Cardiovascular Evaluation of the Selective BET Inhibitor Apabetalone in ACS Patients with Diabetes: Baseline Characteristics of the BETonMACE CV Outcomes Study

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Background

Vascular perturbation in acute coronary syndrome (ACS) is linked to inflammation. Bromodomain and extraterminal (BET) proteins coordinate gene transcription in response to inflammatory insult via epigenetic modulation. Epigenetic changes are particularly important in the pathogenesis of CV events in type 2 diabetes (T2DM) (Ref). Apabetalone (ABL) selectively inhibits binding between BET proteins and acetyl-lysine moieties on histone tails reducing the effects of inflammation. Post-hoc analysis of phase II trials indicated that ABL was associated with a 44% RRR in major adverse cardiac events (MACE) in patients with coronary heart disease, with more pronounced benefit among patients with T2DM or low HDL cholesterol

Purpose

BETonMACE is the first Phase III CVD outcome study with a BET inhibitor. It tests the hypothesis that BET inhibition with ABL reduces MACE in patients with Type 2 DM, recent acute coronary syndrome (ACS), and low HDL-C.

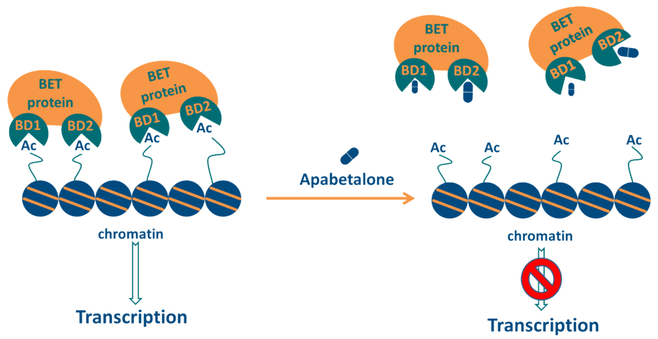
Methods

At 195 centers in 13 countries, BETonMACE includes patients with ACS 7-90 days prior to screening, T2DM, HDL-C <40 mg/dL (males) or <45 mg/dL (females), and treatment with atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily, or the maximum tolerated dose of one of these agents. Eligible patients were randomized 1:1 to treatment with ABL 100 mg orally twice daily or placebo with meals. The primary endpoint is time to first occurrence of CV death, non-fatal myocardial infarction or stroke. The trial will continue until at least 250 primary endpoints have occurred. With an assumed primary event rate of 7 per 100 patient years in the placebo group, the study has 80% power to detect a 29% reduction in MACE with ABL (or 50% power to detect a 24% reduction) with 2400 patients and an average exposure of 1.5 years.

Results

Enrollment of 2,425 patients was completed on July 4, 2018. Baseline characteristics include: male sex 74.5%; mean age 62 (SD 9.5) years; median (interquartile range) LDL-C 65.0 (36.0) mg/dL, HDL-C 33.0 (7.0) mg/dL, HbA1c 7.3 (2.3) %, and blood pressure 129/76 mmHg; eGFR<60 ml/min 11%; treatment with atorvastatin (40/80mg) 51% or rosuvastatin (20/40mg) 49%; dual anti-platelet therapy 87.5%; index ACS event MI 74%; coronary revascularization for index ACS 79%; and median time from index ACS to randomization 34 days.

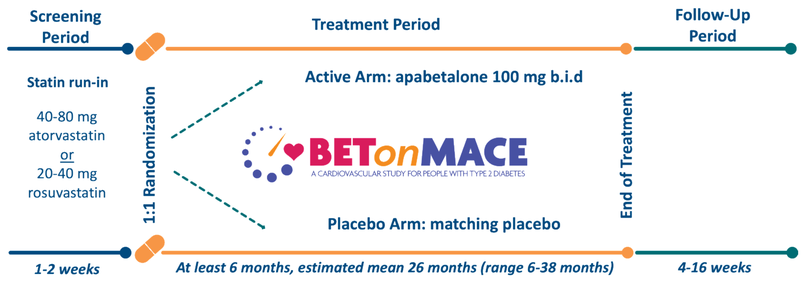
Apabetalone Mechanism of Action



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 cognitive decline. Apabetalone inhibits BET proteins, causing release from chromatin and downregulation of BET sensitive gene expression.

Pill size: selectivity of apabetalone for BD2

BETonMACE Study Design



Inclusion criteria

- Type II Diabetes Mellitus (HbA1c ≥ 6.5% or history of diabetes medications)
- Acute coronary syndrome 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 or stroke)

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

Baseline Demographics

Clinical Characteristic	N	Median (IQR)
Age (yrs)	2,425	62 (13)
Male (%)	1,807	75%
Caucasian (%)	2,115	87%
Inclusion Criteria:		
Myocardial Infarction (%)	1,783	74%
Unstable Angina (%)	640	26%
History of PCI	1,921	79%
Concomitant Medications:		
Atorvastatin	1,244	51%
40-80 mg		45%
Rosuvastatin	1,180	49%
20-40 mg		46%
Insulin (%)	863	36%
Oral T2DM Meds. (%)	2,116	87%
ACE Inhibitors / ARBs (%)	2,216	91%
Dual Antiplatelet Agents (%)	2,122	88%

Baseline Clinical Chemistry

Baseline Clinical Chemistry	N	Median (IQR)
LDL-C (mg/dL)	2,396	65 (36)
HDL-C (mg/dL)	2,414	33 (7.0)
HbA1c (%)	2,367	7.3 (2.3)
eGFR (mL/min/1.73 m^2)	2,413	99 (51)
ALP† (U/L)	2,424	78 (30)
Albumin (g/dL)	2,414	4.3 (0.4)
ApoA-1† (mg/dL)	483*	118 (20)
hsCRP† (mg/dL)	493*	2.8 (4.95)
Fibrinogen† (mg/L)	471*	385 (136)
Platelets (10^9/L)	2,293	249 (94)
NLR (ratio)	2,311	2.6 (1.4)

IQR: Interquartile Range
† results from visit 2/wk 0, whereas all other values are from visit 1/screening
*conducted on a subset only in Hungary and Argentina

Summary and Conclusions

BETonMACE is a unique proof-of-concept trial that will determine if selective BET inhibition with ABL, added to evidence-based treatments, reduces MACE in high-risk patients with T2DM, recent ACS, and low HDL-C.
Results are expected in early 2019.

References: Keating, Plutsky, El-Osta Epigenetic Changes in Diabetes and Cardiovascular Risk. Circ Res. 2016;118:1706-1722