The First-in-Man Randomized Trial of a β3-adrenoceptor Agonist in Chronic Heart Failure - The BEAT-HF Trial

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Background
Cardiac myocyte Na+ overload is important in the pathogenesis of heart failure (HF) and evidence-based treatments facilitate Na+-K+ pump-mediated Na+-export. Since the nitric oxide synthase-coupled β3 adrenoceptor (β3AR) mediates cardiac myocyte Na+-K+ pump stimulation, we hypothesised that β3AR agonists might be beneficial in HF. In support of this, treatment with β3AR agonists improves clinically relevant indices in sheep and rabbit models of HF.

Objective
BEta 3 Agonists Treatment in HF (BEAT-HF) is a randomized, double-blind, placebo-controlled study on effects of the β3AR agonist, Mirabegron (Astellas Pharma, approved for treatment of overactive bladder) in patients with chronic HF. The primary endpoint is increase in left ventricular ejection fraction (LVEF). Secondary endpoints include changes in NT proBNP, left atrial and LV volumes, QT interval and 6-min walking distance, VO2 max and improvement in quality of life.

Methods
The study is designed to include 70 patients to detect a difference in LVEF of 4% with a power of 90% and a 2-sided alpha of 5%, allowing for a drop-out rate of 30%. Inclusion criteria are stable HF, NYHA class II-III, LVEF < 40% on ischemic or non-ischemic basis. Patients have to be on optimal pharmacological treatment that must include a β1 AR-blocker. Exclusion criteria include significant valvular disease, renal failure and treatment with digoxin or tricyclic antidepressants. Patients are randomized 1:1 to oral treatment with Mirabegron or placebo for 6 months, starting at 25 mg x 2, doubled weekly to a target dose of 150 mg x 2 or a predefined maximum tolerated dose. LVEF is assessed by cardiac CT.

Results
The target number of 70 patients have been randomized and will have completed the 6 months follow-up in September 2015. Patients characteristics; age 58±12 years (mean±SD), 62 (89%) men, 31 (44%) had ischemic cardiomyopathy. The median LVEF at entry was 30% (range 10-39); 66 (94%) were in NYHA Class II and 4 (6%) in Class III. Primary and secondary endpoints will be presented.

Conclusions
BEAT-HF is the first-in-man trial to evaluate efficacy of oral treatment with a β3AR agonist in chronic HF. It also explores potential effects on diastolic function, symptoms and repolarisation duration as well as safety (NCT01876433).
Disclosure:

H. Bundgaard: Speakers Bureau; Modest; Speaker fee from MSD, Sanofi-Avensis, Amgen, AstraZeneca, Pfizer. Other; Significant; Together with University of Sydney, Royal North Shore Hospital and Helge H Rasmussen patented the use of beta 3 adrenoceptor agonists in heart failure.

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