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Novartis PARAGON-HF analyses suggest Entresto® benefit beyond HFrEF

- *Entresto (sacubitril/valsartan) demonstrated greatest benefit in HFpEF patients with ejection fractions adjacent to HFrEF, compared to valsartan*[1]
- *Entresto, compared to valsartan, demonstrated reduced risk in total heart failure hospitalizations and cardiovascular death in women, compared to men*[2]
- *Among patients who had been previously hospitalized, those who were screened during or within 30 days of hospitalization showed the greatest treatment effect with Entresto, compared to valsartan*[3]
- *Safety and tolerability of Entresto, where evaluated, were consistent with previously reported findings*[1,2,4,5]
- *New analyses follow full results from the PARAGON-HF trial, which show overall treatment effect, despite narrow miss on statistical significance*[4]

Basel, November 17, 2019 — Novartis announced today new subgroup analyses from its global Phase III PARAGON-HF study of patients with heart failure with preserved ejection fraction (HFpEF), also known as diastolic heart failure[6]. The data suggest that, in specific subgroups, treatment with Entresto may result in greater reductions in heart failure hospitalizations and cardiovascular death, as compared to valsartan. This greater benefit was seen in women with HFpEF and in HFpEF patients recently hospitalized for heart failure[2,3]. In addition, in a pooled analysis of PARAGON-HF (HFpEF) and PARADIGM-HF (heart failure with reduced ejection fraction (HFrEF)), greater treatment benefit was observed in patients with left ventricular ejection fraction (LVEF) below approximately 60%[1]. HFpEF is a type of heart failure that has no currently approved treatment and disproportionately affects women[6-8]. These new analyses were presented at the American Heart Association's (AHA) Scientific Sessions 2019 with simultaneous publication of the gender analysis in *Circulation* and hospitalization analysis in the *Journal of the American College of Cardiology.*

Currently, Entresto (sacubitril/valsartan) is an approved and essential treatment for patients with HFrEF, which is typically defined as ejection fraction less than or equal to 40%[5,7,9-11]. This is based on its superiority to the angiotensin-converting enzyme (ACE) inhibitor enalapril in reducing cardiovascular death and heart failure hospitalizations, as demonstrated in the PARADIGM-HF trial[9,12,13].

The full results of the Phase III PARAGON-HF study were presented at ESC Congress 2019. The study showed a 13% relative reduction in the primary composite endpoint of cardiovascular death and total (first and recurrent) heart failure hospitalizations, but narrowly missed statistical significance[4].

“These new analyses show that the treatment benefit of sacubitril/valsartan may extend to patients with a LVEF higher than the threshold we use to define HFrEF,” said Scott Solomon, M.D., Director of Noninvasive Cardiology at Brigham and Women’s Hospital, Professor at Harvard Medical School and PARAGON-HF Executive Committee Co-Chair. “The data help to provide a greater understanding of the heterogeneous nature of HFpEF and the potential benefit of sacubitril/valsartan for those who are still in need of a treatment option.”

“This new research suggests that sacubitril/valsartan may provide greater benefit in HFpEF patients who have recently been hospitalized for heart failure and suggests the potential benefit of initiating treatment during the vulnerable period following hospitalization in order to reduce further events,” said John McMurray, M.D., Professor of Medical Cardiology at University of Glasgow and PARAGON-HF Executive Committee Co-Chair. “Understanding the correlation between time since hospitalization and treatment benefit may help inform optimization of care for patients with heart failure.”

“Novartis is committed to reimagining outcomes for people with cardiovascular disease and advancing our scientific understanding of heart failure,” said David Soergel, M.D., Global Head of Cardiovascular, Renal and Metabolic Drug Development at Novartis. “These new data, suggesting potential benefit of Entresto beyond HFrEF, represent our ongoing work to develop treatments for patients, including for HFpEF, a complex condition with high unmet patient need.”

About the PARAGON-HF subgroup analyses presented at AHA’s Scientific Sessions
Data from the Phase III PARAGON-HF (n=4,796 patients with heart failure with preserved ejection fraction (HFpEF)) and the PARADIGM-HF (n=8,399 patients with heart failure with reduced ejection fraction (HFrEF)) studies were combined in a pooled analysis to assess cardiovascular death and total heart failure hospitalization, evaluating the effect of Entresto compared with renin-angiotensin-aldosterone system (RAAS) inhibition among different left ventricular ejection fraction (LVEF) categories[1]. In the analysis of the combined groups, total heart failure hospitalizations and cardiovascular death were reduced in patients receiving Entresto compared with RAAS inhibition[1]. Cardiovascular death reduction was driven by the results of the patients with LVEF of 40% or less from the PARADIGM-HF trial[1]. These therapeutic effects of Entresto were stronger within subgroup populations of the study:

- The greatest treatment benefits were observed in patients with LVEF below approximately 60%[1]. Magnitude of reduction in heart failure hospitalizations, cardiovascular death and all-cause mortality decreased with increasing LVEF[1]. The all-cause mortality reduction was driven by the reduction in HFrEF patients[1].
- Treatment benefits persisted up to a higher level of LVEF in women compared with men[1].

A pre-specified subgroup analysis of PARAGON-HF assessed gender differences in heart failure hospitalization and cardiovascular death, compared to valsartan, among patients with HFpEF (n=4,796; 2,479 women and 2,317 men) [2]. In women, Entresto reduced the risk of total heart failure hospitalization, with a 33% relative rate reduction (95% CI: 15-47), and an absolute reduction of 4 events per 100 person-years. In men, there was a 7% relative rate increase in the Entresto group versus the valsartan group, with an absolute increase of 0.9 events per 100 person-years[2]. Men saw improved treatment benefits with Entresto in exploratory secondary endpoints including change in the New York Heart Association (NYHA) class and less worsening in quality of life based on KCCQ Clinical Summary Score at 8 months[2].

In a separate post-hoc analysis in patients from PARAGON-HF (n=4,796), the effect of Entresto on total heart failure hospitalizations and cardiovascular death was compared with that of valsartan, evaluating patients by the time from their last hospitalization[3]. The effect of Entresto on total heart failure hospitalizations and cardiovascular death was greatest among patients screened during or shortly after hospitalization[3]. Entresto was associated with a gradient of risk reduction ranging from patients hospitalized within 30 days of screening (rate ratio, 0.73; 95% CI: 0.53-0.99) to patients never hospitalized (rate ratio, 1.00; 95% CI: 0.80-1.24) [3]. Shorter times from prior heart failure hospitalization were associated with higher risk of total heart failure hospitalizations or cardiovascular death[3].

About PARAGON-HF
PARAGON-HF is the largest clinical trial in heart failure with preserved ejection fraction (HFpEF) conducted to date[14]. The Phase III randomized, double-blind, parallel group, active-controlled, 2-arm, event-driven trial compared the long-term efficacy and safety of Entresto versus valsartan in 4,822 patients with HFpEF[4,14]. The patients in the study represented ambulatory patients with established HFpEF being treated for symptoms and comorbidities, approximately half of whom had a history of heart failure hospitalizations[4]. Results showed a 13% relative reduction in the primary composite endpoint compared to valsartan of total (first and recurrent) heart failure hospitalizations and cardiovascular death, narrowly missing statistical significance (RR=0.87; 95% CI: 0.75, 1.01; p=0.06) [4]. Absolute rate reduction was 1.8 events per 100 person-years. More pronounced effects on the primary endpoint were observed for certain pre-defined subgroups: individuals with an ejection fraction less than or equal to the median of 57% (22% relative reduction; RR=0.78; 95% CI: 0.64, 0.95) (absolute rate reduction = 6.6 events per 100 person-years) and women (27% relative reduction; RR=0.73; 95% CI: 0.59, 0.9) (absolute rate reduction = 3.9 events per 100 person-years) as well as in investigator-reported (non-adjudicated) events (16.3% relative reduction; RR=0.84; 95% CI: 0.74, 0.97) (absolute rate reduction = 2.7 events per 100 person-years) [4].

Secondary endpoint analyses, exploratory in nature, showed that Entresto patients experienced less worsening in quality of life than valsartan patients based on KCCQ Clinical Summary Score (CSS) at 8 months. Change in the New York Heart Association (NYHA) class was also more favorable in the Entresto group than in the valsartan group. Additionally, treatment with Entresto resulted in a reduction in the risk of the composite renal endpoint. No difference in all-cause mortality was observed between groups[4].

Safety and tolerability analyses found:

- Entresto was safe and well tolerated in HFpEF patients, largely as observed in heart failure with reduced ejection fraction (HFrEF) patients in PARADIGM-HF[4,5].
- Hypotension occurred more frequently with Entresto (n=2407; 15.8%) than with valsartan (n=2389;10.8%)[4].
- Overall incidence of confirmed angioedema events was low in the two treatment arms, with 14 events in the Entresto arm (0.6%) and 4 events in the valsartan arm (0.2%); no angioedema events resulted in airway compromise[4].
- Entresto resulted in lower rates of worsening renal function (1.4% versus 2.7% compared to valsartan); and serious adverse events of hyperkalemia compared to valsartan (0.8% versus 1.8%)[4].

PARAGON-HF follows PARAMOUNT-HF, the Phase II trial in HFpEF. Additional studies investigating Entresto on other relevant endpoints in HFpEF are ongoing.

About Entresto for heart failure with reduced ejection fraction
Entresto is a twice-a-day medicine that reduces the strain on the failing heart[12]. It does this by enhancing the protective neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS) [12,15]. Other common heart failure medicines, called angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), only block the harmful effects of the overactive RAAS. Entresto contains the neprilysin inhibitor sacubitril and the ARB valsartan[12,16].

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction[12]. In the United States, Entresto is indicated for the treatment of heart failure (New York Heart Association class II-IV) in patients with systolic dysfunction[16]. It has been shown to reduce the rate of cardiovascular death, heart failure hospitalization and 30-day hospital readmission compared to enalapril, to reduce the rate of all-cause mortality compared to enalapril, and to improve aspects of health-related quality of life (including physical and social activities) compared to enalapril[5,11,17]. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB[12]. Approved indications may vary depending upon the individual country.

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References

1. Solomon S, Packer M, Rouleau J, et al. Effect Of Sacubitril/Valsartan Across The Spectrum Of Ejection Fraction In Heart Failure. Data presented at: AHA Scientific Sessions 2019, Nov 16-18; Philadelphia, USA.
2. McMurray J, Lam C, McGrath M, et al. Effects Of Sacubitril/Valsartan In Women Compared To Men With Heart Failure And Preserved Ejection Fraction. *Circulation.* 2019.
3. Vaduganathan M, Claggett B, Desai A, et al. Prior Heart Failure Hospitalization, Clinical Outcomes, and Response to Sacubitril/Valsartan Compared with Valsartan in HFpEF. *JACC* 2019. doi: 10.1016/j.jacc.2019.11.003.
4. Solomon S, McMurray J, Anand I, et al. Angiotensin-Neprilysin in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019;381:1609-1620. doi: 10.1056/NEJMoa1908655.
5. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004. doi: 10.1056/NEJMoa1409077.
6. Yancy C, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2013;62(16):e147-e239. doi: 10.1016/j.jacc.2013.05.019.
7. Ponikowski P, Voors A, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129–2200. doi:10.1093/eurheartj/ehw128.
8. Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). June 2019. Available at: https://www.fda.gov/media/128372/download. Accessed July 17, 2019.
9. Seferovic P, Ponikowski P, Anker S, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21(10);1169-1186. doi: 10.1002/ejhf.1531.

10. Velazquez E, Morrow D, DeVore, A, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med*. 2019;380:539-548. doi: 10.1056/NEJMoa1812851.
11. Chandra A, Lewis E, Claggertt B, et al. The Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Heart Failure Patients: The PARADIGM-HF Trial. *JAMA Cardiol*. 2018;3(6):498-505. doi: 10.1001/jamacardio.2018.0398.
12. EMA. Entresto (sacubitril/valsartan). Summary of product characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004062/WC500197536.pdf. Accessed July 2019.
13. Yancy C, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137-161. doi: 10.1161/CIR.0000000000000509.
14. Solomon S, Rizkala A, Gong J, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail*. 2017;5(7):471-482. doi: 10.1016/j.jchf.2017.04.013.
15. Langenickel T, Dole W. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today*. 2012;9(4):e131-139. doi: 10.1016/j.ddstr.2013.11.002.
16. ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2019.
17. Desai A, Claggett B, Packer M, et al. Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization. *JACC*. 2016;68(3):241-248. doi: 10.1016/j.jacc.2016.04.047.

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