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Authors

Gilham, Dean
Tsujikawa, Laura
Wasiak, Sylwia
et al.

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Abstracts

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Dean Gilham[1], Laura Tsujikawa[1], Sylwia Wasiak[1], Christopher Halliday[1], Ken Lebioda[1], Kamyar Kalantar-Zadeh[2], Srinivasan Beddhu[3], Vincent Brandenburg[4], Marcello Tonelli[5], Ravi Jahagirdar[1], Norman C. W. Wong[1], Carmine Zoccali[6], Jan O. Johansson[7], Michael Sweeney[7], Mathias Haarhaus[8], Ewelina Kulikowski[1]

[1]*Resverlogix Corp, Calgary, Canada,* [2]*University of California Irvine, School of Medicine, Orange, United States of America,* [3]*The University of Utah, School of Medicine, Salt Lake City, United States of America,* [4]*Rhein-Maas Klinikum, Würselen, Germany,* [5]*University of Calgary, Calgary, Canada,* [6]*CNR-IFC , Reggio Calabria, Italy,* [7]*Resverlogix Inc., San Francisco, United States of America and* [8]*Karolinska University Hospital, Stockholm, Sweden*

INTRODUCTION: Apabetalone is an orally active inhibitor of bromodomain and extraterminal (BET) proteins - epigenetic readers modulating gene expression by bridging acetylated histones or transcription factors with transcriptional machinery. In phase 2 clinical trials, apabetalone reduced major adverse cardiac events (MACE) in patients with cardiovascular disease (CVD), resulting in 44% relative risk reduction on top of standard of care. Chronic kidney disease (CKD) is frequently accompanied by cardiovascular complications, which remain resistant to current therapies. Elevated serum alkaline phosphatase (ALP) contributes to vascular calcification (VC) and endothelial dysfunction. Accordingly, serum ALP is emerging as an independent and novel predictor of MACE and of all-cause mortality.

METHODS: Serum ALP levels were examined post-hoc in CVD patients receiving apabetalone in the 3 month (ASSERT) and 6 month (SUSTAIN & ASSURE) phase 2 trials, including a subset with impaired renal function (eGFR<60 mL/min/1.73m2).

Effects of BET inhibitors (BETi) on expression of tissue-nonspecific ALP (TNAP; gene symbol *ALPL*) was determined in cultured primary human hepatocytes (PHH), the HepaRG cell line, primary human vascular smooth muscle cells (VSMCs) during trans-differentiation to calcifying cells, and vascular endothelial cells. ALP enzyme activity was measured in enzymatic assays.

RESULTS: In phase 2 trials, baseline serum ALP independently predicted MACE (hazard ratio [HR] per SD 1.6, 95% CI 1.2-2.2, p=0.001). In ASSERT, apabetalone dose dependently reduced serum ALP (n=74-76/group; p<0.001 median change vs. placebo). Patients in phase 2 on apabetalone (n=553) had greater reductions in ALP than placebo (n=242; p<0.001). ALP reduction by apabetalone was associated with reduction in MACE (HR 0.58 per SD, 95% CI 0.44-0.77, p<0.001). In the subgroup with eGFR<60, patients on apabetalone (n=69) also had lower on-treatment serum ALP (p=0.008) vs. placebo (n=22). Liver-derived TNAP accounts for ≍50% of ALP enzyme activity in serum. In PHH & HepaRG cells, apabetalone suppressed *ALPL* expression by 60-80%. Vascular expression of *ALPL* also contributes to VC & cardiovascular risk. Compared to basal conditions, trans-differentiation of VSMCs to calcifying cells resulted in 2.5x increase in *ALPL* expression. Apabetalone or JQ1 (BETi with different chemical scaffolds) countered extracellular calcium deposition and suppressed *ALPL* gene expression, TNAP protein levels, and enzyme activity. Apabetalone downregulated *ALPL* expression in human aortic endothelial cells, umbilical vein endothelial cells, and brain microvascular endothelial cells by 50-70%.

CONCLUSIONS: Apabetalone dose dependently lowers serum ALP in patients, which is associated with reduction in cardiovascular events. Decreased *ALPL* expression in cultured hepatocytes with apabetalone is consistent with reduced serum ALP in patients. In addition, apabetalone downregulates *ALPL* expression in vascular cell types including VSMCs and endothelial cells, while reducing VSMC calcification. Involvement of BET proteins in VSMC calcification is a novel discovery. Our data indicate apabetalone has potential to decrease progression of pathological VC and contribute to positive cardiovascular outcomes in CVD patients. The impact of apabetalone treatment on biomarkers, renal function, and CVD outcomes is being evaluated in the phase 3 BETonMACE trial (NCT02586155).