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 adrenergic receptor (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 small and rabbit models of HF. Objective: BEAT 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 and LV volumes, QT interval, 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 a dose of 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 has been randomized and will have completed the 6 months follow-up in September 2015. Patients characteristics; age 56±12 years (means±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% 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 rehospitalisation duration as well as safety (NCT01876433).

Author Disclosures: H. Bundgaard: Speakers Bureau; Modest; Speaker fee from MSD, Sanofi-Avenis, Avenis, AstraZeneca, Pfizer, Other; Significant; Together with University of Sydney, Royal North Shore Hospital and Henning Bundgaard patented the use of β3 adrenergic agonists in heart failure... I. Axelsson: None. I. Kvierson: None. J.H. Thomsen: None. M. Sergaard: None. K. Kofod: None. N.V. Køber: None. H. Krum: None. S. Boegh: None. F. Gustafsson: None. L. Køber: None. H.H. Rasmussen: Other; Significant; Together with University of Sydney, Royal North Shore Hospital and Henning Bundgaard patented the use of beta 3 adrenergic agonists in heart failure.

Key Words: Heart failure, Cell signalling, Catecholamines, Beta-adrenergic receptor agonists, Ion transport

Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Primary Results of a Randomized, 2×2 Factorial, Placebo-Controlled, Double-Blind Clinical Trial

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Introduction: Contemporary adjuvant therapy regimens for early breast cancer are associated with improved survival but at the cost of increased risk of cardiac dysfunction that may progress to clinical heart failure. Preventive neurohormonal blockade may alleviate the decline in cardiac function, but results from randomized, placebo-controlled, double-blind trials are missing. Hypothesis: We tested the hypothesis that cardiotoxicity in patients receiving adjuvant treatment containing anthracyclines with or without trastuzumab and radiation for early breast cancer can be prevented by the concomitant use of the beta-blocker metoprolol and/or angiotensin receptor blocker candesartan.

Methods: PRADA (NCT01434134) is a 2×2 factorial, randomized, placebo-controlled, double-blind clinical trial evaluating the cardioprotective effect of metoprolol succinate and/or candesartan cilexetil vs. placebo administered in parallel with adjuvant anti-cancer therapy. The target dose was 100 mg daily for metoprolol and 32 mg daily for candesartan. Between September 2011 and September 2014 126 women (mean age 50.7 years) with early breast cancer and no serious concomitant illness were validly randomized at a single center. The duration of adjuvant therapy ranged from 10 to 61 weeks. The primary endpoint was change in left ventricular ejection fraction (LVEF) as determined by cardiac magnetic resonance imaging (CMRI) from the completion of adjuvant therapy. Results: There was no evidence of an interaction between assignment to candesartan or metoprolol. In the intention-to-treat analysis, the overall decline in LVEF was 2.6 percentage points (95% confidence interval 1.5 - 3.8) in the placebo group and 0.8 (0.4 - 1.9) in the candesartan group (p=0.026 for between-group difference). In the per-protocol analysis the mean decline was 2.5 (1.4-3.6) percentage points in the placebo group and 0.6 (-0.6-1.8) in the candesartan group (p=0.021 for between-group difference). No effect of metoprolol on the change in LVEF was observed. Conclusions: Concomitant treatment with candesartan, but not metoprolol provides protection against decline in LVEF in women treated for early breast cancer with concomitant anti-cancer treatment.

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Key Words: Cardioprotective drugs, Prevention, Cardiac imaging

Prevention of Acute Kidney Injury by Nitric Oxide During and After Prolonged Cardiopulmonary Bypass. A Double Blind Randomized Controlled Trial

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Background: The most common complication associated with prolonged duration cardiopulmonary bypass (CPB) is acute kidney injury (AKI), which markedly increases the morbidity and mortality. Rationale: Preventing AKI is desirable because it causes hemodynamic instability, adverse drug interactions, sepsis, disseminated intravascular coagulation, and decreased cardiac output and renal perfusion. 2 Reduction of ischemia-reperfusion renal injury and 3. Oxidation of plasma Hb to metHb, which cannot scavenge NO.

Hypothesis: Exposure to NO during and after CPB protects the kidney, by three possible mechanisms: 1. Nitrite and nitrate levels are increased, leading to increased cardiac output and renal perfusion. 2. Reduction of ischemia-reperfusion renal injury and 3. Oxidation of plasma Hb to metHb, which cannot scavenge NO.

Study Design: A single center, prospective, randomized, double blind controlled trial comparing treatment with 80 part per million (ppm) NO (NO group versus N2, control group). Study gas was given via a canister for exchange during CPB and continued for 24 hours post-surgery.

Study Population: 217 consenting adults with normal kidney function undergoing elective multiple valve replacement surgery with CPB. Study Objective: To determine whether NO reduces AKI (primary outcome), and other major complications immediately post-surgery.
A Randomized, Placebo Controlled Trial of Late Na Channel Inhibition (ranolazine) in Coronary Microvascular Dysfunction (CMD): Impact on Angina and Myocardial Ischemia

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Background: Patients with persistent symptoms and signs of myocardial ischemia and no obstructive coronary artery disease (CAD) often have coronary microvascular dysfunction (CMD), as defined by the ISCHEMIA study. CMD is characterized by impaired coronary artery dilation in response to pharmacologic or physiologic stimuli. This study evaluated the safety, pharmacokinetics, and pharmacodynamics of sc administration of ALN-PCSsc, an investigational RNAi therapeutic targeting PCSK9, in individuals with CMD.

Methods: Individuals with CMD were randomized to sc placebo (N=12), or 4 doses of 125 mg-qW (N=6) or 2 doses of 250 mg-qW (N=6) ALN-PCSsc with or without statin. Apheresis was performed before and after the ALN-PCSsc study treatment to evaluate changes in lipoprotein profiles, including total cholesterol, HDL-C, non-HDL-C, ApoB, and Lp(a).

Results: A total of 44 subjects were enrolled, with a mean baseline LDL-C of 146 mg/dl. 24 subjects were enrolled in 5 SAD cohorts and received placebo (N=6) or drug at fixed doses ranging from 25 mg to 800 mg (N=3–6), per group. 45 subjects were enrolled in 6 MD cohorts, and received: placebo (N=6); 4 doses of 125 mg-qW (N=6); or 2 doses of 250 mg-qW (N=6); 300 mg-qM (N=6); 300 mg-qM with statin (N=6). No serious adverse events or discontinuations due to adverse events occurred. Here we report safety and efficacy data (out to 180 days) that support the potential for a robust effect of ALN-PCSsc on LDL-C, of up to 85% maximal reduction of LDL-C, with mean maximal LDL-C reduction of 66%.

Conclusion: ALN-PCSsc is a subcutaneously (sc) delivered RNAi investigational agent that inhibits synthesis of PCSK9 in liver. We previously presented interim data demonstrating up to 94% maximal knockdown of PCSK9 and up to 85% maximal reduction of LDL-C, with mean maximal LDL-C reduction of 66%.

Methods: Individuals were randomized to a single-blind, placebo-controlled, single-ascending dose and multiple dose Phase 1 study to evaluate the safety, pharmacokinetics and pharmacodynamics of sc administered ALN-PCSsc in subjects with elevated LDL-C on and off statins. The primary endpoint was safety and tolerability; secondary endpoints were plasma PK, PCSK9 knockdown, and exploratory endpoints: total cholesterol, HDL-C, LDL-C, Lp(a), ApoB, and Lp(a). Results: A total of 69 subjects were enrolled, with a mean baseline LDL-C of 146 mg/dl. 24 subjects were enrolled in 5 SAD cohorts and received placebo (N=6) or drug at fixed doses ranging from 25 mg to 800 mg (N=3–6), per group. 45 subjects were enrolled in 6 MD cohorts, and received: placebo (N=6); 4 doses of 125 mg-qW (N=6); or 2 doses of 250 mg-qW (N=6); 300 mg-qM (N=6); 300 mg-qM with statin (N=6); 500 mg-qM (N=6); and 500 mg-qM with statin (N=6). ALN-PCSsc was generally well-tolerated; all treatment-emergent adverse events were mild or moderate in severity. No serious adverse events or discontinuations due to adverse events occurred. Here we report safety and efficacy data (out to 160 days) that support the potential for a robust LDL-C lowering (up to a 83% maximal LDL-C reduction, with 44% mean LDL-C reductions remaining 140 days post a single dose) demonstrating the potential for a robust effect of ALN-PCSsc on LDL-C, of up to 85% maximal reduction of LDL-C, with mean maximal LDL-C reduction of 66%.

Conclusion: ALN-PCSsc was generally well-tolerated; all treatment-emergent adverse events were mild or moderate in severity. No serious adverse events or discontinuations due to adverse events occurred. Here we report safety and efficacy data (out to 160 days) that support the potential for a robust LDL-C lowering (up to a 83% maximal LDL-C reduction, with 44% mean LDL-C reductions remaining 140 days post a single dose) demonstrating the potential for a robust effect of ALN-PCSsc on LDL-C, of up to 85% maximal reduction of LDL-C, with mean maximal LDL-C reduction of 66%.

Key Words: Ischemic heart disease, Magnetic resonance imaging