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 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 transcriptional profiles to physiological levels. Post-hoc analysis of 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 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; <45 mg/dL in women). CKD was defined as eGFR 30 to 59 mL/min/1.7m^2, 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/1.7m^2, 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)] include 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 GLP1 receptor agonists (2.1%). The CKD subpopulation differed significantly from the total population with regard to age (71 vs. 62 y. o.), male sex (58% vs. 75%), history of hypertension (92% vs. 88%), history of stroke (9.9% vs. 7.6%), and current smokers (6.5 % vs. 13%). In the 70 year and older (n=469, 19%) subpopulation, 53% (n=246) showed a baseline MoCA score <26, 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.

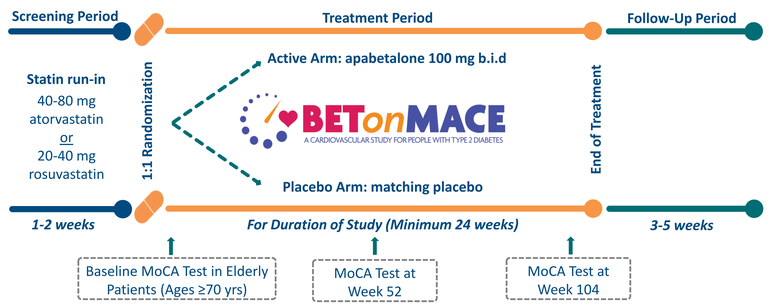
BETonMACE Baseline Characteristics

Clinical Characteristic	All Patients Randomized N	All Patients Randomized %	CKD (eGFR <60 mL/min/1.73 m²) Subgroup N	CKD (eGFR <60 mL/min/1.73 m²) Subgroup %	Non-CKD (eGFR ≥60 mL/min/1.73 m²) Population N	Non-CKD (eGFR ≥60 mL/min/1.73 m²) Population %	CKD Subgroup vs. Non-CKD Population p-value (Chi-Squared X² Test)
Age (yrs) (median) (min, max)	2,425	62 (31, 88)	262	71 (44, 88)	2,163	61 (31, 88)	*< 0.0001**
Sex (male)	1,806	74.5%	152	58.0%	1,654	76.5%	*< 0.0001*
Caucasian	2,115	87.2%	213	81.3%	1,902	87.9%	*0.002*
MoCA (≥70 yrs)	469	19.3%	147	56.1%	322	14.9%	*< 0.0001*
MoCA <26	246	52.5%	80	54.4%	166	51.6%	0.56
Index ACS Event:							
ACS / MI	1,787	73.7%	197	75.2%	1,590	73.5%	0.56
Unstable Angina	625	25.8%	63	24.0%	562	26.0%	0.50
History of PCI	1,930	79.6%	191	72.9%	1,739	80.4%	*0.004*
Medical History							
Diabetes History (median years) (IQR)		6.7 (2.2 – 13.0)		10.2 (3.8 – 18.0)		6.5 (2.1 – 12.4)	*< 0.0001 **
History of DM Medication: Yes (%)	2,301	95.8%	251	95.8%	2,050	94.8%	0.48
History of DM Medication: No (%)	124	4.2%	11	4.2%	113	5.2%	
HbA1c ≥6.5% at Visit 1	1,770	73.0%	190	72.5%	1,580	73.0%	0.86
BMI (kg/m²) (median) (IQR)		29.6 (26.7 – 33.2)		27.3 (24.5 – 30.1)		30.0 (27.0 – 33.6)	*< 0.0001 **
Hypertension	2,144	88.4%	240	91.6%	1,904	88.0%	*0.09*
Tobacco Use	313	12.9%	17	6.5%	296	13.7%	*0.001*
Prior Stroke / TIA	184	7.6%	26	9.9%	158	7.3%	0.13
Concomitant Statins							
Atorvastatin	1,245	51.3%	141	53.8%	1,104	51.0%	0.40
Rosuvastatin	1,180	48.7%	121	46.2%	1,059	49.0%	
Cardiovascular Disease Medications:							
ACE Inhibitors	1,684	69.4%	162	61.8%	1,522	70.4%	*0.005*
ARBs	583	24.0%	82	31.3%	501	23.2%	*0.004*
Beta-Blockers	2,146	88.5%	232	88.5%	1,914	88.5%	0.98
Anti-Platelet Agents	2,392	98.6%	261	99.6%	2,131	98.5%	0.15
DAPT	2,086	86.0%	226	86.3%	1,860	86.0%	0.91
Diabetes Mellitus Medications:							
Insulin	769	31.7%	90	34.4%	679	31.4%	0.33
Diabetes Medications (Ex. Insulins):	2,072	85.4%	208	79.4%	1,864	86.2%	*0.003*
Metformin	1,866	76.9%	169	64.5%	1,697	78.5%	*< 0.0001*
Sulfonylureas	608	25.1%	73	27.9%	535	24.7%	0.27
DPP-4 Inhibitors	157	6.5%	30	11.5%	127	5.9%	*0.001*
SGLT2 Inhibitors	122	5.0%	7	2.7%	115	5.3%	*0.06*
GLP-1 Agonists	51	2.1%	2	0.8%	49	2.3%	0.11

Clinical Chemistry	All Patients Randomized N	All Patients Randomized Median (IQR)	CKD (eGFR <60 mL/min/1.73 m²) Subgroup N	CKD (eGFR <60 mL/min/1.73 m²) Subgroup Median (IQR)	Non-CKD (eGFR ≥60 mL/min/1.73 m²) Population N	Non-CKD (eGFR ≥60 mL/min/1.73 m²) Population Median (IQR)	CKD Subgroup vs. Non-CKD Population p-value (Chi-Squared X² Test)
ALP† (U/L)	2,424	78 (64 – 94)	262	80 (64 – 97)	2,162	77 (64 – 94)	0.07
eGFR (mL/min/1.73m²)	2,413	99 (76 – 127)	262	49 (41 – 55)	2,151	104 (84 – 131)	*< 0.0001*
Albumin (g/dL)	2,413	4.30 (4.10 – 4.50)	262	4.20 (3.90 – 4.40)	2,151	4.30 (4.10 – 4.50)	*< 0.0001*
LDL-C (mg/dL)	2,395	65 (49 – 85)	262	65.5 (48 – 91)	2,133	65 (49 – 85)	0.62
HDL-C (mg/dL)	2,413	33 (30 – 37)	262	34 (30 – 37)	2,151	33 (30 – 37)	0.29
ApoA-1† (mg/dL)	483	118 (109 – 129)	50	119 (108 – 133)	433	118 (109 – 129)	0.95
hsCRP† (mg/dL)	493	2.81 (1.20 – 6.15)	53	3.45 (1.12 – 8.43)	440	2.74 (1.12 – 5.93)	0.23
Fibrinogen† (mg/dL)	471	385 (318 – 454)	51	396 (332 – 452)	420	384 (316 – 454)	0.32
HbA1c (%)	2,369	7.30 (6.40 – 8.70)	257	7.20 (6.40 – 8.50)	2,112	7.30 (6.40 – 8.70)	0.27
Platelets (10⁹/L)	2,295	249 (207 – 301)	251	241 (197 – 307)	2,044	250 (208 – 300)	0.34
NLR (ratio)	2,313	2.57 (1.99 – 3.36)	251	2.87 (2.20 – 3.90)	2,062	2.54 (1.95 – 3.31)	*< 0.0001*

† results from visit 2/wk 0, whereas all other values are from visit 1/screening
IQR: Interquartile Range
** Mann-Whitney U-Test (Wilcoxon Rank-Sum Test)*

BETonMACE Study Design



Inclusion criteria

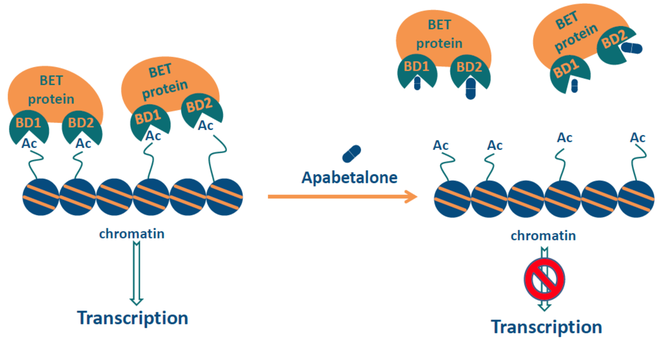
- Type II Diabetes Mellitus (HbA1c > 6.5% or history of diabetes medications)
- CAD event 7 days - 90 days prior to screening including MI, unstable angina or percutaneous coronary intervention
- HDL < 45 mg/dL for males and < 45 mg/dL for females

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 cognitive decline. Apabetalone is a small molecute that binds preferentially BD2 thereby inhibiting BET proteins, causing release from chromatin and downregulation of BET sensitive gene expression.

Pill size: selectivity of apabetalone for BD2

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Summary and Conclusions

- BETonMACE 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.
- BETonMACE will also provide insights about the potential for BET inhibition to modulate renal and cognitive function in prespecified subgroups of patients.