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


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Background

Type II Diabetes Mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) are associated with dementia. Epigenetic dysregulation by bromodomain and extraterminal domain (BD) 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, visuoconstructive 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 administered 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).

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.

Summary and Conclusions

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.

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