BIOBUSINESS BRIEFS

TRIAL WATCH

Dual inhibition shows promise in hypertension

Novartis has reported that LCZ696 — a first-in-class dual-acting angiotensin II (AT_2) receptor and neprilysin inhibitor — demonstrated superior blood-pressure-lowering efficacy in a Phase II trial of patients with hypertension compared with standard treatment with an AT_2 receptor antagonist alone (*Lancet* 16 Mar 2010; doi:10.1016/S0140-6736(09)61966-8).

Although there are multiple treatment options for hypertension — including lifestyle changes, angiotensin converting enzyme inhibitors, AT_2 receptor antagonists, calcium channel blockers or diuretics — blood pressure in many patients with hypertension remains inadequately controlled. "The major problems in the treatment of hypertension today are the inability to maintain long-term control of blood pressure due to the asymptomatic nature of the disease, the presence of other co-morbidities (such as obesity, diabetes and renal dysfunction) that complicate the treatment, and the reluctance of many practitioners to push therapy to achieve recommended blood pressure goals," says Norman Kaplan, professor at the University of Texas Southwestern Medical Center, USA. Moreover, "current medications are limited in their mechanisms of action and fail to take advantage of the body's own blood-pressure-lowering mechanisms," adds John Burnett, professor at the Mayo Clinic, Minnesota, USA.

LCZ696, which combines moieties from the AT_2 receptor antagonist valsartan and the neprilysin inhibitor prodrug AHU377 in a single molecule (*J. Clin. Pharmacol.* 50, 401–414; 2010), has the potential to overcome some of these limitations. "LCZ696 represents a highly innovative drug design. Through inhibition of neprilysin, it simultaneously potentiates the effects of the endogenous natriuretic peptides made by the heart to increase vasodilatation, and promotes sodium excretion and suppresses aldosterone to promote diuresis and lower blood volume. It also blocks the vasoconstricting actions of AT_2 through AT_2 receptor antagonism," explains Burnett.

The results of the recent study, in which 1,328 adult patients with mild-to-moderate hypertension were randomized to receive LCZ696 (100, 200 or 400 mg orally), the appropriate comparator doses of valsartan (80, 160 or 320 mg), AHU377 (200 mg) or placebo daily for 8 weeks, are encouraging. Significantly greater average reductions in mean sitting diastolic and systolic pressures, sitting and ambulatory pulse pressures and 24-hour ambulatory systolic pulse pressure were achieved in patients treated with the two higher doses of LCZ696 than in those treated with the corresponding doses of valsartan. These results therefore demonstrate the complementary effects of the dual mechanism of action of the novel agent.

"LCZ696 appears to be a very effective therapy with virtually no adverse effects," notes Kaplan. Indeed, any adverse events that did occur during the treatment period were generally mild, transient, infrequent and did not show dose dependence. Importantly, there were no signs of angioedema, which has been associated with the once highly promising anti-hypertensive vasopeptidase inhibitors, which act by blocking both neprilysin and angiotensin converting enzyme. "What is needed now is a larger study in more resistant hypertension and testing in black patients, in whom the vasopeptidase inhibitor omipatrilat was more frequently associated with a small risk of angioedema," says Burnett. "Overall, this is an exciting innovative step in drug discovery for the treatment of hypertension, which might herald a substantial advance in cardiovascular therapeutics," he concludes.