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

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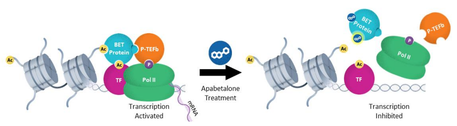
Background

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 targets the second bromodomain of BET proteins and inhibits expression of genes that participate in vascular inflammation and calcification, coagulation and the complement pathway (Figure 1). In CVD patients (pts), apabetalone lowers serum ALP in a dose-dependent manner.

Figure 1: Apabetalone Mechanism of Action

BET proteins control gene transcription through interactions with transcription factors and recruitment of RNA polymerase II. Apabetalone binds to bromodomains in BET proteins, causing their release from chromatin and downregulation of BET sensitive gene expression.



BET: bromodomain and extraterminal proteins
ac: acetylated lysine residue on DNA associated proteins
BD: bromodomain
TF: transcription factor

Methods

In Phase 2 apabetalone studies (n=795) up to 26 weeks' duration in patients with CVD, we assessed the relationship of ALP and CVD events.

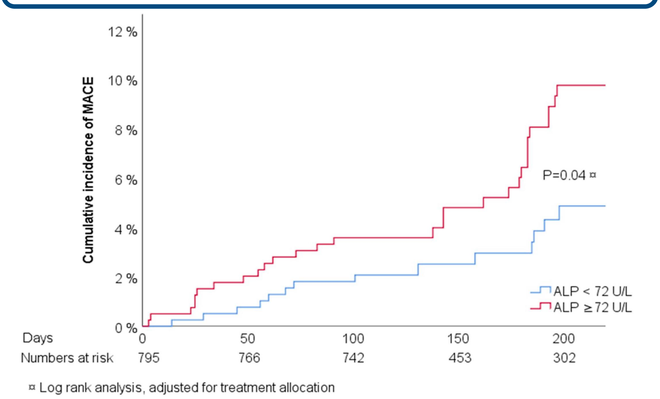
In the recently completed Phase 3 BETonMACE study with apabetalone (n=2,419), baseline cognitive function (Montreal Cognitive Assessment, MoCA) and ALP were measured in pts aged 70 yrs and older (n=469).

Results: ALP and MACE in Phase 2 Studies

In Phase 2 studies:

- Median baseline ALP was 72 U/L. Baseline ALP (dichotomized at 72 U/L) predicted the risk of MACE **(Figure 2)**.
- Apabetalone treatment lowered CVD events (death, non-fatal MI, coronary revascularization, or hospitalization for CV cause) by 44% (p=0.02) **(Figure 3)**.
- ALP was unaffected by treatment with placebo (PBO), but was lowered by a mean of 6.6 U/L (7.9%) from baseline after 12-14 weeks, and by 6.9 U/L (7.9%) from baseline after 24-26 weeks by apabetalone (all p-values <0.0001) **(Figure 4)**.
- Baseline ALP predicted CVD events, independent of high-sensitivity C-reactive protein (hsCRP), sex, age, race, study, cardiovascular risk factors, chronic kidney disease (CKD), liver function markers, and treatment allocation (hazard ratio [HR] per standard deviation [SD] 1.6, 95% CI 1.2 – 2.2, p=0.002).
- A 1 SD (13.0 U/L) reduction in ALP with apabetalone was associated with a MACE HR of 0.68 (95% CI 0.49 – 0.93, p=0.02)**(Figure 5)**.

Figure 2: Phase 2 Results Association of ALP Levels with Risk of MACE



¤ Log rank analysis, adjusted for treatment allocation

Figure 3: Phase 2 Results Apabetalone Lowers Risk of MACE in Patients with CVD

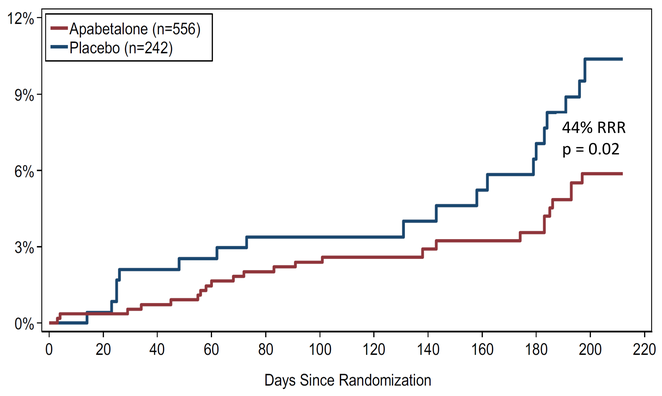
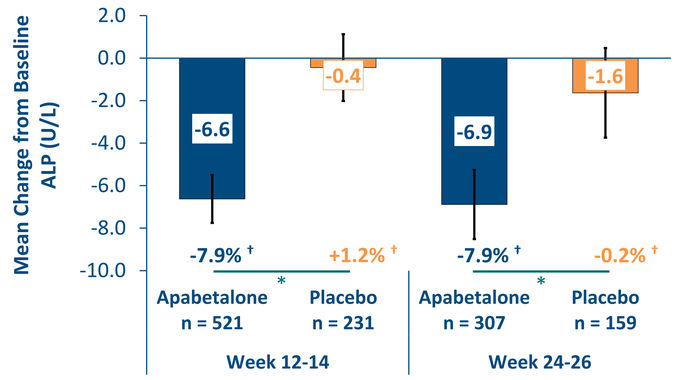


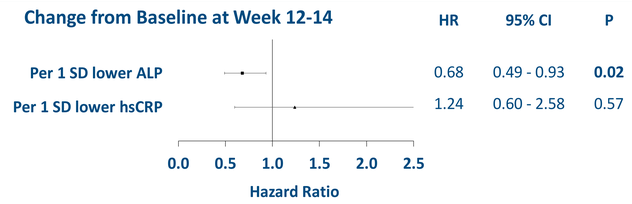
Figure 4: Phase 2 Results Apabetalone Lowers Serum ALP



* p-value <0.0001 (Mann-Whitney U-Test)

† Mean Percent Change from Baseline
Error bars represent 95% CI

Figure 5: Phase 2 Results Higher Baseline Serum ALP Associates with CVD Events



Phase 3 Results: ALP and Cognition in BETonMACE Trial

In the Phase 3 BETonMACE trial, pts aged 70 yrs and older were classified by baseline MoCA ≥26 (normal, n=224), 22-25 (borderline, n=148), or <22 (impaired, n=97).

Pts with impaired cognition (MoCA <22) at randomization had nominally higher ALP (**Figure 6**), lower eGFR (65 vs. 71, p=0.01), and higher hsCRP (4.4 vs.1.9, p=0.03) **(Table 1)**.

Figure 6: Phase 3 Lower MoCA Scores Associate with Higher Serum ALP

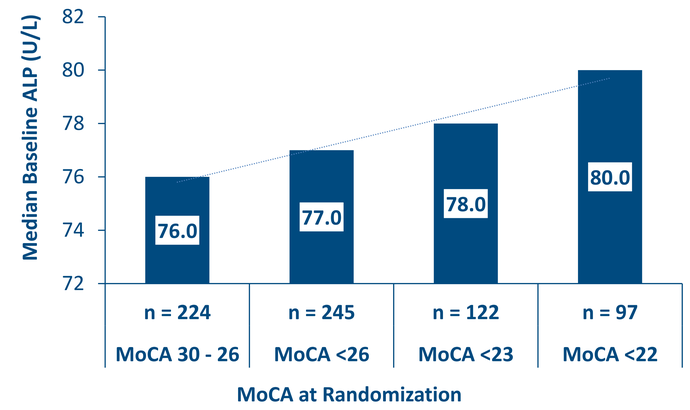


Table 1: Phase 3 BETonMACE Trial Baseline Characteristics

Characteristic	All Patients Randomized		Baseline MoCA ≥26 (Normal) Subgroup		Baseline MoCA <22 (Impaired) Population		MoCA <22 Subgroup vs. MoCA ≥26 Subgroup p-value (Chi-Squared X^2 Test)
	N	%	N	%	N	%	
Age (yrs) (median) (min, max)	2,419	62 (31, 88)	224	73 (70, 88)	97	74 (70, 86)	*0.08* *
Sex (male)	1,801	74.5%	144	64.3%	55	56.7%	0.20

Clinical Chemistry	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	* Mann-Whitney U-Test
ALP† (U/L)	2,419	78 (64 – 94)	224	76 (62 – 92)	97	80 (64 – 95)	0.31
eGFR (mL/min/1.73m^2)	2,415	99 (76 – 127)	224	71 (57 – 88)	97	65 (50 – 80)	***0.01***
LDL-C (mg/dL)	2,416	65 (49 – 85)	224	63 (48 – 82)	96	60 (49 – 82)	0.88
HDL-C (mg/dL)	2,419	33 (30 – 37)	224	34 (31 – 38)	97	34 (31 – 38)	0.78
hsCRP† (mg/dL)	483	2.78 (1.20 – 6.09)	47	1.88 (1.11 – 4.63)	17	4.43 (2.97 – 9.97)	***0.03***
HbA1c (%)	2,397	7.3 (6.4 – 8.7)	220	7.0 (6.3 – 8.1)	97	7.1 (6.4 – 8.6)	0.19

† results from visit 2 / week 0; all other values are from visit 1/screening

IQR: Interquartile Range

Summary and Conclusions

Serum ALP is associated with risk of MACE in patients with CVD. Apabetalone is a BET-inhibitor that lowers serum ALP in CVD pts. In Phase 2 studies, reduction of ALP and CVD events with apabetalone were associated. The current hypothesis-generating findings raise the possibility that ALP-lowering by apabetalone contributes to CVD event reduction.

The effects of apabetalone on MACE and cognitive function (via MoCA) will be reported from the recently completed Phase 3 BETonMACE trial.