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

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Jefferson Medical College 1986

Over 25 years in biotech industry leading clinical development

Immunex, Amgen, Trubion, Gilead, Dermira

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Disclosures

Daniel J. Burge, MD

I disclose the following financial relationship(s) with a commercial interest:

- **Seal Rock Therapeutics, Inc.**
- Evommune, Inc.
- Alterity Therapeutics, Inc.

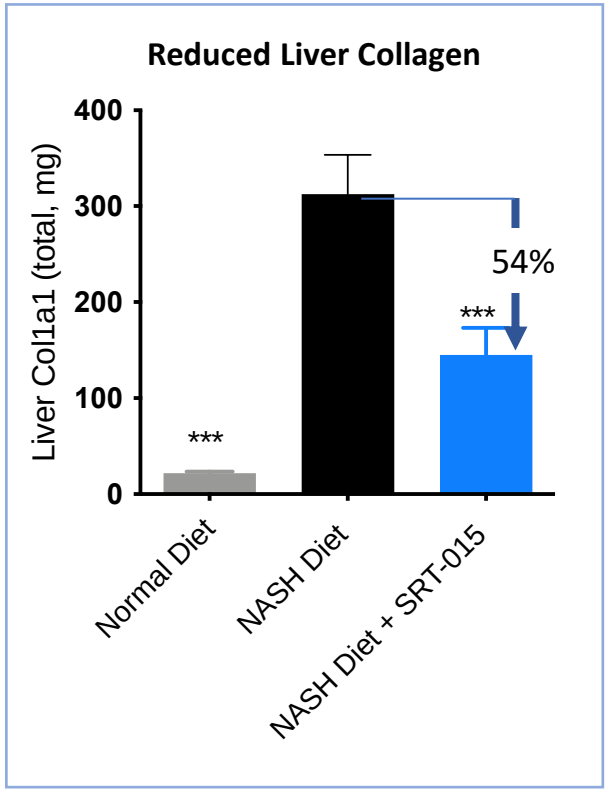
Apoptosis signal-regulating kinase 1 (ASK1)

- ASK1, also known as mitogen-activated protein kinase 5 (MAP3K5), is a member of MAP kinase family
- Ubiquitous kinase activated by various stress including ROS, lipotoxicity, LPS, and ER stress
- Activated ASK1 signals through the JNKs and p38 to execute various cellular responses including cell death, inflammation and fibrosis
- ASK1 is preclinically validated target in diverse liver diseases including alcoholic hepatitis, NASH and primary sclerosing cholangitis

SRT-015: 2nd Generation ASK1 Inhibitor

- Improved ASK1 selectivity
- Improved cardiac safety
- Demonstrated target engagement and dose dependent anti-inflammatory effects in human whole blood
- Efficacious in acute and chronic liver disease models
  - Alcoholic Hepatitis
  - Drug-Induced Liver Injury
  - NASH
    - Reduction of hepatocyte injury
    - Reduction of liver fibrosis, inflammation and apoptosis

Fibrosis



AASLD, 2020

Phase 1, randomized, double-blind, placebo-controlled, Single-Ascending Dose (SAD) and Multiple-Ascending Dose (MAD) Study

- Study drug administered as an oral suspension in a fasting state
- Subjects randomized 3:1 (active:placebo)
- SAD Phase:
  - 5 cohorts of 7-8 subjects
  - Single dose
  - Cohort dose levels: 40mg, 80mg, 160mg, 320mg and 640mg
  - Evaluated for PK and safety for 7 days after a single dose
- MAD Phase:
  - 4 cohorts of 8 subjects
  - Twice daily dosing for 13 doses
  - Cohort dose levels: 40mg BID, 80mg BID, 160mg BID, 320mg BID
  - Evaluated for PK and safety for 14 days (through 7 days after the last dose)

Study Population and Disposition

Key Inclusion Criteria:

- Adults, ages 18-45
- BMI >18 and <32
- Healthy (no clinically significant illnesses)
- No significant safety laboratory or ECG abnormality
- Women excluded if pregnant or breast-feeding

Disposition

- All randomized subjects that received study drug completed the study

Demographics

	SAD N=37	MAD N=32
Mean age: years (range)	26.8 (19-43)	28.3 (18-44)
% Male	51.4%	56.3%
Race: Caucasian Asian Other	 64.9% 35.1%	 65.6% 21.9% 12.5%
Mean weight: kg (range)	71 (51-113)	72 (47-98)
Mean BMI: kg/m^2 (range)	24.3 (19.2-31.8)	24.6 (19.1-31.7)

Safety: SAD

SAD	Placebo (N=10)	40 mg (N=5)	80 mg (N=5)	160 mg (N=5)	320 mg (N=6)	640 mg (N=6)	Total (N=37)
Any AE, n (%)	1 (10.0)	4 (80.0)	--	2 (40.0)	--	2 (33.3)	9 (24.3)
SAE	--	--	--	--	--	--	--
AEs occurring in more than 1 subject, n							
Headache	--	2	--	--	--	1	3
Pain in extremity	--	1	--	1	--	--	2

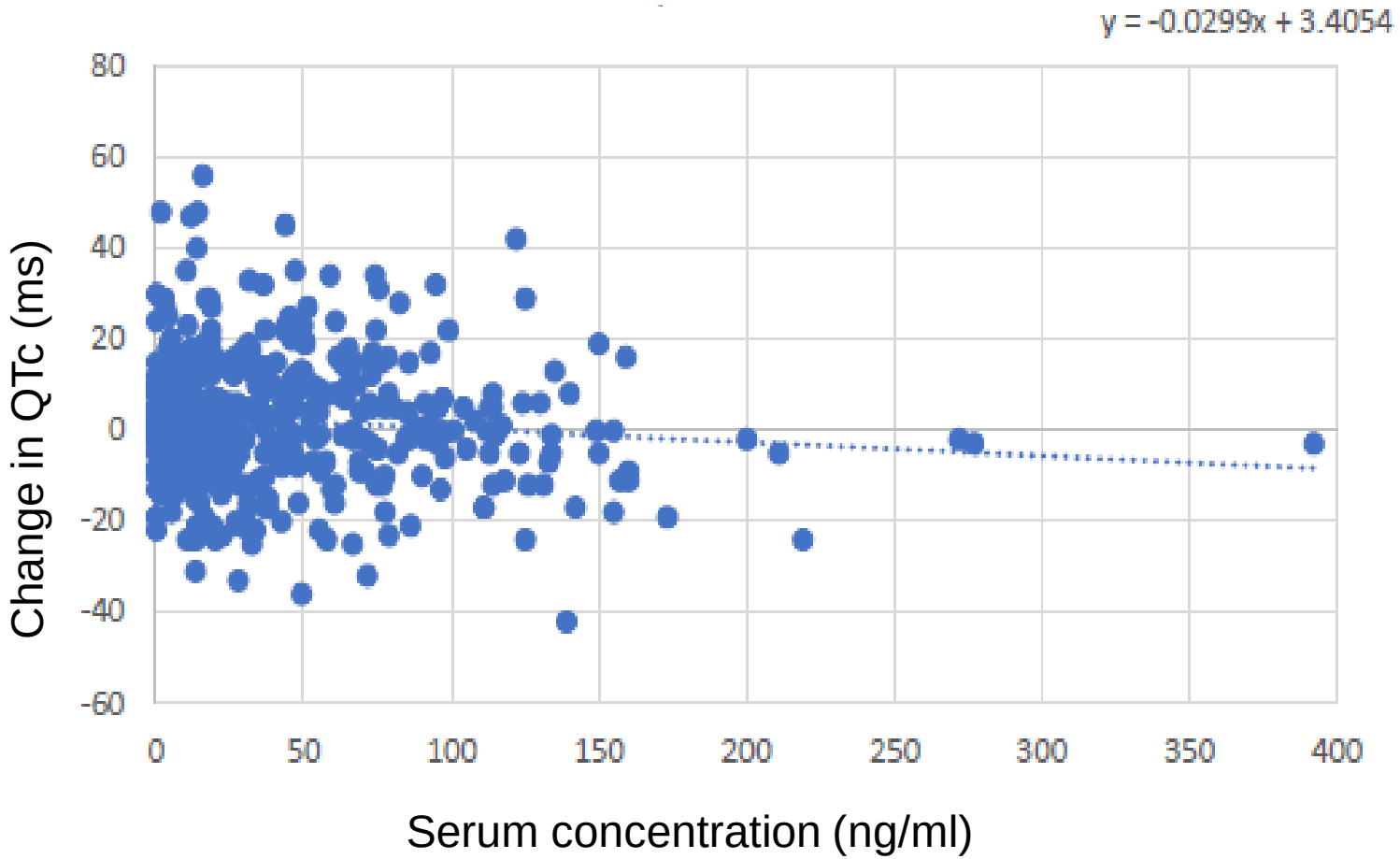
All Adverse events were mild in intensity
No significant changes in safety labs

Safety: MAD

MAD	Placebo (N=8)	40 mg BID (N=6)	80 mg BID (N=6)	160 mg BID (N=6)	320 mg BID (N=6)	Total (N=32)
Any AE, n (%)	3 (37.5)	3 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)	14 (43.8)
SAE	--	--	--	--	--	--
AEs occurring in more than 1 subject, n						
Headache	--	--	2	--	--	2
Contact dermatitis	--	2	--	--	--	2

All adverse events were mild or moderate in intensity
No significant changes in safety labs

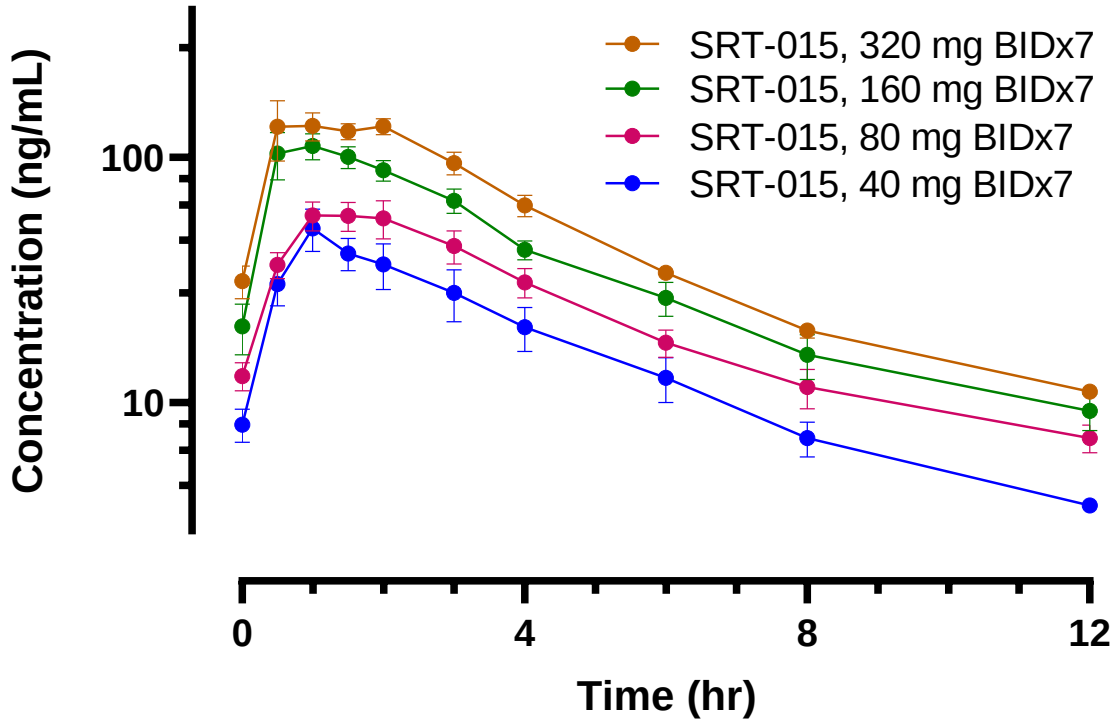
No Drug Effect on QT Interval



- No association between QTc and serum concentration

QTc calculated using Bazett's correction formula

SRT-015 Pharmacokinetics

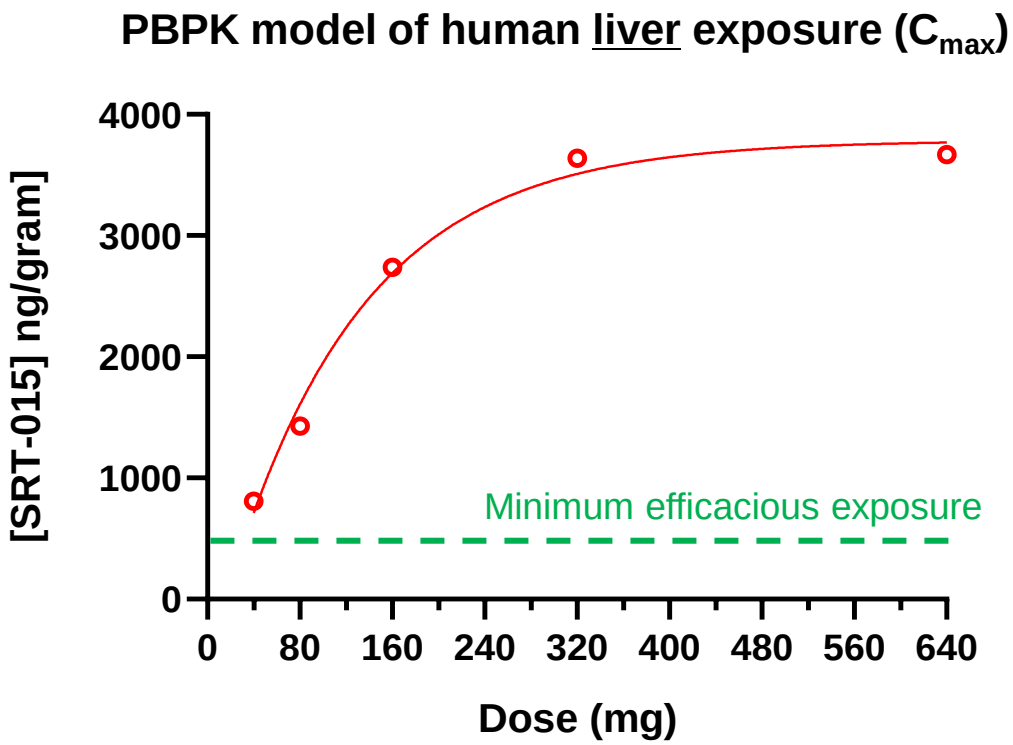


- T_{max} : 1-2 hours
- C_{max} and AUC increased with increasing doses
- $T_{1/2}$: 14 hours
- Data supports once or twice-daily dosing

PBPK model predicts robust liver exposure

- Plasma exposure of SRT-015 within the range predicted by PBPK model.
- Liver exposure of SRT-015 predicted by PBPK model above the minimal efficacious level noted in animal models at all dose levels.
- Predicted human liver concentrations maintains significant safety margin compared with liver exposure in the 4-week toxicology studies

SimulationsPlus



Key Takeaways

- SRT-015 was safe and well tolerated
- Pharmacokinetic profile supports once or twice /day dosing
- Liver exposure of SRT-015 predicted by PBPK model above the minimal efficacious level at all dose levels.

Limitations and Future Directions

- First-in-humans phase 1 study in healthy volunteers
- Short duration of treatment
- Phase 2 studies with SRT-015 in patients with alcoholic hepatitis and NASH are planned

Acknowledgements

- Nucleus Networks (Australia)
- Participants

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