

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG**Entresto improved measures of heart structure and function in HFrEF patients in new Novartis study; additional data complement findings**

- *Results from PROVE-HF trial show significant improvements in measures of cardiac structure and function at six months and one year in heart failure with reduced ejection fraction (HFrEF) patients¹; EVALUATE-HF results complement findings²*
- *PROVE-HF establishes significant correlation between improvement in widely used cardiac biomarker and positive changes in heart structure and ability to pump blood in patients taking Entresto¹*
- *Safety and tolerability of Entresto were comparable to previously reported findings^{1,2,3}*

Basel, September 2, 2019 – Novartis announced today results from two new clinical trials evaluating improvement in heart structure and function and long-term safety of Entresto® (sacubitril/valsartan) in patients with heart failure with reduced ejection fraction (HFrEF). Results suggest that Entresto, an essential treatment for HFrEF, not only positively impacts a biomarker shown to be associated with prognosis of clinical outcomes in HFrEF, but also that the effect is associated with significant improvement in the structural and functional changes, known as cardiac remodeling, that occur with this disease¹⁻¹¹. Safety and tolerability were similar to that in previously reported studies^{1,2,3}.

Cardiac remodeling impairs the heart's ability to pump blood to the body and leads to poor prognosis⁹. Therefore, a positive impact on cardiac remodeling may be important in the treatment of HFrEF as it may result in reversed damage to the heart, which can lead to improved clinical outcomes^{9,12}. These data are the first to demonstrate that Entresto improved heart structure and function, indicative of reversal of cardiac remodeling, and that this improvement is correlated with positive changes in a biomarker^{1,2}. These results, which further support Entresto as a first-choice treatment for HFrEF, were presented as late-breakers at the ESC Congress 2019, the annual meeting of the European Society of Cardiology (ESC) and published in *Journal of the American Medical Association*^{1-5,8}.

“The PROVE-HF and EVALUATE-HF studies provide the first evidence that Entresto may help reverse the damage to the heart caused by HFrEF, which could lead to improved clinical outcomes,” said Marcia Kayath, M.D., Global Head Medical Affairs and Chief Medical Officer, Novartis Pharmaceuticals. “As part of our commitment to reimagining heart failure treatment, we conducted these studies to more deeply understand Entresto’s impact on heart structure and function in HFrEF patients. For the first time, an association was shown between a biomarker and cardiac remodeling improvements in patients treated with Entresto.”

The Phase IV, 52-week, single-arm, open-label PROVE-HF trial showed that treatment with Entresto significantly improved levels of an important biomarker shown to be associated with prognosis of clinical outcomes in HFrEF, N-terminal pro-B-type natriuretic peptide (NT-proBNP), which was linked for the first time to significant improvements in left ventricular remodeling and echocardiographic measures of cardiac structure and function^{1,10,11}. Importantly, the study demonstrated this association between improvement in this biomarker and these positive changes indicative of reversal of cardiac remodeling at six months and one year¹. The study found Entresto’s safety and tolerability to be

largely consistent with that seen in the pivotal PARADIGM-HF trial with the exception of dizziness, which was reported more frequently in PROVE-HF^{1,3}.

Novartis also conducted the Phase IV, multicenter, randomized, double-blind, active-controlled EVALUATE-HF trial to examine Entresto's effect on remodeling of the blood vessels of the heart and ventricular-vascular coupling – a measure of the mechanical efficiency of the heart – compared with enalapril². The study, also presented at ESC Congress 2019, showed that neither Entresto nor enalapril improved the primary endpoint of change in aortic impedance (a measure of vascular stiffness)². It is possible that the short length of the study, as well as the specific patient population, which may already have experienced a degree of improved aortic impedance, may have contributed to this outcome². However, consistent with the findings in PROVE-HF, the study showed that Entresto improved the structure and function of the left ventricle – the chamber that pumps blood to the rest of the body – compared to enalapril, and safety was comparable to that seen in PARADIGM-HF^{1,2,3}.

Entresto is indicated for the treatment of patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure^{13,21}.

About the PROVE-HF Trial

Seven hundred and ninety-four patients with HFrEF, NYHA Class II-IV, were treated in the Phase IV, single-arm, multicenter, open-label PROVE-HF trial in the United States, of which 654 (82.4%) completed the 52-week study¹. From baseline to 12 months, statistically significant correlations were observed between change in NT-proBNP and change in structural cardiac measurements — the primary endpoint of the trial¹. Results showed a clinically and statistically significant reduction in NT-proBNP of 30% from baseline by day 14 (median [interquartile range] NT-proBNP at baseline was 816 [332, 1822] pg/mL), which was maintained throughout 12 months (37% decrease from baseline at 12 months)¹. Clinically and statistically significant improvements were observed in all echocardiographic parameters (LVEF, LAVi, LVEDVi, LVESVi and E/e') at 12 months¹. LVEF increased from a median of 28.2% to 37.8% (difference, 9.4% [8.8, 9.9%]; P <.001), while LVEDVi decreased from a median of 86.93 to 74.15 mL/m² (difference, -12.25 [-12.92, -11.58]; P <.001) and LVESVi decreased from a median of 61.68 to 45.46 mL/m² (difference, -15.29 [-16.03, -14.55]; P <.001)¹. LAVi and E/e' ratio also decreased significantly¹.

Significant correlation was found between change in concentration of NT-proBNP and change in structural cardiac measurements from baseline to six months, with strength of association less than that seen at one year¹. Improvement in all echocardiographic measures was evident at six months, but was more pronounced at one year¹. Among three prespecified subgroups, correlations between change in NT-proBNP and cardiac volume and function were similar to the group as a whole, as was quantitative improvement in cardiac structure and function¹.

Safety and tolerability analyses found:

- Frequency of adverse events was generally consistent with PARADIGM-HF, with the exception of dizziness (16.8% in PROVE-HF vs. 6% in PARADIGM-HF)^{1,3}.
- 65% of patients achieved the target dose of Entresto, 97/103 mg BID, at some point during the 52-week study¹.
- Frequency of positively adjudicated angioedema was low, occurring in only two patients (0.3%), which were resolved with antihistamines or no therapy¹.

About the EVALUATE-HF Trial

Four hundred and sixty-four patients were randomized in the Phase IV, prospective, randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, forced-titration 12-week EVALUATE-HF trial². No statistically significant difference was shown between Entresto and enalapril in the primary endpoint of change from baseline in aortic characteristic impedance at 12 weeks (-2.9 vs -0.7 dyne-sec/cm⁵)².

Entresto improved several structural and functional echocardiographic measures versus enalapril at 12 weeks, including²:

- Left atrial volume index (-2.8 mL/m²; 95% CI: -4.0, -1.6)
- Mitral E/e' ratio (-1.8; 95% CI: -2.8, -0.8)
- Left ventricular end systolic volume index (-1.6 mL/m²; 95% CI: -3.1, -0.03)
- Left ventricular end diastolic volume index (-2.0 mL/m²; 95% CI: -3.7, -0.3)

No significant between-group differences were observed for global longitudinal strain, mitral e' velocity, left ventricular ejection fraction, and ventricular-vascular coupling (Ea/Ees) at 12 weeks².

Safety and tolerability analyses found:

- Frequency of adverse events was generally consistent with PARADIGM-HF and similar between treatment groups^{2,3}.
- 83% of patients achieved the target dose of sacubitril/valsartan 97/103 mg BID².
- One positively-adjudicated angioedema case occurred in the enalapril treatment group².
- One death occurred in each treatment group during the double-blind 12-week period of the study².

About the Novartis Commitment to Heart Failure

Sacubitril/valsartan (approved as Entresto[®] since 2015) is a first-choice treatment in heart failure with reduced ejection fraction (HFrEF), based on superiority it showed in PARADIGM-HF trial to the angiotensin-converting enzyme (ACE) inhibitor enalapril and its ability to significantly reduce cardiovascular death and HFrEF hospitalizations^{3,4,5,8,13}. Entresto plays a critical role in helping people with HFrEF from being hospitalized for heart failure, a disease which has a staggering economic burden, estimated to be \$108 billion globally on an annual basis (accounting for both direct and indirect costs)^{14,15}.

Novartis undertook the largest global clinical program in the heart failure disease area across the pharmaceutical industry to date, called FortiHFy. The program comprises over 40 active or planned clinical studies designed to generate an array of additional data on symptom reduction, efficacy, quality of life benefits and real-world evidence with Entresto, as well as to extend understanding of heart failure.

Through the Entresto scientific program, Novartis is reimagining the standard of care for HFrEF patients and the use of Entresto as a first-choice therapy in HFrEF, as well as Entresto as a therapy in other cardiovascular diseases^{3,4,5,8}.

About NT-proBNP

NT-proBNP is a biomarker commonly used to assess the severity and prognosis of heart failure¹⁰. Levels of NT-proBNP increase when heart muscle cells are subjected to stress (such as stretching) that occurs in people with heart failure¹⁰. Studies suggest that heart failure patients with elevated NT-proBNP are at an increased risk of cardiovascular death or heart failure hospitalization and that reducing levels of NT-proBNP in people with heart failure can be associated with a lower risk of these negative clinical outcomes^{10,11}. Entresto was also shown to reduce plasma NT-proBNP levels compared with enalapril in the PIONEER-HF and PARADIGM-HF trials^{3,6}.

About PARADIGM-HF

PARADIGM-HF was a randomized, double-blind, Phase III study evaluating the efficacy and safety profile of Entresto versus enalapril (a widely studied ACE inhibitor) in 8,442 patients with HFrEF³. The baseline characteristics showed the patients enrolled were typical HFrEF patients with NYHA Class II-IV heart failure³. PARADIGM-HF was specifically designed to see if Entresto could detect a relative reduction of 15% in the risk of cardiovascular mortality.³ Patients received Entresto or enalapril in addition to recommended therapy³. The primary endpoint was a composite of time to first occurrence of either cardiovascular death or heart failure hospitalization. PARADIGM-HF was the largest heart failure study ever done¹⁶.

About Heart Failure

Heart failure (HF) is a chronic and progressive condition, which impacts 26 million people worldwide¹⁴. About half of people with HF have heart failure with reduced ejection fraction (HFrEF), also known as systolic HF^{4,14}. Reduced ejection fraction means the heart does not contract with enough force, so

less blood is pumped out^{17,18,19}. HF presents a major and growing global health-economic burden that currently exceeds \$108 billion annually, which accounts for both direct and indirect costs¹⁵.

About Entresto

Entresto is a twice-a-day medicine that reduces the strain on the failing heart¹³. 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)^{13,20}. 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 Nephilysin inhibitor sacubitril and the ARB valsartan¹³.

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction¹³. In the United States, Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction^{13,21}. 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^{3,7,22}. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB^{13,21}. Approved indications may vary depending upon the individual country.

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About Novartis

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References

1. Januzzi J, Prescott M, Butler J, et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA*. 2019. doi:10.1001/jama.2019.12821.
2. Desai A, Solomon S, Shah A, et al. Effect of Sacubitril-Valsartan Versus Enalapril on Aortic Stiffness in Patients with Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA*. 2019;322(11). doi:10.1001/jama.2019.12843.
3. 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.
4. Ponikowski P, Voors A, Anker S, 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.
5. 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. doi: 10.1002/ejhf.1531.
6. Velazquez E, Morrow D, DeVore A, et al., Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med*. 2018. doi: 10.1056/NEJMoa1812851.
7. Chandra A, Lewis E, Claggert 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.
8. Yancy C, Jessup M, Butler J, 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.
9. Poelzl G, Frick M, Lackner B, et al. Chronic heart failure is associated with vascular remodeling of the brachial artery. *Eur J Heart*. 2005;7(1):43-48.
10. Ndumele C, Matsushita K, Sang Y, et al. NT-proBNP and Heart Failure Risk Among Individuals With and Without Obesity: The ARIC Study. *Circulation*. 2016;133:631-638.
11. Chow S, Maisel A, Anand I, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: A scientific statement from the American Heart Association. *Circulation*. 2017;135:e1054-e1091.
12. Almulleh A, Marbach J, Chih S, et al. Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients. *Am J Cardiovasc Dis*. 2017;7(6):108-113.
13. 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.
14. Savarese G and Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017 Apr; 3(1):7-11.
15. Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. *Int J Cardiol*. 2014;171:368-376.
16. McMurray J, Packer M, Desai A, et al. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014;16:817-825.
17. Yancy C, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;128:e240-e327.
18. Owan T, Hodge D, Herges R, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259.
19. Ejection Fraction Heart Failure Measurement. American Heart Association Website. http://www.heart.org/HEARTORG/Conditions/HeartFailure/SymptomsDiagnosisofHeartFailure/Ejection-Fraction-Heart-Failure-Measurement_UCM_306339_Article.jsp. Updated March 24, 2015. Accessed November 1, 2018.
20. Langenickel T, Dole W. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today*. 2012;4: e131-139.
21. ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; November 2018.

22. 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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