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

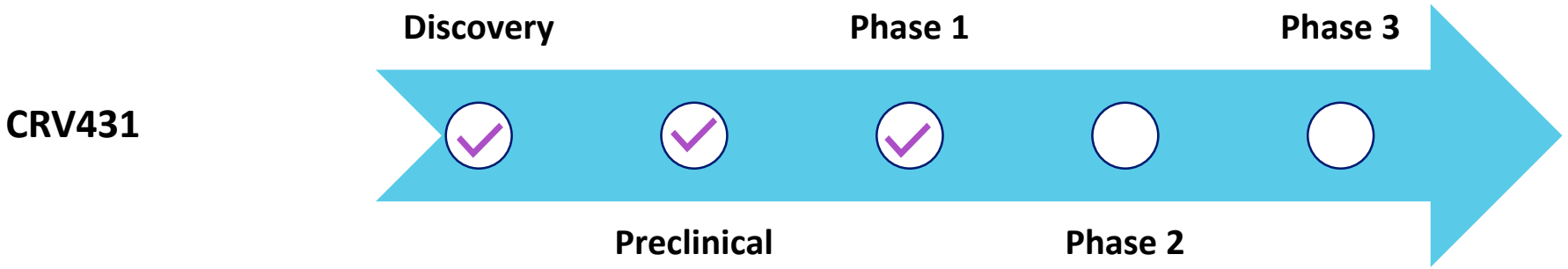
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1804380/

Corporate Overview
Product

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 (Phase 3), and other autoimmune indications (Nasdaq:AUPH) is same core team that has discovered and is developing CRV431

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

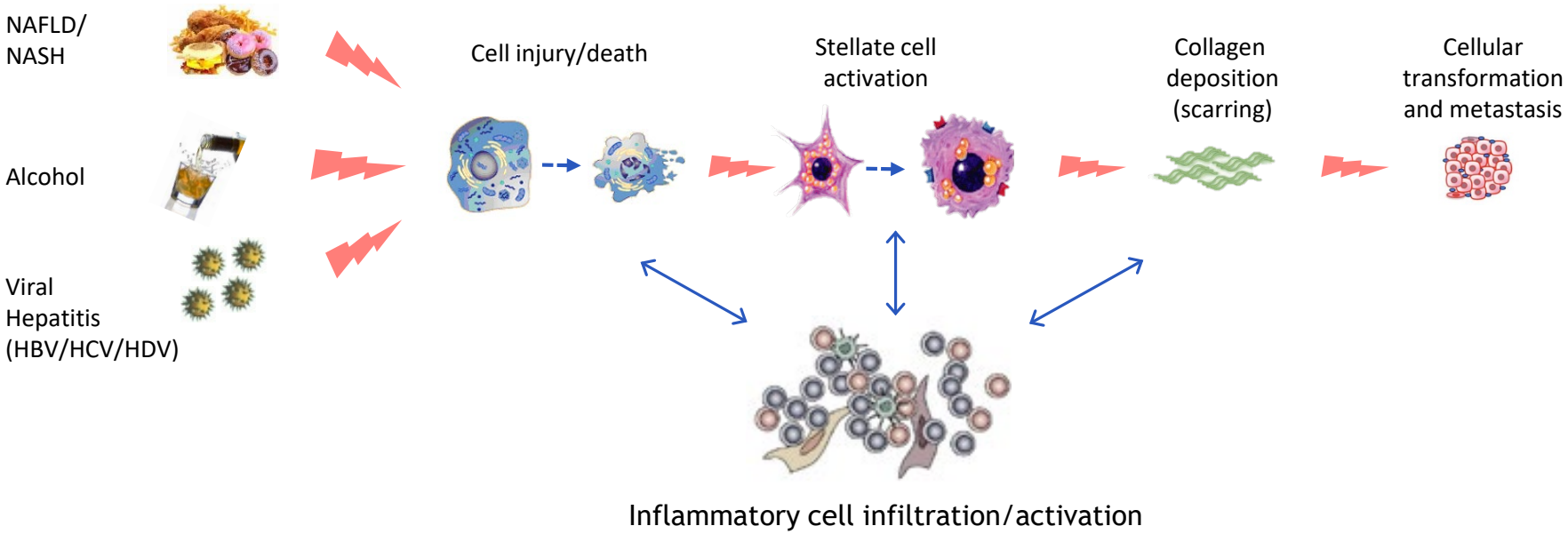
- Suppress pro-inflammatory pathways mediated by extracellular cyclophilin A binding to CD147

FIBROSIS

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

CIRRHOSIS/CANCER

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



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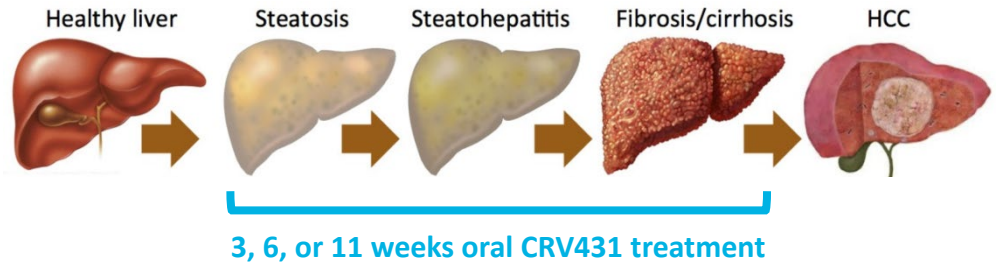
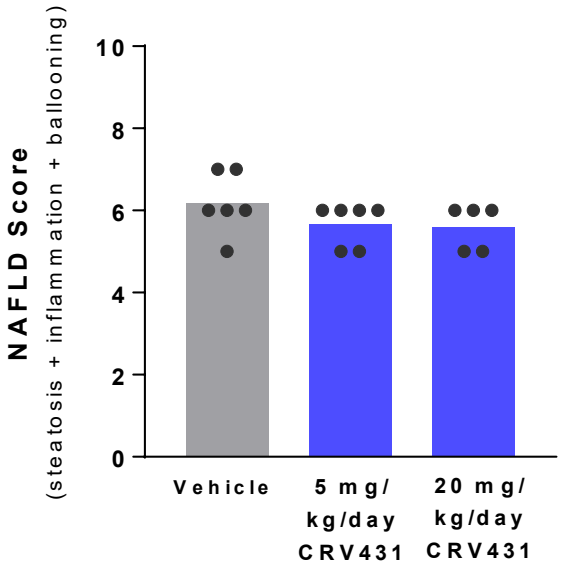
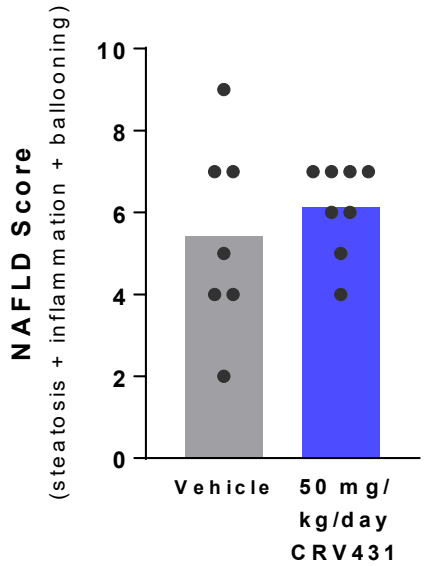
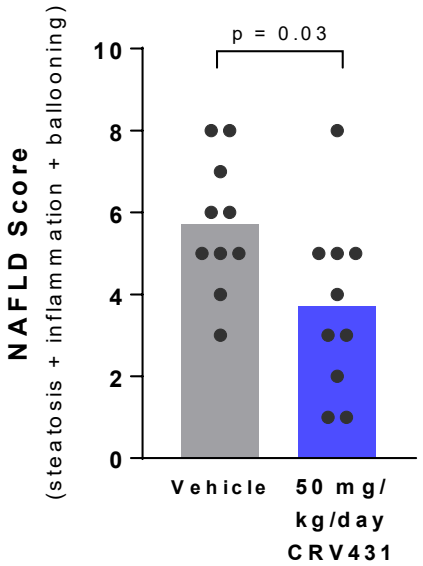
CRV431 Anti-Inflammatory/Steatosis

Efficacy in STAM Murine NASH Model









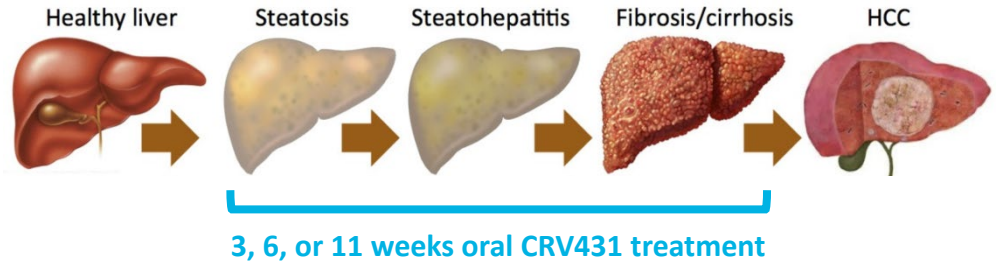
STUDY #1: Stelic Institute (Japan)
3-week, oral CRV431 treatment

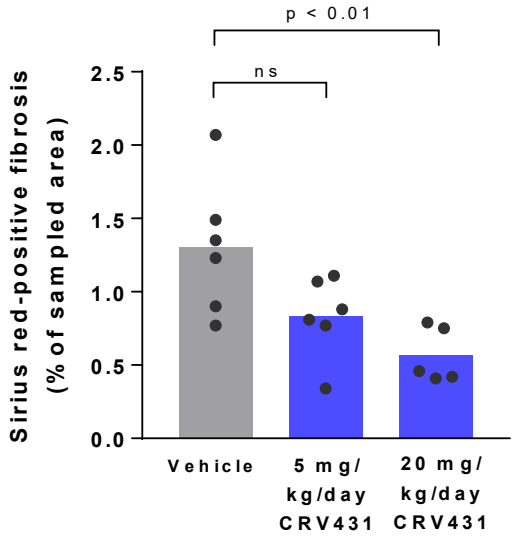
STUDY #2: Scripps Institute (USA)
6-week, oral CRV431 treatment

STUDY #3: Scripps Institute (USA)
11-week, oral CRV431 treatment

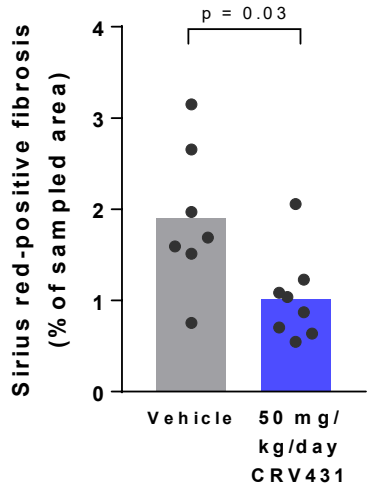
CRV431 Anti-Fibrotic

Efficacy in STAM Murine NASH Model

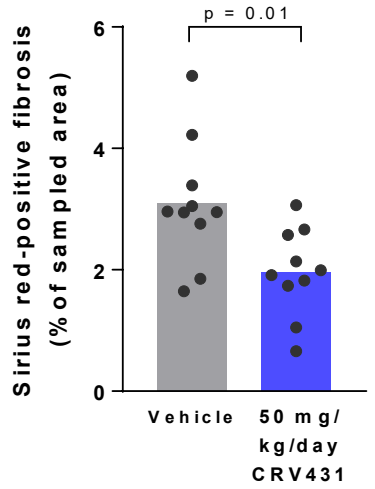




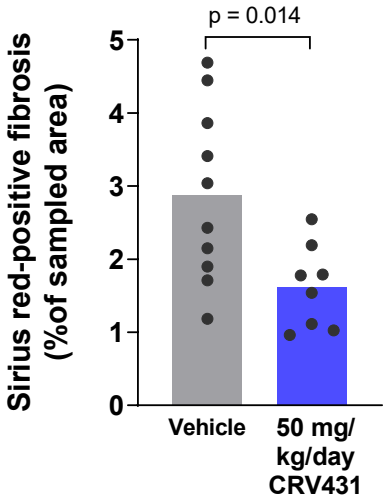
STUDY #1: Stelic Institute
3-week, oral CRV431



STUDY #2: Scripps Institute
6-week, oral CRV431



STUDY #3: Scripps Institute
11-week, oral CRV431



STUDY #4: Scripps Institute
10-week, oral CRV431
(late disease stage)

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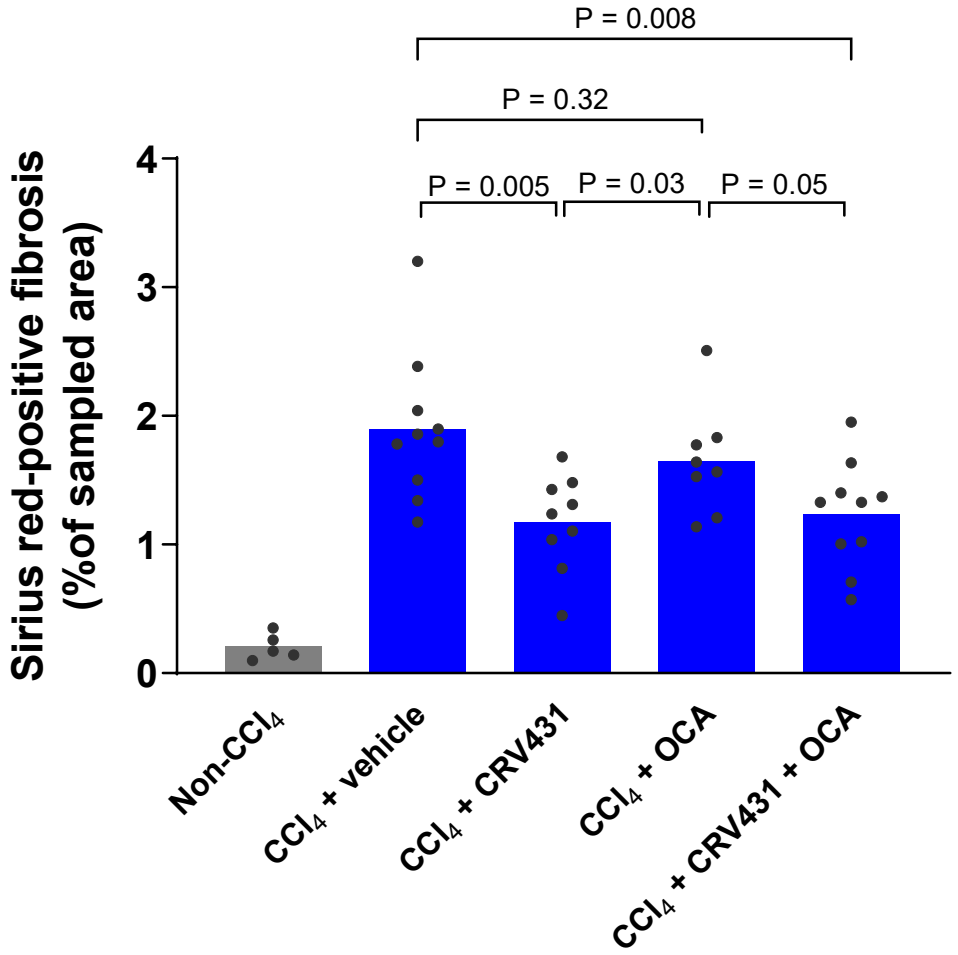
CRV431 Anti-Fibrotic

Efficacy in Carbon Tetrachloride Murine Model



6 weeks carbon tetrachloride (i.p.) + drug treatment (oral):

- Vehicle
- CRV431 50 mg/kg/day
- Obeticholic acid (OCA) 10 mg/kg/day
- CRV431 50 mg/kg/day + OCA 10 mg/kg/day

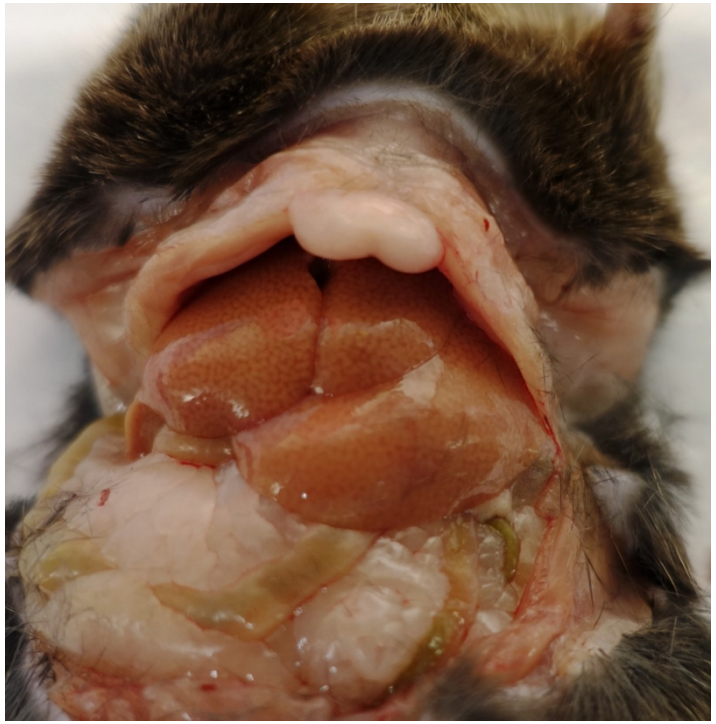
Assess liver fibrosis by Sirius Red staining of liver sections

RESULTS

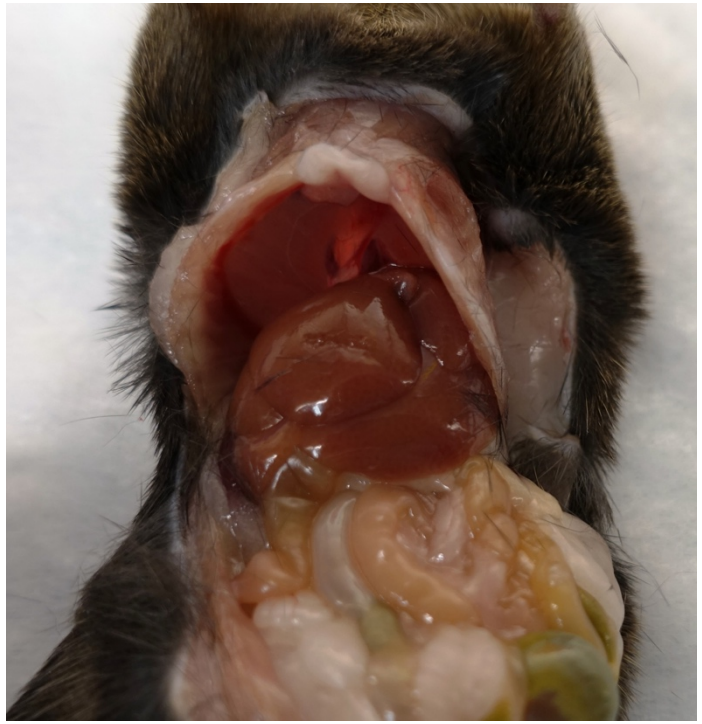
- Second model showing reduction in liver fibrosis by CRV431 (43% decrease *versus* vehicle)
- Lead late-stage NASH drug candidate, OCA, did not demonstrate a statistically significant antifibrotic effect in this CCl4 murine model conducted by us

CRV431 for Liver Disease

Liver morphology in NASH Mice



Vehicle treatment, 11 weeks
(enlarged fatty liver)

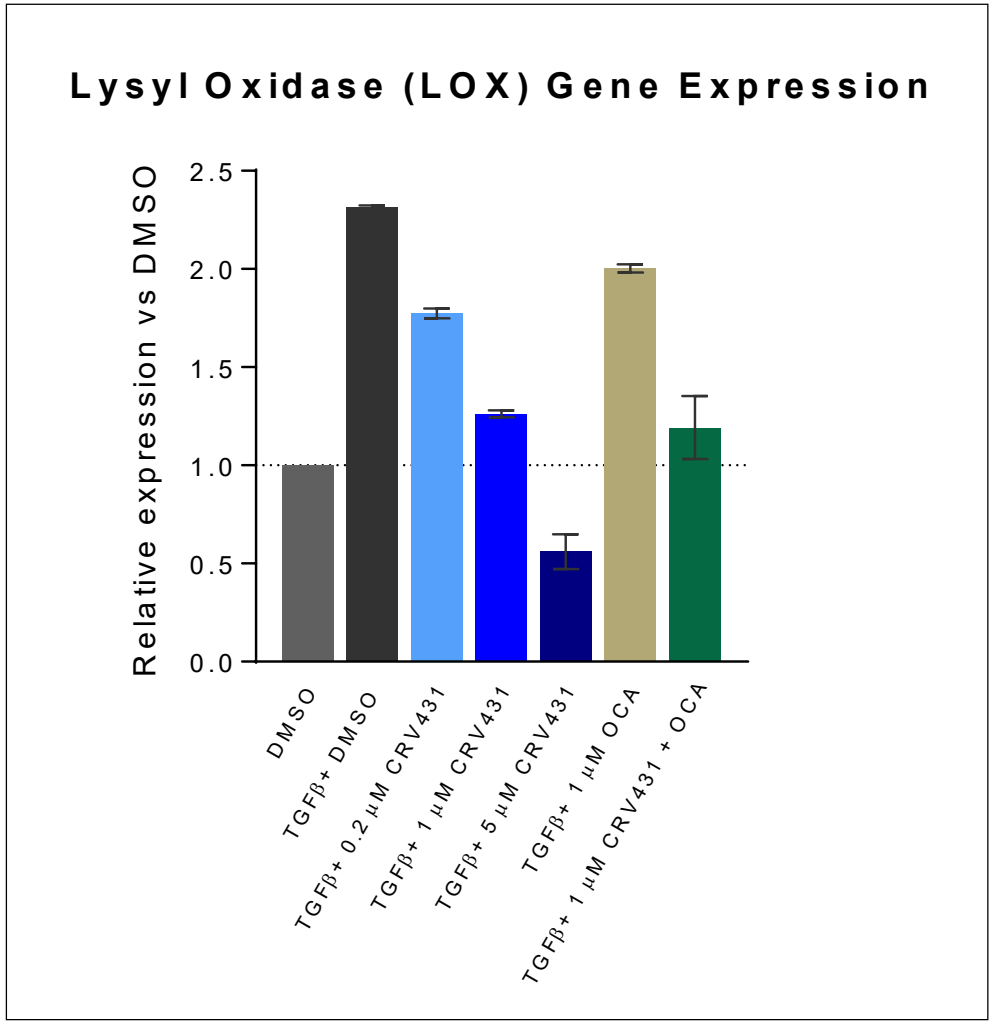


CRV431 treatment, 50 mg/kg, PO, 11 weeks
(normalized liver)

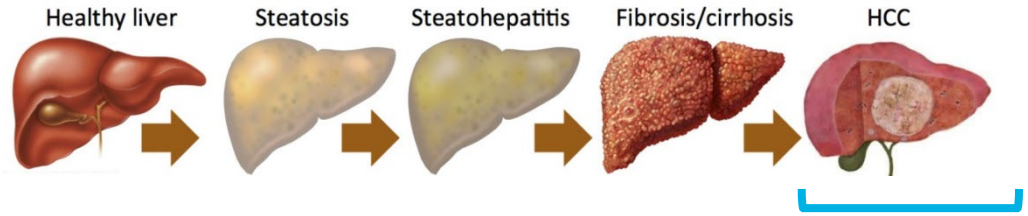
Putative Anti-Fibrotic Mechanism of Action

Collagen reduction

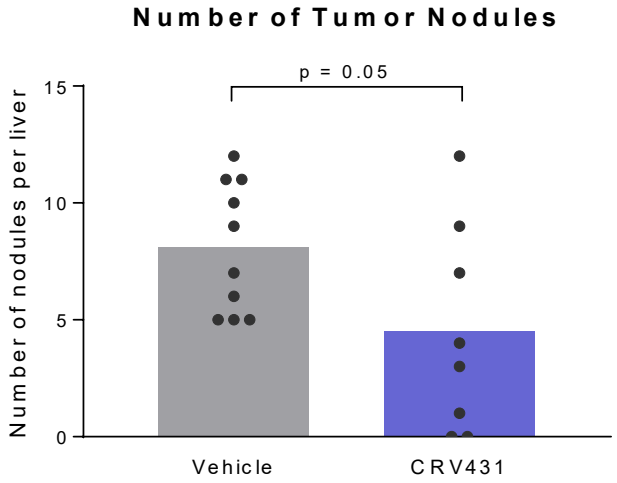
- Role of cyclophilins in formation of collagen involved in at least two ways:
  1. Peptidyl prolyl isomerase (cyclophilin) activity confers CIS-TRANS geometry of procollagen (protein folding)
  2. Hydroxylation of proline and lysine in procollagen are necessary steps for covalent intermolecular cross-linking resulting in formation of the triple helix of collagen
- *In* vitro studies demonstrated that CRV431 reduced expression of lysyl oxidase (LOX) genes involved in fibrotic collagen formation
- Reduction in LOX gene expression observed with CRV431 is dose-dependent
- As a comparison, obeticholic acid (OCA), a farnesoid X receptor agonist has no effect on LOX gene expression

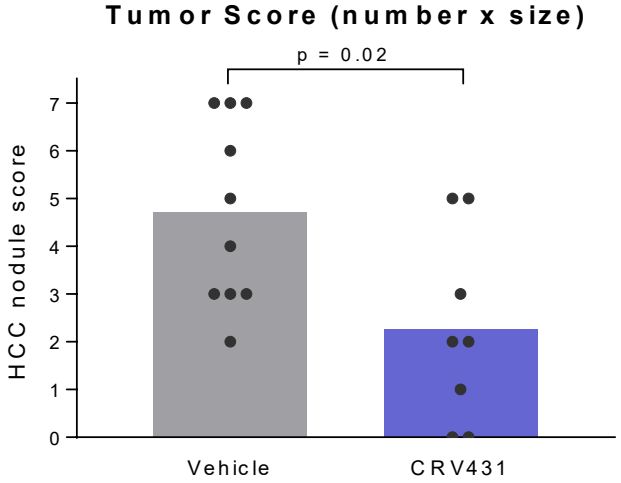


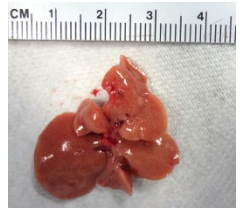
CRV431 Anti-Cancer
Activity in NASH Mice



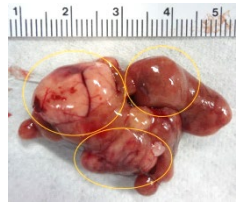
10 weeks oral CRV431 treatment







Score = 0
(no nodules)



Score = 7
(many large nodules)

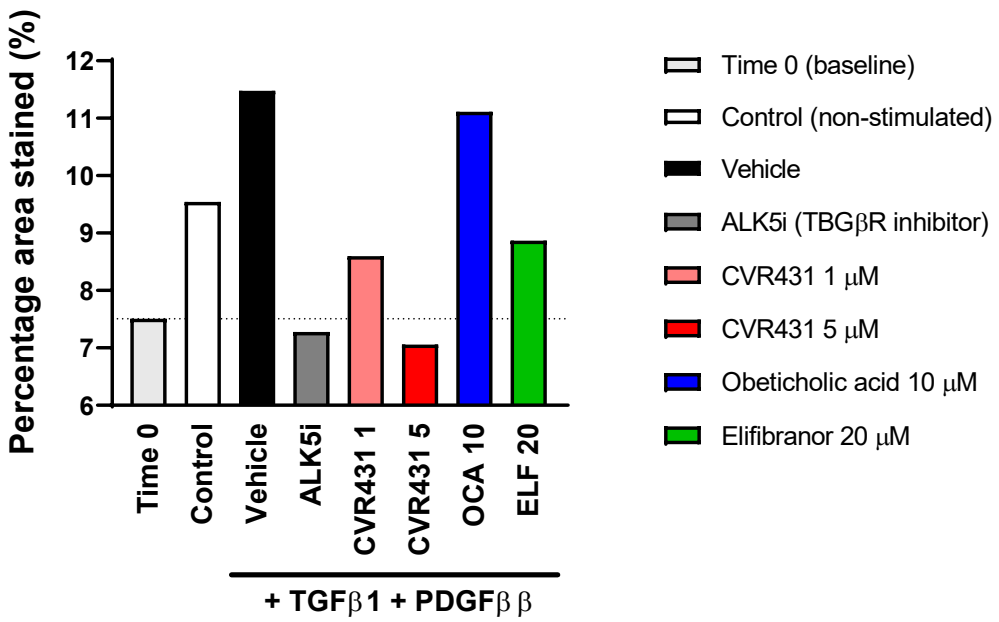
STUDY: Scripps Research Institute (USA)

- 10-week, oral CRV431 treatment, 50 mg/kg once daily
- 44% reduction in tumor number; 52% reduction in tumor score, reflecting number and size of tumors

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)

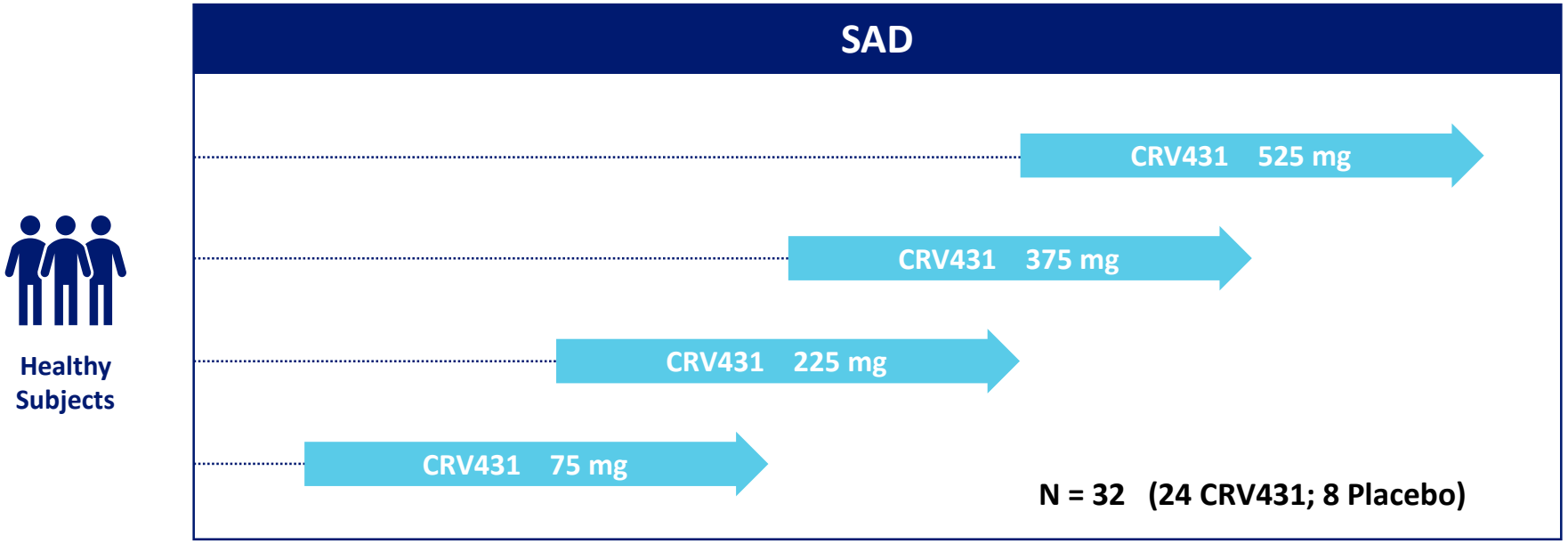
Single Ascending Dose (SAD) Study
(CTRV-CRV431-101)

Objectives

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

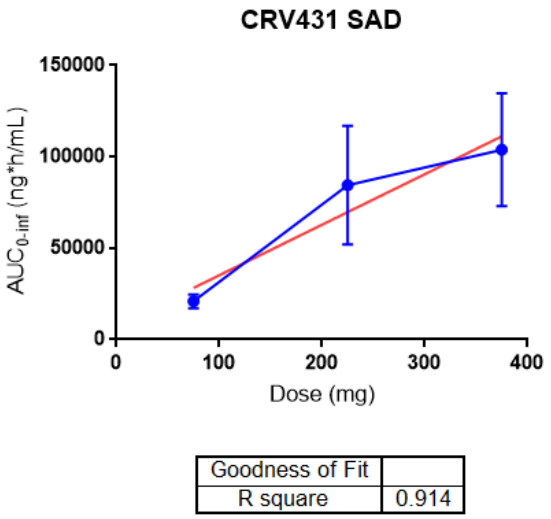
Design

- 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

Viral Hepatitis

Anti-HBV and HCV Activities

CRV431 anti-viral activities toward hepatitis B virus (HBV) and hepatitis C virus (HCV) expected to reduce liver disease arising from viral hepatitis

HBV

CRV431 decreases several HBV markers in cell culture and an animal model, including HBV DNA, HBsAg, HBeAg, cccDNA, pgRNA, and inhibits NTCP-mediated HBV uptake.

HCV

CRV431 inhibits HCV replication by blocking cyclophilin A - NS5A binding.

PLoS One. 2015 Aug 11;10(8):e0134707.
The Novel Cyclophilin Inhibitor CPI-431-32 Concurrently Blocks HCV and HIV-1 Infections via a Similar Mechanism of Action.
Gallay PA, Bobardt MD, Chatterji U, Trepanier DJ, Ure D, Ordonez C, Foster R

CRV431 Advantages
in Treating Liver Disease

- First-in-class 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

Non-Clinical Events

2019

✓ Fibrofind human Precision Cut Liver Slice culture, Part A, data

2019

H2

- In-house *in vitro* - stellate cell, data
- Ongoing Mode of Action studies, ongoing and collaborations

Q4

- Physiogenex rat thioacetamide (Part A), fibrosis data
- Precision cut liver slices (PCLS, Part B), UK, fibrosis data

2020

Q1

- Physiogenex rat thioacetamide (Part B), fibrosis data
- Chronic dosing safety, animals (rat and monkey), initiate

Q2

- Friedman NASH/HCC, *in vivo* model, data, TSRI
- HCC xenograft model, data

H2

- Chronic dosing safety, animals (rat and monkey), data
- Diamond NASH mice, data
- Cyclophilin knockout animal models for NASH/HCC, data

Clinical Timelines/Events

2019

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

2020

H1

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

H2

- Phase 2 NASH pilot study, 1 month, CRV431 repeat dose, biomarker data

2020/2021

Q4/Q1

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

Thank You

Corporate Contact:

Robert Foster

rfoster@hepionpharma.com

Investor Relations:

Stephen Kilmer

skilmer@hepionpharma.com

Tel: 646.274.3580