European Respiratory Society
Annual Congress 2013

Abstract Number: 2493

Publication Number: P3408

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** Treatments **Keyword 3:** Pharmacology

Title: Intracellular accumulation and effects on bile acid transport of endothelin receptor antagonists in sandwich-cultured hepatocytes

Dr. Hunter 12209 Gillies hunter.gillies@gilead.com MD [1], Irene 12210 Lepist irene.lepist@gilead.com [2], William 12211 Smith WilliamSmith@qualyst.com [3], Jia 12212 Hao jia.hao@gilead.com [2], Cassandra 12213 Perry CassandraPerry@qualyst.com [3], Robert 12214 St Claire RobertStclaire@qualyst.com [3], Kenneth 12215 Brouwer KennethBrouwer@Qualyst.com [3] and Adrian 12216 Ray adrian.ray@gilead.com [2]. [1] Clinical Research, Gilead Sciences Inc., Foster City, United States, 94404 ; [2] Drug Metabolism, Gilead Sciences, Foster City, United States, 94404 and [3] Transporter Solutions R&D, Qualyst Inc., Durham, United States, 27713 .

Body: Background: The putative mechanism for hepatic adverse reactions observed with bosentan, an endothelin receptor antagonist (ERA), is inhibition of the hepatic transport of bile acids (Fattinger et al. 2001). In transfected cell lines we have previously shown differences between ERA in their potential to inhibit the bile salt transporters NTCP and BSEP: macitentan > bosentan > ambrisentan. Objective: In order to further our understanding of the potential for ERA to affect the hepatic transport of bile salts, studies were completed in sandwich-cultured human hepatocytes. Methods: The concentration dependent effects of ERA were assessed in studies designed to determine their intracellular accumulation and their effects on the transport of exogenous taurocholate and endogenous glycocholate and glycochenodeoxycholate. The concentration of ERA and bile acids in media and cellular extracts were determined by LC/MS/MS. Results: Differential accumulation in the hepatocytes was observed for the ERA: macitentan (30-600x) > bosentan (10-20x) > ambrisentan (~2x). The effect of ERA on bile acid transport reflected their cellular accumulation with macitentan having the greatest effects, followed by bosentan, and smaller changes observed at the highest concentrations of ambrisentan tested. Sitaxsentan showed results similar to those obtained with bosentan. Conclusions: Significant differences were observed between the ERA. Macitentan had the highest level of accumulation in hepatocytes and caused the greatest effect on bile acids followed by sitaxsentan and bosentan. Ambrisentan showed very low potential to affect bile acids.