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

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- - Study showed significantly more HF-REF patients on LCZ696 regimen were alive, had fewer hospitalizations than those given enalapril regimen(1)
- - On all-cause mortality, LCZ696 doubled the effect that enalapril, an ACE-inhibitor, previously showed vs. placebo when added to current best treatment for HF-REF(1,2)
- - Over 5 million people suffer from heart failure in the United States, facing a high risk of death and poor quality of life, despite currently available medicines(3,4,5,6)

EAST HANOVER, N.J., Aug. 30, 2014 /PRNewswire/ -- 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.[1,7] 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 hospitalized for sudden deterioration of their heart failure than those given ACE-inhibitor enalapril.[1] Patients received LCZ696 or enalapril on top of current best treatment.[7]

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The magnitude of benefit 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:[1]

- reduced the risk of death from cardiovascular (CV) causes by 20% (p=0.00004)
- reduced heart failure hospitalizations 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 hospitalization (p=0.0000002).[1]

"By demonstrating a very significant reduction in cardiovascular deaths while improving quality of life, Novartis' new heart failure medicine, LCZ696, represents one of the most important cardiology advances of the last decade," said David Epstein, Division Head, Novartis Pharmaceuticals. "We want to thank leading cardiologists from around the world for their collaboration with us and their determination in advancing this important new life saving therapy for heart failure patients."

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.[7,8] It acts to enhance the protective neurohormonal systems of the

heart (NP system) while simultaneously suppressing the harmful effects of the overactive RAAS (renin-angiotensin-aldosterone system).[7,8] Currently available medicines for HF-REF work only to block the detrimental effects.[9] Despite existing therapies, the mortality rate remains very high with up to 50% of patients dying within 5 years of a diagnosis of heart failure.[3] Approximately half of patients with heart failure have HF-REF.[10]

Analysis of the safety data from PARADIGM-HF showed side effects were manageable in the study.[1] 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 and non-serious angioedema but less renal impairment, hyperkalemia and cough than the enalapril group. The most common adverse events with LCZ696 (incidence ≥10%) compared to enalapril were elevated serum potassium of more than 5.5 mmol/liter (16.1% vs. 17.3%), symptomatic hypotension (14.0% vs. 9.2%) and cough (11.3% vs. 14.3%).[1]

Novartis plans to file the New Drug Application for review with the US FDA by the end of 2014.

About the PARADIGM-HF study

PARADIGM-HF is a randomized, 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.[7,11,12] The baseline characteristics showed the patients enrolled were typical HF-REF patients with NYHA Class II-IV heart failure.[11] PARADIGM-HF was specifically designed to see if LCZ696 could decrease CV mortality by at least 15% vs. enalapril.[7] 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 hospitalization, and the trial is the largest heart failure study ever done.[7]

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.[7] PARADIGM-HF 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, and that the primary endpoint was met, leading to the trial being stopped early.[13]

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.[7,8] It acts to enhance the protective neurohormonal systems of the heart (NP system) while simultaneously suppressing the effects of the overactive renin-angiotensin-aldosterone system (RAAS).[7,8]

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.[4]

Heart failure presents a major and growing health-economic burden that currently exceeds $30 billion in the United States, which accounts for both direct and indirect costs.[3]

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "being investigated," "thought," "plans," "growing," "mission," 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 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 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.

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Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which 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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