

## MEDIA RELEASE • MEDIA RELEASE • MEDIA RELEASE

**Novartis' new heart failure medicine LCZ696 cuts cardiovascular deaths by 20% vs. ACE-inhibitor in landmark PARADIGM-HF trial**

- *Study showed significantly more HF-REF (heart failure with reduced ejection fraction) patients on LCZ696 regimen were alive, had fewer hospitalisations than those given enalapril regimen<sup>1</sup>*
- *On all-cause mortality, LCZ696 doubled the effect that enalapril, an ACE-inhibitor, showed vs. placebo when added to current best treatment for HF-REF<sup>1,2</sup>*
- *900,000 people in the UK live with heart failure (HF) and HF admissions are projected to rise by 50% over the next 25 years<sup>3</sup>*
- *HF has a poor prognosis: Around 60% of patients in the UK diagnosed with HF die within 5 years<sup>4</sup>*

**Frimley, August 30, 2014** – Today at the European Society of Cardiology congress and published simultaneously in the New England Journal of Medicine, Novartis revealed that its investigational heart failure medicine, LCZ696, was superior to ACE-inhibitor enalapril on key endpoints in the largest heart failure study ever done<sup>1,5</sup>. In PARADIGM-HF patients with heart failure with reduced ejection fraction (HF-REF) who were given LCZ696 were more likely to be alive and less likely to have been hospitalised for sudden deterioration of their heart failure than those given ACE-inhibitor enalapril<sup>1</sup>. Patients received LCZ696 or enalapril on top of current best treatment.

The magnitude of benefits with LCZ696 against enalapril in HF-REF patients was highly statistically significant and clinically important. In the study, the benefit of LCZ696 was seen early, was sustained and was consistent across subgroups. LCZ696:<sup>1</sup>

- reduced the risk of death from cardiovascular causes by 20% ( $p=0.00004$ )
- reduced heart failure hospitalisations by 21% ( $p=0.00004$ )
- reduced the risk of all-cause mortality by 16% ( $p=0.0005$ )

Overall there was a 20% risk reduction on the primary endpoint, a composite measure of CV death or heart failure hospitalisation ( $p=0.0000002$ )<sup>1</sup>.

“This trial has shown that we can clearly and comprehensively do better than ACE inhibitors, which have been our current gold standard bedrock treatment for heart failure. This means we can make our patients live longer and keep them out of hospital.” said Professor John McMurray, Professor of Medical Cardiology in the Institute of Cardiovascular and Medical Sciences at the University of Glasgow, UK and Lead Consultant Cardiologist at the Western Infirmary, Glasgow and Co-principal Investigator of the PARADIGM-HF trial

LCZ696, a twice a day tablet being investigated for heart failure, has a unique mode of action which is thought to reduce the strain on the failing heart<sup>4,6,7</sup>. It acts to enhance the protective neurohormonal systems of the heart (NP [natriuretic peptides] system) while simultaneously suppressing the harmful system (RAAS [renin-angiotensin-aldosterone] system)<sup>4,6</sup>. Currently available medicines for HF-REF work only to block the detrimental

effects<sup>4,6</sup>. Despite existing therapies, the mortality rate remains very high with up to 60% of patients in the UK dying within 5 years of a diagnosis of heart failure<sup>3</sup>. Approximately half of patients with heart failure have HF-REF<sup>8</sup>.

“Heart failure is a major and growing public health problem in the UK” said Nick Hartshorne-Evans, CEO of heart failure charity The Pumping Marvellous Foundation. “Almost 1 million people in the UK live with the syndrome but awareness of it is low. As such, we welcome the results of large scale clinical trials in heart failure such as PARADIGM-HF, especially those that might advance the medical treatment of such an under-invested area.”

Analysis of the safety data from PARADIGM-HF showed that fewer patients on LCZ696 discontinued study medication for any adverse event compared to those on enalapril (10.7% vs 12.3%, respectively,  $p=0.03$ ). The LCZ696 group had more hypotension although this did not lead to greater discontinuation of therapy. The LCZ696 group had less renal impairment, hyperkalemia and cough than the enalapril group. There was no statistically significant difference in angioedema between the two groups.<sup>1</sup>

Novartis plans to file the application for marketing authorisation in the EU in early 2015.

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### **About the PARADIGM-HF study**

PARADIGM-HF is a randomised, double-blind, phase III study evaluating the efficacy and safety profile of LCZ696 versus enalapril (a widely studied ACE inhibitor) in 8,442 patients with HF-REF<sup>4,9</sup>. The baseline characteristics showed the patients enrolled were typical HF-REF patients with NYHA Class II-IV heart failure. PARADIGM-HF was specifically designed to see if LCZ696 could decrease CV mortality by at least 15% vs. enalapril<sup>4</sup>. Patients received LCZ696 or enalapril in addition to current best treatment regimen. The primary endpoint is a composite of time to first occurrence of either cardiovascular death or heart failure hospitalisation, and is the largest heart failure study ever done<sup>4</sup>.

Secondary endpoints are change in the clinical summary score for heart failure symptoms and physical limitations (as assessed by Kansas City Cardiomyopathy Questionnaire) at 8 months; time to all-cause mortality; time to new onset atrial fibrillation; and time to occurrence of renal dysfunction<sup>4</sup>. It was initiated in December 2009 and in March 2014 the Data Monitoring Committee confirmed that patients given LCZ696 were significantly less likely to die from CV causes, leading to the trial being stopped early<sup>10</sup>. The DMC also confirmed the primary endpoint had been met.

### **About LCZ696 in heart failure**

LCZ696 is an ARNI (Angiotensin Receptor Neprilysin Inhibitor) and has a unique mode of action which is thought to reduce the strain on the failing heart<sup>4,6</sup>. It harnesses the body's natural defenses against heart failure, simultaneously acting to enhance the levels of natriuretic and other endogenous vasoactive peptides, while also inhibiting the renin-angiotensin-aldosterone system (RAAS).

Heart failure is a debilitating and potentially life-threatening disease in which the heart cannot pump enough blood around the body. Symptoms such as breathlessness, fatigue and fluid retention can appear slowly and worsen over time, significantly impacting quality of life<sup>11</sup>.

It is a significant and growing public health concern with a high unmet need for new treatments. Every year, HF costs the world economy \$108 billion<sup>12</sup>, and hospitalisations comprise 60-70% of treatment costs<sup>13,14</sup>.

### **Disclaimer**

The foregoing release contains forward-looking statements that can be identified by words such as "being investigated," "thought," "plans," "growing," or similar terms, or by express or implied discussions regarding potential marketing approvals for LCZ696, or regarding potential future revenues from LCZ696. 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 materialise, 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 LCZ696 will be approved for sale in any market, or submitted for approval in any additional markets, or at any particular time. Neither can there be any guarantee that LCZ696 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 LCZ696 will be commercially successful in the future. In particular, management's expectations regarding LCZ696 could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected 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; unexpected 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, eye care, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 135,000 full-time-equivalent associates and sell products in more than 150 countries around the world. For more information, please visit <http://www.novartis.com>.

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<sup>1</sup> McMurray JJV et al. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure, *N Engl J Med* 2014; DOI: 10.1056/NEJMoa1409077

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- <sup>2</sup> Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial, that showed enalapril reduced risk of death by 16% vs placebo; Effect of LCZ69 vs ACE inhibitor derived from PARADIGM-HF trial.
- <sup>3</sup> NICE. Clinical Guideline. Chronic heart failure. Available online at <http://guidance.nice.org.uk/CG108> Last updated August 2013. Last accessed August 2014
- <sup>4</sup> Sutherland K. Bridging the quality gap: heart failure. 2010. Available from: <http://www.health.org.uk/public/cms/75/76/313/583/Bridging%20the%20quality%20gap%20Heart%20Failure.pdf?realName=cXqFcz.pdf>
- <sup>5</sup> McMurray JJ, Packer M, Desai AS, *et al.* Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013;15,1062–1073 (doi:10.1093/eurjhf/hft052)
- <sup>6</sup> Langenickel TH *et al.* Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discovery Today: Therapeutic Strategies*.2012, Vol 9. No.4
- <sup>7</sup> Solomon SD *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;380:1387–95
- <sup>8</sup> Doughty R.N., The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis, *European Heart Journal* 2012;33(14):1750-1757
- <sup>9</sup> Clinicaltrials.gov, [NCT01035255](https://clinicaltrials.gov/ct2/show/study/NCT01035255) last accessed online 19 March 2014
- <sup>10</sup> Novartis press release 'PARADIGM-HF trial of Novartis' LCZ696 for chronic heart failure stopped early based on strength of interim results' issued on March 31, 2014
- <sup>11</sup> Mosterd A, Hoes, A, Clinical epidemiology of heart failure, *Heart* 2007;93:1137
- <sup>12</sup> Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol.* 2014.;171(3):368-76
- <sup>13</sup> Neumann T, Biermann J, Erbel R, Neumann A, Wasem J, Ertl G, *et al.*,. Heart failure: the commonest reason for hospital admission in Germany: medical and economic perspectives. *Dtsch Arztebl Int.* 2009;106:269–75.
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