Late-Breaking Clinical Trial Abstracts

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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).

Author Disclosures: **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 Rsmussen patented the use of beta 3 adrenoceptor agonists in heart failure.. **A. Axelsson:** None. **K. Iversen:** None. **J.H. Thomsen:** None. **M. Sørgaard:** None. **K. Kofoed:** None. **N.V. Køber:** None. **H. Krum:** None. **S. Boesgaard:** 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 adrenoceptor agonists in heart failure.

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

20236

Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Primary Results of a Randomized, 2 x 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 2x2 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 (MRI) from baseline to the completion of adjuvant therapy. **Results:** There was no evidence of an interaction between assignment to candesartan and to 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 decline was 2.6 (1.4-3.8) 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 adjuvant anti-cancer treatment.

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Key Words: Cardioprotective drugs, Prevention, Cardiac imaging

14228

ANNEXA™-R Part 2: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial Demonstrating Sustained Reversal of Rivaroxaban-Induced Anticoagulation in Older Subjects by Andexanet Alfa (PRT064445), a Universal Antidote for Factor XA (FXA) Inhibitors

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Background: Direct FXa inhibitors have superior or comparable efficacy and safety relative to warfarin. A specific antidote for these agents is lacking in case of major bleeding or emergent surgery. Andexanet alfa (AnXa) is a modified, recombinant human FXa molecule under development as a specific antidote for FXa inhibitors. We have reported data for Part 1 of the Phase 3 study in older subjects anticoagulated with rivaroxaban, where an AnXa IV bolus reversed anti-FXa activity and restored thrombin generation (TG). Here we report Part 2 data where AnXa was administered as a bolus-plus-infusion (B+I) regimen in a similar population. Data from the phase 3 study in older subjects anticoagulated with apixaban has also been reported demonstrating rapid and sustained reversal of anti-FXa activity and restored TG with AnXa IV bolus or B+I. **Aims:** To demonstrate immediate and sustained reversal of rivaroxaban anticoagulation following bolus and infusion of AnXa. **Methods:** ANNEXATM is a 4 part, Phase 3, double-blind, placebo-controlled program comprised of 2 studies of AnXa in older subjects treated with rivaroxaban or apixaban. Part 2 investigated a bolus of AnXa plus a 2-hr infusion. In ANNEXA-R Part 2, 39 subjects age 50 to 75 were randomized to receive AnXa or placebo in a 2:1 ratio. All subjects received rivaroxaban 20 mg PO QD for 4 days to achieve steady state plasma levels. AnXa (800 mg IV bolus plus a 2-hr infusion at 8 mg/min) or placebo was administered on Day 4, 4 hrs after the last rivaroxaban dose (~Cmax). Safety data were collected through Day 43. The primary efficacy endpoint is the percent change from baseline in anti-Xa activity at its nadir between 10 min prior to and 5 min after end of infusion. Additional endpoints included reduction in plasma free fraction of rivaroxaban and restoration of TG. **Results:** AnXa rapidly reversed the anticoagulant effect of rivaroxaban and sustained it for the duration of the infusion. AnXa was well tolerated. **Conclusion:** This study continues our investigations of AnXa as an antidote for reversing the anticoagulant effects of rivaroxaban and other FXa inhibitors. Rapid and near complete reversal of the anti-Xa effect of the FXa inhibitors has the potential to improve management of patients with bleeding or those requiring emergent surgery.

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Key Words: Factor xa, Anticoagulants, Biomarkers, Anticoagulation

20991

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 mortality rate. **Rationale:** Prolonged CPB causes hemolysis with high levels of circulating plasma hemoglobin (Hb). Plasma Hb scavenges Nitric Oxide (NO) via the dioxygenation reaction, depleting endogenous NO and causing vasoconstriction, proximal renal tubular injury and AKI. **Hypothesis:** Exposure to NO during and after CPB protects the kidney, by three possible mechanisms: 1. Selective vasodilation of the pulmonary circulation 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 N_2 (N_2 group). Study gas was given via the gas exchanger during CPB and by inhalation for 24h post-operatively in adults. **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,

at 30 days, and 90 days (secondary outcomes). AKI was defined as either an increase of serum creatinine by 50% within 7 days after surgery, or an increase of serum creatinine by 0.3 mg/dl within 48 hrs. **Preliminary results:** are summarized in the tables 1, 2, 3 and 4. **Conclusions**: I) Administration of 80ppm NO for 24 hours was safe. Blood metHb was always below 10%. II) NO decreased the incidence of AKI from 63% to 50% (p=0.04, primary endpoint achieved).

Table. Preliminary Results

Outcomes	N_2 Group n=112	NO Group n=105	RR (95% CI)	p
Renal Complications				
AKI incidence, n (%)	71 (63)	52 (50)	0.78 (0.62-0.99)	0.04
Stage 1	60 (54)	46 (44)	0.82 (0.62-1.08)	0.15
Stage 2	8 (7)	4 (4)	0.53 (0.17-1.72)	0.29
Stage 3	3 (3)	2 (2)	0.71 (0.12-4.17)	0.71
RRT n, (%)	6 (5)	3 (3)	0.53 (0.14-2.08)	0.37
Major AKE, n (%)	72 (64)	52 (50)	0.77 (0.61-0.98)	0.03
Cardiac Complications				
Perioperative MI, n (%)	4 (4)	9 (9)	2.40 (0.76-7.56)	0.13
Non perioperative MI, n (%)	1 (1)	0 (0)	0.36 (0.01-8.63)	0.52
Cardiac arrest, n (%)	1 (1)	1 (1)	1.07 (0.07-16.84)	0.96
Arrhythmia, n (%)	13 (12)	6 (6)	0.49 (0.19-1.25)	0.14
Heart failure, n (%)	4 (4)	1 (1)	0.27 (0.03-2.35)	0.23
Neurological Complications				
Stroke, n (%)	1 (1)	2 (2)	2.13 (0.20-23.18)	0.53
Delirium, n (%)	4 (4)	5 (5)	1.33 (0.37-4.83)	0.66
Respiratory Complications				
Infective				
Pneumonia	50 (45)	42 (40)	0.90 (0.66-1.22)	0.49
ALI/ARDS	28 (25)	27 (26)	1.03 (0.65-1.62)	0.90
Non infective				
ALI/ARDS	22 (20)	10 (10)	0.48 (0.24-0.97)	0.04
Pleural effusion	3 (3)	2 (2)	0.71 (0.12-4.17)	0.71
Pneumothorax	8 (7)	8 (8)	1.07 (0.42-2.74)	0.89
Wound Infection, n (%)	3 (3)	2 (2)	0.71 (0.12-4.17)	0.71
Bleeding, n (%)	3 (3)	0 (0)	0.15 (0.01-2.91)	0.21
Reintubation, n (%)	6 (5)	2 (2)	0.36 (0.07-1.72)	0.20
Prolonged MV, n (%)	5 (4)	5 (5)	1.07 (0.32-3.58)	0.92
Reoperation, n (%)	2 (2)	0 (0)	0.21 (0.01-4.39)	0.32
Readmission, n (%)	3 (3)	2 (2)	0.71 (0.12-4.17)	0.71
Mortality, n (%)	6 (5)	2 (2)	0.36 (0.07-1.72)	0.20

AKI=acute kidney injury; RRT=renal replacement therapy; AKE=adverse kidney event (AKI+death); MI=myocardial infarction; ALI=acute lung injury; ARDS=acute respiratory distress syndrome; MV=mechanical ventilation. Data are expressed as count (%). RR (Risk Ratio) is expressed as Relative Risk of events in NO Group vs N_2 Group with 95% Confidence Interval and p value.

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13496

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), evidenced by limited coronary flow reserve (CFR) on invasive coronary testing and abnormal stress myocardial perfusion reserve on cardiac magnetic resonance imaging (CMRI). Because the mechanistic basis for this syndrome is unclear and outcome trials are lacking, there is no recognized standard of care for such patients. We tested the hypothesis that myocardial ischemia is a mechanistic pathway for angina in CMD using late-Na channel inhibition (ranolazine). **Methods:** We conducted a randomized, double-blinded, placebo-controlled, cross-over trial of oral ranolazine 500-1,000 mg twice daily for 2 weeks in women and men with symptoms and signs of myocardial ischemia, no obstructive CAD, and abnormal CFR or CMRI myocardial perfusion reserve index (MPRI). The outcomes are angina (Seattle Angina Questionnaire [SAQ]) and angina frequency measured by diary (primary), MPRI and diastolic function on CMRI (secondary), and SAQ score change is related to myocardial perfusion change. The Women's Ischemia Syndrome Evaluation (WISE) Coronary Angiography and CMRI core laboratories qualified and analyzed the measures. **Results:** Between March 22, 2011 and April 20, 2015, 435 subjects were screened, 136 (91% women) were enrolled, randomized, and are in follow-up. Baseline data show a mean age 54±12 yrs, 18% diabetes, 54% hypertension, 6% current smoking, body mass index (BMI) of 29±7. The final patient will complete follow-up and data analysis will be concluded by July 30, 2015. The following data will be presented: safety data, efficacy data, SAQ domains (subscale and summary scores), angina diaries, and CMRI variables (global, mid-ventricular and subendocardial MPRI, diastolic function). **Conclusions:** This trial is the first test of the hypothesis that myocardial ischemia is a mechanistic pathway for angina in CMD subjects in the absence of obstructive CAD using late-Na channel inhibition. The results will provide the needed information for design and implementation of a large, definitive outcome trial to improve the morbidity and mortality of patients with CMD.

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Key Words: Ischemic heart disease, Magnetic resonance imaging

23226

ALN-PCSsc, an RNAi Investigational Agent That Inhibits PCSK9 With Potential for Effective Quarterly or Possibly Bi-Annual Dosing: Results of Single-Blind, Placebo-Controlled, Phase 1 Single-Ascending Dose (SAD), and Multi-Dose (MD) Trial in Adults With Elevated LDL-C, on and off Statins

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Background: 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 83% maximal reduction of LDL-C, with mean maximal LDL-C reduction up to 64%. **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 LDL-C; exploratory endpoints included total cholesterol, HDL-C, VLDL, triglycerides, and Lp(a). **Results:** A total of 69 subjects were enrolled, with a mean baseline LDL-C =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=12); 4 doses of 125 mg-qW (N=6); or 2 doses respectively of 250 mg-q2W (N=6); 300 mg-qM (N=6); 300 mg-qM with statin (N=4); 500 mg-qM (N=6); and 500 mg-qM with statin (N=5). 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 180 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 quarterly or possibly bi-annual dosing. In addition, we report for the first time changes in lipoprotein profiles including total cholesterol, HDL-C, non-HDL-c, ApoB, and Lp(a). **Conclusion:** Our results suggest that an investigational RNAi therapeutic targeting PCSK9 can provide a differentiated approach for the treatment of hypercholesterolemia. ALN-PCSsc was generally well-tolerated, resulted in LDL-C lowering to levels similar to those published for PCSK9 monoclonal antibodies, with an extensive duration of action supportive of effective quarterly or possibly bi-annual dosing.

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Key Words: Hyperlipidemia, Cardiovascular therapeutics, PCSK9, LDL