Title

DESIGN FEATURES OF THE BETONMACE CHRONIC KIDNEY DISEASE SUB-STUDY; EFFECTS OF THE SELECTIVE BET-INHIBITOR APABETALONE ON KIDNEY FUNCTION AND MACE IN POST-ACS PATIENTS WITH ESTIMATED GLOMERULAR FILTRATION RATE BELOW 60 AND DIABETES

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INTRODUCTION AND AIMS: Cardio-metabolic disease often contributes to chronic kidney disease (CKD). CKD is an important risk factor for increased cardiovascular events in high risk vascular disease patients. Epigenetic dysregulation and bromodomain and extraterminal domain (BET) proteins are believed to be involved in cardiovascular disease (CVD) and CKD pathogenesis. Treatment with apabetalone, a selective BET inhibitor, over 6-months has illustrated a reduction in alkaline phosphatase (ALP) in phase 2 studies. Additionally, in these phase 2 studies a significant CVD event reduction was highlighted which was most pronounced in patients with diabetes. Therefore an event driven phase 3 trial in CVD patients - BETonMACE - has been initiated.

METHODS: BETonMACE is a multinational, multi-center ($\asymp$200 sites) pivotal phase 3, double blind randomized (1:1), placebo controlled trial in post-Acute Coronary Syndrome (ACS) patient with diabetes mellitus and HDL-cholesterol $<$40 (females) and $<$45 (males) mg/dL investigating if apabetalone 100 mg b.i.d. vs. placebo in addition to standard of care including high intensity statins, beta blockers, ace inhibitors, and dual anti-platelet inhibition treatment, delays the time to major adverse cardiac events (MACE). The study is designed to randomize 2,400 patients and accrue 250 MACE defined as cardiovascular death, non-fatal MI and stroke. Estimated glomerular filtration rate (eGFR) is calculated using the Cockcroft Gault equation. In all patients, eGFR is evaluated at screening, 24 weeks, 52 weeks, 76 weeks, 100 weeks and at the termination of the trial. Evidence of severe renal impairment as determined by an eGFR less than 30 mL/min/1.7m^2 at screening is an exclusion criteria in the BETonMACE study. The substudy will include the assessment of changes in kidney function in a patient population with eGFR below 60 mL/min/1.7m^2 at screening. Therefore, these patients will be classified as stage 3 chronic kidney disease patients. Kidney function assessment is a pre-specified variable comparing change from baseline for active treatment vs. placebo applying standard adjustments including age and baseline eGFR. Markers of kidney disease risk such as alkaline phosphatase, serum chemistry markers and inflammatory markers will also be included in the analysis.

RESULTS: To date, BETonMACE has randomized 2,224 patients of which 11% have screening eGFR below 60. At completion patients will have been treated from 6 to approximately 36 months.

CONCLUSIONS: Kidney function assessment, using eGFR, and MACE reduction is being evaluated in BETonMACE, a phase 3 CVD event trial testing the efficacy of a novel first-in-class BET-inhibitor, apabetalone. The kidney population sub-study, in patients with eGFR below 60 mL/min/1.7m^2 at screening, will provide further insights about epigenetics in kidney function changes and MACE effects of BET-inhibition in approximately 300 post-ACS patients with diabetes, low HDL and CKD.