

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG**Novartis provides update on Phase III PARAGON-HF trial in heart failure patients with preserved ejection fraction (HFpEF)**

- *PARAGON study narrowly misses statistical significance on the primary endpoint; overall safety profile confirmed*
- *Totality of evidence suggests potential clinically important benefit; results will be presented in September at the ESC Congress 2019, the annual meeting of the European Society of Cardiology (ESC)*
- *Novartis plans to engage in conversations with clinical experts and regulators on next steps*

Basel, July 29, 2019 – Novartis today announced topline results from the global Phase III PARAGON-HF study, investigating the safety and efficacy of sacubitril/valsartan versus the active comparator valsartan in HFpEF patients¹. The trial narrowly missed statistical significance for its composite primary endpoint of reducing cardiovascular death and total heart failure hospitalizations¹. Safety and tolerability were consistent with previously reported sacubitril/valsartan data¹.

“Around half of all heart failure patients, some 13 million people worldwide, are estimated to suffer from HFpEF, and there is currently no approved treatment. We embarked upon the landmark Phase III PARAGON-HF trial to determine whether sacubitril/valsartan could have a meaningful impact on the treatment of HFpEF, as it does in the treatment of heart failure with reduced ejection fraction,” said John McMurray, M.D., Professor of Medical Cardiology at University of Glasgow and PARAGON-HF Executive Committee Co-Chair.

“We look forward to presenting and discussing the data from PARAGON-HF, which should inform our understanding and treatment of HFpEF, at the ESC Congress 2019,” said Scott Solomon, M.D., Professor of Medicine at Harvard Medical School and Brigham and Women’s Hospital, and PARAGON-HF Executive Committee Co-Chair.

“The totality of evidence from the trial suggests that treatment with sacubitril/valsartan may result in clinically important benefits in HFpEF. We will be discussing potential next steps with clinical experts and regulators while we prepare to present the full results at the ESC Congress 2019 in September,” said John Tsai, M.D., Global Drug Development and Chief Medical Officer, Novartis, “We thank the patients, investigators and site personnel around the world for their support during the PARAGON-HF study.”

There is currently no approved treatment for HFpEF^{2,3}. Sacubitril/valsartan (approved as Entresto® since 2015) is a first-choice treatment in heart failure with reduced ejection fraction (HFrEF), based on its superiority to the angiotensin-converting enzyme (ACE) inhibitor enalapril and its ability to significantly reduce CV death and HFrEF hospitalizations^{4,5,6}. Novartis continues to study sacubitril/valsartan in HFrEF, with new data on cardiac remodeling being presented at the ESC Congress 2019. Detailed PARAGON-HF results will also be

reported at that time. Additional studies investigating sacubitril/valsartan on other relevant endpoints in HFpEF are ongoing^{8,9}.

About PARAGON-HF

PARAGON-HF is the largest clinical trial in heart failure with preserved ejection fraction (HFpEF) conducted to date⁷. The Phase III randomized, double-blind, parallel group, active-controlled, 2-arm, event-driven trial compared the long-term efficacy and safety of sacubitril/valsartan versus valsartan in 4,822 patients with HFpEF⁷. 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^{1,7}. The primary endpoint of the trial is the composite of total (first and recurrent) heart failure hospitalizations and cardiovascular death⁷. PARAGON-HF is part of FortiHFy, the largest global clinical program in the heart failure disease area across the pharmaceutical industry to date. Established by Novartis, the FortiHFy program comprises more than 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 sacubitril/valsartan, as well as to extend understanding of heart failure.

PARAGON-HF follows the only positive Phase II trial in HFpEF, PARAMOUNT-HF, which demonstrated that sacubitril/valsartan 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 sacubitril/valsartan on other relevant endpoints in HFpEF are ongoing^{8,9}.

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^{2,10,11}. There are two distinct types of heart failure: preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF)¹².

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)¹³. HFpEF can be associated with high hospitalization rates, poor quality of life and increased mortality¹⁴, and it is emerging as the predominant form of HF¹⁵. 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^{16,17}. HFrEF means the heart does not contract with enough force, so less blood is pumped out¹³. There are approved treatment options for people living with HFrEF^{2,5}.

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

Entresto is a twice-a-day medicine that reduces the strain on the failing heart⁴. 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)^{4,18}. 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^{4,19}.

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction⁴. In the United States, Entresto is indicated for the treatment of heart failure (New York Heart Association class II-IV) in patients with systolic dysfunction¹⁹. 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^{20,21,22}. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB^{4,19}. Approved indications may vary depending upon the individual country.

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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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