BETonMACE Chronic Kidney Disease Sub-Study: Effects of the Selective BET-Inhibitor Apabetalone on Kidney Function and MACE in Post-ACS Patients with Diabetes and Estimated Glomerular Filtration Rate Below 60

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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

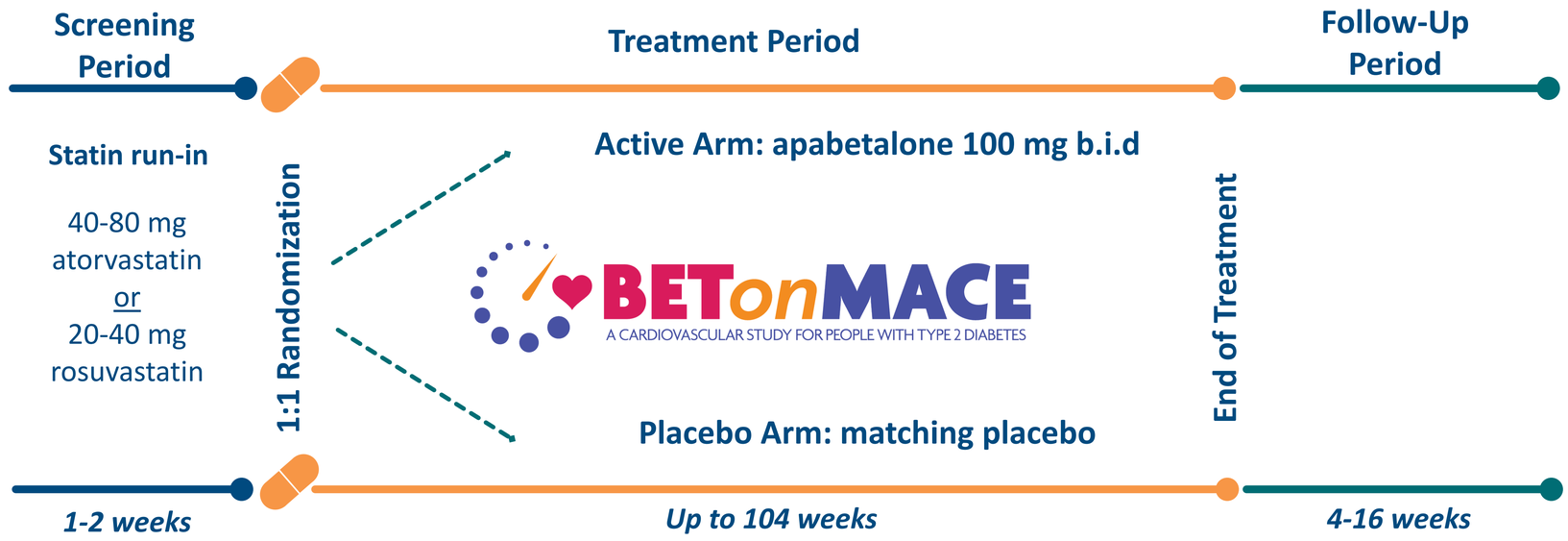
The phase 3 BETonMACE study is an international, multi-center, double-blind, randomized (1:1), placebo controlled trial in post-acute coronary syndrome (ACS) patients with diabetes mellitus and HDL-cholesterol <40 (females) and <45 (males) mg/dL. It is evaluating if apabetalone (100 mg orally b.i.d.) compared to placebo delays the time to major adverse cardiac events (MACE). All patients receive standard of care including high intensity statins, beta blockers, ace inhibitors, and dual anti-platelet inhibition treatment. 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 kidney impairment as determined by an eGFR less than 30 mL/min at screening is an exclusion criteria in the BETonMACE study. The sub-study will include the assessment of changes in kidney function in a patient population with eGFR below 60 mL/min 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 2,416 patients of which 11% have screening eGFR below 60. At completion of the study, patients will have been treated from 6 to approximately 36 months.

BETonMACE Study Design



Inclusion criteria

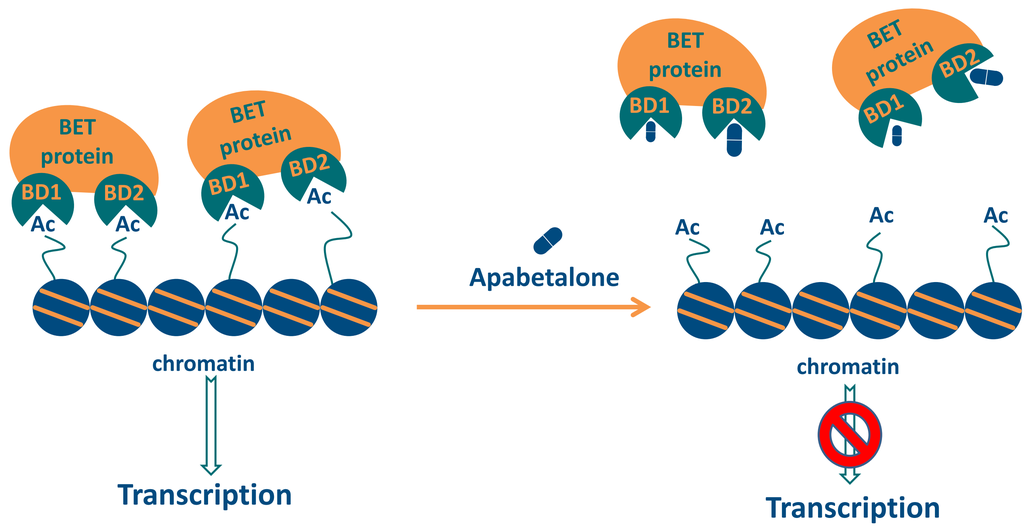
- Type II Diabetes Mellitus (HbA1c > 6.5% or history of diabetes medications)
- CAD event 7 days - 90 days prior to screening including MI, unstable angina or percutaneous coronary intervention
- HDL < 40 mg/dL for males and < 45 mg/dL for females

Primary Endpoint

- Time to first occurrence of adjudication-confirmed narrowly defined MACE (cardiovascular death, non-fatal MI and stroke)

The study is an event-based trial and continues until 250 MACE have occurred

Apabetalone Mechanism of Action



BET proteins bind acetylated lysine (Ac) on histones via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes which drives inflammation and other key markers of kidney disease progression. Apabetalone inhibits BET bromodomain proteins, causing release from chromatin and downregulation of BET sensitive gene expression

Contributed by Dr. O. Kharenko, Dr. E. Campeau, Dr. S. Wasiak, Dr. D. Gilham

Kidney Disease Subgroup Baseline Characteristics

Clinical Characteristic	N	
Age (yrs) (median, IQR)	259	71 (11)
Sex		
Male	149	57.5%
Female	110	42.5%
Concomitant Statins		
Atorvastatin	138	53.3%
Rosuvastatin	121	46.7%

Clinical Chemistry	N	Median (IQR)
eGFR, mL/min	259	49.0 (14.0)
ALP†, U/L	259	81.0 (32.5)
Creatinine, mg/dL	259	1.4 (0.5)
Albumin, g/dL	259	4.2 (0.5)
BUN, mg/dL	259	26.0 (12.0)
NLR, ratio	247	2.9 (1.7)
C-reactive protein†, mg/L	54	3.3 (7.3)
HDL, mg/dL	259	34.0 (7.0)
LDL, mg/dL	259	66.0 (42.5)
Apolipoprotein A-I†, mg/dL	51	120.0 (24.5)
Hba1c, %	254	7.3 (2.1)
Platelets, 10^9/L	247	241.0 (108.0)

† results from baseline, whereas all other values are from screening

Summary and 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 at screening, will provide further insights about epigenetics in kidney function changes and MACE effects of BET-inhibition in more than 250 post-ACS patients with diabetes, low HDL and CKD.