Background

Diabetes (DM) is associated with increased risk of macro/microvascular disease and cognitive decline. Inflammation and heightened 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 transcription profiles to physiological levels. Post-hoc analysis of Phase 2 trials with apabetalone showed 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 (sCRP).

Methods

The double-blind, placebo controlled Phase 3 BETMACE trial is testing the hypothesis that apabetalone 100 mg b.i.d, added to standard of 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; <55 mg/dL in women). CKD was defined as eGFR 30 to 59 mL/min/1.73m², and was included as a predefined subgroup. 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 59 mL/min/1.73m², inflammatory markers, lipids, and ALP as a measure of BET inhibition. In addition the Montreal Cognition Assessment (MoCA) test was performed in patients ≥70 years of age at baseline and annually.

Results

Enrollment of 2,425 patients across 13 countries and 195 centers is now complete. Baseline characteristics (median [IQR]) is as follows: LDL-C 65.0 (49.0 – 85.0) mg/dL, HDL-C 33.0 (30.0 – 37.0) mg/dL, HbA1c 7.3 (6.4 – 8.7) %, hsCRP 2.8 (1.2 – 6.2) mg/L, mean blood pressure 129/76 mmHg, and CKD in 262 patients (10.8%). Background care was based on guideline recommendations. Diabetes medications include metformin (77%), insulin (32%), sulfonylureas (25%), DPP4 inhibitors (6.5%), SGLT2 inhibitors (5.0%) and GLP-1 receptor agonists (2.1%). The CKD subpopulation differed significantly from the total population with regard to age (71 vs. 62 yrs, p<0.0001), sex (58% vs. 75%, p=0.0002), history of hypertension (92% vs. 88%, p=0.0001), history of stroke (9.9% vs. 7.6%), and current smokers (6.5% vs. 3.3%). In the 70 year and older (n4189, 18%) subgroup, 53% (n246) showed a baseline MoCA score <24, suggesting cognitive impairment.

Summary

The BETMACE trial is testing the hypothesis that selective BET inhibition with apabetalone, when added to standard 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.

Clinical Characteristics

<table>
<thead>
<tr>
<th>Age (yr) (median [min, max])</th>
<th>62 (33, 84)</th>
<th>71 (41, 84)</th>
<th>62 (33, 84)</th>
<th>61 (31, 84)</th>
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<tbody>
<tr>
<td>Sex (male)</td>
<td>1,806 (74%)</td>
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<tr>
<td>Cofactors</td>
<td>76 (47%)</td>
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<tr>
<td>Cause</td>
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BETMACE Baseline Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>All Patients Randomized</th>
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BETMACE Study Design

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

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

Exclusion criteria:
- Time to first occurrence of adjudicated endpoint not confirmed normally defined MACE (cardiovascular death, non-fatal MI and stroke)
- Recent PCI
- Recent CABG
- Recent stroke
- History of PCI
- History of CABG
- History of PCI
- NYHA class III/IV
- DVT or PE within 6 months
- History of severe hypothyroidism
- Active malignancy
- Uncontrolled hypertension
- Uncontrolled hyperglycemia
- Uncontrolled macro/microvascular disease
- Uncontrolled severe hyperlipidemia
- Uncontrolled severe hyperuricemia
- Uncontrolled severe proteinuria

Summary and Conclusions

BETMACE is a Phase 3 trial testing the cardiovascular efficacy of apabetalone, a first in class BET inhibitor, in reducing MACE in high-risk patients with DM, recent ACS, and low HDL-C when added on top of established, evidence based treatment. BETMACE will also provide insights about the potential for BET inhibition to modulate renal and cognitive function in prespecified subgroups of patients.