BET Protein Inhibition and Cognition: A Pre-Specified Substudy of the BETonMACE Phase 3 Trial Evaluating Apabetalone in Patients with Diabetes and Acute Coronary Syndrome

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Abstract

Background: Type 2 diabetes (T2D) and cardiovascular disease (CVD) are associated with impaired cognition. Epigenetic dysregulation by bromodomain and extraterminal domain (BET) proteins is implicated in CVD, as well as T2D and dementia. Apabetalone (ABL) is a selective BET inhibitor which in phase 2 trials was associated with a significant 55% reduction in major adverse CV events. Effects of ABL on cognition are unknown.

Methods: The ongoing Phase 3 cardiovascular outcomes trial BETonMACE compares ABL (100 mg orally twice daily) with placebo in 2,425 patients with recent acute coronary syndrome (ACS), T2D, and low HDL cholesterol, enrolled at 195 sites in 13 countries. The primary outcome is time to first occurrence of CV death, myocardial infarction, or stroke. Cognition, a pre-specified secondary outcome, is assessed at baseline and annually in patients 70 years and older by the Montreal Cognition Assessment (MoCA).

MoCA covers several cognitive domains including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A score of ≤25 of 30(31) indicates cognitive impairment. MoCA score change from preliminary blinded data shows a standard deviation of 3.2 points and a sample size of 54 subjects per arm to provide a 90% power to detect a mean between-group difference of 2 points at p<0.05.

Results: Baseline MoCA (versions 7.1, 7.2, and 7.3) was performed in 19.3% of BETonMACE participants (n=467, median age 73). Compared to the entire BETonMACE cohort, the cognition subset is older (median age 73 vs. 62 yrs), comprises more women (36.0% vs. 25.5%), has lower eGFR (70 vs. 99 ml/min) and higher neutrophil/lymphocyte ratio (NLR) (2.77 vs. 2.56) (all p<0.0001). At baseline 53% (n=246) show a MoCA score ≤25, indicating cognitive impairment. Demographics and basic serum chemistry in the MoCA score ≤25 population does not differ significantly from the whole MoCA population.

Conclusions: Cognitive impairment, as assessed by MoCA, is common among elderly patients with diabetes and ACS. BETonMACE will determine whether the first-in-class BET-inhibitor ABL affects the time course of cognitive function in these patients, as well as macrovascular CV events.

Methods

BETonMACE is an international, multi-center, double blind, randomized (1:1), placebo controlled trial of apabetalone (100 mg orally bid) in ~2,400 patients with acute coronary syndrome, type 2 diabetes, and low HDL-cholesterol. All patients receive high intensity statin treatment as well as other evidence-based treatments. The primary outcome is time to first occurrence of CV death, myocardial infarction, or stroke.

A pre-specified secondary analysis of BETonMACE will examine the effects of apabetalone on cognitive function using the Montreal Cognitive Assessment (MoCA). The MoCA is designed as a rapid screening instrument for cognitive impairment and is sensitive to mild changes. It assesses different cognitive domains including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A score of 26 or above is considered normal.

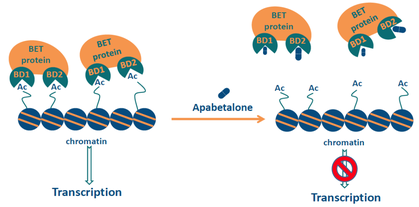
In patients at least 70 years of age the MoCA is administrated at randomization, yearly, and at termination of the trial. Cognition assessment by MoCA is a pre-specified variable comparing change from baseline in both treatment groups, adjusted for age, education, and baseline MoCA score. Additionally, a subgroup of patients with MoCA score ≤25 will be analyzed separately.

Cognition Subgroup Baseline Characteristics

Clinical Characteristic	All Patients Randomized N	All Patients Randomized Median (min, max)	Patients Randomized with Baseline MoCA Completed N	Patients Randomized with Baseline MoCA Completed Median (min, max)	P-value vs. All Randomized Patients (Mann-Whitney)	Patients Randomized with Baseline MoCA ≤ 25 N	Patients Randomized with Baseline MoCA ≤ 25 Median (min, max)	P-value vs. All Randomized Patients (Mann-Whitney)
Age (yrs)		62 (31, 88)		73 (69, 88)	**p < 0.0001**		74 (69, 86)	**p < 0.0001**
Sex (male, %)		74.5%		64.0%			63.8%	
Caucasian (%)	2,425	87.2%	467	88.9%		246	83.7%	
Education (≤12 years, %)		-		68.7%			74.0%	
MoCA Score		-		25 (7, 30)			22 (7, 25)	
Index ACS Event:								
ACS / MI	1,785	73.6%	325	69.6%		176	71.5%	
Unstable Angina	630	26.0%	140	30.0%		70	28.5%	
PCI for Index ACS	1,924	79.3%	342	73.2%		170	69.1%	
Medical History								
Hypertension	2,135	88.0%	442	94.6%		228	92.7%	
Tobacco Use	309	12.7%	29	6.2%		19	7.7%	
Prior Stroke / TIA	250	10.3%	75	16.1%		42	17.1%	
Concomitant Statins								
Atorvastatin	1,245	51.3%	231	49.5%		121	49.2%	
Rosuvastatin	1,180	48.7%	236	50.5%		125	50.8%	
Diabetes Medications:								
Insulin	878	36.2%	154	33.0%		87	35.4%	
Metformin	1,933	79.7%	351	75.2%		182	74.0%	
Sulfonylureas	685	28.2%	148	31.7%		82	33.3%	
GLP-1 Agonists	10	0.4%	2	0.4%		2	0.8%	
DPP-4 Inhibitors	277	11.4%	56	12.0%		32	13.0%	
SGLT2 Inhibitors	266	11.0%	24	5.1%		13	5.3%	
CV Medications:								
ACE Inhibitors	1,746	72.0%	311	66.6%		152	61.8%	
ARBs	693	28.6%	154	33.0%		87	35.4%	
Beta-Blockers	2,180	89.9%	426	91.2%		225	91.5%	
Anti-Platelet Agents	2,394	98.7%	458	98.1%		243	98.8%	
DAPT	2,103	86.7%	390	83.5%		208	84.6%	
Clinical Chemistry								
HDL-C (mg/dL)	2,413	33 (14, 47)	464	34 (20, 46)	**0.008**	243	34 (21, 46)	0.14
ApoA-1† (mg/dL)	483	118 (58, 179)	91	121 (58, 179)	0.36	44	122 (58, 162)	0.17
LDL-C (mg/dL)	2,395	65 (3, 365)	462	64 (10, 365)	0.36	241	64 (10, 247)	0.69
eGFR (mL/min/1.73m²)	2,412	99 (26, 599)	463	70 (28, 599)	**< 0.0001**	242	70 (28, 142)	**< 0.0001**
hsCRP† (mg/dL)	493	2.8 (0.2 162.1)	94	2.5 (0.2, 101.7)	0.45	46	3.2 (0.2, 101.7)	0.81
NLR (ratio)	2,310	2.6 (0.4 16.5)	441	2.8 (0.7, 16.5)	**< 0.0001**	234	2.9 (0.8, 16.5)	**0.001**
ALP† (U/L)	2,424	78 (5, 915)	467	76 (29, 777)	0.14	246	77 (30, 777)	0.46

† results from visit 2/wk 0, whereas all other values are from visit 1/screening

Apabetalone Mechanism of Action

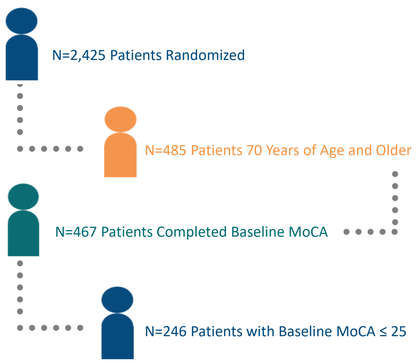


BET proteins bind acetylated lysine (Ac) on histones via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes which drives inflammation and other key markers of cognitive decline. Apabetalone inhibits BET proteins, causing release from chromatin and downregulation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

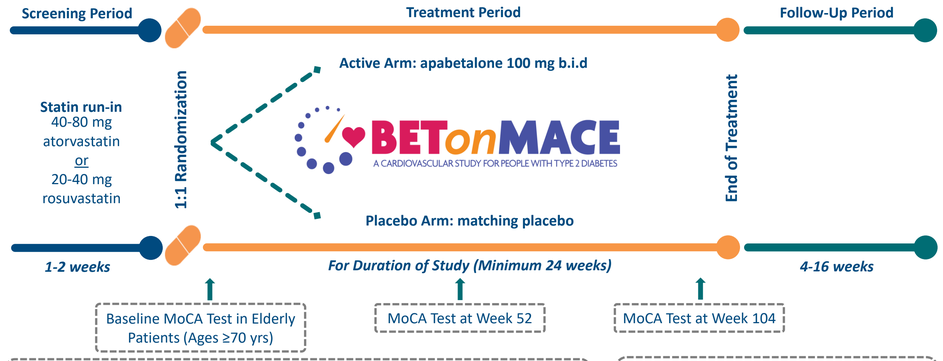
Pill size: selectivity of apabetalone for BD2

Contributed by: Dr. O. Kharenko, Dr. E. Campeau, Dr. S. Wasiak, and Dr. D. Gilham of Resverlogix Corp., Calgary, AB, Canada

Cognition Subgroup



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

Summary and Conclusions

Cognition assessment by MoCA is being evaluated in participants ≥70 years of age in BETonMACE, a phase 3 trial testing the cardiovascular efficacy of a first-in-class BET-inhibitor - apabetalone. Baseline demographics show that the ≥70 y.o. populations compared to the whole BETonMACE population have higher stroke-TIA and hypertension prevalence and serum chemistry data indicates that the cognition subset has lower eGFR (70 vs. 99) and higher NLR (2.77 vs. 2.56). These observations are likely due to the older age of the cognition subgroup relative to the BETonMACE cohort (median age 73 vs. 62 yrs) (p<0.001 for all observations). This is one of the largest cognition assessment of its kind. It will provide insights about the potential for BET inhibition to modulate cognitive function in elderly patients with ASCVD and diabetes.

Disclosure: Dr. Kausik K. Ray is chair of the Resverlogix Corp. Clinical Steering Committee for the Phase 3 BETonMACE trial