New analysis shows Novartis Entresto improves glycemic control in reduced ejection fraction heart failure patients with diabetes

- New post-hoc analysis of PARADIGM-HF data demonstrates Entresto lowered levels of HbA1c (a measure of glycemic control) by 0.26% vs. 0.16% for ACE-inhibitor enalapril in heart failure with reduced ejection fraction (HFrEF) patients who also had diabetes

- New use of insulin was also reduced by 29% among patients taking Entresto compared to enalapril-treated patients

- Up to 40% of HFrEF patients have diabetes, which is associated with worse cardiovascular outcomes

- New analysis presented today at the American College of Cardiology (ACC) Annual Scientific Session and published in The Lancet Diabetes & Endocrinology

Basel, March 18, 2017 – Novartis announced today results of a new post-hoc analysis in a subgroup of patients with reduced ejection fraction heart failure (HFrEF) and diabetes suggesting that Entresto® (sacubitril/valsartan) tablets improved glycemic control, as assessed by hemoglobin A1c (HbA1c) testing, compared to ACE-inhibitor enalapril. HFrEF is also known as systolic heart failure (HF). Entresto is indicated to reduce the risk of cardiovascular (CV) death and hospitalization for HF in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction. It is not indicated to treat diabetes.

Entresto lowered HbA1c levels – a measure of average blood glucose levels for the past two to three months – after one year of treatment for HF, and this effect was sustained over three years of study follow-up. In the analysis, new use of insulin therapy or oral diabetes agents was also reduced in the Entresto group. The findings are based on data from PARADIGM-HF, the largest clinical trial ever conducted in HF, and are simultaneously being presented today at the American College of Cardiology (ACC) 66th Annual Scientific Session & Expo in Washington, D.C. and published in The Lancet Diabetes & Endocrinology.

"Diabetes is a major risk factor in heart failure and is strongly linked to progression of the disease, putting heart failure patients at increased risk of hospitalization and death," said Scott Solomon, MD, Director of Noninvasive Cardiology, Brigham and Women's Hospital, Professor of Medicine, Harvard Medical School, and senior author of the publication. "This analysis suggests that, in addition to the proven heart failure benefits demonstrated in PARADIGM-HF, Entresto may also help tighten glycemic control among heart failure patients with diabetes."

An analysis was conducted of 3,778 HFrEF patients in the PARADIGM-HF trial who were diagnosed with diabetes or had a baseline HbA1c ≥6.5% without a reported diagnosis at screening (98% of patients assessed had type 2 diabetes). The investigators compared the effects of Entresto vs. enalapril on glycemic control by measuring patients' HbA1c levels at screening and at one-, two-, and three-year follow-up visits, and by evaluating patients' initiation of oral antihyperglycemic or insulin therapy during the study.
This post-hoc analysis found that Entresto decreased HbA1c levels by 0.26% during the first year of follow-up, compared to a 0.16% reduction with enalapril (p=0.0023)\(^1\). Over three years, HbA1c levels remained persistently lower in patients treated with Entresto compared to enalapril, with an overall reduction of 0.14% (95% CI [0.06, 0.23]; p=0.0055)\(^1\). In addition, 29% fewer Entresto-treated patients initiated insulin therapy to achieve glycemic control (114 (7%) vs. 153 (10%) patients, HR 0.71, 95% CI, 0.56-0.90; p=0.0052)\(^1\). Entresto was shown to reduce the risk of CV death or HF hospitalization compared with enalapril among patients with or without diabetes at baseline\(^1,6,7\).

“These results show that in addition to its compelling cardiovascular efficacy, Entresto may have important metabolic benefits for HFrEF patients with diabetes,” said Vasant Narasimhan, Global Head, Drug Development and Chief Medical Officer, Novartis. “We are excited about these results and committed to improving our understanding of the benefits of Entresto in different heart failure patient populations.”

**About Heart Failure**

Heart failure (HF) is a debilitating and life-threatening condition, which impacts more than 60 million people worldwide\(^8\). It is the leading cause of hospitalization in people over the age of 65\(^8,9,10\). About half of people with HF have heart failure with reduced ejection fraction (HFrEF)\(^1\). Reduced ejection fraction means the heart does not contract with enough force, so less blood is pumped out\(^12\). HF presents a major and growing health-economic burden that currently costs the world economy $108 billion every year, which accounts for both direct and indirect costs\(^9,13\).

Novartis has established the largest global clinical program in the HF disease area across the pharma industry to date, FortiHFy, comprising 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 Entresto, as well as to extend understanding of heart failure.

**About Entresto**

Entresto is a twice-a-day medicine that reduces the strain on the failing heart. 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)\(^4,14\). Other HF medicines only block the harmful effects of the overactive RAAS\(^6\). Entresto contains the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan\(^6\).

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF). In the United States, Entresto is indicated to reduce the risk of cardiovascular (CV) death and hospitalization for HF in patients with chronic HF (NYHA class II-IV) and reduced ejection fraction\(^14\). Entresto is usually administered in conjunction with other HF therapies, in place of an ACE inhibitor or other angiotensin receptor blocker (ARB). Approved indications may vary depending upon the individual country.

**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\(^15,16\). The baseline characteristics showed the patients enrolled were typical HFrEF patients with NYHA Class II-IV heart failure. PARADIGM-HF was specifically designed to see if Entresto could decrease CV mortality by at least 15% vs. enalapril. Patients received Entresto or enalapril in addition to current best treatment regimen\(^15\). The primary endpoint was a composite of time to first occurrence of either CV death or HF hospitalization, and is the largest HF study ever done\(^15\).
Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "suggests," "may," "suggesting," "excited," "committed," "growing," or similar terms, or by express or implied discussions regarding potential 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 the current beliefs and expectations of management 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 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, management's 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; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; safety, quality or manufacturing issues, 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 provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References
4. Entresto Prescribing Information.


### Novartis Media Relations
Central media line: +41 61 324 2200
E-mail: media.relations@novartis.com

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Agnes Estes
Novartis Global Pharma communications
+41 61 324 1986 (direct)
+41 79 644 1062 (mobile)
agnes.estes@novartis.com

### Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: 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 +1 212 830 2448