/valsartan compared with enalapril in patients with HF with a reduced EF stabilized during hospitalization for acute decompensated HF. Planned enrollment of 882 patients will occur at approximately 140 participating centers in the United States. Patients ≥18 years of age with an EF ≤40% and an amino terminal-pro b-type natriuretic peptide (NT-proBNP) ≥1600 pg/mL or b-type natriuretic peptide (BNP) ≥400 pg/mL are eligible for enrollment irrespective of both the duration of diagnosis (ie, de novo and worsening chronic HF) and prior ACEi and/or ARB status. Patients are enrolled no earlier than 24 hours and up to 10 days from initial presentation while still hospitalized (Table I). Following appropriate management of the acute HF episode, all patients must be *medically stable* as defined by a systolic blood pressure ≥100 mm Hg for the preceding 6 hours, no increase (ie, intensification) in IV diuretics or use of IV vasodilators within the last 6 hours, and no IV inotropes administered for 24 hours prior to randomization. Patients who are currently or were recently prescribed sacubitril/valsartan; who have a history of hypersensitivity, known or suspected contraindications, and/or intolerance to ACEi/ARB/ARNi; or in whom the primary cause of dyspnea is suspected to be due to hemodynamically significant valvular disease or noncardiac causes (eg, acute or chronic respiratory disorders) are excluded from participation.

Treatment protocol and follow-up

The study protocol includes 5 phases: screening (day −10 through day −1), randomization (day 0), in-hospital study drug initiation (day 0 through discharge), outpatient dose titration and follow-up (weeks 1 through 8), and open-label sacubitril/valsartan (weeks 8 through 12) (Figure 1). During the in-hospital initiation phase, patients are randomized in a double-blind fashion 1:1 to sacubitril/valsartan versus enalapril. Patients randomized to enalapril receive the active study drug starting with the first dose, whereas patients randomized to sacubitril/valsartan receive 2 doses of placebo to ensure a minimum 36-hour washout period prior to initiation of ARNi therapy (Figure 2). The third dose is active study medication for all patients and is followed by 6 hours of monitoring for hypotension. Following this observation period, patients can be discharged from the hospital at any point in time at the discretion of the clinician-investigator.

During the outpatient dose titration and follow-up phase, patients continue to receive double-blind treatment with sacubitril/valsartan or enalapril. There are 3 available doses of study drug administered twice daily (Table II).

The starting dose during the in-hospital initiation phase and all subsequent dose changes during the double-blind treatment period are selected using a dose titration algorithm based on SBP (Figure 3). Clinician-investigators are encouraged to uptitrate sacubitril/valsartan to target dose (ie, dose level 3) as tolerated during the open-label phase. Follow-up visits are scheduled for weeks 1 and 2 and for every 2 weeks thereafter for the remainder of the 12-week study (Table III). Blood and urine samples are sent to a central laboratory for hematology, chemistry, and serum and urinary biomarkers. The last dose of blinded study drug is administered the morning of the week 8 visit. To provide a 36-hour washout in both treatment arms, open-label sacubitril/valsartan is started the following evening for the remaining 4 weeks of the study.

Study end points

The primary end point of PIONEER-HF trial is the time-averaged proportional change in NT-proBNP from baseline through weeks 4 and 8 (Table IV). Safety end points of special interest include the incidence of angioedema, symptomatic hypotension, renal insufficiency, and hyperkalemia. Any swelling or edema that may resemble angioedema

Table I
Inclusion and exclusion criteria

Inclusion criteria
• Patients >18 y of age with the capacity to provide written informed consent
• Currently hospitalized for a primary diagnosis of HF, including symptoms and signs of fluid overload
• Randomized no earlier than 24 h and up to 10 d after initial presentation while still hospitalized
• Stable as defined by an SBP >100 mm Hg for the preceding 6 h in the absence of symptomatic hypotension, no increase (ie, intensification) in IV diuretics or use of IV vasodilators within the last 6 h, and no IV inotropes for 24 h prior to randomization
• Left ventricular EF <40% within the past 6 m by echocardiography, MUGA, CT scanning, MRI, or ventricular angiography provided no subsequent study documented an EF >40%
• Elevated NT-proBNP >1600 pg/mL or BNP >400 pg/mL during the current hospitalization
Exclusion criteria
• Currently taking sacubitril/valsartan or any use within the past 30 d
• Enrollment in any other clinical trial involving an investigational agent or device
• History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs including ACEis, ARBs, or sacubitril (neprilysin inhibitor)
• Patient with a known history of angioedema related to previous ACEi or ARB therapy
• Requirement of treatment with both ACEi and ARB eGFR <30 mL/min/1.73 m^2 as measured by the simplified MDRD formula
• Serum potassium >5.2 mEq/L
• ACS, stroke, TIA, coronary or carotid revascularization, or major CV surgery within the past month
• Primary cause of dyspnea due to noncardiac, non-HF causes such as acute or chronic respiratory disorders
• Planned coronary or carotid revascularization within the next 6 m
• Implantation of cardiac resynchronization therapy within the past 3 m or intent to place
• Patients with a history of heart transplant, currently on the transplant list, or with an left ventricular device
• Isolated right HF due to severe pulmonary disease
• Documented untreated ventricular arrhythmia with syncopal episodes within the past 3 m
• Symptomatic bradycardia or second- or third-degree heart block without a pacemaker
• Presence of hemodynamically significant mitral, aortic, or hypertrophic obstructive cardiomyopathy
• History of malignancy or any organ system (other than localized and resectable skin cancers) within the past year with a life expectancy of less than 1 y
• Known hepatic impairment (as evidenced by total bilirubin >3 mg/dL or increased ammonia levels) or history of cirrhosis with evidence of portal hypertension (eg, presence of esophageal varices)
• Pregnant or nursing (lactating) women, where *pregnancy* is defined as the state of a female conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin test result
• *Women of child-bearing potential*, defined as all women physiologically capable of becoming pregnant unless they are using 2 birth control methods

SBP, Systolic blood pressure; *MUGA*, multigated acquisition scan; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *eGFR*, estimated glomerular filtration rate; *MDRD*, Modification of Diet in Renal Disease; *ACS*, acute coronary syndrome; *TIA*, transient ischemic attack.

or angioedema-like events is reviewed by a separate angioedema adjudication committee.[8,9] A secondary objective of PIONEER-HF is to measure change in biomarkers of NP system activation (eg, BNP:NT-proBNP ratio and urinary cyclic guanosine monophosphate), cardiac fibrosis/remodeling (eg, soluble suppressor of tumorigenicity 2), and tissue perfusion/injury (eg, high-sensitivity cardiac troponin). An exploratory objective of PIONEER-HF is to evaluate the time-to-first occurrence of the composite of death, hospitalization for worsening HF, left ventricular assist device implantation, listing for cardiac transplantation, unplanned emergency department or office visits requiring IV diuretics, and *intensification of therapy* defined by an increase in diuretic dose >50% in the outpatient setting. Change in health status is assessed using the disease-specific Kansas City Cardiomyopathy Questionnaire and the generic patient global assessment.

Statistical considerations

The final analytical cohort includes all randomized patients with the exception of those patients who did not qualify for randomization and did not receive any study drug but were inadvertently randomized. The primary end point will be analyzed according to the intention-to-treat principle. The primary hypothesis to be tested is that the ratio of the geometric means of NT-proBNP (ie, the average of values at weeks 4 and 8 divided by the value at baseline) does not differ between the sacubitril/valsartan and enalapril groups. The estimated treatment effect in terms of the ratios of the geometric means, based on the least-squared means from an analysis of covariance model, with logarithmic baseline value as a covariate, and the corresponding 2-sided 95% CI will be reported. The analysis is to be performed based on all available data points with the assumption that data are missing at random. Secondary and exploratory end points will be analyzed using the same approach.

Assuming a threshold for statistical significance of .05 and 85% power, a sample size of 882 patients is needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline in NT-proBNP in the sacubitril/valsartan treatment arm assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85, and a 10% loss to follow-up rate. The assumption of an 18% reduction in the geometric mean for NT-proBNP for the sacubitril/valsartan versus enalapril groups is consistent with the NT-proBNP results previously seen in PARADIGM-HF[9] and other clinical trials.[11,12]

Funding and study organization

The PIONEER-HF trial is run jointly by 2 academic research organizations, the Duke Clinical Research Institute (Durham, NC) and the Thrombolysis in Myocardial Infarction Study Group (Boston, MA), in an academic collaboration with the sponsor Novartis Pharma AG (Basel, Switzerland). Overall responsibility for the oversight and management of the trial lies with the PIONEER-HF Steering Committee which is comprised of senior independent academic investigators who are experts in their field as well as representatives from the sponsor. The PIONEER-HF Data and Safety Monitoring Board includes specialists in HF and an independent statistician responsible for active surveillance of safety data including all adverse and serious adverse events. Members of the Steering Committee and Data and Safety Monitoring Board are listed in Appendix A. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Ethical considerations

The PIONEER-HF trial complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. The institutional review board at each participating center independently approved the protocol, and written informed consent was obtained from all study participants prior to enrollment. PIONEER-HF is registered at clinicaltrials.gov (NCT02554890).

Discussion

PIONEER-HF is a prospective, multicenter, randomized, double-blind, active-controlled trial designed to assess the safety, tolerability, and efficacy of sacubitril/valsartan compared with enalapril in patients

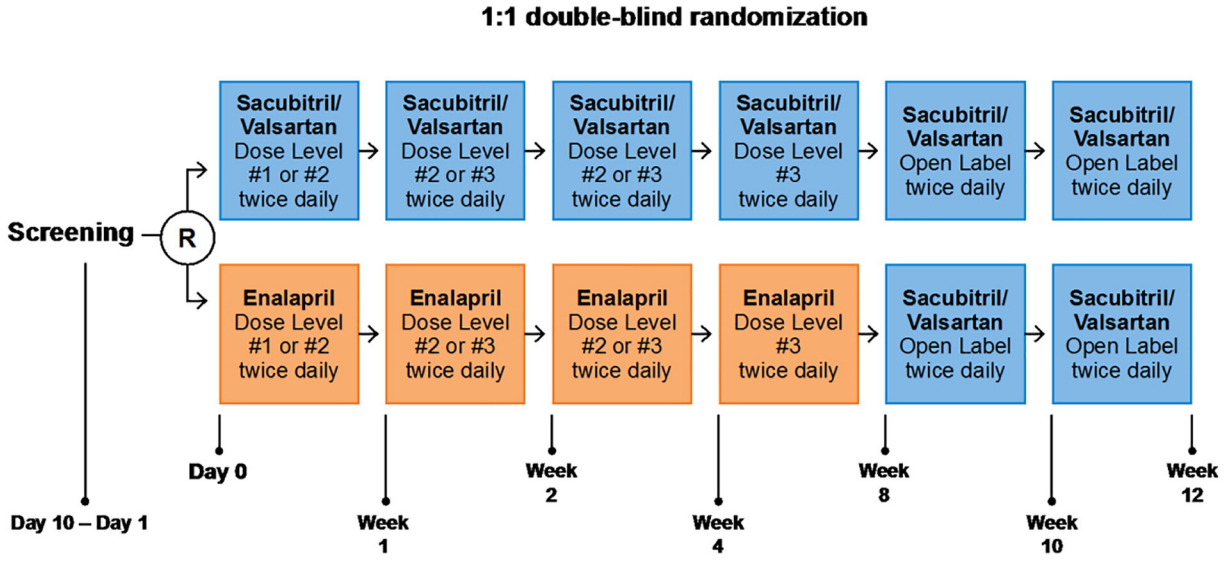

Figure 1. Overview of the study timeline.

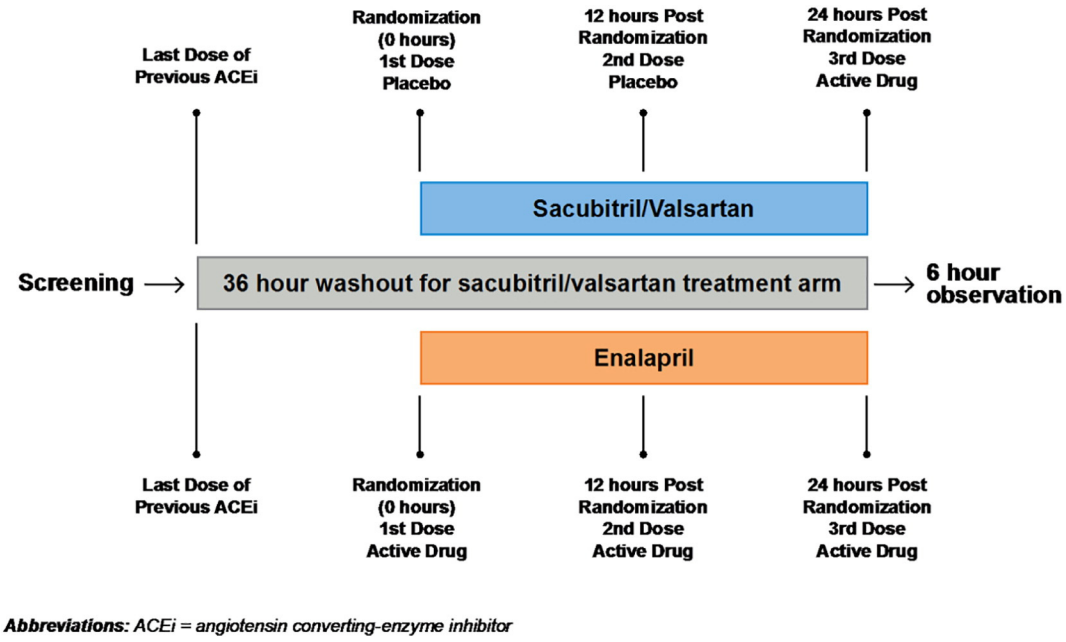

Figure 2. Protocol for the in-hospital initiation phase.

Table II
Treatment dose levels

Dose level	Sacubitril/valsartan	Enalapril
1	24/26 mg BID	2.5 mg BID
2	49/51 mg BID	5 mg BID
3	97/103 mg BID	10 mg BID

BID, Twice daily.

hospitalized for acute decompensated HF with a reduced EF following stabilization but prior to discharge. Despite the conclusive results of PARADIGM-HF, expedited Food and Drug Administration approval, and a strong recommendation in the United States and European guidelines, there is a more limited experience with sacubitril/valsartan in patients hospitalized for acute decompensated HF and patients with severe signs and symptoms of HF.[8,9] In addition, it is well established that in-hospital initiation of evidence-based medications results in greater long-term adherence.[13,14] Given the burden of hospitalizations for worsening HF and the unacceptably high postdischarge event rate, the safe initiation of sacubitril/valsartan in the acute setting may fulfill an important unmet clinical need. There are several salient features of the PIONEER-HF trial which further the existing evidence basis and collective understanding of ARNi therapy in HF with a reduced EF in everyday practice.

The PARADIGM-HF trial predominantly enrolled ambulatory HF patients with a reduced EF and New York Heart Association functional class II and III symptoms, requiring participants to be on a stable dose of an ACEI or an ARB for at least 4 weeks before entering into the study and excluding patients with acute decompensated HF. As a result, nearly 40% of patients reported no prior hospitalizations for worsening HF at baseline, and only 33 patients (0.8%) with New York Heart Association functional class IV symptoms were randomly assigned to sacubitril/valsartan.[15] In addition, patients enrolled in PARADIGM-HF

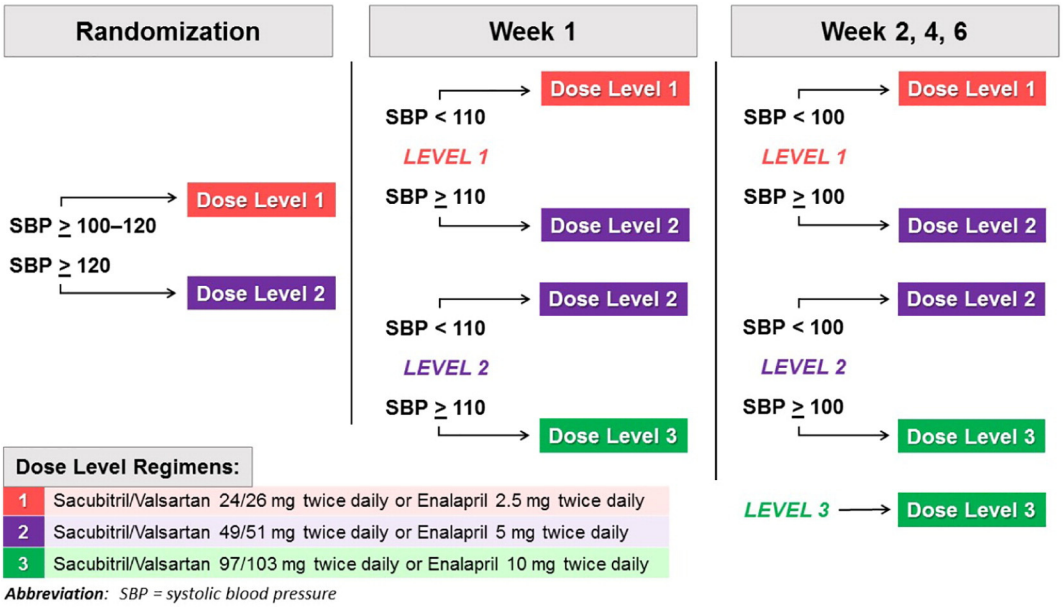

Figure 3. Study drug dose titration algorithm.

Table III
Data collection and schedule of assessments

Phase	Screening/randomization	Double-blind treatment					Open-label treatment	
Week	0	1	2	4	6	8	10	12
Informed consent	X							
Demographics	X							
Medical history	X							
Medication reconciliation	X	X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X	X
Physical examination	X		X			X		X
Electrocardiogram	X							
Hematology	X	X				X		
Chemistry	X	X	X	X		X	X	X
Pregnancy test	X	X		X		X		X
Biomarkers*	X	X	X	X		X		X
Patient-reported outcomes†	X			X		X		X
Medical resource utilization								X
Dispense treatment	X	X	X	X	X	X	X	
Adverse event/serious adverse event	X	X	X	X	X	X	X	X

* BNP/NT-proBNP; High-sensitivity troponin; cystatin C; soluble suppressor of tumorigenicity 2; urinary cyclic guanosine monophosphate; and other cardiac, renal, and drug mechanism of action biomarkers.
† Kansas City Cardiomyopathy Questionnaire and Patient Global Assessment.

Table IV
Study end points

- Primary objective
  - Time-averaged proportional change in NT-proBNP from baseline
- Secondary objectives
  - Change in NT-proBNP at week 8
  - NP system activation (eg, BNP:NT-proBNP ratio and urinary cGMP)
  - Cardiac fibrosis/remodeling (eg, soluble ST2)
  - Tissue perfusion/injury (eg, hs-Tn)
- Exploratory objectives
  - Change in NT-proBNP at wk 1 and 2
  - Time to first occurrence of composite of:
    - I. Death
    - II. Hospitalization for worsening HF
    - III. Left ventricular assist device implantation
    - IV. Listed for cardiac transplantation
    - V. Unplanned emergency department or office visit requiring IV diuretics
    - VI. Increase in diuretic dose >50%
  - Hospitalization or unplanned emergency department or office visit for HF
  - Need for advanced HF therapies (eg, IV inotropes, left ventricular assist device placement, cardiac transplantation)
  - Health-related quality of life as assessed by Kansas City Cardiomyopathy Questionnaire and Patient Global Assessment
  - Change in biomarkers related to NP activation, cardiac fibrosis/remodeling, tissue perfusion/injury, and renal function
  - Change in NT-proBNP in the enalapril during the 4-wk open-label period
  - Medical resource utilization
- Safety end points
  - Incidence of *worsening renal function* (ie, defined as an increase in serum creatinine ≥0.5 mg/dL and worsening of eGFR ≥25%)
  - Incidence of symptomatic hypotension
  - Incidence of *hyperkalemia* (ie, defined as K^+ >5.5 mEq/L)
  - Incidence of angioedema

cGMP, Cyclic guanosine monophosphate; *ST2*, suppressor of tumorigenicity 2; *hsTn*, high sensitivity troponin.

entered sequential single-blind run-in periods of enalapril followed by sacubitril/valsartan to assess for tolerability and ability to achieve the target doses; almost 20% of patients discontinued study drug and did not subsequently undergo randomization.[16]

In contrast, PIONEER-HF is exclusively enrolling patients hospitalized for a primary diagnosis of acute decompensated HF as evidenced by signs and symptoms of volume overload requiring admission for IV therapy. The protocol also requires an elevated BNP and/or NT-proBNP as further objective evidence of acute decompensated HF. There are reasons to believe that ARNi therapy will be effective in this target population, as a number of post hoc analyses of PARADIGM-HF have reported that the benefits of sacubitril/valsartan on CV morbidity and mortality are robust across the spectrum of baseline risk[17] and are irrespective of the occurrence of and/or timing of prior hospitalization for worsening HF.[18] In addition, among patients who required a hospitalization during the trial for a primary diagnosis of HF, 30- and 60-day all-cause and HF-specific readmissions were lower in the sacubitril/valsartan treatment arm.[19] Finally, PIONEER-HF is enrolling patients irrespective of duration of diagnosis of HF or background therapy, making this the first opportunity to assess the safety and tolerability of ARNi therapy among patients with de novo HF and those that are naive of conventional RAS inhibitors.

There are also several notable aspects of the treatments' arms that differ from PARADIGM-HF. PIONEER-HF is the first head-to-head clinical

trial in patients with HF with a reduced EF to include the lowest clinically available dose of sacubitril/valsartan (24/26 mg tablet) as part of the dosing titration protocol. By making use of the full gamut of available doses, this strategy allows a staged assessment of the safety and tolerability of ARNi therapy without a run-in phase, particularly with respect to the incidence of symptomatic hypotension which occurred more frequently in patients who received sacubitril/valsartan (14.0% vs 9.2%, *P* value < .001) in PARADIGM-HF.[20] It is also notable that PIONEER-HF incorporates a double-blind in-hospital initiation phase without a preceding run-in period. In addition, after completing the double-blind treatment phase, all patients in the PIONEER-HF trial will be switched from double-blind treatment to open-label sacubitril/valsartan for the remainder of the trial. This transition provides the unique opportunity to assess the safety and tolerability of switching patients from comparable doses of enalapril to sacubitril/valsartan (ie, compared with continuing sacubitril/valsartan). A notable similarity between PARADIGM-HF and PIONEER-HF is the selection of enalapril and its target dose, which has been criticized for not being the gold standard comparator.[21] Although a single trial tested a higher target dose of enalapril (40 mg daily), the mean daily dose of enalapril achieved in PARADIGM-HF was marginally higher (18.9 mg vs 18.6 mg), and this is the only dose of any ACEi that has been shown to improve survival.[22,23] Notably, in head-to-head trials, ARBs have been shown to be noninferior but not superior to ACEis in terms of mortality.[24,25]

It is also worth noting that the primary end point of PIONEER-HF is the time-averaged proportional change in NT-proBNP from baseline through weeks 4 and 8. Surrogate end points play an important role in clinical trials in HF but should be interpreted with caution. The PARADIGM-HF trial found that patients who were treated with sacubitril/valsartan were almost twice as likely to achieve a reduction in NT-proBNP <1000 pg/mL, a finding which was associated with a lower risk of CV mortality or hospitalization for worsening HF.[26] Although this is not an unexpected finding given that the benefit of sacubitril/valsartan on survival was driven by a reduction in sudden cardiac death and death due to progressive pump failure (ie, worsening HF),[27] PIONEER-HF will uniquely define the time course of NT-proBNP reduction with sacubitril/valsartan during recovery from acute heart failure. In addition, the collection of serum and urinary biomarkers of NP system activation, cardiac fibrosis/remodeling, and perfusion/injury provides valuable insights into the mechanism of action of sacubitril/valsartan and the pathophysiology of HF.

There are several limitations of the data inherent to the conduct of a multicenter randomized clinical trial. First, patients are enrolled at the point of care by the local clinician-investigator without central validation. Although this raises the potential for misclassification, diagnostic criteria for HF were discussed at investigator meetings and include signs and symptoms of congestion requiring IV therapies, an elevated NT-proBNP or BNP, and the absence of an alternative etiology for dyspnea. Second, the in-hospital initiation phase may make it challenging to recruit patients, as participation has the potential to prolong length of stay by 2 or more days. However, this is necessary even in patients who may be ACEi and ARB naïve to preserve blinding and maintain protocol consistency. Third, there will inevitably be patients lost to follow-up and missing data despite the short duration of the PIONEER-HF study. Every effort is being made to contact patients, their caregivers, and/or the treating physician for collateral information, and statistical approaches for imputation and sensitivity analyses will be performed to mitigate the issue of missing data. Fourth, although clinical outcomes including vital status and hospitalizations are being collected, outcomes will not be adjudicated by an independent clinical events committee, and the study may be underpowered to detect differences in these exploratory end points.

Conclusions

In conclusion, hospitalization for worsening HF presents a heretofore untested opportunity to initiate sacubitril/valsartan, allow earlier implementation of this guideline-directed medical therapy, and improve long-term adherence. Thus, the PIONEER-HF trial furthers the existing evidence basis and informs everyday clinical practice by evaluating the safety, tolerability, and efficacy of in-hospital initiation of sacubitril/valsartan in patients admitted for a primary diagnosis of acute decompensated HF with a reduced EF.

Appendix A

Steering Committee:
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Data Monitoring Committee:
Kent Bailey, PhD
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