Apabetalone (RVX-208) is a selective BET protein inhibitor, which reduces the expression of acute phase response markers in vitro and in patients with cardiovascular disease and chronic kidney disease.

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**Abstract**

Apabetalone (RVX-208) is an inhibitor of the epigenetic readers bromodomain and extraterminal (BET) proteins, currently in a phase 3 outcomes trial in patients with cardiovascular disease (CVD) and diabetes mellitus. A post hoc analysis of phase 2b trials demonstrated a 55% relative risk reduction in major adverse cardiac events (MACE) in CVD patients. Elevated inflammatory markers correlate with CVD. Inflammation also accompanies chronic kidney disease (CKD) and CKD patients are at risk of CVD. Previous research has shown that apabetalone modulates pathways that contribute to chronic inflammation, including the acute phase response (APR). Here, pathway analysis of gene microarrays showed downregulation of APR by apabetalone in primary human hepatocytes (PHH). Apabetalone reduces levels of circulating CRP in CVD and CKD patients.

**Results**

1. Apabetalone reduces expression of the acute phase response (APR) pathway in primary human hepatocytes

   **Gene Expression Microarray from Primary Human Hepatocytes (Fold Change)**

   Gene Name | Gene Symbol | Donor 1 | Donor 2
   --- | --- | --- | ---
   Acute phase-binding lectin | MBL2 | 3.07 | 2.32
   Complement component 1, inhibitor | C1INH | 1.03 | 0.94
   Complement component 10 | C10 | 0.94 | 0.94
   Complement component 1, C1r/C1s, OVA, and C2 | C1QC | 1.31 | 0.88
   Complement component 1, C1r/C1s, OVA, and C2 | C1R | 0.47 | 0.79
   Complement component 1, C1r/C1s, OVA, and C2 | C1S | 0.37 | 0.37
   C-reactive protein | CRP | 1.98 | 1.28
   Haptoglobin | HP | 0.88 | 0.84
   Alpha-2-macroglobulin (A2M) | A2M | 0.47 | 0.29
   C1-esterase inhibitor | CI | 1.55 | 1.38
   Serum amyloid P-component | SAA1 | 0.73 | 0.62
   Serum amyloid P-component | SAA2 | 0.66 | 0.47
   Serum amyloid P-component | SAA3 | 0.54 | 0.72
   Serum amyloid P-component | SAA4 | 0.55 | 0.47
   Serum amyloid P-component | SAA5 | 0.73 | 1.04
   Serum amyloid P-component | SAA6 | 0.55 | 0.84
   Serum amyloid P-component | SAA7 | 0.55 | 0.77
   Serum amyloid P-component | SAA8 | 0.56 | 0.62
   Serum amyloid P-component | SAA9 | 0.56 | 0.56
   Serum amyloid P-component | SAA10 | 0.56 | 0.84

   Aggregated expression relative to DMSO-treated primary human hepatocytes.

2. Apabetalone downregulates APR expression in PHH at steady state (A) and in inflammatory conditions (B)

3. Apabetalone reduces expression of APR genes in primary human hepatocytes (PHH)

   **Ingenuity Pathway Analysis (IPA): Acute Phase Response Pathway**

   Fold changes in mRNA abundance in apabetalone vs. DMSO-treated primary human hepatocytes.

   **Disclosure:** Authors were employed by Reverselogix & held stock options.

4. Apabetalone downregulates the APR pathway in CKD or CVD patients

   **Bioinformatics (IPA) Analysis of the Plasma Proteome (SOMAscan)**

   **Trial** | **Acute Phase Response Pathway**
   --- | ---
   Phase 1 | Phase 1
   Phase 2 | Phase 2
   Phase 3 | Phase 3

   **SOMAscan Proteomics Data:** % Change in C-Reactive Protein Abundance in Phase 1 PK Trial in CVD Patients Matched Controls Without CKD

   **Study** | **# of Patients in Study** | **Apabetalone vs. Baseline** | **p-value vs. Baseline**
   --- | --- | --- | ---
   Cohort A: End stage renal disease in dialysis; eGFR < 30 mL/min/1.73m² | n=164 | -7.4 % | 0.04
   Cohort B: Matched subjects, no kidney disease | n=8 | -12.6 % | 0.15

5. Apabetalone reduces levels of circulating CRP in CVD and CKD patients

   **SOMAscan Proteomics Data:** % Change in C-Reactive Protein Abundance in Phase 2 Trials in CVD Patients Receiving Standard of Care

   **Study** | **# of Patients in Study** | **Apabetalone vs. Placebo** | **p-value vs. Placebo**
   --- | --- | --- | ---
   ASSERT (3 months) Cohort A | n=25 | -2.6 % | 0.02
   ASSERT (3 months) Cohort B | n=16 | -12.7 % | 0.01

**Summary**

- Acute phase response (APR) is amongst the top pathways downregulated by apabetalone in primary human hepatocytes and in plasma from treated patients with cardiovascular disease (CVD) or chronic kidney disease (CKD).
- Apabetalone reduces expression of APR genes linked to CVD risk in resting and cytokine-treated primary human hepatocytes.
- Apabetalone downregulates expression of APR genes in a mouse model of inflammation and endotoxemia.
- In three clinical trials, apabetalone reduces circulating levels of C-reactive protein (CRP), an APR protein that correlates with inflammation and independently predicts adverse cardiovascular outcomes.
- Apabetalone-mediated downregulation of the APR pathway in CVD patients may contribute to reductions in MACE observed in clinical trials.