Alkaline Phosphatase Lowering by Selective BET Inhibition, a Novel Mechanism for MACE Reduction in High Risk CVD, Diabetes and CKD Patients; a Post-hoc Analysis of Phase 2b Studies with Apabetalone (RVX-208)

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BACKGROUND

RVX-208 development is focused on reducing major adverse cardiovascular events (MACE) in high risk CVD, diabetes and CKD patients. RVX-208 is a first in class orally active small molecule that binds selectively to the second ligand domain of bromodomain extra-terminal proteins (BET). These proteins are epigenetic readers that recognize acetylated lysines present on histone tails. RVX-208 inhibits this interaction and thereby alters activity of selected genes (see crystallography figure). This has effects on inflammation, reverse cholesterol transport (apoA-I upregulation), and other pathways underlying CVD risk. Reductions in alkaline phosphatase (ALP) have also been observed.

RESULTS

A significant reduction in MACE in all the RVX-208 treated patients (n=331) compared to placebo (n=168) was observed (p<0.02) as well as in those with diabetes (RVX-208 n=127/placebo n=65) (p<0.01). In all patients (n=499), MACMACE patients had higher baseline ALP; 77.0 U/L vs. 72.0 U/L (p<0.05). Similar trends were observed in the diabetes patients, 81.0 U/L vs. 75.5 U/L. RVX-208 treatment significantly lowered ALP vs. placebo in all patients (p<0.0001) and especially in those with a history of diabetes (p<0.0001). In addition, in the RVX-208 treated group, patients who did not experience a MACE had greater reductions of ALP compared to those who experienced a MACE (-8.0 U/L vs. +3.0 U/L) (p<0.05).

CONCLUSIONS

In phase 2b studies in high risk CVD and diabetes patients treated with RVX-208, a select BET-inhibitor, baseline ALP levels were significantly different between the patients who experienced a MACE and those who did not. Furthermore, RVX-208 significantly lowered serum ALP. BETonMACE will examine RVX-208’s potential in reducing MACE in high risk CVD, diabetes and CKD patients and the relationship of any reduction to ALP changes in a large prospective outcomes study.