FDA Briefing Document

Cardiovascular and Renal Drugs Advisory Committee Meeting

December 15, 2020

NDA 207620

Sacubitril / Valsartan

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this application to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Table of Tables

Table of Figures

Glossary

ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
AF	atrial fibrillation and atrial flutter
ASE	American Society of Echocardiography
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CABG	coronary artery bypass graft
CEC	Clinical Endpoint Committee
CI	confidence interval
CSS	Clinical Summary Score
CV	cardiovascular
DBP	diastolic blood pressure
DCN	Division of Cardiology and Nephrology
DM	diabetes mellitus
DMC	Data Monitoring Committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ER	emergency room
ESRD	end-stage renal disease
EQ-5D	EuroQol instrument
FAS	full efficacy analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	heart failure
HHF	hospitalization for heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved left ventricular ejection fraction
HFrEF	heart failure with reduced left ventricular ejection fraction
HR	hazard ratio
HTN	hypertension
IV	intravenous
IQR	interquartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAE	left atrial enlargement
LSM	least squares mean
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LWYY	Lin, Wei, Ying, and Yang model
MI	myocardial infarction

MMSE	Mini-Mental State Examination
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PLS	physical limitation score
RR	rate ratio
SBP	systolic blood pressure
TSS	total symptom score

I FDA Briefing Document

1. Draft Topics for Discussion

The Committee will be asked to opine on ENTRESTO for heart failure with preserved ejection fraction (HFpEF).

ENTRESTO (sacubitril/valsartan) has a claim for the treatment of heart failure with reduced ejection fraction (HFrEF), so this would be a new indication.

Section 505(d) of the 1962 Drug Amendments included a provision requiring manufacturers of drug products to establish a drug's effectiveness by *substantial evidence*, defined as *evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling….* We would like you to provide your insights as such experts. As always, your rationale is more important to us than is your vote.

The study supporting this claim is PARAGON-HF, but this study did not meet its prespecified success criterion for the primary endpoint. Approval under this circumstance is unusual but not unprecedented. Some examples are:

- Enalapril was approved for use in asymptomatic left ventricular dysfunction on the basis of SOLVD-Prevention.
- Digoxin was approved for heart failure on the basis of the DIG study.
- Carvedilol was approved for reduced ejection fraction following myocardial infarction on the basis of the CAPRICORN study.
- Bivalirudin was approved for use after percutaneous coronary intervention on the basis of the post-hoc pooling of the BAT studies.

Like the current case, all of the above involved new indications for approved drugs for relatively common cardiovascular diseases, but the extenuating circumstances were different. For PARAGON-HF, the *p*-value is only slightly above the 0.05 target. The Division encouraged the applicant to submit the supplementary application for the HFpEF indication and suggested some of the post-hoc analyses. PARAGON-HF illustrates two issues of long-standing interest to the Division.

- The value of adjudication is questionable in a blinded study with appropriate investigator expertise. In this case, the investigator-determined and adjudicator findings were virtually identical with respect to their risk ratios; inclusion of additional investigator-determined events resulted in a smaller confidence interval and, had the approach been prospectively planned, would have yielded a p-value < 0.05.

- The typical dichotomization of events wastes information. Use of strict, narrow definitions will declare "events" with a high degree of confidence, but many cases are

adjudicated negatively because of a lack of information (e.g., requirement for the presence of physical examination findings that are not documented in the patient's dossier), or because of alternative practices. Thus, there is a hierarchy of evidence in favor of the occurrence of an "event." We would like to consider giving "partial credit" to events based on the level of evidence provided, e.g., use of an ordinal variable rather than a dichotomous "yes" or "no."

The finding in PARAGON-HF seems mostly driven by subjects with ejection fraction towards the lower end of the range studied, i.e., closer to the range for patients with HFrEF. Had this been anticipated, one could have argued for an alpha level above 0.05 for PARAGON-HF, supported by the data from PARADIGM-HF showing benefit in patients with more reduced ejection fraction. Retrospectively, that still seems relevant.

1. Please comment on the various pre-specified and post-hoc analyses. Which ones contribute to your assessment of the strength of evidence supporting a claim? Which ones do not?
2. Does PARAGON-HF, perhaps supported by previous studies, provide sufficient evidence to support ANY claim?
3. If a claim for ENTRESTO were not granted on the basis of available information, what would be necessary to augment the support for approval?
4. If ENTRESTO warranted a claim, how would you describe the patients in whom such benefit applies?

2. Introduction

Sacubitril/valsartan is currently approved in US for the following indications:

1) To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction

2) For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Sacubitril/valsartan reduces NT-proBNP and is expected to improve cardiovascular outcomes

On April 21, 2020, the Applicant submitted an efficacy supplement for sacubitril/valsartan for the proposed indication: "to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction."

On September 22, 2020, the Applicant revised the proposed indication with the following addition (underlined): "to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction <u>with LVEF below normal</u>."

To support the proposed indication the Applicant submitted the results of a single trial, PARAGON-HF, a phase 3, randomized, double-blind, double-dummy, active-controlled trial comparing sacubitril/valsartan to valsartan in patients with symptomatic NYHA class II-IV heart

failure (HF) with left ventricular ejection fraction (LVEF) ≥ 45%. The primary efficacy endpoint was an adjudicated composite of total hospitalization for heart failure (HHF) (i.e., first hospitalization + recurrent hospitalizations) and cardiovascular (CV) death. The Division of Cardiology and Nephrology (DCN) agreed to the pre-specified threshold of 1-sided $p < 0.024$ in the final analysis to reject the null hypothesis. The trial demonstrated a rate ratio (RR) of 0.87; 95% CI 0.75, 1.01;1-sided $p = 0.029$; 2-sided $p = 0.06$, and thus failed to reject the null hypothesis.

A prespecified exploratory analysis, combining the primary efficacy endpoint with urgent HF visits, yielded a nominally significant result favoring sacubitril/valsartan (RR = 0.86; 95% CI 0.75, 0.99; 2-sided $p = 0.04$).

Post-hoc exploratory analyses and corresponding results included: 1) use of investigator-reported primary efficacy endpoint events in lieu of adjudicated events (RR = 0.84; 95% CI 0.74, 0.97; 2-sided $p = 0.01$); and 2) use of investigator-reported primary efficacy + urgent HF visits (RR = 0.83; 95% CI 0.73, 0.95; 2-sided $p = 0.006$).

In light of the pre-specified and post-hoc exploratory analyses results, the applicant seeks approval for the proposed indication. The applicant also combined data from the PARAGON-HF trial with data from the PARADIGM-HF trial that formed the basis of the HFrEF indication, to establish "totality of evidence" to support an approval for HF within a range of LVEFs that overlap HFrEF and the lower end of HFpEF.

DCN solicits advice from the Cardiovascular and Renal Drugs Advisory Committee on whether the available data support the benefit of sacubitril/valsartan for the treatment of patients with symptomatic HF with LVEF ≥ 45%.

3. Intended Population: Heart Failure with Preserved Ejection Fraction (HFpEF) with LVEF ≥ 45%

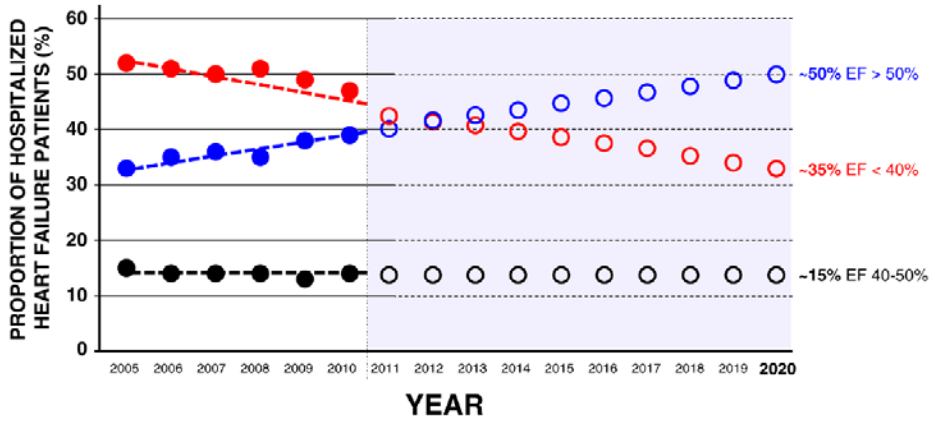
HFpEF is a heterogenous syndrome that is caused or exacerbated by a variety of cardiac and extracardiac abnormalities.[1] Although the definition of HFpEF remains controversial and has been variously defined in HF trials as HF with LVEF ≥ 40%, ≥ 45%, or ≥ 50%,[2] it is considered to be distinct from HFrEF in its pathophysiology and epidemiology.

HF is a chronic condition associated with premature mortality and significant morbidity, with high rates of hospitalization.[3] HF afflicts 1 to 3% of the population worldwide, with a higher prevalence in the elderly, ≥ 10% in those age ≥ 65 years. The annual incidence of HF in the United States (US) is > 650,000 and continues to increase with the aging population.

[1] Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;136:6–19.
[2] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.
[3] Dunlay, S., Roger, V. & Redfield, M. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 14, 591–602 (2017).

Approximately half of the total HF cases are attributed to HFpEF.[4] Fonarow et al reported that the rates of mortality and re-admission during the 60 to 90 days post-hospitalization are similar for patients with HFpEF and HFrEF, i.e., 9.5% vs. 9.8% and 29.2% vs. 29.9%, respectively. The incidence of HFpEF is growing compared to HFrEF (Figure 1).[5,6] HFpEF is a serious condition with significant unmet need. Currently, there is no FDA approved pharmacotherapy to treat patients with HFpEF.

Figure 1. Proportion of Hospitalized Patients with Heart Failure by LVEF Categories by Time



The Changing Landscape of Heart Failure: The Projected Trajectory of HFpEF in Hospitalized Heart Failure Patients Based on results from Get With the Guidelines-Heart Failure (GWTG-HF) Study (Steinberg et al [11••]; N=110,621), using actual data on the proportion of hospitalization patients with three types of HF (HFpEF [EF>50 %]; HFrEF [EF<40 %]; and HF borderline-EF [EF 40–50 %]) at each time point between 2005–2010 The trajectories for 2011–2020 were estimated for HFpEF and HFrEF using linear regression analyses, while HF borderline-EF was held at a constant 14 % proportion of hospitalized HF patients The regression equation for the projected HFpEF trajectory= −0 86(Year)+1771 (*P*=0 015 for the trend of decreasing HFrEF over time); the equation for the projected HFrEF trajectory= 1 086(Year)-2144 (*P*=0 008 for the trend of increasing HFpEF over time)

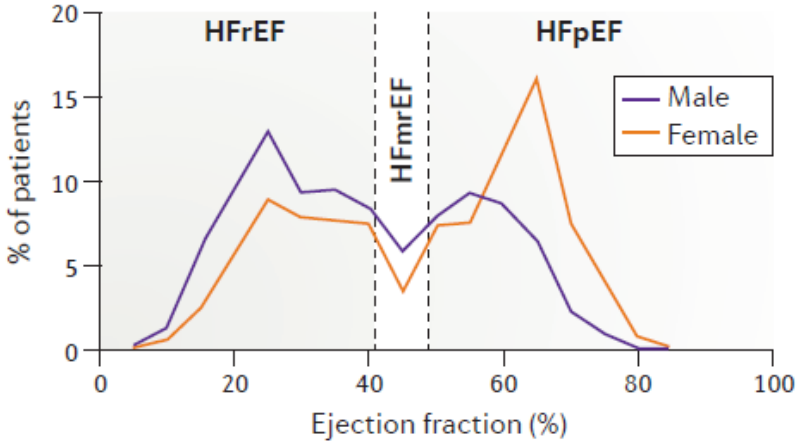
Source: Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10(4):401-410.

Based on epidemiologic data, Dunlay et al 2017 state that a) after adjusting for age and other risk factors, the risk of HFpEF is fairly similar in men and women; however, the risk of HFrEF is much lower in women than men, and that b) the majority of deaths in patients with HFpEF are CV, but the proportion of non-CV deaths is higher in HFpEF than HFrEF. Figure 2 displays the unadjusted incidence rates of HF by LVEF and sex (Dunlay et al 2017).

[4] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

[5] Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126:65–75.

Figure 2. Incidence of Heart Failure by LVEF in Males and Females (Dunlay et al 2017)



Distribution of left ventricular ejection fraction (LVEF) in incident heart failure. The distribution of ejection fraction in 1,223 patients with incident heart failure (defined by Framingham criteria) from Olmsted County, Minnesota, USA, according to gender
HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction

Source: Dunlay, S., Roger, V. & Redfield, M. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 14, 591–602 (2017).

The underlying pathophysiologic mechanisms in HFpEF are diastolic dysfunction, longitudinal left ventricular systolic dysfunction (despite a normal EF), pulmonary hypertension, abnormal exercise-induced vasodilation, abnormal ventricular-arterial and ventriculoatrial coupling, chronotropic incompetence, and extracardiac volume overload.[6] Tromp et al describe that the biological pathways unique to HFpEF are related more to inflammation, neutrophil degranulation, and integrin signaling, whereas in HFrEF are associated with increased metabolism and cellular hypertrophy indicative of distinct mechanism(s) for HFpEF and HFrEF.[7] Compared to HFrEF, patients with HFpEF tend to be older, have a higher prevalence of hypertension and obesity, and a lower prevalence of ischemic heart disease. Established therapies for HFrEF such as angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and spironolactone have not been demonstrated to be efficacious in HFpEF (Table 1).

[6] Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10:401-410.
[7] Tromp J, Westenbrink BD, Ouwerkerk W, van Veldhuisen DJ, Samani NJ, Ponikowski P, Metra M, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Lang CC, Ng LL, Zannad F, Zwinderman AH, Hillege HL, van der Meer P, Voors AA. Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction. J Am Coll Cardiol. 2018;72:1081-1090.

Table 1. Results of Outcome Trials in Heart Failure with Preserved Ejection Fraction

Trial	N	Inclusion, Baseline LVEF	Treatment arms Follow-up Duration	Primary Efficacy Endpoint	Primary Endpoint Results, Intervention vs. Comparator	Total number of HHF/Number of patients (%), intervention vs comparator
CHARM-Preserved, 2003[8]	3023	> 40%, mean: 54%	Candesartan 32 mg vs. Placebo Median: 36.6 months	Time to CV death or HHF	22% vs. 24%, covariate adjusted HR 0.86, CI 0.74-1.0, *p*=0.05	26.5% vs. 37.5%, *p*=0.014
PEP-CHF, 2006[9]	852	> 40%, median: 65%	Perindopril 4 mg vs. Placebo Mean: 26.2 months	Time to all-cause mortality or HHF	Annual incidence of 13.2% vs 12.2%, HR 0.92, CI 0.70-1.21, *p*=0.545	8.0% vs. 12.4% during the first year of follow-up (HR 0.63; CI 0.41–0.97; *p*=0.033)
I-PRESERVE, 2008[10]	4563	≥ 45%, mean: 60%	Irbesartan 300 mg vs. Placebo Mean: 49.5 months	Time to all-cause mortality or CV hospitalization	100.4 and 105.4 per 1000 patient-years, HR 0.95, CI 0.86 to 1.05, *p*=0.35	
TOPCAT, 2014[11]	3445	≥ 45%, median: 56%	Spironolactone 15 to 45 mg vs. Placebo Mean: 3.3 years	Time to CV death or aborted cardiac arrest or HHF	18.6% vs 20.4%, HR 0.89, CI 0.77-1.04, *p*=0.14	6.8 vs. 8.3 per 100 person-years; *p*=0.03

Abbreviations - LVEF: left ventricular ejection fraction, vs.: versus, CV: cardiovascular, HHF: hospitalization for heart failure, HR: hazard ratio, CI: 95% confidence interval, *p*: *p*-value, SBP: systolic blood pressure, DBP: diastolic blood pressure
Source: Reviewer Compilation

HF Classification Based on LVEF

HF is defined as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The 2013 ACCF/AHA guidelines[12] classified HF based on LVEF as HFrEF when LVEF ≤ 40%, HFpEF when LVEF ≥ 50%, HFpEF borderline when LVEF is 41 to 49%, and HFpEF improved when LVEF > 40% in patients who previously had HFrEF. The term HFpEF was proposed to describe patients with HF who do not have a major reduction in systolic function and was not intended to be synonymous with normal LVEF. Historically, HF trials with mortality as the primary endpoint excluded patients with LVEF greater than 35 to 40% as an enrichment strategy. This led to an evidence void in patients with LVEF > 40%. Pfeffer et al describe that the 1997 CHARM-Preserved trial enrolled patients with LVEF >40% to address this "*therapeutic void rather than a mechanistic distinction*.[13]" The term HFpEF was intended to distinguish from the well-studied lower LVEF arms and not to imply normal structure and function. The 2016 European Society of Cardiology Guidelines for

[8] Yusuf S, Pfeffer MA, Swedberg K, et al for the CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet; 362:777-781.
[9] Cleland GF, Tendera M, Adamus J (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J; 27:2338-45.
[10] Massie BM, Carson PE, McMurray JJ, et al for the I-PRESERVE Investigators (2008) Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med; 359:2456-67.
[11] Pitt B, Pfeffer MA, Assmann SF, et al for the TOPCAT Investigators (2014) Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med; 370:1383-92.
[12] 2013 ACCF/AHA Guideline for the Management of Heart Failure
[13] Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. 2019;124:1598-1617. doi:10 1161/CIRCRESAHA.119.313572.

the diagnosis and treatment of acute and chronic HF[14] classify patients with HF with LVEF from 40 to 49% as HF with mid-range ejection fraction (HFmrEF).

LVEF, the most widely used criterion to classify HF, is the proportion of blood ejected during LV systole. It is an indirect measure of global left ventricular systolic function. American Society of Echocardiography (ASE)[15] defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females. The normal reference range for LVEF is derived from a "normal" population that excluded subjects with any of the following criteria: systolic blood pressure (SBP) > 140 mm Hg, diastolic blood pressure > 80 mm Hg, history of drug-treated hypertension, diagnosis of diabetes, impaired fasting glucose > 100 mg/dL, body mass index > 30 kg/m^2, creatinine > 1.3 mg/dL, estimated glomerular filtration rate < 60 mL/min/1.73 m^2 , total cholesterol > 240 mg/dL, low-density lipoprotein cholesterol > 130 mg/dL, and total triglycerides > 150 mg/dL. Table 2 displays normal and abnormal ranges for LVEF by sex. When HFpEF is defined as LVEF ≥ 40 or 45%, it includes patients with HF with mildly abnormal LVEF.

Table 2. Normal and Abnormal Range of Left Ventricular Ejection Fraction (LVEF) by Gender

	Male				**Female**			
	Normal Range	Mildly Abnormal	Moderately Abnormal	Severely Abnormal	Normal Range	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
LVEF (%)	52-72	41-51	30-40	<30	54-74	41-53	30-40	<30

Source: Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.

Proposed Classification of HFpEF Based on Phenotypes

In contrast to HFrEF, drug intervention trials targeting neurohormonal pathways in HFpEF using LVEF diagnostic criteria have failed. This failure has been attributed to distinct systemic and myocardial signaling in HFpEF and to diversity of HFpEF phenotypes. Hence, a different approach of phenotyping HFpEF patients into pathophysiologically homogenous arms has been proposed.[16,17] Patients with HFpEF are predominantly elderly females and have multiple

[14] Piotr Ponikowski, Adriaan A Voors, Stefan D Anker, Héctor Bueno, John G F Cleland, Andrew J S Coats, Volkmar Falk, José Ramón González-Juanatey, Veli-Pekka Harjola, Ewa A Jankowska, Mariell Jessup, Cecilia Linde, Petros Nihoyannopoulos, John T Parissis, Burkert Pieske, Jillian P Riley, Giuseppe M C Rosano, Luis M Ruilope, Frank Ruschitzka, Frans H Rutten, Peter van der Meer, ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200

[15] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.

[16] Reddy YN, Borlaug BA. Heart failure with preserved ejection fraction. Curr Probl Cardiol. 2016;41:145–188. doi: 10.1016/j.cpcardiol.2015.12.002.

[17] Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016;134:73–90. doi: 10.1161/CIRCULATIONAHA.116.021884.

comorbidities such as overweight/obesity (84%),[18] arterial hypertension (60%–80%),[19] type 2 diabetes mellitus (20%–45%), renal insufficiency, and sleep apnea. Rare etiologies of HFpEF such as constrictive pericarditis, valvular heart disease, high-output failure, or infiltrative cardiomyopathies are generally excluded in HFpEF clinical trials. It is theorized that systemic inflammation and/or release of proinflammatory mediators by epicardial tissue may cause microcirculatory dysfunction and myocardial fibrosis of the adjacent tissue, thus impairing left ventricular distensibility, increasing diastolic stiffness and LV filling pressure.[20] Other myocardial structural and chemical perturbations observed in HFpEF include reduced nitric oxide and cyclic guanosine monophosphate because of altered paracrine communication between inflamed microvascular endothelial cells and cardiomyocytes, and left ventricular hypertrophy. This is distinct from HFrEF where cardiac remodeling is primarily driven by cardiomyocyte injury and death due to ischemia, infection, or toxicity.[21]

The proposed HFpEF predisposition phenotypes include: a) overweight/obese/metabolic syndrome/type 2 diabetes mellitus, b) arterial hypertension, c) renal dysfunction, and d) coronary artery disease. Clinical presentation phenotypes include: a) lung congestion, b) chronotropic incompetence, c) pulmonary hypertension, d) skeletal muscle weakness, and e) atrial fibrillation.[8] Compared to non-obese HFpEF patients, obesity-related HFpEF patients display greater biventricular remodeling, volume overload, more right ventricular dysfunction, greater ventricular interaction and pericardial restraint, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation.[22] Usually there is some degree of overlap between the proposed predisposition and clinical phenotypes. There have been no prospective intervention trials that have evaluated treatment based on a phenotypic definition of HFpEF.

Current Management Approach to HFpEF

The 2017 ACC/AHA recommendations[23] to treat patients with HFpEF include the following:

- Class I recommendation to treat hypertension
- Class I recommendation to use of diuretics for symptomatic relief
- Class IIa recommendation for coronary revascularization for concomitant symptomatic (or evidence of significant myocardial ischemia) coronary artery disease; and guideline directed management of atrial fibrillation

[18] Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial.Circ Heart Fail. 2011; 4:324–331. doi: 10.1161/CIRCHEARTFAILURE.110.959890.
[19] Dhingra A, Garg A, Kaur S, Chopra S, Batra JS, Pandey A, Chaanine AH, Agarwal SK. Epidemiology of heart failure with preserved ejection fraction.Curr Heart Fail Rep. 2014; 11:354–365. doi: 10.1007/s11897-014-0223-7
[20] Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 2015;131:550–559.
[21] González A, Ravassa S, Beaumont J, López B, Díez J. New targets to treat the structural remodeling of the myocardium. J Am Coll Cardiol. 2011;58:1833–1843. doi: 10.1016/j.jacc.2011.06.058.
[22] Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. 2017;136(1):6-19. doi:10.1161/CIRCULATIONAHA.116.026807
[23] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–e161.

- Class IIb recommendation to consider use of aldosterone receptor antagonists in appropriately selected patients with HFpEF [with EF ≥ 45%, elevated brain natriuretic peptide (BNP) levels or HF admission within 1 year, estimated glomerular filtration rate (eGFR) >30 mL/min, creatinine < 2.5 mg/dL, potassium <5.0 mEq/L] based on the findings from the Treatment of Preserved Cardiac Function Heart Failure (TOPCAT) trial[4]
- Class IIb recommendation to consider use of ARBs to decrease hospitalizations for patients with HFpEF

4. Regulatory History of Sacubitril/Valsartan

Sacubitril/valsartan (Entresto) is a fixed drug combination of a neprilysin inhibitor (sacubitril) and an angiotensin receptor blocker (valsartan). Sacubitril is a first-in-class neprilysin inhibitor and is converted to the active metabolite sacubitrilat. Sacubitrilat inhibits the enzyme neprilysin thereby increasing the level of vasoactive peptides such as natriuretic peptides, adrenomedullin, endothelin-1, angiotensin II, and bradykinin. Other than angiotensin II, these vasoactive peptides have vasodilatory, natriuretic, and anti-fibrotic effects that are thought to be beneficial in HF. Natriuretic peptides activate membrane bound guanylyl cyclase-coupled receptors, resulting in increased concentration of the second messenger cyclic guanosine monophosphate, thereby promoting vasodilation, natriuresis and diuresis, increased glomerular filtration and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and antifibrotic effects. Angiotensin II causes vasoconstriction, fluid retention, fibrosis, and cardiac remodeling. Valsartan in sacubitril/valsartan attenuates these adverse effects of angiotensin II.

Sacubitril/valsartan was approved to treat patients with HFrEF based on the PARADIGM-HF study that demonstrated superiority of sacubitril/valsartan 200 mg bid compared to enalapril 10 mg bid in symptomatic patients with HFrEF, defined as HF with LVEF ≤ 40%, changed to ≤ 35% by Protocol Amendment 1 (N 8,442) in reducing the incidence of CV death and HHF. Sacubitril/valsartan reduced the time to first composite endpoint of CV death or HHF with a hazard ratio of 0.80; 95% CI 0.73, 0.87; $p < 0.0001$. Table 3 displays the numbers of events and patients with events in the PARADIGM-HF trial. Patients in the sacubitril/valsartan arm experienced 82 and 121 fewer CV death and HHF events, compared to the enalapril group. There were 135 and 121 fewer patients who experienced CV death and HHF, respectively, in the sacubitril/valsartan group than the enalapril group.

Table 3. Treatment Effect for the Primary Composite Endpoint and its Components in PARADIGM-HF in Patients with Heart Failure with Reduced Ejection Fraction

	LCZ696 N = 4,187 n (%)	**Enalapril N = 4,212 n (%)**	**Hazard Ratio (95% CI)**	***p*-value**
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	< 0.0001
Cardiovascular death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events* Cardiovascular death**	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity
**Includes patients who had heart failure hospitalization prior to death

Source: Reviewer compilation

Key safety issues with sacubitril/valsartan include the risks of hyperkalemia, hypotension, renal impairment, and angioedema.

The Applicant has submitted the results of PARAGON-HF to support the claim for reduction in HHF with sacubitril/valsartan compared to valsartan in symptomatic patients with HFpEF defined as HF with LVEF ≥ 45% (N=4822). The dose of sacubitril/valsartan in this document refers to the total dose strength of both components, i.e., 200 mg is equivalent to sacubitril and valsartan component strengths of 97 and 103 mg, respectively.

5. Overview of PARAGON-HF

PARAGON-HF was a phase 3, randomized, double-blind, double-dummy, active-controlled trial that compared sacubitril/valsartan with valsartan in patients with symptomatic HF (NYHA class II-IV) with LVEF ≥ 45%. PARAGON-HF randomized 4,822 adult patients to either sacubitril/valsartan 200 mg or valsartan 160 mg twice daily in a ratio of 1:1 at 755 sites in 43 countries. The study population included 52% women, 83% aged ≥ 65 years [mean age 73 years (range, 50 to 98)], 82% Caucasian, and 36% from Central Europe, 29% Western Europe, 16% Asia/Pacific, 12% North America, and 8% Latin America.

A total of 1903 primary composite endpoints, including 1487 total HHF events (78.1%) and 416 CV deaths (21.9%), were experienced by 1083 patients in the full analysis set (N=4796). Sacubitril/valsartan reduced the rate of the primary efficacy endpoint with a RR of 0.87; 95% CI 0.75, 1.01; *p*=0.06, thus narrowly missing statistical significance. There were 894 (12.8 per 100 patient-years) primary composite events in the sacubitril/valsartan arm compared to 1009 events (14.6 per 100 patient-years) in the valsartan arm, a difference of 115 events. The effect of sacubitril/valsartan on the primary endpoint was driven primarily by the total HHF component.

A total of 690 (9.9 per 100 patient-years) total HHF events occurred in the sacubitril/valsartan arm compared to 797 (11.6 per 100 patient-years) in the valsartan arm, a difference of 107 events

with a relative rate reduction of 15% (RR=0.85; 95% CI: 0.72, 1.00; 2-sided *p*=0.06). There was no difference between treatment arms with regard to CV death risk (HR=0.95; 95% CI: 0.79, 1.16; 2-sided *p*=0.62), but CV death trended in favor of sacubitril/valsartan.

Result of the pre-specified exploratory analysis in PARAGON-HF was as follows:

- Analysis of Clinical Endpoint Committee-confirmed *expanded* primary composite endpoint (which added *urgent HF visits)* demonstrated a RR of 0.86; 95% CI: 0.75, 0.99; *p*=0.04 favoring sacubitril/valsartan. There were 40 and 55 Clinical Endpoint Committee (CEC)-adjudicated urgent HF events in the sacubitril/valsartan and valsartan arms, respectively. The point estimates derived from analyses of the primary and expanded primary composite endpoints are similar, except that the *p*-value was below the pre-specified threshold for the primary composite endpoint (Section 6.2.5).

Results of post-hoc exploratory analyses in PARAGON-HF were as follows:

- Analysis of *investigator-reported* events for the primary composite endpoint of total HHF and CV death demonstrated a RR of 0.84; 95% CI: 0.74, 0.97; *p*=0.01. Investigator-reported events added 226 and 290 HHF events but decreased CV death by 56 and 58 events in the sacubitril/valsartan and valsartan arms, respectively. Hence, a net 170 and 232 events were added to the CEC-reported primary composite endpoint leading to a *p*-value of 0.01, without a significant change in RR (Section 6.2.5).

- Analysis of *investigator-reported expanded* primary composite endpoint events including total HHF, *urgent HF visits*, and CV death demonstrated a RR of 0.83; 95% CI: 0.73, 0.95; *p*=0.006. There were 136 and 173 investigator-reported urgent HF events in sacubitril/valsartan and valsartan arms, respectively (Section 6.2.5).

- Time to first event analysis of CEC-confirmed HHF demonstrated incidences of HHF of 405/2407 (16.83%) versus 433/2389 (18.12%) in the sacubitril/valsartan and valsartan arms, respectively. This yielded a HR of 0.9; 95% CI: 0.79, 1.04; *p*=0.19 (Section 6.2.5).

Thus, the study failed to reject the null hypothesis for the prospectively planned primary efficacy endpoint; however, *reasonable* exploratory analyses, planned an unplanned, were able to reject the null hypothesis.

Subgroup analyses in PARAGON-HF demonstrated a heterogeneity of treatment effect by sex and LVEF. The trial population (N = 4796) was 52% female (n = 2479) and had a median LVEF of 57%. The RR for the primary composite endpoint was 1.02 (95% CI: 0.85, 1.25) and 0.73 (95% CI: 0.59, 0.90) for male versus female, respectively. The RR for the primary composite endpoint was 1.00 (95% CI: 0.81, 1.23) and 0.78 (95% CI: 0.64, 0.95) for patients with LVEF > 57% and ≤ 57%, respectively (Section 6.2.7).

The safety profile of sacubitril/valsartan in patients with HF with LVEF ≤ 40% is well known. No new safety signals were identified in patients with HF with LVEF ≥ 45%. Safety findings in PARAGON-HF will not be discussed in this document.

6. Evidence of Benefit (Efficacy Assessment)

6.1. Design of Clinical Trial/Study Intended to Demonstrate Benefit to Patients

6.1.1. PARAGON-HF Study Design

6.1.1.1. Study Overview

In support of the proposed indication the Applicant conducted a phase 3 study (PARAGON-HF) titled, "A multicenter, randomized, double-blind, parallel arm, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction." The study was conducted between July 18, 2014 and June 7, 2019 at 755 sites in 43 countries. The original protocol for PARAGON-HF dated June 3, 2013 was amended four times. (Section 8.2)

6.1.1.2. Study Design

PARAGON -HF was a phase 3, randomized, double-blind, double-dummy, active-controlled trial designed to evaluate the efficacy and safety of sacubitril/valsartan versus valsartan in patients with symptomatic HF (NYHA class II-IV) with LVEF ≥ 45%. The study enrolled patients ≥ 50 years of age with a LVEF ≥ 45% and evidence of structural heart disease [left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)] within 6 months prior to enrollment, current symptomatic HF (NYHA class II-IV) and symptoms of HF requiring treatment with diuretic therapy for at least 30 days prior to Visit 1. In addition, patients were required to have at least one of the following: (1) a hospitalization for HF within 9 months prior to enrollment and NT-proBNP > 200 pg/mL for patients not in atrial fibrillation (AF) or > 600 pg/mL for patients in AF at Visit 1, or (2) NT-proBNP > 300 pg/mL for patients not in AF or >900 pg/mL for patients in AF at Visit 1. The eligibility criteria were specifically designed to include patients with HFpEF and avoid including patients with borderline HFrEF. All eligible patients were randomized to either sacubitril/valsartan 200 mg bid (dose level 3) with valsartan placebo or valsartan 160 mg bid (dose level 3) with sacubitril/valsartan placebo in a 1:1 ratio at Visit 199/201.

PARAGON-HF had three treatment periods: screening, treatment-run-in, and randomized. Figure 3 displays the study design of PARAGON-HF.

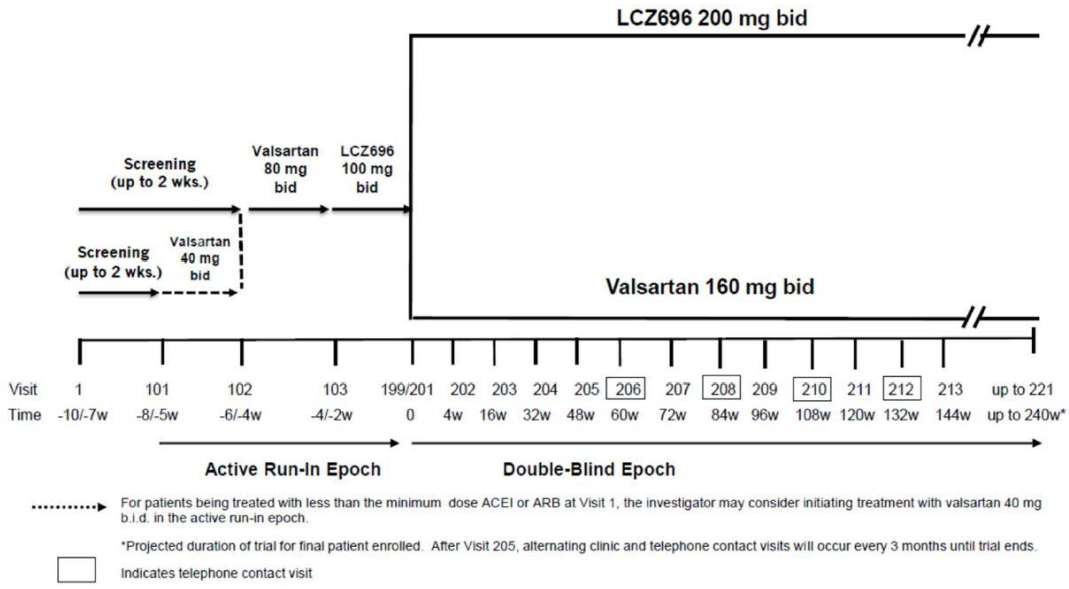
Screening Period (2 weeks): Patient eligibility was determined during the screening period. LVEF measurements were obtained locally from echocardiograms performed within 6 months of Visit 1. If no echocardiogram was available, then an echocardiogram was performed during the screening period. A patient considered to be a screen failure could be re-screened up to two times with a minimum of 2 weeks between re-screenings. Screening NT-proBNP, potassium, eGFR, and liver function tests were assessed at the central laboratory.

Treatment Run-in Period (3-8 weeks): Patients who met the eligibility criteria received single-blind treatment with valsartan 80 mg twice a day for 1 to 2 weeks followed by sacubitril/valsartan 100 mg twice a day for 2 to 4 weeks, if they met the safety monitoring criteria (Table 4). If patients had been on an ACEI or ARB at doses lower than the specified minimum pre-study doses, then they were started on valsartan 40 mg twice a day for 1-2 weeks, titrated up to 80 mg twice a day. The run-in period was used to determine tolerance to half the target doses of the study drugs. Half the target doses were selected because only a small effect on blood pressure was expected with increases in the sacubitril/valsartan dose from 100 to 200 mg twice daily, and in PARADIGM-HF, the majority of the patients who tolerated sacubitril/valsartan 100 mg twice daily were able to tolerate 200 mg twice daily.

Either the local or central laboratory could be used for the assessment of potassium and eGFR at the end-of-treatment run-in visit. Patients who were not able to tolerate study drug at the doses prescribed during the treatment run-in period or who developed angioedema were discontinued and were not eligible to be re-screened. Concomitant use of an open-label ACEI, ARB, or renin inhibitor was strictly prohibited during the treatment run-in period. Background medications could be adjusted if the study drug was not tolerated.

Randomized Treatment Period: Patients who tolerated the study drugs during the treatment run-in period were randomized in a 1:1 ratio to sacubitril/valsartan 200 mg twice daily with valsartan placebo or valsartan 160 mg twice daily with sacubitril/valsartan placebo. For intolerance to study medication, the investigator could consider adjusting background medications prior to down-titrating the study medication, as appropriate. Study drug dose level adjustments were to be based on overall safety and tolerability with special focus on: a) hyperkalemia, b) symptomatic hypotension, and c) clinically significant decreases in eGFR/increases in serum creatinine. The three dose levels were 200, 100, or 50 mg of sacubitril/valsartan or 160, 80, or 40 mg of valsartan twice a day. Patients had to be followed until at least 1847 primary composite events occurred or at least 26 months after the last patient was randomized, whichever occurred last.

Figure 3. Study Design of PARAGON-HF



Source: Sponsor material PARAGON-HF Clinical Study Report Figure 9-1

Table 4. Safety monitoring criteria to be met at Visit 1 (screening), Visit 103 and Visit 199/201

Parameter	Visit 1 (screening)	Visits 103 (treatment run-in) and Visit 199/201 (end of treatment run-in/randomization)
Potassium level	K ≤5.2 mmol/L (mEq/L)	K ≤5.4 mmol/L (mEq/L)
Kidney function	eGFR ≥30 mL/min/1.73m^2	eGFR ≥25 mL/min/1.73m^2 eGFR reduction <35% compared to Visit 1
Blood pressure	SBP ≥110 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥100 mmHg.
AEs or conditions	No conditions that preclude continuation according to the investigator's judgment	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

Source: Sponsor material PARAGON-HF Clinical Study Report Table 9-2

6.1.1.3. Study Objectives and Endpoints

The study objectives/endpoints listed below are according to the Clinical Trial Protocol CLCZ696D2301, Amended Protocol Version 04, dated December 9, 2015.

Primary objective and endpoint: The primary objective was to compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HHF, in patients with HFpEF (NYHA Class II-IV) (LVEF ≥ 45%). The primary endpoint was the rate of the composite endpoint of CV death and total (first and recurrent) HHF.

The Applicant's rationale for the recurrent event primary endpoint was that patients with HFpEF have a higher rate of HHF and a lower rate of CV death compared to patients with HFrEF.[24,25,26] The frequency of repeated HHF increases after the first HHF and is an indicator of disease progression. Investigator-reported trial endpoints were adjudicated.

Secondary objectives and endpoints:

1. To compare sacubitril/valsartan to valsartan on changes in the clinical summary score for HF symptoms and physical limitations, as assessed change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS). The KCCQ CSS includes the total symptom score (TSS) based on HF symptoms and the physical limitation score (PLS).
2. To compare sacubitril/valsartan to valsartan in improving NYHA functional classification at 8 months assessed by change in NYHA functional classification.
3. To compare sacubitril/valsartan to valsartan in 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 (whichever occurs first).
4. To compare sacubitril/valsartan to valsartan in delaying the time to all-cause mortality.

Pre-specified exploratory endpoints:

1. To compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death, total HHF, total non-fatal strokes, and total non-fatal myocardial infarctions (MIs). Total is defined as the first and all recurrent events.
2. To compare sacubitril/valsartan to valsartan on changes in clinical composite assessment (assessed by NYHA, global patient assessment, and major adverse clinical events as defined by CV death and HHF) at 8 months.
3. To compare sacubitril/valsartan to valsartan on patient global assessment at 8 months.

[24] Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalizes for heart failure: A report from the OPTIMIZE-HF registry. J Am Coll Cardiol; 50:768-7.
[25] Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J; 25(14):1214-20.
[26] Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J; 39(20):1770-780

4. To compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death, total non-fatal HHF, total non-fatal strokes, and total non-fatal MIs. Total is defined as the first and all recurrent events.
5. To compare sacubitril/valsartan to valsartan in delaying the time to new onset atrial fibrillation.
6. To compare sacubitril/valsartan to valsartan on changes in the 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 period baseline scores and relative to randomized treatment period baseline scores) and total score of the EQ-5D for health status).
7. To compare sacubitril/valsartan to valsartan in reducing CV deaths and total worsening HF events. A patient will be defined as having a CV death or worsening HF event when the patient has:
    a. CV death or
    b. HHF or
    c. received intravenous (IV) decongestive therapy (diuretics, nesiritide or other natriuretic peptide, inotropes, and nitroglycerin), and did not result in formal inpatient hospital admission, regardless of the setting (i.e., emergency room (ER) setting, physician's office, outpatient treatment facility, etc.).
8. To compare sacubitril/valsartan to valsartan on hospitalizations (all cause and cause specific).
9. To compare sacubitril/valsartan to valsartan on the number of days alive and out of hospital at 12 months.
10. To compare sacubitril/valsartan to valsartan in slowing the rate of decline in eGFR.
11. To compare sacubitril/valsartan to valsartan on delaying time to new onset diabetes mellitus.
12. To compare sacubitril/valsartan to valsartan on reducing healthcare resource utilization, e.g., number of days/stays in intensive care unit, number of re-hospitalizations, and number of ER visits for HF.
13. To compare sacubitril/valsartan to valsartan on 30 day HF hospital readmissions and readmission rate after a prior HHF.
14. To compare sacubitril/valsartan to valsartan on the time between HF hospital readmissions.
15. To compare sacubitril/valsartan to valsartan on the profile of pre-specified biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, inflammatory, and/or other relevant biomarkers) from baseline to predefined time points in a subset of patients.
16. To characterize sacubitril/valsartan and valsartan pharmacokinetics (PK) at steady-state using population modeling and/or non-compartmental based methods in a subset of patients.
17. To compare sacubitril/valsartan to valsartan on the primary composite and secondary endpoints, and key exploratory endpoints in ACEI-intolerant patients.
18. To compare sacubitril/valsartan to valsartan in evaluating the changes in cognitive function (assessed by the Mini-Mental State Examination) at 2 years.

6.1.1.4. Study Population

Key inclusion criteria are listed below:

- Age ≥ 50 years
- LVEF ≥ 45% within 6 months prior to screening
- Evidence of structural heart disease such as LAE or LVH
- HF symptoms – NYHA functional class II-IV
- Requiring diuretic therapy for at least 30 days prior to screening
- 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 HHF. For patients with AF, NT-proBNP > 600 pg/mL if the patient had been hospitalized for HF within the past 9 months or > 900 pg/mL without a recent HHF.
- Patients with AF captured on electrocardiogram (ECG) on Visit 1 were limited to one third of the total study population

All patients were required to have a qualifying echocardiogram for study entry defined as either a locally obtained echocardiogram performed within 6 months prior to Visit 1 or based on a qualifying echocardiogram performed during the screening epoch. No imaging method other than echocardiography was accepted for inclusion into the study. For patients enrolled in India, all ejection fractions were required be performed using 2D volumetric methods. For a subset of approximately 1200 patients at selected centers, the qualifying echocardiograms were sent to a core laboratory for assessment.

Patients had to be on an optimal medical regimen of diuretics and background medications to treat co-morbidities such as hypertension (HTN), diabetes mellitus (DM), AF, and coronary artery disease (CAD).

Key exclusion criteria are listed below:

- Any prior LVEF measurement of < 40%
- Alternative diagnosis that could account for patient's symptoms such as severe pulmonary disease, hemoglobin < 10 g/dL or body mass index (BMI) > 40 kg/m^2
- Current acute decompensated HF
- SBP < 110 or ≥ 180 mm Hg
- Symptomatic hypotension
- SBP > 150 and < 180 mm Hg unless receiving three antihypertensive medications at screening
- Acute coronary syndrome (including MI, cardiac surgery, other major CV surgery), or urgent percutaneous coronary intervention (PCI) within the 3 months prior to Visit 1 or an elective PCI within 30 days prior to Visit 1
- Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF [e.g., MI, coronary artery bypass graft (CABG)], unless an echo measurement was performed after the event confirming the LVEF to be ≥ 45%
- Known history of angioedema

- Patients with either of the following:
  - serum potassium > 5.2 mmol/L (mEq/L) at Visit 1
  - serum potassium > 5.4 mmol/L (mEq/L) at Visit 103 or Visit 199/201
- Patients with one of the following:
  - eGFR < 30 mL/min/1.73m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1, or
  - eGFR < 25 mL/min/1.73m^2 at Visit 103 or Visit 199/201, or
  - eGFR reduction > 35% (compared to Visit 1) at Visit 103 or Visit 199/201

6.1.1.5. Statistical Analysis Plan

The pre-specified analysis for the primary composite endpoint of CV death or HHF was a semi-parametric proportional rates model (Lin et al. 2000), stratified by region, with treatment as a fixed-effect. This recurrent event analysis yields an estimated RR with a corresponding 95% CI and one-sided and two-sided *p*-values. Different analysis methods were specified for components of the composite to accommodate for the type of endpoint event.

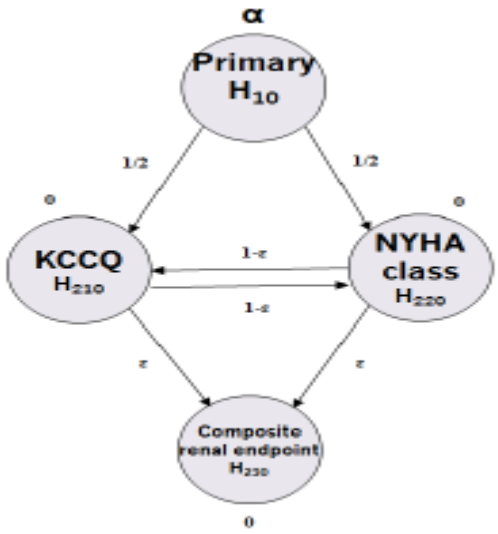
In order to account for the competing risk of CV death, the HHF component was analyzed using a joint gamma frailty model adjusted for region. An estimated RR and 95% CI from this model were used in the results section. The CV death component was analyzed using a Cox regression model stratified by region. A hazard ratio (HR) and corresponding 95% confidence interval were estimated from the model.

The same methods were used for the investigator-reported primary composite endpoint events as well as for the expanded composite endpoint, with the same gamma frailty model used to analyze the urgent HF visits component.

A Bonferroni multiplicity adjustment with an alpha of 0.001 (one-sided) was used to adjust for the planned interim analysis.

A sequentially rejective multiple test procedure with a graphical illustration of weights for alpha reallocation was specified for testing the hypotheses of the primary and secondary endpoints (Figure 4). The null hypothesis for the primary endpoint was tested at full alpha first; therefore, failure to reject this hypothesis would stop the testing procedure. A 1-sided null hypothesis of no or worsening treatment effect was pre-specified against an alternative of a favorable treatment effect. A 1-sided alpha level of 0.024, which was adjusted for the interim analysis, was pre-specified to control the type 1 error rate.

Figure 4. Weights for alpha relocation in the sequentially rejective multiple test procedure for the secondary hypotheses in PARAGON-HF



Source: Figure 9-2 of the Statistical Analysis Plan dated 12-Jun-2019

A post-hoc re-adjudication analysis was run at FDA's request incorporating investigator reported events that were originally negatively adjudicated. A blinded panel of three independent HF experts rated each event with an assigned probability of being a HF event (0%, 25%, 50%, 75%, 100%). These ratings were then averaged to get a single probability for each event.

The probability of being an event was used with a multiple imputation when incorporating the events into the post-hoc recurrent events analysis using the same methodology as described earlier for the primary composite and HHF endpoints. The multiple imputation analysis used 1,000 imputed datasets to incorporate re-adjudicated events with the assigned event probabilities. For each imputation, the probability that a re-adjudicated event was included in that dataset was based on the average re-adjudicated probability.

6.2. Results of Analyses of Clinical Trial/ Study Intended to Demonstrate Benefit to Patients

6.2.1. Demographics

Randomized patients versus patients with run-in failure: The baseline demographic and clinical characteristics of patients in the randomized set versus the run-in failures were generally similar except the median eGFR was 62 and 56 mL/min/1.73 m^2 in patients in the randomized set versus run-in failure, respectively, and patients in the run-in failure arm tended to have a lower mean screening SBP than in the randomized set (134 vs. 137 mmHg).

Full Analysis Set (FAS): The trial population was 81% Caucasian, 13% Asian, 2% Black, and 1% Native American. Sex was nearly evenly divided with 52% females and 48% males. Mean

age was 73 years (range, 50 to 98 years) and mean body mass index was 30 kg/m^2 (range: 15 to 47 kg/m^2). The majority of patients were NYHA class II (72%) with a baseline median LVEF of 57%, median NT-proBNP level of 911 pg/mL (IQR, 464–1613 pg/mL), median blood pressure of 130/75 mm Hg, and median eGFR of 60 mL/min/m^2. The main etiology of HF was non-ischemic (64% with 36% ischemic), 48% patients had a prior HHF, 96% had a history of HTN, 43% had DM, and 53% had a history of AF. Baseline demographic and clinical characteristics were well balanced between the two treatment arms. Table 5 summarizes the baseline demographic and clinical characteristics of the PARAGON trial population.

Table 5. Baseline Demographic and Clinical Characteristics, Full Analysis Set, PARAGON-HF

Characteristic	Category	Sacubitril/valsartan N=2407	Valsartan N=2389
Age 65	Below 65	412 (17.1%)	413 (17.3%)
	At least 65	1995 (82.9%)	1976 (82.7%)
Sex	Male	1166 (48.4%)	1151 (48.2%)
	Female	1241 (51.6%)	1238 (51.8%)
Race	White	1963 (81.6%)	1944 (81.4%)
	Black	52 (2.2%)	50 (2.1%)
	Asian	297 (12.3%)	310 (13.0%)
	Am. Indian Or Alaska Native	28 (1.2%)	23 (1.0%)
	Pacific Islander	0 (0.0%)	1 (0.0%)
	Other	67 (2.8%)	61 (2.6%)
Ethnicity	Hispanic or Latino	241 (10.0%)	224 (9.4%)
	Not Hispanic or Latino	2007 (83.4%)	2004 (83.9%)
	Not Reported	98 (4.1%)	109 (4.6%)
	Unknown	61 (2.5%)	52 (2.2%)
Region	N. America	288 (12.0%)	271 (11.3%)
	W. Europe	699 (29.0%)	691 (28.9%)
	C. Europe	856 (35.6%)	859 (36.0%)
	L. America	191 (7.9%)	179 (7.5%)
	Asia or Other	373 (15.5%)	389 (16.3%)
LVEF Category	Below 60%	1351 (56.1%)	1375 (57.6%)
	At least 60%	1056 (43.9%)	1014 (42.4%)
Diabetes	No	1358 (56.4%)	1369 (57.3%)

Characteristic	Category	Sacubitril/valsartan N=2407	Valsartan N=2389
	Yes	1049 (43.6%)	1020 (42.7%)
Hypertension	No	103 (4.3%)	109 (4.6%)
	Yes	2304 (95.7%)	2280 (95.4%)
NYHA Class	Missing	90 (3.7%)	87 (3.6%)
	1	70 (2.9%)	64 (2.7%)
	2	1792 (74.4%)	1776 (74.3%)
	3	447 (18.6%)	453 (19.0%)
	4	8 (0.3%)	9 (0.4%)
Age	N	2407	2389
	Mean (SD)	72.7 (8.3)	72.8 (8.5)
	Median (Min, Max)	74.0 (50.0, 98.0)	74.0 (50.0, 96.0)
LVEF	N	2407	2389
	Mean (SD)	57.6 (7.8)	57.5 (8.0)
	Median (Min, Max)	57.0 (30.0, 89.0)	57.0 (45.0, 89.0)
BMI	N	2406	2388
	Mean (SD)	30.2 (4.9)	30.3 (5.1)
	Median (Min, Max)	29.8 (15.7, 45.5)	29.9 (15.0, 46.7)
SBP	N	2407	2388
	Mean (SD)	130.5 (15.6)	130.6 (15.3)
	Median (Min, Max)	130.0 (100.0, 200.0)	130.0 (92.0, 185.0)
DBP	N	2407	2388
	Mean (SD)	74.3 (10.6)	74.3 (10.4)
	Median (Min, Max)	75.0 (36.0, 113.0)	75.0 (43.0, 117.0)

LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure

Source Data: FDA analysis of adsleff, adslsub, advs, adsl data sets

6.2.2. Treatment Exposure

Mean follow-up in the trial was 35 months. During the randomized treatment period, 32.5 and 34.5% of patients in sacubitril/valsartan and valsartan arm, respectively, permanently

discontinued treatment prematurely; discontinuations were mainly related to adverse events (AEs). During the randomized treatment period 26% of patients in both treatment arms temporarily interrupted treatment mostly related to AEs. Mean compliance while patients were taking study medication was approximately 96% and was similar in both treatment arms. A total of 52.8% of patients in the sacubitril/valsartan arm and 53.2% of patients in the valsartan arm had a dose reduction or temporarily interrupted study treatment. Approximately half of the patients remained on the target dose throughout the study (200 mg bid sacubitril/valsartan or 160 mg bid valsartan). Similar percentages of patients were on the target dose (200 mg bid) of sacubitril/valsartan (60.4%) or the target dose (160 mg bid) of valsartan (60.7%) at the last available record. The mean duration of study treatment exposure (including temporary interruptions) was 30.96 months in the sacubitril/valsartan group and 30.55 months in the valsartan group. The mean duration of study treatment exposure (excluding temporary interruptions) was 30.52 months in the sacubitril/valsartan group and 30.11 months in the valsartan group. During the randomized period, the mean patient daily doses of sacubitril/valsartan and valsartan were 363 (± 74) and 296 (± 51) mg, respectively. During the randomized period, the median patient daily doses of sacubitril/valsartan and valsartan were 400 and 320 mg, respectively.

6.2.3. Disposition

First patient first visit occurred on July 18, 2014 and last patient last visit occurred on June 07, 2019 with 4822 patients randomized at 755 sites in 43 countries. The trial recruitment and follow-up periods were 2.6 and 2.2 years, respectively. A total of 1903 CEC-confirmed primary composite endpoints (target primary endpoint events: 1847) was observed. April 30, 2019 was the cut-off date for all efficacy endpoints. For safety analysis, all available data were included, regardless of date of onset of the AE.

A total of 10,359 patients were screened; 5747 patients met the eligibility criteria and were enrolled; 5746 patients entered the valsartan run-in period; 5204 patients entered the sacubitril/valsartan run-in period; and 4822 patients who completed the run-in periods were randomized: 2419 to sacubitril/valsartan and 2403 to valsartan. During the run-in period, the median duration of exposure to valsartan was 14 days (IQR 12 to 21 days); the median duration of exposure to sacubitril/valsartan was 19 days (IQR 14 to 23 days). The failure rates for sacubitril/valsartan and valsartan in the run-in period were 7.4 and 9.4 %, respectively. Hypotension, renal impairment, and hyperkalemia were the most common reasons for treatment discontinuation, and frequencies were similar in the sacubitril/valsartan and valsartan run-in periods. The number of patients discontinued from the randomized treatment period was similar in the two treatment arms. There were 26 patients (12 sacubitril/valsartan, 14 valsartan) that were not included in the FAS because of Good Clinical Practice (GCP) violations. 2055 (84.4%) and 2030 (85%) patients completed their randomized treatments in the sacubitril/valsartan and valsartan arms, respectively. The primary reason for non-completion was death, which was similar in both arms. Table 6 summarizes patient disposition.

Table 6. Patient Screening, Randomization, and Disposition for PARAGON-HF

	Sacubitril/valsartan	Valsartan	Total
Screened	.	.	10359
Screen Failure	.	.	4606
Run-in Failure	.	.	925
Not Assigned	.	.	6
Randomized	2419	2403	4822
GCP issues	12 (0.5%)	14 (0.6%)	26
Full Analysis Set	2407	2389	4796
Completed	2055 (85.4%)	2030 (85%)	4085
Died	347 (14.4%)	355 (14.9%)	702
Discontinued	5 (0.2%)	4 (0.2%)	9

Completion is defined as completing through April 30, 2019
Source Data: FDA analysis of adsl, adeff data sets

Protocol Deviations

In the randomized set, 34.6% of patients had at least one protocol deviation during the study. The percentage of patients with protocol deviation(s) was similar in the two treatment groups. The most common protocol deviation was "overall drug compliance < 80%" at one or more medication compliance assessment visit and was similar between the sacubitril/valsartan (16.4%) and valsartan (16.6%) groups. There were 119 (4.9%) and 139 (5.8%) patients in sacubitril/valsartan and valsartan arms, respectively, who used an open-label ACEI, ARB, or renin inhibitor concomitantly while taking study medication at some point in the study. A total of 12 (0.50%) and 14 (0.58%) patients in sacubitril/valsartan and valsartan arms, respectively were excluded from the full analysis set because of protocol deviations for GCP reasons (drug supply issues).

6.2.4. Analysis of the Primary Endpoint

The PARAGON-HF trial randomized 4822 adult patients with symptomatic HF with LVEF ≥45% to sacubitril/valsartan versus valsartan. A total of 1903 primary composite endpoints, including 1487 HHF (78.1%) and 416 CV deaths (21.9%) were experienced by 1083 patients in the FAS (N=4796). Sacubitril/valsartan reduced the rate of the composite endpoint of total (first and recurrent) HHF and CV death with a RR of 0.87; 95% CI 0.75, 1.01; $p = 0.06$. There were 894 (12.8 per 100 patient-years) primary composite events (CEC-confirmed total HHF and CV deaths) in the sacubitril/valsartan arm compared to 1009 (14.6 per 100 patient-years) in the valsartan arm, a difference of 115 events.

The effect of sacubitril/valsartan on the primary endpoint was driven primarily by the total HHF component. Overall, 690 (9.9 per 100 patient-years) total HHF events occurred in the sacubitril/valsartan arm compared to 797 (11.6 per 100 patient-years) in the valsartan arm, a difference of 107 events with a relative rate reduction of 15% (RR=0.85; 95% CI: 0.72, 1.0; 1-

sided p = 0.028; 2-sided p=0.06). There were 28 fewer patients in sacubitril/valsartan arm versus valsartan arm who experienced ≥ 1 HHF.

Note that an alpha of 0.001 (one-sided alpha) was spent for the comparison of primary endpoint at the interim analysis and the rest of alpha (one-sided 0.024) was designated to be utilized for the primary endpoint at the final analysis.

There was no difference between treatment arms with regard to CV death (HR=0.95; 95% CI: 0.79, 1.16; 1-sided p=0.31; 2-sided p=0.62). But CV death trended in favor of sacubitril/valsartan.

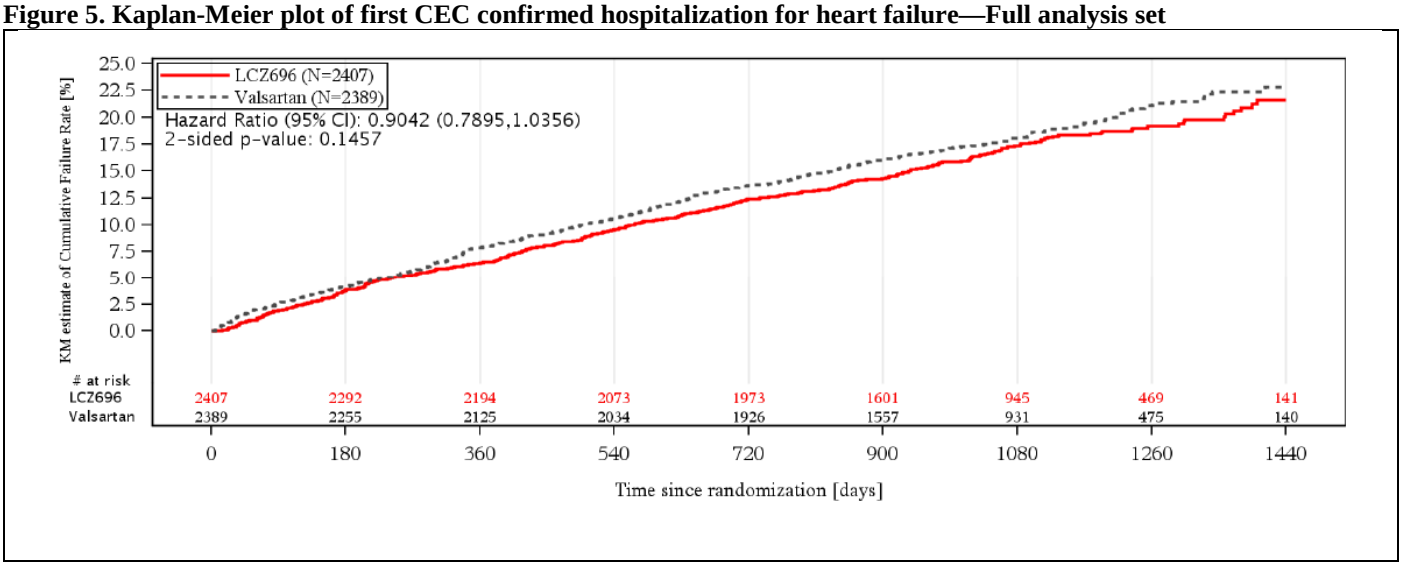
Results of pre-specified exploratory analysis in PARAGON-HF is as follows:

Analysis of CEC-confirmed expanded primary composite endpoint events, including total HHF, urgent HF visits, and CV death, demonstrated a RR of 0.86; 95% CI: 0.75, 0.99; p = 0.04 favoring sacubitril/valsartan. There were 40 and 55 CEC-adjudicated urgent HF events in the sacubitril/valsartan and valsartan arms, respectively. The point estimates derived from analyses of the primary and expanded primary composite endpoints were similar, except that with the addition of 95 urgent HF events, the p-value was below the pre-specified threshold for the primary composite endpoint.

Results of post-hoc exploratory analyses in PARAGON-HF are as follows:

- The analysis of an investigator-reported primary composite endpoint of total HHF and CV death demonstrated a RR of 0.84; 95% CI: 0.74, 0.97; 2-sided p=0.01. Investigator-reported events added 226 and 290 HHF events but decreased CV death by 56 and 58 events in sacubitril/valsartan and valsartan arms, respectively. Hence, a net 170 and 232 total events were added to the CEC-reported primary composite endpoint, leading to a p-value of 0.01, but no significant change in RR.
- The analysis of an investigator-reported expanded primary composite endpoint, including total HHF, urgent HF visits and CV death demonstrated a RR of 0.83; 95% CI: 0.73, 0.95; 2-sided p = 0.006 favoring sacubitril/valsartan. There were 136 and 173 investigator-reported urgent HF events in the sacubitril/valsartan and valsartan arms, respectively.
- A time to first event analysis of CEC-confirmed HHF demonstrated that the incidence of HHF was 405/2407 (16.83%) versus 433/2389 (18.12%) in the sacubitril/valsartan and valsartan arms, respectively. The HR was 0.90; 95% CI: 0.79, 1.04; p = 0.19. Figure 5 displays the Kaplan-Meier plot of time to first CEC-confirmed HHF in PARAGON-HF.

Figure 5. Kaplan-Meier plot of first CEC confirmed hospitalization for heart failure—Full analysis set



Source: Clinical Study Report PARAGON-HF Sponsor Figure 14.2-1.4.3

Concomitant Medications

A total of 27% patients in the sacubitril/valsartan arm and 30% patients in the valsartan arm were taking an aldosterone antagonist. The use of all other background CV and HF therapies was similar in both arms.

Blood Pressure in PARAGON-HF

Throughout the randomized treatment period, patients in the sacubitril/valsartan arm experienced lower systolic and diastolic blood pressure (BP) compared to the valsartan arm. The systolic BP (SBP) changed by - 0.81 and + 2 from baseline to last test in sacubitril/valsartan and valsartan arms, respectively. The diastolic BP (DBP) changed by - 0.26 and + 0.34 from baseline to last test in the sacubitril/valsartan and valsartan arms, respectively. A recurrent events analysis of the treatment effect on the primary composite endpoint adjusted for SBP over time suggests that the treatment effect size was unaffected by SBP [unadjusted RR = 0.87 (95% CI: 0.75, 1.01; 1-sided p = 0.029) vs. SBP adjusted RR = 0.87 (95% CI: 0.74, 1.00; 1-sided p = 0.027)].

6.2.5. Comparative Analyses of Borderline Efficacy Results

Clinical Event Distribution

Endpoint events for CV death, HHF, and urgent HF visits were conveyed as either investigator-reported, adjudicated, or both. Table 7 shows the distribution of the numbers of patients in each arm experiencing HHF and CV death events. Most events were both adjudicated and investigator-reported, but there were more investigator-reported events. There were 2305 and 1903 investigator-reported and adjudicated events, respectively (data not shown). Results based

on the investigator-reported events were examined alongside the pre-specified adjudicated event endpoints to assess the consistency of results.

There are 2407 patients in the sacubitril/valsartan arm with an observed follow up of 6966 patient-years; there are 2389 patients in the valsartan arm with an observed follow up of 6897 patient-years.

Table 7. Event Endpoint distribution for Cardiovascular Death + Total Hospitalization for Heart Failure in PARAGON-HF

N Events	Adjudicated n (%)		Investigator Reported n (%)	
	Valsartan	Sacubitril/valsartan	Valsartan	Sacubitril/valsartan
0	1832 (76.68%)	1881 (78.15%)	1765 (73.88%)	1820 (75.61%)
1	337 (14.11%)	334 (13.88%)	336 (14.06%)	341 (14.17%)
2	126 (5.27%)	108 (4.49%)	150 (6.28%)	142 (5.90%)
3	45 (1.88%)	43 (1.79%)	69 (2.89%)	49 (2.04%)
4	16 (0.67%)	16 (0.66%)	28 (1.17%)	23 (0.96%)
5	14 (0.59%)	10 (0.42%)	15 (0.63%)	12 (0.50%)
6	9 (0.38%)	11 (0.46%)	12 (0.50%)	12 (0.50%)
7	2 (0.08%)	3 (0.12%)	5 (0.21%)	5 (0.21%)
8	3 (0.13%)	0 (0.00%)	4 (0.17%)	1 (0.04%)
9	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
10	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.04%)
11	2 (0.08%)	0 (0.00%)	2 (0.08%)	0 (0.00%)
13	0 (0.00%)	0 (0.00%)	1 (0.04%)	0 (0.00%)
14	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)
15	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.04%)
18	1 (0.04%)	0 (0.00%)	1 (0.04%)	0 (0.00%)
19	0 (0.00%)	0 (0.00%)	1 (0.04%)	0 (0.00%)

Source: Reviewer analysis

Table 8 shows a breakdown of the events as adjudicated only, adjudicated and investigator reported, or negatively adjudicated (investigator reported only). Categories shown in the rows are based on the adjudicated events dataset. There were 30 events that were reported to a different category from which they were adjudicated; these events are classified as “Adjudicated Only” in Table 8. The four events that were adjudicated as urgent HF visits but reported as HHF were not included in some of the investigator reported endpoint analyses. Removing these four events did not make a substantive difference in the investigator reported results.

Events shown in the blue boxes are events that are included in the pre-specified primary composite endpoint. Events shown in the red boxes are included in the investigator-reported primary composite endpoint. Events shown in the yellow boxes are included in the supportive expanded composite endpoint which adds in urgent HF visits. These events are also shown in Figure 6 where the different composites with their event components are broken out separately in side-by-side plots.

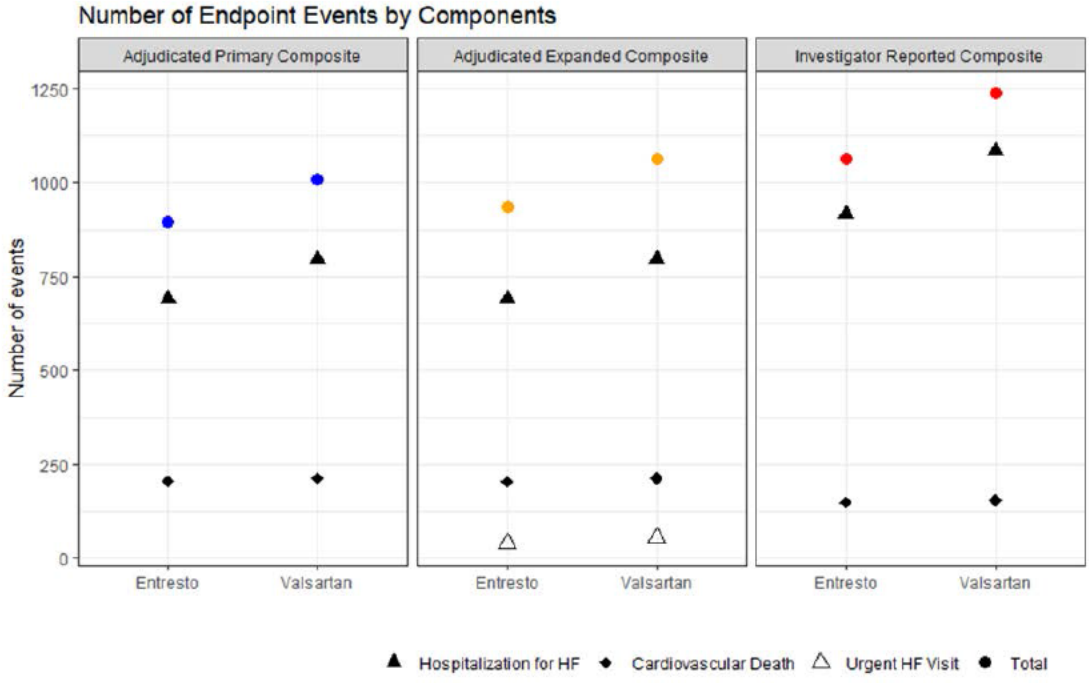
Event ratios are similar for the adjudicated primary composite, the expanded composite, and the investigator-reported composite. However, with greater numbers of events in the expanded composite and the investigator-reported composite, *p*-values reach nominal statistical significance.

Table 8. Endpoint Event Categories by Adjudication Status for PARAGON-HF

		Adjudicated Only	Adj + Inv. Rep.*	Negative Adj.	Category Diff.
Sacubitril/valsartan	HHF	22 (2.35%)	668 (71.29%)	247 (26.36%)	8
	CVD	69 (31.80%)	135 (62.21%)	13 (5.99%)	.
	Urgent HF Visit	2 (1.53%)	38 (29.01%)	91 (69.47%)	1
Valsartan	HHF	28 (2.52%)	769 (69.15%)	315 (28.33%)	18
	CVD	73 (32.16%)	139 (61.23%)	15 (6.61%)	.
	Urgent HF Visit	7 (4.32%)	48 (29.63%)	107 (66.05%)	3

*30 Events which had different Adjudicated and Inv. Rep. categories were included as Adjudicated Only and not included in Inv. Rep. events
Source: Reviewer Analysis

Figure 6. Composite Endpoint Event Breakdowns



Source: Reviewer Analysis

Study Results

Table 9 shows study results for the adjudicated and investigator-reported events in the primary composite, expanded composite, and individual components of the composites. It should be

noted that results for different endpoints are based on different analytical methods as described in the statistical analysis plan. The time until CV death results are expressed as a HR; all other endpoints use a type of recurrent events analysis with results expressed as a RR.

Table 9. Endpoint Results for PARAGON-HF

	n Events			
Endpoint	**Sacubitril/valsartan (N=2407)**	**Valsartan (N=2389)**	**RR/HR (95% CI)**	**2-sided *p*-value**
Primary Composite	894	1009	0.87 (0.75, 1.01)	0.059
HHF	690	797	0.85 (0.72, 1.00)	0.056
HF Events (HHF + Urgent HF Visits)	730	852	0.84 (0.71, 0.98)	0.031
CV Death	204	212	0.95 (0.79, 1.16)	0.624
Expanded Composite	934	1064	0.86 (0.75, 0.99)	0.040
Inv. Reported Primary Composite	1064	1241	0.84 (0.74, 0.97)	0.014
Inv. Reported HHF	916	1087	0.82 (0.71, 0.96)	0.010
Inv. Reported HHF + Urgent HF Visits	1053	1260	0.82 (0.72, 0.94)	0.005
Inv. Reported Expanded Composite	1200	1414	0.83 (0.73, 0.95)	0.006

Observed follow-up time, calculated in 100 patient years, was 69.66 for sacubitril/valsartan and 68.97 for valsartan
RR: risk ratio, HR: hazard ratio, CI: confidence interval
Source: Reviewer's analysis of the adeff data set; cross reference Applicant's results.

The 1-sided *p*-value of 0.029 for the adjudicated primary composite endpoint did not meet the pre-specified criterion of $p<0.024$. So, while the RR shows a trend in favor of sacubitril/valsartan, it fails to reject the null hypothesis of no or worsening treatment effect. Since the primary endpoint failed the hypothesis test, the testing hierarchy stops and no further hypotheses for secondary endpoints will be considered here.

Given the failed hypothesis test for the primary endpoint, establishing evidence of a strong consistency of a treatment effect through other means is needed to build confidence in the results. Treatment benefit in the primary composite is due primarily to a reduction in HF events. When looking only at the first events using a Cox proportional hazards model for the composite and HF event components, there does seem to be a trend showing some benefit favoring sacubitril/valsartan (Table 10). Favorable trends for the composite for first and recurrent events are primarily due to outcomes seen in HF events. Adding more HHF events to the primary composite, as seen with the investigator-reported data, does not have a huge impact on the estimate of treatment effect, but it will improve p-values and confidence intervals.

Table 10. Endpoint Results for First Events in PARAGON-HF

	Events/N		
	Sacubitril/valsartan	**Valsartan**	**HR (95% CI)**
Primary Composite	526 / 2407	557 / 2389	0.92 (0.81, 1.03)
CV Death	204 / 2407	212 / 2389	0.95 (0.79, 1.16)
HHF	405 / 2407	433 / 2389	0.90 (0.79, 1.04)
HHF or Urgent HF Visit	422 / 2407	462 / 2389	0.88 (0.77, 1.00)
Expanded Composite	542 / 2407	585 / 2389	0.90 (0.80, 1.01)
Inv. Reported Primary	587 / 2407	624 / 2389	0.91 (0.81, 1.02)
Inv. Reported HHF	587 / 2407	624 / 2389	0.91 (0.81, 1.02)
Inv. Reported HHF or Visit	573 / 2407	620 / 2389	0.88 (0.79, 0.99)
Inv. Reported Expanded Composite	573 / 2407	620 / 2389	0.88 (0.79, 0.99)

HR: hazard ratio, CI: confidence interval, CV: cardiovascular, HHF: hospitalization for heart failure, HF: heart failure, Inv.: investigator
Source: Reviewer's analysis on adeff and adttee, cross reference Sponsor's results

Post-hoc Re-adjudication Analysis Results

All 566 negatively adjudicated HHF events, including the four that were previously positively adjudicated as urgent HF visits, were sent for re-adjudication (section 6.1.1.5). The four (1 sacubitril/valsartan, 3 valsartan) events which were reported as HHF but adjudicated as urgent HF visits were not included in the FDA re-adjudication analysis. The re-adjudication event probability distribution for the average event probability is shown in Table 11.

Table 11. Average Re-Adjudicated HHF Event Probability Distribution

Re-Adj. Prob.	**Sacubitril/valsartan**	**Valsartan**	**Total**
1	11	6	17
0.92	12	17	29
0.83	17	19	36
0.75	20	13	33
0.67	9	33	42
0.58	23	23	46
0.50	22	23	45
0.42	17	17	34
0.33	18	22	40
0.25	15	32	47
0.17	21	29	50
0.08	22	26	48
0	40	55	95
Total	247	315	562

HHF: hospitalization for heart failure, Re-Adj.: readjudicated, Prob.: probability
Source: Reviewer's analysis

One thousand imputation datasets were created. The average re-adjudication probability associated with the 562 negatively adjudicated events was used as the probability for whether an

event was included in each dataset. Results from the MI were combined using Rubin's rule. This added approximately 104 events to the sacubitril/valsartan arm, and 124 events to the valsartan arm. Results based on this re-adjudication analysis are shown in Table 12. Point estimates for the primary composite and HHF are the same, but because there are more events upon which to estimate the treatment effect, we see tighter confidence intervals around these estimates. Adding in these additional events does not seem to change the point estimates. The statistical implications from adding events are as we would expect, tighter confidence intervals which also directly links with a smaller *p*-value.

Table 12. Post-hoc Re-adjudication Analysis Results

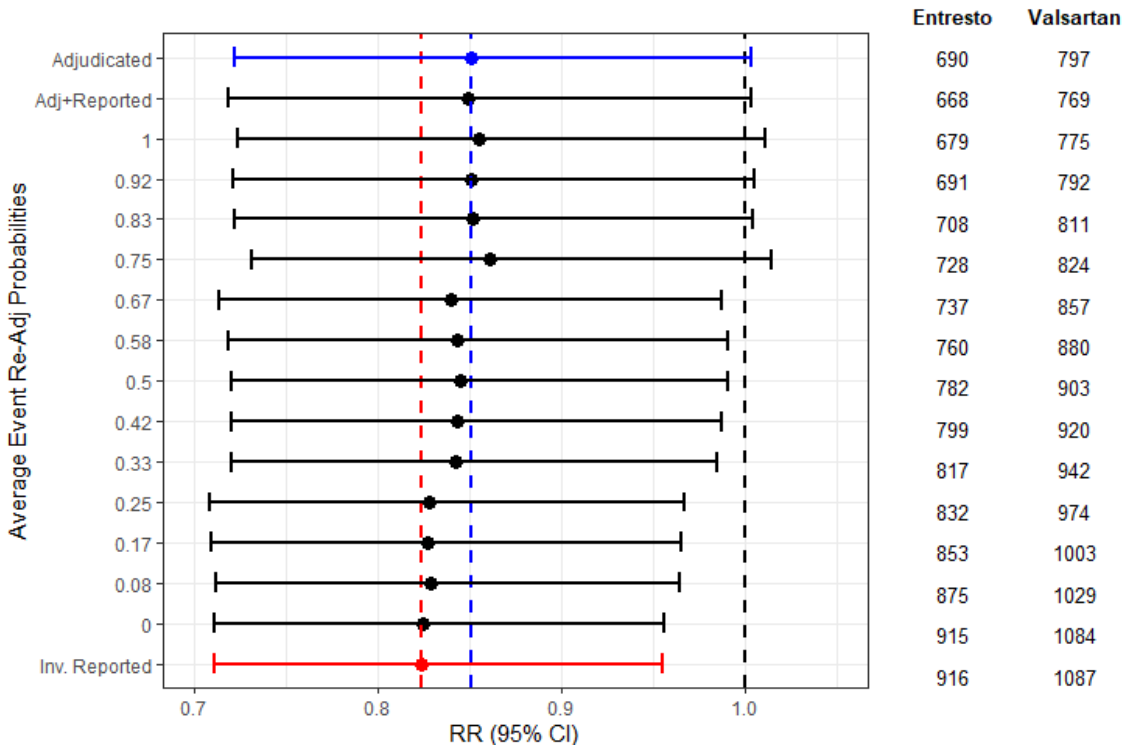
Endpoint	RR (95% CI)	2-sided *p*-value
Primary Composite	0.87 (0.75, 0.997)	0.0453
HHF	0.85 (0.72, 0.99)	0.0392

Source: Reviewer's analysis

The re-adjudication analysis can be viewed as a hybrid of the adjudicated events and the investigator reported events analysis results. The point estimates for the treatment effect line up with the results seen in the adjudicated events analysis showing consistency, and the additional events contribute to the tighter confidence bands around the point estimate.

The re-adjudicated event probabilities can further be used to connect the adjudicated and investigator-reported events. Figure 7 shows analysis results for HHF using the adjudicated events data, adding in events based on re-adjudicated probabilities until all investigator reported events were added in. The analyses were based on the total number of events shown in the columns to the right of the plot. Results using the adjudicated HHF events are shown in blue. Results based on events that were both adjudicated and investigator-reported (column 2 of Table 8) are shown below that. Negatively adjudicated events are added back in for each line of the forest plot based on re-adjudication probabilities. Results based on the investigator-reported events are shown in red. Given the similarities between the adjudicated and the investigator-reported events analyses, the forest plot can be viewed as a roadmap to see how additional events affect both the point estimate and confidence intervals. The scale upon which the RR is plotted is quite small, so changes in this context are also small. A combination of adding in events along with ratios of additional events that favored sacubitril/valsartan helped to improve the RR slightly relative to the investigator-reported results.

Figure 7. HHF Recurrent Events Analysis results for Adjudicated, Re-Adjudicated, and Investigator reported events



Source: Reviewer's analysis

In general, the post-hoc re-adjudication analysis results are supportive in showing consistency with the pre-specified adjudicated composite primary endpoint.

Discussion of the Statistical Results

In hypothesis testing, alpha is used to define the cut-off for the rejection region. After a study has closed and been analyzed, the only conclusions we can make regarding the hypothesis test is whether the statistical test rejects the pre-specified null hypothesis defined by the cut-off for the rejection region. The *p*-value is a summary measure of the evidence in the study centered around the null hypothesis. Based solely on the data from this study as summarized by the *p*-value, there is not enough evidence against the null to meet the pre-specified cut-off, thus we fail to reject the null hypothesis for the PARAGON-HF study.

Failure to reject a null hypothesis should not be interpreted as evidence that sacubitril/valsartan does not have any effect. Rather, we interpret this as the study itself does not provide the level of evidence for a treatment effect that was laid out in the protocol using the pre-specified primary endpoint and analysis population. Weaker than anticipated evidence against the null hypothesis should be considered in context with the rest of the study results.

Pre-specification of the study attributes and statistical testing criteria are essential when conducting a Phase 3 confirmatory study. We have a greater assurance of the credibility and strength of the study findings when protocols are implemented, and the completed data meet the pre-specified levels of evidence around which the study is designed to achieve. Failure to meet these levels does not completely nullify the study results, and therefore should be considered when assessing the strength of evidence that this study provides. Results based on endpoints and analyses that were not pre-specified with a necessary level of evidence for/against a hypothesis do provide some level of support, but they do not have the rigor to provide the strength of evidence that pre-specification provides.

6.2.6. Secondary Endpoint Results

Given that the primary endpoint failed to reach statistical significance, the secondary efficacy endpoint results are considered only exploratory and are described below:

a) Change from baseline in KCCQ clinical summary score at Month 8: The KCCQ clinical summary score (CSS) included HF symptoms and physical limitation domains. The mean change from baseline to Month 8 in the KCCQ CSS was -1.51 points in the sacubitril/valsartan arm and -2.53 points in the valsartan arm with a mean difference between the two arms of 1.03 points in favor of sacubitril/valsartan (95% CI: 0.005, 2.06; 2-sided $p = 0.05$).[27]

b) Change in NYHA class from baseline to Month 8: Mean change in NYHA class was not reported. At Month 8, NYHA functional class improved in 15.0 and 12.6% of patients in the sacubitril/valsartan and valsartan arms, respectively. No change in NYHA class was reported in 76 and 78% patients in the sacubitril/valsartan and valsartan arms, respectively.

c) Time to first occurrence of the composite renal endpoint: The incidence of composite renal endpoint, defined as renal death, reaching ESRD, or experiencing a ≥ 50% decline in eGFR relative to baseline, was 33/2407 (1.37%) and 64/2389 (2.68%) in sacubitril/valsartan and valsartan arms, respectively with a HR of 0.50, $p = 0.001$. This difference in renal composite endpoint was driven by the ≥ 50% decline in eGFR component, which was observed in 27/2407 (1.12%) and 60/2389 (2.51%) patients in sacubitril/valsartan and valsartan arms, respectively.

   The rate of change in eGFR was -0.21 mL/min/1.73 m^2 per month in the valsartan arm, and -0.16 mL/min/1.73m^2 per month in the sacubitril/valsartan arm. The rate at which the eGFR declined was significantly slower by 0.04 mL/min/1.73m^2 per month (0.48 mL/min/1.73m^2 per year) in the sacubitril/valsartan arm relative to the valsartan arm during the randomized treatment period.

[27] Even if this were a valid finding, the effect observed is not clinically relevant.

d) Time to all-cause mortality: There was no difference in all-cause mortality: all-cause mortality was 342/2407 (14.21%) and 349/2389 (14.61%) in the sacubitril/valsartan and valsartan arms, respectively.

6.2.7. Subgroup Analyses

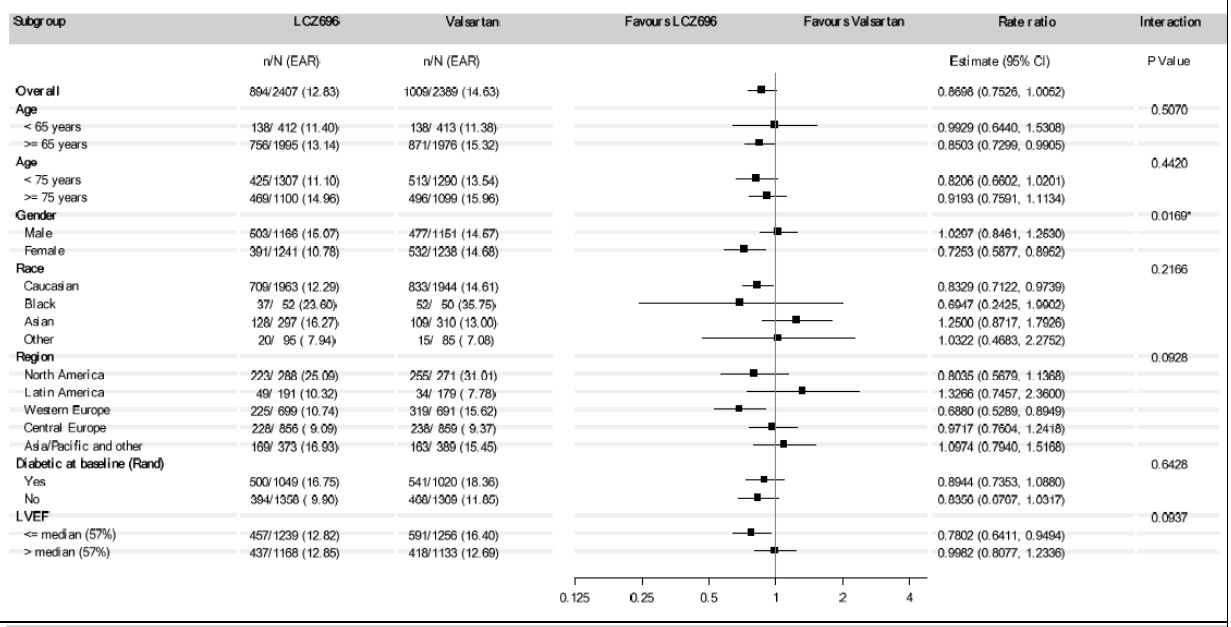
Prespecified subgroup analyses were conducted to explore consistency of treatment effect across 14 subgroups: age groups (<65, ≥65; <75, ≥75 years), sex, race (Caucasian, Black, Asian, Other), region, DM (yes/no), baseline LVEF (≤ median and > median), baseline AF on ECG (yes/no), baseline AF by history (yes/no), baseline NT-proBNP (≤ median and > median), baseline SBP (≤ median and > median), baseline aldosterone antagonist use (yes/no), ACEI intolerant (yes/no), baseline eGFR (< 60 vs ≥ 60 mL/min/1.73 m^2), and baseline NYHA class (I/II vs III/IV).

In a univariate analysis, the treatment effect of sacubitril/valsartan was generally consistent across these subgroups except for LVEF, sex, and region.

In females, subgroup analyses indicated a stronger trend (27% reduction) in the RR of the composite endpoint of total HHF and CV death in favor of sacubitril/valsartan than in males (none to slightly worsening effect). This effect seems to be driven by a reduction in the RR of total HHF (joint frailty analysis results of approximately 31%). In patients with LVEF ≤ 57%, subgroup analyses indicated a stronger trend (22% reduction) in the RR of the composite endpoint of total HHF and CV death in favor of sacubitril/valsartan than in patients with LVEF > 57% (none to slightly worsening effect). These findings suggest that sacubitril/valsartan has a greater treatment effect in females and in patients with LVEF at the lower end of the spectrum for HFpEF i.e.; LVEF ≤ 57% where there may be some overlap with patients with HFrEF.

Figure 8 shows the subgroup forest plot for the primary composite endpoint of CEC-confirmed total HHF and CV death.

Figure 8. Subgroup Forest Plot of Rate Ratios (95% CIs) from LWYY for Recurrent CEC Confirmed Primary Composite Endpoint (Cardiovascular Death and Total Hospitalizations for Heart Failure) (Full Analysis Set)



Within subgroup estimated treatment effect, 95% CI and subgroup-by-treatment interaction *p*-value are based on the proportional rate model (abbreviated as LWYY) with treatment, subgroup and subgroup-by-treatment fixed effect factors and stratified by region (the region stratification is waived for the region subgroup analysis). n: Total number of events; N: Total number of patients; T(100 patient years): total up-to-terminal-event/censoring duration summarized over patients in the respective treatment arm; EAR (Exposure-adjusted rate per 100 patient years) = n/T. Events occurred in randomized treatment epoch up to April 30, 2019 are included in the analysis.
* indicates 2-sided nominal *p*-value <0.05.

Source: PARAGON-HF Clinical Study Report Figure 11-7

7. Review Issues

7.1. Does PARAGON-HF provide Evidence of Efficacy in Heart Failure Patients with LVEF ≥ 45%?

Consistent Rate Ratio Across Various Efficacy Endpoint Analyses

PARAGON-HF was designed to have 95% power to detect a RR of 0.78 for the primary efficacy endpoint of CEC-confirmed total HHF and CV death. However, the observed RR was 0.87. With a smaller treatment effect than estimated, PARAGON-HF failed to meet statistical significance. However, the RR observed with the pre-specified exploratory expanded endpoint of total HHF, urgent HF visits, and CV death; with post-hoc exploratory endpoints of investigator-reported total HHF and CV death; investigator-reported total HHF, urgent HF visits and CV death; and re-adjudicated total HHF and CV death demonstrated consistent RRs ranging from 0.87 to 0.83 (section 6.2.4).

Generally, even when the results of clinical trials are statistically significant, statistical significance should not be used to compare the magnitude of treatment effect because the magnitude of statistical significance is largely dependent on the number of patients studied or events observed. For example, a small trial of a highly effective therapy could have a statistically significant result with a *p*-value that is greater (i.e., less persuasive) than a result from a large trial of a modestly effective treatment.[28] In PARAGON-HF the primary efficacy analysis failed to reject the null hypothesis. Several post-hoc analyses that added events to both treatment arms resulted in similar RRs; however, the nominal *p*-value decreased (became more persuasive), which was merely a reflection of an increased number of events. The added events do not change the interpretation of magnitude of treatment effect as demonstrated on the basis of the primary efficacy analysis in PARAGON-HF.

Borderline Trial Results

The effect of sacubitril/valsartan on the primary endpoint was driven primarily by the total HHF component. Overall, 690 (9.9 per 100 patient-years) total HHF events occurred in the sacubitril/valsartan arm compared to 797 (11.6 per 100 patient-years) in the valsartan arm, a difference of 107 events with a relative rate reduction of 15% (RR=0.85; 95% CI: 0.72, 1.0; 1-sided $p = 0.028$; 2-sided $p = 0.06$). Analysis of the CEC-confirmed expanded primary composite endpoint of total HHF, urgent HF visits, and CV death added 40 and 55 CEC-adjudicated urgent HF events in the sacubitril/valsartan and valsartan arms, respectively. This analysis demonstrated a point estimate for the RR that was similar to the primary endpoint analysis; however, with an additional 95 urgent HF events, the nominal *p*-value was below the pre-specified threshold for the primary composite endpoint (RR = 0.86; 95% CI: 0.75, 0.99; $p = 0.04$ favoring sacubitril/valsartan) (Section 6.2.4).

[28] Faraone SV. Interpreting estimates of treatment effects: implications for managed care. P T. 2008;33(12):700-711.

Investigator Versus Adjudicated Endpoints

The investigator-reported events added 226 and 290 HHF events but decreased CV deaths by 56 and 58 events in sacubitril/valsartan and valsartan arms, respectively. Hence, a net 170 and 232 total events were added to the CEC-reported primary composite endpoint leading to a nominal *p*-value of 0.01, but no significant change in RR (Section 6.2.4).

A Cochrane Meta-analysis[29] of 47 randomized controlled trials (RCTs) (275,078 patients) demonstrated that there was no significant difference in treatment estimates between investigators' (blinded) assessments and those of adjudication committees. The primary endpoint results based on CEC-adjudicated versus investigator-reported events in PARAGON-HF are consistent with this finding.

Adjudicated Versus Re-adjudicated Endpoints

With respect to the adjudication of HHF events, the CEC charter was set up to assure high specificity (with low sensitivity) based on the documentation available in the source documents. There were several patients who appeared to have had HHF events; however, documentation was inadequate in the source documents to make a positive adjudication. Thus, FDA advised the Applicant to consider re-adjudicating the negatively-adjudicated investigator-reported HHF events to decrease the loss of true HHF events that were not classified such because of inadequate documentation (Section 6.2.4).

With re-adjudication of 566 negatively adjudicated HHF events, approximately 104 and 124 events were added to the sacubitril/valsartan and valsartan groups, leading to a nominal *p*-value of 0.05, but no significant change in RR (Section 6.2.4).

Urgent HF visits

Urgent HF visits were events of new or worsening HF, defined similarly to HHF, except that no overnight hospitalization was required for treatment. We believe that urgent HF visits are an important measure of morbidity associated with chronic HF; the distinction between HHF and urgent visits can simply reflect local clinical practice approaches to management of HF. PARAGON-HF did not prospectively include urgent HF visits in the primary efficacy endpoint, rather this was analyzed as a pre-specified exploratory analysis. Of the 4,796 patients in Full Analysis Set, 884 patients experienced a first episode of HHF or urgent HF visit, of which 818 (92.5%) were HHF and 66 (7.5%) were urgent HF visits. The baseline characteristics of patients who experienced a first event of urgent HF visit versus a first event of HHF in PARAGON-HF (Table 13) were generally similar, except that patients who experienced urgent HF visits had a

[29] Ndounga Diakou LA, Trinquart L, Hróbjartsson A, Barnes C, Yavchitz A, Ravaud P, Boutron I. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. Cochrane Database Syst Rev. 2016 Mar 10;3(3):MR000043.

lower prevalence of females, more patients with NYHA class II, a higher prevalence of AF, and higher NT-proBNP and eGFR.

Table 13. Baseline Characteristics of Patients Who Experienced First Hospitalization for Heart Failure Versus Urgent Heart Failure Visit Versus no Heart Failure Event—FAS, PARAGON-HF

Baseline Characteristic	Urgent Heart Failure Visit	Heart Failure Hospitalization	*p-value* (Urgent HF visit vs HF Hospitalization)	No Heart Failure Event	*p-value* (across all 3 groups)
	n = 66	n = 818		n = 3912	
Age (years)	74 ± 9	74 ± 9	0.89	73 ± 8	<0.001
Females	29 (43.9%)	408 (49.9%)	0.35	2042 (52.2%)	0.22
NYHA Class II	51 (77.3%)	581 (71.1%)		3074 (78.6%)	
NYHA Class III	10 (15.2%)	207 (25.3%)		715 (18.3%)	
Atrial Fibrillation	30 (45.5%)	293 (36.0%)	0.12	1229 (31.5%)	0.004
Screening NT-proBNP (pg/mL)	1209 (723, 2019)	1161 (578, 2106)	0.69	858 (45, 1523)	<0.001
Estimated glomerular filtration rate (mL/min/1.73m^2)	63 ± 19	60 ± 19	0.21	63 ± 19	<0.001
Left ventricular ejection fraction (%)	57 ± 8	57 ± 8	0.6	57 ± 8	0.13

Source: Sponsor Correspondence dated September 10, 2020

Use of Active Control – Valsartan in PARAGON-HF

BP reduction is known to be associated with reduced risk for HHF. Hence, an exploratory analysis was conducted to ascertain an association between blood pressure effects and the clinical outcome of PARAGON-HF.

In PARAGON-HF, SBP and DBP decreased by approximately 4 and 2 mm Hg, and 7 and 3 mm Hg in valsartan and sacubitril/valsartan arm, respectively from screening to last visit. Patients randomized to valsartan 320 mg daily experienced increases in mean SBP and DBP by +2 ± 19.6 and +0.34 ± 12.2 mm Hg [change from baseline (on sacubitril/valsartan 200 mg daily) to last test]. Whereas, patients randomized to sacubitril/valsartan 400 mg daily dose experienced decreases in mean SBP and DBP by - 0.81 ± 17.9 and - 0.34 ± 11.7 mm Hg [change from baseline (on sacubitril/valsartan 200 mg daily) to last test]. These data indicate that valsartan is a less potent antihypertensive compared to sacubitril/valsartan in patients with HF with LVEF ≥ 45%. Although a recurrent events analysis of the treatment effect on the primary composite endpoint adjusted for SBP over time appears to suggest that the treatment effect size in PARAGON-HF was unaffected by SBP [unadjusted RR 0.87 (95% CI 0.75 – 1.01; 1-sided p=0.029) vs. SBP adjusted RR 0.87 (95% CI 0.74 – 1.00; 1-sided p = 0.027)], but some benefit from greater BP reduction with sacubitril/valsartan compared to valsartan cannot be completely excluded.

7.2. Heterogeneity of Treatment Effect of Sacubitril/Valsartan by LVEF and Gender

In this section we show a number of exploratory analyses on LVEF, sex, and NT-proBNP. The results shown should be construed as hypothesis generating and not as definitive evidence for or against a treatment effect within particular subgroups.

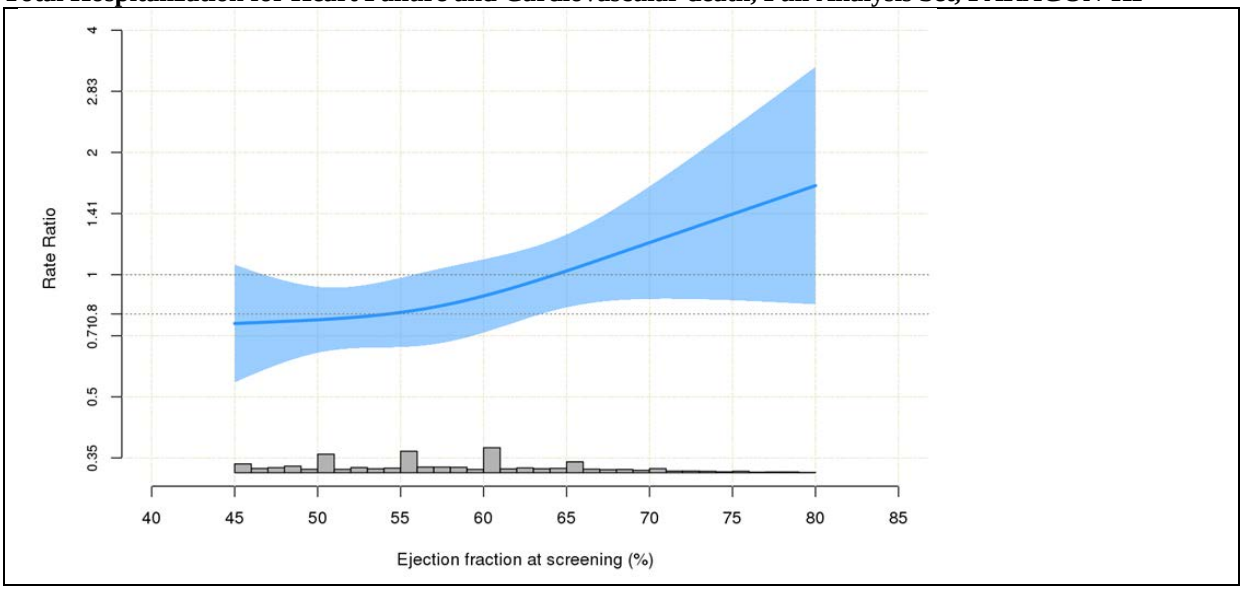
Figure 9 displays the estimated treatment effect (RR) of sacubitril/valsartan compared to valsartan against LVEF at screening as a continuous variable. The estimated RR and 95% confidence intervals are plotted for recurrent CEC-confirmed total HHF and CV death as a function of LVEF at screening. The RR is < 0.8 in patients with LVEF between 45 to 55% and between 0.8 and 1 in patients with LVEF between 55 and 65%.

In PARAGON-HF, 70% (3371/4796) of the patients had an LVEF of < 60%. Table 14 and Figure 10 present the distribution of patients in PARAGON-HF by treatment arm by LVEF categories in increments of 5%. There was only one patient with LVEF < 45% in the FAS in PARAGON-HF.

The relationship between the level of NT-proBNP at screening and treatment response was explored. Figure 11 displays the estimated treatment effect (RR) of sacubitril/valsartan compared to valsartan plotted against NT-proBNP at screening for recurrent CEC-confirmed total HHF and CV death. The RR is consistent across the range of NT-proBNP levels at screening.

These findings show that the therapeutic benefit with sacubitril/valsartan tends to be more pronounced at the lower range of LVEF, though there may be some effect in patients with higher LVEFs. The treatment effect did not vary with screening NT-proBNP levels in PARAGON-HF.

Figure 9. Treatment Effect (rate ratio) against Ejection Fraction at Screening for Recurrent CEC-Confirmed Total Hospitalization for Heart Failure and Cardiovascular death, Full Analysis Set, PARAGON-HF



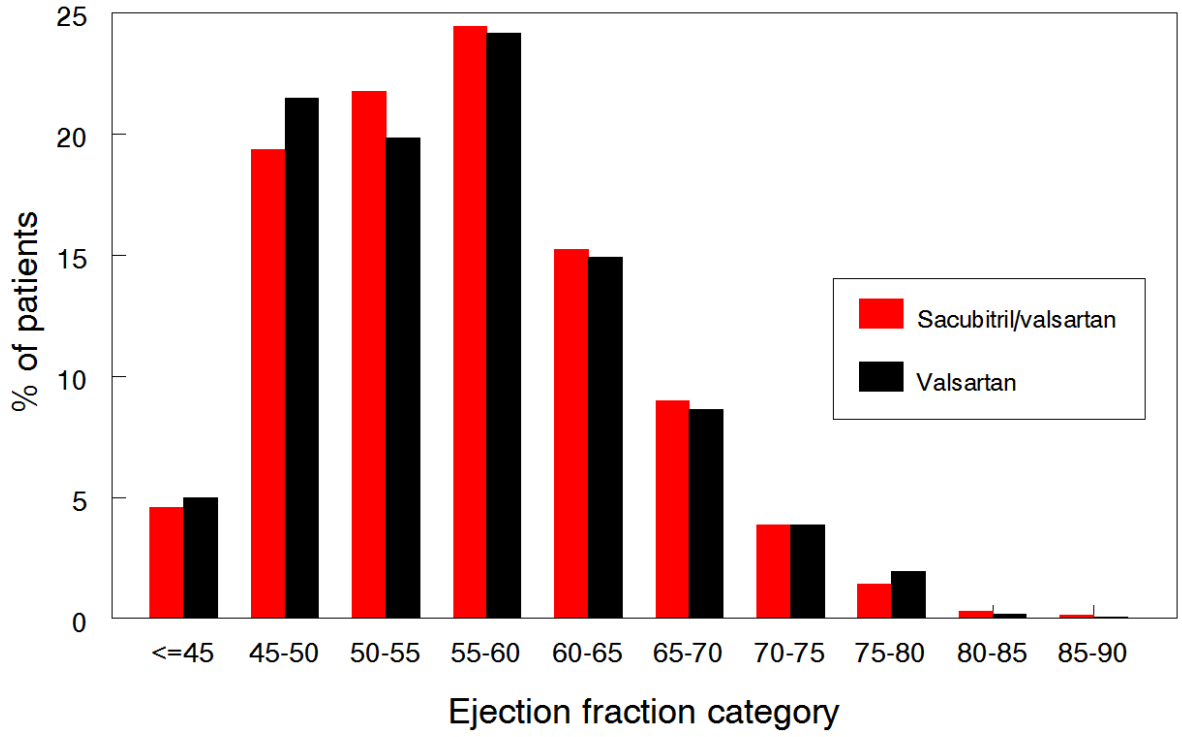
Source: NDA 207620/S-018 – Applicant Response to FDA Information Request dated May 27, 2020

Table 14. Distribution of Patients by Treatment Arm by LVEF Categories, PARAGON-HF, Full Analysis Set

LVEF Range	Sacubitril/valsartan 200 mg bid	Valsartan 160 mg bid	Total
LVEF≤45	110 4.57%	119 4.98%	229
45-50	466 19.36%	513 21.47%	979
50-55	524 21.77%	474 19.84%	998
55-60	588 24.43%	577 24.15%	1165
60-65	366 15.21%	356 14.9%	722
65-70	216 8.97%	206 8.62%	422
70-75	93 3.86%	92 3.85%	185
75-80	34 1.41%	46 1.93%	80
80-85	7 0.29%	4 0.17%	11
85-90	3 0.12%	2 0.08%	5
Total	2407	2389	4796

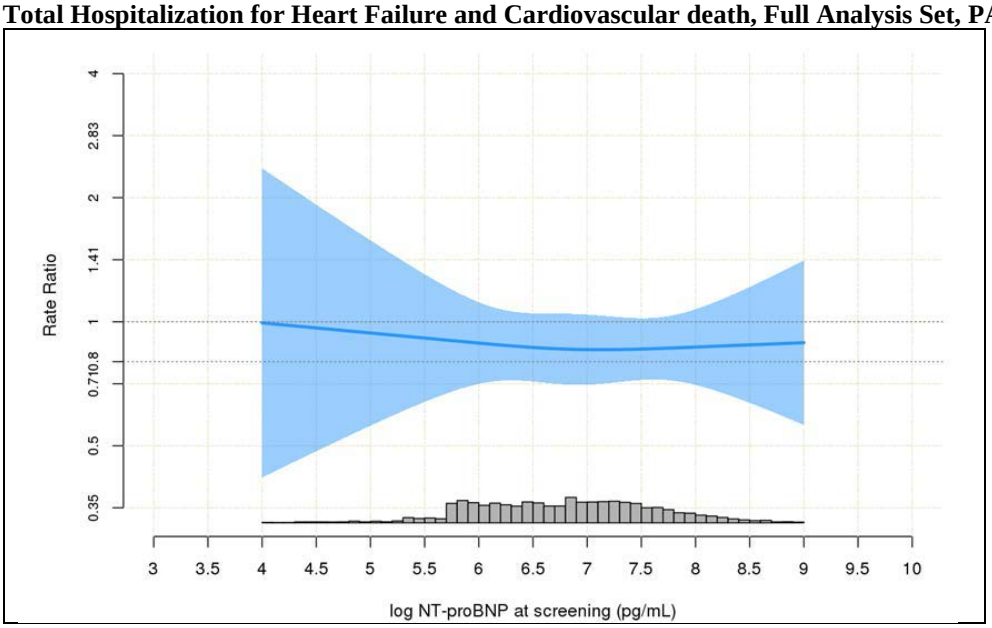
LVEF: Left ventricular ejection fraction
Source: Reviewer's Analysis

Figure 10. Distribution of Patients by Treatment Arm by LVEF Categories, PARAGON-HF, Full Analysis Set



LVEF: Left ventricular ejection fraction
Source: Reviewer's Analysis.

Figure 11. Treatment Effect (rate ratio) against NT-proBNP at Screening for Recurrent CEC-Confirmed Total Hospitalization for Heart Failure and Cardiovascular death, Full Analysis Set, PARAGON-HF



Source: NDA 207620/S-018 – Applicant Response to FDA Information Request dated May 27, 2020

Given the noticeable differential trend in treatment effect by LVEF and gender, we used descriptive statistics to break down these subgroups into sub-subgroups to understand if there was potential confounding between them (Table 15). The breakdown between sub-subgroups was fairly even with the largest sub-subgroups being males with LVEF below the median and females with LVEF above the median. Females with LVEF below the median only made up 23% of the study population and had an overall event rate slightly lower than, but close to, their male counterparts. Based on these general descriptive statistics, confounding does not seem to be an issue.

Breaking down event rate by treatment arms (Table 16), we see that females with lower LVEF on valsartan had the highest event rate of all sub-subgroups and those on sacubitril/valsartan had the lowest.

Table 15. Breakdown of Proportion of Patients in Subgroups by LVEF and Gender, Full Analysis Set, PARAGON-HF

		LVEF≤57	LVEF>57	Total
Male	n (%)	1395 (29.09%)	922 (19.22%)	**2317 (48.31%)**
	events per 100 patient years	15.06 (597 / 3964)	14.47 (383 / 2647)	**14.82 (980 / 6612)**
Female	n (%)	1100 (22.94%)	1379 (28.75%)	**2479 (51.69%)**
	events per 100 patient years	14.08 (451 / 3204)	11.66 (472 / 4047)	**12.73 (923 / 7251)**
Total	n (%)	**2495 (52.02%)**	**2301 (47.98%)**	**4796**
	events per 100 patient years	**14.62 (1048 / 7168)**	**12.77 (855 / 6694)**	**13.73 (1903 / 13863)**

LVEF: left ventricular ejection fraction
Source: Reviewer's analysis

Table 16. Subgroup Results by LVEF and Gender, Full Analysis Set, PARAGON-HF

	n (events per 100 patient years)		
Subgroup	**Sacubitril/valsartan**	**Valsartan**	**RR (95% CI)**
Male	1166 (15.06)	1151 (14.57)	1.03 (0.84, 1.25)
Female	1241 (10.78)	1238 (14.68)	0.73 (0.59, 0.90)
LVEF≤57	1239 (12.82)	1256 (16.40)	0.78 (0.64, 0.95)
LVEF>57	1168 (12.85)	1133 (12.69)	0.99 (0.80, 1.23)
Male, LVEF≤57	686 (15.03)	709 (15.09)	0.99 (0.77, 1.27)
Male, LVEF>57	480 (15.13)	442 (13.74)	1.11 (0.81, 1.54)
Female, LVEF≤57	553 (10.15)	547 (18.06)	0.57 (0.42, 0.76)
Female, LVEF>57	688 (11.28)	691 (12.04)	0.91 (0.69, 1.21)

LVEF: left ventricular ejection fraction
Source: Reviewer's analysis

The sub-subgroup of females with LVEF below the median seem to be achieving the most benefit from the study treatment. Conversely, it is questionable whether males in any sub-subgroup of this study population are gaining benefit from treatment (Table 16). An unexplained poor response to valsartan evidenced by a higher event rate in female patients with lower LVEF might be explored further. Additional studies designed to test these hypotheses would be needed to confirm these findings.

Table 17 displays the prevalence of some baseline co-morbidities / clinical characteristics that are associated with, or can worsen, HF, by gender in the randomized set. Males had a higher prevalence of atherosclerotic CV disease, atrial fibrillation/flutter and prior HHF; and females had a higher prevalence of hypertensive cardiomyopathy and depression. These differences do not help explain a potential difference in response to sacubitril/valsartan. Note that the observed HR in CHARM-PRESERVED and I-PRESERVE did not differ by gender. It is possible that the heterogeneity of treatment effect observed in the subgroups by gender and LVEF in PARAGON-HF is a chance finding.

Table 17. Baseline Prevalent Co-morbidities in Randomized Set (N=4822) by Gender

Clinical Characteristic	Female N 2491/ 2479	Male N 2331/ 2317
Primary Heart Failure Etiology		
Ischemic	671 (27%)	1052 (45%)
Hypertensive	1651 (66%)	1156 (50%)
Diabetic	287 (12%)	236 (10%)
One heart failure hospitalization within 12 months prior to screening	852 (34 %)	894 (39%)
Baseline LVEF (%) Mean ± SD	59 ± 8	56 ± 8
Baseline LVEF (%) Median	60	55
LA volume index (ml/m^2) Mean ± SD overall	47 ± 17	46 ± 18
LA volume index (ml/m^2) Mean ± SD in patients with atrial fibrillation	52 ± 17	51 ± 20
LV septal wall thickness (cm) Mean ± SD	1.21 ± 0.22	1.27 ± 0.23
LV posterior wall thickness (cm) Mean ± SD	1.13 ± 0.21	1.20 ± 0.23
NT-proBNP (pg/ml) Mean ± SD overall	1245 ± 1397	1362 ± 1667
Angina Pectoris	664 (27%)	724 (31%)
Coronary Artery Bypass Graft	172 (7%)	398 (17%)
Percutaneous Coronary Intervention	369 (15%)	608 (26%)
Peripheral Vascular Disease	176 (7%)	238 (10%)
Prior Stroke	260 (10%)	258 (11%)
Dyslipidemia	1475 (59%)	1440 (62%)
Hypertension	2392 (96%)	2192 (94%)
Diabetes	1001 (40%)	1061 (46%)

Source: FDA analyses of ADBS, ADCM data sets.

Conclusion

PARAGON-HF failed to reject the null hypothesis for the prospectively planned primary efficacy endpoint, however, various pre-specified and post-hoc analyses suggest that sacubitril/valsartan compared to valsartan reduces HF events in patients with HF with LVEF ≥ 45%.

Sacubitril/valsartan has demonstrated efficacy in reduction in HHF and CV death in an adjacent patient population of HF with LVEF < 40% in PARADIGM trial. Although there are underlying differences in the pathophysiology and epidemiology of patients with HFrEF and HFpEF, the LVEF boundaries separating the two patient populations is ill-defined. In PARAGON-HF, 70% of the patients had an LVEF < 60% (Table 14), which is considered to be a reduced LVEF by echocardiography. It is conceivable that there is some overlap in pathophysiology between patients with LVEF < 40% and LVEF ≥ 45% evaluated in PARADIGM and PARAGON-HF, respectively. In PARAGON-HF, the relationship of RR with LVEF as a continuous variable (Figure 22) indicates that the patients in the lower LVEF range benefit the most with sacubitril/valsartan.

The prevalence of HF with LVEF ≥ 45% is increasing in the US, with increasing life expectancy, and epidemics of metabolic syndrome and DM. These patients experience significant morbidity associated with recurrent HHF with no approved treatment. The overall benefit-risk

considerations may support approval of sacubitril/valsartan to treat patients with HF with LVEF ≥ 45%.

II Appendices

8. PARAGON-HF: Trial Design and Results Additional Information

8.1. Dose selection rationale

Per Applicant, the 200 mg bid dose of sacubitril/valsartan was chosen because it was similar to the approved regimen to treat patients with HFrEF and based on biomarker and modeling data was expected to reach approximately 90% of its maximal neprilysin inhibition. Twice daily dosing schedule was considered necessary for sustained neprilysin inhibition over a 24-hour period and was anticipated to reduce the incidence of hypotension in HF patients, particularly in the elderly. Patients were instructed to take the study drug at approximately 8:00 AM and 7:00 PM, with or without food.

Valsartan was selected as an active comparator in this trial because current management of HFpEF allows use of ACEI or ARB to treat comorbidities in this patient population. Approximately 85% of the patients in TOPCAT[30] were on an ACEI or ARB at baseline. Valsartan being a component of sacubitril/valsartan, using valsartan as the comparator will allow demonstration of incremental benefit of sacubitril/valsartan versus valsartan. Note that the valsartan component of sacubitril/valsartan is more bioavailable than the valsartan in Diovan and other marketed tablet formulations, i.e., 26 mg, 51 mg, and 103 mg of valsartan in sacubitril/valsartan provides similar valsartan exposure as 40, 80 and 160 mg of valsartan in Diovan and other marketed tablet formulations, respectively.

Study Drug Dose Adjustment, Interruption or Discontinuation: Study drug dose could be adjusted or interrupted for patients unable to tolerate protocol-specified randomized dosing scheme, despite adjustment of concomitant medications. A patient could continue to receive the lower dose or be off the study treatment for a recommended period of 1 to 4 weeks prior to being re-challenged with the next higher dose. Other reasons for temporary or permanent study drug discontinuation included open-label use of AEI, ARB or renin inhibitor; or pregnancy or lactation period. Open-label ACEIs, ARBs or a renin inhibitor could be used during the study only if the patient had study treatment discontinued, temporarily or permanently. Study treatment was permanently discontinued for withdrawal of informed consent, suspected angioedema, investigator decision for patient safety, severe suspected drug-related AE, protocol deviation resulting in serious risk to patient safety, or after emergency unblinding.

[30] Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014 Apr 10;370(15):1383-92.

Concomitant CV Medications: Caution was recommended when co-administering sacubitril/valsartan with atorvastatin or other statins (e.g. simvastatin, pravastatin) that are substrates of OATP1B1 and OATP1B3 because of the potential to raise plasma statin levels.

8.2. Protocol Amendments

The original protocol for PARAGON-HF is dated June 3, 2013. There were 4 amendments to the PARAGON-HF study protocol dated June 10, 2014; May 6, 2015; December 4, 2015; and December 9, 2015. On February 18, 2016 a protocol addendum was added to Protocol V03 and V04. Relevant changes in these protocol amendments are listed below:

Amended Protocol Version 01 dated June 10, 2014 was updated with:

1. Results of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial.
2. Decision of the Data Monitoring Committee (DMC) to stop PARADIGM-HF study ahead of schedule because compared to enalapril, patients treated with sacubitril/valsartan were less likely to die from CV causes or be admitted to the hospital with worsening HF.

Amended Protocol Version 02 dated May 06, 2015 was changed as follows:

1. Secondary objective of comparing sacubitril/valsartan to valsartan on changes in the clinical summary score for HF symptoms and physical limitations (as assessed by KCCQ) at 8 months was added as number 1 secondary objective.
2. The endpoint of time to first occurrence of a composite renal endpoint, defined as: renal death, or reaching ESRD, or ≥ 50% decline in eGFR relative to baseline was changed from exploratory to secondary objective number 3.
3. The alpha relocation in sequentially rejective multiple test procedure for the secondary hypotheses was updated.
4. Secondary objective of comparing sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death, total non-fatal HF hospitalizations, total nonfatal strokes, and total non-fatal MIs was changed to an exploratory objective.
5. Secondary objective of comparing sacubitril/valsartan to valsartan in delaying the time to new onset atrial fibrillation (NOAF) in patients with no history of AF and without AF on ECG at baseline was changed to an exploratory objective.
6. Objective to compare effect of sacubitril/valsartan to valsartan on changes in cognitive function assessed by Mini-Mental State Examination (MMSE) at 2 years was added.
7. Subgroup by baseline eGFR (<60 vs ≥60 mL/min/1.73 m2) was added to the planned subgroup analyses.
8. Cardiac monitoring sub study to measure atrial fibrillation burden in approximately 600 patients was removed.
9. Age inclusion criteria was changed from ≥ 55 to ≥ 50 years to include younger patients.
10. Patients who had HHF within 9 months prior to Visit 1 also needed to have NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF on Visit 1 ECG to be eligible.

11. Exclusion criteria of any prior echocardiogram measurement of LVEF <45% was changed to <40%.
12. Exclusion criteria for SBP was changed from < 105 to < 100 mm Hg at Visit 103 (end of treatment run-in) or Visit 199/201 (randomization visit).
13. Exclusion criteria of eGFR <25 mL/min/1.73m2 at Visit 103 (end of treatment run-in) or Visit 199/201 was added.
14. Assessment of endpoints - total non-fatal MIs, non-fatal strokes, KCCQ overall summary score and subdomain scores, new onset atrial fibrillation, mini-mental state examination score was added.
15. The efficacy interim analysis plan was changed from 50% to when two-thirds of target number of adjudicated primary events are obtained (approximately 1148 instead of 860 events).
16. Plan to conduct a futility analysis during interim efficacy analysis if superiority boundary was unlikely to be crossed was removed.

Amended Protocol Version 03 dated December 4, 2015:

There were 1508 patients randomized into the trial at the time of this amendment.

1) Sample size was increased from 4300 to 4600 to increase statistical power from 81 to 85% to detect a 25% reduction in recurrent HHF. The sample size re-estimation was based on analysis of recurrent HF hospitalization in the PARADIGM-HF, which showed that sacubitril/valsartan resulted in approximately a 25% reduction in recurrent HHF relative to enalapril. The target number of primary events was also increased to 1847, which corresponded to conducting the interim efficacy analysis when ~1231 primary composite events have been confirmed by adjudication. A 25% reduction in recurrent HHF was expected to correspond to an overall 19% reduction in the primary endpoint (CV deaths and total recurrent HHF).
2) The target number of primary events was increased to 1847.
3) Statistical stopping rules for superiority of sacubitril/valsartan over valsartan were modified from one-sided *p*-value of <0.0001 for the primary endpoint to one sided *p*-value of <0.001 for both the primary endpoint and CV death at the interim efficacy analysis.
4) Source documentation verification to ensure adherence to the study eligibility criteria as needed was incorporated.

Amended Protocol Version 04 dated December 9, 2015 was updated with additional study visits for Japan and India, and LVEF assessment in India had to be performed using 2D volumetric methods.

8.3. Endpoint Adjudication

The CEC was comprised of the CEC chairman, physician reviewers, administrator and project manager/coordinator. Investigator reported events, which could potentially fulfill criteria for

primary, secondary, or other clinical endpoints were assessed by the CEC for adjudication. The CEC was accountable for review and adjudication of the following events:

- All deaths
- Total HHF
- Urgent HF visits
- MIs and all hospitalizations for myocardial ischemia (Note: hospitalizations for
- myocardial ischemia were not endpoints in this study, but were
- adjudicated for possible MIs)
- Stroke/Transient ischemic attack (TIA) (Note: TIA was not an endpoint in this study but was adjudicated for possible strokes)
- ESRD
- New onset atrial fibrillation/atrial flutter (NOAF)
- New onset diabetes mellitus (NODM)
- Angioedema or angioedema-like event

The source documents required to adjudicate an HHF event included discharge summary, admitting history and physical, medication logs, clinic notes, cardiac marker reports if available, and chest x-ray report if done. Investigator-reported endpoints were randomly assigned to two independent physician reviewers. It the two reviewers agreed on adjudication results then the potential endpoint was not required to be presented to the CEC. If the results of adjudication did not match between the two reviewers, then the potential endpoint was presented to the CEC to decide the final outcome.

The PARAGON-HF Endpoint Definition for HHF event was as follows:
Presentation to an acute care facility requiring an overnight hospitalization (change in calendar day) with an exacerbation of HF requiring treatment meeting the following criteria:

1. Symptoms and signs of HF: One or more of the following symptoms consistent with HF: a. Increasing dyspnea b. Worsening orthopnea c. Paroxysmal nocturnal dyspnea d. Increasing fatigue/ decreasing exercise tolerance e. Worsening edema/anasarca

AND

Two or more of the following signs consistent with HF: a. Rapid weight gain b. Pulmonary edema or rales c. Elevated jugular venous pressure d. Radiologic signs of HF e. Peripheral edema f. Increasing abdominal distension or ascites g. S3 gallop h. Hepatojugular reflux i. Elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (> most recent baseline) j. Congestive hepatomegaly (i.e. not related to intrinsic liver disease) k. Invasive/Non-invasive tests showing cardiac filling pressures or low cardiac output

AND

2. Treatment with intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump for hemodynamic compromise.

Initiation of standing oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify as treatment.

Note: Adjudicated HF events associated with elevation in cardiac biomarkers (e.g. cardiac troponin) not thought to be evidence of an associated MI will be noted by the CEC.

The PARAGON-HF Endpoint Definition for Urgent Heart Failure Visit was as follows:

Urgent, unscheduled office/practice or emergency department visit for HF management not requiring overnight hospitalization

1. New or worsening signs and symptoms of HF, defined by the same criteria as for the HHF end point above

AND

2. Receives intravenous (IV) decongestive therapy [IV diuretics, IV neseritide or other natriuretic peptide, IV inotropes, and IV nitroglycerin (NTG)], and does not result in formal inpatient hospital admission*, regardless of the setting (i.e. in an ER setting, in the physician's office, an outpatient treatment facility, etc.).
* "formal inpatient hospital admission" refers to presentation to an acute care facility requiring an overnight hospitalization (change in calendar day).

Data Monitoring Committee: An independent DMC regularly reviewed accumulating study data and the results of pre-specified interim analyses. The committee membership and responsibilities were defined by a written charter and included cardiology, nephrology, and statistical expertise. The Applicant submitted minutes for meetings of the DMC which did not raise any concerns about trial conduct. An external independent statistician and programmer performed analyses and generated reports for the DMC according to a pre-specified analysis plan.

8.4. Other Findings

GCP Deviations: Site 3305 was prematurely closed due to significant GCP deviations which affected the integrity of the data. As a result, the 26 randomized patients at this site were excluded from the efficacy analyses but were included in the safety analyses. Protocol deviations were assigned to these patients.

Treatment Unblinding: A total of 5 patients were unblinded during the study leading to treatment discontinuation.

Protocol Deviations: In the randomized set, 34.6% of patients had at least one protocol deviation during the study. The percentage of patients with protocol deviation(s) was balanced between the two treatment arms. He most common protocol deviation was "overall drug compliance < 80%" at one or more medication compliance assessment visit and was similar between sacubitril/valsartan (16.4%) and valsartan (16.6%) arms. There were 119 (4.9%) patients in the and 139 (5.8%) patients in sacubitril/valsartan and valsartan arms, respectively who used an open-label ACEI, ARB, or renin inhibitor concomitantly while taking study medication at some point in the study. A total of 12 (0.50%) and 14 (0.58%) patients in sacubitril/valsartan and valsartan arms, respectively were excluded from the full analysis set due to protocol deviations for GCP reasons.

Other Analyses

a) Number of days alive out of the hospital: Analysis based on ANCOVA model with treatment and region as fixed-effect factors were conducted evaluating days alive out of the hospital and days alive out of HHF (Table 18). During the randomized period, patients in LCZ696 group had approximately 7 more days alive out of the hospital adjusted for the duration of exposure compared to valsartan group.

b) NT-proBNP: The ratio of NT-proBNP to baseline levels was approximately 19% and 17% lower in the sacubitril/valsartan arm as compared to the valsartan arm at Week 16 and Week 48 post randomization, respectively (Table 19).

Table 18. Number of Days Alive Out of the Hospital in PARAGON HF by Treatment Arm—Full Analysis Set

Parameter	Sacubitril/valsartan N=2407	Valsartan N=2389	Sacubitril/valsartan - Valsartan
	LSM (SE)	LSM (SE)	LSM of difference (95% CI)
DAOOH during first 12 months in the randomized treatment period	356 (0.80)	354 (0.81)	1.78 (-0.45, 4.01)
DAOOH during randomized treatment period adjusting for follow-up time	1046 (4.68)	1039 (4.70)	7.14 (-5.86, 20.15)
Days alive out of heart failure hospitalization during first 12 months in the randomized treatment period	359 (0.76)	357 (0.76)	1.99 (-0.12, 4.10)
Days alive out of heart failure hospitalization during randomized treatment period adjusting for follow-up time	1056 (4.63)	1049 (4.65)	6.49 (-6.36, 19.38)

LSM: Least Square Mean; DAOOH: days alive out of hospital; SE: Standard Error of Mean; CI: Confidence Interval;

Source: Reviewer Compilation

Table 19. N-Terminal Pro-Brain Natriuretic Peptide by Treatment Arm, PARAGON HF—Full Analysis Set

	LCZ696 N=1400		Valsartan N=1374		LCZ696 vs. Valsartan	
Visit	n	LSM of ratio: E/B Geometric Mean (95% CI)	n	LSM of ratio: E/B Geometric Mean (95% CI)	LSM of ratio: LCZ696/ Valsartan	(95% CI)
Visit 203 (Week 16)	1345	0.7644 (0.7362, 0.7937)	1315	0.9450 (0.9097, 0.9816)	0.8089	(0.7668, 0.8534)
Visit 205 (Week 48)	1273	0.8062 (0.7724, 0.8415)	1229	0.9666 (0.9254, 1.0095)	0.8341	(0.7847, 0.8866)

(1) Includes patients in the Full analysis set who had NTproBNP samples available for analysis at either V101 or V102 Baseline is Visit 101 or 102, whichever occurs first The change from baseline in logarithmic scale is analyzed using a repeated measure ANCOVA model with treatment, region, visit, treatment-by-visit interaction as fixed-effect factors, log transformed baseline value as a covariate, and a common unstructured covariance matrix among visits for each treatment arm The analysis is using all available data up to Visit 205 (week 48) based on likelihood method with an assumption of missing at random (MAR) for missing data Ratio: E/B=Endpoint/Baseline; CI=Confidence interval; Geometric mean= back-transformed from the LS mean based on the ANCOVA model The same transformation is applied to the 95% CI

Source: PARAGON-HF Clinical Study Report Table 11-19

8.5. Schedule of Assessments

NT-proBNP

NT-proBNP was analyzed for all patients that provided a sample at the pre-valsartan run-in visit (Visit 1, 101/102), (N= 2774 patients). Sampling occurred prior to study drug administration at five visits: baseline (pre-valsartan run in visit V101/V102); pre-sacubitril/valsartan run-in (V103), randomization (V199/V201), Week 16 (V203) and Week 48 (V205). The central lab

performed all biomarker analyses in complete patient sets by laboratory personnel blinded to treatment allocation and clinical outcomes.

Table 20 displays the Schedule of Assessments.

Table 20. Schedule of Assessments

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/SS	1	101†	102	103	199/201††	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221°	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
Obtain informed consent	S	x																				
Inclusion/Exclusion criteria	DS	x																				
Safety monitoring criteria	DS			(x)[1][5]	x	x[§]																
Relevant Medical History/Current Medical Conditions /Demography	DS	x																				
Medical History Possibly Contributing to Liver Dysfunction	DS	x																				
HF and Diabetes History/Smoking History/Alcohol History	DS	x																				

Epoch		Screen	Treatment Run-in			Randomized Treatment															
Visit	DS/SS	1	101†	102	103	199/201††	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
Concomitant Medications	DS	x	x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visit Contact Information	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
NYHA Classification (HF Signs/Symptoms)	DS	x		x	x	x§	x	x	x	x		x		x		x		x		x	x	x
Physical Exam[1]	S	x		x	x	x	x	x	x	x		x		x		x		x		x	x	x
Vital signs (BP and pulse)	DS	x	x	x	x	x§	x	x	x	x		x		x		x		x		x	x	x
Height	DS	x																				
Weight	DS	x				x§	x	x	x	x		x		x		x		x		x	x	x
Waist/hip circumference	DS					x§																x
ECG[2]	DS	x				x				x				x				x		X[2]	(x)	x

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/SS	1	101†	102	103	199/201††	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
Echocardiography[3]	DS	x																				
QOL Questionnaire (KCCQ)[4]	DS		x			x		x	x	x				x				x		X		x
Patient Global Assessment[4]	DS					x		x	x	x				x				x		X		x
EuroQol (EQ-5D)[4]	DS					x		x	x	x				x				x		X		x
Mini-Mental State Examination (MMSE)[16]	DS					x				x				x				x		X		x
Complete Laboratory Evaluations[5]	DS	x			x	x§		x		x				x				x		x[13]		x
Abbreviated Laboratory Evaluations[6]	DS			(x)			x		x			x				x				x[13]	(x)	
Local Laboratory[15] Evaluation				(x)	(x)	(x§)															(x)	
Urinalysis	DS	x				x		x		x				x				x			(x)	x

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/S	1	101†	102	103	199/201†	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
FSH[7]	DS	x																				
Plasma NT-proBNP[8]	DS	x	x		x	x		x		x												
Biomarkers/Biobanking[9]	DS		x		x	x		x		x												
1st morning void (urine)[9]	DS		x		x	x		x		x												
Pharmacogenomics[14]	DS				x			x		x												
Pharmacogenetics[10]	DS				x																	
Pharmacokinetic Sampling[11]	DS					x		x		x												
Serum/Urine Pregnancy Test[12]	DS	x	x	x	x	x§	x	x	x	x		x		x		x		x		x	(x)	x
AEs/SAEs	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/S	1	101†	102	103	199/201†	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
Drug Accountability	DS			x	x	x§	x	x	x	x		x		x		x		x		x	(x)	x
Contact IVRS/IWRS	S	x	x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispense Study Medication	S		x	x	x	x	x	x	x	x		x		x		x		x		x	(x)	
Screening Disposition	DS	x																				
Endpoint Information	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Run-in Disposition	DS					x§																
Treatment Disposition	DS																					x

UNS = Unscheduled visit
EOS = End of Study
DS = assessment to be recorded in clinical database
S = assessment to be recorded on source document
(x) = optional assessment

† = Visit performed only for patients that entered the treatment run-in epoch due to having been on an ACEI or ARB medication at doses lower than the total daily dose or per the investigator's discretion based on the patient's clinical status.

†† = Visit 199/201 completed for all patients who entered the treatment run-in epoch. For patients that were randomized, Visit 199/201 was to be combined into one clinic visit. For patients who discontinued during the treatment run-in epoch, only procedures with "§" were performed and no Visit 201 was conducted.

††† = Visit 299 (end of randomized treatment visit) completed for all patients that entered the randomized treatment epoch

° Indicates study visits to be conducted as a telephone contact visit, except for patients enrolled in Japan where these visits were conducted as clinic visits with procedures similar to Visit 202 with the exception that study medication dispensing, drug accountability and serum/urine pregnancy tests were not required.

§ At Visit 199/201, only procedures marked with "§" were performed for patients who discontinued during the run-in epoch.

[1] Complete physical examination required at Visit 1 and 201 and annually thereafter (Visit 205, 209, 213, 217, 221) up until Visit 299 (EOS). Short physical exam required at all interim visits.

[2] ECG performed at Visits 1, 201, and annually thereafter.

[3] Qualifying LVEF measurements/documentation of structural heart disease was based on locally obtained echocardiograms (echo) performed ≤ 6 months prior to Visit 1. If an echo performed ≤ 6 months prior to Visit 1 was not available, an echo was to be performed during the screening epoch.

[4] Patient Global Assessment was not evaluated at Visit 201; patients were asked to remember how he/she felt at Visit 201, throughout the study the patient was asked to rate how he/she felt compared to at the randomization visit (Visit 201). KCCQ value was assessed at the beginning of run-in, i.e. Visit 101 or 102 (whichever occurred first), If the study extended beyond Visit 221, KCCQ, Patient Global Assessment, and EuroQOL would be conducted annually.

[5] Complete laboratory evaluations were collected and sent to the central lab at all specified visits for all patients. If the study was extended beyond Visit 221 a complete laboratory evaluation was performed annually. Complete blood chemistry laboratory was evaluated at Visit 103.

[6] Abbreviated laboratory includes: blood urea nitrogen (BUN), creatinine, potassium and eGFR. If the study extended beyond Visit 221 an abbreviated laboratory evaluation was performed at all interval visits except annual visits.

[7] Not required for males or pre-menopausal women.

[8] Visits 1, 101/102 (whichever was first), 103, 199/201, 203 and 205 (central lab) for all patients. Only the Visit 1 NT-proBNP results were reported to the investigator and the sponsor.

[9] For patients participating in the biomarker substudy. If patient had biomarker sampled at Visit 101, biomarker sample at Visit 102 was not needed.

[10] If the pharmacogenetics substudy sample was not obtained at Visit 103, it could be obtained at any time during the study.

[11] Patients participating in the PK substudy were also to participate in the biomarker substudy; however patients could participate in the biomarker substudy without having to participate in the PK substudy.

Source: PARAGON-HF Clinical Study Report Table 9-5