HEPION PHARMACEUTICALS

CORPORATE PRESENTATION • 2019

Nasdaq: HEPA

Forward-Looking
Statements

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Snapshot

A Liver Disease Company

Committed to developing pleiotropic drug therapy for treatment of chronic liver diseases, including NASH (non-alcoholic steatohepatitis) and other liver diseases (HBV, HCV, HDV)

"…Nearly 45% of all deaths in the developed world are attributed to some type of chronic fibroproliferative disease. Therefore, the demand for antifibrotic drugs that are both safe and effective is likely to be enormous..."

– J Clin Invest. 2007 Mar;117(3):524-9. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases.
Wynn TA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1804380/

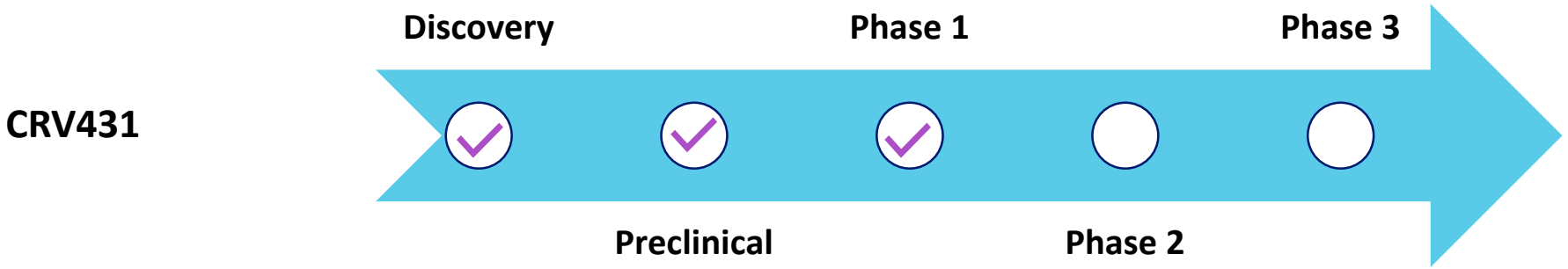
Corporate Overview

Lead Asset

CRV431: Novel, high-potency, cyclophilin inhibitor that targets multiple stages of liver disease, including NASH

- Anti-fibrotic, anti-viral, and anti-cancer properties (pleiotropic)
- Strong preclinical proof of concept
- Strong safety profile in preclinical and Phase 1 clinical studies
- Orally active, once daily
- Robust IP
- Built upon 30 years' experience in this very specific field of chemistry
  - Core team that founded Aurinia Pharmaceuticals, and discovered and developed voclosporin through to phase 2
  - Voclosporin met all primary and secondary endpoints in a Phase 3 trial for lupus nephritis (NDA submission, H1 2020)

Development Phase



- IND for HBV – Phase 1 Single Ascending Dose completed
- IND for HBV – Multiple Ascending Dose in progress, Q3-2019
- IND for NASH – Approved, Q3-2019

"In our large combined tertiary center cohorts, patients with concomitant NASH and CHB (chronic hepatitis B) had more advanced fibrosis, and shorter time to development of liver-related outcomes of death, compared to patients with CHB alone. Among patients with advanced fibrosis, superimposed NASH predicted poorer clinical outcomes in our cohort" *H.S.J. Choi et al., Hepatology, 68(1, suppl.), 2018*

CRV431 in NASH

Cyclophilin Inhibitors Target Multiple Liver Disease Stages

INJURY/STEATOSIS

- Antiviral activity (HBV, HCV, HDV, HIV-1)
- Suppress cell death by inhibiting mitochondrial pore regulator, cyclophilin D

INFLAMMATION

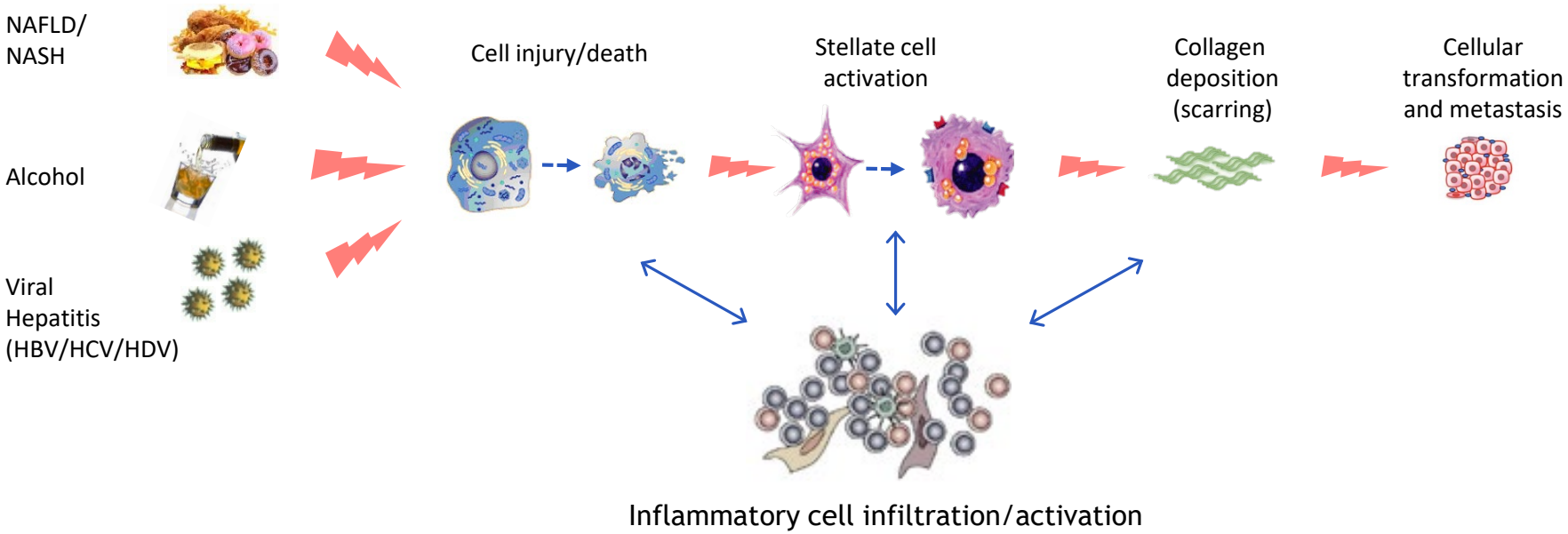
- Suppress pro-inflammatory pathways mediated by extracellular cyclophilin A binding to CD147

FIBROSIS

- Reduce collagen production from hepatic stellate cells
- Reduce collagen hydroxyl-ation and crosslinking

CIRRHOSIS/CANCER

- Block cancer cell adaptation to hypoxia
- Suppress metastasis-related gene expression
- Suppress cell proliferation
- Sensitize to cell death



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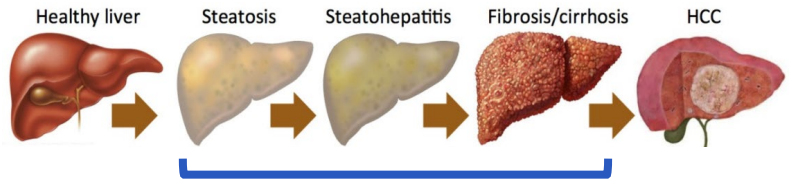
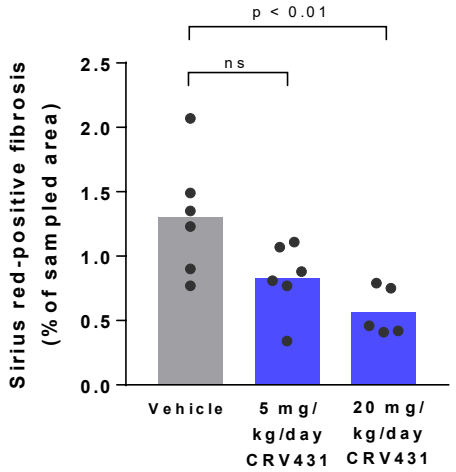
Anti-Fibrotic Activity in NASH Models

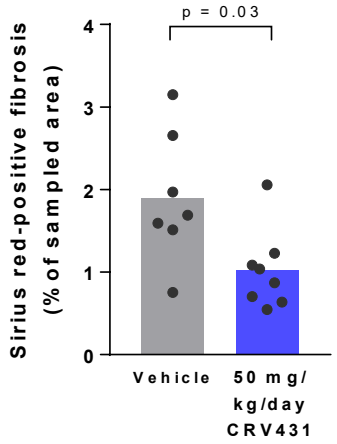
STAM Mouse Model
(High fat diet + streptozotocin)



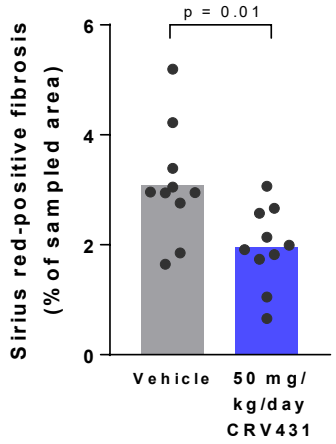
3 - 11 weeks oral CRV431 treatment



3 weeks treatment
<u>57%</u> reduction in fibrosis

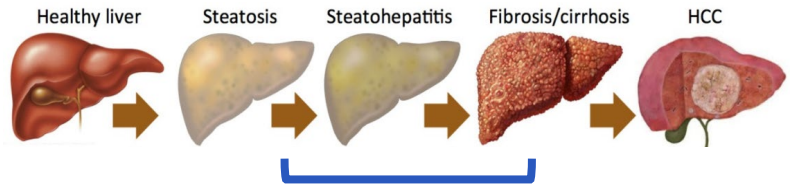


6 weeks treatment
<u>46%</u> reduction in fibrosis

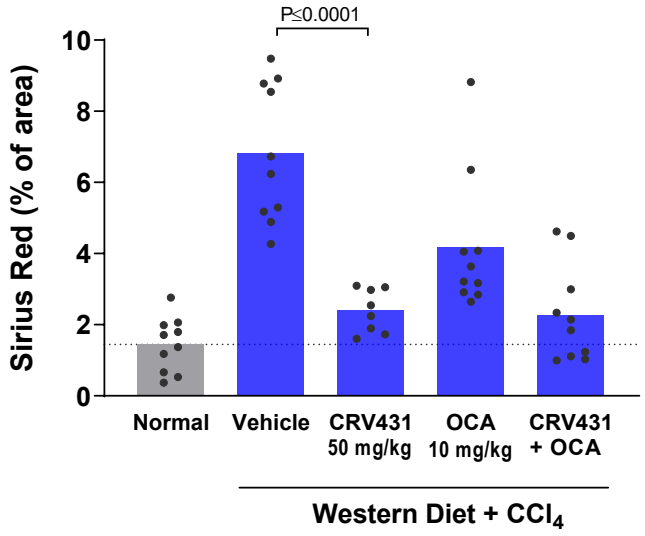


11 weeks treatment
<u>37%</u> reduction in fibrosis

"Friedman" Mouse Model
(Western diet + CCl_4)



6 weeks oral CRV431 treatment



6 weeks treatment: <u>82%</u> reduction in fibrosis

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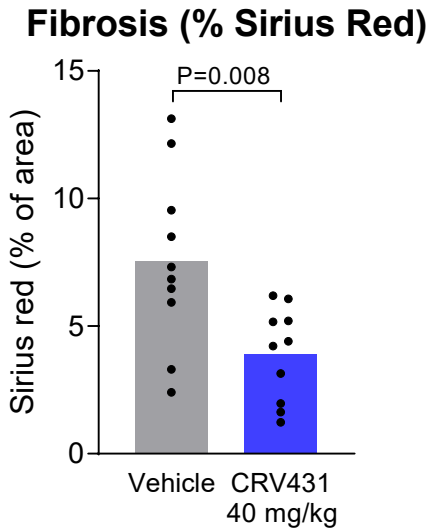
Anti-Fibrotic Activity in Liver Toxin Models

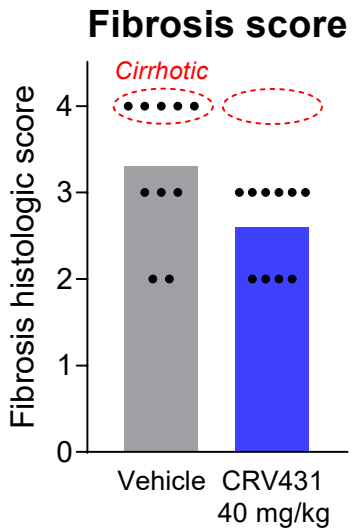
Rat Thioacetamide Model

9 weeks thioacetamide

9 weeks vehicle or CRV431



9 weeks treatment
<u>48%</u> reduction in fibrosis

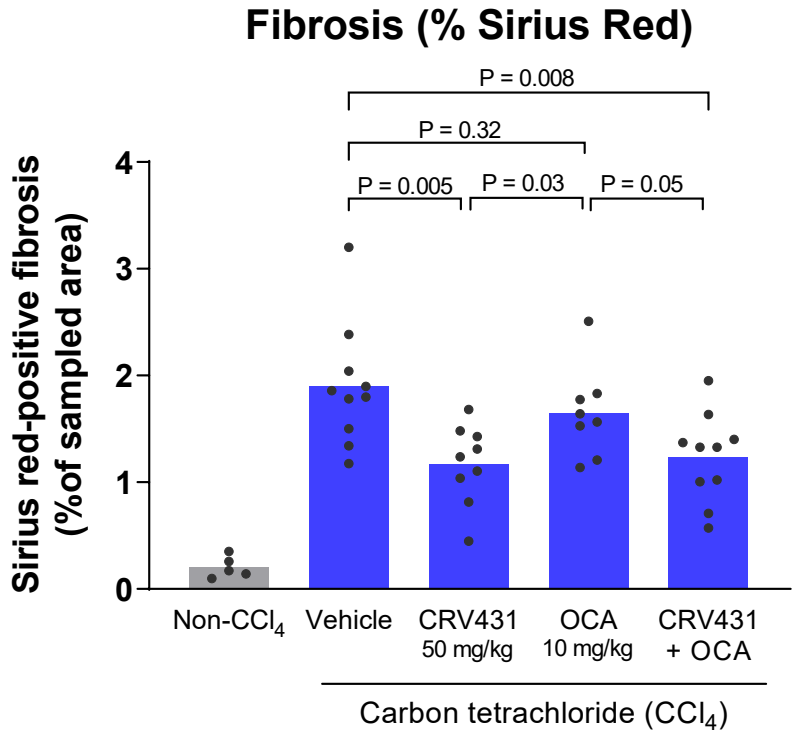


No cirrhotic livers
in CRV431 treatment group

Carbon Tetrachloride Mouse Model

6 weeks CCl_4

6 weeks vehicle, CRV431, or obeticholic acid (OCA)



6 weeks treatment: <u>43%</u> reduction in fibrosis

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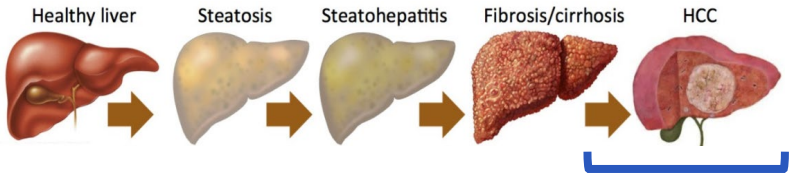
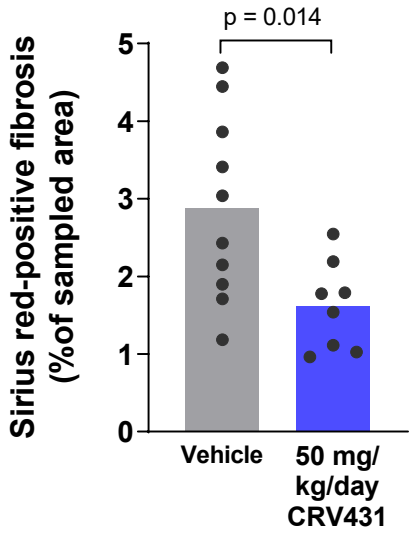
Anti-Cancer Activity in Late-Stage NASH Model

STAM Mouse Model

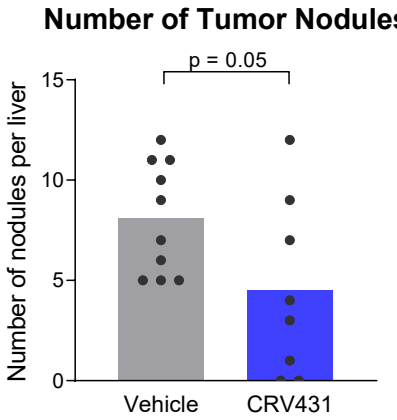
(streptozotocin + high fat diet)



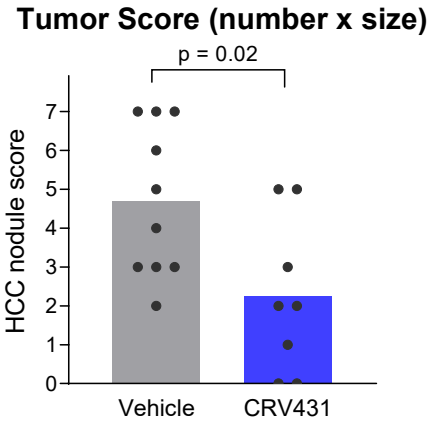
10 weeks oral CRV431 treatment



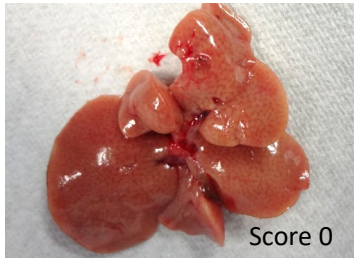
10 weeks treatment
<u>44%</u> reduction in fibrosis

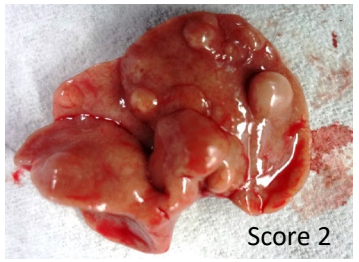


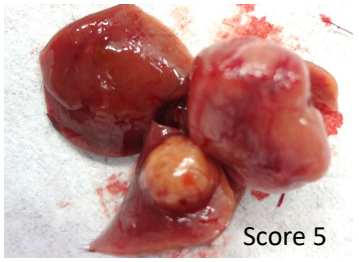
<u>44%</u> reduction in tumor number

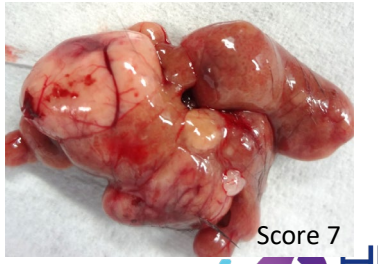


<u>52%</u> reduction in tumor composite score









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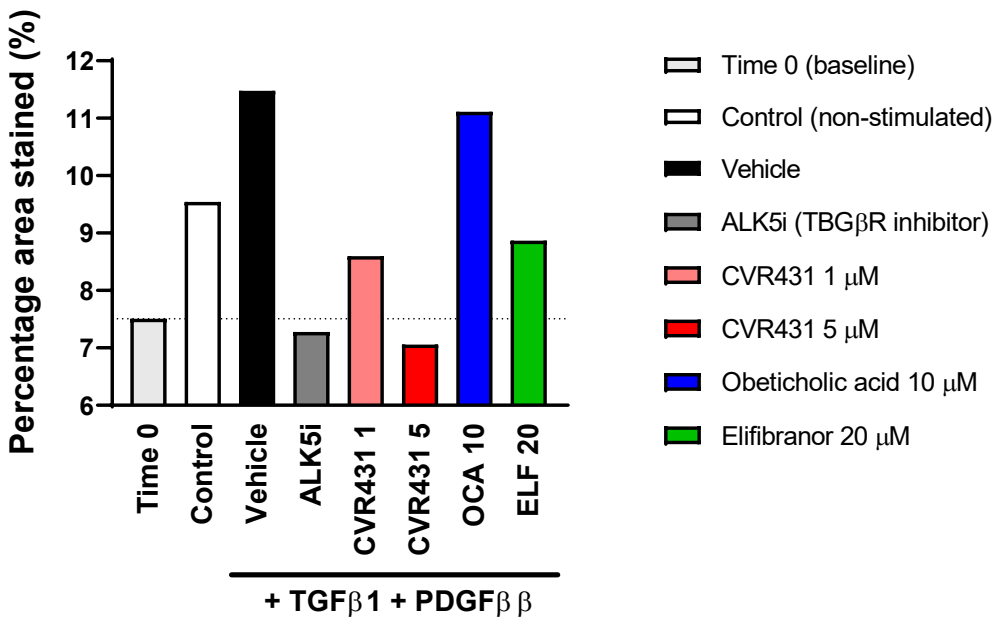
CRV431 on Human Precision Cut Liver Slices

CRV431 Decreases Inflammation and Fibrosis (UK Study Group)

Picrosirius Red Staining of Fibrotic Collagen



- CRV431 5 μM completely prevented the Day 0-4 increase in fibrosis in similarity to TGFβ receptor inhibition (Alk5i)
- CRV431 was more efficacious than OCA and elafibranor

CONCLUSIONS

- TGFβ +PDGF stimulation increased inflammation and fibrosis markers, and TGFβ/PDGF receptor inhibition (Alk5i) blocked the effects
- CRV431 decreased all markers of inflammation and fibrosis:
  - GENE EXPRESSION – e.g. collagen, IL-6
  - SECRETED CYTOKINES AND EXTRACELLULAR MATRIX PROTEINS
  - FIBROTIC TISSUE COLLAGEN
- CRV431 had similar or better efficacy than OCA (FXR agonist) and elafibranor (PPAR agonist)

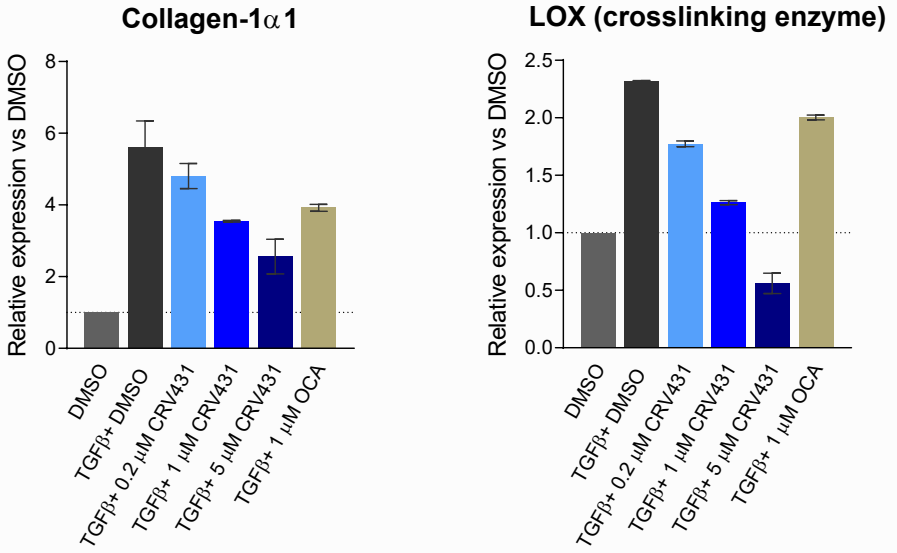
Anti-Fibrotic Mechanisms of Action

CRV431 is proposed to decrease fibrosis by affecting two processes in hepatic stellate cells, the primary, collagen-producing cell type in hepatic fibrosis:

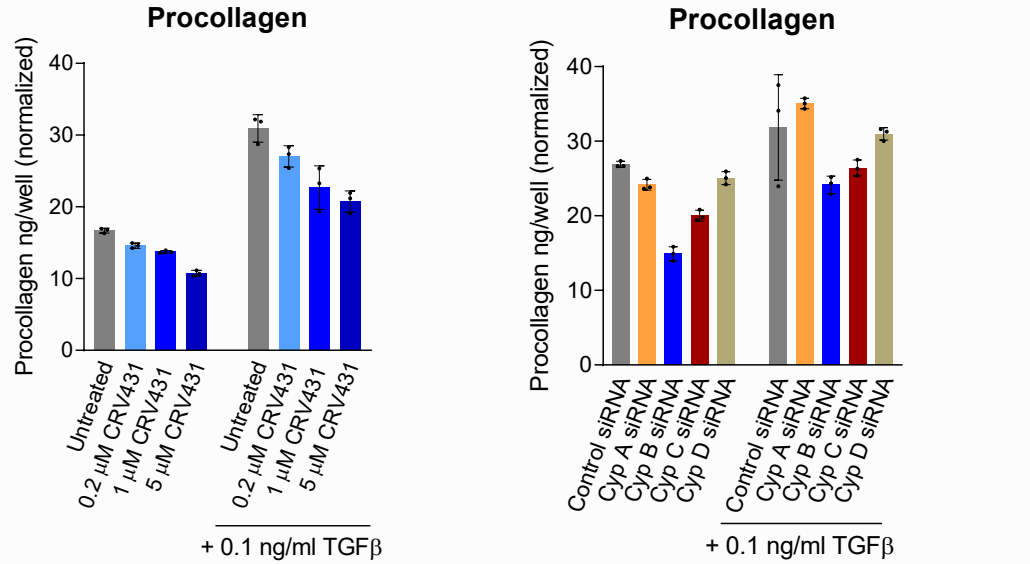
- decrease expression of fibrosis-related genes
- decrease cyclophilin B-dependent collagen synthesis and secretion

Representative Experiments on LX-2 Hepatic Stellate Cells

Fibrosis-related gene expression reduced by CRV431



Procollagen secretion reduced by CRV431 or Cyp B knockdown



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Summary of Nonclinical Anti-fibrotic Activities

Species	Model	Location	Treatment Duration	Fibrosis Reduction (% Sirius Red)	Other CRV431 Effects
Mice	Friedman NASH model (CCl_4 + Western diet)	Scripps (USA)	6 weeks	82% ↓	Weight gain ↓
Mice	STAM NASH model (streptozotocin + HFD)	Stelic (Japan)	3 weeks	57% ↓	none
Mice	STAM NASH model (streptozotocin + HFD)	Scripps (USA)	6 weeks	46% ↓	none
Mice	STAM NASH model (streptozotocin + HFD)	Scripps (USA)	11 weeks	37% ↓	Weight gain ↓ NAS score ↓
Mice	STAM NASH model (streptozotocin + HFD)	Scripps (USA)	10 weeks (late disease)	44% ↓	Liver tumor number and size 52% ↓ Liver weight ↓
Mice	Carbon tetrachloride (CCl_4)	Scripps (USA)	6 weeks	44% ↓	none
Rats	Thioacetamide	Physiogenex (France)	9 weeks	48% ↓	Prevented progression to cirrhosis
Human	Precision cut liver slice (PCLS) cultures with TGFβ+PDGF-BB	FibroFind (UK)	4 days	100% ↓	RNA levels and secretion of inflammatory/fibrotic proteins ↓
Human	LX-2 hepatic stellate cell cultures (± TGFβ)	Hepion	1-2 days	30-50% ↓ collagen secretion	Fibronectin secretion ↓ Fibrotic gene expression ↓

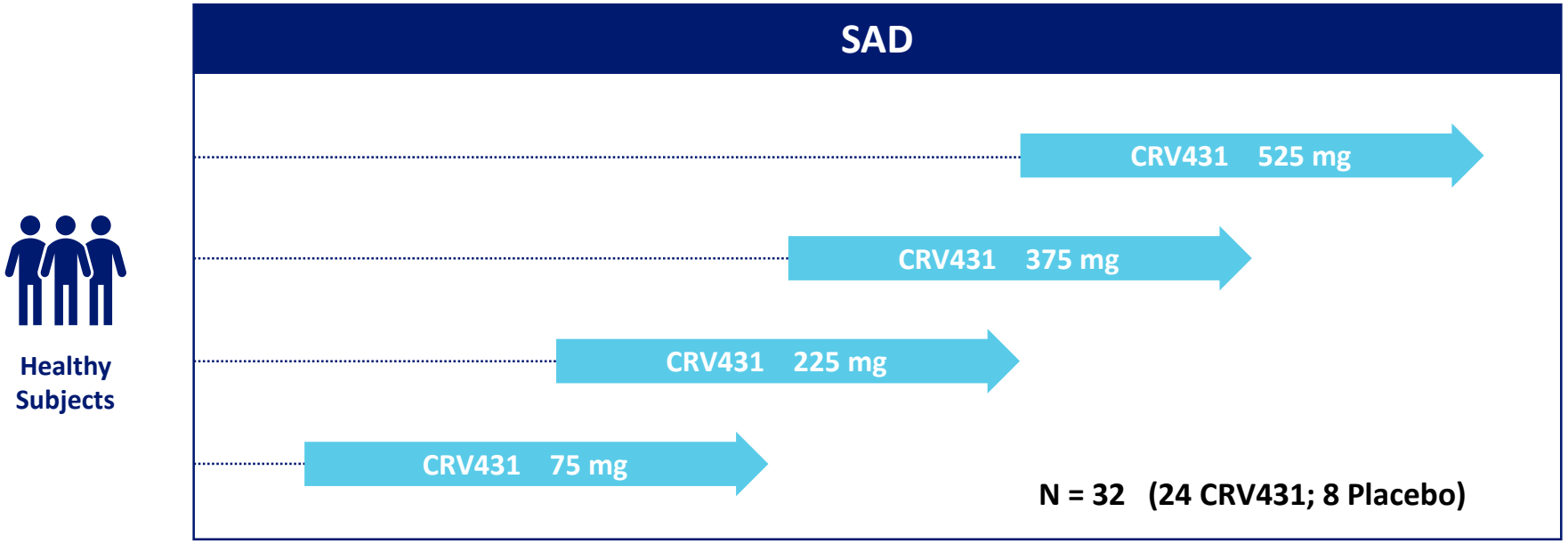
Single Ascending Dose (SAD) Study
(CTRV-CRV431-101)

Objectives

- To evaluate the safety and tolerability of single oral doses of CRV431 at increasing dose levels
- To evaluate the pharmacokinetics of CRV431

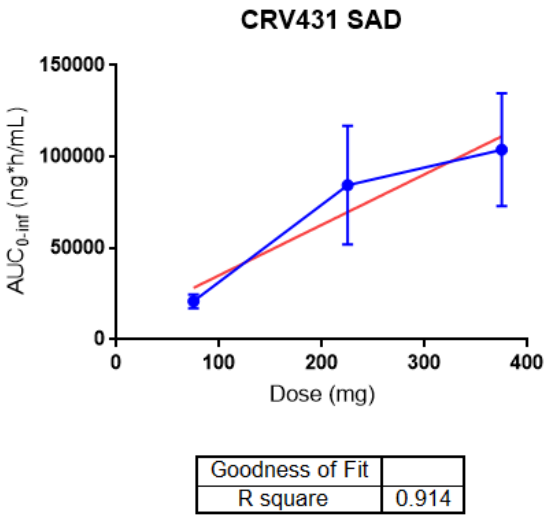
Design

- Randomized, Partially blinded, Placebo-controlled, sequential SAD Study in healthy volunteers



CRV431
Mean Pharmacokinetic Parameters

Dose	$T_{max, h}$ (range)	$C_{max, ng/mL}$ (SD)	AUC_{0-inf}, ng*h/mL (SD)	t½, h (SD)
75 mg	4 (2-10)	334±106	20,917±3,780	73.6±15.2
225 mg	1.3 (1-2)	1,368±221	84,422±32,373	97.3±18.4
375 mg	1.5 (1-3)	1,488±176	103,833±30,916	110.8±36.2
525 mg	1 (1-1)	1,655±250	102,087±43,612	98.5±24.1



- Drug exposure is linear up to 375mg (r^2=0.914)
- Pharmacokinetic profile supports once daily dosing.

Safety Profile and Conclusions
SAD Study

Safety Profile

- No SAE's were reported in the SAD Study
- AE's from the SAD study have been mild to moderate and mostly unrelated to study drug
- There were no Grade 3 or Grade 4 laboratory abnormalities
- Vital signs and ECGs were unremarkable

Conclusions

- In the SAD doses were tested up to 525 mg with no concerns
- The collective data from the SAD demonstrate a favorable pharmacological, pharmacokinetic, and safety profile for CRV431 with acceptable safety margins that support the proposed clinical development program

CRV431 Advantages
in Treating Liver Disease

- Cyclophilin inhibitor (inhibits peptidyl prolyl isomerase)
- Broad range of liver-protective mechanisms (pleiotropic) due to targeting multiple cyclophilins
- **The only investigational drug targeting *both* viral hepatitis and liver disease**
- Later-stage disease focus (fibrosis, HCC) differentiates CRV431 from many NASH compounds in development
- Accumulates to 5-fold higher concentrations in the liver compared to blood
- Excellent safety profile in preclinical and clinical studies is backed up by approximately 35 years of cyclosporine A experience

Of the histologic features of NASH, fibrosis is considered the strongest predictor of adverse clinical outcomes, including liver-related death.

… the FDA encourages sponsors to focus drug development on the area of greatest need and potential effect on health (i.e., non-cirrhotic NASH with liver fibrosis).

Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment
FDA Guidance for Industry, December 2018

Clinical Timelines/Events

2019

- ✓ NASH IND, authorization to proceed
- ✓ Initiated Clinical 28-day study, oral CRV431 escalating dose, once daily repeat doses

2020

H1

- Data from Clinical 28-day study, oral CRV431 Multiple Ascending Dose (MAD), once daily
- Initiate Phase 2 NASH biomarker pilot study, 1-month CRV431 repeat dose

Q3

- Data from Phase 2 NASH pilot study, 1 month, CRV431 repeat dose

2020/2021

Q4/Q1

- Initiate Phase 2 NASH, approx. 100 subjects, CRV431 orally, once daily for 24 weeks

Non-Clinical Events

2019

✓ Data from Human Precision Cut Liver Slice culture

2019

H2

- Data from In-house *in vitro* - stellate cells
- Ongoing Mode of Action studies, ongoing and collaborations

Q4

✓ Data from rat thioacetamide, fibrosis study
✓ Data from NASH Western Diet, fibrosis study
- Data from Precision Cut Liver Slices (PCLS, Part B), UK, fibrosis study

2020

Q1

- Initiate chronic dosing safety, animals (rat and monkey),

Q2

- Data from NASH Western Diet, *in vivo* model, TSRI, HCC
- Data from HCC xenograft model

H2

- Data from chronic dosing safety, animals (rat and monkey),
- Data from Diamond NASH mice
- Data from cyclophilin knockout animal models for NASH/HCC

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Thank You

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