MINI-FOCUS ISSUE: HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)

STATE-OF-THE-ART REVIEW

Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction

Rationale and Design of the PARAGON-HF Trial

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CME/MOC Objective for This Article: After reading this article, the reader should be able to: 1) identify the key molecular targets of angiotensin receptor neprilysin inhibitors (ARNIs); 2) discuss the key inclusion criteria of the PARAGON-HF clinical trial; and 3) discuss the key pathophysiological mechanisms that underlie heart failure with preserved ejection fraction.

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Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial is designed to determine the efficacy and safety of the angiotensin receptor neprilysin inhibitor sacubitril/valsartan compared with valsartan in patients with chronic heart failure and preserved ejection fraction (HFpEF).

BACKGROUND HFpEF is highly prevalent, associated with substantial morbidity and mortality, and in need of effective therapies that improve outcomes. The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan, which has been shown to benefit patients with heart failure (HF) and reduced ejection fraction, demonstrated favorable physiologic effects in a phase II HFpEF trial.

METHODS The PARAGON-HF trial is a randomized, double-blind, parallel group, active-controlled, event-driven trial comparing the long-term efficacy and safety of valsartan and sacubitril/valsartan in patients with chronic HFpEF (left ventricular ejection fraction ≥45%), New York Heart Association functional class II to IV symptoms, elevated natriuretic peptides, and evidence of structural heart disease. Before randomization, all patients entered sequential single-blind run-in periods to ensure tolerability of both drugs at half the target doses (i.e., valsartan titrated to 80 mg bid followed by sacubitril/valsartan 49/51 mg [100 mg] bid). The primary outcome is the composite of cardiovascular death and total (first and recurrent) HF hospitalizations.

CONCLUSIONS PARAGON-HF will determine whether sacubitril/valsartan is superior to angiotensin receptor blockade alone in patients with chronic symptomatic HFpEF. (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]; NCT01920711) (J Am Coll Cardiol HF 2017;5:471–82) © 2017 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) accounts for a large proportion of patients with heart failure (HF), is associated with substantial morbidity and mortality, and is rising in prevalence as the population ages (1–3). Several pathophysiological alterations could play a role in HFpEF, including left ventricular hypertrophy (LVH) and fibrosis, leading to reduced chamber compliance; impaired diastolic relaxation with resultant left ventricular filling pressure elevation (4); subtle left ventricular systolic dysfunction (5,6); abnormalities of ventricular-vascular coupling (7);

increased cardiomyocyte stiffness; and comorbidity-induced systemic inflammation (8). Four outcome trials using inhibitors of the renin-angiotensin-aldosterone system (RAAS) did not meet their primary endpoints (9–12), and currently, no therapy has received regulatory approval to reduce morbidity and mortality (13,14).

The first-in-class angiotensin receptor neprilysin inhibitor sacubitril/valsartan (formerly known as LCZ696) simultaneously blocks the RAAS and the endopeptidase neprilysin (15). Neprilysin is a ubiquitous enzyme that is responsible for the breakdown of

many vasoactive peptides, including the bio-logically active natriuretic peptides (NPs), adrenomedullin, endothelin-1, and angio-tensin. Sacubitril/valsartan is a crystalline compound composed of both the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril that dissociates into its component parts after ingestion. Sacubitril is further esterified to its active form, sacubitrilat. Sacubitril/valsartan reduced cardiovascular and all-cause mortality, as well as HF hospitalizations (HFHs), in patients with HF with reduced ejection fraction (HFrEF) compared with enalapril (16).

Patients with HFpEF can have an impaired atrial natriuretic peptide, renal cyclic gua-nosine monophosphate (cGMP), and natri-uretic response to acute volume expansion (17), as well as upregulation of phosphodies-terase 9 in the hypertrophied cardiomyocyte, which degrades cGMP stimulated by NPs (18). Neprilysin inhibition augments endogenous biologically active NPs and other vasoactive compounds, with increased generation of cGMP, reported to be reduced in myocardial cells in HFpEF (19). Moreover, NP augmen-tation induces diuresis, vasodilation, natri-uresis, and can reduce myocardial fibrosis and improve myocardial relaxation (20). In a phase II HFpEF trial, sacubitril/valsartan was superior to valsartan in reducing N-terminal pro-brain natriuretic peptide (NT-proBNP), decreasing left atrial (LA) size, and improving New York Heart Association (NYHA) functional class (21). These latter findings provided the rationale for an outcomes trial in HFpEF, and here we describe the design of the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial.

TRIAL DESIGN AND METHODS

PARAGON-HF is a randomized, double-blind, parallel group, active-controlled, 2-arm, event-driven trial comparing the long-term efficacy and safety of valsartan and sacubitril/valsartan in patients with chronic symptomatic HFpEF. The trial was designed by members of the steering committee in collabora-tion with the sponsor. The trial has been registered (NCT01920711).

PATIENTS. The final eligibility criteria are summa-rized in Table 1. Briefly, patients were ≥50 years of age, had a left ventricular ejection fraction (LVEF) ≥45% by

echocardiography within the 6 months before screening and symptoms of HF (NYHA functional class II to IV), required diuretic therapy for at least 30 days before screening, and had NT-proBNP >200 pg/ml if the patient had been hospitalized for HF within the past 9 months or >300 pg/ml without a recent HFH. The NT-proBNP requirement was tripled if patients were in atrial fibrillation at screening. In addition, patients had to have evidence of structural heart dis-ease, including either LVH (i.e., septal or posterior wall thickness ≥1.1 cm) or LA enlargement (i.e., width ≥3.8 cm, length ≥5.0 cm, area ≥20 cm^2, volume ≥55 ml, or volume index ≥29 ml/m^2).

The key exclusion criteria included prior LVEF <40% using echocardiography, an alternative diagnosis that could account for the patient's symp-toms, and systolic blood pressure <110 or ≥180 mm Hg. Patients with SBP >150 mm Hg were excluded unless they were receiving at least 3 antihypertensive medications at screening. Those patients with atrial fibrillation at screening were limited to approximately 33% of the study sample.

Enrollment in PARAGON-HF began on July 18, 2014, after protocol approval by the ethics commit-tees and institutional review boards affiliated with each investigative site. Patients were enrolled at 788 centers in 43 countries distributed across all major geographic regions. The study is being conducted in accordance with Good Clinical Practice and the Declaration of Helsinki 2002.

STUDY DESIGN. Sequential run-in period. The overall study design is summarized in the **Central Illustration**. After screening, in which NT-proBNP, serum potassium, and estimated glomerular filtra-tion rate for eligibility were measured in a central laboratory, patients entered a sequential run-in phase in which they first received 1 to 2 weeks of single-blind treatment with valsartan 40 mg or 80 mg twice daily (bid). Those started on the lower dose had their doses up-titrated to valsartan 80 mg bid after 1 to 2 weeks. Patients who tolerated valsartan 80 mg bid, as defined by criteria in Online Table 1, were switched to sacubitril/valsartan 49/51 mg bid (LCZ696 100 mg bid) for 2 to 4 weeks. Patients who tolerated sacubitril/valsartan 49/51 mg bid, per criteria in Online Table 1, were eligible for randomization. Other background medications (except for angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs] and renin inhibitors) were continued during the run-in periods.

Randomized double-blind treatment period. Patients who tolerated both run-in periods were randomized to

TABLE 1 Eligibility Criteria

Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed
2. ≥50 years of age, male or female
3. LVEF ≥45% by echocardiography during the screening epoch, or within 6 months prior to screening visit (any local LVEF measurement made using echocardiography only)
4. Symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening visit
5. Current symptom(s) of HF (NYHA functional class II to IV) at screening visit
6. Structural heart disease evidenced by at least 1 of the following echocardiography findings (any local measurement made during the screening epoch or within the 6 months prior to screening visit):
   a) LA enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 ml or LA volume index ≥29 ml/m^2
   b) LVH defined by septal thickness or posterior wall thickness ≥1.1 cm
7. Patients with at least 1 of the following:
   a) HF hospitalization (defined as HF listed as the major reason for hospitalization) within 9 months prior to screening visit and NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF on screening ECG, or
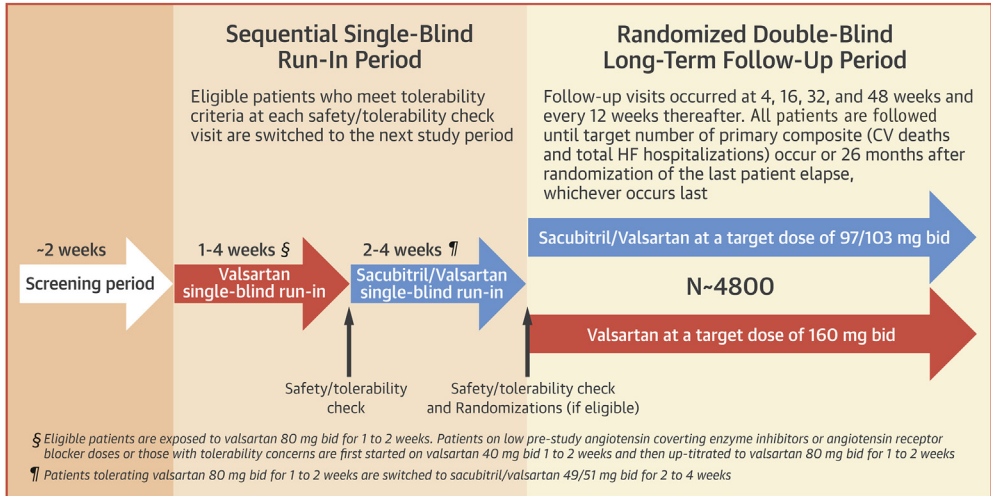   b) NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on the screening visit ECG

Exclusion criteria

1. Any prior echocardiographic measurement of LVEF <40%
2. Acute coronary syndrome (including MI), cardiac surgery, other major cardiovascular surgery, or urgent PCI within the 3 months prior to visit 1 or an elective PCI within 30 days prior to visit 1
3. Any clinical event within the 6 months prior to visit 1 that could have reduced the LVEF (e.g., MI, CABG), unless an echocardiographic measurement was performed after the event confirming the LVEF to be ≥45%
4. Current acute decompensated HF requiring augmented therapy with diuretic agents, vasodilator agents, and/or inotropic drugs
5. Patients who require treatment with 2 or more of the following: an ACEI, an ARB, or a renin inhibitor
6. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
7. Patients with a known history of angioedema
8. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue), such as significant pulmonary disease (including primary pulmonary hypertension), anemia, or obesity. Specifically, patients with the following are excluded:
   a) Severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) or
   b) Hemoglobin <10 g/dl, or
   c) Body mass index >40 kg/m^2
9. Patients with any of the following:
   a) Systolic blood pressure (SBP) ≥180 mm Hg at visit 1, or
   b) SBP >150 mm Hg and <180 mm Hg at visit 1 unless the patient is receiving 3 or more antihypertensive drugs. Antihypertensive drugs include but are not limited to a thiazide or other diuretic, mineralocorticoid (MRA), ACEI, ARB, beta blocker, and calcium channel blocker, or
   c) SBP <110 mm Hg at visit 1, or
   d) SBP <100 mm Hg or symptomatic hypotension as determined by the investigator at visit 103 or visit 199/201
10. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
11. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy-induced cardiomyopathy, or viral myocarditis
12. Evidence of right-sided HF in the absence of left-sided structural heart disease
13. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy
14. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF
15. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator
16. Stroke, transient ischemic attack, carotid surgery, or carotid angioplasty within the 3 months prior to visit 1
17. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial
18. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and AF or atrial flutter with a resting ventricular rate >110 beats per minute
19. Patients with a cardiac resynchronization therapy device
20. Patients with prior major organ transplant or intent to transplant (i.e., on transplant list)
21. Any surgical or medical condition that in the opinion of the investigator may place the patient at higher risk from his/her participation in the study or is likely to prevent the patient from complying with the requirements of the study or completing the study
22. Any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following: any history of pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury within the past 5 years
23. Evidence of hepatic disease as determined by any 1 of the following: SGOT (AST) or SGPT (ALT) values exceeding 3× the upper limit of normal, bilirubin >1.5 mg/dl at visit 1
24. Patients with 1 of the following:
   a) eGFR <30 ml/min/1.73 m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at visit 1, or
   b) eGFR <25 ml/min/1.73 m^2 at visit 103 or visit 199/201, or
   c) eGFR reduction >35% (compared with visit 1) at visit 103 or visit 199/201
25. Presence of known functionally significant bilateral renal artery stenosis
26. Patients with either of the following:
   a) Serum potassium >5.2 mmol/l (mEq/l) at visit 1
   b) Serum potassium >5.4 mmol/l (mEq/l) at visit 103 or visit 199/201
27. History or presence of any other disease with a life expectancy of <3 years
28. History of noncompliance to medical regimens and patients who are considered potentially unreliable
29. History or evidence of drug or alcohol abuse within the past 12 months
30. Persons directly involved in the execution of this protocol
31. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
32. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test
33. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days off study drug

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; LA = left atrial; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

CENTRAL ILLUSTRATION Study Schematic and Mechanism of Action of Sacubitril/Valsartan
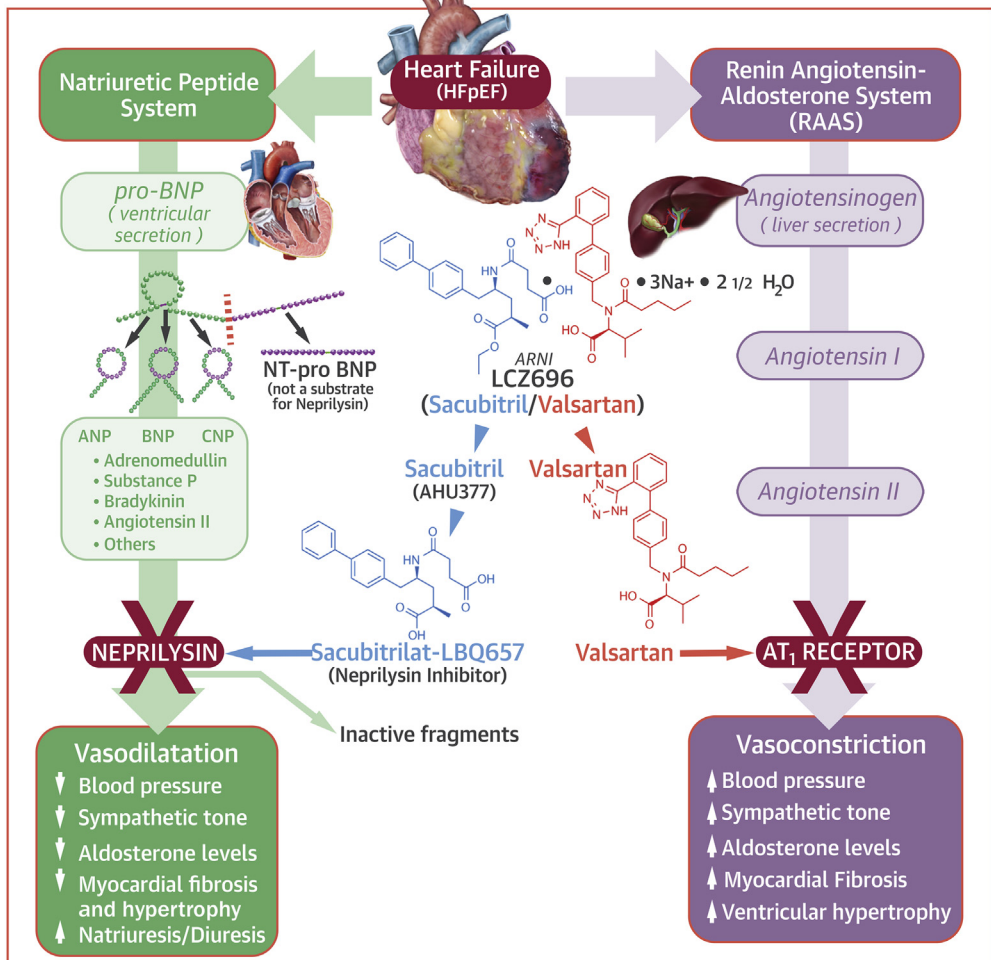
Solomon, S.D. et al. J Am Coll Cardiol HF. 2017;5(7):471–82.

double-blind treatment with either valsartan 160 mg bid or sacubitril/valsartan 97/103 mg bid (LCZ696 200 mg bid). In this ongoing study, study visits occur every 4 to 16 weeks during the first 48 weeks and every 12 weeks thereafter. Visits are conducted telephonically or in-person at the study site in an alternating manner beginning at week 60 and continuing until the end of the trial, with additional telephonic or in-person unscheduled visits at the discretion of the investigator. Patients are treated with optimal diuretic regimens and other background medications (except for ACE inhibitors, ARBs, and renin inhibitors) to effectively manage comorbidities. Investigators are instructed to make every effort to control patients' blood pressure in accordance with international and local treatment guidelines.

Patients are asked to complete the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline before the start of any study medication; at randomization; at 16, 32, and 48 weeks after the start of the double-blind period; and annually thereafter. Patients are administered the Mini Mental State Examination at randomization and annually thereafter.

Monitoring of safety and tolerability during double-blind period. Patients are assessed at each study visit for adverse events. Blood samples to assess blood biochemistry are collected at the screening visit and at every study visit, and samples for hematology are collected at the screening visit; after valsartan run-in; after sacubitril/valsartan run-in/randomization; at 16 and 48 weeks; and annually thereafter. Patients who do not tolerate the target study drug dose can have the dose down-titrated at the investigator's discretion, with encouragement for rechallenging these patients.

Key substudies. An echocardiographic substudy designed to characterize cardiac structure and function at screening is being performed with core laboratory assessment in approximately 1,200 patients. A biomarker substudy has been designed to compare the effects of sacubitril/valsartan and valsartan on relevant cardiac and renal biomarkers at several time points, with samples collected before study medication, after valsartan single-blind run-in, after sacubitril/valsartan single-blind run-in, and at 16 and 48 weeks after randomization.

STUDY OBJECTIVES. The primary objective of this study is to evaluate the efficacy of sacubitril/valsartan compared with valsartan in reducing the rate of the composite endpoint of cardiovascular death and total (first and recurrent) HFHs. Secondary objectives include comparing sacubitril/valsartan and valsartan in: 1) improving the KCCQ clinical summary score for HF symptoms and physical limitations at 8 months; 2) improving NYHA functional classification at 8 months; 3) delaying the time to first occurrence of either a ≥50% in estimated glomerular filtration rate relative to baseline, attainment of end-stage renal disease, or renal death; and 4) delaying the time to all-cause death. Exploratory objectives are listed in **Table 2**.

Protocol amendments. The modifications implemented in the 4 PARAGON-HF protocol amendments to date are summarized in Online Table 2.

STUDY MANAGEMENT AND COMMITTEES. PARAGON-HF is conducted by Novartis under the guidance and leadership of an academic steering committee. An independent external Data Monitoring Committee (DMC) oversees the safety of the patients in the trial and reviews the results of the interim efficacy analysis. An Endpoint Adjudication Committee is responsible for classifying all deaths and adjudicating all nonfatal events. A separate committee is responsible for adjudicating suspected cases of angioedema.

STATISTICAL CONSIDERATIONS. The primary efficacy variable is the cumulative number of primary composite endpoint events, that is, the total number of Endpoint Adjudication Committee–confirmed HFHs, as well as cardiovascular death, for each subject over time. The analysis is based on a semiparametric proportional rates model (22), the LWYY method, which is a modified Anderson and Gill model

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CENTRAL ILLUSTRATION Continued

Heart failure (HF) stimulates both the renin-angiotensin system and the natriuretic peptide system. LCZ696 is composed of 2 molecular moieties, the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril (AHU377). Valsartan blocks the angiotensin type I (AT₁) receptor. Sacubitril is converted enzymatically to the active neprilysin inhibitor LBQ657, which inhibits neprilysin, an enzyme that breaks down atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), as well as other vasoactive substances. N-terminal pro-BNP (NT-proBNP) is not a substrate for neprilysin. Adapted with permission from Vardeny et al. (15) (mechanism of action panel).

TABLE 2	Study Objectives

Primary objective

To compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of cardiovascular death and total (first and recurrent) HF hospitalizations in HF patients (NYHA functional class II to IV) with preserved EF (LVEF ≥45%)

Secondary objectives

To compare the effects of sacubitril/valsartan and valsartan on:
- Changes in the clinical summary score for HF symptoms and physical limitations, as assessed by the KCCQ at 8 months
- Improving NYHA functional classification at 8 months
- Delaying the time to first occurrence of a composite renal endpoint, defined as:
  ○ Renal death, or
  ○ Reaching end-stage renal disease (ESRD), or
  ○ ≥50% decline in eGFR relative to baseline
- Delaying the time to all-cause mortality

Exploratory objectives

To compare the effects of sacubitril/valsartan and valsartan on:
- Reducing the rate of the composite endpoint of cardiovascular death, total HF hospitalizations, total nonfatal strokes, and total nonfatal MIs (total is defined as the first and all recurrent events)
- Changes in clinical composite assessment (assessed by NYHA functional class, global patient assessment, and major adverse clinical events as defined by cardiovascular death and hospitalization for HF) at 8 months
- Patient global assessment at 8 months
- Reducing the rate of the composite endpoint of cardiovascular death, total nonfatal HF hospitalizations, total nonfatal strokes, and total nonfatal MIs (total is defined as the first and all recurrent events)
- Delaying the time to new-onset AF
- Changes in health-related quality of life (assessed by overall summary score, clinical summary score, and individual scores of the subdomains from the KCCQ [relative to treatment run-in epoch baseline scores and relative to randomized treatment epoch baseline scores] and total score of the EQ-5D for health status)
- Reducing cardiovascular deaths and total worsening HF events. A subject will be defined as having a cardiovascular death or worsening HF event when the subject has:
  ○ Cardiovascular death, or
  ○ A hospitalization for HF, or
  ○ Received IV decongestive therapy (IV diuretic agents, IV nesiritide or other natriuretic peptide, IV inotropes, and IV nitroglycerin) that does not result in formal inpatient hospital admission, regardless of the setting (i.e., in an ED setting, in the physician's office, an outpatient treatment facility, and so on)
- Hospitalizations (all cause and cause specific)
- The number of days alive and out of hospital at 12 months
- Slowing the rate of decline in eGFR
- Delaying time to new-onset diabetes mellitus
- Reducing healthcare resource utilization (e.g., number of days/stays in intensive care unit, number of rehospitalizations, and number of ED visits for HF)
- 30-day HF hospital readmissions and readmission rate after a prior HF hospitalization
- Time between HF hospital readmissions
- The profile of pre-specified biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, inflammatory, and/or other relevant biomarkers) from baseline to pre-defined time points in a subset of patients
- The primary composite and secondary endpoints, and key exploratory endpoints in ACEI-intolerant patients
- Evaluating the changes in cognitive function (assessed by the MMSE) at 2 yrs
- To characterize sacubitril/valsartan and valsartan PK at steady state using population modeling and/or noncompartmental based methods in a subset of patients

ED = emergency department; EF = ejection fraction; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; MMSE = Mini Mental State Examination; PK = pharmacokinetics; other abbreviations as in Table 1.

(23) with a robust variance estimator to account for the dependency of within-subject recurrent events, with treatment group as a factor and stratified by geographic region. As part of the primary analysis, the

components in the composite endpoint (total HFHs, cardiovascular death) will also be analyzed separately to quantify the respective treatment effects and assess consistency. A joint gamma frailty model (24) approach, which models total HFHs with the Poisson regression model and cardiovascular death with the exponential regression model and joins the 2 models through a gamma frailty, will be used for the component analyses to address the potential bias of cardiovascular death as a semicompeting risk and to account for the correlation between HFH and cardiovascular death.

Sample size and power were calculated through simulations with the pseudo-data generated using the parametric joint gamma frailty model. The control group rate of total HFHs and cardiovascular death rate were estimated in 2 steps. First, based on the candesartan group of the CHARM-Preserved (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved) study for patients with LVEF ≥45%, the joint model, we estimated a Poisson baseline intensity of 0.00032 HFHs per day per patient and an exponential hazard rate of 0.000136 cardiovascular deaths per day per patient, with the estimated gamma shape parameter of 0.193, which resulted in annualized rates of 0.083 for time to first primary event and 0.036 for cardiovascular mortality. We then increased these rates by 8% and adjusted the corresponding Poisson intensity and exponential hazard rates proportionally to annualized rates of 0.09 and 0.04 for time to first primary event and cardiovascular death, respectively, reflecting the requirement for elevated NPs, recent HFHs, and imaging evidence of structural heart disease for enrollment. For various combinations of effect size scenarios and sample sizes, 3,000 studies were simulated with uniform patient enrolment over 29 months and a minimum follow-up of 26 months, and the primary analysis was performed using a 1-sided alpha level of 0.025. It was estimated that 4,600 patients would provide 95% power for the primary analysis, assuming approximately 1,847 primary events had accrued, if the true primary endpoint rate reduction were 22%, which approximately corresponds to a 30% reduction for total HFHs and 10% for cardiovascular death, under the assumed model. For a smaller reduction of 19% in the primary endpoint rate, corresponding to a 25% reduction for total HFHs and 10% for cardiovascular death, the study would have 84% power for the primary analysis.

For secondary endpoints, change from baseline in KCCQ clinical summary score at 8 months will be analyzed using a repeated-measures ANCOVA model,

together with the mixed-effect logistic responder analyses for 5-point deterioration and 5-point improvement; change from baseline in NYHA functional class at 8 months will be analyzed using a repeated-measures proportional cumulative odds model; time to first renal impairment composite outcome and time to all-cause death will also be analyzed with Cox proportional hazard models. The multiplicity for the comparisons across the primary and secondary endpoints will be adjusted on the basis of a sequentially rejective multiple test procedure (25). If the primary endpoint is statistically significant at the significance-level alpha (e.g., 1-sided level of 0.024 at the end), then the KCCQ and NYHA endpoints will be tested at level alpha/2. If one of them is statistically significant at this level, the other can be tested at level alpha. If both KCCQ and NYHA endpoints are statistically significant, the composite renal endpoint can be tested at level alpha. The all-cause mortality endpoint will be tested at level alpha, after the rejection of the primary hypothesis. The endpoints for the exploratory objectives in Table 2 will also be analyzed using appropriate methods.

Study duration, interim analyses, and early termination. PARAGON-HF is an event-driven trial, and all randomized patients will be followed up until at least 1,847 total (first and recurrent) HFHs and cardiovascular deaths occur, with follow-up of ≥26 months after randomization for all noncensored patients to obtain the target power, unless the DMC recommends that the study be stopped earlier for efficacy or safety reasons. The minimum follow-up duration can be blindly re-estimated using the power simulation model with the target power and updated estimated model parameters based on the data collected around the time of the efficacy interim analysis. The total trial length depends on the overall duration of the patient recruitment period and the time taken to accrue the pre-specified number of primary events.

One interim efficacy analysis is planned to assess the primary endpoint when approximately two-thirds of the target number of primary events have been adjudicated, using a 1-sided alpha of 0.001. The study can be stopped earlier in the interim analysis for superiority only when both the primary endpoint and cardiovascular death are statistically significant at a one-sided alpha of 0.001. The significance level of alpha to be used for the final analysis will be adjusted for the interim analysis to control the overall type I error at 0.025 (1-sided). Interim safety analyses are conducted by the DMC biannually.

DISCUSSION

HFpEF is morbid and costly and accounts for a growing proportion of patients with HF, yet current therapy for HFpEF remains empiric. Neprilysin inhibition represents a potentially novel therapeutic strategy, with promising experimental and phase II mechanistic data. Four prior outcomes trials in HFpEF that have focused on inhibiting the RAAS with ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists have not been successful. In contrast to prior HFpEF outcomes trials, PARAGON-HF uses a novel therapy, was preceded by a positive phase II trial, and was designed to address many of the perceived shortcomings of these prior trials.

We chose an active comparator, valsartan, because RAAS inhibitors are widely used in HFpEF patients, predominantly to treat comorbidities such as hypertension (11,12). Because sacubitril/valsartan cannot be administered in conjunction with an ACE inhibitor because of the increased risk of angioedema, we standardized the active RAAS inhibitor comparator arm in PARAGON-HF. The choice of RAAS inhibitor, valsartan, differed from that used in PARADIGM-HF (where the comparator was enalapril) because, unlike in HFrEF, there is no standard of care for RAAS inhibition in HFpEF. The target dose of sacubitril/valsartan was based on the PARADIGM-HF and PARAMOUNT trials and is the dose that achieves similar systemic exposure as 160 mg bid of the valsartan international formulation, as well as 90% of the maximum neprilysin inhibition (16,21).

There has been concern that the failure of prior trials in HFpEF might have been related to inclusion criteria, as well as aspects of the trial design and execution. Because the diagnosis of HF can be difficult when LVEF is preserved, it is likely that some patients enrolled in prior HFpEF trials may not have truly had HF, as was likely the case for many patients enrolled from Russia and Georgia in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) (26). This issue remains a concern in all HFpEF trials, and the possibility that misdiagnosis might have played a role in the failure of other trials cannot be ruled out. Other problems, such as dropout and crossover, might have further compromised prior HFpEF trials (10).

The inclusion criteria of PARAGON-HF were designed to mitigate issues that might have been problematic for prior HFpEF trials (Table 3). To ensure

TABLE 3	Comparison of PARAGON-HF and Prior HFpEF Trials				
	CHARM-P (n = 3,023)	**PEP-CHF** (n = 850)	**I-PRESERVE** (n = 4,128)	**TOPCAT** (n = 3,445)	**PARAGON-HF** (n = 4,800)
Treatment arms	Candesartan vs. placebo	Perindopril vs. placebo	Irbesartan vs. placebo	Spironolactone vs. placebo	Sacubitril/valsartan vs. valsartan
Key inclusion criteria	NYHA functional class II to IV, prior CVH	Clinical diagnosis of DHF with signs/symptoms of HF, ≥2 of the following: LAE/LVH/impaired LV filling/AF	NYHA functional class II-IV + any corroborating evidence (e.g., HF sign), LVH or LAE considered optional corroborating evidence, HFH required unless in NYHA functional class III-IV	Yes. ≥1 HF symptom + ≥1 HF sign, elevated NP, or HFH	Yes. NYHA functional class II-IV, elevated NT-proBNP. Mildly elevated NT-proBNP if prior HFH, structural heart disease (LAE or LVH)
Endpoint	First of either CVD or HFH	First of either all-cause death or HFH	First of either all-cause death or CVH	First of either CVD, HFH, or RSD	CVD and total HFH (first and recurrent)

CHARM-P = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved; CVD = cardiovascular disease; CVH = cardiovascular hospitalization; DHF = diastolic heart failure; HFH = heart failure hospitalization; HFpEF = heart failure with preserved ejection fraction; I-PRESERVE = Irbesartan in Heart Failure With Preserved Ejection Fraction; LAE = left atrial enlargement; LV = left ventricular; NP = natriuretic peptide; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction; PEP-CHF = Perindopril in Elderly People With Chronic Heart Failure; RSD = resuscitated sudden death; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; other abbreviations as in Table 1.

that patients enrolled had HF and that their signs and symptoms were not simply due to other disease states, all patients enrolled in PARAGON-HF after an early protocol amendment were required to have mild NP elevation, regardless of whether they were hospitalized for HF in the recent past. This criterion was designed to ensure that a patient would not be enrolled solely on the basis of an HFH, which might be difficult to verify. Additionally, all patients in PARAGON-HF were required to have structural heart disease, some degree of LVH or LA enlargement, both of which are known to be markers of risk in HFpEF (27,28). These criteria were not specifically required in all patients by prior HFpEF outcomes trials (Table 3).

PARAGON-HF uses a novel primary endpoint, reduction in first and recurrent HFHs and cardiovascular death, with a recurrent event analysis method. All prior HFpEF outcomes trials and most trials in HF in general have used time-to-first-event analysis for the primary endpoint assessment. However, patients with HFpEF experience recurrent hospitalizations, with each event contributing to the patient's burden and resource utilization. The use of recurrent events, therefore, might allow for better assessment of the true disease burden, and post hoc reanalysis of total events in the CHARM-Preserved trial (nearly double that of first events) using several recurrent event methods demonstrated significant reduction in hospitalizations in patients who were given candesartan (29). PARAGON-HF will use the LWYY semiparametric proportional rates model approach to assess the primary endpoint, an approach that has been vetted and accepted by regulatory authorities. This variation on the Andersen-Gill (23) method uses a robust variance estimator and makes no assumption of event independence.

Prior modeling of this method using data from CHARM-Preserved suggested that it would provide an improvement in statistical power compared with the conventional time-to-first-event approach. Event rate estimations were further informed after the TOPCAT data became available.

Several substudies and exploratory endpoints will complement the primary analyses. Echocardiography assessment at screening will help characterize cardiac structure and function in this population. A cognitive function study using the Mini Mental State Examination is being performed to explore the theoretical risk that inhibition of neprilysin would attenuate the breakdown of neurotoxic amyloid-beta peptides in the brain and contribute to the risk of impairment in cognitive function. There are currently no human data supporting this risk with sacubitril/valsartan (30), and data from PARADIGM-HF did not demonstrate an increased risk of dementia in patients treated with this drug (31). Indeed, cognitive function might improve in the sacubitril/valsartan group if the test treatment is effective. Prevention of HFHs could be important, because episodes of critical illness are associated with marked cognitive decline over the subsequent 12 months (32). Similarly, improved cardiac function and cerebral blood flow in HF patients might improve cognitive function.

STUDY LIMITATIONS. As with any clinical trial, the design of PARAGON-HF has several limitations that should be considered. The requirement for elevation in NPs might exclude some patients with HFpEF without such elevation. In addition, PARAGON-HF excludes patients with body mass index >40 kg/m² because of the difficulty of diagnosing HF in this population. These exclusions could limit the

generalizability of the PARAGON-HF results in specific populations. Moreover, PARAGON-HF uses an ejection fraction cutoff for HFpEF that has been commonly used in prior trials. More recently, the European Society of Cardiology guidelines proposed a new nomenclature categorizing HF patients in the LVEF 40% to 50% range "heart failure with mid-range ejection fraction (HFmREF)." PARAGON-HF will include patients in part but not all of this range.

CONCLUSIONS

PARAGON-HF will assess in patients with HFpEF the benefit of sacubitril/valsartan, a drug that has

been proven to reduce morbidity and mortality in HFrEF and that has demonstrated efficacy in a phase II trial in patients with HFpEF. The design of PARAGON-HF, the largest phase III HFpEF trial to date, has considered several concerns from prior neutral clinical trials in HFpEF and has the potential to provide an evidenced-based therapeutic option for patients with this syndrome.

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KEY WORDS angiotensin receptor neprilysin inhibitor, heart failure with preserved ejection fraction, sacubitril, valsartan

APPENDIX For a list of the PARAGON-HF study co-chairs and committee members as well as supplemental tables, please see the online version of this article.

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