Favorable Cognitive Effects of the BET Protein Inhibitor Apabetalone in Patients 70 and Older

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

[1]Resverlogix Corporation, Calgary, Alberta, Canada; [2]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; [3]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, United States of America; [4]Victorian Heart Institute, Monash University, Melbourne, Australia; [5]Cicarrone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America; [6]Division of Nephrology and Hypertension, University of California Irvine, Irvine, California, United States of America; [7]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; [8]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; [9]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden; [10]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; [11]UK Dementia Research Institute at UCL, London, United Kingdom; [12]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom; [13]Imperial Centre for Cardiovascular Disease Prevention, Imperial College, London, United Kingdom

Background

Cognitive decline in late life including Alzheimer's disease (AD) and vascular dementia (VaD) may be caused by epigenetic change. Bromodomain and extra-terminal (BET) proteins are epigenetic transcriptional "readers" found to contribute to chronic disease. Apabetalone, a small molecule BET protein inhibitor for oral administration, was assessed for therapeutic effects on cognitive performance in a randomized trial of patients at high risk for cardiovascular disease (CVD).

Methods

In the BETonMACE post-acute coronary syndrome (ACS) trial in type 2 diabetes mellitus patients were randomized to apabetalone capsule 100 mg b.i.d. or placebo (n=2,425). The Montreal Cognitive Assessment (MoCA) was performed on all patients 70 years or older at baseline (n=464) and yearly in the embedded cognition 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).

Results

Apabetalone exposure was equivalent in each of the three MoCA-score defined groups. Apabetalone treatment over approximately two years was associated with an increased total MoCA score in participants with baseline MoCA score of ≤ 21 (p = 0.02). Onset of cognition benefit appeared after 12 months treatment. There was no significant difference in change from baseline in the treatment groups with higher MoCA scores.

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)

P-values comparing groups were calculated using chi-square tests for categorical variables and Wilcoxon tests (*) or z-tests (†) for continuous variables. P-values of <0.05 are considered statistically significant and are highlighted in **bold**.

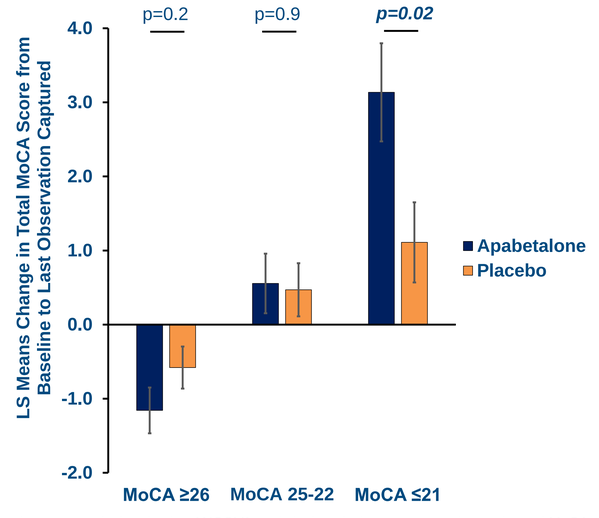
Table 2. Medication Use at Baseline

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%)

Table 3. Baseline MoCA and Biochemical Parameters

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)
MoCA Score, points†	27 (26 – 29)	28 (26 – 29)	24 (23 – 25)	24 (23 – 25)	18.5 (16 – 20)	18 (16 – 20)
HbA1c, % *	6.9 (6.3 – 7.9)	7.1 (6.3 – 8.2)	7.3 (6.5 – 8.1)	7.0 (6.2 – 7.9)	7.3 (6.5 – 8.9)	7.0 (6.4 – 8.5)
Serum glucose, mg/dL *	134.5 (116.9 – 157.9)	129.7 (107.2 – 161.1)	137.3 (112.3 – 182.7)	127.2 (109.9 – 167.7)	140.1 (106.8 – 179.5)	130.6 (100.2 – 183.0)
Total cholesterol, mg/dL *	126.1 (108.2 – 149.6)	129.2 (113.3 – 155.5)	123.4 (102.4 – 143.8)	129.9 (109.0 – 149.7)	117.2 (103.3 – 140)	133.8 (110.6 – 150.8)
LDL cholesterol, mg/dL *	62.8 (46 – 85)	63.4 (50.9 – 81.0)	66.3 (46.5 – 81.7)	66.3 (50.1 – 85.0)	57.0 (45.5 – 77.3)	64.0 (52.7 – 82.4)
HDL cholesterol, mg/dL *	**33.3 (29.8 – 37.1)**	**34.8 (31.7 – 38.7)**	32.9 (30.1 – 37.1)	34.0 (31.3 – 37.5)	33.6 (29.3 – 37.3)	34.8 (31.3 – 37.9)
Triglycerides, mg/dL *	146.6 (118.9 – 192.2)	158.5 (128.0 – 205.0)	139.9 (108.9 – 184.2)	143.0 (104.1 – 174.5)	130.6 (103.2 – 179.8)	146.1 (128.4 – 191.3)
Alkaline phosphatase, 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)
Alanine aminotransferase, U/L *	19 (14.5 – 26)	20.0 (15.3 – 27.8)	18.0 (14.0 – 23.3)	19.0 (15.0 – 27.0)	19.0 (13.5 – 25.5)	19.0 (15.0 – 25.0)
Systolic BP (mmHg) *	131 (122.8 – 140)	132.0 (122.0 – 140.0)	130.0 (125.0 – 136.0)	131.5 (121.8 – 140.0)	**135.5 (128.0 – 145.0)**	**129.0 (120.0 – 137.0)**
Diastolic BP (mmHg) *	77 (70 – 80)	78.0 (70.5 – 83.0)	75.5 (70.0 – 80.0)	73.5 (67.8 – 80.0)	77.0 (68.0 – 83.0)	74.0 (70.0 – 80.0)
Total bilirubin, umol/L *	9.6 (7.3 – 12.6)	9.9 (7.6 – 13.0)	9.5 (8.0 – 11.8)	9.3 (7.2 – 13.4)	9.6 (7.2 – 14.1)	9.8 (8.5 – 13.8)
hsCRP, mg/L *	**3.5 (1.7 – 6)** [n = 23]	**1.3 (0.8 – 2.3)** [n = 23]	2.1 (1.1 – 3.7) [n = 16]	1.7 (0.4 – 5.5) [n = 10]	2.2 (0.8 – 5.1) [n = 4]	5.2 (3.3 – 10.3) [n = 13]
NLR, ratio *	2.8 (2.1 – 3.7)	2.5 (2.1 – 3.5)	3.0 (2.2 – 3.9)	3.0 (2.2 – 3.8)	2.9 (2.1 – 3.8)	2.5 (2.2 – 3.6)

Change in Total MoCA Score from Baseline to Last Observation Captured



P-values were calculated using ANCOVA statistical analysis to compare change in total MoCA from baseline to last observation captured between apabetalone-treated patients and placebo with baseline total MoCA serving as a covariate and treatment arm as a factor.

Conclusions

In the BETonMACE trial epigenetic BET protein inhibition by apabetalone capsule 100 mg b.i.d. vs placebo was associated with improved cognition as measured by MoCA in patients with baseline scores of ≤ 21. It is feasible to embed cognition assessment in randomized Phase 3 CVD endpoint studies. BET protein inhibitors warrant further investigation for late life cognitive disorders.