Title

ALP Levels Predict Adverse Cardiovascular Outcomes and Cognitive Impairment in High Risk Patients

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Abstract: Background: Serum alkaline phosphatase (ALP) is associated with incident cardiovascular disease (CVD) , coronary artery disease, vascular calcification, cerebral small vessel disease and ischemic stroke. Recent studies also associate elevated ALP with impaired cognition, suggesting neuronal or neurovascular dysfunction. To date there is no specific pharmacological means to lower ALP. Bromodomain & extraterminal (BET) proteins bind to acetylated histones on chromatin and regulate gene transcription. Apabetalone (ABET) targets the second bromodomain of BET proteins and inhibits expression of genes that participate in vascular inflammation and calcification, coagulation and the complement pathway. In CVD patients (pts) , ABET lowers serum ALP in a dose-dependent manner.

Methods: In phase 2 ABET studies (n=795) up to 26 weeks' duration in CVD pts, we assessed the relationship of ALP and CVD events. In the ongoing phase 3 BETonMACE study with

ABET (n=2,425) , baseline cognitive function (Montreal Cognitive Assessment, MoCA) and ALP were measured in pts aged 70 yrs and older (n=467) .

Results: In phase 2 studies, CVD events (death, non-fatal MI, coronary revascularization, or hospitalization for CV cause) were lowered by 44% (p=0.02) with ABET. Baseline ALP (median 72 U/L) independently predicted CVD events (hazard ratio [HR] per standard deviation [SD] 1.6, 95% CI 1.2-2.1, p<0.001) . Mean ABET decrease in ALP from baseline was 8.45% (p<0.001) , or 6.6 U/L. A 1 SD (13.0 U/L) reduction in ALP with ABET was associated with a HR for MACE of 0.58 (95% CI 0.43-0.78, p<0.001) . In the BETonMACE trial pts were classified by baseline MoCA >26 (normal, n=221) , 21-25 (borderline, n=161) , or <21 (impaired, n=85) . Pts with impaired cognition had higher ALP (trend p-value 0.006) , lower eGFR (66 vs. 71, p=0.04) , and higher hsCRP (4.8 vs.1.8, p=0.03) .

Conclusion: Serum ALP is associated with coronary and cerebral vascular disease. ABET is a BET-inhibitor that lowers serum ALP in CVD pts. In phase 2 studies reduction of ALP and CVD events with ABET were associated. In the ongoing phase 3 BETonMACE CVD outcomes trial to report in 2019, higher ALP was associated with lower MoCA. We hypothesize that ALP-lowering by ABET contributes to CVD event reduction and prevention of cognitive decline.