Title

SP071APABETALONE (RVX-208), A SELECTIVE BROMODOMAIN AND EXTRA-TERMINAL (BET) PROTEIN INHIBITOR, DECREASES ABUNDANCE AND ACTIVITY OF COMPLEMENT PROTEINS IN VITRO, IN MICE AND IN CLINICAL STUDIES

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RENAL PATHOLOGY. EXPERIMENTAL AND CLINICAL - 1

SP071 **APABETALONE (RVX-208), A SELECTIVE BROMODOMAIN AND EXTRA-TERMINAL (BET) PROTEIN INHIBITOR, DECREASES ABUNDANCE AND ACTIVITY OF COMPLEMENT PROTEINS IN VITRO, IN MICE AND IN CLINICAL STUDIES**

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Introduction and Aims: RVX-208, an orally active small molecule, reduced incidence of major acute cardiac events in patients with cardiovascular disease (CVD) and potentially improved eGFR in a subpopulation with chronic kidney disease (CKD) in phase II clinical studies. RVX-208 inhibits the epigenetic readers bromodomain and extraterminal (BET) proteins by competing with acetylated lysines on histones tails that are associated with active transcription. Previously, microarray studies of primary human hepatocytes (PHH) have shown a downregulation of several complement genes (19 of 26). Since activation of complement in the kidney has been associated with renal disease and reduction in complement activation is beneficial for kidney function, we have examined the effect of RVX-208 on complement expression and activity in vitro, in mice and in clinical samples.

Methods: Effects of RVX-208 on mRNA expression and secretion of complement proteins was examined in cultured PHH. Expression of complement genes was studied in mice treated with RVX-208 (150 mg/kg, 3 days, b.i.d.). Circulating complement proteins and complement activity were quantified in clinical samples using proteomics approaches and hemolytic assays, respectively.

Results: RVX-208 downregulated basal and inflammatory mRNA expression and protein secretion of complement C3, C4, C5 and C9 in cultured PHH by 10%-100%. Chimeric mice with humanized livers treated with RVX-208 decreased expression of C4, C9 and MBL2 mRNA by 36%, 46% and 61%, respectively. Proteomic analysis of clinical samples showed a significant decrease in circulating complement proteins following treatment with RVX-208 (between -5% and -20%, vs. baseline). To establish if the observed decrease in protein abundance affected activity, CH50 and AH50 hemolytic assays were performed on 11 plasma samples from patients with CVD at baseline and after 26 weeks of RVX-208 treatment. A significant decrease in activity of approximately 26% ($p<0.01$) was observed in both assays. No increase in infections was reported in phase II trials.

Conclusions: RVX-208 decreases complement component expression and cascade activity, which may result decreased pathologic activation of complement in CKD. The potential of RVX-208 for the treatment of high-risk diabetes and CKD patients is currently being explored in the phase III BETonMACE clinical study.