Kidney & Blood Pressure Research

Kidney Blood Press Res 2018;43:449-457
DOI: 10.1159/000488257
Published online: March 22, 2018
Accepted: March 13, 2018





**Original Paper**

# Apabetalone Mediated Epigenetic Modulation is Associated with Favorable Kidney Function and Alkaline Phosphatase Profile in Patients with Chronic Kidney Disease

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**Key Words**
Epigenetic • Alkaline phosphatase • Vascular calcification • eGFR

**Abstract**
***Background/Aims:*** The association between serum alkaline phosphatase (ALP) with adverse cardiovascular outcomes, in Chronic Kidney Disease (CKD) patients has previously been reported and may be a result of increased vascular calcification and inflammation. Here we report, for the first time, the effects of pharmacologic epigenetic modulation on levels of ALP and kidney function via a novel oral small molecule BET inhibitor, apabetalone, in CKD patients. ***Methods:*** A post-hoc analysis evaluated patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m$^2$, who participated in the apabetalone phase 2 randomized controlled trials (SUSTAIN and ASSURE). 48 CKD subjects with a history of cardiovascular disease (CVD) were

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treated with 100mg twice-daily of 24 and 26 weeks of apabetalone or placebo. ALP and eGFR were measured prior to randomization and at final visits. ***Results:*** Patients who received apabetalone (n=35) versus placebo (n=13) over 6 months showed significantly (p=0.02) lowered serum ALP -14.0% (p<0.0001 versus baseline) versus -6.3% (p=0.9 versus baseline). The eGFR in the apabetalone group increased by 3.4% (1.7 mL/min/1.73 $m^2$) (p=0.04 versus baseline) and decreased by 5.8% (2.9 mL/min/1.73 $m^2$) (p=0.6 versus baseline) in the placebo group. Apabetalone was well tolerated. ***Conclusion****:* A post-hoc analysis of CKD subjects from the SUSTAIN and ASSURE randomized controlled trials demonstrated favorable effects of apabetalone on ALP and eGFR, and generated the hypothesis that epigenetic modulation by BET inhibition may potentially offer a novel therapeutic strategy to treat CVD and progressive kidney function loss in CKD patients. This is being examined in the phase III trial BETonMACE.



## Introduction

Chronic kidney disease (CKD) encompasses a set of heterogeneous disorders that negatively affect the structure and function of the kidneys [1]. These disorders typically include diabetes, hypertension, CVD, obesity, and others that contribute to progressive kidney damage [1]. The goal of CKD management is to prevent or slow the progression of kidney damage, reduce CVD complications and associated disorders (anemia, bone disease and hypertension), and improve quality of life. Current interventions typically include anti-hypertensive medications, oral hyperglycemic agents, and lipid-modifying medications. However, these approaches do not address some of the key drivers of CKD which include calcification, inflammation, and oxidative stress [2]. The high-burden of CVD-related complications and mortality observed in CKD patients remains despite available treatments [2]. Novel approaches targeting vascular calcification and inflammation to reduce the increased CVD outcomes associated with CKD are warranted.

Bromodomain and extra-terminal (BET) proteins are a family of bromodomain (BD) containing proteins that bind acetylated lysines on chromatin thereby regulating gene transcription [3]. Through this epigenetic mechanism, BET proteins have been shown to regulate the increased expression of proteins implicated in the development of many disease states [4]. Importantly, in two recent studies, the impact of inhibiting these proteins using a BET inhibitor has been investigated in kidney disease. In animal studies, JQ1, a non-clinical BET inhibitor, abrogated renal inflammation in murine models of unilateral ureteral obstruction, anti-basal glomerular nephritis, and infusion of Angiotensin II [5]. JQ1 reduces the expression at the transcriptional level of several key pro-inflammatory genes: interleukin-6 (IL-6), C-C motif chemokine-2 (CCL-2), and C-C motif chemokine (CCL-5) [5]. Additionally, a clinical BET inhibitor candidate, IBET-151, decreased the activation of multiple signaling pathways associated with renal fibroblast activation in an animal model of renal fibrosis, thus demonstrating the potential of BET inhibition to attenuate renal fibrosis [6]. These results demonstrate that BET inhibition reduces renal fibrosis and inflammation, suggesting a potential therapeutic application in CKD.

Apabetalone (RVX-208) is an oral small molecule that targets the second bromodomain of BET proteins BRD2, BRD3, and BRD4 and is currently being developed for the treatment of CVD [7]. Apabetalone functions by inhibiting the transcriptional interactions of BET proteins with acetylated lysines on histone tails and other transcription factors [7,8]. Pan-BET inhibitors target the BET proteins by binding to bromodomains 1 (BD1) and 2 (BD2) with equal affinity, apabetalone, however binds preferentially to BD2 [8]. Apabetalone is the first BET inhibitor to be evaluated in human clinical trials for treatment of chronic disease, and has been shown to target multiple processes that underlie CVD, including reverse cholesterol transport, atherogenesis, thrombosis and vascular inflammation [9, 10]. A recent pharmacokinetic study of apabetalone treatment in patients with late stage CKD revealed that a single dose of apabetalone rapidly downregulated multiple CKD and CVD

protein markers, and associated molecular pathways [11]. Moreover, in the phase II clinical studies with apabetalone, patients treated with apabetalone were less likely to experience a major adverse cardiovascular event (MACE) and experienced reductions in CKD risk factors such as ALP [9]. ALP catalyzes the breakdown of inorganic pyrophosphate, which functions as an important inhibitor of calcification and mineralization [12]. Expressed by vascular smooth muscle cells, ALP has been previously associated with vascular calcification [13]. Higher ALP levels are correlated with increased risk of cardiovascular disease, calcification, and mortality in populations with and without CKD [14-16]. Pharmacological inhibition of ALP improves vascular calcification, cardiac hypertrophy and survival in an animal model of vascular ALP overexpression [17]. Serum ALP has also been associated with CKD progression and proteinuria [13, 18]. However, the effect of ALP inhibition on CKD progression has not yet been investigated. Here we perform a post-hoc analysis of the pooled SUSTAIN and ASSURE studies and evaluate the effects of apabetalone on the levels of ALP and other CKD risk factors in patients with established coronary artery disease and estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m$^2$.

## Materials and Methods

*Study Design: SUSTAIN and ASSURE*

The full rationale and design of the two studies, SUSTAIN (NCT01423188) and ASSURE (NCT01067820) have been published previously [19]. The phase IIb SUSTAIN and ASSURE trials were designed to evaluate the effects of apabetalone on lipid parameters and progression of coronary atherosclerosis using serial intravascular ultrasound, respectively. Both trials enrolled patients with established CVD receiving standard of care therapy, including statins and then randomized to receive either apabetalone or placebo for a period of 6 months. Similarities in the clinical trial design included the inclusion criteria, identical dosing regimen of apabetalone, comparable treatment durations (24 and 26 weeks, respectively) and the replicate placebo groups, providing rationale for the data to be pooled and analyzed. The major differences of the two trials were in the severity of the CVD. In the SUSTAIN study, patients were required to have documented stable coronary artery disease whereas in the ASSURE study patients were scheduled to undergo coronary angiography for a clinical indication. This difference provided a broader and more integrated analysis of the effects of apabetalone over 6 months of treatment.

*Post-hoc Subgroup Determination*

After combining data from the two trials, a total of 499 subjects received either 100mg b.i.d. of apabetalone (n=331) or placebo (n=168). In the SUSTAIN study, a total of 28 patients had baseline eGFR<60 mL/min/1.73 m$^2$, with 18 randomized to the apabetalone group and 10 to the placebo group. In the ASSURE study, a total of 20 patients had baseline eGFR<60 mL/min/1.73 m$^2$, with 17 randomized to the apabetalone group and 3 to the placebo group. A total of 48 patients were included in this post-hoc analysis.

*Biochemical Measures*

A central laboratory performed all biochemical determinations including creatinine and ALP (ACM, Rochester, NY, USA; and York, UK). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the eGFR [20].

*Statistical analysis*

Categorical variables are summarized using frequencies (%), while laboratory parameters are reported as median (min, max) as data was not normally distributed. All patients treated with apabetalone were compared with those receiving placebo in terms of clinical characteristics, biochemical parameters, and investigator-reported serious adverse events (SAEs). The Fisher's exact test was used to examine the difference in clinical characteristics and the Mann-Whitney test was used to examine the differences in biochemical parameters between treatment groups at baseline. The median percent change from baseline to 24/26 weeks (SUSTAIN/ASSURE) in the renal parameters was analyzed using a 2-sided Van Elteren test

of apabetalone vs placebo, stratified by study in the safety population. Baseline was defined as the last non-missing value prior to randomization. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

*Serious Adverse Events*

System organ classes and preferred terms are coded using the MedDRA Dictionary (Version 13.0 and 14.1). A subject with multiple occurrences of an AE is counted only once in the System Organ Class and Preferred Term category.

## Results

A total of 48 CKD patients were included in the post-hoc analysis, 35 who received apabetalone treatment and 13 on placebo (Fig. 1). One patient from the placebo group was lost due to death and one patient in the apabetalone group discontinued the study.

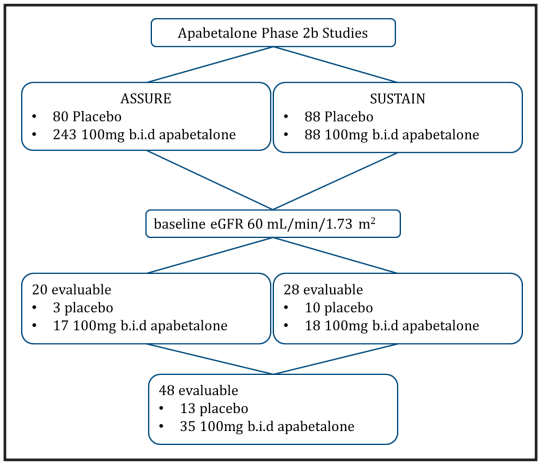


**Fig. 1.** Disposition of Patients Eligible for Post-hoc Analysis

Baseline clinical characteristics and concomitant medication use are summarized in Table 1. Due to the small sample size of each treatment group, there were some differences in baseline characteristics between apabetalone and placebo groups. Patients treated with apabetalone were more likely to have higher levels of creatinine (1.3 mg/dL vs 1.1 mg/dL; p=0.002). Although this difference was observed, the baseline eGFR measurements between the two treatment groups were similar (p=0.7). Patients in the apabetalone treatment group were more likely to be male (77.1% vs 30.8%; p=0.003). The concomitant statin allocation was different between treatment groups as apabetalone treated patients were more likely to be co-administered rosuvastatin (77.1% vs. 38.5%; p=0.02) while placebo treated patients were more likely to be co-administered atorvastatin (61.5% vs 22.9%; p=0.02).

Six months of apabetalone treatment yielded a reduction in ALP versus baseline of 14.0% (12.0 U/L) (p<0.0001 vs baseline) compared to a reduction of 6.3% (4.5 U/L) (p=0.9 vs baseline) in the placebo group. The difference between groups was significant (p = 0.02) (Table 2). eGFR in the apabetalone group increased by 3.4% (1.7 mL/min/1.73 $m^2$) (p=0.04 vs baseline) and decreased by 5.8% (2.9 mL/min/1.73 $m^2$) (ns vs baseline) in the placebo group (Table 2). Reductions in blood urea nitrogen (BUN) were similar between the two groups, and did not differ statistically (data not shown). Changes in additional markers of bone metabolism and liver function such as serum calcium, serum phosphate, serum lactate dehydrogenase, serum alanine aminotransferase, serum aspartate transaminase, and serum gamma-glutamyl transferase did not show any differences between treatment groups (data not shown).

Apabetalone was well tolerated with fewer patients in the apabetalone group experiencing an SAE compared to the placebo group (5/35, 14.3% compared to 2/13, 15.4%) (Table 3). In the apabetalone group, all of the SAEs were assessed by the Investigator unrelated to treatment with the study drug.

**Table 1.** Patient demographics, concomitant medications, and baseline laboratory values in placebo- and apabetalone treated patients with baseline eGFR<60 mL/min/1.73 $m^2$ from the pooled SUSTAIN and ASSURE studies. Categorical variables are summarized using frequencies N(%), while laboratory parameters are reported as median (min, max); eGFR estimated glomerular filtration rate, hsCRP high-sensitivity C-reactive protein, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

| Parameter | All (n=48) | Placebo (n=13) | Apabetalone (n=35) | p-value |
|---|---|---|---|---|
| Age, yrs | 67.5 (43 – 83) | 68 (55 – 83) | 67 (43 – 81) | 0.2 |
| Male | 31 (64.6) | 4 (30.8) | 27 (77.1) | 0.006 |
| Caucasian | 36 (75.0) | 10 (76.9) | 26 (74.3) | 1.0 |
| Body mass index, kg/$m^2$ | 29.5 (17.3 – 49.4) | 29.8 (20.0 – 48.1) | 29.4 (17.3 – 49.4) | 0.8 |
| Hypertension | 42 (87.5) | 12 (92.3) | 30 (85.7) | 1.0 |
| Hyperlipidemia | 29 (60.4) | 6 (46.2) | 23 (65.7) | 0.3 |
| Cardiovascular Disease History | 46 (95.8) | 13 (100.0) | 33 (94.3) | 1.0 |
| Diabetes | 24 (50.0) | 6 (46.2) | 18 (51.4) | 1.0 |
| Smoker | 8 (16.7) | 3 (23.1) | 5 (14.3) | 0.7 |
| | | | | |
| Statin Use | | | | |
| Atorvastatin | 16 (33.3) | 8 (61.5) | 8 (22.9) | 0.02 |
| Rosuvastatin | 32 (66.7) | 5 (38.5) | 27 (77.1) | 0.02 |
| | | | | |
| Concomitant Medications | | | | |
| ACE Inhibitors | 20 (41.7) | 4 (30.8) | 16 (45.7) | 0.5 |
| Beta Blockers | 28 (58.3) | 10 (76.9) | 18 (51.4) | 0.2 |
| Anticoagulants | 39 (81.3) | 9 (69.2) | 30 (85.7) | 0.2 |
| Diabetes Medications | 24 (50.0) | 6 (46.2) | 18 (51.4) | 1.0 |
| | | | | |
| Baseline Chemistry | | | | |
| Alkaline Phosphatase, U/L | 76 (39 – 156) | 70 (59 – 156) | 77 (39 – 134) | 0.4 |
| eGFR, mL/min per 1.73 $m^2$ | 53.6 (40.0 – 59.7) | 53.0 (42.0 – 59.7) | 54.4 (40.0 – 59.1) | 0.7 |
| Creatinine, mg/dL | 1.3 (1.0 – 1.6) | 1.1 (1.0 – 1.5) | 1.3 (1.0 – 1.6) | 0.002 |
| hsCRP, mg/L | 2.1 (0.4 – 22.5) | 2.3 (0.9 – 22.5) | 1.8 (0.4 – 11.3) | 0.06 |
| HDL-C, mg/dL | 39.0 (23.0 – 56.0) | 44.0 (31.0 – 56.0) | 38.5 (23.0 – 54.0) | 0.09 |
| Apolipoprotein A-I, mg/dL | 121.5 (79.8 – 168.7) | 134.8 (90.1 – 168.7) | 121.4 (79.8 – 159.3) | 0.3 |
| LDL-C, mg/dL | 91.5 (42.0 – 190.3) | 98.1 (51.4 – 151.0) | 89.6 (42.0 – 190.3) | 0.3 |

**Table 2.** Effects of Apabetalone on ALP and eGFR in the subgroup of patients with baseline eGFR<60 mL/min/1.73 $m^2$ from the pooled SUSTAIN and ASSURE studies

| Parameter | Placebo (n =13) Percent Change From Baseline | p-value vs. baseline | Apabetalone (n=35) Percent Change From Baseline | p-value vs. baseline | p-value between groups |
|---|---|---|---|---|---|
| Alkaline Phosphatase, U/L | -6.3 | 0.9 | -14.0 | <0.0001 | 0.02 |
| eGFR, mL/min per 1.73$m^2$ | -5.8 | 0.6 | +3.4 | 0.04 | 0.3 |

## Discussion

Changes in the epigenetic landscape are a recognized consequence of chronic kidney disease. Pathogenic signaling initiated by heightened levels of oxidative stress, advanced glycation end-products, pro-inflammatory cytokines, and uremic toxins induce changes in epigenetic modifications, including methylation and acetylation, on chromatin associated proteins [21-23]. Apabetalone is the first epigenetic oral therapeutic, in the bromodomain

**Table 3.** Treatment-emergent Serious Adverse Events (SAEs)

| System Organ Class/Preferred Term | All (N=48) | Placebo (N=13) | Apabetalone (N=35) | p-value |
|---|---|---|---|---|
| Number of Subjects with at least one SAE | 7 (14.6) | 2 (15.4) | 5 (14.3) | |
| Cardiac disorders | 2 (4.2) | | 2 (5.7) | 1.0 |
| Angina Pectoris | 2 (4.2) | | 2 (5.7) | 1.0 |
| General disorders and administration site conditions | 1 (2.1) | 1 (7.7) | | 0.3 |
| Death | 1 (2.1) | 1 (7.7) | | 0.3 |
| Hepatobiliary disorders | 1 (2.1) | | 1 (2.9) | 1.0 |
| Cholecystitis Acute | 1 (2.1) | | 1 (2.9) | 1.0 |
| Infections and infestations | 1 (2.1) | | 1 (2.9) | 1.0 |
| Infectious Mononucleosis | 1 (2.1) | | 1 (2.9) | 1.0 |
| Nervous system disorders | 1 (2.1) | 1 (7.7) | | 0.3 |
| Syncope | 1 (2.1) | 1 (7.7) | | 0.3 |
| Skin and subcutaneous tissue disorders | 1 (2.1) | | 1 (2.9) | 1.0 |
| Angioedema | 1 (2.1) | | 1 (2.9) | 1.0 |
| Vascular disorders | 1 (2.1) | | 1 (2.9) | 1.0 |
| Peripheral Vascular Disorder | 1 (2.1) | | 1 (2.9) | 1.0 |

and extra-terminal (BET) protein inhibitor class that preferentially targets the second bromodomain of BET family members [8]. These domains are a family of evolutionary conserved modules that bind to acetylated lysine residues which are found on the tails of histones and other transcription factors. The interaction between the BET protein and the acetylated lysines via the bromodomain plays a key role in chromatin organization and regulation of gene transcription. Apabetalone acts by inhibiting BET proteins from binding to acetylated lysine thus representing a mechanism by which gene expression can be modulated [8]. This single target approach has the potential to impact multiple dysregulated genes and biological pathways that are known to drive vascular disease. Recent findings have demonstrated apabetalone treatment can reduce expression of calcification and vascular inflammation biomarkers, as well as factors both in the fibrin clotting cascade and the complement system [9, 10]. These pathways play a potential role in the biology underlying the pathogenesis of diabetes and CKD as well as cardiovascular disease.

In this post-hoc sub-analysis of the SUSTAIN and ASSURE phase II studies, involving patients with eGFR <60 mL/min/1.73m$^2$ at baseline, a statistically significant (p=0.02) reduction in ALP was observed in the apabetalone group of -14.0% compared to -6.3% in the placebo group, even in this small sub-population. Previously, serum ALP levels have been linked with increased CVD risk in diabetic and CKD patients [18], and associated with higher mortality and calcification in CKD as well as in dialysis patients [24]. Correlation analysis has also illustrated that higher ALP levels are associated with increased hazard ratios for CVD and ESRD risk as well as for overall mortality in multiple analyses, providing evidence of increased ALP and poorer CVD outcomes across all CKD stages [25]. By decreasing ALP, apabetalone treatment may therefore improve CVD outcomes in these patients. This hypothesis is supported by the finding of a more pronounced reduction of ALP in apabetalone treated patients who did not develop a MACE compared to patients who developed a MACE in the pooled analysis of all patients included in the SUSTAIN and ASSURE trials. These data are compatible with the hypothesis that ALP is part of an array of inter-correlated risk factors that contribute to CVD and CKD. It can also be hypothesized that since ALP has a role in the vasculature, where it inactivates pyrophosphate thereby promoting medial arterial vascular calcification, apabetalone may also prevent calcification.

Apabetalone treatment also resulted in an increase in eGFR of +3.4%, which was statistically significant compared to baseline, even in this small sub-population. Estimated glomerular filtration rate is the most widely utilized test for assessing kidney function. The CKD-EPI equation utilizes a patients' blood creatinine level, along with age, race and gender

to calculate this value. Extensive reporting of eGFR has provided an indirect correlation between lower GFR and higher CVD risk in diabetics and CKD patients [26]. Although serum ALP has previously been associated with CKD progression, the underlying mechanisms are still unclear. However, we demonstrate for the first time a pharmacologic reduction of serum ALP activity and an improvement of eGFR. These data suggest that BET inhibition by apabetalone may be beneficial for kidney function.

A number of limitations of the current study should be noted. Patient urine was not collected and as such no data on proteinuria data is available. Additionally, this post-hoc analysis represents a small subgroup from two larger studies, which were shorter in duration than previous evaluations of CVD therapies. The small sample size in each treatment group represents a limitation to the study as there were some differences in baseline characteristics. Whether a continued favorable impact of apabetalone might be observed during a longer period of follow-up is part of a pre-specified CKD sub-group in BETonMACE, a phase III clinical trial currently enrolling high-risk diabetes and CKD patients.

## Conclusion

Apabetalone has beneficial effects on ALP and eGFR and is a potential novel therapeutic for the treatment of CKD. Currently, apabetalone is being evaluated in BETonMACE, a trial enrolling high risk post-acute coronary syndrome patients with diabetes, of which approximately 10-15% will have stage III CKD. Key clinical endpoints will include MACE reduction, renal function, and changes in CKD markers in the CKD patients in the trial. Furthermore, based on these observations, a phase IIa study in ESRD patients on hemodialysis (HD) is planned, with the evaluation of ALP levels, serum creatinine, serum calcium, inflammatory and metabolic biomarkers associated with CVD risk in dialysis patients as endpoints.

## Disclosure Statement

EK, JJ, MS, CH, KL, and NW are salaried employees of Resverlogix Corp. and shareholders of Resverlogix Corp which supported the study financially. MH, VB, SB, MT, CZ and KKZ are members of the renal clinical advisory board of Resverlogix Corp. KKZ are supported by the NIDDK grants R01-DK095668 and K24-DK091419 as well as philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, Dr. Joseph Lee and AVEO.

## References

1 Levey AS, Coresh J: Chronic kidney disease. Lancet 2012;379:165-180.
2 Schlieper G, Hess K, Floege J, Marx N: The vulnerable patient with chronic kidney disease. Nephrol Dial Transplant 2016;31:382-390.
3 Filippakopoulos P, Knapp S: The bromodomain interaction module. FEBS Lett 2012;586:2692-2704.
4 Brown JD, Lin CY, Duan Q, Griffin G, Federation AJ, Paranal RM, Bair S, Newton G, Lichtman AH, Kung AL, Yang T, Wang H, Luscinskas FW, Croce KJ, Bradner JE, Plutzky J: Nf-kappab directs dynamic super enhancer formation in inflammation and atherogenesis. Mol Cell 2014;56:219-231.
5 Suarez-Alvarez B, Morgado-Pascual JL, Rayego-Mateos S, Rodriguez RM, Rodrigues-Diez R, Cannata-Ortiz P, Sanz AB, Egido J, Tharaux PL, Ortiz A, Lopez-Larrea C, Ruiz-Ortega M: Inhibition of bromodomain and extraterminal domain family proteins ameliorates experimental renal damage. J Am Soc Nephrol 2017;28:504-519.
6 Xiong C, Masucci MV, Zhou X, Liu N, Zang X, Tolbert E, Zhao TC, Zhuang S: Pharmacological targeting of bet proteins inhibits renal fibroblast activation and alleviates renal fibrosis. Oncotarget 2016;7:69291-69308.

7 McLure KG, Gesner EM, Tsujikawa L, Kharenko OA, Attwell S, Campeau E, Wasiak S, Stein A, White A, Fontano E, Suto RK, Wong NC, Wagner GS, Hansen HC, Young PR: RVX-208, an inducer of ApoA-I in humans, is a BET bromodomain antagonist. PLoS One 2013;8:e83190.

8 Picaud S, Wells C, Felletar I, Brotherton D, Martin S, Savitsky P, Diez-Dacal B, Philpott M, Bountra C, Lingard H, Fedorov O, Muller S, Brennan PE, Knapp S, Filippakopoulos P: RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. Proc Natl Acad Sci U S A 2013;110:19754-19759.

9 Gilham D, Wasiak S, Tsujikawa LM, Halliday C, Norek K, Patel RG, Kulikowski E, Johansson J, Sweeney M, Wong NC: Rvx-208, a bet-inhibitor for treating atherosclerotic cardiovascular disease, raises apoa-i/hdl and represses pathways that contribute to cardiovascular disease. Atherosclerosis 2016;247:48-57.

10 Wasiak S, Gilham D, Tsujikawa LM, Halliday C, Norek K, Patel RG, McLure KG, Young PR, Gordon A, Kulikowski E, Johansson J, Sweeney M, Wong NC: Data on gene and protein expression changes induced by apabetalone (rvx-208) in ex vivo treated human whole blood and primary hepatocytes. Data Brief 2016;8:1280-1288.

11 Wasiak S, Tsujikawa LM, Halliday C, Stotz SC, Gilham D, Jahagirdar R, Kalantar-Zadeh K, Robson R, Sweeney M, Johansson JO, Wong NC, Kulikowski E: Benefit of Apabatalone on Plasma Proteins in Renal Disease. Kidney Int Rep 2017; DOI: 10.1016/j.ekir.2017.12.001.

12 Schoppet M, Shanahan CM: Role for alkaline phosphatase as an inducer of vascular calcification in renal failure? Kidney Int 2008;73:989-991.

13 Haarhaus M, Brandenburg V, Kalantar-Zadeh K, Stenvinkel P, Magnusson P: Alkaline phosphatase: A novel treatment target for cardiovascular disease in ckd. Nat Rev Nephrol 2017;13:429-442.

14 Kovesdy CP, Ureche V, Lu JL, Kalantar-Zadeh K: Outcome predictability of serum alkaline phosphatase in men with pre-dialysis ckd. Nephrol Dial Transplant 2010;25:3003-3011.

15 McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H, Rafiq M, Jones S: Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: A large community based cohort study. PLoS One 2013;8:e74996.

16 Tonelli M, Curhan G, Pfeffer M, Sacks F, Thadhani R, Melamed ML, Wiebe N, Muntner P: Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation 2009;120:1784-1792.

17 Sheen CR, Kuss P, Narisawa S, Yadav MC, Nigro J, Wang W, Chhea TN, Sergienko EA, Kapoor K, Jackson MR, Hoylaerts MF, Pinkerton AB, O'Neill WC, Millan JL: Pathophysiological role of vascular smooth muscle alkaline phosphatase in medial artery calcification. J Bone Miner Res 2015;30:824-836.

18 Taliercio JJ, Schold JD, Simon JF, Arrigain S, Tang A, Saab G, Nally JV, Jr., Navaneethan SD: Prognostic importance of serum alkaline phosphatase in ckd stages 3-4 in a clinical population. Am J Kidney Dis 2013;62:703-710.

19 Nicholls SJ, Gordon A, Johannson J, Ballantyne CM, Barter PJ, Brewer HB, Kastelein JJ, Wong NC, Borgman MR, Nissen SE: Apoa-i induction as a potential cardioprotective strategy: Rationale for the sustain and assure studies. Cardiovasc Drugs Ther 2012;26:181-187.

20 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J: A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-612.

21 Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, Kanbay M, Mallamaci F, Parati G, Rossignol P, Wiecek A, London G: The systemic nature of CKD. Nat Rev Nephrol 2017;13:344-358.

22 Witasp A, Van Craenenbroeck AH, Shiels PG, Ekstrom TJ, Stenvinkel P, Nordfors L: Current epigenetic aspects the clinical kidney researcher should embrace. Clin Sci (Lond) 2017;131:1649-1667.

23 Wing MR, Ramezani A, Gill HS, Devaney JM, Raj DS: Epigenetics of progression of chronic kidney disease: fact or fantasy? Semin Nephrol 2013;33:363-374.

24 Regidor DL, Kovesdy CP, Mehrotra R, Rambod M, Jing J, McAllister CJ, Van Wyck D, Kopple JD, Kalantar-Zadeh K: Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. J Am Soc Nephrol 2008;19:2193-2203.

25 Abramowitz M, Muntner P, Coco M, Southern W, Lotwin I, Hostetter TH, Melamed ML: Serum alkaline phosphatase and phosphate and risk of mortality and hospitalization. Clin J Am Soc Nephrol 2010;5:1064-1071.

26 Solini A, Penno G, Bonora E, Fondelli C, Orsi E, Arosio M, Trevisan R, Vedovato M, Cignarelli M, Andreozzi F, Nicolucci A, Pugliese G: Diverging association of reduced glomerular filtration rate and albuminuria with coronary and noncoronary events in patients with type 2 diabetes: The renal insufficiency and cardiovascular events (riace) italian multicenter study. Diabetes Care 2012;35:143-149.