Apabetalone (RVX-208) treatment lowered alkaline phosphatase (ALP) in CVD patients in phase II studies. Apabetalone inhibits the interaction of BET (bromodomain extra terminal) proteins & acetyl-lysine marks on histone tails. BET proteins control recruitment of transcriptional machinery to coordinate gene transcription of sensitive genes, including factors that contribute to vascular calcification. Vascular calcification is an underlying process in CKD pathogenesis and is directly associated with increased mortality. We examined the effect of apabetalone on markers known to contribute to vascular calcification in vitro & in the clinic.

To examine markers of vascular calcification, microarrays of human whole blood (WB) & primary human hepatocytes (PHH) treated with apabetalone were analyzed. Expression of vascular calcification markers were further evaluated using real-time PCR in PHH & U937 macrophages. In the SUSTAIN and ASSURE phase 2b clinical studies, high risk CVD patients were treated with 100 mg b.i.d RVX-208 or placebo for up to 26 weeks duration. Proteomic analysis of plasma samples (n=47 apabetalone; n=47 placebo) from phase II CVD trials was performed using SOMAscan™. SOMAscan™ uses aptamers which are highly specific for their cognate protein, to assess levels of ~1300 proteins.

In WB treated with apabetalone (A), microarrays showed suppression of a variety of vascular inflammation & calcification factors. Expression of additional calcification related genes was also reduced in PHH including ALP, RANKL, CCL2, IL8, OPG & BMP2 (B). Expression of osteopontin (SPP1), a proinflammatory molecule, is reduced in LPS stimulated U937 macrophages (-94%) as well as in PHH (-82%) (C). Apabetalone treatment significantly lowered ALP vs. placebo in all patients in phase 2 studies (p<0.0001) (D). In the 26 week ASSURE trial, circulating levels of OPG (associated with higher incidence of arterial calcification) & IBSP (major component of bone matrix) were reduced by 14% & 18% (p<0.05) versus placebo (E).

**RESULTS**

**BACKGROUND**

Apabetalone (RVX-208) treatment lowered alkaline phosphatase (ALP) in CVD patients in phase II studies. Apabetalone inhibits the interaction of BET (bromodomain extra terminal) proteins & acetyl-lysine marks on histone tails. BET proteins control recruitment of transcriptional machinery to coordinate gene transcription of sensitive genes, including factors that contribute to vascular calcification. Vascular calcification is an underlying process in CKD pathogenesis and is directly associated with increased mortality. We examined the effect of apabetalone on markers known to contribute to vascular calcification in vitro & in the clinic.

**METHODS**

To examine markers of vascular calcification, microarrays of human whole blood (WB) & primary human hepatocytes (PHH) treated with apabetalone were analyzed. Expression of vascular calcification markers were further evaluated using real-time PCR in PHH & U937 macrophages. In the SUSTAIN and ASSURE phase 2b clinical studies, high risk CVD patients were treated with 100 mg b.i.d RVX-208 or placebo for up to 26 weeks duration. Proteomic analysis of plasma samples (n=47 apabetalone; n=47 placebo) from phase II CVD trials was performed using SOMAscan™. SOMAscan™ uses aptamers which are highly specific for their cognate protein, to assess levels of ~1300 proteins.

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In WB treated with apabetalone (A), microarrays showed suppression of a variety of vascular inflammation & calcification factors. Expression of additional calcification related genes was also reduced in PHH including ALP, RANKL, CCL2, IL8, OPG & BMP2 (B). Expression of osteopontin (SPP1), a proinflammatory molecule, is reduced in LPS stimulated U937 macrophages (-94%) as well as in PHH (-82%) (C). Apabetalone treatment significantly lowered ALP vs. placebo in all patients in phase 2 studies (p<0.0001) (D). In the 26 week ASSURE trial, circulating levels of OPG (associated with higher incidence of arterial calcification) & IBSP (major component of bone matrix) were reduced by 14% & 18% (p<0.05) versus placebo (E).

**CONCLUSIONS**

BET inhibition by apabetalone decreases expression and circulating levels of markers known to contribute to vascular calcification. Epidemiology data link vascular calcification to risk of Congestive Heart Disease and CVD morbidity/mortality, especially in CKD patients. The potential of apabetalone to prevent CVD in post-ACS with diabetes is being explored in the phase III BETonMACE outcomes trial. Approximately 10-15% of patients in BETonMACE will have CKD as defined by an eGFR of 30-60 mL/min/1.73m². In addition, a PK study in severe renally impaired patients (eGFR < 30 mL/min/1.73m² not on dialysis) was completed in anticipation of future studies in the ESRD-CKD-dialysis populations.