NOVARTIS

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

December 15, 2020

Entresto®

(sacubitril/valsartan)

for

Chronic Heart Failure and Preserved Ejection Fraction

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

1 Table of contents

1.1 List of tables

1.2 List of figures

2 List of Abbreviations

6MWD	Six-minute walk distance
AAC	Angioedema adjudication committee
ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AHA	American Heart Association
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
b.i.d.	Twice a day
BMI	Body mass index
CEC	Clinical endpoint committee
CI	Confidence interval
cGMP	Cyclic guanosine monophosphate
CHF	Chronic heart failure
CKD	Chronic kidney disease
CSS	Clinical Summary Score
CV	Cardiovascular
EAIR	Exposure-adjusted incidence rate
EAR	Exposure-adjusted rate
ECG	Electrocardiogram
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESRD	End stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HF	Heart failure
HFH	Heart failure hospitalization
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IMT	Individualized medical therapy
IQR	Interquartile range
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrial
LCZ696	Sacubitril/valsartan
LSM	Least squares mean
LVEF	Left ventricular ejection fraction
LWYY	Lin, Wei, Ying and Yang

MRA	Mineralocorticoid antagonist
MTP	Multiple testing procedure
NEP	Neprilysin
NMQ	Novartis MedDRA Queries
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PT	Preferred term
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RAP	Re-adjudication panel
RAS	Renin angiotensin system
RR	Rate ratio
RRR	Relative rate reduction
SAE	Serious adverse event
Sac/Val	Sacubitril/valsartan
SBP	Systolic blood pressure
SCTI	Standardized Data Collection for Cardiovascular Trials Initiative
SD	Standard deviation
SMQ	Standardized MedDRA Query
sNDA	Supplemental New Drug Application
TTFE	Time to first event
US	United States
Val	Valsartan

3 Executive Summary

Introduction

Novartis Pharmaceuticals Corporation (hereafter referred to as Novartis) submitted a supplemental New Drug Application (sNDA) on 20-Apr-2020, seeking to expand the use of Entresto® (sacubitril/valsartan) from the currently approved indication for the treatment of chronic heart failure (CHF) patients with reduced ejection fraction (HFrEF) to include the adjacent population of patients with preserved ejection fraction (HFpEF) who have a left ventricular ejection fraction (LVEF) below normal.

HFpEF is among the most challenging clinical syndromes for drug development in cardiovascular medicine. While patients with HFrEF have benefited from medical advancements and a growing list of available therapeutic agents, patients with HFpEF continue to wait as there are no approved therapies to treat the morbidity or mortality of their disease. The burden of morbidity for HFpEF patients is similar to HFrEF, yet HFpEF patients are generally only treated through the management of their comorbidities. Therefore, there remains a significant unmet medical need for therapies for patients with HFpEF.

Encouraged by the positive results from the Phase 2 PARAMOUNT trial in HFpEF and the robust efficacy from the Phase 3 PARADIGM-HF trial in HFrEF, Novartis initiated a large outcomes trial, PARAGON-HF, to understand if sacubitril/valsartan could be an effective drug for the treatment of HFpEF.

Entresto® was first approved by the Food and Drug Administration (FDA) for the treatment of patients with HFrEF in 2015 based on the PARADIGM-HF trial, in which sacubitril/valsartan demonstrated a 20% reduction in the risk of the primary endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF) relative to enalapril.

Entresto® is approved in 115 countries worldwide for the treatment of HFrEF, with more than 2.6 million patient-years of exposure to date. Entresto® has also been endorsed by international HF treatment guidelines as first-line therapy for HFrEF patients with a Class I recommendation, and has significantly advanced pharmacological HF management by reducing morbidity and mortality in these patients.

The purpose of this Advisory Committee meeting is to discuss the totality of evidence supporting the demonstration of effectiveness of sacubitril/valsartan in reducing worsening HF events (HF hospitalization and urgent HF visits) in HFpEF patients with LVEF below normal.

In the phase 3 HFpEF study (PARAGON-HF), sacubitril/valsartan reduced the rate of the primary composite endpoint of total HF hospitalization and CV death by 13% relative to the active comparator valsartan, but narrowly missed statistical significance. Considering the significant unmet need and lack of approved treatment options, Novartis engaged with the FDA to discuss the totality of evidence generated in PARAGON-HF to assess if the data could support the use of sacubitril/valsartan in HFpEF patients. As agreed with the FDA, the sNDA included pre-specified and supportive analyses of the primary endpoint that consistently showed a similar magnitude of the treatment effect and achieved nominal p-values below the threshold for statistical significance, supporting demonstration of a true treatment effect. In addition, pre-specified subgroup analyses demonstrated a greater treatment effect in two relevant subgroups:

women and patients with LVEF below the study population median. A pre-specified combined analysis of the two pivotal active-controlled HF trials with sacubitril/valsartan (PARADIGM-HF in HFrEF and PARAGON-HF in HFpEF) demonstrated a clinically meaningful benefit across the spectrum of LVEF up to normal levels (approximately 60%), with women deriving benefit to a higher LVEF than men.

This briefing document reviews the totality of evidence in support of the proposed indication expansion as indicated in bold text below:

Sacubitril/valsartan is indicated for the treatment of chronic heart failure:

- *to reduce cardiovascular death and hospitalization for heart failure in patients with HFrEF;*
- ***to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with HFpEF with left ventricular ejection fraction below normal***

With this new proposed indication, sacubitril/valsartan would provide a safe and effective treatment for a broader range of HF patients, including those with HFpEF, a prevalent, progressive and debilitating condition with no approved treatment option.

Disease background

Chronic heart failure is a complex clinical syndrome that affects an estimated 6.2 million adults in the US. The prevalence of HF is increasing; projections show that it will increase to > 8 million adults by 2030. As such, it is a major public health problem and a leading cause of morbidity, mortality and diminished quality of life (Virani SS et al 2020, Benjamin et al 2019).

Chronic heart failure is caused by an impairment of cardiac structure and/or function leading to progressive decline, reduced or inadequate cardiac output and/or elevated intracardiac pressures and an inability to adequately perfuse organ systems throughout the body. Patients with CHF often exhibit a collection of signs (e.g., edema, gallop, rales) and symptoms (e.g., dyspnea, fatigue, exertional intolerance) (Keulenaer et al 2011) which have a significant negative impact on their quality of life and sense of wellbeing. In addition to these debilitating disease manifestations, CHF is also associated with a high rate of CV events, including frequent hospitalizations for acute exacerbations of HF signs and symptoms, and CV death.

The burden of CHF affects patients and their families. Patients struggle socially, physically and emotionally, and the loss of independence for patients places an increased burden on families and caregivers (Fry et al 2016, Humphrey L et al. 2013). Chronic heart failure is also associated with a high burden on the health care system. The American Heart Association (AHA) reported 809,000 hospital discharges, 414,000 emergency department (ED) visits, and 1,932,000 physician office visits with a primary diagnosis of HF in 2016 (Virani SS et al 2020). In 2014, the majority (82%) of emergency department visits for primary HF resulted in hospital admission or transfer to another facility. The economic burden of CHF on the health care system is also high, driven by hospitalization costs. The estimated mean cost for each hospitalization with a primary diagnosis of HF was $11,552, and the total estimated cost was > $11 billion. Total direct medical costs for CHF as a whole were also estimated at $30.7 billion in 2012 and are projected to increase to $69.7 billion by 2030 (Jackson et al 2018).

Classification of Heart Failure

Chronic heart failure may result from any disorder of the heart structure but most patients experience symptoms due to impaired left ventricular function. Chronic heart failure is often considered to be a continuum most commonly classified as HFrEF and HFpEF, and can occur across the range of LVEF, a widely used measure of heart function (Rigolli and Whalley 2013). LVEF is easily measured and can be determined using cardiac imaging techniques, such as echocardiography, to assess the volume of blood ejected from the left ventricle with each contraction expressed as a percentage of the total blood volume when the heart is relaxed. Its measured values are often dependent on the imaging technique used, method of analysis, and operator function. The American Society of Echocardiography and European Association of Cardiovascular Imaging define normal LVEF and normal range (±2 standard deviations) as 62% (range: 52%–72%) in men and 64% (range: 54%–74%) in women (Lang et al 2015).

Chronic HF has historically been classified into two major groups based on the LVEF value:

- Chronic heart failure with reduced ejection fraction (HFrEF) includes patients with LVEF up to approximately 40% who are considered to have marked systolic dysfunction. This type of HF is often a consequence of acute myocardial infarction or longstanding coronary artery disease. It is a well-recognized type of HF, largely due to its ease of diagnosis, and has been well researched in clinical trials leading to the approval of multiple therapeutic modalities.
- Chronic heart failure with preserved ejection fraction (HFpEF) generally includes patients whose LVEF is greater than 40%, though cut-off criteria ranging from >40% to >49% have been used in clinical trials to select these patients. The etiology of HF in this group of patients is less clearly understood than the etiology of the disease in HFrEF and includes common conditions, such as longstanding hypertension and ischemic heart disease, as well as less common conditions, such as transthyretin amyloidosis. Obesity, atrial fibrillation, chronic kidney disease, diabetes mellitus, coronary artery disease and pulmonary hypertension are common comorbidities. Heart failure with preserved ejection fraction encompasses a heterogeneous group of patients with both normal and below normal LVEF values, and many patients have some degree of systolic dysfunction. In most patients, abnormalities of systolic and diastolic dysfunction coexist in varying degrees, irrespective of LVEF.
- More recently, both the American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines have recognized the existence of an intermediate group of HFpEF patients with LVEF below normal and mild systolic dysfunction (AHA/ACC 2013, ESC 2016).

Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction is a common disease; published reports suggest that approximately 50% of patients with CHF have preserved ejection fraction and greater than 70% of CHF patients aged 65 and older have HFpEF (Pfeffer et al 2019, Shah et al 2017, Dunlay et al 2017). In the past 20 years, epidemiologic trends demonstrate an increasing prevalence of patients with HFpEF but relatively stable or even decreasing prevalence of patients with HFrEF (Savarese and Lund 2017). Analysis of data from 275 hospitals participating in the AHA's Get

With the Guidelines-Heart Failure initiative from 2005-2010 showed that hospitalization for HFpEF is increasing relative to HFrEF (Steinberg BA et al 2012).

Patients with HFpEF tend to be older and more commonly women with relatively high prevalence of CV and metabolic comorbidities (e.g., hypertension, atrial fibrillation, diabetes, renal disease, and obesity) compared to HFrEF (Maeder and Kaye 2009, Lenzen et al 2004). HFpEF encompasses a heterogeneous population, which includes patients with normal LVEF, as well as patients with mildly reduced LVEF. The latter intermediate group of HFpEF patients with LVEF below normal has more recently become recognized by international HF guidelines as a separate phenotype of HF patients as this group shares some characteristics of both HFrEF and HFpEF with normal LVEF, specifically, "mild systolic dysfunction, but with diastolic features" (Ponikowski et al 2016). Guidelines and the medical community have described this population in a number of ways, including 'heart failure with mid-range ejection fraction', 'heart failure with mildly reduced ejection fraction', or 'heart failure with preserved ejection fraction, borderline'. Increasing evidence suggests that this group of HFpEF patients may benefit from therapies proven effective in HFrEF (Nauta et al 2017).

In HFpEF, the burden of disease is characterized by frequent and recurrent worsening symptoms or HF events, in particular, severe dyspnea, requiring escalation of care leading to hospitalization to stabilize these patients and manage their disease. Therefore, HF hospitalization is common and frequent in HFpEF patients and is a clinically significant problem. For HF hospitalization, the median length of stay is 3 days (interquartile range, 2–6 days) and approximately 40% of HFpEF patients are re-admitted within 1 year of hospital discharge (Jackson 2018, Cheng et al 2014). Each HF hospitalization or urgent outpatient visit (to an emergency department or urgent care clinic) for worsening HF is indicative of disease progression and portends a higher risk of hospitalization (or readmission) and subsequent death (Bello et al 2014). The rate of hospitalization (first and recurrent) is similar in HFpEF and HFrEF patients, although overall mortality rates are lower in HFpEF patients, with a higher proportion of non-CV death compared to CV death (Solomon et al 2020). Repeated worsening HF events directly contribute to the poor quality of life of HFpEF patients. Therefore, in HFpEF, an important goal of treatment is to reduce these frequent and recurring worsening HF events.

Treatment Landscape and Unmet Medical Need

There is no approved therapy available for the treatment of HFpEF.

International HF treatment guidelines recommend diuretics to alleviate symptoms such as edema, orthopnea and dyspnea. In addition, guidelines recommend treatment of comorbidities such as hypertension, atrial fibrillation, coronary artery disease and diabetes.

Several therapeutic agents that inhibit the renin-angiotensin-aldosterone system (RAAS) have been studied in HFpEF outcome trials, but none are approved for use in HFpEF. Hence, there remains a significant unmet medical need to develop a treatment to reduce recurrent events related to worsening of disease in HFpEF patients.

HFpEF Registration Program and Regulatory Framework

The sacubitril/valsartan HFpEF clinical registration program was designed in consultation with global health authorities, including FDA. The PARAGON-HF trial was initiated following the positive results of PARAMOUNT (Phase 2 study in HFpEF) and PARADIGM-HF (Phase 3 study in HFrEF). Key design features of PARAGON-HF were discussed and agreed with the FDA, including the study endpoints, the use of valsartan as a comparator and the recurrent event analysis.

Sacubitril/valsartan Registration Program

PARADIGM-HF (Study CLCZ696B2314)
Event driven, randomized, double-blind, active-controlled Phase 3 study evaluating the effect of sacubitril/valsartan compared to enalapril on the time to first composite endpoint of CV death or HF hospitalization in HF patients with reduced ejection fraction (HFrEF; LVEF≤ 40%) with New York Heart Association (NYHA) Class II-IV (N = 8442)

PARAMOUNT (Study CLCZ696B2214)
12-week (with 24-week extension) randomized, double-blind, active-controlled Phase 2 study evaluating the effect of sacubitril/valsartan compared to valsartan on N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac structure and function, and HF symptoms/signs in HF patients with preserved ejection fraction (HFpEF; LVEF ≥ 45%) with NYHA Class II-IV (N = 301)

PARAGON-HF (Study CLCZ696D2301)
Event driven, randomized, double-blind, active-controlled Phase 3 study evaluating the effect of sacubitril/valsartan compared to valsartan on the composite endpoint of total (first and recurrent) HF hospitalizations and CV death in HF patients with preserved ejection fraction (HFpEF; LVEF ≥ 45%) with NYHA Class II-IV (N = 4822)

Pre-filing meetings with FDA were held following the completion of PARAGON-HF. During these discussions, FDA recommended that Novartis provide additional analyses in the sNDA to support the treatment effect. In particular, FDA recommended a blinded, independent re-adjudication of investigator-reported HF hospitalizations that were not confirmed by the clinical endpoint committee (CEC). This recommendation was intended to address concerns that the original CEC adjudication process may have discarded a number of true HF hospitalization events. The independent adjudication panel assigned probabilities that these investigator-reported events were true HF hospitalizations based on clinical judgment, rather than binary assessments (i.e., yes/no) based on a strict endpoint definition as in the CEC charter. An analysis of the primary endpoint including additional events identified in the CEC-unconfirmed HF hospitalizations re-adjudication process was conducted to estimate the treatment effect based on a more holistic approach of qualitative evaluation of events to maximize the value of information from these endpoints. This provided further supportive evidence of sacubitril/valsartan's treatment benefit in reducing HF hospitalizations in patients with HFpEF.

In December 2019, FDA issued a guidance entitled, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." While the standards of demonstrating effectiveness have not changed, the guidance further describes how the evidentiary standard for establishing substantial evidence of effectiveness to support regulatory approval can be fulfilled beyond the traditional approach of two adequate, well-controlled trials clinical trials or a single, large multicenter trial. The guidance establishes a third approach based on one adequate well-controlled trial plus confirmatory evidence. Different sources of data can be used to provide the

confirmatory evidence, including study/ies in closely related approved indications, or data from studies that provide strong mechanistic support. In keeping with the December 2019 guidance, evidence of effectiveness for sacubitril/valsartan for the proposed HFpEF indication is based on the totality of evidence including:

1. The phase 3 trial PARAGON-HF, an adequate and well-controlled clinical trial assessing efficacy and safety in HFpEF, and confirmatory evidence from:
2. The established efficacy in the closely related adjacent HFrEF population from the phase 3 trial, PARADIGM-HF,
3. The strong mechanistic support provided by biomarker and cardiac remodeling data from the phase 2 trial in HFpEF, PARAMOUNT.

Overview of supportive data from HFrEF: PARADIGM-HF

In the PARADIGM-HF study, sacubitril/valsartan reduced morbidity and mortality and improved quality of life in symptomatic HFrEF patients (NYHA class II – IV) with LVEF ≤ 40% (N = 8,442) (McMurray et al 2014). Relative to enalapril administered at a target dose of 10 mg b.i.d., sacubitril/valsartan given at a target dose of 200 mg b.i.d. resulted in 20% risk reduction in the first event of the primary composite endpoint of CV death or HF hospitalization, 20% risk reduction of CV death alone, 21% risk reduction for HF hospitalization alone, and 16% risk reduction of all-cause death (all with p<0.001). There was also less deterioration in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) (relative difference 1.64 points, p = 0.0014; odds ratio [OR] for 5-point deterioration 0.82; p<0.0001) in the sacubitril/valsartan group. Of note, the rate of the composite of total (first and recurrent) HF hospitalizations and CV death was reduced by 21% (rate ratio [RR] 0.79; 95% confidence interval [CI] 0.71 – 0.87; p <0.001), which was partly driven by a 25% relative rate reduction (RRR) in total HF hospitalizations (RR 0.75; 0.66 – 0.86; p<0.001) (Mogensen et al 2018).

Overview of phase 2 data in HFpEF: PARAMOUNT

PARAMOUNT was a double-blind, active controlled phase 2 study that was performed prior to initiation of PARAGON-HF. Patients with HFpEF (LVEF ≥ 45%), elevated NT-proBNP levels, and with mild to moderate HF symptoms (NYHA class II-IV) were randomized to receive either sacubitril/valsartan at a target dose of 200 mg b.i.d. or valsartan at a target dose of 160 mg b.i.d. for 12 weeks in a 1:1 ratio (N = 301) followed by a 24-week double-blind extension period.

Patients receiving sacubitril/valsartan had a 23% relative reduction in the primary endpoint of NT-proBNP (a predictor of long-term outcomes in HF) at week 12 compared to valsartan (p = 0.005). Similarly, there was a greater reduction in the secondary endpoint of left atrial volume in sacubitril/valsartan treated patients compared with valsartan patients (-5.70 ml relative to valsartan; p = 0.0034) at week 36. In addition, although there was no difference between treatments in change in KCCQ CSS, a higher percentage of sacubitril/valsartan patients experienced a favorable change in NYHA functional class than valsartan patients (22.8% vs. 13.6%; p = 0.0488). Sacubitril/valsartan and valsartan were similarly well-tolerated.

The favorable biomarker and cardiac remodeling effects of sacubitril/valsartan demonstrated in PARAMOUNT, together with data suggestive of improved functionality, provided support to

the hypothesis that sacubitril/valsartan could improve long-term HF outcomes in HFpEF patients, which provided further rationale for proceeding to the phase 3 PARAGON-HF outcomes trial.

PARAGON-HF study design and population

PARAGON-HF is the largest and only active-controlled Phase 3, randomized, double-blind, morbidity and mortality study in HFpEF, involving 4,822 symptomatic HFpEF patients (NYHA class II-IV; LVEF $\geq$ 45%). The primary objective of the study was to compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death. The study also included CEC-adjudicated urgent HF visits as an additional component of a pre-specified exploratory expanded composite endpoint to capture the inpatient and outpatient burden of the disease.

Patients were followed for a median duration of 35 months, with final vital status known for all but 9 patients (7 patients withdrew consent and 2 patients were lost to follow-up) in the full analysis set, indicating high quality of study execution and data completeness.

Efficacy Discussion

PARAGON-HF evaluated the long-term efficacy and safety of sacubitril/valsartan in a broad HFpEF population. Sacubitril/valsartan reduced the **primary composite endpoint** of CEC-confirmed total (first and recurrent) HF hospitalizations and CV death by 13% versus the active comparator valsartan (RR = 0.87; 95% CI 0.75 – 1.01; 2-sided p = 0.0587). The effect was driven by a 15% reduction in the rate of total HF hospitalizations (RR = 0.85; 95% CI 0.72 – 1.00; 2-sided p = 0.0556). While the primary analysis narrowly missed the threshold for statistical significance, pre-specified and supportive analyses of the primary endpoint, which added clinically important events to the primary endpoint, consistently produced a treatment effect of similar magnitude with nominal p-values below the threshold for statistical significance. These added events include 1) the pre-specified exploratory expanded composite endpoint adding CEC-confirmed urgent HF visits to the primary endpoint events, 2) investigator-reported primary endpoints using total events reported by investigators in the trial, and 3) a re-adjudication analysis of CEC-unconfirmed HF hospitalization events. These analyses, which improve the precision (reduce variance) of the treatment effect estimate, provide strong confidence in a true sacubitril/valsartan treatment benefit in HFpEF patients:

- **Expanded composite endpoint (CEC-confirmed total worsening HF events [HF hospitalizations and Urgent HF visits] and CV death):** Sacubitril/valsartan reduced the rate of the pre-specified exploratory expanded composite endpoint by 14% (RR = 0.86; 95% CI 0.75 – 0.99; 2-sided p = 0.0403) compared to valsartan, which was driven by a 16% reduction in the rate of total worsening HF events (RR = 0.84; 95% CI 0.71 – 0.98).
- **Investigator-reported primary composite endpoint (regardless of CEC-confirmation):** Sacubitril/valsartan reduced the rate of investigator-reported events for the primary composite endpoint by 16% (RR = 0.84; 95% CI 0.74 – 0.97; 2-sided p = 0.0140) compared to valsartan, which was driven by an 18% reduction in rate of investigator-reported total HF hospitalizations (RR = 0.82; 95% CI 0.71 – 0.96).
- **Re-adjudication analysis of CEC-unconfirmed HF hospitalization events:** CEC-unconfirmed HF hospitalization events assessed by an independent blinded panel of

three HF experts for probability of being true HF hospitalizations and incorporated into the analysis of the primary composite endpoint showed that sacubitril/valsartan reduced the rate of the primary composite endpoint by 14% relative to valsartan (RR = 0.86; 95% CI 0.75 – 1.00; 2-sided p = 0.0429), which was driven by a 16% reduction in the rate of total HF hospitalizations (RR = 0.84; 95% CI 0.72 – 0.99).

Secondary endpoints: Beneficial effects of sacubitril/valsartan were also observed across the efficacy secondary endpoints relative to valsartan, demonstrating directional consistency with the observed benefit in the primary endpoint:

- Patient-reported HF symptoms and physical limitations measured by the KCCQ CSS were improved on average by 1.0 point at 8 months [95% CI -0.0 – 2.1], resulting in a 30% greater odds of experiencing ≥5-point improvement (OR = 1.30; 95% CI 1.04 – 1.61),
- Physician-assessed functional status as measured by change in NYHA class at 8 months was more favorable (OR = 1.45; 95% CI 1.13 – 1.86),
- There was a lower risk of experiencing the composite renal outcome of death due to renal causes, reaching end stage renal disease, or having ≥50% drop in estimated glomerular filtration rate (eGFR) (HR = 0.50; 95% CI 0.33 – 0.77).
- The results for the different secondary endpoints were consistent with the results observed for the same endpoints in HFrEF patients in PARADIGM-HF with the exception of all-cause mortality where there was no difference between treatment groups (HR = 0.97; 95% CI 0.84 – 1.13) in PARAGON-HF.

In PARAGON-HF, pre-specified subgroup analyses for heterogeneity across multiple baseline characteristics, including median LVEF and gender, were conducted for the primary and secondary endpoints. A larger treatment effect was observed in the primary endpoint in patients with LVEF ≤ the median (57%) and women compared to other patients.

In HFpEF patients with LVEF ≤ median, a 22% reduction in the rate of the primary composite endpoint of total HF hospitalizations and CV death in favor of sacubitril/valsartan was observed (RR = 0.780; 95% CI 0.641 – 0.949). This effect was driven by a 25% reduction in the rate of total HF hospitalizations (RR = 0.75; 95% CI 0.60 – 0.95), with a very similar effect on total worsening HF (RR = 0.74; 95% CI 0.60 – 0.93). A larger treatment effect in patients with lower LVEF is highly credible, has strong biological plausibility and is supported by the proven effectiveness of sacubitril/valsartan in patients with systolic dysfunction and HFrEF ≤ 40% (the adjacent HF population studied in PARADIGM-HF). A greater treatment benefit in HFpEF patients with lower LVEF also has external validation as this was also observed in prior HFpEF trials (Lund et al 2018; Solomon et al 2016).

A pre-specified combined analysis of the two pivotal active-controlled HF trials with sacubitril/valsartan, PARADIGM-HF in HFrEF and PARAGON-HF in HFpEF, demonstrated a clinically relevant benefit across the spectrum of LVEF that extended up to approximately 60% in HFpEF patients, with women deriving benefit to a higher LVEF than men. While a treatment-by-sex interaction was not seen in other HFpEF trials, these studies did show that women derived a benefit to a higher LVEF than men.

Of note, the RRR in total HF hospitalizations in HFpEF patients with LVEF below normal in PARAGON-HF was 25%, which is similar to the RRR of the same endpoint observed in HFrEF patients in PARADIGM-HF (25%).

Safety

The safety profile of sacubitril/valsartan in HF has been well-characterized based on both substantial clinical trial experience from more than 23,600 patients, as well as extensive post-marketing experience for more than 5 years for the treatment of patients with HFrEF (with ~ 2.6 million patient-years of exposure). The safety profile of sacubitril/valsartan in HFpEF is consistent with that observed in HFrEF patients.

In PARAGON-HF, the overall incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation and AEs leading to dose adjustment or temporary interruption were similar between the sacubitril/valsartan and valsartan treatment groups.

In PARAGON-HF, the same types of adverse reactions as those already known for angiotensin receptor blockers (ARBs) like valsartan were observed, and were consistent with those already identified for sacubitril/valsartan in the HFrEF population:

- Hypotension: while a greater proportion of patients in the sacubitril/valsartan group experienced mild and moderate hypotension events compared to valsartan, the incidence of more clinically important hypotension such as SAEs and AEs that led to treatment discontinuation was low and comparable between the treatment groups.
- Hyperkalemia: the incidence of hyperkalemia, including SAEs and AEs leading to treatment discontinuation, was lower for sacubitril/valsartan compared to valsartan.
- Renal impairment: the incidence of renal impairment, including SAEs and AEs leading to treatment discontinuation, was lower for sacubitril/valsartan compared to valsartan.
- Angioedema: The overall incidence of angioedema was low. Although the incidence of angioedema was numerically higher in the sacubitril/valsartan treatment group than in the valsartan treatment group, the majority of angioedema events were mild to moderate in severity, with no cases of angioedema events involving airway compromise or death.

The safety profile of sacubitril/valsartan was consistent across subgroups, including patients with LVEF below the median.

Overall Benefit-Risk in HFpEF

HFpEF is a prevalent, progressive, debilitating disease with no approved therapy. Although HFpEF has been historically defined as HF patients with LVEF > 40%, it is a heterogeneous population encompassing patients with both mildly reduced LVEF and normal LVEF. More recently, there has been recognition that the patients with mildly reduced LVEF represent a distinct phenotype within HFpEF. The clinical course of HFpEF is characterized by recurrent events of worsening symptoms, in particular severe dyspnea, that frequently requires escalation of care leading to hospitalization in order to stabilize these patients, and dramatically impairs quality of life. Keeping patients feeling well and out of the hospital is a key objective in managing HFpEF.

PARAGON-HF was a large, well conducted, active-controlled CV outcomes study that enrolled a broad HFpEF patient population. In this study, sacubitril/valsartan reduced the rate of the primary composite endpoint of CEC-confirmed total HF hospitalizations and CV death by 13% compared to valsartan, narrowly missing statistical significance. The effect was driven primarily by a 15% reduction in the relative rate of total HF hospitalizations.

The magnitude of the treatment effect in the primary composite endpoint was consistently observed (RRR of approximately 13% to 16%) in several pre-specified and supportive analyses, which added clinically important HF events to the primary endpoint. The consistency of benefit observed across these supportive analyses of the primary endpoint achieving nominal p-values below the threshold for statistical significance and directional consistency of secondary endpoint results support demonstration of a true treatment effect in the overall study. These include an analysis of events for the contemporary expanded composite endpoint (Section 6.3.1.1), events reported by the investigators (Section 6.3.1.2), and a blinded re-adjudication that incorporated CEC-unconfirmed HF hospitalizations (Section 6.3.1.3).

The pre-specified subgroup analyses of PARAGON-HF and combined analyses of sacubitril/valsartan pivotal trials across CHF demonstrated a clinically meaningful treatment effect in reduction of worsening HF events of approximately 20% in HFpEF patients with LVEF up to approximately 60%. A greater treatment effect of reducing hospitalizations in HFpEF patients with LVEF below normal has strong credibility with biologic plausibility, and is similar to the established efficacy in reducing hospitalizations in the adjacent HFrEF population, with internal consistency and external validity. The safety profile of sacubitril/valsartan in patients with HFpEF was in line with that of ARBs and is consistent with the already characterized safety profile in HFrEF. Safety is manageable through current product labelling and standard CHF patient management.

In summary, in PARAGON-HF, the consistency of the treatment effect across different supportive analyses of the primary endpoint achieving nominal p-values below the threshold for statistical significance and the consistent benefit across secondary endpoints support the conclusion of a true treatment effect of sacubitril/valsartan in the overall study. This is supported by confirmatory evidence, consistent with the December 2019 FDA Guidance, from both PARADIGM-HF in the approved closely-related HFrEF population, and the Phase 2 study PARAMOUNT which provides mechanistic support based on biomarker and cardiac remodeling data in HFpEF patients. The totality of evidence from these three studies provide evidence of effectiveness of sacubitril/valsartan in HFpEF. HFpEF patients with LVEF below normal experienced substantially greater benefit and are therefore the population that is proposed to be indicated for treatment with sacubitril/valsartan. The favorable benefit/risk profile supports expansion of the existing indication to CHF patients with preserved EF below normal who have no approved treatment options.

4 Overview of heart failure with preserved ejection fraction (HFpEF)

4.1 Disease Background

Heart failure is a hemodynamic condition where the heart fails to keep up with the circulatory demand of the body due to impairment of ventricular filling or ejection. This results in a reduced or inadequate cardiac output and/or elevated intracardiac pressures at rest or during stress. Heart failure is highly prevalent, affecting 6.2 million adults in the US and disproportionately affecting older individuals. It is a major and growing public health problem with prevalence expected to increase to greater than 8 million American adults by 2030 (Virani et al 2020). Heart failure is a progressive clinical syndrome associated with shortness of breath, fatigue, fluid retention, and poor quality of life, which lead to limitations in daily physical and social activities, as well as emotional symptoms (Ponikowski et al 2014). The gradual decline of patients with HF, often marked by episodes of acute deterioration, recurrent hospitalizations, or sudden unexpected death can have devastating effects on both patients and their families. Moreover, HF is associated with substantial healthcare resource utilization and cost, in large part related to high rates of patient hospitalizations. Direct medical costs associated with this disease in the US are projected to be approximately $40 billion in 2020 (Go et al 2013).

Once diagnosis of HF is established, it is generally categorized based on the degree of compromise of cardiac systolic function, which is most commonly assessed using LVEF, a measure of how well the heart pumps out blood though the circulation. The American Society of Echocardiography estimates normal LVEF in men and women at 62 ± 5% and 64 ± 5%, respectively (Lang et al 2015), although normal ranges also differ by age and ethnicity (The EchoNoRMAL Collaboration 2015). Historically, HF clinical trials investigating therapies for significant systolic compromise recruited patients with LVEF of approximately 40% or lower, i.e., frankly reduced LVEF, a group that was categorized as HF with reduced ejection fraction (HFrEF). Consequently, all other HF patients, i.e., all those with LVEF above approximately 40%, were categorized as HF with preserved ejection fraction (HFpEF). These HFpEF patients, who comprise approximately half of the overall HF population, encompass a phenotypically heterogeneous patient group, including patients with normal LVEF values, as well as patients with mildly reduced LVEF. This intermediate phenotype of patients with LVEF below normal, which lies between the HFrEF group and HF patients with normal LVEF, has been increasingly recognized by the community and international guidelines (e.g. ACC/AHA and ESC guidelines) and described in a number of ways, including ‘heart failure with mid-range ejection fraction’, ‘heart failure with mildly reduced ejection fraction’, or ‘heart failure with preserved ejection fraction, borderline’ (Yancy et al 2013; Ponikowski et al 2016). International HF guidelines have generally defined this intermediate phenotype to have LVEF of approximately 40 to 50% (Yancy et al 2013; Ponikowski et al 2016), but more recently some have estimated its upper limit to extend to a higher LVEF based on normative values and response patterns to neurohormonal therapies (Campbell et al 2018; Böhm et al 2020). This group has been characterized as having mild systolic dysfunction; echocardiographic measures of systolic dysfunction inversely correlate with increasing LVEF among HFpEF patients (Ponikowski et al 2016; Kraigher-Krainer et al 2014). Importantly, although systolic

dysfunction is greatest among patients with HFrEF and less so as LVEF increases, women tend to have systolic dysfunction at a higher LVEF than men across the continuum (Gori et al 2014).

Heart failure with reduced ejection fraction has been well recognized and well researched, leading to the approval of multiple therapeutic modalities shown to reduce morbidity and mortality in HFrEF. Consequently, mortality among HFrEF patients has gradually decreased over the last 20 years (Tsao et al 2018). On the other hand, the prevalence of HFpEF is increasing, affecting more women than men; patients also tend to be older than HFrEF patients. Rising prevalence may potentially be due to the aging population and increasing prevalence of comorbidities associated with this disease. Comorbidities, such as obesity, hypertension, atrial fibrillation, chronic kidney disease (CKD), and diabetes mellitus, are common among HFpEF patients and etiologic or pathophysiologic factors may be different in patients with these varying conditions (Blanche et al 2010, Gerber et al 2015, Tsao et al 2018). As a result of increasing prevalence, HFpEF will soon become the dominant form of HF.

Despite these differences, HFrEF and HFpEF patients present with similar signs and experience similarly significant symptoms, including dyspnea on exertion, exercise intolerance, peripheral and pulmonary edema, and fatigue, all of which dramatically reduce their quality of life. Also, HFrEF and HFpEF patients often experience recurrent episodes of acute exacerbation of these symptoms, requiring inpatient hospitalization or treatment in urgent care setting with intravenous (IV) medications, which result in further deterioration of their quality of life and mental and emotional wellbeing. Of note, while the risk of CV death is lower among patients with HFpEF, the rate of recurrent hospitalizations for acute decompensated HF is similar across HFpEF and HFrEF (Mogensen et al 2018; Solomon et al 2019). Approximately 40% of HF patients are re-admitted within 1 year of hospital discharge. These episodes of worsening HF are highly symptomatic for the patient and are typically characterized by worsening dyspnea, orthopnea and other symptoms. It is also noteworthy that acute HF exacerbations, which lead to either inpatient hospitalization or urgent care in an outpatient facility, are associated with significantly increased risk of all-cause mortality among both HFpEF and HFrEF patients in the long term.

Consequently, preventing HF hospitalizations and improving patients' HF symptoms and functionality are HFpEF treatment goals of the highest priority.

4.2 Treatment Landscape

No therapy has been approved to treat HFpEF. Hence, current treatment of HFpEF is largely empiric and symptom focused. International guidelines for management of HFpEF recommend diuretics to manage symptoms of fluid overload, such as dyspnea, orthopnea, and peripheral and pulmonary edema. Also, they recommend chronic management of CV and non-CV comorbidities such as diabetes mellitus, hypertension, renal insufficiency, atrial fibrillation, and coronary artery disease often using RAAS inhibitors (Yancy et al 2017). While previous HFpEF trials have not resulted in the approval of products tested for patients based on their primary results, post hoc analyses of trials for RAAS blockers suggest some limited benefit in reducing HF hospitalizations in these patients compared to placebo and provide evidence suggesting that this intermediate group of patients with LVEF below normal may benefit from therapies proven effective in HFrEF (Lund et al 2018, Abdul-Rahim et al 2018, Khan MS et al 2017, Solomon et al 2016).

Given that there is no approved treatment for HFpEF, there is a significant unmet medical need. This includes treatment options to reduce major adverse HF events, such as hospitalizations or urgent outpatient visits for HF, as these events represent a highly symptomatic exacerbation of the disease. Therefore, a development program to investigate the treatment benefit of sacubitril/valsartan in HFpEF was initiated.

5 Product Overview

5.1 Sacubitril/valsartan Background

Entresto® is a combination of sacubitril and valsartan and is the only dual blocker of the RAAS and neprilysin. Sacubitril is converted to the active metabolite sacubitrilat, a neprilysin inhibitor, which plays a key role in counteracting many of the pathological processes underlying HF, including reducing sympathetic tone, fibrosis, blood pressure and hypertrophy. Valsartan optimizes the effects of sacubitril by blocking the actions of angiotensin II, thereby reducing vasoconstriction and countering fibrosis and cardiac hypertrophy. Together, the two components of Entresto® alleviate the state of neurohormonal imbalance that exists in HF.

Entresto® was first approved by the FDA in 2015 for the treatment of patients with HFrEF based on the PARADIGM-HF trial, and is approved in 115 countries worldwide. Since approval, international HF treatment guidelines have given sacubitril/valsartan a class I recommendation to be used as first line therapy in HFrEF patients (Ponikowski et al 2016; Yancy et al 2016). Entresto® has been used by over a million patients and has played a significant role in keeping patients with HF alive and out of the hospital; considerable evidence has been published on its benefits in HFrEF over the last 5 years.

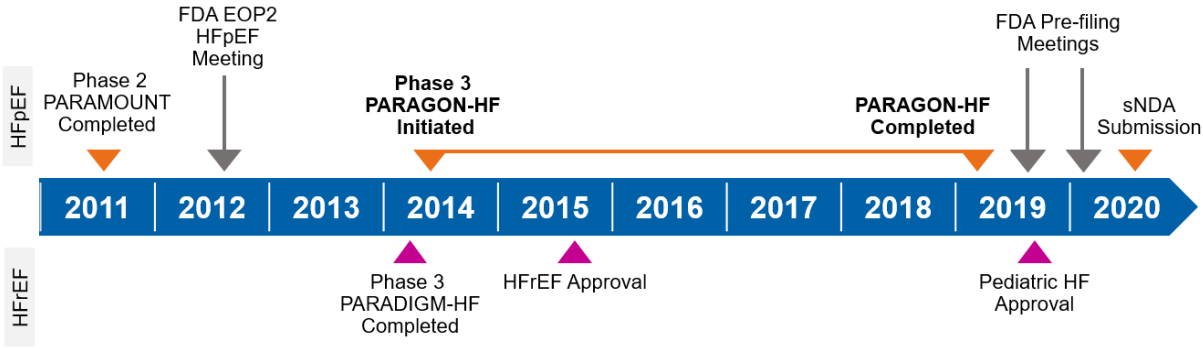
5.2 Clinical Registration Program and US Regulatory History

The sacubitril/valsartan clinical registration program was designed in close collaboration with FDA (Figure 5-1) and other Health Authorities.

The HFpEF pivotal outcomes study, PARAGON-HF, was initiated in July 2014 following completion of the Phase 2 HFpEF study, PARAMOUNT, and the positive results of the Phase 3 pivotal outcomes study PARADIGM-HF in HFrEF.

PARAMOUNT demonstrated that sacubitril/valsartan reduced NT-proBNP (a biomarker that is prognostic of long-term outcomes in HFpEF), improved NYHA functional class, and reversed left atrial remodeling in HFpEF patients (Solomon et al 2012) (Section 6.1).

Figure 5-1 US Regulatory History



Following the completion of PARAGON-HF, Novartis met with the FDA in August 2019 and January 2020 to discuss the results in advance of the sNDA submission. FDA and Novartis discussed potential approaches to the regulatory assessment of PARAGON-HF. FDA indicated that despite the primary analysis p-value narrowly missing the statistical significance level, it may be possible to support a new indication in HFpEF if the totality of evidence based on the available data demonstrated substantial evidence of efficacy.

Consistent with the **FDA Guidance for Industry** – *Demonstrating Substantial Evidence of Effectiveness (Dec 2019)*, FDA encouraged Novartis to submit the sNDA and to provide additional analyses from PARAGON-HF to support a treatment effect. FDA agreed that the sNDA should reference the totality of the evidence from the registration program, including data from PARAGON-HF, with confirmatory evidence of efficacy from PARADIGM-HF (Phase 3 study in a related population, HFrEF) and PARAMOUNT (Phase 2 study in HFpEF), to establish substantial evidence of effectiveness in HFpEF (Section 5.3). Discussions also focused on investigator-reported HF hospitalizations that were excluded from the primary analysis due to the strict requirements applied by the CEC during the adjudication process, even though many of these events were considered by the CEC to be hospitalizations for HF based on their clinical judgment. FDA encouraged a further review of the data and recommended re-adjudication of HF hospitalizations that were unconfirmed by the CEC (Section 6.3.1.3).

5.3 Regulatory framework

A drug's effectiveness must be established by "substantial evidence" which was defined in 505(d) of the Federal Food, Drug, and Cosmetic Act in 1962. Generally, this has been interpreted as requiring at least two adequate and well-controlled clinical investigations to establish effectiveness. Following the enactment of the Modernization Act, FDA issued a guidance in 1998 entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." The 1998 guidance described the quantity and quality of evidence necessary to support an effectiveness claim, including that this can be met by a single large multicenter trial. More recently, in December 2019, FDA issued a draft guidance on "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." The guidance notes that FDA's evidentiary standard for effectiveness has not changed and provides more granular detail on several scenarios by which one adequate and well-controlled study plus confirmatory evidence could be used to establish effectiveness. Two relevant examples of acceptable approaches are "*one adequate and well-controlled clinical*

investigation on a new indication for an approved drug, supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of the drug for its other, closely related approved indication(s)" (section IV B.1) and "*one adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support*" (section IV B.2).

Consistent with the December 2019 FDA guidance, the evidence of effectiveness of sacubitril/valsartan in the proposed new indication is based on the totality of evidence from:

- PARAGON-HF, an adequate and well controlled phase 3 trial in HFpEF, and confirmatory evidence from:
- PARADIGM-HF, an adequate and well-controlled clinical phase 3 trial that demonstrated the effectiveness of sacubitril/valsartan in the closely related approved indication of HFrEF,
- PARAMOUNT, a phase 2 trial in HFpEF providing strong mechanistic rationale.

While the FDA does not refer to particular clinical endpoints to establish evidence of effectiveness, it is well established that the effect shown in the adequate and well-controlled clinical trials must be clinically meaningful. FDA issued a draft guidance in June 2019 on "*Treatment for Heart Failure: Endpoints for Drug Development*" to emphasize the importance of endpoints demonstrating a reduction in morbidity for regulatory decision making, and clarifying that demonstration of a mortality benefit is not a requirement, "*A drug that improves symptoms or function when added to standard of care would be valuable even if it did not improve survival or hospitalization.*"

In this guidance, the FDA also clarifies the acceptance of outpatient interventions as a measure of clinically important worsening symptoms, "*As heart failure treatment moves away from the inpatient setting, FDA will consider alternative endpoints that reflect clinically important worsening symptoms leading to an intervention (e.g., treatment in an emergency department, a same-day access clinic, or an infusion center) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic.*" The guidance also indicates that different approaches are acceptable to quantify hospitalization and outpatient interventions, including analysis of recurrent events.

These two recent FDA guidances demonstrate the evolving regulatory framework to establish substantial evidence of effectiveness for the registration of new therapies and new indications for the treatment of HF.

5.4 Phase 3 Trial in HFrEF: PARADIGM-HF

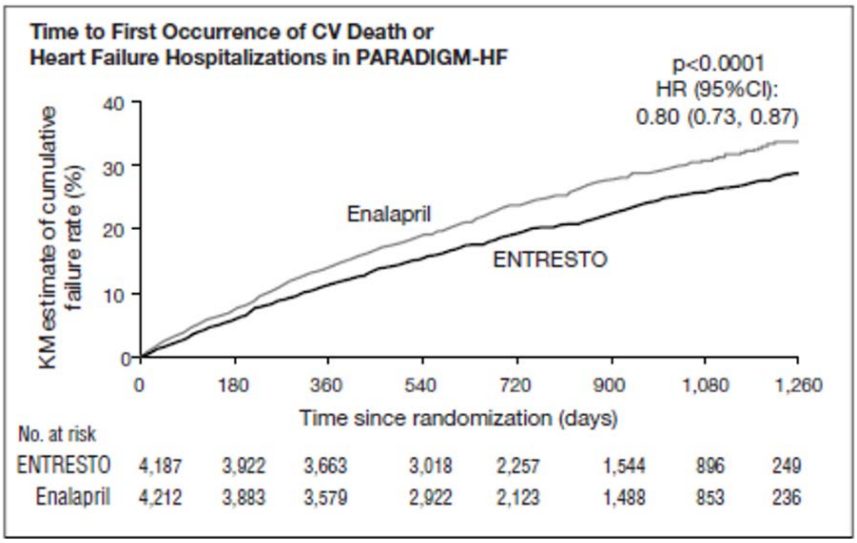
PARADIGM-HF was a large, randomized, double-blind, active controlled, Phase 3 study designed to evaluate the efficacy and safety of sacubitril/valsartan (target dose of 97/103 mg b.i.d., henceforth referred to as 200 mg b.i.d.) compared to enalapril (target dose of 10 mg b.i.d.) on mortality and morbidity in HFrEF patients. The primary objective of this large outcome study (N = 8,442) was to demonstrate that sacubitril/valsartan was superior to enalapril in delaying the time to first occurrence of the composite endpoint of CV death or HF hospitalization. The study was specifically powered to demonstrate a CV mortality benefit over enalapril. Eligible patients were men and women ≥ 18 years of age with a diagnosis of CHF in NYHA class II-IV and LVEF ≤ 40%.

PARADIGM-HF was terminated early by the Data Monitoring Committee due to overwhelming efficacy of sacubitril/valsartan over enalapril. In PARADIGM-HF, sacubitril/valsartan demonstrated robust evidence of efficacy based on a 20% reduction in the risk of the time to first event of composite primary endpoint of CV death or HF hospitalization (Figure 5-2), 20% risk reduction in CV death, 21% risk reduction in HF hospitalization, and 16% risk reduction in all-cause mortality compared to enalapril in HFrEF patients (McMurray et al 2014). Of note, sacubitril/valsartan reduced the rate of the recurrent endpoint of total HF hospitalizations and CV death by 21% relative to enalapril (LWYY model RR = 0.79; 95% CI 0.71 – 0.87; p<0.001). The rate of total (first and recurrent) HF hospitalizations component was reduced by 25% relative to that of enalapril (joint frailty model RR = 0.75; 95% CI 0.66 – 0.86; p<0.001) (Mogensen et al 2018).

Change in the KCCQ CSS for HF symptoms and physical limitations at 8 months favored sacubitril/valsartan over enalapril. The adjusted mean change from baseline to month 8 in the KCCQ clinical summary score was -2.99 in the sacubitril/valsartan group and -4.63 in the enalapril group (treatment difference 1.64 points; 95% CI, 0.63 – 2.65; one-sided p = 0.0007), although the difference did not meet the threshold for significance using the conservative multiple testing procedure (MTP) at an alpha = 0.0002 as pre-specified in the Statistical Analysis Plan. At Month 8, there were more patients with an improved NYHA functional class (15.8% vs. 14.0%) and fewer patients with a worsened NYHA functional class (10.2% vs. 12.6%) in the sacubitril/valsartan group compared with the enalapril group (OR = 1.34; 95% CI 1.13 – 1.58; p = 0.0006). Moreover, in a post hoc analysis, sacubitril/valsartan reduced the risk of the composite of ≥ 50% decline in eGFR or reaching end stage renal disease (ESRD), a conventional renal endpoint commonly used in renal outcome trials, by a third relative to enalapril (HR 0.63; 95% CI 0.42 – 0.95; p = 0.0276).

The results from PARADIGM-HF provided definitive evidence that sacubitril/valsartan is superior to enalapril in reducing mortality and morbidity in patients with frankly reduced LVEF (≤ 40%) and formed the basis for registration of sacubitril/valsartan for the treatment of HFrEF.

Figure 5-2 PARADIGM-HF: Kaplan-Meier Plot for the Primary Composite Endpoint



6 Efficacy, Safety, and Benefit-Risk Evaluation in HFpEF

6.1 Phase 2 trial: PARAMOUNT

PARAMOUNT was a Phase 2, double-blind, randomized, active-controlled study in HFpEF (N = 301) comparing the effect of sacubitril/valsartan to valsartan on changes in NT-proBNP (a potential predictor for clinical outcomes), cardiac structure and function, and HF symptoms/signs (Solomon et al 2012). PARAMOUNT included symptomatic HFpEF patients (NYHA class II-IV) with elevated NT-proBNP and LVEF ≥ 45%. Patients were randomized to either sacubitril/valsartan 200 mg b.i.d. or valsartan 160 mg b.i.d. in a 1:1 ratio for 12 weeks and then followed on their randomized treatment in a 24-week extension.

After 12 weeks of treatment, sacubitril/valsartan reduced NT-proBNP (primary endpoint) by 23% (Geometric mean ratio: 0.77; 95% CI 0.64, 0.92; 2-sided p = 0.005) relative to valsartan. This treatment effect was consistent with that which was later observed in PARAGON-HF (Section 10, Appendix 3). This treatment effect was consistent within all pre-specified subgroups and was independent of sacubitril/valsartan's blood pressure lowering effects. At 36 weeks sacubitril/valsartan treated patients experienced greater reduction in left atrial (LA) size (i.e., reverse cardiac remodeling; left atrial volume between-group difference -5.70 mL, p = 0.0034). While there was no difference between treatments in KCCQ CSS, more patients experienced an improvement in NYHA HF functional class at 36 weeks in the sacubitril/valsartan group than in the valsartan group (22.8% vs. 13.6%; p = 0.0488). Moreover, there was less deterioration in renal function among sacubitril/valsartan-treated patients than among the valsartan patients as evaluated by changes in eGFR (between-group difference in eGFR at 36 weeks = 3.46 ml/min/1.73m^2; 95% CI 0.64 – 6.27 ml/min/1.73m^2).

Overall, sacubitril/valsartan was well tolerated in the HFpEF population.

PARAMOUNT provided the first indication of benefit of sacubitril/valsartan in the treatment of HFpEF. The biomarker and cardiac remodeling data, as well as the HF functional change and renal data generated in PARAMOUNT provided relevant pharmacodynamic, mechanistic, renal and symptom benefit information supporting further development of sacubitril/valsartan in HFpEF patients.

6.2 Phase 3 trial: PARAGON-HF

6.2.1 Study Design

PARAGON-HF was a Phase 3, randomized, double-blind, active controlled, event driven morbidity and mortality study designed to evaluate the efficacy and safety of sacubitril/valsartan compared to valsartan in symptomatic HFpEF patients (NYHA class II-IV) with preserved LVEF (LVEF ≥ 45%).

Inclusion Criteria: The inclusion criteria were aimed at enrolling patients with symptomatic and physical features of HFpEF to ensure proper patient selection. Eligible patients were patients with symptomatic HF failure, NYHA class II-IV, with LVEF ≥ 45% by echocardiography and treated with diuretics for at least 30 days. They were required to have evidence of structural heart disease within 6 months prior to enrollment in the form of either left atrial enlargement or left ventricular hypertrophy. Eligible patients were also required to

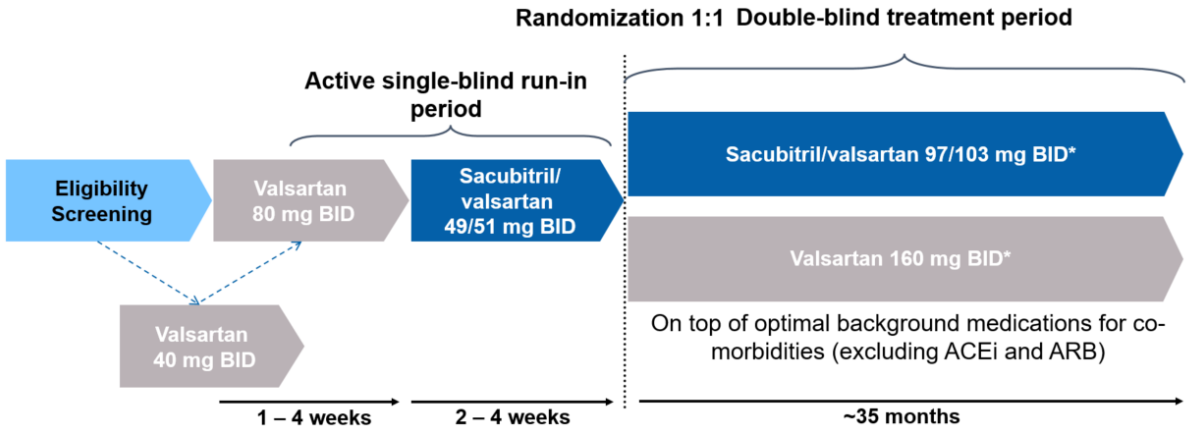
have elevated NT-proBNP (> 300 pg/ml or > 200 pg/ml if they were hospitalized for HF within the nine months immediately before screening). Required NT-proBNP levels were tripled for patients with atrial fibrillation/flutter on the screening electrocardiogram (ECG).

Exclusion Criteria: patients were excluded if they had history of LVEF < 40% at any time prior to screening, any alternative diagnosis that may explain their HF symptoms (e.g., severe pulmonary disease, obesity (BMI >40 kg/m^2), or anemia [hemoglobin <10 g/dL]), or uncontrolled hypertension (SBP ≥180 mmHg or SBP >150 mmHg and <180 mmHg being treated with fewer than 3 antihypertensive medications).

The PARAGON-HF trial design is depicted in Figure 6-1. Eligible patients entered a sequential run-in period in which they were treated with valsartan titrated to a dose of 80 mg b.i.d. (half of the target dose) for 1 to 2 weeks followed by sacubitril/valsartan titrated to a dose of 49/51 mg b.i.d. (half target dose, from here forward will be referred to as 100 mg b.i.d.) for 2 to 4 weeks. The goal of the sequential run-in period was to optimize safety in an older vulnerable population, maximize adherence to the treatment, and minimize risk of lost to follow-up. The treatment run-in period was similar to those in previous HF trials (The SOLVD Investigators 1991, McMurray et al 2014).

Patients who demonstrated adequate tolerability (by assessing hyperkalemia, symptomatic hypotension, and renal dysfunction) to both sequential treatment regimens were randomized in a 1:1 ratio to receive either sacubitril/valsartan at the full target dose of 97/103 mg b.i.d. (from here forward will be referred to as 200 mg b.i.d.) or valsartan at the full target dose of 160 mg b.i.d. The sacubitril/valsartan dosing regimen was identical to that studied in PARAMOUNT, PARADIGM-HF and currently approved in HFrEF. The trial was event driven with a target total of 1,847 primary endpoint events to be accrued.

Figure 6-1 PARAGON-HF design



Primary Endpoint: Composite endpoint of total (first and recurrent) HF hospitalizations and CV death

Secondary Endpoints:

- Changes in the KCCQ CSS for HF symptoms and physical limitations at 8 months
- Improvement in NYHA functional classification at 8 months
- Time to first occurrence of the composite renal endpoint, which was defined as (1) renal death, (2) reaching end stage renal disease, or (3) ≥ 50% decline in eGFR relative to baseline
- Time to all-cause mortality

Urgent HF visits, unscheduled visits to outpatient healthcare facilities for emergent treatment of HF, were also prospectively adjudicated by the CEC. Biomarkers related to cardiac failure/injury and associated comorbidities were collected prior to start of study medication and during the double-blind period in a subset of patients (Appendix 3).

Please refer to the sections below for the rationale for the above endpoints and how they were included in the analyses.

The clinical endpoint committee (CEC) and the adjudication process

The CEC adjudicated all investigator-reported deaths (to identify the cause of death), HF hospitalizations, urgent HF visits, and end stage renal disease events.

The PARAGON-HF CEC reviewed and adjudicated all investigator-reported worsening HF (total HF hospitalizations and urgent HF visits) and CV death events based on strict standardized criteria. HF hospitalizations and urgent HF visits had largely similar strict definitions as the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) (Hicks et al 2018). The PARAGON-HF definition of HF hospitalization endpoint required documentation of (1) an in-patient admission involving a change in calendar date, (2) at least one HF symptom, (3) at least two HF signs, and (4) qualifying treatment directed at treating HF. Qualifying treatments were IV diuretics, IV vasodilators, IV 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 also qualified as treatment.

Urgent HF visits also required at least one symptom and at least two signs consistent with heart failure but were defined as unscheduled office/practice, acute care facility, or hospital emergency department visit for HF management requiring IV therapy, but not requiring overnight hospitalization (change in calendar day).

Re-adjudication process of CEC-unconfirmed HF hospitalizations

CEC-adjudication was based on strict criteria pre-specified in a charter. In PARAGON-HF, if a potential HF hospitalization event did not fulfill all of the strict criteria pre-specified in the CEC charter, the CEC did not confirm the case as a HF hospitalization event, even if the CEC thought the event reflected a HF hospitalization based on their clinical opinion of the submitted source documents. There are a few reasons why an investigator-reported HF hospitalization may not be confirmed by the CEC, including content, quality and insufficient detail in the documentation provided.

While the use of a CEC to adjudicate events was intended to assist in assuring systematic application of a standard definition, especially for non-fatal events, it can result in quantifying HF hospitalization events in a prescriptive approach and dichotomizes the overall clinical judgement of HF events into a binary (yes/no) decision. This approach increases the specificity of the endpoint detection process, but at the expense of reducing sensitivity. This may have occurred in PARAGON-HF because of the high hurdle for positive CEC-confirmation due to the strict HF hospitalization definition stated above.

During the pre-filing meetings to discuss the PARAGON-HF results, FDA recommended re-adjudication of investigator-reported HF hospitalizations not confirmed by the original CEC. This recommendation was intended to address concerns that the original CEC adjudication process may have discarded a number of true HF hospitalization events. An analysis of the primary endpoint by including additional events identified in the CEC-unconfirmed HF hospitalizations re-adjudication process was conducted to estimate the treatment effect based on a more holistic approach of qualitative evaluation of events to maximize the value of information from these endpoints.

The re-adjudication process to assess HF hospitalization events not confirmed by the CEC was developed in consultation with the FDA. A re-adjudication panel (RAP) was formed of three external HF experts who each individually and independently reviewed each CEC-unconfirmed HF hospitalization event. Information taken into consideration for this assessment included clinical history of the episode, symptoms and physical examination findings, laboratory and imaging data, hemodynamic or device data (such as pulmonary artery catheterization, CardioMEMS), and treatment (i.e., addition or intensification of HF therapy (Section 6.2.2.3)). The panelists independently performed this task while blinded to the treatment assignment of the patients and the CEC's reason(s) for not confirming the events. Each panelist reviewed only the clinical documents originally supplied by investigators to the CEC and assessed the likelihood of the event being a hospitalization for HF based on their clinical judgement using the following scale: definitely (probability of 100%), likely (probability of 75%), possibly (probability of 50%), less likely (probability of 25%), and definitely not a HF hospitalization (probability of 0%). Note that since the specificity of CEC adjudication using Hicks rules is known to be very high, the goal of the panel was not to evaluate the investigator-reported HF hospitalization events that had already met the stringent criteria and had been confirmed by the CEC, but rather specifically assess the likelihood of the CEC-unconfirmed HF hospitalizations being true episodes of hospitalizations for acute decompensated HF.

6.2.1.1 Rationale for selection of valsartan as active comparator

In the absence of approved therapies in HFpEF, previous trials in this patient population were conducted against placebo, including CHARM-Preserved and TOPCAT (Yusuf et al 2003, Solomon et al 2016). For the design of PARAGON-HF, valsartan was chosen as the active comparator as it was acknowledged that the majority of HFpEF patients have hypertension and/or diabetic nephropathy, which require RAAS inhibition [i.e., angiotensin converting enzyme inhibitor (ACEI) or ARB] per standard of care. Indeed, this was confirmed in PARAGON-HF, in which prior to run-in, the majority of patients (86%) were on either an ACEI or an ARB (Solomon et al 2019). It would not have been reasonable or feasible to withdraw RAAS blockade in these patients and, therefore, a placebo comparator was not appropriate.

Moreover, the addition of sacubitril/valsartan to a background ACEI therapy would also have been impracticable as concomitant use with an ACEI is contraindicated due to potential increased risk of angioedema. To ensure similar RAAS blockade in both treatment groups, valsartan was chosen as the comparator ARB at the dose of 160 mg b.i.d., which is the dose approved for treatment of HF. Also, valsartan administered at the target dose of 160 mg b.i.d. was the comparator in the Phase 2 HFpEF study, PARAMOUNT. Of note, because of greater bioavailability of the form of valsartan delivered via the sacubitril/valsartan 97/103 mg formulation, 103 mg of valsartan in sacubitril/valsartan provides similar plasma levels as 160 mg delivered via the other marketed formulation of valsartan (Diovan®). Thus, both treatment groups in PARAGON-HF were provided with similar degree of anti-RAAS inhibition.

As noted above, previous data suggest that RAAS inhibition provides some benefit in reducing HF hospitalizations (Yusuf et al 2003, Rogers et al 2014, Pitt et al 2014). In a post hoc analysis of the CHARM-Preserved study, candesartan was shown to reduce the investigator-reported recurrent endpoint of total HF hospitalizations and CV death by 25% relative to placebo (RR = 0.75; 95% CI 0.62 – 0.91; p = 0.003 based on negative binomial analysis) (Rogers et al 2014). In addition, there are data from observational research that supports a benefit of RAAS inhibiting agents in a HFpEF population. An analysis in 16,216 HFpEF patients (LVEF ≥ 40%) from the Swedish Heart Failure Registry comparing all-cause mortality in RAAS-treated and RAAS-untreated patients showed a crude 1-year survival of 86% (95% CI 86% – 87%) for treated patients vs 69% (95% CI 68% – 71%) for untreated patients, with a propensity score-adjusted HR of 0.90 (95% CI 0.85 – 0.96; p = 0.001) (Lund et al 2012). Thus, the effects induced by sacubitril/valsartan in PARAGON-HF should be considered as incremental to the effect achieved by RAAS blockade with valsartan over placebo.

The use of valsartan as the comparator was agreed to by FDA, European Medicines Agency (EMA) and other global Health Authorities. The incremental benefit of sacubitril/valsartan is demonstrated relative to the effect of valsartan alone at its maximal approved dose. Sacubitril cannot be studied alone as neprilysin also affects angiotensin II degradation (Jhund et al 2014). Neprilysin (NEP) inhibition alone would increase angiotensin II concentrations, potentially resulting in deleterious effects on the development and progression of HF.

6.2.1.2 Rationale for the primary endpoint

The major goals of HF treatment are to reduce both major non-fatal and fatal consequences of this illness, which include HF hospitalizations and CV death. Therefore, the primary endpoint of PARAGON-HF was the composite of total HF hospitalizations and CV death. However, CV death occurs at a substantially lower rate in HFpEF patients and the ratio of non-CV to CV death is higher in this population than in HFrEF, while recurrent HF hospitalizations are a common part of the clinical course in many HFpEF patients. Importantly, HF hospitalization reflects progression of the HF syndrome and portends high subsequent risk, both of readmission and death (Solomon et al 2007, Ahmed et al 2008).

Traditionally, outcomes studies have assessed composite endpoints using a time-to-first event analysis. Limitations of this approach have been increasingly recognized (Neaton et al 2005, Cohn et al 2009, Pocock et al 2012). Time-to-first event analytical approaches only focus on the first occurring event and do not consider subsequent events, leading to a substantial loss of information. A review of HF studies found that approximately 40% of all CV deaths and HF

hospitalizations are ignored in a time-to-first event analysis (Anker and McMurray 2012). This would be particularly problematic in HFpEF, which, as noted above, is characterized by a high frequency of recurrent HF hospitalizations and relatively low CV mortality. Moreover, time-to-first event analysis ignores CV deaths if they were preceded by a HF hospitalization. Thus, an endpoint that includes all events as applied to a progressive disorder such as HF has the benefit of more accurately capturing the patient's clinical course and better reflects the true burden of the illness on the patient and the healthcare system. This understanding of HF and its treatment has led to the choice of a disease-specific composite outcome of total HF hospitalizations and CV death as the primary composite endpoint in PARAGON-HF. Use of this novel primary composite endpoint was endorsed by global Health Authorities, including FDA at time of the end of phase 2 meeting and has since been included in the June 2019 FDA guidance "*Treatment for Heart Failure: Endpoints for Drug Development*" (Section 5.3). Although the primary analysis of the study was based on the CEC-confirmed events, supportive analysis based on investigator-reported events was pre-planned.

6.2.1.3 Rationale for the secondary endpoints

The secondary endpoints of PARAGON-HF are further described below:

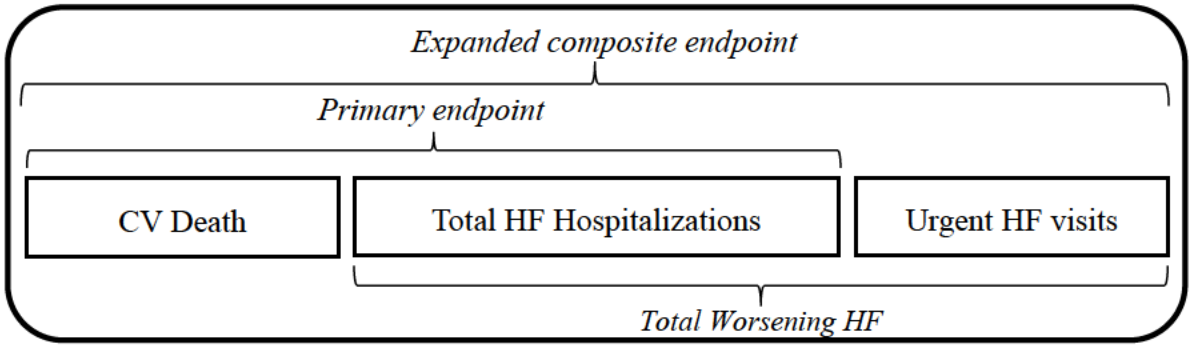
- The **KCCQ** is a validated patient-reported outcomes instrument for assessing quality of life (QoL) and health status in HF patients. The clinical summary score, which is derived from the physical limitations and HF symptoms domains of the KCCQ, is a valid measure for assessing the patient's health aspects that may be influenced by CV medications. Given the symptomatic burden of HF and its associated physical limitations, this endpoint is of relevance to patients and is an important goal of HF treatment. The KCCQ clinical summary score has been used as an endpoint in other trials. KCCQ clinical summary score was analyzed at month 8 to minimize the number of missing data points.
- **NYHA classification** is an accepted measure of functional status and provides important information on disease progression from the perspective of the treating physician. NYHA classification was analyzed at month 8 to minimize the number of missing data points.
- The **composite renal endpoint** of renal death (i.e., death from worsening renal function), ESRD, or ≥ 50% decline in eGFR relative to baseline is frequently used in clinical trials of renal disease. This endpoint is of clinical significance because renal dysfunction is common in HF patients, is associated with poorer clinical outcomes, and complicates clinical management. Also, commonly used medications to treat comorbidities in HFpEF patients, such as ACEIs and ARBs, are often sub-optimally prescribed due to concerns of further worsening renal function. Thus, prevention of renal dysfunction is of considerable clinical importance and, therefore, warranted further investigation in all HF patients including the HFpEF population.
- **All-cause mortality** is a standard safety endpoint that is routinely assessed in morbidity and mortality trials.

6.2.1.4 Rationale for the expanded composite endpoint

The composite of the CEC-confirmed primary endpoint and CEC-confirmed urgent HF visits, also referred to as the expanded composite endpoint, was a pre-specified exploratory endpoint

in PARAGON-HF. As shown in Figure 6-2, the expanded composite endpoint consisted of total worsening HF events (i.e., HF hospitalizations and urgent HF visits) and CV death.

Figure 6-2 Expanded composite endpoint (Total Worsening HF and CV Death)



The importance of inclusion of urgent HF visits in the definition of the expanded composite endpoint is twofold. First, it is reflective of the changing trends in increasing efforts in many countries around the world to treat decompensated HF on an out-patient basis and the urgent visit is indicative of a symptomatic deterioration the patient's condition (Bradley et al 2013). Thus, including urgent HF visits with HF hospitalizations in the expanded primary endpoint captures the burden of the disease more comprehensively. Second, there is strong evidence linking decompensated HF treated on an outpatient basis to poor outcomes that is in line with decompensated HF treated in the hospital (Okumura et al 2016; Skali et al 2014). Consequently, urgent HF visits were defined and prospectively adjudicated by the CEC. Those were unscheduled office or emergency department visits for management of worsening signs and symptoms of HF (defined by the same criteria used for HF hospitalization endpoint) and requiring treatment with IV decongestive therapy, but did not involve overnight admission.

When PARAGON-HF was in the design stage, urgent HF visits were only beginning to be recognized as a relevant endpoint that predicted patient outcomes and it was considered for inclusion in the primary endpoint of the study. However, given the novel nature of the recurrent event analysis of the primary endpoint in PARAGON-HF, it was decided not to include CEC-confirmed urgent HF visits in the primary composite endpoint, and to instead include them as an exploratory objective to assess the recurrent composite endpoint of total worsening HF events and CV death. Following the design of PARAGON-HF and as a result of the evolving management trends of HF patients as described above, urgent HF visits have been included as an additional component within the primary composite endpoint in more contemporary trials, such as DAPA-HF in HFrEF (McMurray et al 2019b) and DELIVER in HFpEF (AstraZeneca 2020) to fully capture the major burden of disease across HF in the inpatient and outpatient setting. Urgent HF visits are also recognized as a reflection of clinically important worsening symptoms leading to an intervention in the June 2019 FDA guidance "*Treatment for Heart Failure: Endpoints for Drug Development*" (Section 5.3).

6.2.2 Statistical Methods

All efficacy analyses are based on the Full Analysis Set (FAS) and follow the intent-to-treat principle. The FAS consisted of all randomized patients with the exception of patients from one site with major Good Clinical Practice (GCP) violations.

6.2.2.1 Analysis of the primary endpoint

The primary efficacy endpoint of PARAGON-HF consisted of the times to total (first and recurrent) hospitalizations due to HF and time to death due to CV reasons during the patient's follow-up. The primary estimand was the rate ratio of primary composite endpoint events while being alive, regardless of treatment discontinuation and dose level. The estimand may also be interpreted as rate ratio of the number of primary endpoint events per expected unit time alive in the sacubitril/valsartan group and the number of primary endpoint events per expected unit time alive in the valsartan group, which is considered a clinically meaningful estimand.

A semiparametric proportional rates model (abbreviated as LWYY model) (Lin et al 2000) with treatment as factor and stratified by region was utilized for testing and quantifying the treatment effect on the primary composite endpoint. The LWYY model can be considered a natural extension of the conventional Cox regression model for the corresponding time-to-first-event endpoint. It is also widely known as the Andersen-Gill model with a robust variance estimate. The LWYY model accounts for the correlation of repeat events within subjects. Simulation studies have shown that the LWYY model preserves the type 1 error rate and provides an adequate estimator in settings where the treatment effect on HF hospitalization and CV death are in the same direction. The LWYY approach was preferred over the alternative negative binomial model approach because it is more flexible (e.g., it allows the event rate to change over time as opposed to assuming a constant event rate) and is less dependent on model assumptions (unlike the negative binomial approach, the LWYY method does not assume that events from the same subject are independent, i.e. the method adjusts for the dependence of intra-subject events) (Lin et al 2000, Lawless 1987, Mogensen et al 2018).

For the analysis of the HF hospitalization component and characterization of the respective treatment effect, the joint modeling (frailty model) approach (Cowling et al 2006) with treatment and region as fixed-effect factors was used to account for the correlation between HF hospitalizations and CV death. A Cox proportional hazards model with a fixed treatment group factor and stratified by region was used for the analysis of the CV death component.

The cumulative rates of HF hospitalizations over time by treatment group were plotted as cumulative incidence curves using the non-parametric Ghosh and Lin method, accounting for the competing risk of death (Ghosh & Lin 2000). For all clinical endpoint analyses a data-cutoff was pre-specified in the statistical analysis plan. Only events up to April 30, 2019 were included in the analysis.

6.2.2.2 Analysis of secondary endpoints

Changes from baseline in KCCQ clinical summary score at Month 8 were analyzed based on a repeated measures analysis of covariance (ANCOVA) model in which treatment, region, visit, and treatment-by-visit interaction were included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance matrix among visits for each treatment group. For patients who died, the KCCQ scores were imputed by zero at all subsequent scheduled visits. In addition, to assess the clinical relevance of the difference between the two groups in the mean change from baseline, a responder analysis for KCCQ clinical summary score change from baseline at Month 8 (defined as patients with at least 5 point improvement / deterioration) was performed based on a generalized mixed effect model with similar covariates

described above and a common compound symmetry covariance matrix among visits for each treatment group.

A repeated measures proportional cumulative odds model was used for analyzing NYHA class change. The response variable was the category change from baseline to any scheduled time point up to Month 8 (improved, unchanged, worsened). NYHA class change after a patient died was categorized as 'worsened'. The model included patient as a random effect and the randomized treatment phase baseline NYHA class, region, treatment, visit and treatment-by-visit interaction as fixed effect factors. This model assumed that the treatment effect sizes across measurement categories were the same. Model fittings were based on likelihood method with all available data up to Month 8.

Time-to-first occurrence of composite renal endpoint events was analyzed using a Cox proportional hazard model with treatment as a fixed effect factor, stratified by region. The estimated hazards ratio and the corresponding two-sided 95% confidence interval were provided.

All-cause mortality was analyzed using a Cox proportional hazards model with a fixed treatment group factor and stratified by region.

For the primary and secondary analyses, a sequentially rejective MTP was defined. The formal hypothesis testing of secondary endpoints required statistical significance of the primary analysis at a 2-sided alpha of 4.8% (adjusted for interim analysis). The hypotheses related to KCCQ and NYHA were then to be tested at 2-sided alpha of 2.4% each and if one of them was statistically significant, the other one could be tested at a 2-sided alpha of 4.8%. If both the KCCQ and NYHA endpoints were statistically significant, the renal composite endpoint could be tested at a 2-sided alpha of 4.8%. The all-cause mortality endpoint was not incorporated in the MTP and planned to be tested at a full level of alpha, after the rejection of the primary hypothesis.

In this document, along with point estimates and 95% confidence intervals, nominal p-values are presented for the 4 secondary endpoint analyses. Supportive analyses and selected exploratory endpoint analyses are also presented with point estimates, 95% confidence intervals and descriptive nominal p-values without adjustment for multiplicity.

6.2.2.3 Analysis of the re-adjudication process of CEC-unconfirmed HF hospitalizations

The analysis of the FDA-recommended re-adjudication process of CEC-unconfirmed HF hospitalizations was pre-specified in a separate analysis plan prior to having access to re-adjudication results. For each investigator-reported CEC-unconfirmed HF hospitalization, the information on whether it represented a primary endpoint event or not was imputed based on an event-specific average probability p, that was derived from the 3 re-adjudication panel (RAP) members' probability ratings (i.e., average of three probabilities).

The analysis followed a standard multiple imputation approach (Rubin, 1987). One thousand complete datasets were simulated. Each dataset consisted of all the CEC-confirmed primary events and a number of imputed HF hospitalizations events, based on the assigned RAP average probability (p's) for each of the CEC-unconfirmed HF hospitalizations.

Each of the resulting 1000 simulated complete datasets was analyzed using the above specified primary analysis LWYY model. This yielded 1000 sets of model parameter estimates and associated covariance matrices. Applying Rubin's rules to these estimates, the overall rate ratio estimate and its confidence interval, as well as the associated p-value, were derived, which adequately captured the uncertainty of confirming HF hospitalizations from RAP members and the variation in generating imputed events. The HF hospitalization component was analyzed and presented using the same methodology, since the LWYY model was computationally more feasible than the joint frailty model. Of note, since there was only a small between-group difference in CV death, the RR based on the joint frailty model is expected to be well-approximated by the RR based on the LWYY model.

6.2.2.4 Subgroup analyses

Subgroup analyses were performed for the primary and secondary endpoints. To explore the homogeneity of beneficial effects among subgroups, the estimated effect sizes, their 95% confidence intervals, and p-value for the test for the treatment-by-subgroup interaction were provided for each of the subgroups based on the analysis models. The analysis models included treatment, subgroup, and treatment-by-subgroup as fixed-effect factors. In order to account for the multiplicity and correlations among the investigated subgroups, a multivariable interaction analysis was performed based on 12 of the 15 pre-specified subgroup factors (age with cut-off at 65 years and atrial fibrillation based on screening ECG were excluded because these variables were represented twice with different definitions and ACEI intolerant status was excluded because the subgroup was extremely small and added at specific health authority's request). The model included 17 interaction terms because the categorical variables race and region were included as multiple binary variables. A simultaneous test of all interaction terms (global test for heterogeneity) was performed.

6.2.2.5 Analysis of PARAGON-HF Totality of Evidence

In order to quantify the strength of the totality of evidence provided by the PARAGON-HF trial, a post-hoc analysis was performed to combine information across the primary endpoint and the four secondary endpoints, following a similar approach as described by (Li et al 2020) and (Ristl et al 2019).

For each endpoint, a z-score (estimated treatment difference divided by its standard error) was calculated as a measure of strength of evidence for a treatment effect, with negative numbers representing outcomes in favor of sacubitril/valsartan). The average of the five z-scores was used to reflect the aggregated strength of evidence across endpoints.

To facilitate a large number of permutation analyses (random shuffling of treatment assignments) in a computationally efficient way, z-scores were based on the negative binomial model for the primary endpoint, ANCOVA for KCCQ CSS change at Month 8, and proportional cumulative odds model for NYHA class change at Month 8, all with region and treatment as fixed factors. The original Cox model stratified by region with treatment as the fixed factor was used to calculate the z-scores for the renal composite endpoint and the all-cause death endpoint. Of note, the approximation through simplified models is conservative in the sense that individual z-scores and the average z-score based on the simplified models were slightly less favorable for sacubitril/valsartan than those based on the original models.

To simulate the treatment effect distribution under the null hypothesis, 100,000 random treatment permutations were generated and for each permutation, the average z-score was estimated based on the five endpoints. The probability to observe the aggregated PARAGON-HF result (or more extreme) if there was no treatment effect (2-sided p-value) was obtained as the proportion of permuted average z-scores with absolute value greater or equal to the absolute value of the observed average z-score in PARAGON-HF. Of note, this approach implicitly accounts for the correlation among the endpoints.

6.2.2.6 Statistical power assumptions

PARAGON-HF was designed to randomize 4,600 patients in a 1:1 ratio to sacubitril/valsartan and valsartan groups for a target accrual of 1847 primary events with a minimum follow-up of 26 months. Annualized event rates in the control group of 9% for the first primary endpoint event and 4% for CV death were assumed. Using simulations based on a joint frailty model (assuming a Poisson distribution for HF hospitalization, an exponential distribution for CV death and a gamma distribution for the frailty) with parameters and correlation structure informed by CHARM-Preserved, the study ensured approximately 80% power for the primary analysis if the true rate reduction for HF hospitalization given the frailty was 25% and the true hazard reduction for CV death given the frailty was 10%, which approximately corresponds to a primary endpoint rate reduction of 19%. With 1882 primary events, the power for the primary analysis was estimated to be 85%.

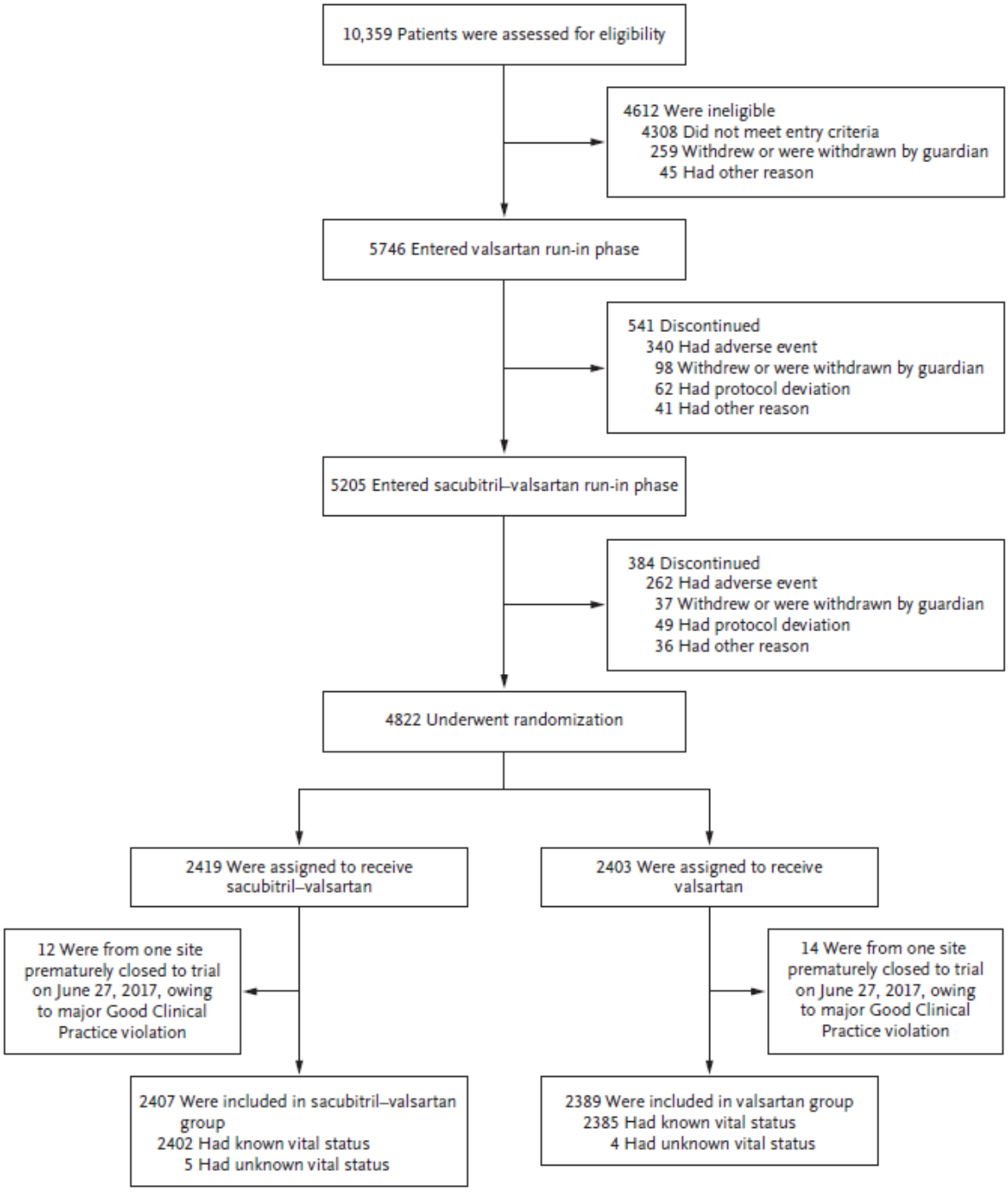
6.2.3 Enrolled Population

6.2.3.1 Subject Disposition

Figure 6-3 provides an overview of patient disposition.

A total of 5,747 patients entered the single-blind sequential run-in in PARAGON-HF. Of those, 541 patients discontinued from the valsartan run-in (9.4% of valsartan run-in patients) and 384 patients discontinued from the sacubitril/valsartan run-in (7.4% of sacubitril/valsartan run-in patients). The most common reason for run-in failure was adverse events, including protocol-specified laboratory criteria requiring discontinuation regardless of investigator's assessment. Ultimately, 4,822 patients were randomized; 2,419 were randomized to sacubitril/valsartan and 2,403 were randomized to valsartan. One site, which randomized 26 patients, was terminated prematurely due to serious GCP violations, leaving the FAS used for efficacy analyses with 2,407 patients and 2,389 patients in the sacubitril/valsartan and valsartan groups, respectively. Median follow-up in the randomized, double-blind period was 35 months in both groups. The fatal and non-fatal outcomes of all patients were known by the end of the study, except for 9 patients (5 on sacubitril/valsartan and 4 on valsartan), including 7 patients who withdrew informed consent and 2 patients who were lost to follow-up, indicating high quality of study execution and data completeness.

Figure 6-3 Patient disposition in PARAGON-HF



The median duration of the valsartan run-in phase was 15 days (interquartile range, 12 to 22). One patient completed the valsartan run-in phase and underwent randomization without entering the sacubitril/valsartan run-in phase. The median duration of the sacubitril/valsartan run-in phase was 19 days (interquartile range, 15 to 23). One patient completed screening and entered the sacubitril/valsartan run-in phase without having entered the valsartan run-in phase (Solomon et al 2019).

6.2.4 Demographics and Baseline Characteristics

PARAGON-HF enrolled patients broadly representative of HFpEF. Table 6-1 provides an overview of the key baseline characteristics and medical history of the PARAGON-HF patients. Patient characteristics and medical history were similar across the treatment groups and were consistent with the general HFpEF population (Dunlay et al 2017). Patients in PARAGON-HF tended to be elderly with an average age of 72.7 years and mostly women (52%); mean LVEF was 57.5%. Overall, 77% and 19% of patients were in NYHA functional class II and III, respectively. The vast majority of patients (96%) had hypertension; 53% had atrial fibrillation, and 43% had diabetes mellitus. Approximately 49% of patients had CKD as defined by an eGFR < 60 ml/min/1.73m^2. Consistent with the protocol's entry criteria, 95.6% of patients were receiving a diuretic. At screening, 86% of patients were on either an ACEI or an ARB, while nearly 80% were on a beta blocker. Except for a slight imbalance in the use of mineralocorticoid receptor antagonists (MRAs) at randomization (more patients in the valsartan group taking MRAs), the two treatment groups were well balanced in terms of their baseline characteristics.

Table 6-1 PARAGON-HF: Baseline characteristics and medical history (FAS)

Variable	Sac/Val N = 2407	Val N = 2389	Overall N = 4796
Age (years), mean ± SD	72.7 ± 8.3	72.8 ± 8.5	72.7 ± 8.4
Females, n (%)	1241 (51.6)	1238 (51.8)	2479 (51.7)
Race, n (%)			
Caucasian	1963 (81.6)	1944 (81.4)	3907 (81.5)
Black	52 (2.2)	50 (2.1)	102 (2.1)
Asian	297 (12.3)	310 (13.0)	607 (12.7)
Native American	28 (1.2)	23 (1.0)	51 (1.1)
All others	67 (2.8)	62 (2.6)	129 (2.7)
BMI (kg/m^2), mean ± SD	30.2 ± 4.9	30.3 ± 5.1	30.2 ± 5.0
Estimated GFR (ml/min/1.73m^2), mean ± SD	62.7 ± 18.9	62.5 ± 19.3	62.6 ± 19.1
Estimated GFR <60 ml/min/1.73m^2, n (%)	1164 (48.4)	1177 (49.3)	2341 (48.8)
SBP (mmHg), mean ± SD	130.5 ± 15.6	130.6 ± 15.3	130.6 ± 15.5
NYHA class at randomization, n (%)			
Class I	73 (3.0)	64 (2.7)	137 (2.9)
Class II	1866 (77.5)	1840 (77.0)	3706 (77.3)
Class III	458 (19.0)	474 (19.8)	932 (19.4)
Class IV	8 (0.3)	11 (0.5)	19 (0.4)
Missing	2 (0.1)	0 (0.0)	2 (<0.1)
LVEF (%), mean ± SD	57.6 ± 7.8	57.5 ± 8.0	57.5 ± 7.9
LVEF category, n (%)			
<50%	348 (14.5)	381 (16.0)	729 (15.2)
≥50% - ≤60%	1340 (55.7)	1302 (54.5)	2642 (55.1)
>60%	719 (29.9)	706 (29.6)	1425 (29.7)
NT-proBNP (pg/ml), median (IQR)	904 (475 – 1596)	915 (453 – 1625)	911 (464 – 1613)
Medical history, n (%)			
Hospitalization for HF*	1135 (47.2)	1171 (49.0)	2306 (48.1)
Atrial fibrillation**	1246 (51.8)	1275 (53.4)	2521 (52.6)
Hypertension	2304 (95.7)	2280 (95.4)	4584 (95.6)

Variable	Sac/Val N = 2407	Val N = 2389	Overall N = 4796
Diabetes mellitus	1046 (43.5)	1016 (42.5)	2062 (43.0)
Myocardial infarction	561 (23.3)	522 (21.9)	1083 (22.6)
Stroke	266 (11.1)	242 (10.1)	508 (10.6)
Angina pectoris	714 (29.7)	674 (28.2)	1388 (28.9)
Concomitant medication, n (%)			
Diuretics at randomization	2294 (95.3)	2291 (95.9)	4585 (95.6)
ACE inhibitor or ARB at screening	2074 (86.2)	2065 (86.4)	4139 (86.3)
MRA at randomization	592 (24.6)	647 (27.1)	1239 (25.8)
Beta-blocker at randomization	1922 (79.9)	1899 (79.5)	3821 (79.7)

BMI = body mass index; FAS = full analysis set; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; SD = standard deviation; IQR = interquartile range.

*Hospitalization for HF within 9 months: sacubitril/valsartan 37.6% vs valsartan 39.2%

**Patients with atrial fibrillation/flutter on screening ECG: sacubitril/valsartan 32.2% vs valsartan 32.5%

6.3 Efficacy Results

6.3.1 Primary Composite Endpoint (Total HF hospitalizations and CV death) and supportive analyses

Table 6-2 summarizes key results of the CEC-confirmed recurrent primary endpoint and its components. Based on the pre-specified primary analysis, using a proportional rates model with treatment as fixed-effect factor, and stratified by region, there was a 13% relative rate reduction (RRR) in the primary composite endpoint compared to valsartan, a treatment effect that narrowly missed statistical significance (RR = 0.87; 95% CI 0.75 – 1.01; 2-sided p = 0.059). The effect of sacubitril/valsartan on the primary endpoint was driven primarily by a 15% RRR in the total HF hospitalizations component (RR = 0.85, 95% CI 0.72 – 1.00; 2-sided p = 0.056). The differential effect of sacubitril/valsartan over valsartan on the primary composite endpoint appeared early and was constant throughout the duration of the follow-up period (Figure 6-4). There was no relevant difference between treatment groups with regards to CV death risk (HR = 0.95; 95% CI 0.79 – 1.16; 2-sided p = 0.624). An LWYY model of the primary composite endpoint adjusted for systolic blood pressure (SBP) over time showed that the treatment effect size induced by sacubitril/valsartan was unaffected by SBP.

Table 6-2 PARAGON-HF: Primary efficacy analysis of recurrent events for the CEC-confirmed primary composite endpoint (CV death and total hospitalizations for HF) and its components (FAS)

	Sac/Val		Val			p-value
Endpoint	n/N	n/T EAR (95% CI)	n/N	n/T EAR (95% CI)	Rate ratio/ Hazard ratio (Sac/Val vs Val) (95% CI)	2-sided
Primary composite	894/2407	894/69.65 12.835 (12.007, 13.705)	1009/2389	1009/68.97 14.630 (13.741, 15.561)	0.8698 (0.7526, 1.0052)	0.0587
Total hospitalizations for heart failure	690/2407	690/69.65 9.906 (9.181, 10.674)	797/2389	797/68.97 11.556 (10.768, 12.387)	0.8511 (0.7216, 1.0039)	0.0556
Cardiovascular death	204/2407	204/69.65 2.929 (2.541, 3.359)	212/2389	212/68.97 3.074 (2.674, 3.517)	0.9531 (0.7863, 1.1551)	0.6241

Primary composite endpoint is analyzed using the proportional rates model (LWYY) with treatment as fixed-effect factor and stratified by region and with robust (sandwich) variance estimate. Total hospitalizations for heart failure is analyzed using the joint frailty model with treatment and region as fixed-effect factors. Cardiovascular death is analyzed using a Cox proportional hazard model with treatment as fixed-effect factor and stratified by region.

A rate ratio < 1 indicates an effect in favor of Sac/Val.

n: Total no. of events; N: Total no. of patients; T(100 patient years): Total exposure up to event/censoring; Exposure-adjusted rate per 100 patient years (EAR)=n/T.

Figure 6-4 PARAGON-HF: Mean cumulative function of CEC-confirmed primary composite endpoint (cardiovascular death and total hospitalizations for heart failure) (FAS)

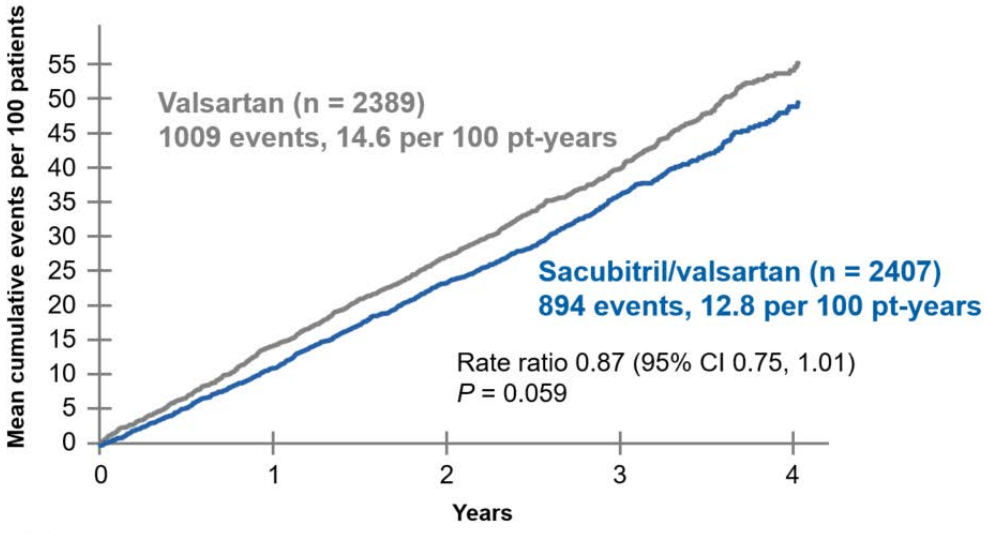


Figure includes estimates of the (unconditional) mean number of CEC-confirmed primary endpoint events (Table 6-2) over time allowing for death as terminal event according to Ghosh and Lin 2000.

Several key pre-specified and supplementary analyses support the replicability of the benefit of sacubitril/valsartan in reducing HF events in the overall study. These included results of the:

- CEC-confirmed expanded primary composite endpoint,
- Investigator-reported primary composite endpoint, and
- FDA-recommended re-adjudication analysis of CEC-unconfirmed HF hospitalizations.

As shown below, all three analyses include the addition of clinically relevant endpoint events. In each of these analyses, the magnitude of the point estimate of the rate ratio of sacubitril/valsartan's treatment effect is preserved, while improving the precision of its 95% CI. This pattern provides confidence that there is a true treatment effect in the overall study.

6.3.1.1 Expanded composite endpoint: CEC-confirmed total worsening HF events (total HF hospitalization and urgent HF visits) and CV death

A pre-specified exploratory analysis which added 40 and 55 CEC-confirmed urgent HF visits in the sacubitril/valsartan and valsartan groups respectively to the primary composite endpoint showed that treatment with sacubitril/valsartan resulted in a 14% rate reduction in the CEC-confirmed expanded composite endpoint relative to valsartan (RR = 0.86; 95% CI 0.75 – 0.99) (Table 6-3) achieving a nominal p-value below the threshold for statistical significance. This effect was driven by a 16% reduction in the rate of total worsening HF events (total HF hospitalizations and urgent HF visits) (RR = 0.84; 95% CI 0.71 – 0.98). Analysis of the expanded composite endpoint based on investigator-reported events was consistent with CEC-confirmed events and showed a 17% rate reduction with sacubitril/valsartan relative to valsartan (RR = 0.83; 95% CI 0.73 – 0.95).

Table 6-3 PARAGON-HF: Primary efficacy analysis of recurrent events for CEC-confirmed expanded composite endpoint (total worsening HF events and CV death) (FAS)

	Sac/Val		Val			p-value
Endpoint	n/N	n/T EAR (95% CI)	n/N	n/T EAR (95% CI)	Rate ratio/ Hazard ratio (Sac/Val vs Val) (95% CI)	2-sided
Expanded composite endpoint	934/2407	934/69.65 13.409 (12.563, 14.297)	1064/2389	1064/68.97 15.427 (14.514, 16.383)	0.8613 (0.7467, 0.9934)	0.0403
Total worsening HF events*	730/2407	730/69.65 10.480 (9.734, 11.269)	852/2389	852/68.97 12.353 (11.538, 13.212)	0.8379 (0.7138, 0.9836)	0.0306

Expanded composite endpoint consisted of CEC-confirmed total worsening HF events (HF hospitalizations and urgent HF visits) and CV death. Total worsening HF events include 40 and 55 urgent HF visits in the sacubitril/valsartan arm and the valsartan arm, respectively.
The analyses for the expanded composite endpoint is based on the proportional rates model (LWYY) with treatment as fixed-effect factor and stratified by region and robust (sandwich) variance estimate. A rate ratio <1 indicates an effect in favor of sacubitril/valsartan. n: Total no. of events; N: Total no. of patients. T(100 patient years): total up-to-terminal-event/censoring duration-time summarized over patients in the respective treatment group; EAR (Exposure-adjusted rate per 100 patient years)=n/T.
* Total worsening heart failure is analyzed using the joint frailty model with treatment and region as fixed-effect factors.

6.3.1.2 Investigator-reported primary composite endpoint

Recognizing that investigators in this study were cardiologists and clinicians experienced in treating HF patients and diagnosing acute episodes of HF decompensation requiring in-patient and/or intensification of treatment, a pre-specified analysis of the primary composite endpoint based on all investigator-reported events (regardless of CEC confirmation decision) was conducted.

Based on this analysis there was a 16% RRR in favor of sacubitril/valsartan (RR = 0.84; 95% CI 0.74 – 0.97) (Table 6-4), achieving a nominal p-value below the threshold for statistical significance. The effect was driven by an 18% RRR in the total HF hospitalizations component (RR = 0.82; 95% CI 0.71 – 0.96).

Table 6-4 PARAGON-HF: Primary efficacy analysis of recurrent events for investigator-reported primary composite endpoint (total hospitalizations for HF and CV death) (FAS)

	Sac/Val		Val			p-value
Endpoint	n/N	n/T EAR (95% CI)	n/N	n/T EAR (95% CI)	Rate ratio/ Hazard ratio (Sac/Val vs Val) (95% CI)	2-sided
Primary composite	1064/2407	1064/69.65 15.275 (14.371, 16.222)	1241/2389	1241/68.97 17.994 (17.006, 19.023)	0.8429 (0.7355, 0.9660)	0.0140
Total hospitalizations for HF	916/2407	916/69.65 13.151 (12.313, 14.031)	1087/2389	1087/68.97 15.761 (14.838, 16.726)	0.8241 (0.7109, 0.9553)	0.0103
Cardiovascular death	148/2407	148/69.65 2.125 (1.796, 2.496)	154/2389	154/68.97 2.233 (1.894, 2.615)	0.9514 (0.7592, 1.1923)	0.6654

Primary composite endpoint is analyzed using the proportional rates model (LWYY) with treatment as fixed-effect factor and stratified by region and with robust (sandwich) variance estimate. Total hospitalizations for heart failure is analyzed using the joint frailty model with treatment and region as fixed-effect factors. Cardiovascular death is analyzed using a Cox proportional hazard model with treatment as fixed-effect factor and stratified by region.
A rate ratio < 1 indicates an effect in favor of sacubitril/valsartan
n: Total no. of events; N: Total no. of patients; T(100 patient years): Total up-to-terminal-event/censoring duration-time summarized over patients in the respective treatment group; EAR=n/T.

Of note, investigator-reported HF hospitalization was associated with similar rates of subsequent all-cause death regardless of whether it was confirmed by the CEC (EAR 18.6/100 patient-years; 95% CI 16.1 – 21.3) or not (EAR 18.7/100 patient-years; 95% CI 14.9 – 23.1). These rates were substantially higher than rates of all-cause death in patients who did not have any investigator-reported HF hospitalizations (3.7 per 100 patient-years; 95% CI 3.3 – 4.0). This indicates that the investigator-reported HF hospitalizations were similarly associated with an increased risk of death regardless of whether or not the available documentation described these hospitalization episodes with sufficient details to allow for confirmation by the CEC.

6.3.1.3 Re-adjudication analysis of CEC-unconfirmed HF hospitalizations

As requested by FDA, re-adjudication of 566 CEC-unconfirmed HF hospitalization events was conducted, and added the equivalent of 105 HF hospitalization events to the sacubitril/valsartan

group and 126 additional HF hospitalization events to the valsartan group (see Section 6.2.2.3 for the methodology). When these events were incorporated into the analysis of the CEC-confirmed primary composite endpoint, sacubitril/valsartan reduced the rate of the primary composite endpoint by 14% relative to valsartan (RR = 0.86; 95% CI 0.75 – 1.00) (Table 6-5), achieving a nominal p-value below the threshold for statistical significance. This effect was driven by a 16% RRR in HF hospitalizations (RR = 0.84; 95% CI 0.72 – 0.99). This analysis demonstrated consistency with the primary analysis of the CEC-adjudicated primary endpoint and further supports the reliability of the treatment effect.

Table 6-5 PARAGON-HF: Analysis of CEC-confirmed primary endpoint incorporating CEC-unconfirmed HF hospitalization events based on their average re-adjudication probabilities (FAS)

	Average no. of events/N EAR		Sac/Val vs. Val	
Endpoint	Sac/Val	Val	Rate ratio (95% CI)	2-sided p-value
Primary composite endpoint	999/2407 (14.338)	1135/2389 (16.458)	0.8647 (0.7512, 0.9954)	0.0429
Total HF hospitalizations	795/2407 (11.409)	923/2389 (13.384)	0.8446 (0.7207, 0.9897)	0.0368

The analysis is using a binomial model which imputes unconfirmed HF hospitalizations into confirmed events with average probabilities calculated from three re-adjudicators' evaluations. 1000 complete datasets are created based on a multiple imputation approach and LWYY is fitted, yielding 1000 sets of parameter estimates and associated covariance matrices. Final statistics are based on Rubin's rules.

6.3.1.4 Other sensitivity and supportive analyses

Table 6-6 summarizes results of other sensitivity and supportive analyses. Recurrent event analysis of the primary composite endpoint using the negative binomial method was in line with other analyses described above showing a treatment effect of 13% to 14% rate reduction of sacubitril/valsartan relative to valsartan. Time to first event analysis using a Cox proportional hazards model, which included 526 patients (21.9%) in the sacubitril/valsartan group and 557 patients (23.3%) in the valsartan group who experienced at least one HF hospitalization or CV death, indicated an 8% reduction in the risk of experiencing a HF hospitalization or CV death in favor of sacubitril/valsartan (HR = 0.917; 95% CI 0.814 – 1.033). Due to the chronicity of HFpEF and potential occurrence of multiple events, quantifying total HF hospitalizations and CV death compared to time to first event more completely captures the patient experience. Sacubitril/valsartan showed more robust effects on recurrent HF hospitalizations compared with first HF events in PARAGON-HF.

Of note is the supportive analysis of the primary composite endpoint stratified *by country* as opposed to *by region*. As discussed in Section 6.2.2.1, the primary analysis of the primary composite endpoint used a proportional rates model (LWYY) with treatment as fixed-effect factor, which was stratified by region. Because the standard of care with respect to hospitalization for HF may differ significantly among countries within the same region (e.g., within the Asia/Pacific region there is considerable heterogeneity in terms of treatment standards), stratifying by country would have been more clinically appropriate than stratifying

by region as it reduces the potential heterogeneity in the model. However, it was decided when designing the study to stratify the primary analysis model by region to avoid excluding data of small countries that may experience no event. After database lock, it was noted that all countries had primary endpoint events, which allowed running a supportive country-stratified analysis, without losing any data. In the analysis of PARAGON-HF utilizing the LWYY model stratified by country, sacubitril/valsartan reduced the CEC-confirmed recurrent primary endpoint rate by 14% relative to valsartan (RR = 0.86; 95% CI 0.75 – 1.00; 2-sided p = 0.045). This was driven by a 16% rate reduction in total HF hospitalization in the sacubitril/valsartan group relative to valsartan (RR = 0.84; 95% CI 0.71 – 0.99).

Table 6-6 PARAGON-HF: Primary results and other analyses supporting the effect of sacubitril/valsartan in the overall HFpEF population

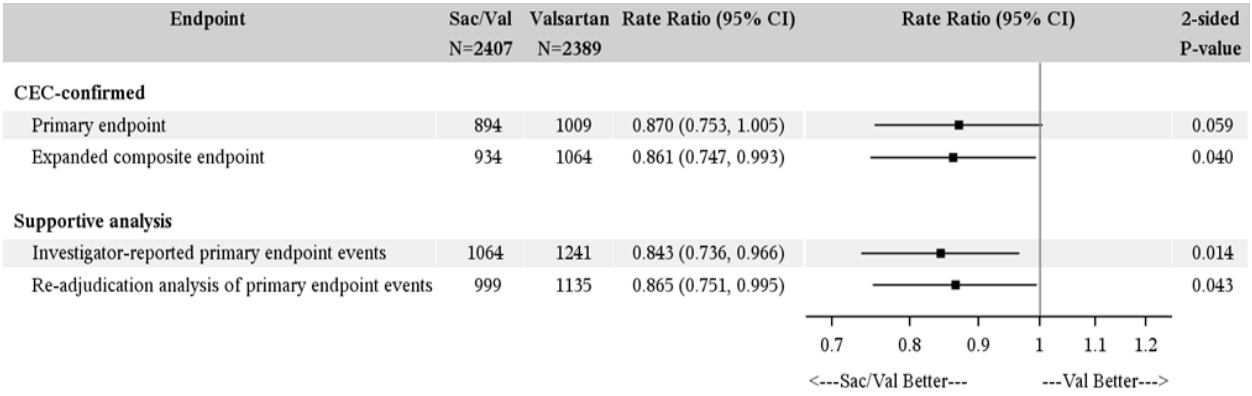
Endpoint/analysis	Sac/Val treatment effect (95% CI)	2-sided p-value
Primary results: Recurrent primary endpoint/LWYY (stratified by region)*	**RR = 0.870 (0.753 – 1.005)**	**0.0587**
Recurrent primary endpoint/LWYY (stratified by country)**	RR = 0.863 (0.748 – 0.997)	0.0449
Recurrent primary endpoint/negative binomial	RR = 0.865 (0.742 – 1.01)	0.0664
Primary endpoint/Cox proportional hazard (time to first event)	HR = 0.917 (0.814 – 1.033)	0.1531

*Regions were (1) North America (Canada and the United States), (2) Latin America (Argentina, Brazil, Colombia, Guatemala, Mexico, Peru), (3) Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK), (4) Central Europe (Bulgaria, Croatia, Czech Republic, Hungary, Poland, Republic of Slovakia, Romania, Russia, Serbia, Slovenia, Turkey), and (5) Asia/Pacific and other (Israel, South Africa, Australia, China, India, Japan, Republic of Korea, Philippines, Singapore, Taiwan).
**The recurrent primary endpoint/LWYY analysis stratification by country was conducted as a post hoc analysis.

6.3.1.5 Consistency of treatment effect across multiple analyses of the primary endpoint

Figure 6-5 summarizes multiple lines of evidence supporting the treatment effect of sacubitril/valsartan in the overall study population based on the primary endpoint of total HF hospitalizations and CV death and the more contemporary expanded composite endpoint of total worsening HF events and CV death. In these analyses, precision is improved by adding related clinically important events. As noted in Section 6.3.1.4, precision is also improved when the analysis model is stratified *by country* rather than *by region*, resulting in a nominally significant treatment effect (RR = 0.863; 95% CI 0.748 – 0.997; p = 0.0449), which is also in line with the magnitude based on other analyses shown in Figure 6-5.

Figure 6-5 PARAGON-HF: CEC-confirmed primary and expanded composite endpoint analyses and supportive analyses incorporating all investigator reported events and HF hospitalization re-adjudication analyses (FAS)



While the primary endpoint narrowly missed statistical significance, the observation that a consistent treatment effect of 13% to 16% rate reduction with nominal p-value below the threshold of statistical significance is achieved across the described various analyses provides confidence that sacubitril/valsartan reduces recurrent non-fatal HF events in HFpEF compared to valsartan alone.

6.3.2 Secondary endpoints

Table 6-7 summarizes the results of the efficacy secondary endpoints of the PARAGON-HF study. Consistent with the results on the primary endpoint, the results of the efficacy secondary endpoints showed a treatment effect in favor of sacubitril/valsartan over valsartan.

The mean change from baseline to month 8 in the patient-reported KCCQ CSS was −1.51 points in the sacubitril/valsartan group and −2.53 points in the valsartan group (treatment difference: 1.03 points). Patients on sacubitril/valsartan had a 30% greater odds of experiencing a clinically relevant improvement in KCCQ CSS of at least 5 points relative to the valsartan group (33.0% in the sacubitril/valsartan group and 29.6% in the valsartan group; OR = 1.30; 95% CI 1.04 – 1.61); the odds of experiencing clinically relevant deterioration in KCCQ by at least 5 points were similar between the two groups (33.5% in the sacubitril/valsartan group and 34.5% in the valsartan group).

Favorable change from baseline at month 8 in the investigator-reported NYHA class was experienced by 15.0% and 12.6% of patients in the sacubitril/valsartan group and the valsartan group, respectively, while a smaller percentage of patients had an unfavorable change in the sacubitril/valsartan (8.7% vs. 9.6%). This corresponded to a 45% greater odds of experiencing a favorable change in the sacubitril/valsartan group compared to valsartan (OR = 1.45; 95% CI 1.13 – 1.86).

The risk of the pre-specified 3-component composite renal endpoint was 50% lower in the sacubitril/valsartan group relative to the valsartan group (HR = 0.504; 95% CI 0.331– 0.767). This was driven by a 56% lower risk of ≥ 50% decline in eGFR in the sacubitril/valsartan group (27 patients) compared with the valsartan group (60 patients) (HR = 0.44; 95% CI 0.28 – 0.69). Although the total number of patients experiencing ESRD or death due to renal causes favored

sacubitril/valsartan (8 vs. 13), the overall incidence of these types of events in the HFpEF population enrolled in this study was low. In line with findings for the composite renal endpoint, eGFR declined at a slower rate (mean difference 0.53 mL/min/1.73 m^2 per year; 95% CI 0.27 – 0.80; p<0.0001) in the sacubitril/valsartan group relative to the valsartan group during the randomized treatment period.

There was no significant difference in the endpoint of all-cause mortality between treatment groups (HR = 0.97; 95% CI 0.84 – 1.13; p = 0.68) using a Cox proportional hazards model.

Table 6-7 Results of the efficacy secondary endpoints in PARAGON-HF

Endpoint	Sac/Val N = 2407	Valsartan N = 2389	LSM of difference or OR/HR	2-sided p-value
KCCQ CSS change at 8 months – n	2250	2226		
Change from baseline, LSM (SE)	**-1.51 (0.37)**	**-2.53 (0.37)**	**1.03 (-0.01 – 2.06)**	**0.0510**
≥5-point improvement	33.0%	29.6%	1.30 (1.04 – 1.61)	0.0186
≥5-point deterioration	33.5%	34.5%	0.93 (0.76 – 1.14)	0.4672
NYHA class change at 8 months – n	2316	2302	**1.45 (1.13 – 1.86)**	**0.0035**
Improved	15.0%	12.6%		
Unchanged	76.3%	77.9%		
Worsened	8.7%	9.6%		
Composite renal endpoint	**1.4%**	**2.7%**	**0.50 (0.33 – 0.77)**	**0.0014**
Renal death	<0.1%	<0.1%	0.93 (0.06 – 14.86)	0.9588
Reaching ESRD	0.3%	0.5%	0.58 (0.23 – 1.47)	0.2484
≥50% decline in eGFR from baseline	1.1%	2.5%	0.44 (0.28 – 0.69)	0.0004

eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HR = hazard ratio; NYHA = New York Heart Association; KCCQ CCS = Kansas City Cardiomyopathy Questionnaire clinical summary score; LSM = least square mean; OR = odds ratio

NYHA class treatment effect is presented as an OR; treatment effects of the renal composite endpoint and its components are presented in hazard ratios.

LSM of difference >0 favors and OR/HR <1 favor sacubitril/valsartan.

6.3.3 Conclusion of overall efficacy of sacubitril/valsartan in the HFpEF population

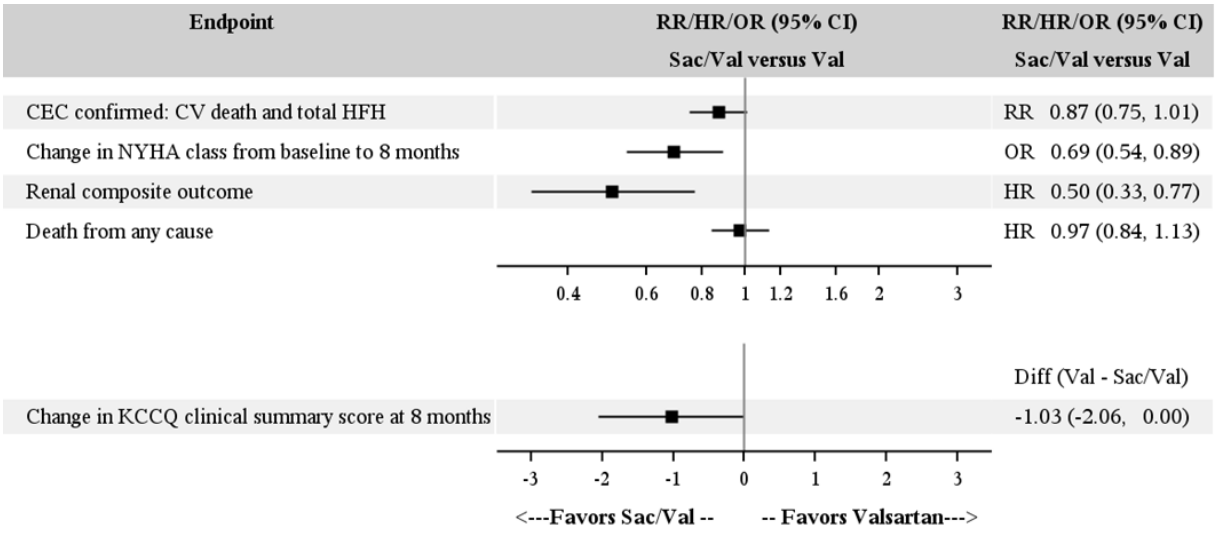
Figure 6-6 summarizes the treatment effect across the primary and secondary endpoints. Sacubitril/valsartan treated patients experienced greater morbidity benefits, specifically reduction in total worsening HF events (HF hospitalizations and urgent HF visits), improved HF symptoms and physical limitations as indicated by higher KCCQ CSS, more favorable change in NYHA HF functional class, and better preserved renal function, compared to valsartan-treated patients. All-cause and CV death were similar between the two treatments.

The consistency and the totality of the benefits of sacubitril/valsartan across the main and supportive analyses of the primary and secondary endpoints provide strong evidence for a true treatment effect in the overall study.

In a post-hoc analysis, the aggregated strength of evidence from PARAGON-HF was quantified based on the mean z-score across the primary and four secondary endpoints, which resulted in a value of z = -2.00 (see Section 6.2.2.5 for the methodology). The probability to observe such a favorable z score ≤ -2.00 if there was no difference between the treatment groups, is extremely

low (2-sided p = 0.0008) indicating that the totality of evidence strongly supports a true treatment effect.

Figure 6-6 Sacubitril/valsartan treatment effect across the primary and secondary endpoints in PARAGON-HF



While the data summarized above shows sacubitril/valsartan's benefit to be a 13% to 16% reduction in the primary endpoint of total HF hospitalization and CV death in the overall study population (Section 6.3.1), pre-specified subgroup analyses detailed below indicate that two subgroups experienced notably larger benefits, namely women and patients with lower LVEF.

6.3.4 Efficacy analyses by key subgroups

6.3.4.1 Subgroup analyses of the primary composite endpoint

Univariate analyses

In PARAGON-HF, pre-specified univariate subgroup analyses were performed for the CEC-confirmed primary endpoint. The effect of sacubitril/valsartan was generally consistent across the majority of subgroups; however, treatment-by-subgroup interactions, using a univariate interaction p-value of < 0.1, were observed for region (2 sided p = 0.0928), sex (2-sided p = 0.0169), and LVEF (above vs. at or below median LVEF of 57%; 2-sided p = 0.0937). As always, results from these interaction p-values and corresponding subgroup analyses should be interpreted with caution, as there is a non-negligible chance of false positive and false negative findings.

Figure 6-7 PARAGON-HF: Subgroup forest plot of rate ratios (95% CIs) from LWYY for recurrent CEC confirmed primary composite endpoint (CV death and total hospitalizations for HF) (FAS)

Subgroup	Sac/Val	Valsartan	Favors Sac/Val	Favors Valsartan	Rate Ratio	
	n/N (EAR)	n/N (EAR)			Estimate (95% CI)	P Value
Overall	894/2407 (12.83)	1009/2389 (14.63)			0.8698 (0.7526, 1.0052)	
Age						0.5070
< 65 years	138/412 (11.40)	138/413 (11.38)			0.9929 (0.6440, 1.5308)	
≥ 65 years	756/1995 (13.4)	871/1976 (15.32)			0.8503 (0.7299, 0.9905)	
Age						0.4420
< 75 years	425/1307 (11.10)	513/1290 (13.54)			0.8206 (0.6602, 1.0201)	
≥ 75 years	469/1100 (14.96)	496/1099 (15.96)			0.9193 (0.7591, 1.1134)	
Gender						0.0169*
Male	503/1166 (15.07)	477/1151 (14.57)			1.0297 (0.8461, 1.2530)	
Female	391/1241 (10.78)	532/1238 (14.68)			0.7253 (0.5877, 0.8952)	
Race						0.2166
Caucasian	709/1963(12.29)	833/1944 (14.61)			0.8329 (0.7122, 0.9739)	
Black	37/52 (23.60)	52/50 (35.75)			0.6947 (0.2425, 1.9902)	
Asian	128/297 (16.27)	109/310 (13.00)			1.2500 (0.8717, 1.7926)	
Other	20/95 (7.94)	15/85 (7.08)			1.0322 (0.4683, 2.2752)	
Region						0.0928
North America	223/288 (25.09)	255/271 (31.01)			0.8035 (0.5679, 1.1368)	
Latin America	49/191 (10.32)	34/179 (7.78)			1.3266 (0.7457, 2.3600)	
Western Europe	225/699 (10.74)	319/691 (15.62)			0.6880 (0.5289, 0.8949)	
Central Europe	228/856 (9.09)	238/859 (9.37)			0.9717 (0.7604, 1.2418)	
Asia/Pacific and other	169/373 (16.93)	163/389 (15.45)			1.0974 (0.7940, 1.5168)	
Diabetic at baseline (Rand)						0.6428
Yes	500/1049 (16.75)	541/1020 (18.36)			0.8944 (0.7353, 1.0880)	
No	394/1358 (9.90)	468/1369 (11.85)			0.8356 (0.6767, 1.0317)	
LVEF						0.0937
≤ median (57%)	457/1239 (12.82)	591/1256 (16.40)			0.7802 (0.6411, 0.9494)	
> median (57%)	437/1168 (12.85)	418/1133 (12.69)			0.9982 (0.8077, 1.2336)	

Subgroup	Sac/Val	Valsartan	Favors Sac/Val	Favors Valsartan	Rate Ratio	
	n/N (EAR)	n/N (EAR)			Estimate (95% CI)	P Value
AF based on ECG at baseline (Rand)						0.5398
Yes	279/717 (13.33)	314/679 15.93)			0.8091 (0.6297, 1.0397)	
No	607/1672 (12.59)	694/1698 (14.19)			0.8907 (0.7458, 1.0639)	
AF based on history at baseline (Rand)						0.4068
Yes	520/1246 (14.29)	620/1275 (16.72)			0.8278 (0.6863, 0.9985)	
No	374/1161 (11.24)	389/1114 (12.20)			0.9377 (0.7478, 1.1759)	
NT-proBNP at Screening						0.8602
≤ median (911 pg/mL)	329/1199 (9.20)	379/1180 (10.89)			0.8508 (0.6693, 1.0816)	
> median (911 pg/mL)	558/1189 (16.74)	625/1189 (18.61)			0.8742 (0.7285, 1.0489)	
SBP at Screening						0.8695
≤ median (137 mmHg)	461/1220 (13.19)	523/1230 (14.87)			0.8802 (0.7238, 1.0704)	
> median (137 mmHg)	433/1185 (12.49)	486/1159 (14.38)			0.8592 (0.6943, 1.0632)	
Use of MRA at baseline (Rand)						0.1115
Yes	218/592 (12.88)	327/647 (17.58)			0.7286 (0.5617, 0.9452)	
No	676/1815 (12.82)	682/1742 (13.54)			0.9384 (0.7896, 1.1153)	
ACEi intolerant						0.9976
Yes	40/123 (10.72)	46/139 (11.48)			0.8701 (0.4589, 1.6497)	
No	854/2284 (12.95)	963/2250 (14.82)			0.8692 (0.7493, 1.0084)	
Baseline (Rand) eGFR						0.1119
< 60 mL/min/1.73/m2	493/1164 (14.85)	622/1177 (18.77)			0.7901 (0.6559, 0.9518)	
≥ 60 mL/min/1.73/m2	401/1243 (11.00)	386/1211 (10.78)			1.0053 (0.7975, 1.2674)	
NYHA at baseline (Rand)						0.4581
I/II	670/1939 (11.95)	732/1904 (13.29)			0.8984 (0.7612, 1.0602)	
III/IV	222/466 (16.44)	277/485 (19.96)			0.7916 (0.5919, 1.0585)	

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 group; 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.

Multivariable interaction analysis

A simultaneous test of all interaction terms (global test for heterogeneity) provided statistical evidence for a heterogeneous treatment effect among subgroups (Table 6-8), suggesting that HFpEF encompasses a heterogeneous patient population with respect to response to sacubitril/valsartan relative to valsartan. After adjusting for covariates with continuous covariates treated as continuous, instead of using the pre-specified dichotomization, there was a strong signal for heterogeneity (p = 0.0087 for the test for heterogeneity), which was mainly driven by LVEF and sex; these two covariates are discussed in detail below.

Table 6-8 PARAGON-HF: Multivariable interaction analysis of the primary endpoint (Total HF hospitalizations and CV death)

Treatment-Covariate Interaction (continuous variables treated as continuous)	Effect modification rate ratio (95% CI)	P-value
LVEF (per 10% lower)	0.76 (0.63, 0.92)	0.0044*
Female sex	0.65 (0.48, 0.88)	0.0053*
MRA use	0.74 (0.55, 1.01)	0.0588
Region (Central Europe)	1.08 (0.53, 2.20)	0.1268
Region (Latin America)	1.25 (0.50, 3.15)	
Region (North America)	0.75 (0.37, 1.55)	
Region (Western Europe)	0.70 (0.35, 1.43)	
eGFR (per 10ml/min/1.73m2 lower)	0.94 (0.86, 1.02)	0.1618
History of AF	0.88 (0.64, 1.21)	0.4315
SBP (per 10mmHg)	0.98 (0.89, 1.09)	0.7530
NT-proBNP (per log)	1.06 (0.87, 1.30)	0.5424
Age (per 10 years)	1.05 (0.85, 1.29)	0.6354
NYHA Class III/IV	0.99 (0.71, 1.37)	0.9405
Diabetic	1.04 (0.78, 1.38)	0.8031
Race (Asian)	1.22 (0.58, 2.57)	0.9611
Race (Black)	0.96 (0.31, 2.98)	
Race (Other)	1.04 (0.41, 2.62)	
Test for heterogeneity		**0.0087***

Estimated rate ratios, confidence intervals, and p-values based on the LWYY model with treatment-covariate interactions. The analysis is based on 1888 events. The p-values shown are for the hypothesis that all interaction coefficients for a covariate are equal to zero. Asia/Pacific served as reference category for region and Caucasian as a reference category for race.
* indicates nominal 2-sided p<0.05

6.3.4.2 Treatment effect by patient's sex

Table 6-9 and Table 6-10 summarize the results of the primary endpoint of PARAGON-HF, its components and the secondary endpoints, respectively, by sex subgroup (men vs. women). Women appeared to have experienced a 27% reduction in the primary endpoint relative to valsartan, driven by a 31% rate reduction in total HF hospitalizations. However, men experienced a negligible increase of 3% in the rate of the primary endpoint relative to valsartan, largely due to an apparent 5% increase in the relative rate of total HF hospitalizations, which was off-set by a non-significant 9% risk reduction in CV death. Overall, there was no difference

between women and men in terms of the treatment effect on CV death. With respect to the secondary endpoints, the magnitude of the sacubitril/valsartan treatment effect was similar in women and men, except in change from baseline in KCCQ CSS at 8 months in which men experienced a larger treatment benefit than women (2.0 vs. -0.0).

Table 6-9 PARAGON-HF: Summary of the primary endpoints by sex subgroup (FAS)

	Effect size (95% CI)	
	Women	**Men**
Primary composite endpoint	RR = 0.73 (0.59 – 0.90)	RR = 1.03 (0.85 – 1.25)
Total HF hospitalizations	RR = 0.69 (0.55 – 0.87)	RR = 1.05 (0.83 – 1.32)
CV death	HR = 1.01 (0.76 – 1.35)	HR = 0.91 (0.67 – 1.17)

CV = cardiovascular; HF = heart failure; HR = hazard ratio; RR = rate ratio
A rate or hazard ratio < 1 indicates an effect in favor of sacubitril/valsartan

Table 6-10 Sacubitril/valsartan treatment effect size (95% CI) on the secondary endpoints by sex

Endpoint	Females	Males
KCCQ CSS change at 8 months; LSM	-0.0 (-1.3 – 1.3)	2.1 (0.8 – 3.4)
NYHA class favorable change at 8 months; OR	1.47 (1.08 – 2.00)	1.42 (1.04 – 1.95)
Renal composite endpoint; HR	0.49 (0.27 – 0.89)	0.52 (0.29 – 0.93)
All-cause death; HR	0.96 (0.77 – 1.20)	0.98 (0.80 – 1.19)

CI = confidence interval; HR = hazard ratio; KCCQ CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score; LSM = least square mean; NYHA = New York Heart Association; OR = odds ratio
LSM >1 indicates an effect in favor of sacubitril/valsartan
HR <1 indicates an effect in favor of sacubitril/valsartan
OR >1 indicates an effect in favor of sacubitril/valsartan

It is understood that subgroup analyses need to be interpreted with caution. While there may be some biologic plausibility to the treatment-by-sex interaction on the primary endpoint, it was an unexpected finding. Women are known to have anatomically smaller hearts and variable patterns of LV remodeling compared with men (Lin FY et al 2008). In addition, lower natriuretic peptide levels in women and differences in visceral adiposity may also play a role. However, no prior studies in HFpEF have shown a similar interaction and no sex interaction was observed in PARADIGM-HF (p-value for treatment-by-sex interaction = 0.63) with sacubitril/valsartan. Further, there was no difference between men and women in hemodynamic response to treatment as indicated by changes in blood pressure, NT-proBNP, or urinary cGMP/creatinine ratio (McMurray et al 2020). Moreover, as discussed above, men appeared to have experienced a 2.1-point improvement with sacubitril/valsartan relative to valsartan in mean change in KCCQ CSS at month 8 (95% CI 0.8 – 3.4), while women experienced almost no difference between treatments in this secondary endpoint. The conflicting directional behavior of the primary composite endpoint (i.e., greater benefit in women) and the KCCQ CCS secondary endpoint (i.e., greater benefit in men) indicates a lack of internal consistency within this subgroup.

In contrast, a greater treatment effect in the lower LVEF group has strong credibility with biologic plausibility, internal consistency and substantial external validity (i.e., replication). This subgroup is reviewed in detail in Section 6.3.4.3 below.

6.3.4.3 Treatment effect by patient's LVEF

A potential interaction of LVEF on treatment effect was considered based on the understanding of heart failure across the LVEF continuum, precedent trials of RAAS blockers in HFpEF, and the established efficacy of sacubitril/valsartan in HFrEF. Accordingly, a pre-specified analysis of the primary endpoint of PARAGON-HF and its components was conducted by LVEF subgroup (≤ median vs. > median). As shown in Table 6-11, sacubitril/valsartan-treated patients with LVEF at or below the median experienced a 22% rate reduction in the primary endpoint relative to their valsartan-treated counterparts, which was driven by a 25% RRR in total HF hospitalizations. Patients with higher LVEF appeared to experience substantially less benefit in the primary endpoint. A similar trend was observed in the analysis of the expanded composite endpoint, for which sacubitril/valsartan treated patients with LVEF ≤ the median experienced a 22% rate reduction, driven by a 26% RRR in total worsening heart failure. Sacubitril/valsartan's effect on death from CV causes in PARAGON-HF was similar regardless of LVEF subgroup, with broad confidence intervals.

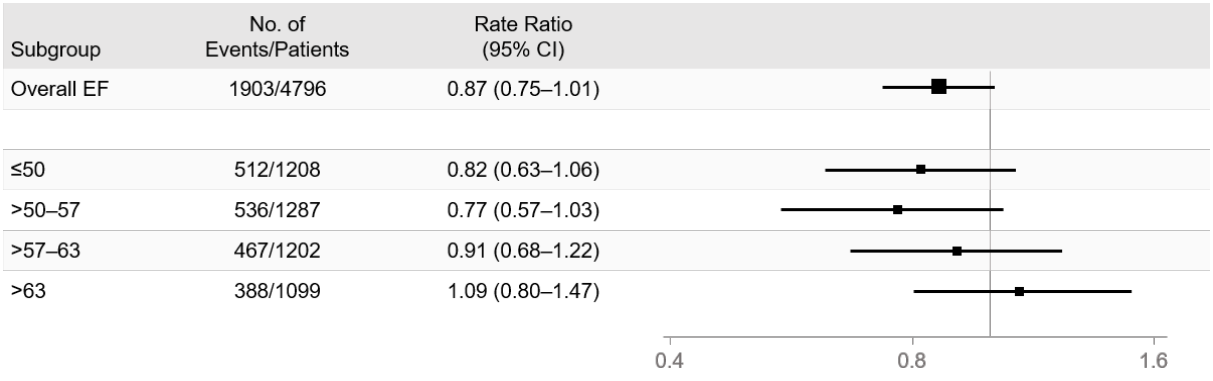
Table 6-11 PARAGON-HF: Summary of the primary and expanded composite endpoints by LVEF subgroup (FAS)

	Effect size (95% CI)	
	LVEF ≤ median	**LVEF > median**
Primary composite endpoint	RR = 0.78 (0.64 – 0.95)	RR = 1.00 (0.81 – 1.23)
Total HF hospitalizations	RR = 0.75 (0.60 – 0.95)	RR = 0.99 (0.78 – 1.26)
CV death	HR = 0.99 (0.77 – 1.26)	HR = 0.91 (0.67 – 1.24)
Composite endpoint of total worsening HF and CV death	RR = 0.78 (0.64 – 0.94)	RR = 0.98 (0.79 – 1.21)
Total worsening HF	RR = 0.74 (0.60 – 0.93)	RR = 0.97 (0.77 – 1.23)

CV = cardiovascular; HF = heart failure; HR = hazard ratio; RR = rate ratio
A rate or hazard ratio < 1 indicates an effect in favor of sacubitril/valsartan

To better understand the treatment effect on the primary endpoint at a more granular level, a post hoc subgroup analysis was performed by LVEF quartiles (Figure 6-8). The clinically relevant treatment effect favored sacubitril/valsartan in the bottom two quartiles in patients with LVEF below the median. The treatment effect, appeared to gradually diminish as LVEF increased in the top two quartiles.

Figure 6-8 Sacubitril/valsartan treatment effect on the primary endpoint by LVEF quartile



The sacubitril/valsartan treatment effect on the secondary endpoints was not modified by LVEF subgroup, with the exception of the composite renal endpoint, for which patients with LVEF ≤ the median experienced a greater reno-protective effect than patients with LVEF > the median (HR = 0.36 vs. 0.78) (Table 6-12).

Table 6-12 Sacubitril/valsartan treatment effect size (95% CI) on the secondary endpoints by LVEF

Endpoint	LVEF ≤ median	LVEF > median
KCCQ CSS change at 8 months; LSM	1.2 (-0.2 – 2.5)	0.9 (-0.5 – 2.2)
NYHA class favorable change at 8 months; OR	1.27 (0.94 – 1.73)	1.66 (1.21 – 2.28)
Renal composite endpoint; HR	0.36 (0.20 – 0.64)	0.78 (0.42 – 1.46)
All-cause death; HR	1.02 (0.84 – 1.25)	0.90 (0.72 – 1.14)

HR = hazard ratio; KCCQ CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score; LSM = least square mean; NYHA = New York Heart Association; OR = odds ratio
LSM >1 indicates an effect in favor of sacubitril/valsartan
HR <1 indicates an effect in favor of sacubitril/valsartan
OR >1 indicates an effect in favor of sacubitril/valsartan

As noted above, the greater treatment effect of sacubitril/valsartan on the primary endpoint among HFpEF patients with lower LVEF is considered to have strong biological plausibility. In PARADIGM-HF, sacubitril/valsartan was shown to significantly reduce morbidity and mortality in HFrEF patients who have significant systolic dysfunction. It is plausible that these beneficial effects can extend across the ejection fraction spectrum to patients immediately adjacent to HFrEF population; these patients have a LVEF in the HFpEF range, but still have a mild degree of systolic dysfunction. This is an increasingly recognized subpopulation within HFpEF as described in Section 4.1.

In PARAGON-HF, the 22% RRR in total HF hospitalizations and CV death (driven by 25% RRR in total HF hospitalizations) in HFpEF patients with lower LVEF is consistent with the 21% RRR in the same endpoint (driven in part by 25% RRR in total HF hospitalizations) in PARADIGM-HF HFrEF patients who have LVEF ≤ 40% (Mogensen et al 2018). Moreover, the larger treatment effect among HFpEF patients with lower LVEF has external validity, as this same finding was reported in prior trials, such as the CHARM program (Lund 2018) and TOPCAT (Solomon et al 2016). In these trials, treatment with candesartan and spironolactone respectively, appeared to elicit greater benefits among HFpEF patients with lower LVEF (Section 8, Appendix 1).

Thus, the differential treatment effect of sacubitril/valsartan by LVEF observed in the PARAGON-HF subgroup analysis has significant credibility. Section 6.3.5 below provides additional pre-specified analyses that further elucidate the relationship between LVEF and treatment effect.

6.3.5 Sacubitril/valsartan treatment effect across the LVEF continuum

Because PARAGON-HF and PARADIGM-HF included HF patients across the spectrum of LVEF, a pre-specified pooled analysis was performed to better understand the treatment effect in patients with mildly reduced LVEF by evaluating the relationship between baseline LVEF and the treatment effect of sacubitril/valsartan compared with the active control (i.e., valsartan (PARAGON-HF) or enalapril (PARADIGM-HF), which were considered to be exchangeable

in this modeling approach). This pooled analysis of the combined dataset of PARAGON-HF and PARADIGM-HF included 13,195 patients who were divided into septiles by baseline LVEF value and was performed on the rate of the composite endpoint of recurrent CEC-confirmed total HF hospitalizations and CV death (Table 6-13). Of note, only the >36% to ≤50% septile group (N = 2,013) included patients from both PARAGON-HF (N = 1,207) and PARADIGM-HF (N = 806). The lower septiles (LVEF ≤36%) consisted of patients from PARADIGM-HF and patients in the higher septiles (>50%) were all from PARAGON-HF. In addition, Figure 6-9 provides a plot of estimated treatment effect (rate ratio) against ejection fraction at screening for recurrent events of CEC-confirmed CV death and total HF hospitalizations (pooled data from PARAGON-HF and PARADIGM-HF, adjusted for baseline covariates).

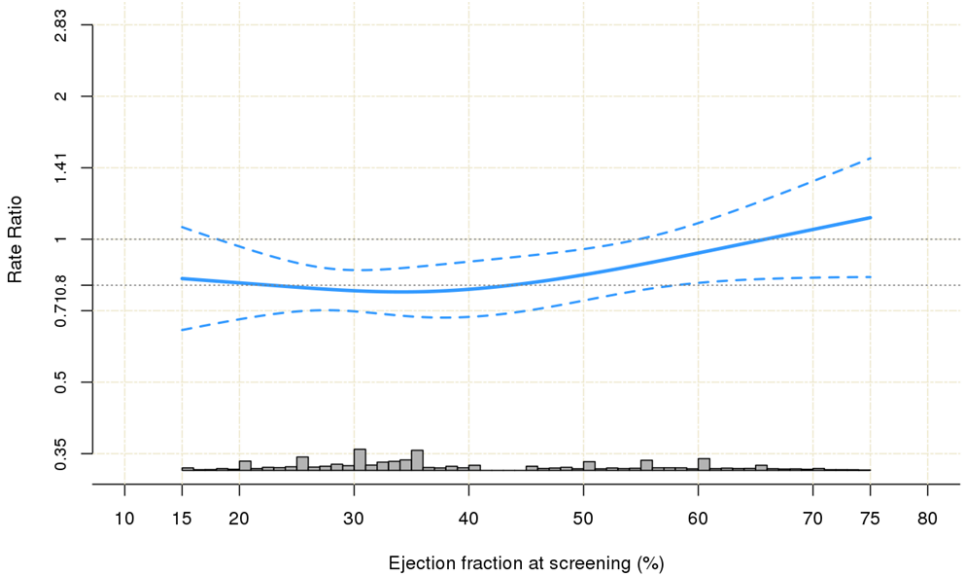
In this combined assessment of treatment effect dependent on LVEF, the treatment effect of sacubitril/valsartan on the primary composite endpoint of total HF hospitalizations and CV death appears to extend across the spectrum of LVEF up to a LVEF of 60%. In the highest septile (LVEF > 60%), the direction of the treatment effect is reversed, which appears to be related to a large drop in the rate of events in the comparator group, while the event rate remains relatively stable across the higher septiles in the sacubitril/valsartan group. The cause of this difference is unclear.

Table 6-13 Total HF hospitalizations and CV death by LVEF septile across pooled dataset of PARAGON-HF and PARADIGM-HF (FAS)

	Sacubitril/valsartan N=6594		Comparator* N=6600		
LVEF Septile	**n/N**	**EAR**	**n/N**	**EAR**	**Rate Ratio (95% CI)**
≤25%	451/1148	18.8	583/1205	23.0	0.82 (0.68 to 0.97)
>25 to ≤30%	346/1092	14.9	467/1070	20.7	0.72 (0.59 to 0.88)
>30 to ≤33%	190/622	14.6	235/607	18.9	0.77 (0.58 to 1.02)
>33 to ≤36%	275/928	12.9	340/921	16.7	0.76 (0.59 to 0.98)
>36 to ≤50%	364/973	13.1	442/1040	15.1	0.88 (0.71 to 1.09)
>50 to ≤60%	402/1112	12.4	466/1051	15.4	0.79 (0.63 to 1.00)
>60	275/719	13.3	248/706	11.8	1.12 (0.85 to 1.46)

Within subgroup estimated treatment effect, 95% CI and interaction p-value are based on the proportional rate model (abbreviated as LWYY) with treatment, subgroup and subgroup-by-treatment interaction fixed effect factors.
n: Total no. of events; N: Total no. of patients; Events occurred in randomized treatment epoch up to respective cutoff dates are included in the analysis. * valsartan in PARAGON-HF and enalapril in PARADIGM-HF

Figure 6-9 Plot of estimated treatment effect (rate ratio) against ejection fraction at screening for recurrent events of CEC-confirmed CV death and total heart failure hospitalizations (pooled data from PARAGON-HF and PARADIGM-HF, adjusted for baseline covariates) (FAS)



Estimated treatment effect and its 95% pointwise confidence intervals are plotted for ejection fraction (EF) ranged between 15% and 75%. Less than 2% of patients had an EF outside of the plotting range. The analysis uses a proportional rates model (LWYY) under the generalized additive models framework with restricted cubic splines (3 knots) applied to all continuous covariates in the model. This model includes region, treatment, EF, treatment by EF interaction as fixed factors, and adjusts for pre-specified baseline covariates. Rate ratio < 1 favors sacubitril/valsartan.

Table 6-14 summarizes results of additional analyses from PARAGON-HF in HFpEF patients with LVEF ≤ the median in comparison with results in HFrEF patients from PARADIGM-HF with LVEF ≤40%. As described in Section 6.3.4.3, among HFpEF patients with LVEF ≤ the median, there was a clinically meaningful treatment effect of sacubitril/valsartan with a 22%

RRR in the recurrent primary endpoint of total HF hospitalizations and CV death, which was driven by a 25% RRR in total HF hospitalizations. These effects were consistent with the established treatment effect in HFrEF patients demonstrated in PARADIGM-HF. The risk of CV death among PARAGON-HF patients with LVEF ≤ the median was similar in the two treatment groups (HR = 0.99; 95% CI 0.77 – 1.26).

Table 6-14 Results of additional analyses of PARAGON-HF patients with LVEF ≤the median in comparison to similar analyses of PARADIGM-HF patients with LVEF ≤40%

Study/Endpoint	Sac/Val EAR (95% CI)	Comparator EAR (95% CI)	RR/HR (95% CI)
PARAGON-HF (LVEF ≤ the median)		**Valsartan**	
Total HF hospitalizations and CV death (LWYY)	12.8 (11.7 – 14.0)	16.4 (15.1 – 17.8)	0.78 (0.64 – 0.95)
Total HF hospitalizations (joint frailty)	9.3 (8.3 – 10.4)	12.9 (11.7 – 14.1)	0.75 (0.60 – 0.95)
CV death (TTFE)	3.5 (2.9 – 4.2)	3.6 (3.0 – 4.2)	0.99 (0.77 – 1.26)
PARADIGM-HF (LVEF ≤40%)		**Enalapril**	
Total HF hospitalizations and CV death (LWYY)	15.1 (14.4 – 15.9)	19.2 (18.3 – 20.1)	0.79 (0.71 – 0.87)
Total HF hospitalizations (joint frailty)	9.1 (8.5 – 9.8)	11.7 (11.0 – 12.4)	0.75 (0.66 – 0.86)
CV death (TTFE)	6.0 (5.5 – 6.5)	7.5 (7.0 – 8.1)	0.80 (0.71 – 0.89)

EAR = exposure adjusted rate; HR = hazard ratio; LWYY = semi-parametric proportional rates model by Lin, Wei, Yang, and Ying for analysis of recurrent events; RR = rate ratio; TTFE = time to first event analysis using Cox proportional hazards.

Thus, although there is evidence supporting the efficacy of sacubitril/valsartan in reducing HF events in the overall HFpEF population, a substantially larger and more clinically relevant treatment effect exists among patients with LVEF ≤ the median, which represents a value that is just below the average normal LVEF. This differential effect is both biologically plausible and externally validated (given it has been observed in other prior HFpEF studies) and impacts a large, well-defined population that is immediately adjacent to the HFrEF population on the LVEF spectrum.

Events prevented by treating 1000 patients for 3 years

Table 6-15 summarizes the estimated number of events that would be prevented if 1000 patients are treated for 3 years based on the observed treatment effects in PARAGON-HF (HFpEF patients) and PARADIGM-HF (HFrEF patients). Although 54 primary composite events (including 49 HF hospitalizations) would be prevented if 1000 HFpEF patients were treated with sacubitril/valsartan for 3 years, treating HFpEF patients with LVEF ≤ the median in PARAGON-HF would prevent substantially more events, specifically, 108 primary composite events (including 106 HF hospitalizations). Sacubitril/valsartan HF event-sparing effects in HFpEF patients with LVEF below normal are in line with effects in HFrEF patients, namely 122 primary composite events prevented (including 76 HF hospitalizations). The larger projected HF hospitalization-sparing effect in HFpEF patients with LVEF below normal

compared to HFrEF patients may be due to the lower rate of the competing risk of CV death in HFpEF compared to HFrEF.

Table 6-15 Number of events prevented if 1000 patients are treated for 3 years

Study/cohort	Primary composite events prevented	HF hospitalizations prevented
PARAGON-HF/Overall	54	49
PARAGON-HF/LVEF ≤median	108	106
PARADIGM-HF	122	76

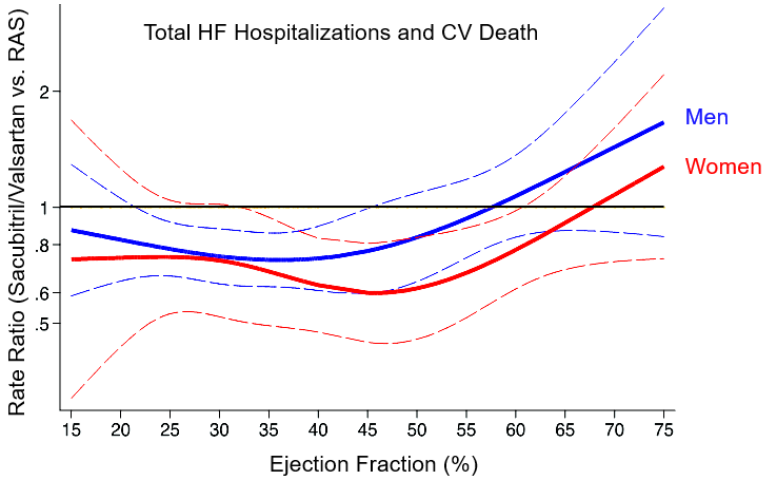
Treatment effect by LVEF and Sex

In light of the sex interaction observed in PARAGON-HF, the treatment effect on the recurrent composite endpoint of total HF hospitalizations and CV death was analyzed across the LVEF spectrum by sex using the pooled data from PARAGON-HF and PARADIGM-HF. The relationship was illustrated graphically using LVEF as a continuous variable. Figure 6-10 demonstrates the behavior of the treatment effect of sacubitril/valsartan across the LVEF continuum in men and women separately (Solomon et al 2020). The data indicates that while there is no meaningful difference in treatment effect in HFrEF, women derive benefit from sacubitril/valsartan to a higher LVEF than men in HFpEF. Unlike the treatment-by-sex interaction discussed in Section 6.3.4.2, which was not observed in prior HFpEF outcome trials, the interplay of LVEF and sex with respect to treatment effect has been observed with mineralocorticoids and with the ARB candesartan (Dewan et al 2020).

As noted in Section 4.1, international HF guidelines (AHA/ACC 2013, ESC 2016) recognize an intermediate group of HFpEF patients with mildly reduced LVEF. Different terminology has been used across guidelines and in the published literature, and there is debate as to how far this intermediate group spans (Campbell et al 2018, Böhm et al 2020).

The results of PARAGON-HF support that patients with an LVEF up to approximately 60% benefit from sacubitril/valsartan, with women deriving benefit to a higher LVEF than men.

Figure 6-10 Estimated treatment effect (rate ratio) against baseline LVEF and sex for CEC-confirmed total (first and recurrent) HF hospitalizations and CV death (pooled data from PARAGON-HF and PARADIGM-HF)



6.3.6 Summary of efficacy in PARAGON-HF

Multiple lines of evidence support a real and consistent treatment effect of sacubitril/valsartan in the overall study ranging from a 13% to 16% reduction in the primary endpoint relative to valsartan. While the primary composite endpoint analysis narrowly missed statistical significance, three supportive analyses achieved nominal p-values below the threshold of statistical significance by including additional clinically important worsening of HF endpoints and demonstrating a similar magnitude of effect:

- Analysis of the investigator-reported primary endpoint showed a 16% RRR, driven by an 18% RRR in total HF hospitalizations
- Re-adjudication analysis of CEC-unconfirmed HF hospitalizations combined with the CEC-confirmed primary endpoint resulted in a 14% RRR in the primary endpoint, driven by a 16% RRR in total HF hospitalizations
- Analysis of the CEC-confirmed expanded primary endpoint (including CEC-confirmed urgent HF visits) showed a 14% RRR, driven by a 16% RRR in CEC-confirmed total worsening HF events (HF hospitalizations and urgent HF visits)

Moreover, results of secondary endpoints favored sacubitril/valsartan, for quality of life as measured by the KCCQ, NYHA functional class, and risk of the composite renal endpoint. These findings were largely consistent with the results observed for the same endpoints in PARADIGM-HF.

There was no relevant difference in CV death or all-cause mortality between treatment groups.

A greater treatment effect of sacubitril/valsartan was observed in HFpEF patient with LVEF at or below the median and in women:

- A greater treatment effect of sacubitril/valsartan was observed in HFpEF patients with LVEF in the lower end of the spectrum. HFpEF patients with LVEF $\leq$ the median experienced a 22% RRR in the primary endpoint of total HF hospitalization and CV death, driven by a 25% RRR in total HF hospitalizations. This effect was in line with what was observed in HFrEF patients with LVEF $\leq$ 40% in PARADIGM-HF. A larger treatment effect among HFpEF patients with lower LVEF has also been observed in prior HFpEF studies. Thus, treatment-by-LVEF interaction has strong credibility with biologic plausibility and substantial external validity (i.e., replication).
- Although the treatment-by-sex interaction has limited biological basis and was not observed in prior HFpEF studies, rendering it less credible than the treatment-by-LVEF interaction, the data show that women benefit from sacubitril/valsartan to a higher LVEF than men.

In conclusion, the PARAGON-HF results in HFpEF patients, supported by established efficacy and consistent results of the PARADIGM-HF study in the adjacent population of HFrEF patients and the mechanistic data from PARAMOUNT, provide substantial evidence of clinically important benefit of sacubitril/valsartan in patients with HFpEF with LVEF below normal.

6.4 Safety Results

Overall, the safety of sacubitril/valsartan has been well characterized based on extensive clinical evaluation in more than 23,600 patients and 5 years of post-marketing experience, with over 2.6 million patient years of exposure in HFrEF.

In PARAGON-HF, the safety profile was in line with that of valsartan and the already characterized safety in HFrEF patients. The two large pivotal outcome studies, PARAGON-HF and PARADIGM-HF, demonstrated a consistent safety profile across the HF continuum.

Extent of Exposure in PARAGON-HF

The randomized population of PARAGON-HF included 4,822 patients with a median follow-up of 35 months, accounting for 6,241 patient years of experience on sacubitril/valsartan in this study.

During the treatment run-in epoch in PARAGON-HF, 5,746 patients were exposed to 40 mg to 80 mg b.i.d. of valsartan, followed by 5,205 patients exposed to 100 mg b.i.d. of sacubitril/valsartan. Because of this run-in design, the adverse reaction rates described below are likely lower than in a study without run-in period. Safety analyses were performed based on the Safety set, which included all randomized patients who received at least one dose of study drug during the double-blind period of the study. Patients were analyzed according to the treatment received. Following the treatment run-in epoch, 4,822 patients were randomized to either sacubitril/valsartan 200 mg b.i.d. (2,419 patients) or valsartan 160 mg b.i.d. (2,403 patients) in a 1:1 ratio. However, one patient in the randomized valsartan treatment group did not receive study medication and therefore 4,821 patients were included in the Safety set (2,419 patients in the sacubitril/valsartan group and 2,402 patients in the valsartan group).

The mean duration of study drug exposure (excluding temporary interruptions) in the randomized treatment epoch was comparable between the two treatment groups (30.5 and 30.1 months in the sacubitril/valsartan and valsartan groups, respectively). At the final visit, among the patients who were continuing therapy, 82.0% and 85.1% were taking the target dose in the sacubitril/valsartan and valsartan groups, respectively.

6.4.1 Overview of Adverse Events

An overview of the safety profile in PARAGON-HF is shown in Table 6-16. The overall incidence of AEs, SAEs, and other significant events was comparable between the sacubitril/valsartan and valsartan treatment groups.

Table 6-16 PARAGON-HF: Overall summary of adverse events (double-blind period) (Safety set)

	Sac/Val 200 mg BID N=2419 n (%)	Val 160 mg BID N=2402 n (%)
Subjects with any AE(s)	2301 (95.12)	2294 (95.50)
Death*	347 (14.34)	357 (14.86)
Subjects with any SAE(s)	1424 (58.87)	1416 (58.95)
Dose adjustment or interruption due to any AE(s)	856 (35.39)	846 (35.22)
Discontinued study treatment due to any AE(s)	493 (20.38)	520 (21.65)

* Deaths refer to those that were investigator-reported.

6.4.2 Most Frequently Occurring Adverse Events

In PARAGON-HF, the overall incidence of AEs was balanced between the sacubitril/valsartan and valsartan treatment groups (Table 6-17).

Hypotension AEs occurred at a higher incidence (> 2% difference between treatment arms) in patients treated with sacubitril/valsartan compared to valsartan, which is consistent with the greater blood pressure-lowering effect of sacubitril/valsartan. No other AE occurred at a > 2% higher incidence in sacubitril/valsartan compared to valsartan. AEs occurring at a lower incidence (> 2% difference between treatment arms) in sacubitril/valsartan treated patients compared to those on valsartan included cardiac failure, hyperkalemia, renal impairment and hypertension.

Safety topics of interest are detailed in Section 6.4.7.

Table 6-17 PARAGON HF: Common adverse events by PT (≥5% in any treatment arm) in the Randomized treatment epoch (Safety Set)

Preferred term	Sac/Val N=2419 n (%)	Val N=2402 n (%)
Number of patients with at least one TEAE	2301 (95.12)	2294 (95.50)
Hypotension	562 (23.23)	408 (16.99)
Cardiac failure	494 (20.42)	560 (23.31)
Atrial fibrillation	364 (15.05)	342 (14.24)
Renal impairment	301 (12.44)	356 (14.82)
Urinary tract infection	274 (11.33)	309 (12.86)
Hyperkalemia	252 (10.42)	328 (13.66)
Pneumonia	246 (10.17)	253 (10.53)
Dyspnea	244 (10.09)	272 (11.32)
Dizziness	241 (9.96)	200 (8.33)
Hypertension	237 (9.80)	328 (13.66)
Anemia	216 (8.93)	261 (10.87)
Nasopharyngitis	207 (8.56)	178 (7.41)
Bronchitis	206 (8.52)	228 (9.49)
Cough	191 (7.90)	149 (6.20)
Diarrhea	187 (7.73)	193 (8.03)
Edema peripheral	172 (7.11)	192 (7.99)
Back pain	159 (6.57)	179 (7.45)
Arthralgia	154 (6.37)	159 (6.62)
Upper respiratory tract infection	147 (6.08)	143 (5.95)
Acute kidney injury	136 (5.62)	159 (6.62)
Fall	135 (5.58)	110 (4.58)
Non-cardiac chest pain	127 (5.25)	120 (5.00)
Influenza	125 (5.17)	119 (4.95)
Angina pectoris	123 (5.08)	123 (5.12)

-A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the greatest severity.
-Preferred terms are presented in descending order of frequency as reported in sacubitril/valsartan column.
-MedDRA Version 22.0 has been used for the reporting of adverse events.

6.4.3 Most frequently Occurring Severe Adverse Events

In PARAGON-HF, the incidence of severe AEs was balanced between the sacubitril/valsartan and valsartan treatment groups (Table 6-18).

Table 6-18 PARAGON-HF: Common severe adverse events (≥1% in any treatment arm) in the Randomized treatment epoch (Safety Set)

Preferred term	Sac/Val 200 mg BID N=2419 n (%)	Val 160 mg BID N=2402 n (%)
Total	947 (39.15)	957 (39.84)
Cardiac Failure	180 (7.44)	193 (8.03)
Pneumonia	85 (3.51)	98 (4.08)
Atrial fibrillation	54 (2.23)	49 (2.04)
Acute kidney injury	53 (2.19)	60 (2.50)
Cardiac failure acute	41 (1.69)	39 (1.62)
Cardiac failure congestive	41 (1.69)	42 (1.75)
Acute myocardial infarction	33 (1.36)	35 (1.46)
Hypotension	32 (1.32)	35 (1.46)
Anemia	30 (1.24)	41 (1.71)
Respiratory failure	29 (1.20)	23 (0.96)
Sepsis	28 (1.16)	30 (1.25)
Cerebrovascular Accident	27 (1.12)	24 (1.00)
Myocardial infarction	27 (1.12)	28 (1.17)
Renal failure	22 (0.91)	27 (1.12)
Chronic obstructive pulmonary disease	21 (0.87)	27 (1.12)
Dyspnea	21 (0.87)	26 (1.08)
Urinary tract infection	20 (0.83)	25 (1.04)
Renal impairment	18 (0.74)	40 (1.67)
Cardiac arrest	18 (0.74)	31 (1.29)
Hyperkalemia	14 (0.58)	31 (1.29)

-A patient with multiple adverse events within a primary system organ class is counted only once in the total row
-A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the greatest severity.
-Preferred terms are presented in descending order of frequency as reported in sac/val column.
MedDRA Version 22.0 has been used for the reporting of adverse events.

6.4.4 Deaths

CV death was a component of the primary endpoint in PARAGON-HF. CV deaths are presented in Section 6.3.1. The results across groups were consistent when using investigator-reported cause of death or CEC-adjudicated death. Therefore, further description of deaths in this section will be focused on non-CV deaths as reported by the investigator (Table 6-19), in line with the safety standard approach to evaluate deaths.

Non-CV deaths occurred at a similar frequency in the sacubitril/valsartan group compared with the valsartan group, with no meaningful difference between treatment groups with respect to the individual causes of death.

The proportion of patients for whom the investigator reported death due to unknown cause was similar in the sacubitril/valsartan group compared with the valsartan group.

Table 6-19 PARAGON-HF: Deaths in Randomized treatment epoch as reported by the investigator (Safety Set)

Primary cause of death/ Subcategory	Sac/Val 200 mg BID N=2419 n (%)	Val 160 mg BID N=2402 n (%)
Number of deaths	347 (100.0)	357 (100.0)
CV deaths	150 (43.23)	155 (43.42)
Non-CV deaths	138 (39.77)	146 (40.90)
Other	59 (17.00)	56 (15.69)
Malignancy	26 (7.49)	29 (8.12)
Infection	21 (6.05)	19 (5.32)
Pulmonary failure	18 (5.19)	22 (6.16)
Accidental/trauma	3 (0.86)	7 (1.96)
Gastrointestinal	3 (0.86)	7 (1.96)
Renal failure	6 (1.73)	4 (1.12)
Suicide	2 (0.58)	2 (0.56)
Unknown	59 (17.00)	56 (15.69)

Causes of death were determined by an independent adjudication committee.

6.4.5 Overview of Serious Adverse Events

The proportion of patients with at least one SAE was comparable between the sacubitril/valsartan and valsartan groups in PARAGON-HF (58.9% vs 59.0% respectively) (Table 6-20). No individual SAE term was reported with ≥1% higher incidence in the sacubitril/valsartan group relative to the valsartan group.

Table 6-20 PARAGON-HF: Serious adverse events ≥2% in any treatment group in Randomized treatment epoch, regardless of study drug relationship (Safety Set)

Preferred term	Sac/Val N=2419 n (%)	Val N=2402 n (%)
Number of patients with at least one SAE	1424 (58.87)	1416 (58.95)
Cardiac failure	340 (14.06)	380 (15.82)
Atrial fibrillation	162 (6.70)	145 (6.04)
Pneumonia	162 (6.70)	178 (7.41)
Acute kidney injury	90 (3.72)	110 (4.58)
Cardiac failure congestive	86 (3.56)	83 (3.46)
Cardiac failure acute	85 (3.51)	77 (3.21)
Anemia	68 (2.81)	67 (2.79)
Acute myocardial infarction	60 (2.48)	54 (2.25)
Urinary tract infection	54 (2.23)	68 (2.83)
Hypotension	52 (2.15)	47 (1.96)
Angina unstable	50 (2.07)	43 (1.79)
Angina pectoris	42 (1.74)	50 (2.08)
Chronic obstructive pulmonary disease	42 (1.74)	67 (2.79)
Dyspnea	42 (1.74)	64 (2.66)
Syncope	41 (1.69)	57 (2.37)
Renal impairment	24 (0.99)	48 (2.00)

6.4.6 Adverse Events Leading to Study Drug Discontinuation

The proportion of patients with an AE that led to study drug discontinuation was comparable between the sacubitril/valsartan and valsartan groups in PARAGON-HF (Table 6-21), with no meaningful difference in the individual AEs terms that led to discontinuation.

Table 6-21 PARAGON-HF: Adverse events (≥1% in any treatment group) leading to study drug discontinuation in Randomized treatment epoch, regardless of study drug relationship (Safety Set)

Preferred term	Sac/Val 200 mg BID N=2419 n (%)	Val 160 mg BID N=2402 n (%)
Total	493 (20.38)	520 (21.65)
Hypotension	51 (2.11)	48 (2.00)
Renal impairment	42 (1.74)	52 (2.16)
Cardiac failure	33 (1.36)	42 (1.75)
Hyperkalemia	26 (1.07)	35 (1.46)

6.4.7 Safety Topics of Interest

The following safety topics of interest were evaluated in detail (analysis of AEs and laboratory test results) in PARAGON-HF and PARADIGM-HF, based on the mechanism of action or the known effects of sacubitril/valsartan:

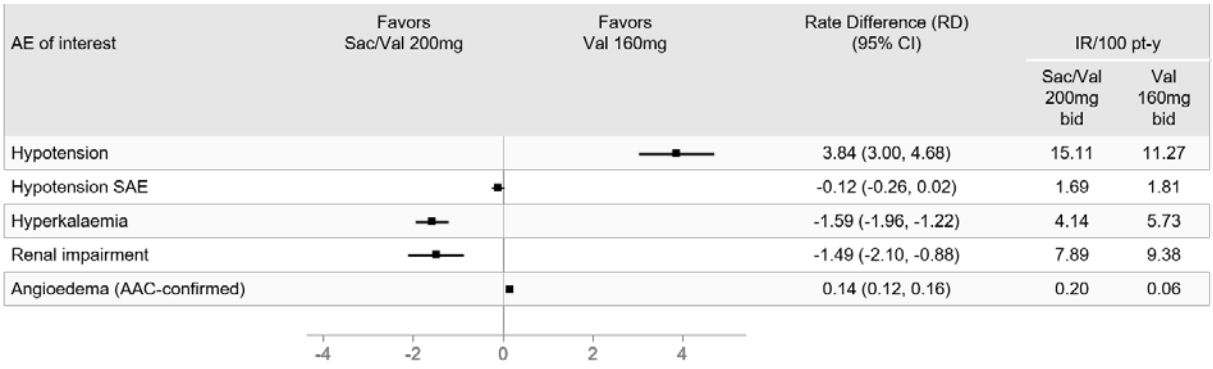
- Hypotension
- Hyperkalemia
- Renal impairment
- Angioedema

Analysis of AEs of the safety topics of interest were conducted using SMQs (standard groupings of terms provided by the MedDRA organization) or NMQs (Novartis MedDRA Queries) for which no adequate SMQ exists.

In PARAGON-HF, for hypotension and angioedema, the rate difference and 95% CI favored the valsartan treatment group. While the total number of patients presenting with hypotension events was higher on sacubitril/valsartan, the incidence of more clinically relevant hypotension-related events like SAEs and hypotension-related AEs that led to permanent discontinuation of study treatment was low and comparable between the sacubitril/valsartan and valsartan groups. The majority of angioedema events were mild to moderate in severity, with no cases of angioedema events involving airway compromise or death.

For hyperkalemia and renal impairment, the rate difference favored the sacubitril/valsartan treatment group (Figure 6-11).

Figure 6-11 PARAGON-HF: Exposure adjusted incidence rate of AEs of interest in Randomized treatment epoch (Safety Set)



AAC=angioedema adjudication committee; IR=incidence rate; Sac/Val=sacubitril/valsartan; pt-y=patient treatment years; RD=rate difference; Val=valsartan
- IR/100 pt-y: EAIR per 100 person-years is calculated by n (number of patients with events)/ total exposure time (in 100 years) of double-blind treatment, summed up from all patients in the treatment group. Exposure time is the duration from Day 1 to the 1st event for patients with at least one event or the duration of treatment in Randomized treatment epoch for patients with no event reported. Rate difference (RD) is based on IR.

Overall, the pattern of AEs observed in PARAGON-HF was consistent with the known safety profile of sacubitril/valsartan observed in PARADIGM-HF (Table 6-22). Reported rates of hypotension and renal impairment AEs in PARAGON-HF were higher than those in PARADIGM-HF, whereas the rate of hyperkalemia AEs in PARAGON-HF showed no relevant differences compared to PARADIGM-HF. These differences similarly affected both treatment

arms in each study suggesting that it rather reflects differences between the study populations and study design (e.g., partial vs. complete run-in periods) than a difference in the safety profile of sacubitril/valsartan. The difference between sacubitril/valsartan and its respective comparators for the safety topics of interest was consistent across populations. The rate of angioedema was consistent in both PARAGON-HF and PARADIGM-HF studies for patients on sacubitril/valsartan: 0.20 vs 0.20, respectively.

Table 6-22 Exposure adjusted incidence rate of AEs of interest in Randomized treatment epoch (Safety set) (PARAGON-HF and PARADIGM-HF)

	PARAGON-HF		PARADIGM-HF	
AE of Interest	Sac/Val 200mg BID N=2419 n (%) IR/100 pt-y (95% CI)	Val 160 mg BID N=2402 n (%) IR/100 pt-y (95% CI)	Sac/Val 200mg BID N=4203 n (%) IR/100 pt-y (95% CI)	Enalapril 10 mg BID N=4229 n (%) IR/100 pt-y (95% CI)
Hypotension	804 (33.24) 15.11 (14.08,16.19)	645 (26.85) 11.27 (10.42,12.17)	1027 (24.43) 13.16 (12.37,13.99)	786 (18.59) 9.50 (8.84,10.19)
Hyperkalemia	272 (11.24) 4.14 (3.66,4.66)	363 (15.11) 5.73 (5.15,6.35)	500 (11.90) 5.71 (5.22,6.23)	605 (14.31) 7.08 (6.53,7.67)
Renal impairment (Narrow SMQ)	492 (20.34) 7.89 (7.21,8.62)	569 (23.69) 9.38 (8.62,10.18)	605 (14.39) 6.91 (6.37,7.49)	679 (16.06) 7.90 (7.31,8.51)
Angioedema (AAC-confirmed)	14 (0.58) 0.20 (0.11,0.34)	4 (0.17) 0.06 (0.02,0.15)	19 (0.45) 0.20 (0.12,0.31)	10 (0.24) 0.11 (0.05,0.20)

IR/100 pt-y: exposure-adjusted incidence rate per 100 person-years is calculated by n (number of patients with events)/ total exposure time (in 100 years) of randomized treatment, summed up from all patients in the treatment group. Exposure time is the duration from Day 1 to the 1st event for patients with at least one event or the duration of treatment in randomized period for patients with no event reported.

6.4.7.1 Hypotension

Sacubitril/valsartan has a blood pressure-lowering effect based on its dual ARB and NEP inhibition properties, including decreased effects of angiotensin II on the vasculature (causing decreased vascular tone) and the kidney (causing decreased sodium and water reabsorption).

Consistent with its mechanism of action, in PARAGON-HF the exposure adjusted incidence of hypotension related AEs was greater in the sacubitril/valsartan group (33.2%) than in the valsartan group (26.9%) (Table 6-22). In line with the higher frequency of hypotension-related events reported in the sacubitril/valsartan group, greater proportions of patients presented with SBP < 100 mmHg and/or ≥ 30 mmHg drop in SBP from baseline in the sacubitril/valsartan group compared with the valsartan group (Table 6-23).

However, the incidence of the more clinically relevant events of syncope, pre-syncope or loss of consciousness, which could be potentially related to hypotension, as well as SAEs and AEs leading to permanent discontinuation of study treatment due to hypotension was low and comparable between the sacubitril/valsartan and valsartan groups. The incidence of hypotension related AEs by PT reported during the randomized treatment epoch is presented in Table 6-23.

Table 6-23 Hypotension in PARAGON-HF (Safety set)

PT/Group Term	Sac/Val 200 mg BID N=2419 n (%) or EAIR	Valsartan 160 mg BID N=2402 n (%) or EAIR
Hypotension-related events (NMQ*)	804 (33.24)	645 (26.85)
Hypotension	562 (23.23)	408 (16.99)
Dizziness	241 (9.96)	200 (8.33)
Syncope	78 (3.22)	114 (4.75)
Loss of consciousness	6 (0.25)	7 (0.29)
Presyncope	18 (0.74)	20 (0.83)
Hypotension AE requiring dose adjustment/interruption	366 (15.13)	240 (9.99)
Hypotension, severe	32 (1.32)	35 (1.46)
Hypotension SAE	52 (2.15)	47 (1.96)
Hypotension AE/SAEs leading to study drug discontinuation	51 (2.11)	48 (2.00)
Simultaneous SBP <100 mmHg and ≥ 30 mmHg drop in SBP from baseline	161 (6.66)	115 (4.79)

* AE based on Novartis medical query definition as included
AE and SAE data are for the single preferred term of 'hypotension'

Per the product label, if hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs and treatment of other causes of hypotension (e.g., hypovolemia) should be considered. If hypotension persists despite such measures, it can be managed by dose reduction or temporary discontinuation of sacubitril/valsartan.

6.4.7.2 Renal impairment

Renal impairment occurs frequently in HFpEF patients and renal function can be further compromised by HF therapies that block the renin angiotensin system (RAS) by decreasing glomerular filtration. However, NEP inhibition results in natriuresis and vasodilation; in the kidney, this vasodilatory effect reduces intraglomerular pressure (Judge et al 2015). Therefore, NEP inhibitors have the potential to increase renal blood flow while lowering intraglomerular pressure and provide a renal protective effect (Dries et al 2000, Cao et al 2001, Taal et al 2001).

Results from PARAGON-HF indicate that the risk of renal impairment is lower for sacubitril/valsartan compared with valsartan, which is consistent with observations in the HFrEF population in PARADIGM-HF.

In PARAGON-HF, the incidence of renal impairment AEs was lower in the sacubitril/valsartan group. While no difference was observed in mild renal impairment events, there was a lower incidence of moderate and severe events. Consistent with the reduction of the more severe AEs, there was a lower incidence of renal impairment SAEs (Table 6-24) and a slight lower incidence of renal impairment AEs leading to study drug discontinuation.

Table 6-24 Renal impairment in PARAGON-HF (Safety set)

PT/Group Term	Sac/Val 200 mg BID N=2419 n (%)	Val 160 mg BID N=2402 n (%)
Renal Impairment (narrow SMQ)	492 (20.34)	569 (23.69)
Mild	186 (7.69)	186 (7.74)
Moderate	215 (8.89)	261 (10.84)
Severe	91 (3.76)	122 (5.08)
Renal Impairment SAE (SMQ)	139 (5.75)	173 (7.20)
Renal Impairment AE leading to study drug discontinuation (SMQ)	67 (2.77)	80 (3.33)
Creatinine		
>2.0 mg/dl	264 (10.91)	332 (13.82)
>2.5 mg/dl	93 (3.84)	106 (4.41)
>3.0 mg/dl	38 (1.57)	40 (1.67)
>50% eGFR decline from baseline*	131 (5.42)	203 (8.45)

SMQ=standardized MedDRA query

*Baseline is defined as the last non-missing value on or before the first double-bling treatment dose date.

In PARAGON-HF, more patients in the valsartan group exceeded pre-defined renal impairment-related clinical thresholds (eGFR decline from baseline, serum creatinine increase from baseline, serum creatinine level) than the sacubitril/valsartan group. This is similar to what was observed in PARADIGM-HF, in which patients in the enalapril group experienced a greater decline in eGFR from baseline to month 12 than the sacubitril/valsartan group.

Despite the lower risk in the sacubitril/valsartan group, the potential for renal impairment remains a concern for patients with HF, and renal function should be monitored. Down-titration of sacubitril/valsartan should be considered for patients who develop a clinically significant decrease in renal function.

6.4.7.3 Hyperkalemia

Hyperkalemia may occur as a result of RAS blockade inhibiting secretion of aldosterone, particularly in patients who have chronic renal insufficiency or are using MRAs concomitantly. For the majority of patients treated with RAS inhibitors, the decline in serum aldosterone concentration associated with RAS inhibitor therapy is not sufficient to cause hyperkalemia.

Overall, treatment with sacubitril/valsartan resulted in a lower rate of hyperkalemia AEs and SAEs compared to valsartan, as well as a slightly lower rate of discontinuation of study drug due to hyperkalemia.

Table 6-25 Hyperkalemia in PARAGON-HF (Safety set)

PT/Group Term	Sac/Val 200 mg BID N=2419 n (%)	Val 160 mg BID N=2402 n (%)
Hyperkalemia (SMQ)	272 (11.24)	363 (15.11)
Mild	172 (7.11)	210 (8.74)
Moderate	86 (3.56)	121 (5.04)
Severe	14 (0.58)	32 (1.33)
Hyperkalemia SAE (SMQ)	19 (0.79)	42 (1.75)
Hyperkalemia AE (SMQ) leading to study drug discontinuation	26 (1.07)	35 (1.46
Potassium*		
≥5.5 mmol/L	426 (17.76)	466 (19.57)
>6 mmol/L	75 (3.13)	101 (4.24)

SMQ=standard MedDRA query

* Biochemistry laboratory results meeting specified criteria post-baseline by treatment

Consistent with the AE profile for hyperkalemia events in PARAGON-HF, the proportion of patients with increased serum potassium levels in the laboratory results during the Randomized treatment epoch was lower in the sacubitril/valsartan group than in the valsartan group (Table 6-25). These results are consistent with the results for PARADIGM-HF, where slightly lower proportions of patients in the sacubitril/valsartan group than in the enalapril group had potassium > 5.5 mmol/L (15.5% vs. 16.5%) or > 6 mmol/L (5.6% vs. 6.7%).

The lower incidence of hyperkalemia events in both PARAGON-HF and PARADIGM-HF may be explained by the natriuretic and diuretic effect of sacubitril/valsartan through NEP inhibition.

Patients with HF often have comorbidities that increase the risk for hyperkalemia (e.g., renal impairment, diabetes mellitus, hypoaldosteronism) or are on a high potassium diet or taking MRAs, which are also risk factors for hyperkalemia. Periodic monitoring of serum potassium levels in patients receiving sacubitril/valsartan is recommended.

6.4.7.4 Angioedema

NEP inhibition by the sacubitril component in sacubitril/valsartan has the potential to increase levels of the substrate bradykinin and cause angioedema. The ARB valsartan is known to have a lower risk of angioedema compared to ACEIs (Irons and Kumar 2003, Fryer et al 2008, Toh et al 2012). Therefore, angioedema or angioedema-like events were carefully evaluated. Known or suspected events were documented by the investigators utilizing a supplied adjudication questionnaire and sent for adjudication to an Angioedema Adjudication Committee (AAC).

The overall incidence of AAC confirmed angioedema events was low in PARAGON-HF. During the treatment run-in, there were 6 patients (0.10%) with confirmed angioedema events in the valsartan group and 3 patients (0.06%) in the sacubitril/valsartan group. Five of the 6 cases receiving valsartan were severity grade I (no treatment administered or antihistamines only) and 1 case was severity grade II (treated with catecholamines or steroids); all 3 cases in the sacubitril/valsartan run-in period were severity grade I.

During the randomized treatment phase, a greater proportion of patients in the sacubitril/valsartan group (14 patients (15 total events), 0.58%) had AAC-confirmed

angioedema compared with the valsartan group (4 patients, 0.17%). Four patients (0.17%) in the sacubitril/valsartan group and no patients in the valsartan group had events of angioedema within 30 days from the start of randomized treatment; thereafter, events occurred sporadically. Of the 14 patients who experienced an AAC-confirmed angioedema event in the sacubitril/valsartan group, 5 had a severity I event, 5 had a severity II event, and 4 had a severity IIIa (no airway compromise) event. Of the patients in the valsartan group, 2 had a severity I event, 1 had a severity II event, and 1 had a severity IIIa event. No cases of severe angioedema events involving airway compromise or death were reported on either study treatment.

Overall, there was no meaningful difference in severity of events between Black and Non-Black patients. However, there were relatively few Black patients in PARAGON-HF; hence, caution should be exercised when interpreting results in terms of the incidence of angioedema in this subgroup.

The findings for AAC-confirmed angioedema in PARAGON-HF were consistent with those in PARADIGM-HF, with the same EAIRs in both studies for patients on sacubitril/valsartan: 0.20 vs 0.20, respectively (Table 6-22), although incidence rates were lower in the valsartan group (comparator in PARAGON-HF) compared to the enalapril group, as expected.

In summary, the incidence of angioedema in PARAGON-HF was low in both treatment groups, but, as expected, was numerically higher in the sacubitril/valsartan group than in the valsartan group. Consistent with PARADIGM-HF, no angioedema events in PARAGON-HF resulted in respiratory compromise or death. Measures to manage the risk of angioedema are reflected in labeling and include a contraindication for concomitant use with an ACEI. Discontinuation is recommended if angioedema occurs during sacubitril/valsartan use.

Key safety subgroup analyses

The safety profile for sacubitril/valsartan by subgroups (sex and median LVEF) was consistent with the known safety profile of sacubitril/valsartan as seen in the overall study population.

In the subgroups of patients by LVEF, the incidence of AEs, SAEs, and discontinuations due to AEs was similar in sacubitril/valsartan and valsartan groups within each of the subgroups (Table 6-26). Consistent with the safety profile in the overall population, while there was a higher incidence of hypotension AEs in the sacubitril/valsartan compared to the valsartan group, the rates of hypotension SAEs and hypotension AEs leading to discontinuation were similar across treatment arms within each subgroup. Hyperkalemia and renal impairment were less frequently observed in the sacubitril/valsartan than in the respective valsartan groups. The incidence of angioedema was low in both groups.

When comparing across subgroups, higher incidences of AEs were generally observed in the LVEF > median subgroup, except for hyperkalemia or deaths which were more frequently observed in the LVEF ≤ median subgroup. These differences in rates of events affected in a similar manner both treatment arms within each subgroup, thus indicating differences in the population included in the subgroups and not a drug effect.

Table 6-26 Overall safety by median LVEF – PARAGON-HF

	LVEF ≤ median		LVEF > median	
	Sac/val N=1246 n(%)	Val N=1259 n(%)	Sac/val N=1173 n(%)	Val N=1143 n(%)
Patients with at least one AE	1181 (94.8)	1191 (94.6)	1120 (95.5)	1103 (96.5)
AEs of interest				
Hypotension*	254 (20.3)	189 (15.0)	308 (26.3)	219 (19.2)
Hypotension SAE*	24 (1.9)	21 (1.7)	28 (2.4)	26 (2.3)
Hyperkalemia	156 (12.5)	194 (15.4)	116 (9.9)	169 (14.8)
Renal impairment	230 (18.5)	294 (23.4)	262 (22.4)	275 (24.1)
Angioedema (AAC confirmed)	5 (0.4)	2 (0.2)	9 (0.8)	2 (0.2)
Patients with at least one SAE	724 (58.1)	730 (58.0)	700 (59.7)	686 (60.0)
Patients who died	202 (16.2)	201 (16.0)	145 (12.4)	156 (13.6)
Patients who discontinued due to AEs	260 (20.9)	275 (21.8)	233 (19.9)	245 (21.4)

*Based on PTs

In summary, the safety profile in the subgroups by LVEF was consistent with the overall population of PARAGON-HF.

Regarding subgroups by sex, the safety profile in each of the subgroups was also consistent with that seen in the overall population. The incidence of AEs, SAEs, and discontinuations due to AEs was similar in sacubitril/valsartan and valsartan groups in men and women. While there was a higher incidence of hypotension AEs in the sacubitril/valsartan compared to the valsartan group, the rates of hypotension SAEs were similar across treatment arms within each subgroup. Hyperkalemia and renal impairment were less frequently observed in the sacubitril/valsartan than in the respective valsartan groups. The incidence of angioedema was low in both men and women.

When comparing across the subgroups, there was a higher risk for women than for men to present with hypotension and angioedema when treated with sacubitril/valsartan compared to valsartan. The incidence of hypotension AEs in women was 25.3% and 17.2% in sacubitril/valsartan and valsartan, respectively, compared to 21.0% and 16.8% in men. However, similar rates to valsartan were observed for women in the more clinically relevant hypotension SAEs (1.9% and 2.1% for sacubitril/valsartan and valsartan, respectively) or hypotension AEs leading to discontinuation (2.4% and 2.2% for sacubitril/valsartan and valsartan groups, respectively) and these were similar to men. This suggests that the more pronounced numerical increase in hypotension report rates observed in women is of limited clinical relevance. As expected (Kostis et al 2018), angioedema was slightly more frequently observed in women, with 11 (0.9%) and 3 (0.2%) women presenting with angioedema in sacubitril/valsartan and valsartan groups, respectively, compared to 3 (0.3%) and 1 (0.1%) in men, respectively. Otherwise, the incidence of other AEs was similar in men and women.

6.4.8 Summary of Safety

The safety profile of sacubitril/valsartan is well-characterized, with more than 23,600 patients treated across multiple studies in the sacubitril/valsartan development program and 5 years of post-marketing experience with 2.6 million patient-years of exposure in HFrEF patients. The

safety data in HFpEF patients from PARAGON-HF was similar between sacubitril/valsartan and valsartan treatment groups and was consistent with the known safety profile in HFrEF patients. No new safety signals have been identified and risks are manageable through current product labelling and standard patient management.

6.5 Other Clinical Studies in HFpEF

6.5.1 PARALLAX-HF

PARALLAX-HF was designed to generate data in response to a request by the German health technology assessment decision body (G-BA) to compare sacubitril/valsartan to individualized medical treatment (IMT) based on their pre-study anti-RAAS treatment (ACEI, ARB, or no RAAS inhibition). Several design features of this study, including the comparator, endpoints, some entry criteria and some study procedures were incorporated based on agreements reached with G-BA and differed from the sacubitril/valsartan registration trials in HF.

PARALLAX-HF was a randomized, active-controlled 24-week study comparing sacubitril/valsartan to IMT on NT-proBNP (change from baseline at 12 weeks), exercise capacity (6-minute walking distance [6MWD] at 24 weeks), and HF symptoms and physical limitations (change from baseline in KCCQ CSS at 24 weeks) in patients with HFpEF (N = 2566). In contrast to other trials in the sacubitril/valsartan development program, which did not restrict eligibility to a specific HF symptom/physical limitation extent, patients enrolled in PARALLAX-HF had to have a KCCQ clinical summary score <75 to be eligible for inclusion. Eligible patients were randomized to either sacubitril/valsartan at a target dose of 200 mg b.i.d. or IMT comparator in a 1:1 ratio based on the anti-RAAS treatment the patient was receiving prior to entering the study. The IMT comparators were enalapril 10 mg b.i.d., valsartan 160 mg b.i.d., or placebo b.i.d. for patients who were in the prior ACE inhibitor treatment stratum (N = 1066), the prior ARB treatment stratum (N = 1174), or the no prior RAAS inhibitor stratum (N = 326), respectively. In this trial, the investigators were encouraged but not required to increase the dose to the target dose of sacubitril/valsartan or IMT.

Sacubitril/valsartan was shown to be superior to IMT in reducing NT-proBNP at 12 weeks (relative reduction 16%; 2-sided p <0.0001), one of two primary endpoints and a biomarker of clinical interest in HF. There was no difference between the two groups with respect to the second primary endpoint of change from baseline in 6MWD at week 24 (sacubitril/valsartan mean change 9.7 m vs. IMT mean change 12.2 m; adjusted mean difference -2.5 m; 95% CI -8.5 m – 3.5 m; 2-sided p = 0.42). Of note, recently reported studies of other HF disease modifying therapies, such as empagliflozin and vericiguat, also have not shown benefits in improving this endpoint relative to placebo (Boehringer Ingelheim 2019; Armstrong PW 2020). There was an initial greater improvement among sacubitril/valsartan patients in change from baseline in KCCQ clinical summary score after 4 weeks of treatment (adjusted mean difference 1.5); however, after 24 weeks of treatment both groups had improved considerably and there was no significant difference between groups (sacubitril/valsartan mean change 12.3 vs. IMT 11.8; adjusted mean difference 0.5; 95% CI -0.9 – 2.0; 2-sided p = 0.48). Similarly, both groups had similar odds of experiencing a favorable change in investigator-reported NYHA functional class (OR = 0.98; 95% CI 0.81 – 1.18; p = 0.831). In line with renal findings of PARAGON-HF and PARADIGM-HF, sacubitril/valsartan patients experienced less decline in eGFR over this 24-week study (adjusted mean change -1.5 ml/min/1.73m^2) compared to the

IMT patients (adjusted mean change -2.6 ml/min/1.73m^2), a difference that was statistically significant (1.1 ml/min/1.73m^2; 95% CI 0.0 – 2.0 ml/min/1.73m^2; p = 0.016).

Adverse events were more frequently reported in the sacubitril/valsartan group than in the IMT group: (84.9%) vs. (80.2%), respectively. The majority of AEs were mild or moderate in severity, and there was no imbalance in the overall incidence of SAEs between the treatment groups (14.5% in the sacubitril/valsartan vs 14.9% in the IMT, respectively). The rate of death during the double-blind treatment epoch was low in both groups (sacubitril/valsartan 23 patients [1.8%] vs. IMT 17 patients [1.3%]). The small difference was mainly driven by non-cardiovascular deaths. Study treatment discontinuation due to AEs was low. Overall, the safety of sacubitril/valsartan in PARALLAX-HF was consistent with the known safety profile in previous studies.

Although it was not an efficacy objective in PARALLAX HF, the risk of experiencing a cardiac failure SAE (grouped MedDRA SMQ term) was lower in the sacubitril/valsartan group (39 events in 30 patients) than in the IMT group (61 events in 51 patients) (HR = 0.58; 95% CI 0.37 – 0.91). The lower risk of events with sacubitril/valsartan relative to IMT remained when patients who experienced investigator-reported CV deaths were combined with those who experienced cardiac failure SAEs (HR = 0.64; 95% CI 0.42 – 0.97). These findings are consistent with the results of PARAGON-HF in which the rate of worsening HF events in the sacubitril/valsartan group was lower compared with the valsartan group.

6.6 Benefit/Risk Evaluation

6.6.1 Benefits

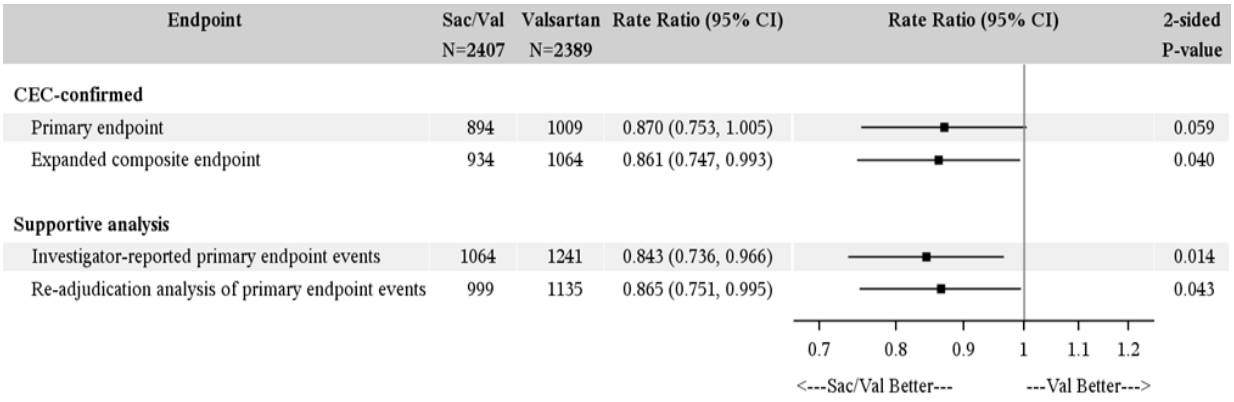
The totality of evidence supporting the registration of sacubitril/valsartan in HFpEF patients with LVEF below normal is based on the results from the phase 3 PARAGON-HF trial in HFpEF, supported by the confirmatory evidence from the Phase 3 PARADIGM-HF trial which established efficacy in the closely related approved indication of HFrEF, and the Phase 2 PARAMOUNT trial in HFpEF that provided mechanistic evidence of efficacy (reduced NT-proBNP and reversed left atrial remodeling).

PARAGON-HF is the largest completed Phase 3, randomized, double-blind, active controlled outcomes study in HFpEF, evaluating 4,822 symptomatic HFpEF patients. Patients were followed throughout the study for a median duration of 35 months with vital status known for all but 9 patients, indicating high quality of study execution and data completeness.

While the primary endpoint narrowly missed the threshold of statistical significance, the evidence of benefit for sacubitril/valsartan in PARAGON-HF is based on the consistent reduction in the rate of the CEC-confirmed primary endpoint of total HF hospitalizations and CV death and the pre-specified and supportive analyses, including the expanded composite endpoint including urgent HF visits, the investigator-reported primary endpoint, and the analysis of the primary endpoint incorporating the re-adjudicated CEC-unconfirmed HF hospitalizations. Adding clinically important HF events, these supportive analyses showed a magnitude of effect similar to the primary endpoint and achieved nominal p-values below the threshold for statistical significance supporting demonstration of a true treatment effect of sacubitril/valsartan in the overall study (Figure 6-12). According to these analyses, the

magnitude of the benefits of sacubitril/valsartan on the primary composite endpoint across the overall study population was a 13% to 16% rate reduction relative to valsartan.

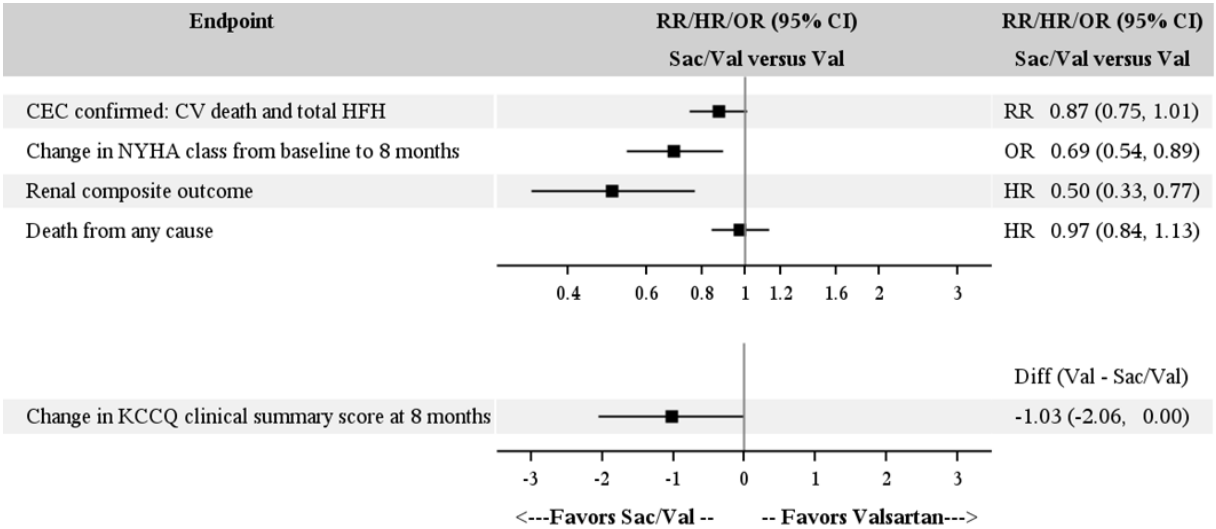
Figure 6-12 PARAGON-HF: Primary and expanded composite endpoint and analyses incorporating all investigator reported events and HF hospitalization re-adjudication analyses (FAS)



CEC = Clinical Endpoint Committee

In addition, secondary efficacy endpoints which assessed HF symptoms, physical limitations and functionality, as well as the risk of the composite renal endpoint, consistently favored sacubitril/valsartan compared to valsartan (Figure 6-13).

Figure 6-13 PARAGON-HF: Efficacy benefits for the primary and secondary endpoints (FAS)



CEC = Clinical Endpoint Committee; Diff = difference; HFH = heart failure hospitalization; HR = hazard ratio; NYHA = New York Heart Association; OR = odds ratio; Val = valsartan; Sac/Val = sacubitril/valsartan.
For NYHA, the treatment effect was expressed in terms of the odds for **unfavorable** NYHA class changes so that **favorable** changes for sacubitril/valsartan appear on the left side of the figure (note that 0.69 = 1/1.45)

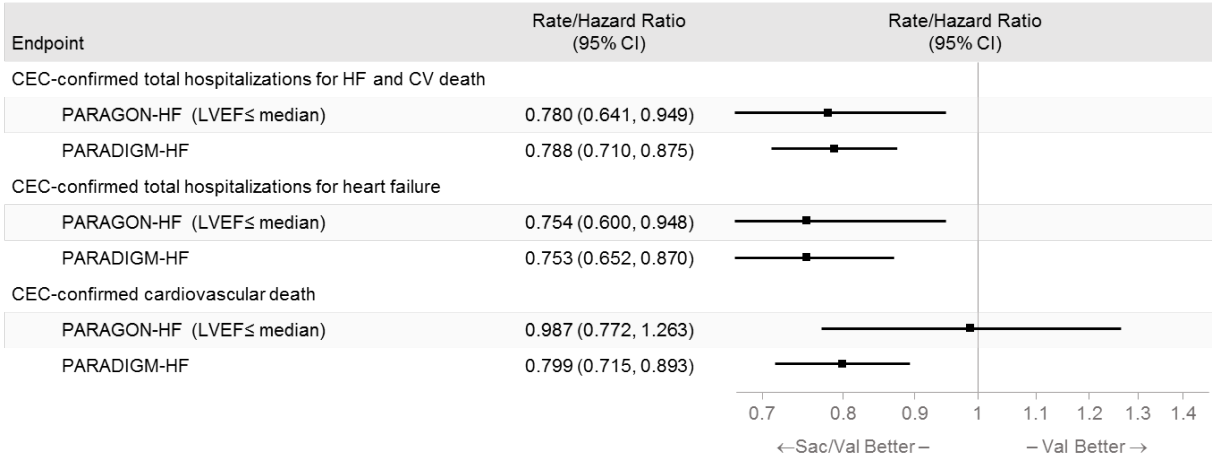
While not approved for treatment of HFpEF, ARBs, such as valsartan are thought to provide some benefits in reducing the rate of non-fatal HF outcomes compared to placebo (Böhm et al 2020). The treatment effects induced by sacubitril/valsartan in PARAGON-HF should therefore

be considered as incremental to the effect achieved by RAAS blockade with valsartan over placebo.

Taken together, the consistency of treatment effect in favor of sacubitril/valsartan compared to valsartan across the different supportive analyses of the primary endpoint achieving nominal p-values below the threshold for statistical significance and the consistent benefit across key secondary endpoints support the conclusion of a true, albeit modest, treatment effect of sacubitril/valsartan in the overall study population.

Importantly, patients with LVEF below normal experienced a greater and clinically relevant benefit with a 22% RRR in the CEC-confirmed primary composite endpoint (RR = 0.78; 95% CI 0.64 – 0.95), driven by a 25% RRR in total HF hospitalizations (RR = 0.75; 95% CI 0.60 – 0.95), and very similar reduction in total worsening HF including total HF hospitalizations and urgent HF visits (RR = 0.74; 95% CI 0.60 – 0.93). This translates into an absolute treatment benefit of 106 prevented HF hospitalizations in 1,000 HFpEF patients with LVEF below normal treated with sacubitril/valsartan instead of valsartan for three years (Table 6-15). The treatment effect of sacubitril/valsartan in HFpEF patients with LVEF below normal in reducing the rate of total HF hospitalizations and CV death is very similar to its effect in the adjacent HFrEF patient group enrolled in PARADIGM-HF, 21% RRR in total HF hospitalizations and CV death (RR = 0.79; 95% CI 0.71 – 0.87), which was driven in part by a 25% RRR in total HF hospitalizations (RR = 0.75; 95% CI 0.65 – 0.87) (Figure 6-14).

Figure 6-14 Recurrent primary composite endpoint and its components in HFpEF patients with LVEF ≤ the median in PARAGON-HF in comparison to the same endpoint in PARADIGM-HF HFrEF patients with LVEF ≤ 40%



CEC=Clinical Endpoint Committee; CI=confidence interval; Sac/Val=sacubitril/valsartan; Val=valsartan

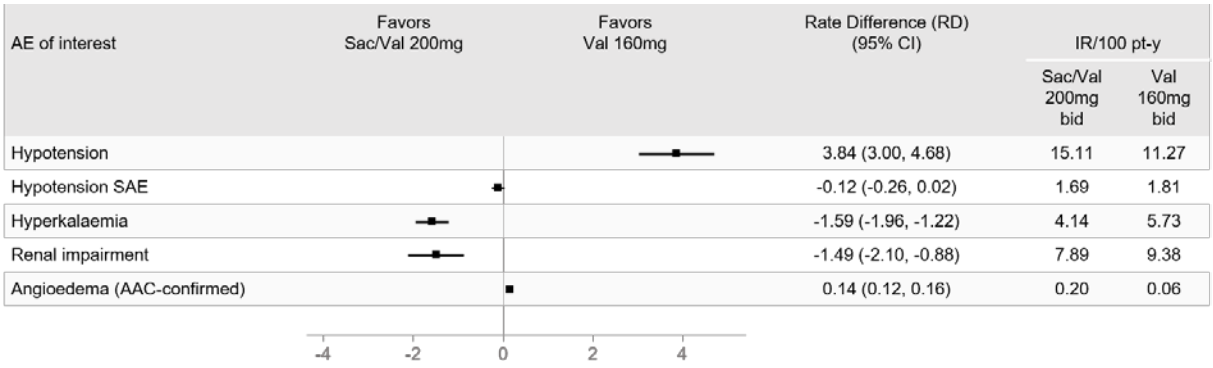
A pre-planned pooled analysis of the PARAGON-HF and PARADIGM-HF was conducted to assess the efficacy of sacubitril/valsartan across the entire LVEF continuum of heart failure. The results demonstrated that the benefits of sacubitril/valsartan extend beyond HFrEF up to the normal range of LVEF (~ 60%) (Figure 6-9), with women continuing to derive benefits to a higher LVEF than men (Figure 6-10). Similar observation of beneficial treatment effect above markedly reduced ejection fraction has also been recently described with other neurohormonal therapies in CHARM-Preserved and TOPCAT, with an attenuation of benefit relative to placebo

as LVEF increases. In addition, analyses from these studies have also observed that women derived benefit to a higher LVEF than men (Lund et al 2018; Solomon et al 2016).

6.6.2 Risks

Based on the well-understood mechanism of action and data from more than 23,600 patients across multiple randomized clinical studies in the sacubitril/valsartan development program, in addition to over 2.6 million patient-years of post-marketing safety data in HFrEF, the safety profile of sacubitril/valsartan is well characterized. The main safety risks for sacubitril/valsartan include hypotension, renal impairment, hyperkalemia and angioedema. While the incidence of mild and moderate hypotension was higher in the sacubitril/valsartan arm than in the valsartan arm in PARAGON-HF, the incidence of clinically relevant hypotension including SAEs and AEs leading to discontinuation was low and similar between treatment groups. The incidence of angioedema was low albeit numerically higher than that of valsartan. The majority of angioedema events were mild to moderate in severity, with no cases leading to airway compromise or death. The incidence of hyperkalemia and renal impairment was lower in patients treated with sacubitril/valsartan than those who received valsartan (Figure 6-15). These risks are manageable through current product labelling and standard CHF patient management. There was no relevant difference observed in the safety profile of any of the subgroups.

Figure 6-15 PARAGON-HF: Exposure-adjusted incidence rate of AEs of interest in Randomized treatment epoch (Safety Set)



AAC=angioedema adjudication committee; IR=incidence rate; Sac/Val=sacubitril/valsartan; pt-y=patient treatment years; RD=rate difference; Val=valsartan
- IR/100 pt-y: EAIR per 100 person-years is calculated by n (number of patients with events)/ total exposure time (in 100 years) of double-blind treatment, summed up from all patients in the treatment group. Exposure time is the duration from Day 1 to the 1st event for patients with at least one event or the duration of treatment in Randomized treatment epoch for patients with no event reported. Rate difference (RD) is based on IR.

Overall, the safety profile of sacubitril/valsartan in the HFpEF population was in line with the already known safety profile of ARBs like valsartan, and consistent with the safety profile in the HFrEF population. No new risks or meaningful changes in the rate or severity of the known adverse reactions were identified; thus, no changes in the safety labeling have been proposed.

6.7 Conclusion

Heart failure with preserved ejection fraction is a highly morbid and symptomatic condition in which patients experience frequent acute worsening HF events, generally characterized by severe dyspnea and breathlessness and often requiring inpatient hospitalization or the need for

immediate treatment in an urgent care setting to alleviate their worsening symptoms. Acute exacerbations of HFpEF are highly symptomatic events that have a significant impact on patient quality of life and their sense of wellbeing. These events are indicative of disease progression and are associated with an increased risk of hospitalization (or readmission) and subsequent death (Bello et al 2014).

Currently, there is no approved therapy for this disease. Increasing knowledge of HFpEF has led to the recognition of the heterogeneity of the population it encompasses, with the emergence of a patient phenotype characterized by mild systolic dysfunction at the lower end of the HFpEF LVEF range. International guidelines and the medical community have described this phenotype of HF as 'heart failure with mid-range ejection fraction', 'heart failure with mildly reduced ejection fraction', or 'heart failure with preserved ejection fraction, borderline'. Increasing evidence suggests that this group of patients may benefit from therapies proven effective in HFrEF (Nauta et al 2017).

PARAGON-HF was a large, well-designed and well-executed study which demonstrated that treatment with sacubitril/valsartan reduced the rate of the primary composite endpoint of CEC-confirmed total HF hospitalizations and CV death by 13% compared to valsartan, an effect driven primarily by a 15% reduction in the relative rate of total HF hospitalizations. Despite narrowly missing statistical significance on the primary analysis, the consistency of magnitude of benefit observed across the primary endpoint and its pre-specified and supportive analyses achieving nominal p-values below the threshold for statistical significance (treatment effect of 13 to 16% RRR) and directional consistency of clinically relevant secondary endpoint results (KCCQ, NYHA and renal endpoint) support a true treatment benefit in the overall study.

Importantly, HFpEF patients with LVEF below normal experienced substantially greater benefits and are therefore the proposed population to be indicated for treatment with sacubitril/valsartan. Specifically, these patients experienced a 22% RRR in total HF hospitalizations and CV death and a 26% RRR in total worsening HF (HF hospitalizations and urgent HF visits). In line with the recognition of an intermediate phenotype of HFpEF patients with mild systolic dysfunction, these clinically meaningful benefits are consistent with what was observed in the adjacent HFrEF population in which sacubitril/valsartan is indicated and recommended as first line therapy by international HF treatment guidelines. The results support that patients with LVEF below normal (up to approximately 60%) continue to observe benefit from sacubitril/valsartan in reducing the morbidity of heart failure.

The safety profile of sacubitril/valsartan in patients with HFpEF was in line with that of ARBs, and is consistent with the existing safety profile of sacubitril/valsartan in HFrEF. Safety is manageable through current product labelling and standard CHF patient management.

The results from PARAGON-HF, in the context of established effectiveness in HFrEF from PARADIGM-HF and pharmacodynamic and structural improvements observed in the Phase 2 study PARAMOUNT collectively provide substantial evidence of effectiveness consistent with the FDA guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Dec 2019)* and supports the extension of the indication for sacubitril/valsartan to HFpEF patients with LVEF below normal.

Sacubitril/valsartan has the potential to address an important unmet medical need in these HF patients who currently do not have treatment options to manage their disease, to enable them to feel well and remain out of the hospital. Novartis is appreciative of the opportunity to discuss this application with the Committee and looks forward to your input and guidance as to how best to communicate these benefits to physicians and patients.

7 References

[Abdul-Rahim AH, Shen L, Rush CJ et al 2018] Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. Eur J Heart Fail 2018;20:1139-1145.

[Ahmed A, Allman RM, Fonarow GC, et al (2008)] Incident heart failure hospitalization and subsequent mortality in chronic heart failure: A propensity-matched study. J Card Fail; 14(3):211-8.

[Anker SD, McMurray JJV (2012)] Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials? Eur Heart J; 33(22):2764-5.

[Armstrong PW (2020)] The VITALITY-HFpEF Trial (Evaluate the Efficacy and Safety of the Oral sGC Stimulator Vericiguat to Improve Physical Functioning in Daily Living Activities of Patients With Heart Failure and Preserved. Heart Fail Association of the European Society of Cardiology Annual Meeting Late breaker session. (Internet). Available at: < https://www.escardio.org/vgn-ext-templating/Sub-specialty-communities/Heart-Failure-Association-of-the-ESC-(HFA)/Research-and-Publications/HFA-Discoveries> (Accessed 3-Sep-2020).

[AstraZeneca (2020)] NCT03619213: Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) (Internet). Available from: <clinicaltrials.gov/ct2/show/NCT03619213?term=NCT03619213&draw=2&rank=1> (Accessed 13-Mar-2020).

[Benjamin EF, Muntner P, Alonso A et al (2019)] Heart disease and stroke statistics – 2019 update: A report from the American Heart Association. Circulation:139 e56-e528.

[Bello NA, Claggett B, Desai AS et al (2014)] Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. Circ Heart Fail. 2014;7(4):5909-595.

[Blanche C, Fumeaux T, Polikar R (2010)] Heart failure with normal ejection fraction (HFNEF): is it worth considering? Swiss Med Wkly;140:66–72.

[Boehringer Ingelheim (2019)] Boehringer Ingelheim and Lilly provide update on empagliflozin phase 3 exercise ability studies in chronic heart failure. (Internet). Available at: <wwwboehringer-ingelheim.com/print/245118> (Accessed 09-Jan-2020).

[Böhm M, Bewarder Y, Kindermann I (2020)] Ejection fraction in heart failure revisited - where does the evidence start? Eur Heart J; 41(25):2363-2365.

[Bradley EH, Curry L, Horwitz LI, et al (2013)] Hospital strategies associated with 30-day readmission rates for patients with heart failure. Circ Cardiovasc Qual Outcomes; 6:444-50.

[Campbell RT, Jhund PS, Castagno D et al (2012)] What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol; 60(23):2349-56.

[Campbell RT, Petrie MC, McMurray J (2018)] Redefining heart failure phenotypes based on ejection fraction. Eur J Heart Fail;20(12):1634-1635.

[Cao Z, Burrell LM, Tikkanen I, et al (2001)] Vasopeptidase inhibition attenuates the progression of renal injury in subtotal nephrectomized rats. Kidney Int;60(2):715-21.

[Cheng PP, Chambless LE, Shahar E, et al (2014)] Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study) Am J Cardiol. 2014;113:504–510.

[Cleland JGF, Tendera M, Adamus J, et al (2006)] The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J; 27(19):2338-45.

[Cohn J, Cleland JGF, Lubsen J, et al (2009)] Unconventional end points in cardiovascular clinical trials: should we be moving away from morbidity and mortality? J Card Fail; 15(3):199-205.

[Cowie MR, Anker SD, Cleland JGF, et al (2014)] Improving care for patients with acute heart failure: before, during and after hospitalization. ESC Heart Fail; 2:110-145.

[Cowling BJ, Hutton JL, Shaw JEH (2006)] Joint modeling of event counts and survival times. Appl Stat; 55(1):31-9

[Dewan P, Jackson A, Lam C et al (2020)] Interactions between left ventricular ejection fraction, sex and effect of neurohormonal modulators in heart failure. Eur J Heart Fail; 22(5):898-901.

[Dries DL, Exner DV, Domanski MJ, et al (2000)] The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardio;35(3): 681-9.

[Dunlay SM, Roger VL, Redfield MM (2017)] Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol; 14(10):591-602.

[Fry M, McLachlan S, Purdy S, et al (2016)] The implications of living with heart failure; the impact of everyday life, family support, co-morbidities and access to healthcare: a secondary qualitative analysis.

[Fryer RM, Segreti J, Banfor PN, et al (2008)] Effect of bradykinin metabolism inhibitors on evoked hypotension in rats: rank efficacy of enzymes associated with bradykinin-mediated angioedema. Br J Pharmacol; 153(5):947-55.

[Gerber Y, Weston SA, Redfield MM, et al (2015)] A contemporary appraisal of the heartfailure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med; 175(6): 996–1004.

[Ghosh D, Lin DY (2000)] Nonparametric analysis of recurrent events and death. Biometrics; 56:554–62.

[Go AS, Mozaffarian D, Roger VL, et al (2013)] Heart disease and stroke statistics – 2013 Update. A report from the American Heart Association. Circulation; 127:e6-e245.

[Gori M, Lam CSP, Gupta DK, et al (2014)] Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur J Heart Fail; 16:535-542.

[Hicks KA, Mahaffey KW, Mehran R, et al (2018)] 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. JACC; 71(9):1021-34.

[Humphrey L, Kulich K, Deschaseaux C (2013)] The Caregiver Burden Questionnaire for Heart Failure (CBQ-HF): face and content validity. Health and Quality of Life Outcomes; 11:84.

[Irons BK, Kumar A (2003)] Valsartan-Induced Angioedema. Ann Pharmacother; 37(7-8):1024-7.

[Jackon SL, Tong X, King R, et al (2018)] National burden of heart failure events in the United States, 2006 to 2014. Circ Heart Fail; 11(12):e004873.

[Jhund PS, Claggett B, Packer M, et al (2014)] Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. Eur J Heart Fail; 16(6):671-7.

[Judge P, Haynes R, Landray MJ, et al (2015)] Neprilysin inhibition in chronic kidney disease. Nephrol Dial Transplant; 30(5):738-43.

[Keulenaer GW, Brutsaert DL (2011)] Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation;123:1996–2005.

[Khan MS, Fonarow GC, Khan H, et al (2017)] Renin–angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Fail; 4: 402–408.

[Kostis WJ, Shetty M, Chowdhury YS, et al (2018)] ACE Inhibitor-Induced Angioedema: a Review. Curr Hypertens Rep;20(7):55.

[Kraigher-Krainer E, Shah AM, Gupta DK, et al (2014)] Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol; 63(5):447-56.

[Lang MR, Badano LP, Mor-Avi V, et al (2015)] 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; 28: 1-39.

[Lawless, J. F. (1987)]. Negative binomial and mixed Poisson regression. The Canadian Journal of Statistics, 15(3):209-225.

[Lenzen MJ, Scholte op Reimer WJM, Boersma E, et al (2004)] Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart FailureSurvey. Eur Heart J; 25(14):1214-20.

[Li D, McDonald CM, et al (2020)] Assessment of Treatment Effect With Multiple Outcomes in 2 Clinical Trials of Patients With Duchenne Muscular Dystrophy. JAMA Network Open;3(2):e1921306.

[Lin FY, Devereux RB, Roman MJ, et al (2008)] Cardiac chamber volumes, function, and mass as determined by 64-multidetector row computed tomography. JACC Cardiovasc Imging; 1(6):782-6.

[Lin DY, Wei LJ, Yang I, et al (2000)] Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc; B, 62:711–730.

[Lund LH and Benson L (2012)] Losartan vs candesartan for heart failure. JAMA; 308(4):336.

[Lund LH, Claggett B, Liu J, et al 2018] Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail;20:1230-1239.

[Lund LH (2018)] Heart Failure with Mid-range Ejection Fraction: Lessons from CHARM. Card Fail Rev; 4(2):70-2.

[Lund LH, Claggett B, Liu J, et al (2018)] Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J HF; 20(8):1230-1239.

[Maeder MT and Kaye DM (2009)] Heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol; 53(11):905-18.

[McMurray JJV, Packer M, Desai AS, et al (2014)] Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med; 371(11):993-1004.

[McMurray JJV, Solomon SD, Inzucchi SE, et al (2019b)] Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med; 381(21):1995-2008.

[McMurray J, Jackson AM, Lam C, et al (2020)] Effects of sacubitril/valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction. Circulation; 141(5):338-351.

[Mogensen UM, Gong J, Jhund PS, et al (2018)] Effect of sacubitril/valsartan on Recurrent Events in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). Eur J Heart Fail; 20(4):760-68.

[Nauta JF, Hummel YM, van Melle JP, et al (2017)] What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail;19:1569-1573.

[Neaton JD, Gray G, Zuckerman BD, et al (2005)] Key issues in end point selection for heart failure trials: composite end points. J Card Fail; 11(8):567-75.

[Okumura N, Jhund PS, Gong J, et al (2016)] Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF). Circulation; 133(23):225462.

[Pfeffer MA, Shah AM and Borlaug BA (2019)] Heart failure with preserved ejection fraction in perspective. Circ. Res.2019. 124: 1598-1671.

[Pitt B, Pfeffer MA, Assmann SF, et al (2014)] Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med; 370(15):1383-92.

[Pocock SJ, Ariti CA, Collier TJ, et al (2012)] The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J; 33(2):176-82.

[Ponikowski P, Voors AA, Anker SD, et al. (2016)] 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). Eur J Heart Fail; 18(8):891-975.

[Rigolli M and Whalley GA (2013)] Heart failure with preserved ejection fraction. J Geriatr Cardiol; 10: 369−376.

[Ristl R, Urach S, Rosenkranz G, Posch M et al (2019)]. Methods for the analysis of multiple endpoints in small populations: a review. J Biopharm Stat;29(1):1-29. doi:10.1080/10543406.2018.1489402.

[Rogers JK, Pocock SJ, McMurray JJ, et al (2014)] Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail; 16(1):33-40.

[Rubin, Donald (9 June 1987)]. Multiple imputation for nonresponse in surveys. Wiley Series in Probability and Statistics. doi:10.1002/9780470316696. ISBN 9780471087052.

[Savarese G and Lund HR (2017)] Global public health burden of heart failure. Card Fail Rev; 3(1):7-11.

[Shah AM, Clagett B, Loehr LR et al (2017)] Heart failure stages among older adults in the community: The atherosclerosis risk in communities study. Circul. 2017; 135: 224-240.

[Skali H, Dwyer EM, Goldstein R, et al (2014)] Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. Eur J Heart Fail; 16(5):560-5.

[Solomon SD, Claggett B, Lewis EF et al 2016] Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J;37:455-462.

[Solomon SD, Dobson J, Pocock S, et al (2007)] Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation; 116(13):1482-7.

[Solomon SD, Zile M, Pieske B, et al (2012)] The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure With Preserved Ejection Fraction: A Phase 2 Double-Blind Randomised Controlled Trial. Lancet; 280(9851):1387-95.

[Solomon SD, Claggett B, Lewis EF, et al. (2016)] Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J; 37(5):455-62.

[Solomon SD, McMurray JJV, Anand IS, et al. (2019)] Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med; 381(17):1609-20.

[Solomon SD, Vaduganathan M, Claggett BL, et al (2020)] Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation;141:352–361.

[Steinberg BA, Zhao X, Heidenreich PA, et al 2012] Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction. Circulation;126:65-75.

[Taal MW, Nenov VD, Wong W, et al (2001)] Vasopeptidase inhibition affords greater renoprotection than angiotensin-converting enzyme inhibition alone. J Am Soc Nephrol; 12(10):2051-9.

[The EchoNoRMAL Collaboration (2015)] Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function. The EchoNoRMAL Study. Echocardiographic normal ranges meta-analysis of the left heart collaboration. JACC Cardiovasc Imaging; 8(6):656-65.

[The SOLVD Investigators (1991)] Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med;325(5):293-302.

[Toh S, Reichman ME, Houstoun M, et al (2012)] Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med; 172(20):1582-9.

[Tsao CW, Lyass A, Enserro D, et al (2018)] Temporal trends in the incidence of and mortality associated With heart failure with preserved and reduced ejection fraction. JACC Heart Fail; 6(8):678-85.

[Virani SS, Alonso A, Benjamin E, et al (2020)] Heart disease and stroke statistics – 2020 update: A report from the American Heart Association. Circulation; 141(9):139-596.

[Yancy CW, Jessup M, Bozkurt B, et al (2013)] 2013 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;62:e147–239.

[Yancy CW, Jessup M, Bozkurt B, et al (2017)] 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; 136:e137–e161.

[Yusuf S, Pfeffer MA, Swedberg K, et al (2003)] Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet; 362(9386):777-81.

8 Appendix 1 Prior HFpEF studies: Treatment effect by LVEF in CHARM program and TOPCAT study

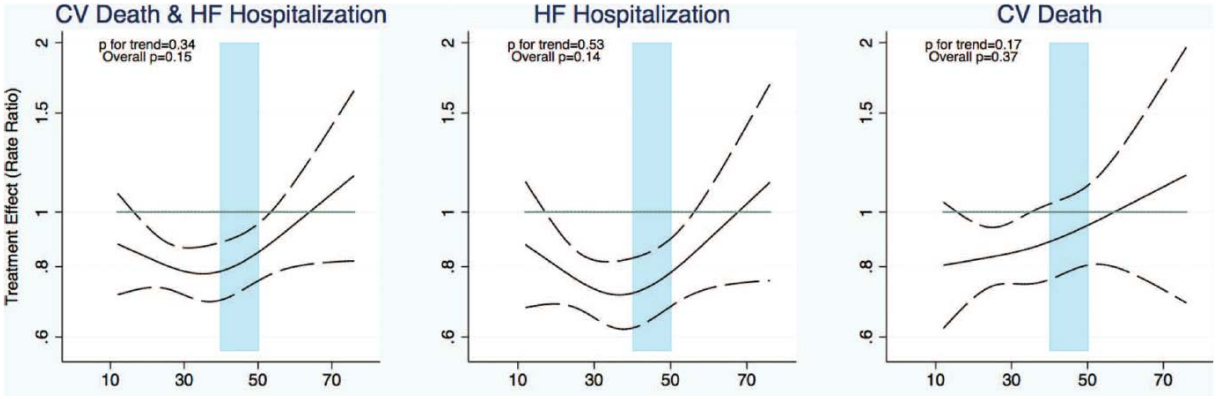
CHARM

A total of 7,598 patients were enrolled in the three studies of the CHARM program (CHARM-Added, CHARM-Alternative and CHARM-Preserved). A *post hoc* analysis evaluated the effect of candesartan compared to placebo across the spectrum of LVEF looking at differences in patient characteristics as well as treatment effect differences among the populations defined as HFrEF (LVEF ≤ 40%, n = 4,323), HF mid-range EF (LVEF 40 – 49%, n = 1,322) and HFpEF (LVEF ≥ 50%, n = 1,953) (Lund et al 2018). Interestingly, the population with an LVEF of 40 – 49% resembled the population with a LVEF ≤ 40% (HFrEF) regarding most characteristics including age, systolic blood pressure, gender, previous myocardial infarction and atrial fibrillation.

For the primary endpoint, time-to-first event for CV death or HF hospitalization, the unadjusted HR was 0.82 (95% CI 0.75 – 0.91), 0.76 (95% CI 0.61 – 0.96) and 0.95 (95% CI 0.79 – 1.14) for the 3 groups, LVEF ≤ 40%, 40 – 49%, and ≥ 50%, respectively.

Similarly, when looking at LVEF as a continuous variable, there was a declining effect of candesartan at higher LVEF values (Figure 8-1).

Figure 8-1 Effect of candesartan by ejection fraction as a continuous variable (CHARM program)

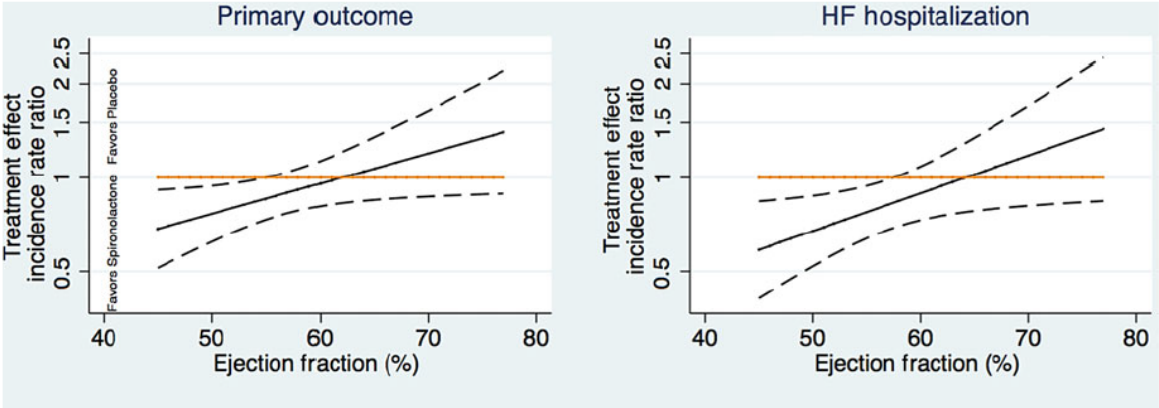


TOPCAT

Similar results are seen in the TOPCAT trial, which randomized 3,444 patients with HFpEF (LVEF ≥ 45%) to either spironolactone or placebo. Left ventricular ejection fraction modified the spironolactone treatment effect for the primary endpoint (time to first event of CV death, aborted cardiac arrest or HFH) ($p < 0.046$ for continuous LVEF-by-treatment interaction) and for HF hospitalization ($p < 0.039$ for continuous LVEF-by-treatment interaction), with stronger estimated benefits for spironolactone at the lower end of the LVEF range (Solomon et al 2016). The HR for the primary endpoint by LVEF category was as follows: LVEF < 50%, HR = 0.72 (95% CI 0.50 – 1.05); LVEF 50 – 54.99%, HR = 0.85 (95% CI 0.61 – 1.18), LVEF 55 – 59.99%, HR = 0.94 (95% CI 0.68 – 1.29); and LVEF ≥ 60%: HR = 0.97 (95% CI 0.76 – 1.23). An

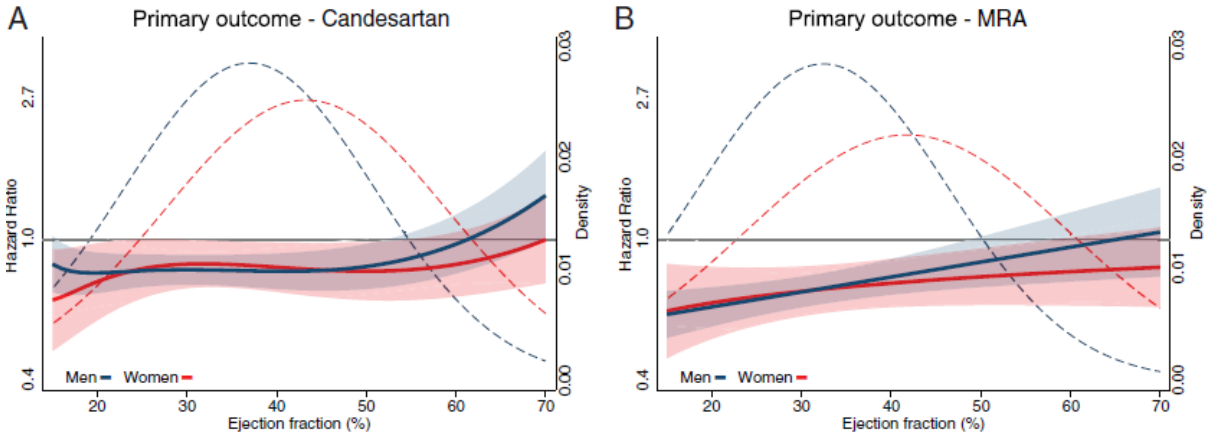
attenuation of the spironolactone treatment effect at higher LVEF values could be observed (Figure 8-2).

Figure 8-2 Effect of spironolactone by ejection fraction as a continuous variable (TOPCAT)



Thus, the results of both the CHARM program and those of TOPCAT are consistent with those observed in PARADIGM-HF and PARAGON-HF, all of which showed a greater effect of treatment in the lower LVEF range in HFpEF with an attenuation of that effect in the higher LVEF range.

9 Appendix 2 Treatment effect of candesartan and mineralocorticoid receptor antagonists on time to first CV death or heart failure hospitalization



Figures taken from Dewan et al 2020. Dotted curves show normalized distribution of LVEF in men (blue) and women (red). Solid lines show a continuous hazard ratio for the primary composite of CV death or HF hospitalizations. The shaded areas represent the 95% confidence intervals. Candesartan data are based on the CHARM program (candesartan vs. placebo). Mineralocorticoid (MRA) data are based on RALES, EMPHASIS-HF, and TOPCAT (MRA vs. placebo). Figures show that the treatment effect of candesartan and mineralocorticoid

receptor antagonists appears to be greatest in lower LVEF and diminishes as LVEF increases, but women appear to derive benefit from these treatments to a higher LVEF than men.

10 Appendix 3 Supportive Pharmacodynamic data for PARAGON-HF

Biomarkers related to the pathophysiology of HF or study drug mechanism of action were analyzed. NT-proBNP and high sensitivity Troponin T were analyzed as markers related to cardiac stress. Soluble ST2 (suppressor of tumorigenicity 2), PINP (aminoterminal propeptide of type 1 procollagen), PIIINP (N-terminal propeptide of type III procollagen), TIMP-1 (tissue inhibitor of metalloproteinases-1), and CITP (C-terminal telopeptide of type I collagen) were analyzed as markers related to fibrosis and cardiac remodeling. Urinary cGMP (cyclic guanosine monophosphate), a mediator of vasodilation, was analyzed as a mechanism of action marker for sacubitril/valsartan.

Table 10-1 summarizes the between treatment analysis results of NT-proBNP and other biomarkers at specified times during the double-blind period using Visit 101 or 102 (whichever occurred first) as baseline.

The ratio of NT-proBNP to baseline levels was approximately 19% and 17% lower in the sacubitril/valsartan group as compared to the valsartan group at Week 16 and Week 48 post-randomization, respectively (both 2-sided p<0.0001).

Table 10-1 Repeated measures analysis of biomarkers in PARAGON-HF (FAS)

		Sacubitril/Valsartan		Valsartan		Sac/Val vs. Val	
Visit	Biomarker	n	LSM of ratio: E/B Geometric Mean (95% CI)	n	LSM of ratio: E/B Geometric Mean (95% CI)	LSM of ratio: Sac/Val / Valsartan (95% CI)	p-value
Visit 203 (Week 16)	NT-proBNP	1345	0.76 (0.74, 0.79)	1315	0.95 (0.91, 0.98)	0.81 (0.77, 0.85)	<0.0001
	hsTnT	554	0.94 (0.92, 0.97)	540	1.04 (1.01, 1.06)	0.91 (0.88, 0.94)	<0.0001
	CITP	538	1.07 (1.05, 1.10)	528	1.03 (1.01, 1.06)	1.04 (1.01, 1.07)	0.0137*
	PINP	546	1.00 (0.98, 1.03)	532	1.02 (0.99, 1.04)	0.99 (0.95, 1.02)	0.4496
	PIIINP	546	1.02 (0.99, 1.04)	531	1.05 (1.03, 1.08)	0.97 (0.94, 1.00)	0.0378
	sST2	554	0.95 (0.94, 0.97)	537	1.00 (0.98, 1.02)	0.96 (0.93, 0.98)	0.0015
	TIMP-1	541	0.94 (0.92, 0.96)	529	1.02 (1.00, 1.04)	0.92 (0.90, 0.95)	<0.0001
	Urine cGMP	527	1.71 (1.61, 1.81)	513	0.94 (0.89, 1.00)	1.81 (1.67, 1.98)	<0.0001

		Sacubitril/Valsartan		Valsartan	Sac/Val vs. Val	
Visit	**Biomarker**	**n**	**LSM of ratio: E/B Geometric Mean (95% CI)**	**n**	**LSM of ratio: E/B Geometric Mean (95% CI)**	**LSM of ratio: Sac/Val / Valsartan (95% CI)**	**p-value**
	Urine cGMP/ Creatinine	526	1.70 (1.63, 1.76)	513	0.95 (0.91, 0.98)	1.79 (1.70, 1.88)	<0.0001
Visit 205 (Week 48)	NT-proBNP	1273	0.81 (0.77, 0.84)	1229	0.97 (0.93, 1.01)	0.83 (0.78, 0.89)	<0.0001
	hsTnT	520	0.97 (0.95, 1.00)	500	1.09 (1.06, 1.12)	0.89 (0.86, 0.93)	<0.0001
	CITP	499	1.11 (1.08, 1.14)	486	1.08 (1.05, 1.11)	1.03 (0.99, 1.07)	0.1365
	PINP	513	1.00 (0.97, 1.03)	495	1.02 (0.99, 1.06)	0.97 (0.93, 1.02)	0.2394
	PIIINP	509	1.01 (0.98, 1.04)	494	1.04 (1.01, 1.07)	0.97 (0.93, 1.01)	0.1195
	sST2	523	0.98 (0.96, 1.00)	499	1.02 (1.00, 1.04)	0.96 (0.94, 0.99)	0.0100
	TIMP-1	491	0.96 (0.94, 0.98)	470	1.02 (1.00, 1.04)	0.94 (0.91, 0.97)	<0.0001
	Urine cGMP	501	1.59 (1.49, 1.70)	474	0.95 (0.89, 1.01)	1.68 (1.53, 1.85)	<0.0001
	Urine cGMP/ Creatinine	499	1.67 (1.61, 1.73)	471	1.00 (0.93, 1.01)	1.72 (1.63, 1.82)	<0.0001

CI=confidence interval; E/B=endpoint/baseline ratio; LSM=least square mean
(1) Biomarker measurements are only performed for patients with V101/V102 samples available for analysis.
- The change from baseline in logarithmic scale is analyzed using a repeated measure ANCOVA model with treatment, region, visit, and 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 group. 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.