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BET-inhibition with Apabetalone in Post-ACS Patients with Diabetes: Design and Baseline Characteristics of the BETonMACE trial

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Background: Diabetes (DM) is associated with increased risk of macro/microvascular disease and cognitive decline. Inflammation and vascular calcification may be contributing factors. Bromodomain and extraterminal (BET) proteins coordinate gene transcription and modify the transcriptional response to hyperglycemia, and inflammation. Apabetalone competitively and selectively inhibits binding between BET proteins and acetyl-lysine marks on histone tails: normalizing transcriptional profiles to physiological levels; reducing in vitro alkaline phosphatase (ALP) transcription and in vivo plasma ALP in a dose-dependent manner. Phase 2 trials with apabetalone show improved renal function in the chronic kidney disease (CKD) subgroups. Furthermore, treatment showed a 55% reduction in CVD events with more pronounced benefit among patients with DM, low HDL-cholesterol (HDL-C) and high sensitivity C-reactive protein (hsCRP).

Methods: The double-blind, placebo controlled phase 3 BETonMACE trial is testing the hypothesis that apabetalone 100 mg b.i.d., added to standard care, reduces major adverse cardiovascular events (MACE: CV death, non-fatal myocardial infarction or stroke) in patients with DM, acute coronary syndrome (ACS) within the preceding 7–90 days, low HDL-C ($<$40 mg/dL in men; $<$45 mg/dL in women), and estimated glomerular filtration rate (eGFR) $>$30 mL/min/1.7m^2. The trial will continue until at least 250 MACE, providing 80% power to detect a 30% reduction. Secondary endpoints include changes in eGFR in patients with baseline eGFR 30 to $<$60 mL/min/1.7m^2, inflammatory markers, lipids, and ALP. In addition the Montreal Cognition Assessment (MoCA) test was performed in patients $\geq$70 years of age at baseline and annually.

Results: Enrollment of 2425 patients across 13 countries and 195 centers is now complete. Baseline characteristics [median (IQR)] include LDL-C 65.0 (36) mg/dL, HDL-C 33.0 (7) mg/dL, HbA1c 7.3 (2.3) %, hsCRP 2.8 (4.9) mg/L, mean blood pressure 129/76 mmHg, and CKD in 266 patients (10.8%). Background care was based on guideline recommendations. Diabetes medications include metformin (79%), insulin (36%), sulfonylureas (28%), DPP4 inhibitors (11%), SGLT2 inhibitors (9.7%) and GLP1 receptor agonists (0.3%). The CKD subpopulation vs. total population differed significantly from the whole population with regard to age (71 vs. 62 y. o.), male sex (58% vs. 75%), history of hypertension (46% vs. 88%), history of stroke (1.5% vs. 7.5%), and current smokers (6.1% vs. 13%). In the 70 year and older (n=466, 19%) population 54% (n=243) showed a baseline MoCA score 25 and lower suggesting cognitive impairment.

Summary: The BETonMACE trial is testing the hypothesis that selective BET-inhibition with apabetalone, added to established, evidence-based treatment, reduces MACE in high-risk patients with DM, recent ACS, and low HDL-C. The study will also assess apabetalone's effect on renal function and cognition.