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 (ac) lysine [4a] on histones via bromodomains, 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.

All Study Groups

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


1Cleveland Clinic, Cleveland, Ohio, USA; 2Karolinska Institute, Stockholm, Sweden; 3Neurology, UC San Francisco, California, United States of America; 4Neurology, Oregon Health Sciences University, Portland, Oregon, USA; 5Karolinska Institute, Stockholm, Sweden; 6University of California Irvine, School of Medicine, Division of Nephrology & Hypertension, Irvine, CA, United States of America; 7Monash Cardiovascular Research Centre; 8School of Medicine, Aurora, CO, United States of America; 9Imperial College, Department of Primary Care and Public Health, London, United Kingdom

Objectives

Type 2 diabetes (T2D) and cardiovascular disease (CVD) associate with cognitive impairment, likely to be of vascular origin. Epigenetic dysregulation by bromodomain and extramembranous 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 downregulates 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 unclear.

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 135 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 12-48 months). Cognition, a pre-specified exploratory outcome, is assessed at baseline and annually in patients 70 years and older by the Montreal Cognitive 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, 7.3, and 7.5 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. 30% 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=233), 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.

BET on MACE Study Design

N=2,425 Patients Randomized

N=469 Patients 70 Years of Age and Older

N=46 Patients with Baseline MoCA ≤25

MoCA Domain Scores

Summary and Conclusions

- Cognitive impairment is common among elderly patients with T2D and ACS.
- Cognitive 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.