

**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 patients<sup>1</sup>. The trial narrowly missed statistical significance for its composite primary endpoint of reducing cardiovascular death and total heart failure hospitalizations<sup>1</sup>. Safety and tolerability were consistent with previously reported sacubitril/valsartan data<sup>1</sup>.

“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<sup>2,3</sup>. Sacubitril/valsartan (approved as Entresto<sup>®</sup> 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<sup>4,5,6</sup>. 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<sup>8,9</sup>.

#### **About PARAGON-HF**

PARAGON-HF is the largest clinical trial in heart failure with preserved ejection fraction (HFpEF) conducted to date<sup>7</sup>. 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 HFpEF<sup>7</sup>. 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<sup>1,7</sup>. The primary endpoint of the trial is the composite of total (first and recurrent) heart failure hospitalizations and cardiovascular death<sup>7</sup>. 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.<sup>8,9</sup>

#### **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<sup>2,10,11</sup>. There are two distinct types of heart failure: preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF)<sup>12</sup>.

#### **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)<sup>13</sup>. HFpEF can be associated with high hospitalization rates, poor quality of life and increased mortality<sup>14</sup>, and it is emerging as the predominant form of HF<sup>15</sup>. There is currently no approved treatment for HFpEF<sup>2,3</sup>.

#### **About HFrEF**

HFrEF is a certain type of long-lasting heart failure, also known as systolic HF<sup>16,17</sup>. HFrEF means the heart does not contract with enough force, so less blood is pumped out<sup>13</sup>. There are approved treatment options for people living with HFrEF<sup>2,5</sup>.

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

Entresto is a twice-a-day medicine that reduces the strain on the failing heart<sup>4</sup>. 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)<sup>4,18</sup>. 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<sup>4,19</sup>.

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction<sup>4</sup>. 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<sup>19</sup>. 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<sup>20,21,22</sup>. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB<sup>4,19</sup>. Approved indications may vary depending upon the individual country.

### **Disclaimer**

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 “plans,” “next steps,” “to date,” “could,” “continues,” “being presented,” “look forward,” “will,” “investigating,” “ongoing,” “planned,” “emerging,” “potential,” “expectations,” “suggests,” “may,” “prepare,” 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](http://www.novartis.com).

Novartis is on Twitter. Sign up to follow @Novartis at <http://twitter.com/novartis> or follow @NovartisNews for the latest media releases and updates at <https://twitter.com/novartisnews> For Novartis multimedia content, please visit [www.novartis.com/news/media-library](http://www.novartis.com/news/media-library) For questions about the site or required registration, please contact [media.relations@novartis.com](mailto:media.relations@novartis.com)

### **References**

1. Novartis data on file.
2. Ponikowski P, Voors A, 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.
3. 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.
4. 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](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004062/WC500197536.pdf). Accessed July 2019.
  5. Yancy C, Jessup M, 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.
  6. Seferovic P, Ponikowski P, 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.
  7. Solomon S, Rizkala A, 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.
  8. Solomon S, Zile M, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380(9851):1387-1395. doi: 10.1016/S0140-6736(12)61227-6.
  9. Ndumele C, Matsushita K, et al. NT-proBNP and Heart Failure Risk Among Individuals With and Without Obesity: The ARIC Study. *Circulation*. 2016;133:631-638. doi: 10.1161/CIRCULATIONAHA.115.017298.
  10. What is Heart Failure? American Heart Association. Website. [http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/What-is-Heart-Failure\\_UCM\\_002044\\_Article.jsp#.WvB9T6iPKyJ](http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/What-is-Heart-Failure_UCM_002044_Article.jsp#.WvB9T6iPKyJ). Updated March 7, 2018. Accessed July 20, 2019.
  11. Savarese G, Lund L. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3(1):7-11. doi: 10.15420/cfr.2016:25:2.
  12. Borlaug B, Redfield M. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation*. 2011;123(18):2006-214. doi: 10.1161/CIRCULATIONAHA.110.954388.
  13. Ejection Fraction Heart Failure Measurement. American Heart Association. Website. <https://www.heart.org/en/health-topics/heart-failure/diagnosing-heart-failure/ejection-fraction-heart-failure-measurement>. Published March 24, 2015. Accessed July 17, 2019.
  14. Dunlay S, Roger V, et al. Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*. 2017;14:591-602. doi: 10.1038/nrcardio.2017.65.
  15. Oktay A, Rich J, et al. The Emerging Epidemic of Heart Failure with Preserved Ejection Fraction. *Curr Heart Fail Rep*. 2013;10(4):401-410. doi:10.1007/s11897-013-0155-7.
  16. Yancy C, Jessup M, 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.
  17. Owan T, Hodge D, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259. doi: 10.1056/NEJMoa052256.
  18. 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.
  19. ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; November 2018.
  20. Desai A, Claggett B, 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.
  21. McMurray J, Packer M, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004. doi: 10.1056/NEJMoa1409077.
  22. Chandra A, Lewis E, 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.

###

**Novartis Global External Communications**

E-mail: [media.relations@novartis.com](mailto:media.relations@novartis.com)

Peter Züst

Sophia Hosseini

Novartis Global External Communications  
+41 61 324 6383 (direct)  
[peter.zuest@novartis.com](mailto:peter.zuest@novartis.com)

Novartis Division Communications  
+44 7920 467679 (mobile)  
[sophia.hosseini@novartis.com](mailto:sophia.hosseini@novartis.com)

Eric Althoff  
Novartis US External Communications  
+1 646 438 4335  
[eric.althoff@novartis.com](mailto:eric.althoff@novartis.com)

**Novartis Investor Relations**

Central investor relations line: +41 61 324 7944  
E-mail: [investor.relations@novartis.com](mailto:investor.relations@novartis.com)

Central  
Samir Shah +41 61 324 7944  
Pierre-Michel Bringer +41 61 324 1065  
Thomas Hungerbuehler +41 61 324 8425  
Isabella Zinck +41 61 324 7188

North America  
Richard Pulik +1 862 778 3275  
Cory Twining +1 862 778 3258