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PARADIGM-HF trial stopped early for benefit

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The latest update on the trial, describing the design and baseline characteristics of patients, was presented today at the Heart Failure Congress 2014 by Professor Milton Packer, co-principal investigator. The Congress is the main annual meeting of the Heart Failure Association of the European Society of Cardiology.

Professor John McMurray, co-principal investigator, said: "There are very few breakthroughs in heart failure and so the fact that this new therapy reduced on the primary composite endpoint and on cardiovascular mortality alone, as announced by Novartis in March is remarkable and hopefully very promising for patients."

PARADIGM-HF tested the hypothesis that LCZ696 200 mg bid was superior to enalapril 10 mg bid in reducing mortality and morbidity in patients with heart failure and reduced ejection fraction (HF-REF).1 Patients were randomised in a 1:1 ratio to double-blind treatment with one of the two drugs.

ACE inhibitors are the gold standard treatment in heart failure and act by blocking the renin-angiotensin-aldosterone system (RAAS). Enalapril was chosen because it was the ACE inhibitor shown to reduce mortality and hospitalisation of HF-REF patients in the SOLVD-T trial. LCZ696, which is an angiotensin receptor blocker-neprilysin inhibitor (ARNI), simultaneously blocks RAAS and augments endogenous natriuretic peptides (and other endogenous vasoactive substances) by blocking the enzyme that degrades them, called neprilysin or neutral endopeptidase.

Professor McMurray said: "The novel aspect about LCZ696 is that it also enhances the body's natural defences against heart failure. For example, natriuretic peptides are produced by the failing heart in increased amounts to protect the body against sodium and water overload."

The primary objective of the trial was to evaluate the effect of LCZ696 compared with enalapril, in addition to standard heart failure treatment, in delaying time to either cardiovascular death or heart failure hospitalisation (the primary composite endpoint). The trial was deliberately designed so that it was large enough to detect whether LZC696 also had an effect on cardiovascular death alone. Between December 2009 and January 2013, 8 442 patients were randomised at 985 sites in 47 countries.

The baseline characteristics of patients in PARADIGM-HF are presented for the first time today. They reveal that compared to contemporary heart failure trials, the patients in PARADIGM-HF were particularly well treated, with the highest rate of beta-blocker (over 90%) and of mineralocorticoid receptor antagonist (60%) use of any trial.

Professor McMurray said: "This shows that we tested LCZ696 on top of the best available pharmacological treatment. The benefits we have shown are hopefully, therefore, an important advance in the treatment of HF-REF patients."

The trial was due to conclude around October 2014 but the Data Monitoring Committee (DMC) recommended stopping it in March because of a benefit to patients that was overwhelmingly statistically significant. The DMC rules were that the trial could only be stopped if there was a strongly statistically significant benefit on both the primary composite endpoint and on the cardiovascular mortality endpoint.

Professor McMurray said: "The trial was stopped for benefit and that doesn't happen very often. We don't know the results, as the data are still being analysed. However, the pre-specified guidelines for stopping the trial early required a highly statistically significant reduction in both the primary composite endpoint and cardiovascular death. We also don't know about tolerability and safety but no safety issue has been raised during the past four years by the DMC. For these reasons we hope that LCZ696 will be an important breakthrough in the management of patients with HF-REF."

The trial is currently closing out and the final data will then be analysed. The investigators have applied to present their results at ESC Congress 2014 in Barcelona, Spain.

Provided by European Society of Cardiology