Apabetalone (RVX-208), a First-in-Class Epigenetic BET Inhibitor, has Effects on ALP and eGFR in Subjects with CVD and CKD; a Post-hoc Analysis of ASSERT, SUSTAIN and ASSURE Clinical Trials

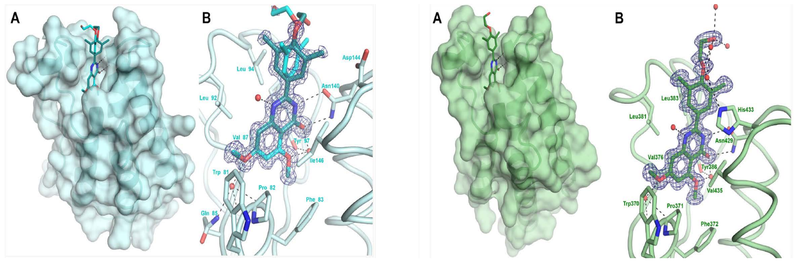
Kamyar Kalantar-Zadeh[1], Jan Johansson[2], Michael Sweeney[2], Ewelina Kulikowski[3], Ken Lebioda[3], Christopher Halliday[3], Norman Wong[3]

[1]University of California Irvine School of Medicine, Irvine, CA, [2]Resverlogix Corp, Clinical Development, San Francisco, CA, [3]Resverlogix Corp, R&D, Calgary, AB, CANADA

BACKGROUND

RVX-208 is a first in class orally active small molecule that binds selectively to the second ligand domain of bromodomain extra-terminal proteins (BET). These proteins are epigenetic readers that bind acetylated lysine present in the tail of histones thus affecting chromatin structure. RVX-208 inhibits acetylated lysine from binding to BET proteins and thereby alters activity of selected genes (see crystallography figure). The epigenetic BET inhibitor RVX-208 is characterized by anti-inflammatory effects, activation of apolipoprotein A-I (apoA-I) transcription and improved metabolic effects. Reductions in alkaline phosphatase (ALP) have also been observed.

RVX-208 binds selectively to BD2 of BET proteins.



Each BET protein is comprised of dual bromodomains (BD1 and BD2) that bind to acetylated lysines on histone tails and thereby affect chromatin function. RVX-208 binds selectively to BD2.

METHODS

A subpopulation analysis from the placebo controlled phase 2 program in cardiovascular disease (CVD) identified subjects with CKD based on eGFR < 60 ml/min/1.73m^2. The effect of selective BET inhibition on key renal parameters in this subgroup was assessed. A total of 81 subjects (RVX-208 n=58/Placebo n=23) were treated with either RVX-208 200mg daily, RVX-208 300mg daily or placebo for 3 months and 48 subjects (RVX-208 n=35/Placebo n=13) were treated with RVX-208 200mg daily or placebo for 6 months. A pooled analysis was performed assessing changes in eGFR and ALP at 3 and 6 months. Analysis of lipid markers included ApoA-I, HDL-C and HDL particle parameters by nuclear magnetic resonance (NMR).

RESULTS

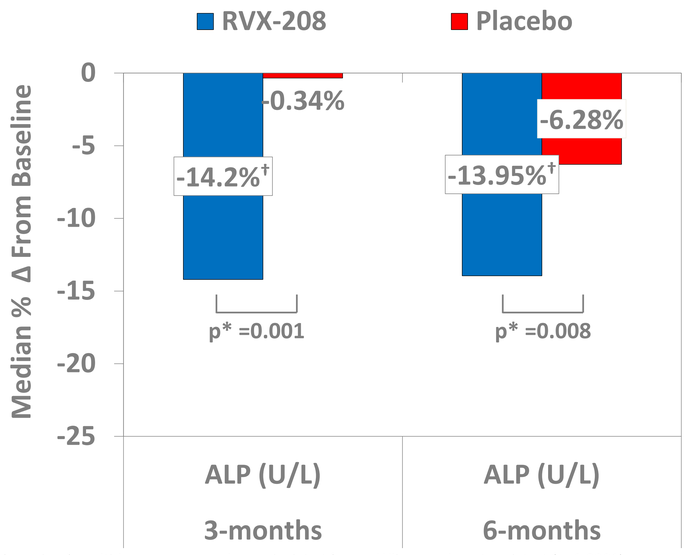
In CKD subjects receiving RVX-208 there was no change in eGFR compared to a decrease of -3.7% in patients receiving placebo at 3 months. Following 6 months of RVX-208 treatment, an increase of +3.4% eGFR (p=0.04 vs. baseline) was observed compared to a decrease of -5.9% in placebo (Figure A). Changes in ALP for RVX-208 and placebo were -14.2% and -0.3% at 3 months (p<0.05 vs. placebo) and -13.9% vs. -6.3% (p<0.05 vs. placebo) at 6 months (Figure B). Changes in lipid parameters over placebo at 6 months included, an increase of +5.2% in ApoA-I (mg/dL) (p=0.007 vs. baseline), an increase of +7.6% in HDL-c (mg/dL) (p=0.03 vs. baseline), an increase of +24.3% in large HDL particles (umol/L) (p=0.001 vs. baseline), an increase of +1.2% in HDL size (nm) (p<0.1 vs. baseline) (Figure C).

A. RVX-208 improves eGFR in patients with eGFR<60 treated for 6 months.

Treatment Group	N	Median % Δ from baseline	p vs baseline†
Placebo	13	-5.9	0.64
RVX-208	35	+3.4	0.04

† p-value for within group comparison calculated from a Wilcoxon signed-rank test

B. RVX-208 lowers ALP in patients with eGFR<60 treated for 3 and 6 months.



† p-value for within group comparison calculated from a Wilcoxon signed-rank test (p<0.0001)
* p-value for between group comparison calculated from a 2-sided Van Elteren test. Stratified by study

C. RVX-208 improves markers of RCT in patients with eGFR<60 treated for 6 months.

Biomarker	Within Treatment Results Median % Δ from baseline				Between Treatment Difference
	RVX-208 (n=35)	p-value vs baseline	Placebo (n=15)	p-value vs baseline	
HDL-C (mg/dL)	+5.4	0.03	-2.17	0.84	+7.57
ApoA-I (mg/dL)	+5.8	0.007	+0.54	0.91	+6.3
Large HDL particles (µmol/L)	+29.1	0.001	+4.76	0.85	+24.3
HDL size (nm)	+1.2	0.08	0.0	0.76	+1.2

† p-value for within group comparison calculated from a Wilcoxon signed-rank test

CONCLUSIONS

Apabetalone (RVX-208) selective BET inhibition shows a gradual improvement in eGFR following up to 6 months of treatment, significant reductions in ALP and improved lipid parameters. These findings may have implications for patients with CKD and high CVD risk. Additional clinical trials in high risk CVD, diabetes and CKD populations are warranted.