

## Entresto improved measures of heart structure and function in HFrEF patients in new Novartis study; additional data complement findings

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- - 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) patients;(1) EVALUATE-HF results complement findings(2)
- - 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 Entresto(1)
- - Safety and tolerability of Entresto were comparable to previously reported findings(1,2,3)

EAST HANOVER, N.J., Sept. 2, 2019 /PRNewswire/ -- 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 disease.<sup>1-11</sup> Safety and tolerability were similar to that in previously reported studies.<sup>1,2,3</sup>

Cardiac remodeling impairs the heart's ability to pump blood to the body and leads to poor prognosis.<sup>9</sup> 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.<sup>9,12</sup> 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.<sup>1,2</sup> 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.<sup>1-5,8</sup>

"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.<sup>1,10,11</sup> 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 year.<sup>1</sup> 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.<sup>1,3</sup>

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 enalapril.<sup>2</sup> 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).<sup>2</sup> 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 outcome.<sup>2</sup> 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.<sup>1,2,3</sup>

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.<sup>13</sup>

### 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 study.<sup>1</sup> 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 trial.<sup>1</sup> 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).<sup>1</sup> Clinically and statistically significant improvements were observed in all echocardiographic parameters (LVEF, LAVi, LVEDVi, LVESVi and E/e') at 12 months.<sup>1</sup> 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/m<sup>2</sup> (difference, -12.25 [-12.92, -11.58]; P <.001) and LVESVi decreased from a median of 61.68 to 45.46 mL/m<sup>2</sup> (difference, -15.29 [-16.03, -14.55]; P <.001).<sup>1</sup> LAVi and E/e' ratio also decreased significantly.<sup>1</sup>

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 year.<sup>1</sup> Improvement in all echocardiographic measures was evident at six months, but was more pronounced at one year.<sup>1</sup> 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 function.<sup>1</sup>

### 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).<sup>1,3</sup>
- 65% of patients achieved the target dose of Entresto, 97/103 mg BID, at study endpoint during the 52-week study.<sup>1</sup>

- Frequency of positively adjudicated angioedema was low, occurring in only two patients (0.3%), which were resolved with antihistamines or no therapy.<sup>1</sup>

#### 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 trial.<sup>2</sup> 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/cm<sup>5</sup>).<sup>2</sup>

Entresto improved several structural and functional echocardiographic measures versus enalapril at 12 weeks, including:<sup>2</sup>

- Left atrial volume index (-2.8 mL/m<sup>2</sup>; 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/m<sup>2</sup>; 95% CI: -3.1, -0.03)
- Left ventricular end diastolic volume index (-2.0 mL/m<sup>2</sup>; 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 weeks.<sup>2</sup>

Safety and tolerability analyses found:

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

#### About the Novartis Commitment to Heart Failure

Sacubitril/valsartan (approved as Entresto<sup>®</sup> 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.<sup>3,8,13</sup> 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).<sup>14,15</sup>

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.<sup>3,4,5,8</sup>

#### About NT-proBNP

NT-proBNP is a biomarker commonly used to assess the severity and prognosis of heart failure.<sup>10</sup> Levels of NT-proBNP increase when heart muscle cells are subjected to stress (such as stretching) that occurs in people with heart failure.<sup>10</sup> 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.<sup>10,11</sup> Entresto was also shown to reduce plasma NT-proBNP levels compared with enalapril in the PIONEER-HF and PARADIGM-HF trials.<sup>3,6</sup>

#### 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 HFrEF.<sup>3</sup> The baseline characteristics showed the patients enrolled were typical HFrEF patients with NYHA Class II-IV heart failure.<sup>3</sup> PARADIGM-HF was specifically designed to see if Entresto could detect a relative reduction of 15% in the risk of cardiovascular mortality.<sup>3</sup> Patients received Entresto or enalapril in addition to recommended therapy.<sup>3</sup> 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 done.<sup>16</sup>

#### About Heart Failure

Heart failure is a chronic and progressive condition, which impacts approximately 6 million Americans and is one of the leading causes of hospitalization among Americans over the age of 65.<sup>17,18,19</sup> About half of people with heart failure have heart failure with reduced ejection fraction (HFrEF), also known as systolic heart failure.<sup>20,21</sup> Reduced ejection fraction means the heart does not contract with enough force, so less blood is pumped out.<sup>22</sup> Heart failure presents a major and growing health-economic burden that exceeds \$30 billion in the United States, which accounts for both direct and indirect costs.<sup>23</sup>

#### About Entresto

Entresto is a prescription medicine used to reduce the risk of cardiovascular death and heart failure hospitalization in people with certain types of long-lasting (chronic) heart failure (HFrEF).<sup>13</sup> Entresto is usually used with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB) therapy.<sup>13</sup> Entresto is a twice-a-day prescription medicine that works by enhancing the beneficial neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS).<sup>13,24</sup> Most other heart failure medicines only block the harmful effects of the overactive RAAS. Entresto contains the neprilysin inhibitor sacubitril and the ARB valsartan.<sup>13</sup> Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg and 97/103 mg (sacubitril/valsartan).<sup>13</sup> These doses are referred to as 50 mg, 100 mg and 200 mg in the clinical trial literature including The New England Journal of Medicine publication of the results of PARADIGM-HF.<sup>3</sup> The target maintenance dose of Entresto is 97/103 mg twice daily as tolerated by the patient.<sup>13</sup>

#### IMPORTANT SAFETY INFORMATION

Entresto can harm or cause death to an unborn baby. Patients should talk to their doctor about other ways to treat heart failure if they plan to become pregnant. If a patient gets pregnant while taking Entresto, she should tell her doctor right away.

Patients are not to take Entresto if they are allergic to sacubitril or valsartan or any of the ingredients in Entresto; have had an allergic reaction including swelling of the face, lips, tongue, throat or trouble breathing while taking a type of medicine called an ACE inhibitor or ARB; or take an ACE inhibitor medicine. Patients are not to take Entresto for at least 36 hours before or after they take an ACE inhibitor medicine. Patients should talk with their doctor or pharmacist before taking Entresto if they are not sure if they take an ACE inhibitor medicine. Patients are not to take Entresto if they have diabetes and take a medicine that contains aliskiren.

Before they take Entresto, patients should tell their doctor about all of their medical conditions, including if they have kidney or liver problems; or a history of hereditary angioedema; are pregnant or plan to become pregnant; are breastfeeding or plan to breastfeed. Patients should either take Entresto or breastfeed. They should not do both.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. They should especially tell their doctor if they take potassium supplements or a salt substitute; nonsteroidal anti-inflammatory drugs (NSAIDs); lithium; or other medicines for high blood pressure or heart problems such as an ACE inhibitor, ARB, or aliskiren.

Entresto may cause serious side effects including serious allergic reactions causing swelling of the face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death. Patients are to get emergency medical help right away if they have symptoms of angioedema or trouble breathing. Patients are not to take Entresto again if they have had angioedema while taking Entresto. People who are black or who have had angioedema may have a higher risk of having angioedema if they take Entresto. Entresto may cause low blood pressure (hypotension). Patients are to call their doctor if they become dizzy or lightheaded, or they develop extreme fatigue. Entresto may cause kidney problems or an increased amount of potassium in the blood.

The most common side effects were low blood pressure, high potassium, cough, dizziness, and kidney problems.

Please see full Prescribing Information, including Boxed WARNING available at <http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf>.

Patients are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.

Novartis is committed to providing patients with affordable access and resources through Entresto Central. For more information, please call 1-888-ENTRESTO or visit [www.entresto.com](http://www.entresto.com).

#### Disclaimer

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