Effects of the Epigenetic BET-Inhibitor Small Molecule Apabetalone on Cognition in Patients with Diabetes and Cardiovascular Disease

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Objectives

Type 2 diabetes (T2D) and cardiovascular disease (CVD) associate with cognitive impairment, likely to be of vascular origin. Epigenetic dysregulation by bromodomain and extraterminal domain (BET) proteins is implicated in CVD, T2D and dementia. Apabetalone is a selective BET-inhibitor that in phase 2 studies showed reduction in CVD events. Apabetalone counters the expression of cytokines and endothelial adhesion molecules which have been associated with neuroinflammation and cognitive impairment in preclinical models. Apabetalone clinical studies show time, dose-dependent and significant reduction in serum Alkaline Phosphatase (ALP), a reported marker of vascular calcification and cognitive risk. Effects of apabetalone on human cognition are unknown.

Methods

The ongoing phase 3 trial BETonMACE compares apabetalone (100 mg orally twice daily) with placebo in 2,425 patients with recent acute coronary syndrome (ACS), T2D, and low HDL cholesterol, at 195 sites in 13 countries. The primary outcome is time-to-first-occurrence of CV-death, myocardial infarction, or stroke. Average treatment-duration is expected to be 26 months (range 12-40 months). Cognition, a pre-specified exploratory outcome, is assessed at baseline and annually in patients 70 years and older by the Montreal Cognition Assessment (MoCA). A score of ≤25 indicates cognitive impairment. MoCA score change from historical data shows a standard deviation of 3.2 points predicting a necessary 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.

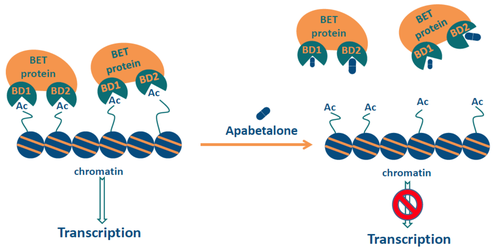
Results

Baseline MoCA (versions 7.1, 7.2, and 7.3 depending on language) was performed in 19% of BETonMACE participants (n=469, median age 73). The MoCA population included relatively more women than the total population, i.e. 36% vs. 25.5%. At baseline 52% (n=246) showed a MoCA score ≤25, indicating cognitive impairment. Demographics and basic serum chemistry in the MoCA score ≤25 population did not differ significantly from the population with MoCA >25 (n=223), except low MoCA was associated with higher serum ALP. Lower MoCA was mostly contributed by memory, language, attention, and visuospatial/executive function domains.

Conclusions

Cognitive impairment is common among elderly patients with T2D and ACS. BETonMACE will determine whether the first-in-class BET-inhibitor apabetalone affects cognitive function in these patients.

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

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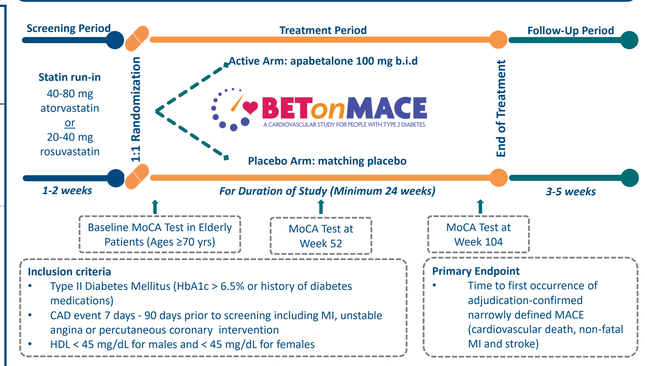
Cognition Subgroup Baseline Characteristics

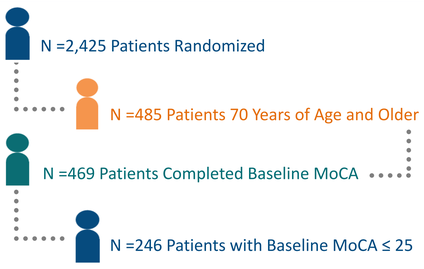
Clinical Characteristic	All Patients Randomized N	All Patients Randomized %	Cognition Subgroup N	Cognition Subgroup %	Patients Randomized with Baseline MoCA >25 N	Patients Randomized with Baseline MoCA >25 %	Patients Randomized with Baseline MoCA ≤25 N	Patients Randomized with Baseline MoCA ≤25 %	Patients with MoCA >25 vs. Patients with MoCA ≤25 p-value (Fisher Exact Test)
Age (yrs) (median) (min, max)	2,425	62 (31, 88)	469	73 (69, 88)	223	73 (70, 88)	246	74 (69, 86)	0.13 *
Sex (male)	1,806	74.5%	300	64.0%	144	64.6%	156	63.4%	0.85
Caucasian	2,115	87.2%	417	88.9%	211	94.6%	206	83.7%	**0.0002**
Education (≤12 years)	-	-	360	76.8%	162	72.6%	198	80.5%	**0.05**
MoCA Score (mean) (SD)	-		24.4 (4.1)		27.7 (1.4)		21.4 (3.4)		**<0.0001 ***
Domains (mean scores) (SD):									
Visuospatial / Executive Function (/5)	-	-	3.8 (1.2)		4.3 (0.8)		3.3 (1.3)		**<0.0001 ***
Naming (/3)	-	-	2.9 (0.4)		3.0 (0.1)		2.8 (0.5)		**<0.0001 ***
Attention (Digits, Letters, Subtraction) (/6)	-	-	4.7 (1.4)		5.5 (0.8)		4.0 (1.5)		**<0.0001 ***
Language (Repetition, Fluency) (/3)	-	-	2.1 (0.9)		2.6 (0.7)		1.6 (0.9)		**<0.0001 ***
Abstraction (/2)	-	-	1.7 (0.6)		1.9 (0.4)		1.5 (0.7)		**<0.0001 ***
Memory (Recall) (/5)	-	-	2.8 (1.6)		3.8 (1.1)		1.9 (1.4)		**<0.0001 ***
Orientation (/6)	-	-	5.8 (0.7)		6.0 (0.2)		5.7 (0.9)		**<0.0001 ***
Index ACS Event:									
ACS / MI	1,787	73.7%	327	69.7%	150	67.3%	177	72.0%	0.31
Unstable Angina	625	25.8%	139	29.6%	70	31.4%	69	28.0%	0.48
History of PCI	1,930	79.6%	343	73.1%	173	77.6%	170	69.1%	**0.05**
Medical History									
Diabetes History (median years) (IQR)		6.7 (10.8)		9.8 (12.7)		10.0 (13.6)		9.7 (11.4)	0.81 *
History of taking Diabetes Medication: Yes (%)	2,322	95.8%	445	94.9%	212	95.1%	233	94.7%	1.00
History of taking Diabetes Medication: No (%)	103	4.2%	24	5.1%	11	4.9%	13	5.3%	
HbA1c ≥6.5% at Visit 1	1,770	73.0%	317	67.6%	148	66.4%	169	68.7%	0.62
BMI (kg/m^2) (median) (IQR)		29.6 (6.6)		28.7 (6.3)		28.7 (5.8)		28.6 (6.6)	0.31 *
Hypertension	2,144	88.4%	445	94.9%	217	97.3%	228	92.7%	**0.03**
Tobacco Use	313	12.9%	30	6.4%	10	4.5%	20	8.1%	0.13
Prior Stroke / TIA	184	7.6%	55	11.7%	24	10.8%	31	12.6%	0.57
Concomitant Statins									
Atorvastatin	1,245	51.3%	232	49.5%	111	49.8%	121	49.2%	0.93
Rosuvastatin	1,180	48.7%	237	50.5%	112	50.2%	125	50.8%	
Diabetes Mellitus Medications:									
Insulin	907	37.4%	157	33.5%	68	30.5%	89	36.2%	0.20
Diabetes Medications (Excluding Insulins):	2,139	88.2%	407	86.8%	194	87.0%	213	86.6%	1.00
Metformin	1,954	80.6%	355	75.7%	172	77.1%	183	74.4%	0.52
Sulfonylureas	699	28.8%	152	32.4%	68	30.5%	84	34.1%	0.43
GLP-1 Agonists	79	3.3%	6	1.3%	1	0.4%	5	2.0%	0.22
DPP-4 Inhibitors	292	12.0%	58	12.4%	25	11.2%	33	13.4%	0.49
SGLT2 Inhibitors	290	12.0%	28	6.0%	14	6.3%	14	5.7%	0.85
Cardiovascular Disease Medications:									
ACE Inhibitors	1,764	72.7%	319	68.0%	162	72.6%	157	63.8%	**0.05**
ARBs	709	29.2%	157	33.5%	67	30.0%	90	36.6%	0.14
Beta-Blockers	2,193	90.4%	428	91.3%	203	91.0%	225	91.5%	0.87
Anti-Platelet Agents	2,396	98.8%	460	98.1%	217	97.3%	243	98.8%	0.32
DAPT	2,116	87.3%	393	83.8%	185	83.0%	208	84.6%	0.71
Clinical Chemistry		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
ALP† (U/L)	2,424	78 (30)	469	76 (30)	223	76 (30)	246	77 (31)	0.63 *
eGFR (mL/min/1.73m^2)	2,413	99 (51)	467	70 (29)	223	71 (32)	244	70 (28)	0.21 *
Albumin (g/dL)	2,413	4.3 (0.4)	467	4.2 (0.4)	223	4.2 (0.4)	244	4.2 (0.5)	**0.04 ***
LDL-C (mg/dL)	2,395	65 (36)	465	64 (35)	223	63 (34)	242	64 (36)	0.73 *
HDL-C (mg/dL)	2,413	33 (7.0)	467	34 (6.0)	223	34 (7.0)	244	34 (6.0)	0.47 *
ApoA-1† (mg/dL)	483	118 (20)	91	121 (22)	47	117 (25)	44	122 (14)	0.34 *
hsCRP† (mg/dL)	493	2.81 (4.95)	94	2.46 (5.19)	48	1.82 (3.45)	46	3.16 (5.68)	0.28 *
Fibrinogen† (mg/dL)	471	385 (136)	91	387 (118)	47	388 (110)	44	386 (142)	0.75 *
HbA1c (%)	2,369	7.3 (2.3)	456	7.0 (1.8)	216	7.0 (1.8)	240	7.1 (2.1)	0.38 *
Platelets (10^9/L)	2,295	249 (94)	442	237 (93)	208	243 (95)	234	231 (89)	0.56 *
NLR (ratio)	2,313	2.57 (1.37)	445	2.76 (1.52)	209	2.68 (1.54)	236	2.87 (1.55)	0.54 *

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

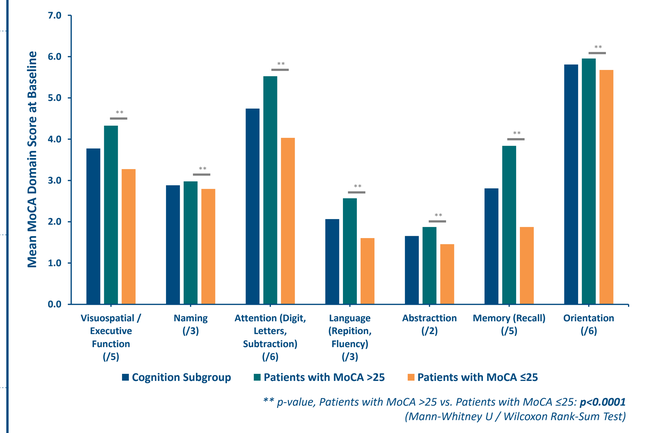
BETonMACE Study Design



Cognition Subgroup



MoCA Domain Scores



*** p-value, Patients with MoCA >25 vs. Patients with MoCA ≤25: **p<0.0001** (Mann-Whitney U / Wilcoxon Rank-Sum Test)*

Summary and Conclusions

- Cognitive impairment is common among elderly patients with T2D and ACS.
- 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.
  - This is one of the largest cognition assessment of its kind.
- BETonMACE will provide insights about the potential for BET inhibition to modulate cognitive function in elderly patients with ASCVD and diabetes, as well as macrovascular CV events.