SRT-015: Novel Therapeutic for Cholestatic Liver Diseases

K. Elias [1], S. Brown[1], N. McDonnell[1], A. Plonowski [1]

[1]Seal Rock Therapeutics Inc., Seattle WA, USA

Contact Information
kelias@sealrocktx.com
www.sealrocktx.com

EASL CONGRESS Milan, Italy 5-8 June 2024

Abstract 811
TOP-156

Seal Rock THERAPEUTICS

Introduction

SRT-015 is an oral second-generation apoptosis signal-regulating kinase 1 (ASK1) inhibitor with liver-preferred distribution and demonstrated:

- Direct dose-dependent anti-apoptotic, anti-inflammatory and antifibrotic effects in vitro (1).
- Efficacy in acute rodent models of liver injury including alcohol-related liver disease and acetaminophen overdose (2).
- Efficacy in a chronic therapeutic, diet-induced obese mouse MASH model with biopsy-confirmed fibrosis (1)
- Generally well-tolerated with a favorable safety profile in human volunteers in a phase 1 clinical trial (3).

Aim

To evaluate SRT-015 effects on fibrosis in a rat 14-day Bile Duct Ligation (BDL) model of severe cholestatic disease.

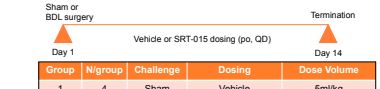
Method

Protocol
Male Sprague Dawley rats (7 - 8 weeks) were randomized into four treatment groups as shown. BDL surgery included ligation of the common bile duct below the junction of the hepatic ducts and above the pancreatic duct entrance. Sham animals underwent laparotomy without ligation. SRT-015 or vehicle was dosed po (80:20 Capryol90: Labrafil M 1944 CS, % v/v) starting at Day1, 1 h before surgery, then daily for 14 days.

Endpoints
On terminal Day 14, 2 h after the last dose, whole blood was collected for blood chemistry evaluation. Livers were evaluated for SRT-015 concentrations, fibrosis by biochemical hydroxyproline (HP) content, picrosirius red staining (PSR), and stellate cell activation (alpha-smooth muscle actin staining) by histomorphometry (Aperio ImageScope analysis software).

Statistics: Results are presented as mean ± S.E.M. Statistical analysis was performed by One-way ANOVA followed by Dunnett's multiple comparison test using GraphPad Prism. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$ compared to BDL + Vehicle group.

Physiologically based pharmacokinetic (PBPK) model: Using an established PBPK model based on preclinical plasma and liver exposures, and clinical data (4), the SRT-015 liver exposure levels from this study were modeled to predict human liver exposures.

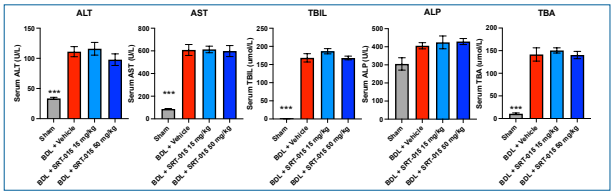


Group	N/group	Challenge	Dosing	Dose Volume
1	4	Sham	Vehicle	5ml/kg
2	10	BDL	Vehicle	5ml/kg
3	10	BDL	SRT-015 15 mg/kg	5ml/kg
4	10	BDL	SRT-015 50 mg/kg	5ml/kg

Endpoints:
BW, LW, liver enzymes
Fibrosis: Hydroxyproline, PSR
Stellate cell activation: alpha-SMA IHC

Results

All BDL groups had elevated blood chemistries compared to sham vehicle



The BDL-elevated blood chemistries were unchanged with SRT-015 treatment.

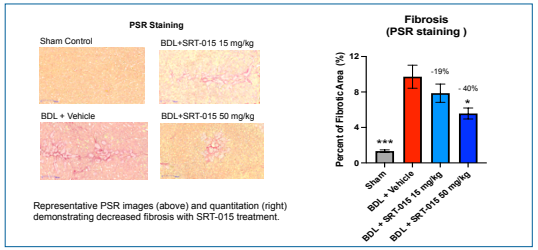
The BW of all BDL groups was decreased, and liver weight increased, compared to sham group and unchanged with SRT-015 treatment (data not shown).

Acknowledgements

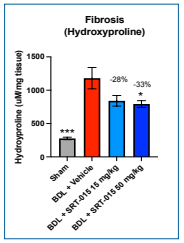
Thanks to PharmaLegacy and Simulations Plus for performing the animal studies and modeling analysis, respectively

Results

SRT-015 significantly and dose-dependently decreased BDL-induced fibrosis as demonstrated by PSR staining and HP analysis

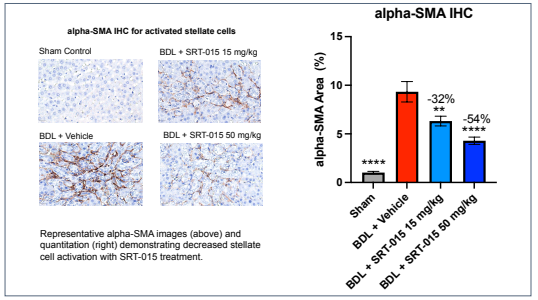


Representative PSR images (above) and quantitation (right) demonstrating decreased fibrosis with SRT-015 treatment.



SRT-015 treatment significantly decrease BDL-induced fibrosis by both morphometric and biochemical methods in this severe model.

SRT-015 significantly and dose-dependently decreased BDL-induced stellate cell activation



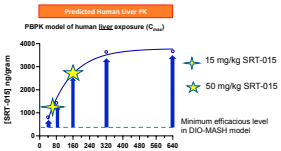
Representative alpha-SMA images (above) and quantitation (right) demonstrating decreased stellate cell activation with SRT-015 treatment.

SRT-015 liver concentrations within range of the predicted hepatic exposure in the phase 1 clinical trial using a PBPK model

Dose	Liver (ng/g)
15 mg/kg	1,232 +/- 168
50 mg/kg	2,757 +/- 680

SRT-015 liver exposure 2hrs post last dose ($\sim C_{max}$) in BDL study

Using an established PBPK model, the SRT-015 liver concentrations from this BDL study are demonstrated clinically achievable in this simulated model.



Conclusions

- SRT-015 significantly and dose-dependently decreased BDL-induced fibrosis as demonstrated by decreased PSR and HP after 14 days of treatment in this severe model. A significant and dose-dependent decrease of stellate cell activation (fibrosis generating cells) was also observed.
- These antifibrotic data suggests that SRT-015 is a promising therapeutic for human cholestatic liver diseases with an established safe clinical dosing regimen.

References

1 Elias K et al. Anti-fibrotic and anti-inflammatory mechanisms of best-in-class ASK1 inhibitor SRT-015. Hepatology. 2020;71:1009A
2 Elias K et al. SRT-015, best-in-class apoptosis signal-regulating kinase 1 inhibitor, demonstrates preclinical efficacy in acute models of liver injury. EASL 2023
3. Burge D et al. Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose Study of the Safety, Tolerability and Pharmacokinetics of the ASK1 Inhibitor SRT-015 in Healthy Adults, AASLD 2022
4. Plonowski A et al. Development of physiologically based pharmacokinetic model to predict liver exposure of SRT-015, a next-generation inhibitor of apoptosis signal-regulating kinase. EASL 2023