Title
Apabetalone Downregulates Factors That Promote Vascular Calcification and Contribute to Cardiovascular Events

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Abstract: Introduction: Apabetalone, an orally active BET inhibitor, reduced incidence of major adverse cardiac events (MACE) in patients with CVD and improved eGFR in a subpopulation with chronic kidney disease (CKD) in phase 2 trials. Because vascular calcification (VC) is associated with MACE and is a predictor of all-cause mortality, modulation of processes associated with VC through BET inhibition were examined.

Methods: Plasma proteomic profiling was conducted in CVD patients receiving 100 mg of apabetalone b.i.d. in 3 month (ASSERT) and 6 month (SUSTAIN & ASSURE) phase 2 trials, as well as in patients with stage 4 CKD receiving a single 100 mg dose in a phase 1 trial. Cell culture systems were used to examine the effects of apabetalone on expression of VC markers, differentiation of coronary artery VSMCs in osteogenic conditions and extracellular calcium deposition.

Results: Apabetalone significantly reduced circulating levels of VC markers in phase 2 trials in CVD patients, including alkaline phosphatase (ALP), osteopontin and osteoprotegerin. Plasma proteomics of CKD patients (n=8) demonstrated activation of molecular pathways driving calcification including "BMP-2 signaling" and "RANK signaling in osteoclasts" versus matched individuals. Both pathways were downregulated by apabetalone 12 hours post dose in the CKD cohort. Mechanistic effects of apabetalone were examined in vitro. In primary human hepatocytes (PHH), apabetalone downregulated ALP expression by 60-80% and reduced expression of osteopontin in PHH and U937 macrophages. Differentiation of primary human VSMCs with osteogenic conditions induced expression of ALP, osteoprotegerin, RUNX2 and WNT5A, which was opposed by apabetalone. Further, apabetalone dose dependently countered calcium deposition in VSMCs.

Conclusions: Apabetalone mediates downregulation of factors and pathways associated with VC. Simultaneous effects on multiple contributing cell types suggest apabetalone may oppose pathologic VC to decrease MACE in patients with high CVD risk. The potential impact of chronic apabetalone treatment on biomarkers, renal function & CVD outcomes in patients with impaired kidney function is currently being studied in a substudy of the phase 3 BETonMACE CVD outcomes trial.