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Rationale, Design and Baseline Characteristics of the PARAGLIDE-HF Trial: Sacubitril/Valsartan vs Valsartan in HFmrEF and HFpEF With a Worsening Heart Failure Event

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ABSTRACT

Background: The PARAGON-HF trial studied the effect of sacubitril/valsartan (Sac/Val) compared with valsartan (Val) on clinical outcomes in patients with chronic heart failure with preserved ejection fraction (HFpEF) or mildly reduced EF (HFmrEF). Further data are needed regarding the use of Sac/Val in these groups with EF and with recent worsening heart failure (WHF) events and in key populations not broadly represented in the PARAGON-HF trial, including those with de novo HF, the severely obese and Black patients.

Methods: The PARAGLIDE-HF trial is a multicenter, double-blind, randomized, controlled trial of Sac/Val vs Val that enrolled patients at 100 sites. Medically stable patients $\geq$ 18 years old with EF $>$ 40%, amino terminal-pro B-type natriuretic peptide (NT-proBNP) levels $\geq$ 500 pg/mL and within 30 days of a WHF event were eligible for participation. Patients were randomly assigned 1:1 to Sac/Val vs Val. The primary efficacy endpoint is time-averaged proportional change in NT-proBNP from baseline through Weeks 4 and 8. Secondary endpoints include clinical outcomes during follow-up and additional biomarker assessments. Safety endpoints include symptomatic hypotension, worsening renal function and hyperkalemia.

Results: The trial enrolled 467 participants from June 2019 through October 2022 (52% women, 22% Black, age 70 $\pm$ 12 years, median (IQR) BMI 33 (27$-$40) kg/m^2). The median (IQR) EF was 55% (50%$-$60%), 23% with HFmrEF (LVEF 41%$-$49%), 24% with EF $>$ 60% and 33% with de novo HFpEF. Median screening NT-proBNP was 2009 (1291$-$3813) pg/mL, and 69% were enrolled in the hospital.

Conclusions: The PARAGLIDE-HF trial enrolled a broad and diverse range of patients with heart failure with mildly reduced or preserved ejection fraction and will inform clinical practice by providing evidence about the safety, tolerability and efficacy of Sac/Val vs Val in those with a recent WHF event. (*J Cardiac Fail 2023;00:1$-$9*)

Key Words: acute decompensated HFpEF, HFmrEF, sacubitril/valsartan, natriuretic peptides, clinical outcomes.

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The PARAMOUNT and PARAGON-HF trials investigated the effect of sacubitril/valsartan (Sac/Val) compared with valsartan (Val) on biomarkers and clinical outcomes in patients with chronic heart failure with preserved ejection fraction (HFpEF) and mildly reduced EF (HFmrEF), defined as left ventricular ejection fraction (LVEF) $\geq$ 45%, with initiation of treatment in the outpatient setting.[1,2] The PARAMOUNT study was a phase 2 trial of Sac/Val vs Val in 301 patients with LVEF $\geq$ 45%.[1] The primary endpoint, change in amino terminal-pro B-type natriuretic peptide (NT-proBNP) levels from baseline to 12 weeks, was significantly reduced in the Sac/Val group compared with the Val group (ratio of change from baseline: 0.77, 95% CI 0.64−0.92; $P = 0.005$). PARAGON-HF was a randomized, double-blind, active-controlled phase 3 trial of Sac/Val vs Val in 4822 patients with chronic HFpEF; the primary endpoint was total hospitalizations for HF and death due to cardiovascular causes. The trial excluded patients with current acute decompensated HF. Over a median follow-up duration of 35 months, there was a 13% relative rate reduction in the primary composite endpoint with Sac/Val compared to Val, a possible treatment effect that narrowly missed statistical significance (RR = 0.87; 95% CI: 0.75−1.01; $P = 0.0587$).[2] In a prespecified subgroup analysis, there was a 22% rate reduction in the primary composite endpoint in patients with an LVEF less than or equal to the median (57%) (RR = 0.78; 95% CI: 0.64−0.95).[2] No new safety signals were seen in PARAGON-HF, and safety assessments were consistent with PARADIGM-HF, a HF with reduced ejection fraction (HFrEF) study comparing Sac/Val to enalapril.[3] Thus, PARAGON-HF narrowly missed the primary endpoint, but benefits were observed in patients with EF below normal, and Sac/Val is now indicated for treatment of chronic HF in the United States and approximately 38 other countries, noting that the benefits are greatest when LVEF is below normal.

The period subsequent to a worsening heart failure (WHF) event—an episode of exacerbation of signs and symptoms of HF requiring an escalation of therapy (in either the inpatient or outpatient setting)—occurs when patients are most vulnerable for hospitalization, rehospitalization and increased mortality rates.[4] In a post hoc analysis of PARAGON-HF, the patients who were recently hospitalized had a 2−3-fold higher risk of rehospitalization and cardiovascular death compared to those not previously hospitalized.[5] Specifically, 622 (13% of the total randomized) patients had at least 1 hospitalization within 30 days of trial screening. The event rates in the Val group were 26.7 per 100 patient-years in those with an HF hospitalization within 30 days vs 7.9 per 100 patient-years in those without recent hospitalization. Furthermore, the treatment benefit with Sac/Val vs Val was larger in those with a recent HF hospitalization. The absolute risk reduction for the primary endpoint in patients enrolled $\leq$ 30 days after hospitalization was 6.4% in the group receiving Sac/Val compared to Val, and this effect decreased as time from hospitalization increased (absolute risk reduction of -0.02% in those never hospitalized).

Patients with HFpEF/HFmrEF and WHF commonly have markedly elevated levels of BNP and NT-proBNP, which are reduced following adequate treatment and stabilization of cardiac decompensation. Similar to the PARAGON-HF data described above, in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) trial, patients with both recent hospitalizations and elevated NT-proBNP ($>$ 360 pg/mL) levels had greater risks of cardiovascular death and subsequent hospitalization due to HF.[6] Management that reduces natriuretic peptide levels is associated with improved clinical outcomes.[7,8] Therefore, it is relevant to evaluate therapeutic strategies that can lead to superior reductions in NT-proBNP levels in patients with HFpEF/HFmrEF with recent WHF.

The PIONEER-HF trial evaluated the effect of in-hospital initiation of Sac/Val vs enalapril in patients with HFrEF who had been stabilized during hospitalization for acute decompensated HF.[9] The PIONEER-HF trial demonstrated greater reduction in NT-proBNP levels with Sac/Val vs enalapril, assessed as time-averaged proportional change in NT-proBNP levels from baseline to Weeks 4 and 8 (ratio of change with Sac/Val vs enalapril 0.71 [0.63−0.81]; $P < 0.001$) and a decrease in the exploratory clinical composite outcome of death, rehospitalization for HF, left ventricular assist device implantation, or listing for cardiac transplant.[9,10]

Based on these considerations, the PARAGLIDE-HF trial was designed to assess the efficacy, safety and tolerability of Sac/Val vs Val in patients with HFpEF and HFmrEF (LVEF $>$ 40%) with a WHF event who have been stabilized and have initiated Sac/Val at the time of or within 30 days post-decompensation. Further data are also needed regarding the use of Sac/Val in key populations not broadly represented in PARAGON-HF, including newly diagnosed HF, severely obese, recently hospitalized, and Black patients in North America.

Study Design

The methods described here are based on Protocol version number 4, dated December 8, 2021.

Overview

PARAGLIDE-HF is a multicenter, double-blind, randomized, controlled trial designed to assess the effect of Sac/Val vs Val on changes in NT-proBNP, safety and tolerability in patients with HFmrEF or HFpEF and with a WHF event (HF decompensation is defined as hospitalization, emergency department visit or out-of-hospital urgent HF visit, all requiring IV diuretics) who have been stabilized and have initiated Sac/Val at the time of or within 30 days post-decompensation (Figure 1) (Table 1). Supplementary Table 1 summarizes protocol amendments over the course of the trial. Planned enrollment of approximately 450 patients was projected to occur at participating centers in the United States and Canada.

Medically stable patients $\geq$ 18 years with diagnoses of HF, EF $>$ 40% and NT-proBNP levels $\geq$ 500 pg/mL (or BNP $\geq$ 150pg/mL) for patients in normal sinus rhythm (NT-proBNP $\geq$ 1000 pg/mL or BNP $\geq$ 300 pg/mL in atrial fibrillation) were eligible for participation during a current hospitalization for WHF or within 30 days of a WHF event (Table 1). Patients were eligible for enrollment irrespective of both the duration of diagnosis (ie, de novo or worsening chronic HF) and prior status of taking of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs). Patients with HF with improved EF were eligible (prior EF $<$ 40% with current EF $>$ 40% for at least 3 months), and there was not a specific exclusion criterion for body mass index (BMI) (in the final amendment following removal of the BMI $>$ 50 kg/m^2 exclusion on December 8, 2021). Patients with Sac/Val use within the past 60 days, serum potassium $>$ 5.2 mEq/L, eGFR $<$ 20mL/min/1.73 m^2, isolated right HF, or hypersensitivity to study drugs (including prior angioedema) were not eligible. The criterion of serum potassium $>$ 5.2 mEq/L was chosen for consistency with prior Sac/Val trials, including PIONEER-HF and PARAGON-HF. In addition, those with significant valvular heart disease that was likely to require intervention within the duration of the trial as well as those with genetic hypertrophic cardiomyopathy or infiltrative cardiomyopathy, including suspected or confirmed amyloid heart disease, were ineligible. In order to provide for a necessary 36-hour washout of prior ACEi treatment before receiving Sac/Val, eligible patients were randomized no earlier than 36 hours after their last ACEi dose. Following management of the acute WHF episode, all patients were required to be medically stable, as defined by a systolic blood pressure $>$ 100 mmHg for the preceding 6 hours, no increase (ie, intensification) in IV diuretics or use of IV vasodilators within the past 6 hours, and no IV inotropes administered for 24 hours prior to randomization. PARAGLIDE-HF is registered at clinicaltrials.gov (NCT03988634).

Treatment Protocol and Study Schedule

Patients were randomly assigned 1:1 to Sac/Val titrated to a target dosage of 97/103 mg twice daily vs Val titrated to 160 mg twice daily, as tolerated. See Supplementary Table 2 for full details about study drug's initiation and titration. In brief, the initial dose at randomization was determined based

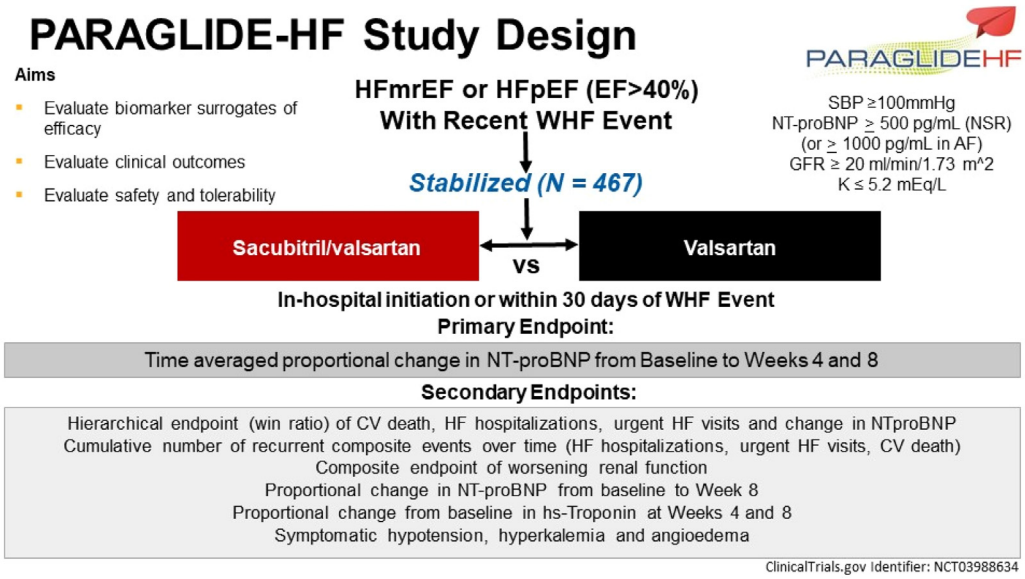

Fig. 1. PARAGLIDE-HF trial overview.

Table 1. Inclusion and exclusion criteria

Patients eligible for inclusion in this study must meet *all* of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Patients must be ≥18 years of age, male or female.
3. Patients must be currently hospitalized for WHF (HFpEF decompensation), or be within 30 days of discharge following a WHF event (defined as hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics).
4. Randomized patients will have been hemodynamically stable, defined in this study as having:
   a. SBP ≥100 mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension;
   b. No increase (intensification) of IV diuretic dosage within past 6 hours prior to randomization;
   c. No IV inotropic drugs for 24 hours prior to randomization;
   d. No IV vasodilators, including nitrates, within past 6 hours prior to randomization.
5. HFpEF with most recent LVEF >40% (within the past 3 months)
6. NT-proBNP or BNP at the time of acute HFpEF decompensation or post-decompensation screening (and within 72 hours for post-decompensation randomization, if applicable)
   - Patients not in AF at the time of biomarker assessment: NT-proBNP ≥ 500 pg/mL or BNP ≥ 150 pg/mL; patients in AF at the time of biomarker assessment: NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL
7. Have not taken an ACEi for 36 hours prior to randomization.

Patients meeting any of the following criteria are not eligible for inclusion in this study:

1. Any clinical event within the 90 days prior to randomization that could have reduced the LVEF (ie, myocardial infarction, coronary artery bypass graft), unless an echo measurement was performed after the event, confirming the LVEF to be >40%;
2. Sacubitril/valsartan usage within the past 60 days;
3. eGFR <20mL/min/1.73 m^2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula;
4. Serum potassium >5.2 mEq/L;
5. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major cardiovascular (CV) surgery, percutaneous coronary intervention or carotid angioplasty within 30 days prior to randomization;
6. Probable alternative diagnoses that, in the opinion of the investigator, could account for the patient's HF symptoms (ie, dyspnea, fatigue), such as significant pulmonary disease (including primary pulmonary hypertension), anemia or obesity;
7. Isolated right HF in the absence of left-sided structural heart disease;
8. History of hypersensitivity (ie, including angioedema), known or suspected contraindications or intolerance to any of the study drugs, including ARNIs (ie, sacubitril/valsartan) and/or ARBs;
9. Patients with known histories of angioedema due to any etiology;
10. Patients with histories of heart transplantation or left ventricular assist devices, being currently on the transplant list or with planned intent to implant a left ventricular assist device or undergoing cardiac resynchronization therapy;
11. A cardiac resynchronization therapy device within the initial 3 months of enrollment during the trial;
12. A cardiac or noncardiac medical condition other than HF with an estimated life expectancy of <6 months;
13. Known pericardial constriction, genetic hypertrophic cardiomyopathy or infiltrative cardiomyopathy, including suspected or confirmed amyloid heart disease (amyloidosis);
14. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 bpm;
15. Clinically significant congenital heart disease believed to be the cause of the patient's symptoms and signs of HF;
16. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention within the duration of the trial;
17. Any surgical or medical condition which, in the opinion of the investigator, may place the patient at higher risk due to 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;
18. Known hepatic impairment (as evidenced by total bilirubin >3 mg/dL or increased ammonia levels, if performed) or history of cirrhosis with evidence of portal hypertension such as varices;
19. Participation in any other clinical trial involving investigational agents or devices within the past 30 days;
20. Current confirmed COVID-19 infection;
21. Past COVID19 infection with persistent symptom burden suspected to be due to COVID19;
22. Pregnant or nursing (lactating) women, in whom pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive laboratory test for human chorionic gonadotropin;
23. 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 of the investigational drug and for 7 days off the study drug.

on the patient's previous dose of (or lack of) ACEis/ARBs immediately prior to the current WHF event (HF decompensation), or at the time of post-decompensation randomization (dose 1 or 2). As detailed in the protocol, every attempt was made to titrate to and maintain patients on the target study drug's dosage level for as long as possible throughout the study. However, maximal dosages of the study's medication were determined by the investigator on the basis of the patients' clinical status. Dosage adjustments to lower dosage levels could be made at any time at both scheduled and unscheduled visits if clinically indicated for reasons of blood pressure or tolerability. Adjustments to increase dosage levels

could be made at any time on the basis of clinical need or investigator judgment. The concomitant use of open-label ACEis or ARBs was prohibited while the patient was receiving the study's medication. The planned maximum duration of treatment was up to approximately 20 months of double-blind treatment, and the last patient randomized was followed for a minimum of 8 weeks.

Supplementary Table 3 includes the study's visit schedule and assessment details. In brief, screening occurs during the index hospitalization or within 30 days of a WHF event. Following randomization and baseline assessment, study visits occur at day 7 (Week 1), followed by day 28 (Week 4), day 56 (Week 8), and then approximately every 112 days (16 weeks/4 months).

Study Endpoints

The primary efficacy endpoint is the time-averaged proportional change in NT-proBNP levels from baseline to Weeks 4 and 8. Secondary objectives include a win-ratio-based composite hierarchical outcome consisting of: (1) time to cardiovascular death; (2) number and times of HF hospitalizations during follow-up; (3) number and times of urgent HF visits during follow-up; and (4) time-averaged proportional change in NT-proBNP levels (from baseline to Weeks 4 and 8). Additional secondary clinical outcomes include the cumulative number of recurrent composite events over time, ie, the total number of composite events of HF hospitalizations, urgent HF visits, and cardiovascular death; the incidences of a composite endpoint of worsening renal function, defined as (1) renal death, (2) reaching end-stage renal disease or (3) $\geq$ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline. Tolerability and the incidence of adverse events of special interest during treatment will be assessed including the incidence of symptomatic hypotension, hyperkalemia (potassium $>$ 5.5 mEq/L), angioedema and worsening renal function, defined as an increase in serum creatinine of $\geq$ 0.5mg/dL and worsening of the eGFR by at least 25%. A summary of study endpoints is included in Table 2.

Table 2. Study endpoints

Primary Endpoint
• The time averaged proportional change in NT-proBNP levels from baseline to Weeks 4 and 8.
Secondary Endpoints
• The composite hierarchical outcome consisting of: (1) time to CV death, (2) number and times of HF hospitalizations during follow-up, (3) number and times of urgent HF visits during follow-up, and {4) time-averaged proportional change in NT-proBNP levels (from baseline to Weeks 4 and 8); • The cumulative number of recurrent composite events over-time, ie, the total number of composite events of HF hospitalizations, urgent HF visits and cardiovascular death. • The incidences of a composite endpoint of worsening renal function, defined as: ○ renal death; ○ reaching end-stage renal disease; ○ ≥50% decline in eGFR relative to baseline. • Proportional change in NT-proBNP levels from baseline to Week 8; • Proportional change from baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8; • Dosing levels and discontinuations; • Incidence of symptomatic hypotension during treatment; • Incidence of hyperkalemia (potassium >5.5 mEq/L); • Incidence of angioedema; • Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5 mg/dL and worsening of the eGFR by at least 25%.

Statistical Considerations

The primary null hypothesis (H_{10}) to be tested is that the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8) divided by baseline for the Sac/Val and Val groups are equal vs the alternative hypothesis (H_{1a}) that the ratio of the geometric means of NT-proBNP are not equal. The treatment effect, in terms of ratios of geometric means, will be estimated based on the least-squared means (LS-means) from an ANCOVA model, and the corresponding 95% 2-sided confidence interval will be provided. Secondary and exploratory endpoints will be analyzed as detailed in the protocol and statistical analysis plan.

A sample size of approximately 450 patients will have 85% power to detect a 23% reduction in the geometric mean of the proportional change from baseline to an average of Weeks 4 and 8 of NT-proBNP for the Sac/Val treatment group. The power is estimated assuming a 2-sided significance level of 0.05, a common standard deviation of 0.85 for change in log transformed NT-proBNP, and a 15% rate of missingness in NT-proBNP at both Week 4 and Week 8. More complete statistical details are provided in the Supplement.

Funding and Study Organization

The PARAGLIDE-HF trial was led by an academic Steering Committee in collaboration with the sponsor, Novartis. Overall responsibility for the oversight and management of the trial lay with the Steering Committee, which comprised senior independent academic investigators, who are experts in their field, as well as representatives of the sponsor. The Data and Safety Monitoring Board included 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 Supplementary Table 4. The authors were solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

Ethical Considerations

The PARAGLIDE-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.

Baseline Characteristics

The trial enrolled 467 participants from June 2019 through October 2022. The trial population included 52% women and 22% Black individuals with a mean ± SD age of 70 ± 12 years and a median (IQR) BMI of 33 (27−40) kg/m^2 (Table 3). The IQR EF was 55% (50%−60%), 23% had an HFmrEF (EF 41%−49%), and 24% had an EF > 60%. Overall, 33% had de novo HF, 29% had an HF hospitalization prior to the qualifying WHF event, and 69% were enrolled while in the hospital (31% were enrolled while outpatients and within 30 days of the event). Regarding screening natriuretic peptide levels, median NT-proBNP level (available n = 258, 55%) was 2009 (1291−3813) pg/mL, and median BNP (available n = 207, 44%) was 517 (350−911) pg/mL. Ischemic etiology was documented in only 18% of patients. With regard to renal function, mean ± SD baseline eGFR was 52 ± 19 mL/min/1.73 m^2. Background comorbidities included the following: 49% had diabetes mellitus, and 59% had histories of atrial fibrillation/flutter (51% had ongoing AF/AFL). Baseline ACEi/ARB, beta-blocker, mineralocorticoid receptor antagonist (MRA), and SGLT2i use were 77%, 76%, 29%, and 12%, respectively.

Discussion

PARAGLIDE-HF will provide important information regarding the efficacy, safety and tolerability of initiating Sac/Val therapy in patients with a WHF event (HFmrEF and HFpEF decompensation) who were hemodynamically stabilized during a hospitalization for WHF or experienced an outpatient WHF event requiring IV diuretics. These data from PARAGLIDE-HF will complement the PARAGON-HF trial, which focused on Sac/Val investigation in chronic HFpEF,[2] and the specific secondary analysis assessing treatment effects based on time from prior HF hospitalization.[5] The analytic plan includes prespecified analyses pooling the PARAGLIDE-HF participants with the aforementioned similar participants in the PARAGON-HF trial. Comparing these trial

Table 3. Baseline characteristics

Variables	Total Randomized Patients n = 467
Age, years	69.8 (11.8)
Gender, n (%)	
Female	243 (52.0)
Male	224 (48.0)
Race, n (%)	
White	353 (75.6)
Black or African American	102 (21.8)
Asian	6 (1.3)
Native Hawaiian or other Pacific Islander	2 (0.4)
American Indian or Alaska Native	4 (0.9)
Ethnicity, n (%)	
Hispanic or Latino	28 (6.0)
Not Hispanic or Latino	437 (93.6)
Unknown	2 (0.4)
Country, n (%)	
USA	424 (90.8)
Canada	43 (9.2)
SBP (mmHg)	128 (117−145)
Heart rate (bpm)	74 (65−87)
BMI (kg/m^2)	32.9 (27.2−40.2)
eGFR (mL/min/1.73m^2)	49 (38−64)
Plasma NT-proBNP (pg/mL), local laboratory at screening	2009 (1291−3813)
n	258
BNP (pg/mL), local laboratory at screening	517 (350−911)
n	207
Clinical Features of HF	
History of HF prior to the qualifying HF event, n (%)	314 (67.2)
Ischemic etiology, n (%)	82 (17.6)
Randomization Location	
In hospital	322(69.0%)
Out of hospital	145(31.0%)
LVEF (%)	
Mean (SD)	55.4 (8.07)
Median	55
Q1, Q3 (IQR)	50.0, 60.0 (10.0)
Min, Max	41.0, 80.0
LVEF Category, n (%)	
LVEF 41%−49%	107 (22.9)
LVEF 50%−60%	250 (53.5)
LVEF >60%	110 (23.6)
Medical History, n (%)	
Hypertension	448 (95.9)
Diabetes mellitus	227 (48.6)
Atrial fibrillation/atrial flutter	273 (58.5)
Ongoing atrial fibrillation/atrial flutter	240 (51.4)
Stroke	48 (10.3)
Prior heart failure hospitalization	183 (39.2)
Myocardial infarction	27 (5.8)
Previous Use of Medication, n (%)	
ACEi or ARB	360 (77.1)
MRA	135 (28.9)
BB	354 (75.8)
SGLT2i	56 (12.0)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Table 4. Comparison of PARAGLIDE-HF to several recent HF trials*

	Sac/Val Trials				SGLT2 inhibitor trials in worsening HF	
	PARAMOUNT	PARAGON-HF	PIONEER-HF	PARAGLIDE-HF	SOLOIST-WHF	EMPULSE
Total n	301	4822	881	467	1222	530
n with LVEF >40% or ≥50%	n = 301 (100%) with LVEF ≥45%	n = 4822 (100%) with LVEF ≥45%	n = 0 with LVEF >40%	n = 467 (100%) with LVEF >40%	n = 256 (20.9%) with LVEF ≥50%	n = 169 (31.9%) with LVEF >40%
Setting	Chronic outpatient	Chronic outpatient	Inpatient WHF	Within 30 days of WHF event	In-hospital or recent discharge with WHF	Inpatient WHF
Treatment groups	Sac/Val vs Valsartan	Sac/Val vs Valsartan	Sac/Val vs Enalapril	Sac/Val vs Valsartan	Sotagliflozin vs placebo	Empagliflozin vs placebo
EF criterion	≥45%	≥45%	≤40%	>40%	All eligible	All eligible
Age (years)	70.9 (9.4)*	72.7 (8.3)	61 (14)	70 (12)	69 (63–76)*	71 (62–78)*
Women	57%*	52%*	28%	52%	33.7%	34%
Black	NR	2.2%*	36%	22%	4.1%	7.9%
EF (%)	58 (7.3)*	57.6 (7.8)*	24 (18-30)	55 (50–60)	35 (28–47)*	31.0 (23.0-45.0)*
NT-proBNP (pg/mL)	828 (460–1341)*	904 (475–1596)*	4812 (3050–8745) [screening]	2009 (1291–3813)	1816.8 (854.7–3658.5)*	3,299 (1,843–6130)*
BMI, kg/m^2	30.1 (5.5)*	30.2 (4.9)	30.5 (25.9–37.1)*	33 (27–40)	30.4 (26.3–34.3)*	28.35 (24.54–32.46)*
eGFR (mL/min/1.73 m^2)	67 (19)	63 (19)	58 (48–72)	52 (19)	49.2 (39.5–61.2)*	50.0 (36.0–65.0)*

Presented as mean (SD) or median (IQR).
*Presented as investigational treatment group value.NR, not reported.

populations (Table 4), PARAGON-HF had a mean age of 73 years compared to 70 years in PARAGLIDE-HF. Both studies included > 50% women, whereas PARAGLIDE-HF recruited 22% Black individuals (n = 102) compared to 2% in PARAGON-HF (n = 102). The median EF in PARAGON was 57% compared to 55% in PARAGLIDE-HF. Ischemic etiology was lower in PARAGLIDE-HF compared to PARAGON-HF. MRA use at baseline was relatively similar in the 2 trials, at just over 25%. With regard to SGLT2i use, 12% of the PARAGLIDE-HF population was taking an SGLT2i at baseline, whereas PARAGON-HF had a lower percentage of SGLT2i use, given guideline recommendations and available evidence at the time of trial enrollment.

PARAGLIDE-HF will also complement TRANSITION and PIONEER-HF, which examined the safety and efficacy of Sac/Val in hospitalized patients who were hemodynamically stabilized after an acute decompensated HFrEF event.[9,11] Comparing the PARAGLIDE-HF population to the PIONEER-HF population (Table 4), PIONEER-HF recruited a younger age group with lower BMIs and higher screening NT-proBNP levels. In both PIONEER-HF and PARAGLIDE-HF, approximately one-third of patients had de novo HF.

Recent studies have also explored sodium-glucose cotransporter-2 (SGLT2) inhibitors initiated in patients with a WHF event. The SOLOIST-WHF trial (a multicenter, randomized, double-blinded, placebo-controlled, phase 3 study evaluating the cardiovascular efficacy of sotagliflozin vs placebo) investigated the SGLT2 and SGLT1 inhibitor sotagliflozin in patients with diabetes (n = 1222) and a recent WHF event (regardless of EF) and showed an improvement in clinical outcomes compared with placebo. Patients were randomized either in the hospital or within 3 days of hospital discharge. The study population had a median age of 70 years (similar to the PARAGLIDE-HF trial). Approximately 40% of the population had baseline EF > 40%, and the baseline median NT-proBNP was approximately 1800 pg/mL (less than in PARAGLIDE-HF, even with the inclusion of patients with HFrEF in SOLOIST-WHF). The EMPULSE trial assessed in-hospital initiation of the SGLT2 inhibitor empagliflozin vs placebo in 530 patients hospitalized with acute HF (regardless of EF) and showed a net clinical benefit in a hierarchical composite of death, HF events and quality-of-life change through 90 days using win ratio methodology. The study population had a median age similar to that in the PARAGLIDE-HF trial and included 34% women and 78% white individuals. Approximately 30% of the EMPULSE population had baseline EF > 40%, and the baseline median NT-proBNP level was > 3000 pg/mL.

Thus, compared to these recent SGLT2-inhibitor studies, PARAGLIDE-HF includes only those with EF > 40% and has greater representation of women and Black individuals and a smaller overall sample size but a larger absolute number of patients with HFpEF. Also, in comparison to SOLOIST-WHF and EMPULSE, the PARAGLIDE-HF trial is unique because it has an active comparator, Val, an ARB. In the 2022 AHA/

ACC/HFSA Guideline for the Management of Heart Failure, ARBs have a 2b recommendation for HFmrEF and HFpEF (particularly at the lower end of this LVEF spectrum).[12] PARAGLIDE-HF is uniquely positioned to assess the potential incremental benefit of Sac added to Val in the patient population studied.

In conclusion, the PARAGLIDE-HF trial will inform clinical practice by providing evidence about the safety, tolerability and efficacy of Sac/Val vs Val in a diverse population with HFmrEF and HFpEF and with a recent WHF event to complement the data from PARAGON-HF in chronic HFmrEF/HFpEF as well as the data from PARADIGM-HF and PIONEER-HF, which focused on chronic HFrEF and stabilized acute HFrEF, respectively.

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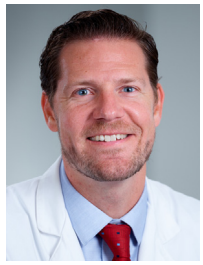
Lay Summary

Prior studies have shown the benefits of a medication called sacubitril/valsartan on outcomes in patients with heart failure and an ejection fraction (or "heart squeeze") of 45% or more. More information is needed regarding the effect and safety of the medication when started in those with recent worsening of their heart failure requiring a hospitalization, ED visit or urgent clinic visit. The PARAGLIDE-HF trial studied the effect of sacubitril/valsartan on a heart failure biomarker ("blood test") and clinical outcomes in patients with heart failure with an ejection fraction $>$ 40% and a recent worsening heart failure event.



Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.02.001.

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