Levosimendan improves event free survival by 50 percent in end-stage heart failure

May 27 2013

Ambulatory levosimendan improves event free survival by 50% compared to placebo, according to results from the LevoRep Study presented today during the late breaking trial session1 of the Heart Failure Congress 2013. In a second study, the third generation mineralocorticoid receptor antagonist (MRA) BAY 94-8862 showed improved potassium and kidney tolerance in heart failure patients with chronic kidney disease (CKD).

Heart Failure 2013 is the main annual meeting of the Heart Failure Association of the European Society of Cardiology and is being held 25-28 May in Lisbon, Portugal (1)

The prevalence of end-stage heart failure is increasing significantly and is associated with frequent hospital admissions and high costs. LevoRep is the largest trial of repetitive ambulatory administration of an inotrope in end-stage heart failure. The study focused on the safety and efficacy of levosimendan in an ambulatory setting.

LevoRep was a multicentre study in which 120 patients with end-stage heart failure were randomised to receive biweekly 0.2 mcg/kg/min levosimendan for 6 hours over 6 weeks or placebo. The study met its secondary endpoints and showed that ambulatory levosimendan was safe and improved event free survival by 50% compared with placebo. However, the study failed to show significant improvements in functional capacity and quality of life which were the primary endpoints.

Presenter Dr Gerhard Poelzl (Austria) said: "Future studies with more patients and higher dosing or higher repetition frequencies of levosimendan in an outpatient setting could show positive results for the primary endpoints. The improvement in event-free survival shown in this study may revive an old concept of ambulatory treatment of end-stage heart failure patients which has been largely dismissed because of the excessive mortality with intropes."

The MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) was a randomised, double blind, phase 2 trial of BAY 94-8862 in patients with chronic heart failure and mild/moderate chronic kidney disease. First (spironolactone) and second (eplerenone) generation MRAs have safety issues including risk of hyperkalemia and worsened renal function. Their use is limited in patients with poor renal function, a frequent comorbidity in patients with heart failure.

The fourth generation MRA BAY 94-8862 is non-steroidal and BAY 94-8862 is thought to be more kidney friendly. This is due to its pharmacokinetics of distribution where the drug tends to be compartmentalised to a greater extent in the heart than the kidneys when compared to spironolactone and eplerenone in rodents, suggesting targeted action on the cardiovascular system with fewer effects on the kidney.

Part B of the ARTS trial, presented today, randomised 393 patients with heart failure and moderate CKD to BAY 94-8862 (2.5, 5, or 10mg once daily or 5mg twice daily), placebo or the standard dose of spironolactone.

All BAY 94-8862 doses were safe and well tolerated and BAY 94-8862 was associated with less hyperkalemia and better kidney tolerance than spironolactone. Both drugs produced an almost equal effect on brain natriuretic peptide (BNP), a hemodynamic biomarker of remodelling of

the heart.

Presenter Professor Faiez Zannad (France) said: "This fourth generation drug is better tolerated when it comes to potassium and the kidney even in patients at higher risk because of pre-existing moderate CKD. There is a real unmet need in this population because while MRAs are not contraindicated, many doctors are wary of using them because of the side effects in the kidney. This study is the first important step towards investigating newer and wider indications for MRAs."

He concluded: "Future studies will investigate BAY 94-8862 novel indications: patients with heart failure and either moderate CKD or diabetes hospitalized for worsening chronic heart failure, and kidney protection in diabetics."

Provided by European Society of Cardiology