BET-Inhibition by Apabetalone and Cognitive Effects: A Pre-Specified MoCA Analysis Nested in the BETonMACE Randomized Controlled Trial

Jeffrey Cummings[1], Gregory G. Schwartz[2], Stephen J. Nicholls[3], Aziz Khan[4], Christopher Halliday[4], Peter P. Toth[5], Michael Sweeney[6], Jan O. Johansson[6], Norman C.W. Wong[4], Ewelina Kulikowski[4], Kamyar Kalantar-Zadeh[7], Kenneth Lebioda[4], Henry N. Ginsberg[8], **Bengt Winblad**[9], Henrik Zetterberg[10,11,12], and Kausik K. Ray[13]

[1]Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, Nevada, United States of America; [2]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, United States of America; [3]Victorian Heart Institute, Monash University, Melbourne, Australia; [4]Resverlogix Corporation, Calgary, Alberta, Canada; [5]Cicarrone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America; [6]Resverlogix Corporation, San Francisco, California, United States of America; [7]Division of Nephrology and Hypertension, University of California Irvine, Irvine, California, United States of America; [8]Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY Department of Neurobiology, New York City, New York, United States of America; [9]Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Solna, Sweden, and Karolinska University Hospital, Theme Inflammation and Aging, Huddinge, Sweden; [10]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden; [11]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; [12]UK Dementia Research Institute at UCL, London, United Kingdom and Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom; [13]Imperial Centre for Cardiovascular Disease Prevention, Imperial College, London, United Kingdom

Background

Epigenetic changes may contribute importantly to cognitive decline in late life including Alzheimer's disease (AD) and vascular dementia (VaD). Bromodomain and extra-terminal (BET) proteins are epigenetic "readers" that may distort normal gene expression and contribute to chronic disorders.

Objectives

To assess the effects of apabetalone, a small molecule BET protein inhibitor, on cognitive performance of patients 70 years or older participating in a randomized trial of patients at high risk for major cardiovascular events (MACE).

Methods

The Montreal Cognitive Assessment (MoCA) was performed on all patients 70 years or older at the time of randomization. 464 participants were randomized to apabetalone or placebo in the cognition sub-study. In a prespecified analysis, participants were assigned to one of three groups: MoCA score ≥ 26 (normal performance), MoCA score 25 – 22 (mild cognitive impairment), and MoCA score ≤ 21 (dementia). Exposure to apabetalone was equivalent in the treatment groups in each MoCA-defined group.

Results

Apabetalone was associated with an increased total MoCA score in participants with baseline MoCA score of ≤ 21 ($p = 0.02$) mostly contributed by the abstraction and recall domains (both $p<0.1$). There was no significant difference in change from baseline in the treatment groups with higher MoCA scores. Serum ALP was significantly and consistently reduced by apabetalone across the cohorts, regardless of MoCA baseline category. In the cognition study, more patients randomized to apabetalone discontinued study drug for adverse effects (11.3% vs 7.9%).

Table 1. Baseline Patient Characteristics

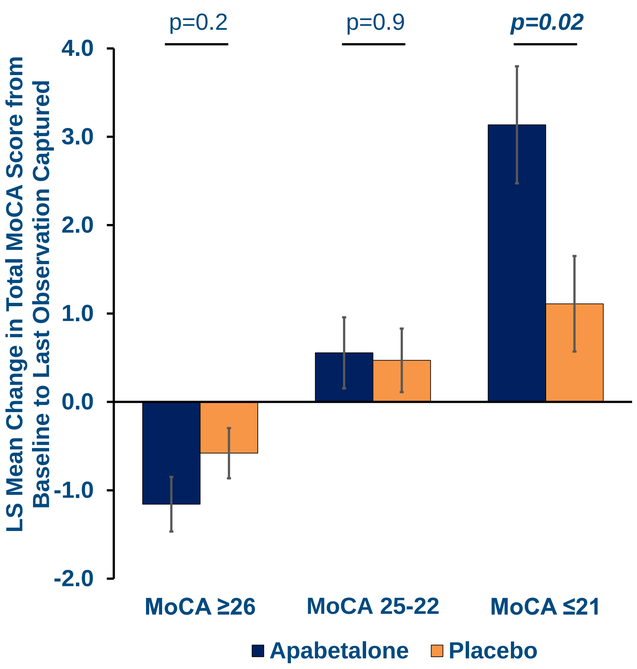
Characteristic	Patients with MoCA ≥ 26		Patients with MoCA 25 – 22		Patients with MoCA ≤ 21	
	Apabetalone (N=104)	Placebo (N=119)	Apabetalone (N=64)	Placebo (N=80)	Apabetalone (N=44)	Placebo (N=53)
Age (years) *	73 (71 - 76)	73 (71 - 76)	73 (71 - 77)	73.5 (71 - 76)	73.5 (71 - 76)	75 (72 - 77)
Males, n (%)	72 (69.2%)	72 (60.5%)	45 (70.3%)	53 (66.3%)	25 (56.8%)	30 (56.6%)
Caucasian, n (%)	98 (94.2%)	113 (95.0%)	57 (89.1%)	71 (88.8%)	**30 (68.2%)**	**47 (88.7%)**
Body mass index (kg/m^2) †	29.5 (4.5)	29.5 (4.3)	29.4 (4.2)	29.2 (5.2)	28.4 (4.9)	29.0 (4.8)
Hypertension, n (%)	100 (96.2%)	117 (98.3%)	60 (93.8%)	71 (88.8%)	43 (97.7%)	49 (92.5%)
Current or ex-smoker, n (%)	6 (5.8%)	4 (3.4%)	6 (9.4%)	7 (8.8%)	3 (6.8%)	1 (1.9%)
Duration of diabetes (years) †	10.9 (8.7)	10.9 (9.1)	10.2 (8.4)	10.1 (6.8)	13.3 (9.7)	11.0 (9.5)
Index ACS event						
STEMI, n (%)	28 (41.8%)	28 (35.0%)	15 (35.7%)	24 (40.7%)	19 (57.6%)	21 (56.8%)
Non-STEMI, n (%)	39 (58.2%)	52 (65.0%)	27 (64.3%)	35 (59.3%)	14 (42.4%)	16 (43.2%)
Unstable angina, n (%)	35 (33.7%)	35 (30.2%)	22 (34.4%)	20 (25.3%)	11 (25.0%)	15 (28.3%)
Time from index ACS to randomization (days) *	31 (23 - 63)	30 (23 - 52)	31 (24 - 62)	39 (27 - 59)	41 (28 - 67)	37 (25 - 62)

Table 2. Medication Use at Baseline

Medication	Patients with MoCA ≥ 26		Patients with MoCA 25 – 22		Patients with MoCA ≤ 21	
	Apabetalone (N=104)	Placebo (N=119)	Apabetalone (N=64)	Placebo (N=80)	Apabetalone (N=44)	Placebo (N=53)
Cardiovascular Medications						
Atorvastatin, n (%)	50 (48.1%)	61 (51.3%)	34 (53.1%)	40 (50.0%)	22 (50.0%)	24 (45.3%)
Rosuvastatin, n (%)	54 (51.9%)	58 (48.7%)	30 (46.9%)	40 (50.0%)	22 (50.0%)	29 (54.7%)
High-intensity statin, n (%)	89 (85.6%)	99 (83.2%)	56 (87.5%)	65 (81.3%)	38 (86.4%)	47 (88.7%)
Ezetimibe, n (%)	2 (1.9%)	6 (5.0%)	1 (1.6%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
ACE inhibitor/ARBs, n (%)	99 (95.2%)	112 (94.1%)	57 (89.1%)	74 (92.5%)	41 (93.2%)	48 (90.6%)
Beta-blockers, n (%)	96 (92.3%)	107 (89.9%)	62 (96.9%)	72 (90.0%)	39 (88.6%)	47 (88.7%)
Anti-platelet agents, n (%)	100 (96.2%)	117 (98.3%)	63 (98.4%)	79 (98.8%)	44 (100.0%)	52 (98.1%)
Diabetes Medications						
Metformin, n (%)	78 (75.0%)	97 (81.5%)	**52 (81.3%)**	**52 (65.0%)**	38 (86.4%)	42 (79.2%)
Insulin, n (%)	30 (28.8%)	38 (31.9%)	26 (40.6%)	25 (31.3%)	20 (45.5%)	17 (32.1%)
Sulfonylureas, n (%)	35 (33.7%)	33 (27.7%)	26 (40.6%)	20 (25.0%)	17 (38.6%)	19 (35.8%)
DPP4 inhibitors, n (%)	13 (12.5%)	19 (16.0%)	13 (20.3%)	14 (17.5%)	6 (13.6%)	5 (9.4%)
SGLT2 inhibitors, n (%)	6 (5.8%)	9 (7.6%)	6 (9.4%)	3 (3.8%)	0 (0.0%)	3 (5.7%)
GLP1 receptor agonists, n (%)	0 (0.0%)	2 (1.7%)	1 (1.6%)	1 (1.3%)	0 (0.0%)	2 (3.8%)

P-values comparing groups at baseline were calculated using chi-square test for categorical variables, z-test (†) for normal continuous variables, and Mann-Whitney Wilcoxon test (*) for non-normal continuous variables.
P-values of <0.05 are considered statistically significant and are highlighted in **bold**.

Change in Total MoCA Score from Baseline to Last Observation Captured

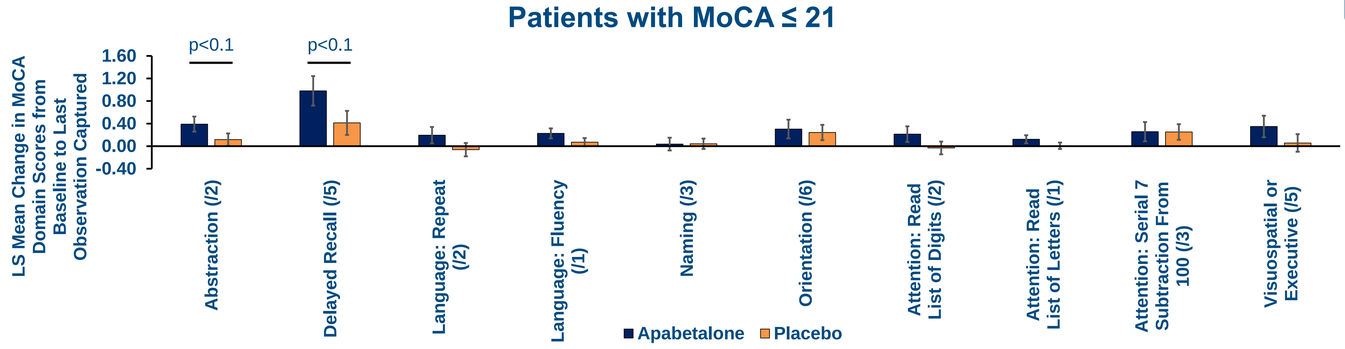


P-values were calculated using ANCOVA statistical analysis to compare change in MoCA scores from baseline to last observation captured between apabetalone-treated patients and placebo with baseline MoCA scores serving as a covariate and treatment arm as a factor.
Data shown as LS Mean Change (Standard Error of the Mean).

Table 3. MoCA and Alkaline Phosphatase (ALP)

Parameter	Patients with MoCA ≥ 26		Patients with MoCA 25 – 22		Patients with MoCA ≤ 21	
	Apabetalone (N=104)	Placebo (N=119)	Apabetalone (N=64)	Placebo (N=80)	Apabetalone (N=44)	Placebo (N=53)
Baseline MoCA Score, points †	27 (26 – 29)	28 (26 – 29)	24 (23 – 25)	24 (23 – 25)	18.5 (16 – 20)	18 (16 – 20)
Baseline ALP, U/L *	76 (63 – 92.3)	77.0 (61.0 – 91.0)	74.0 (61.8 – 84.0)	76.5 (61.0 – 93.3)	81.0 (59.8 – 101.3)	77.0 (66.0 – 92.0)
Patients with subsequent MoCA measurements	N=85	N=101	N=55	N=69	N=30	N=45
Baseline ALP, U/L	76.0 (64.0 – 88.0)	76.0 (61.0 – 91.0)	74.0 (60.5 – 84.5)	76.0 (61.0 – 94.0)	82.5 (65.8 – 101.8)	73.0 (65.0 – 95.0)
Follow-Up, U/L (median of all time points)	67.0 (55.0 – 78.0)	74.5 (60.0 – 90.5)	65.0 (55.0 – 73.0)	74.0 (63.0 – 95.0)	75.0 (60.3 – 94.9)	70.0 (61.0 – 92.0)
Percent Change, % *	**-10.6 (-20.5 – -3.4)**	**0.0 (-9.0 – 10.6)**	**-13.7 (-19.9 – -3.9)**	**-1.1 (-12.0 – 6.8)**	**-10.2 (-18.6 – -5.1)**	**-5.3 (-11.5 – 2.2)**

Change in MoCA Domain Scores from Baseline to Last Observation Captured in Patients with MoCA ≤ 21



Conclusions

In this randomized controlled study, apabetalone was associated with improved cognition as measured by MoCA scores in those with baseline scores of 21 or less.
BET protein inhibitors warrant further investigation for late life cognitive disorders.