Abstract

Background: RVX-208 affects epigenetics by inhibiting bromodomain and extraterminal (BET) proteins from binding to their natural ligand, acetyl-lysine marks on histone tails and thereby modulates gene activity. In SUSTAIN and ASSURE phase IIb trials of CVD patients (n=499), giving 200 mg/d of RVX-208 orally lead to a 55% relative risk reduction in major adverse cardiovascular events (MACE) vs. placebo. This marked reduction in MACE is unlikely due to RVX-208’s modest induction of ApoA-1/HDL, thus prompting studies of RVX-208 for its benefits beyond lipids.

Methods: included microarray surveys of human whole blood (WB) or primary hepatocytes (PH) exposed to RVX-208. Cytokines were assayed in U937 macrophage and peripheral blood mononuclear cells (PBMC) exposed to RVX-208. Plasma samples from phase IIb patients were measured using SOMAscan proteomic analysis.

Results: of the microarray studies using WB showed a potential anti-atherogenic effect of RVX-208 because it suppressed activity of 37/46 pro-atherogenic while inducing 8/18 anti-atherogenic genes. Additionally, RVX-208 had potential anti-thrombogenic properties by affecting 18 genes related to platelet function (e.g. downregulation of CD64 and thrombospondin 1). RVX-208 had anti-inflammatory effects on the expression of >25 cytokines including IL-6, MCP-1, VCAM-1, PARC and osteopontin (OPN).

Summary: RVX-208 inhibits BET proteins to impact cellular epigenetics that in turn affects expression of genes with known roles in CVD. This activity may underlie RVX-208’s anti-atherogenic, anti-thrombotic and anti-inflammatory effects in reducing MACE observed in clinical trials.

Conclusions

- RVX-208 reduces Fmo3 expression which affects TMAO production.
- RVX-208 reduces circulating CVD markers.
- RVX-208, reduces expression of genes involved in atherogenesis, vascular inflammation and platelet function in vitro.
- RVX-208 reduces circulating CVD markers in patients.
- RVX-208 reduces Fmo3 expression which may lower TMAO levels.
- RVX-208 induces transcriptional changes that may impact CVD and lower incidence of MACE observed in the ASSURE and SUSTAIN trials.

Apabetalone (RVX-208) has Anti-atherosclerotic, Anti-Thrombotic and Anti-Inflammatory Effects in Patients with Cardiovascular Disease.

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