Discovery of RTY-406, a Positive Functional Modulator of ABCB4 and BSEP (ABCB11) as a Disease-Modifying Therapy for the Treatment of Primary Sclerosing Cholangitis

Nathan O. Fuller, Eric Bell, Pol Boudes, Robert Hughes, John Miller, Todd Bosanac, Renata Franca, Alastair Garfield, Eitan Hoch, Youhwa Jo, Adrianne Kolpak, Jon Moore, Pui Yee Ng, Bharat Reddy, Patrick Stoiber, Jennifer Truong.

Rectify Pharmaceuticals, 24 School Street, 2nd floor, Boston, MA 02108

Primary sclerosing cholangitis (PSC) is a bile duct disease in which inflammation and fibrosis lead to biliary strictures. PSC is predominantly driven by changes in bile composition that render it toxic to duct epithelial cells (cholangiocytes). This bile duct injury further leads to cholangitis, cholestasis, and increased risk of cholangiocarcinoma. PSC ultimately progresses to cholestatic liver cirrhosis and liver failure. There is no approved drug for this severe disease.

Positive functional modulators (PFMs) are molecules which directly bind their cellular protein target to facilitate proper trafficking of the protein to the cell surface, thereby increasing the protein's abundance, effectively increasing its functional output. Rectify hypothesized that a dual PFM for the hepatocyte transporters ABCB4 and BSEP (bile salt export pump, also known as ABCB11), necessary for biliary homeostasis, would provide therapeutic benefit to PSC patients. The enhanced activity of ABCB4 would increase phospholipid secretion to restore the formation of biliary micelles and decrease bile toxicity, while enhanced BSEP function would restore normal bile flow, decreasing the residence time of toxic bile in the ducts, retention of bile acids in hepatocytes, and their resulting negative consequences on the liver. Here, Rectify describes our approach to identify dual PFMs for ABCB4 and BSEP.

Screening provided a series of indole carboxamide compounds which increased ABCB4 and BSEP protein levels. Optimization efforts increased potency and lowered projected human dose. CryoEM demonstrated direct binding to both target proteins. In primary hepatocytes *in vitro*, optimized compounds increased ABCB4 and BSEP protein expression and conferred corresponding functional improvements. This work led to the discovery of RTY-406, a dual, equipotent PFM of ABCB4 and BSEP. In an *in vivo* mouse model of PSC, RTY-406 reduced cholestasis, cholelithiasis, cholangitis, ductular reaction, and fibrosis. RTY-406 has advanced to Phase 1 clinical trials as a potential new treatment for PSC.