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CHRONIC KIDNEY DISEASE. PATHOPHYSIOLOGY, PROGRESSION & RISK FACTORS - 2

SP323

EFFECTS OF RVX-208, A FIRST IN CLASS EPIGENETIC BET INHIBITOR, ON KEY RENAL PARAMETERS IN SUBJECTS WITH A HISTORY OF CVD, AND CHRONIC KIDNEY DISEASE (CKD); A POST-HOC ANALYSIS OF PATIENTS FROM THE ASSERT, SUSTAIN AND ASSURE CLINICAL TRIALS

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Introduction and Aims: RVX-208 is a first in class of orally active small molecules that binds selectively to the second ligand domain of bromodomain extra-terminal proteins (BET). These proteins are epigenetic readers that bind acetylated lysine present in the tail of histones thus affecting chromatin structure. RVX-208 inhibits acetylated lysine from binding to BET proteins and thereby alters activity of selected genes. The epigenetic BET inhibitor RVX-208 is characterized by anti-inflammatory effects, activation of apolipoprotein A-I (apoA-I) transcription and improved metabolic effects. Reductions in alkaline phosphatase (ALP) have also been observed. A subpopulation analysis from the double-blind placebo controlled phase 2b program in cardiovascular disease (CVD) identified 81 subjects with CKD based on eGFR < 60 ml/min/1.73m2. The effect of selective BET inhibition on key renal parameters in this subgroup was assessed.
Methods: Total of 81 CKD subjects (RVX-208 n=58/Placebo n=23) were treated with either RVX-200mg b.i.d, RVX-208 300mg b.i.d or matching placebo for 3 months and 48 subjects (RVX-208 n=35/Placebo n=13) were treated with RVX-208 200mg b.i.d or matching placebo for 6 months. A pooled analysis was performed to assess the changes from baseline for eGFR, ALP and creatinine at 3 and 6 months. Additional lipid markers assessed included ApoA-I, HDL-cholesterol and HDL particle parameters by nuclear magnetic resonance (NMR.)
Results: In CKD subjects receiving RVX-208 there was no change in eGFR compared to a decrease of -3.7% in patients receiving placebo at 3 months. Following 6 months of RVX-208 treatment, an increase of +3.4% (p=0.04 vs. baseline) was observed compared to a decrease of -5.9% in the placebo group. The respective changes in ALP for RVX-208 and placebo were -14.2% and -0.34% at 3 months (p<0.05 vs. placebo) and -13.9% vs. -6.28% (p<0.05 vs. placebo) at 6 months. No change of creatinine was observed following treatment with RVX-208 at 3 months and a decrease was observed at 6 months (-2.82%, p=0.07 vs. baseline) compared to increases in the placebo group of +3.0% and +4.85%, respectively. Changes in lipid parameters over placebo at 6 months included, an increase of +5.23% in ApoA-I (mg/dL) (p=0.007 vs. baseline), an increase of +7.57% in HDL-c (mg/dL) (p=0.03 vs. baseline), an increase of +24.3% in large HDL particles (umol/L) (p=0.001 vs. baseline), an increase of +1.2% in HDL size (nm) (p<0.1 vs. baseline).
Conclusions: Selective BET inhibition via RVX-208 significantly lowers serum ALP, improves lipid parameters, lowers creatinine and appears to improve eGFR at 6 months. These findings may have implications for patients with CKD and high cardiac risk. Additional clinical trials in target CKD populations are warranted.