RTY-406, a candidate drug for Primary Sclerosing Cholangitis (PSC), a dual-acting ABCB4/MDR3 and ABCB11/BSEP positive functional modulator, demonstrates proof of mechanism in non-human primates

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Introduction

ATP binding cassette subfamily B members 4 (ABCB4/MDR3) and 11 (ABCB11/BSEP) translocate phosphatidylcholine (PL) and bile acids (BA) from hepatocytes to bile ducts, respectively. RTY-406, a novel dual-acting ABCB4/BSEP positive functional modulator (PFM), has demonstrated efficacy in rodent models of cholestasis, and validating target modulation and safety in a higher species de-risks clinical translation. We used non-human primates to assess and validate mechanism of action and hepatobiliary health serum biomarkers to support early clinical development. RTY-406 demonstrated a favorable profile with no adverse signals in liver function tests. ALT and AST levels confirmed the absence of hepatocellular injury. Cholesterol, ALP, and GGT levels were all dose-dependently reduced, indicating appropriate target modulation consistent with the anticipated mechanism of action of RTY-406.

Methods

Study design: Healthy naïve cynomolgus monkeys aged 3 to 5 years old were obtained from Beijing Vafory Technology Co. and animals were quarantined for 3 weeks prior to initiating 28 days of QD dosing. Animals were provided water ad libitum and fed twice daily except during overnight food fasting prior to blood collection for clinical chemistry. Animals were randomized on weight into study groups (Table 1). Three of four groups are presented. All study activities were in accordance with Pharmaron (Beijing) TSP's IACUC policies and procedures.

Formulation and dosing: Dose formulations were prepared weekly, aliquoted for daily usage and stored refrigerated (5±3°C) before use. The vehicle was 30% PEG400/5% TPGS/2% HPMC-E5/pH 3 citrate buffer (0.1M) (v/v/w/v). RTY-406 was formulated at 1 mg/mL and 2 mg/mL to achieve 5 mg/kg and 10 mg/kg dose using 5 mL/kg dose volume.

Clinical Chemistry: Clinical chemistry parameters of alanine transaminase (ALT) and aspartate aminotransferase (AST) were used to monitor liver toxicity. Total cholesterol, alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) were used to monitor target modulation (Table 2). All analytes were measured using a HITACHI 7180 Chemistry Analyzer. Data is presented as the mean ± standard error of the mean for the percent change from baseline to day 28.

Table 1. Study Groups

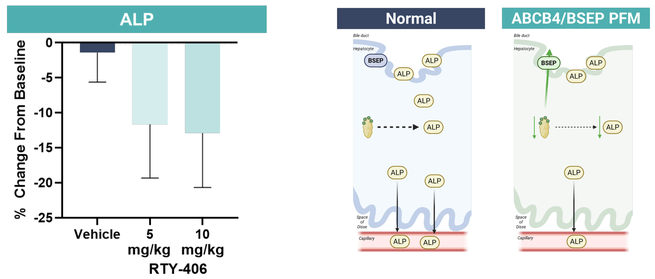
Treatment	Dose Level (mg/kg/day)	Dose Frequency	Number (M/F)
Vehicle	0	QD	5/5
RTY-406	5	QD	3/3
RTY-406	10	QD	5/5

Results

Table 2. Pharmacodynamic endpoints used to determine ABCB4/BSEP target modulation

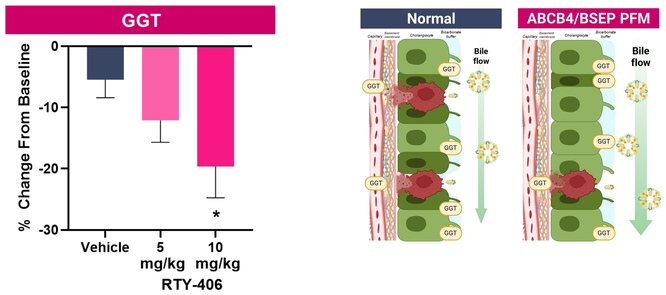
Target	Translational biomarker	Relevance
BSEP	ALP	Marker of reduced hepatic BA
ABCB4	GGT	Marker of cholangiocyte turnover
BSEP	Total Cholesterol	Marker of reduced hepatic BA

Figure 1. RTY-406 reduced serum ALP after 28 days of QD dosing



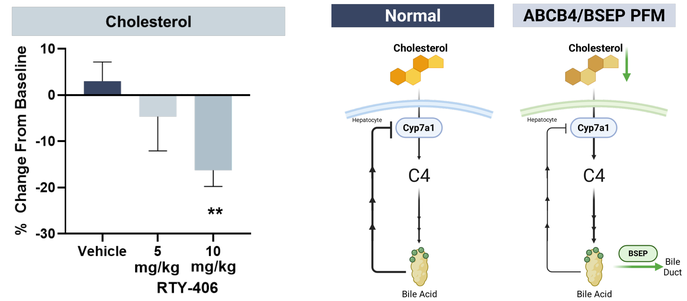
- RTY-406 reduced serum ALP levels
- BA regulate hepatic expression of ALP[1], and increased BSEP activity reduces hepatic BA resulting in reduction in ALP production and leak into capillaries

Figure 2. RTY-406 dose dependently reduced serum GGT levels after 28 days of QD dosing



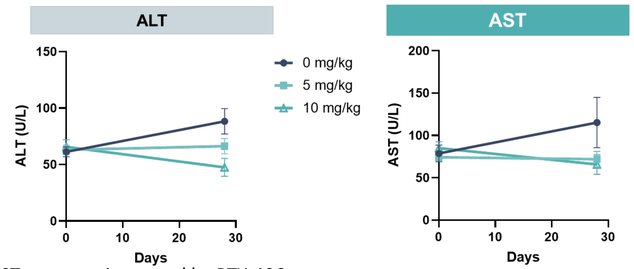
- RTY-406 dose-dependently reduced serum GGT levels
- Basal turnover of cholangiocytes in bile ducts act as a source of serum GGT under normal conditions[2, 3, 4]
- Increased ABCB4/BSEP activity increases bile flow and micelle formation to reduce cholangiocyte turnover

Figure 3. RTY-406 dose dependently reduced serum cholesterol levels after 28 days of QD dosing



- RTY-406 reduced cholesterol, the substrate for de novo BA synthesis
- Increased BSEP activity reduces hepatic BA resulting in de-repression of C4 synthesis from cholesterol

Figure 4. RTY-406 does not induce liver toxicity as measured by ALT and AST after 28 days of QD dosing



- ALT and AST were not increased by RTY-406
- Absolute levels all remained within normal limits

Conclusions

This cynomolgus monkey study establishes a translatable biomarker profile for RTY-406. Use of bile acid synthesis markers combined with ALP, GGT, ALT, and AST provides a robust panel for parallel monitoring of target modulation and hepatobiliary health. These data de-risk translation to human studies, offering a specific set of serum biomarkers that further support clinical development of RTY-406 for PSC.

References

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