Effects of Apabetalone (RVX-208) on Serum Albumin in Subjects with CVD, Diabetes and Chronic Kidney Disease; a Post-hoc Analysis of the ASSURE and SUSTAIN Clinical Trials

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Abstract

INTRODUCTION AND AIMS:

Albumin and Glomerular Filtration Rate (GFR) are known markers of Cardiovascular Disease (CVD) risk and renal function in chronic kidney disease (CKD) and diabetes mellitus (DM) patient populations. A strong relationship exists between high or constant albumin levels in blood and improved renal function. Additionally, albumin levels have been associated with (CVD) risk and major adverse cardiovascular events (MACE) outcomes in DM and CKD patients. Apabetalone is a first-in-class orally active bromodomain and extraterminal domain (BET) inhibitor with BD2 selectivity. Apabetalone in phase 2 studies showed a MACE-reduction in patients with a history of CVD accounted for by effects in DM patients. BET inhibition by apabetalone has been shown to regulate activation of pathways that underlie CVD, DM and CKD including, vascular inflammation and mineralization, coagulation and complement. Additionally, an improvement of estimated GFR has been reported in a subpopulation analysis of CVD patients with baseline eGFR < 60 ml/min/1.73m^2 (n=35 in apabetalone group; n=13 placebo group) from the phase 2 clinical trials.

METHODS:

In the phase 2 clinical studies, high risk CVD patients (n=331 in apabetalone group; n=168 in placebo group) were treated with 100 mg b.i.d apabetalone or placebo for 6 months. Patients with a history of DM (n=127 in apabetalone group; n=65 in placebo group) were evaluated as a subgroup as well as patients with baseline eGFR < 60 ml/min/1.73m^2 (n=35 in apabetalone group; n=13 placebo group). Serum albumin was collected during trial visits at screening, 3 months and 6 months**.** Analysis was performed in each group assessing changes in albumin from screening to 3 and 6 month visits. Plasma Alkaline phosphatase (ALP) activity was assessed at the same time points.

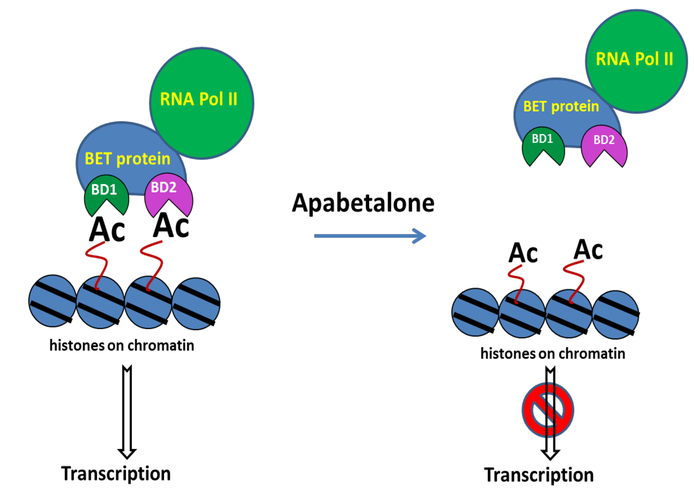
RESULTS:

Following 6 months of apabetalone treatment, a 1.3% improvement in serum albumin level versus placebo ($p<0.05$) was observed in all CVD patients. In the DM subgroup, a 2.1% increase in albumin versus placebo ($p<0.10$) was observed. In patients with baseline eGFR<60 ml/min/1.73m^2, the difference in albumin between those on apabetalone treatment and those receiving placebo was 5.2% ($p=0.15$). Additionally, an increase in eGFR of 3.4% ($p=0.04$ vs. baseline) was observed in these patients compared to a decrease of 5.9% in the placebo group. The changes in plasma ALP activity for apabetalone and placebo were -14.0% vs. -6.3%, respectively ($p<0.05$).

CONCLUSIONS:

In all CVD patients, BET inhibition via apabetalone significantly increased serum albumin levels versus placebo, with the similar or more pronounced numerical effects in the smaller DM and eGFR <60 ml/min/1.73m patients. The parallel observation of increase in eGFR by apabetalone treatment suggests further potential for renal function improvement in patients with CKD and high risk CVD. Apabetalone is currently being evaluated in the phase 3 clinical trial, BETonMACE, which is targeting acute coronary syndrome patients with DM in which an estimated 15% will have CKD.

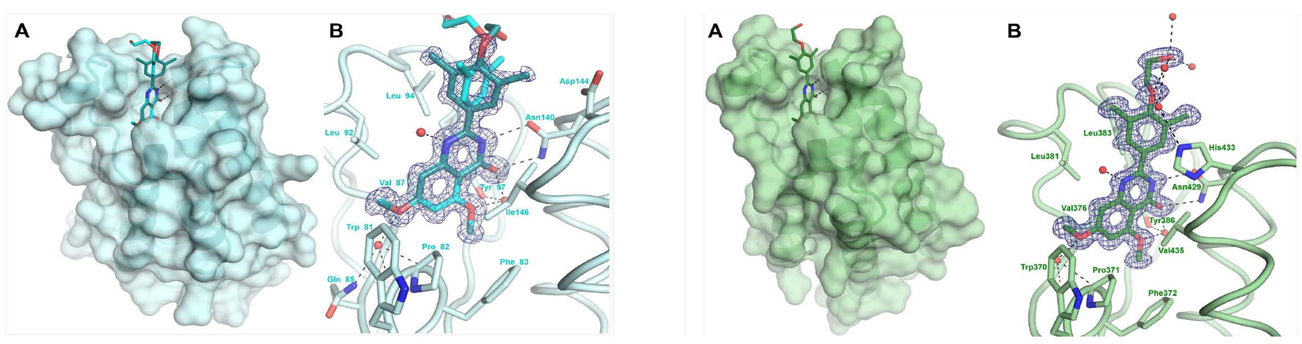
Mechanism of Action



BET proteins, such as BRD4, bind acetylated lysine (Ac) on proteins such as histones via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes. Apabetalone inhibits BET bromodomains, causing release from chromatin and downregulation of BET sensitive gene expression.

Acknowledgment: Figure originally developed by Dr. Olesya Kharenko

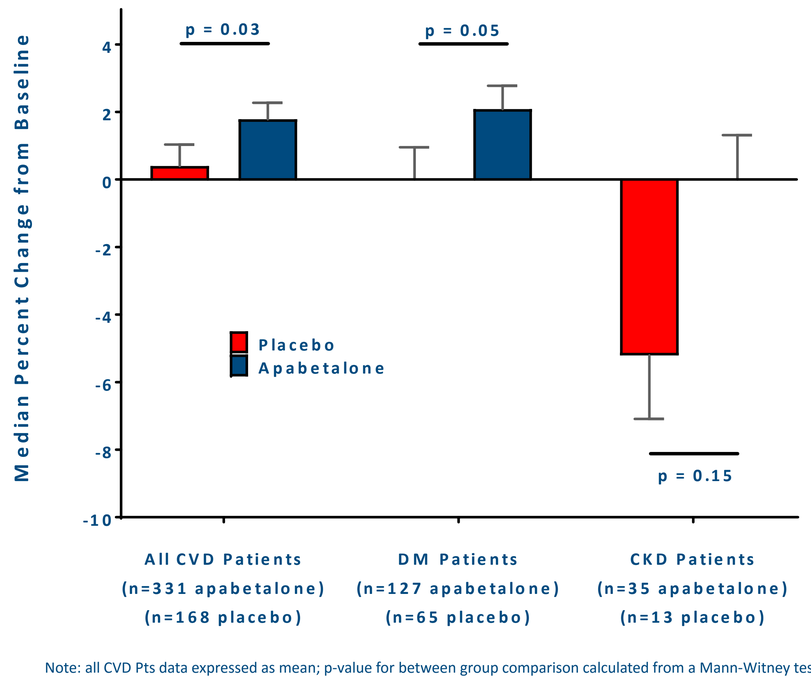
Apabetalone binds selectively to BD2 of BET proteins.



Each BET protein is comprised of dual bromodomains (BD1 [left panel] and BD2 [right panel]). Apabetalone binds selectively to BD2.

Results

Apabetalone effects on serum albumin in (A) All CVD Pts; (B) DM Pts; (C) CKD Pts



Note: all CVD Pts data expressed as mean; p-value for between group comparison calculated from a Mann-Witney test

Apabetalone effects on eGFR and serum ALP in CKD Pts

Parameter	Placebo (n=13)	p vs baseline	Apabetalone (n=35)	p vs baseline	p vs placebo
eGFR	-5.9%	ns	+3.4%	0.04	ns
ALP	-6.3%	ns	-14.0%	<0.0001	0.02

p-value for within group comparison calculated from a Wilcoxon signed-rank test and p-value vs placebo calculated from a 2-sided Van Elteren test stratified by study

Summary

- **Apabetalone significantly increased serum albumin in all CVD patients, with similar or more pronounced numerical effects in the DM and CKD patient subgroups in phase 2 studies**
- **Apabetalone significantly reduced serum ALP in patients with eGFR<60 and illustrated slight improvement in eGFR compared to baseline**
- **Approximately 15% of the acute coronary syndrome patients in the phase 3 BETonMACE study will have CKD which will elucidate the effects of apabetalone in a CKD patient population**