

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG**Novartis PARAGON-HF trial suggests Entresto® benefit in HFpEF patients but narrowly misses primary endpoint**

- *Entresto (sacubitril/valsartan) reduced the composite of total (first and recurrent) heart failure hospitalizations and cardiovascular death although narrowly missed statistical significance ($p = 0.059$)¹*
- *Totality of evidence, including improvement in various measures of symptoms, quality of life, and renal function, suggests clinically important benefits in HFpEF¹*
- *Entresto was well tolerated and the overall safety profile was comparable to previous findings in HFrEF patients¹*

Basel, September 1, 2019 – Novartis announced today full results from its global Phase III PARAGON-HF study, investigating the efficacy and safety of Entresto (sacubitril/valsartan) versus the active comparator valsartan in heart failure patients with preserved ejection fraction (HFpEF). Entresto reduced the composite primary endpoint of total (first and recurrent) heart failure hospitalizations and cardiovascular (CV) death by 13 percent ($p = 0.059$)¹. The result was primarily driven by a nearly 15 percent reduction ($p = 0.056$) in total heart failure hospitalizations (first and recurrent)¹.

The full body of evidence from the trial suggests that treatment with Entresto may result in clinically important benefits in HFpEF, a heterogeneous type of heart failure with no approved treatment, in particular subgroups^{2,3}. Pre-specified subgroup analyses suggest even greater effects in individuals with a left ventricular ejection fraction equal to or below the median of 57% (22 percent reduction in primary endpoint; 95% CI: 0.641, 0.949) and in women (27.5 percent reduction in primary endpoint; 95% CI: 0.588, 0.895)¹. Safety and tolerability were consistent with previously reported findings in HFrEF patients¹. Currently, Entresto is an approved and essential treatment for patients with HFrEF, which is typically defined as ejection fraction less than 40%^{2,4-7}. These results were presented at the ESC Congress 2019, the annual meeting of the European Society of Cardiology, and published in *The New England Journal of Medicine*¹.

“Novartis is proud of PARAGON-HF’s significant contribution to the body of scientific evidence in HFpEF. This study highlights the critical need for treatment options for this complex disease,” said David Soergel, M.D., Global Head of Cardiovascular, Renal and Metabolic Drug Development at Novartis. “Novartis is committed to reimagining heart failure treatment, and our next step is to further explore these results from PARAGON-HF. We also look forward to continuing conversations with clinical experts and regulators to determine next steps.”

“While the reduction in the primary endpoint was not statistically significant, the totality of evidence from PARAGON-HF suggests potential overall benefit of sacubitril/valsartan compared with valsartan in HFpEF, particularly in patients with ejection fraction below normal. It also highlights the complexity of HFpEF and may suggest that some treatments have a more pronounced impact in certain patient groups, including women, who are more likely to

suffer from this condition than men,” said Scott Solomon, M.D., Director of Noninvasive Cardiology at Brigham and Women’s Hospital, Professor, Harvard Medical School, and PARAGON-HF Executive Committee Co-Chair.

“PARAGON-HF provides a wealth of data that will advance our understanding of HFpEF and the patients it affects,” said John McMurray, M.D., Professor of Medical Cardiology at University of Glasgow and PARAGON-HF Executive Committee Co-Chair. “When considered in the context of the PARADIGM-HF trial, it is not surprising that sacubitril/valsartan might have a greater treatment effect in HFpEF patients with an ejection fraction in the lower part of the range we studied in PARAGON-HF.”

Sacubitril/valsartan (approved as Entresto® since 2015) is a first-choice and essential treatment in HFrEF^{2,4-7}, based on its superiority to the angiotensin-converting enzyme (ACE) inhibitor enalapril and its ability to significantly reduce CV death and HF hospitalizations^{5,8,9}.

About PARAGON-HF

PARAGON-HF is the largest clinical trial in heart failure with preserved ejection fraction (HFpEF) conducted to date¹⁰. 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 HFpEF¹⁰. 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^{1,10}. Results showed a 13% reduction in the primary composite endpoint of total (first and recurrent) heart failure hospitalizations and cardiovascular death, narrowly missing statistical significance (RR=0.870; 95% CI: 0.753, 1.005; p=0.059). More pronounced effects on the primary endpoint were observed for additional pre-defined subgroups, including individuals with an ejection fraction less than or equal to the median of 57% (22% reduction; RR=0.780; 95% CI: 0.641, 0.949) and women (27.5% reduction; RR=0.725; 95% CI: 0.588, 0.895) as well as in investigator-reported (non-adjudicated) events (15.7% reduction; RR=0.843; 95% CI: 0.736, 0.966; p=0.0140)¹.

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 significant reduction in the risk of the composite renal endpoint. No difference in all-cause mortality was observed between groups¹.

Safety and tolerability analyses found:

- Entresto was safe and well tolerated in HFpEF patients, largely as observed in HFrEF patients in PARADIGM-HF.
- Hypotension occurred more frequently with Entresto (23.2%) than with valsartan (17%), but rates of discontinuation due to hypotension were similar (2.4% and 2.3%, respectively).
- Overall incidence of confirmed angioedema events was low in the two treatment arms, with 15 events in the Entresto arm (0.58%) and 4 events in the valsartan arm (0.17%); no angioedema events resulted in airway compromise or death.
- Entresto resulted in lower rates of renal dysfunction and hyperkalemia compared to valsartan, as well as lower rates of discontinuation of study medication due to these events¹.

PARAGON-HF follows the only positive, previously announced, Phase II trial in HFpEF, PARAMOUNT-HF, which demonstrated that Entresto reduced NT-proBNP (a biomarker of cardiac strain) to a greater extent than valsartan at 12 weeks and was associated with improvement in NYHA class at 36 weeks. Additional studies investigating Entresto on other relevant endpoints in HFpEF are ongoing^{11,12}.

About Heart Failure

Heart failure (HF) is a progressive and serious condition, affecting approximately 26 million people worldwide, where the heart cannot pump enough blood to the body^{2,13,14}. There are two distinct types of heart failure: preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF)¹⁵.

About HFpEF

HFpEF is a distinct type of heart failure where the heart muscle contracts normally but the ventricles do not relax as they should during ventricular filling (or when the ventricles relax)¹⁶. HFpEF can be associated with high hospitalization rates, poor quality of life and increased mortality¹⁷, and it is emerging as the predominant form of HF¹⁸. There is currently no approved treatment for HFpEF^{2,3}.

About HFrEF

HFrEF is a certain type of long-lasting heart failure, also known as systolic HF^{19,20}. HFrEF means the heart does not contract with enough force, so less blood is pumped out¹⁶. There are approved treatment options for people living with HFrEF^{2,21}.

About Entresto for Heart Failure with Reduced Ejection Fraction (HFrEF)

Entresto is a twice-a-day medicine that reduces the strain on the failing heart⁸. 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)^{8,22}. 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^{8,23}.

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction⁸. In the United States, Entresto is indicated for the treatment of heart failure (New York Heart Association class II-IV) in patients with systolic dysfunction²³. 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^{4,7,24}. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB^{8,23}. Approved indications may vary depending upon the individual country.

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This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “next steps,” “to date,” “could,” “investigating,” “ongoing,” “emerging,” “suggests,” “may,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Entresto, or regarding potential future revenues from Entresto. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Entresto will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Entresto will be commercially successful in the future. In particular, our expectations regarding Entresto could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost

containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach more than 750 million people globally and we are finding innovative ways to expand access to our latest treatments. About 108,000 people of more than 140 nationalities work at Novartis around the world. Find out more at www.novartis.com.

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