Apabetalone (An Epigenetic BET-Inhibitor Small Molecule): A Substudy Evaluating Effects on Cognition in Diabetes Patients with Cardiovascular Disease

J. Cummings[1], J. Johansson[2], E. Kulikowski[3], N.C. Wong[3], C. Halliday[3], K. Lebioda[3], B. Winblad[4], H. Zetterberg[5], K. Kalantar-Zadeh[6], S.J. Nicholls[7], G.G. Schwartz[8], K.K. Ray[9] and M. Sweeney[2]

[1]Cleveland Clinic Lou Ruvo, Center for Brain Health, Las Vegas, USA, [2]Resverlogix Corp., Research and Development, San Francisco, USA; [3]Resverlogix Corp., Research and Development, Calgary, Canada; [4]Karolinska Institute, Department of NVS, Division of Neurogeriatrics, Huddinge, Sweden; [5]Sahlgrenska Academy at the University of Gothenburg, Department of Psychiatry and Neurochemistry- Institute of Neuroscience and Physiology, Gothenburg, Sweden; [6]School of Medicine, Division of Nephrology & Hypertension, Irvine, USA; [7]University of Adelaide, South Australian Health & Medical Research, Adelaide, Australia; [8]University of Colorado, School of Medicine, Denver, USA; [9]Imperial College, Department of Primary Care and Public Health, London, United Kingdom

Background

Type II Diabetes Mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) are associated with dementia. Epigenetic dysregulation by bromodomain and extraterminal domain (BET) proteins is believed to be involved in ASCVD and dementia pathogenesis.

Apabetalone is a selective (BD2) BET inhibitor. In phase 2 studies it was associated with significant major adverse cardiovascular event (MACE) reduction which was most pronounced in patients with diabetes and elevated inflammation. Therefore a phase 3 trial - BETonMACE - has been initiated with primary MACE outcomes.

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.

Methods

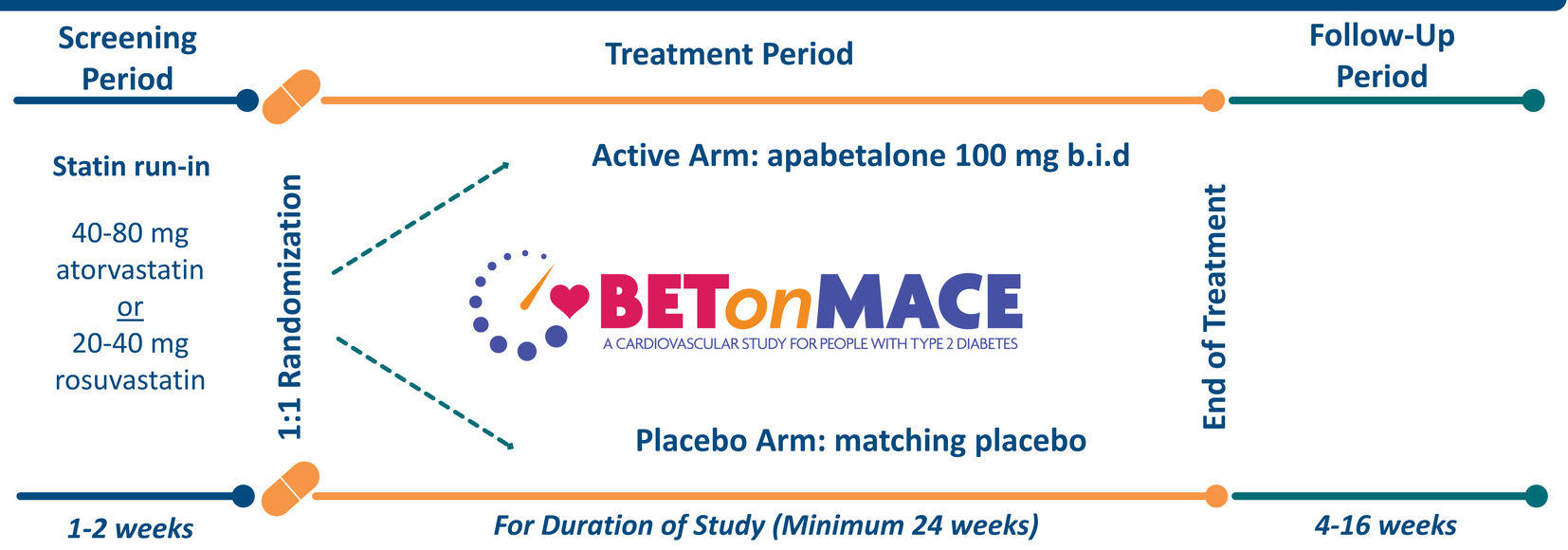
A pre-specified secondary analysis of BETonMACE will examine the effects of apabetalone on cognitive function using the Montreal Cognitive Assessment (MoCA). The MoCA is designed as a rapid screening instrument for cognitive impairment and is sensitive to mild changes. It assesses different cognitive 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.

Results

To date, 2,418 patients have been randomized in the BETonMACE study, of which 20% are 70 years and older. The MoCA test (Versions 7.1, 7.2, and 7.3) has been administered by trained and certified site investigators across 220 sites in 14 countries and 17 languages. Upon completion of the study, it is estimated that approximately 500 patients will have undergone MoCA testing with a median exposure to study treatment of 18 months (range 6-36).

BETonMACE Study Design

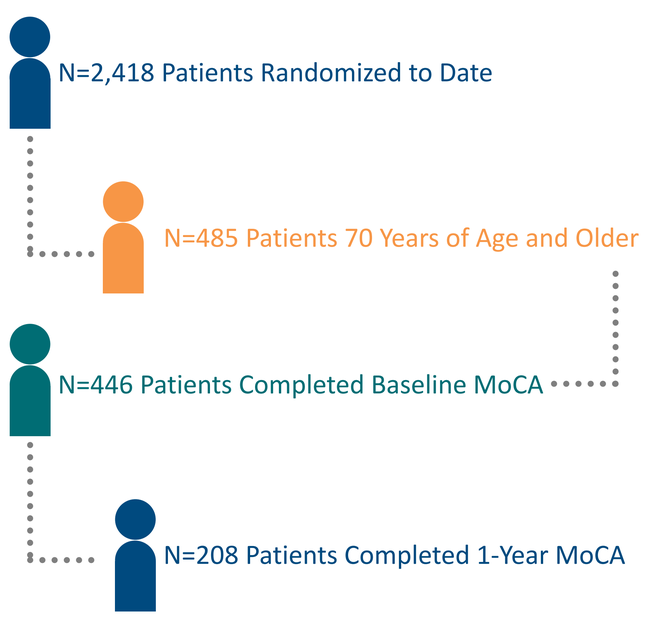


Inclusion criteria
- Type II Diabetes Mellitus (HbA1c > 6.5% or history of diabetes medications)
- CAD event 7 days - 90 days prior to screening including MI, unstable angina or percutaneous coronary intervention
- HDL < 45 mg/dL for males and < 45 mg/dL for females

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

Cognition Subgroup

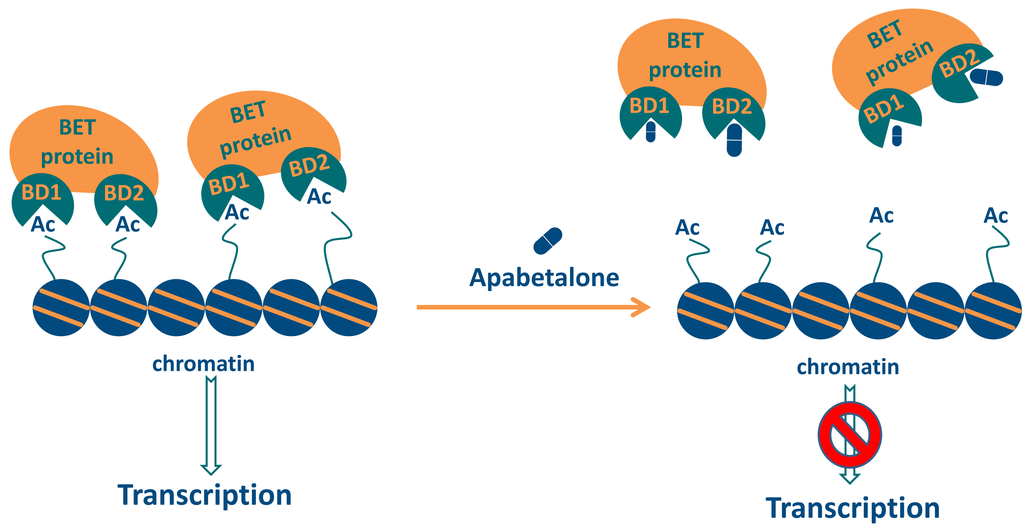


Cognition Subgroup Baseline Characteristics

Clinical Characteristic	Patients Randomized with Baseline MoCA Completed		Patients Randomized with Baseline MoCA ≤ 25	
	N	Median (min, max)	N	Median (min, max)
Age (yrs)	446	73 (69, 88)	238	
Sex (male, %)		65.2%		65.5%
Education (≤12 years, %)		68.2%		71.0%
MoCA		25 (7, 30)		23 (7, 25)
Concomitant Statins				
Atorvastatin	221	49.6%	116	48.7%
Rosuvastatin	225	50.4%	122	51.3%
Clinical Chemistry				
HDL-C (mg/dL)	444	34 (20, 46)	236	34 (21, 46)
ApoA-1† (mg/dL)	89	121 (58, 179)	44	122 (58, 162)
LDL-C (mg/dL)	442	63.5 (10, 365)	234	64.5 (10, 247)
hsCRP† (mg/dL)	92	2.5 (0.2, 101.7)	46	3.2 (0.2, 101.7)
NLR (ratio)	424	2.8 (0.7, 16.5)	228	2.9 (0.8, 16.5)
ALP† (U/L)	446	76.5 (29, 777)	238	77 (37, 777)

† 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, Dr. D. Gilham

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. This analysis will provide insights about the potential for BET inhibition to modulate cognitive function in elderly patients with ASCVD and diabetes.