HEPION PHARMACEUTICALS

CORPORATE PRESENTATION • 2020

Nasdaq: HEPA

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Corporate Overview

Lead Asset: CRV431, a cyclophilin inhibitor

Novel molecule 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 (protection in major markets including US, Europe, Australia, Canada, China, Japan, Korea) with exclusivity until 2039 with potential further regulatory exclusivity to 2044
- Built upon 30 years' experience in this very specific field of chemistry
  - Core team that founded Aurinia Pharmaceuticals (NASDAQ:AUPH), and discovered and developed voclosporin through to Phase 2

Development Phase

CRV431

Discovery

Synthesized and screened ~200 molecules

Identified CRV431 as lead molecule

Preclinical

Efficacy Models:
5 *in vivo*
5 *in vitro* fibroblast
2 human explants - liver and lung

Toxicology
In vitro and *in vivo*

CMC

ADME

Pharmacology and MOA

Phase 1

Single ascending dosing completed

Multiple ascending dosing in progress, completion in Q3, 2020

May 2020
Announced advancement to 4th dose level

Phase 2

May 2020
Announced advancement to Phase 2a Trial ("AMBITION") for NASH Fibrosis

June 2020
Projected start of AMBITION trial; results expected by YE, 2020

Phase 3

Projected Launch

2026

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 hydroxylation and crosslinking

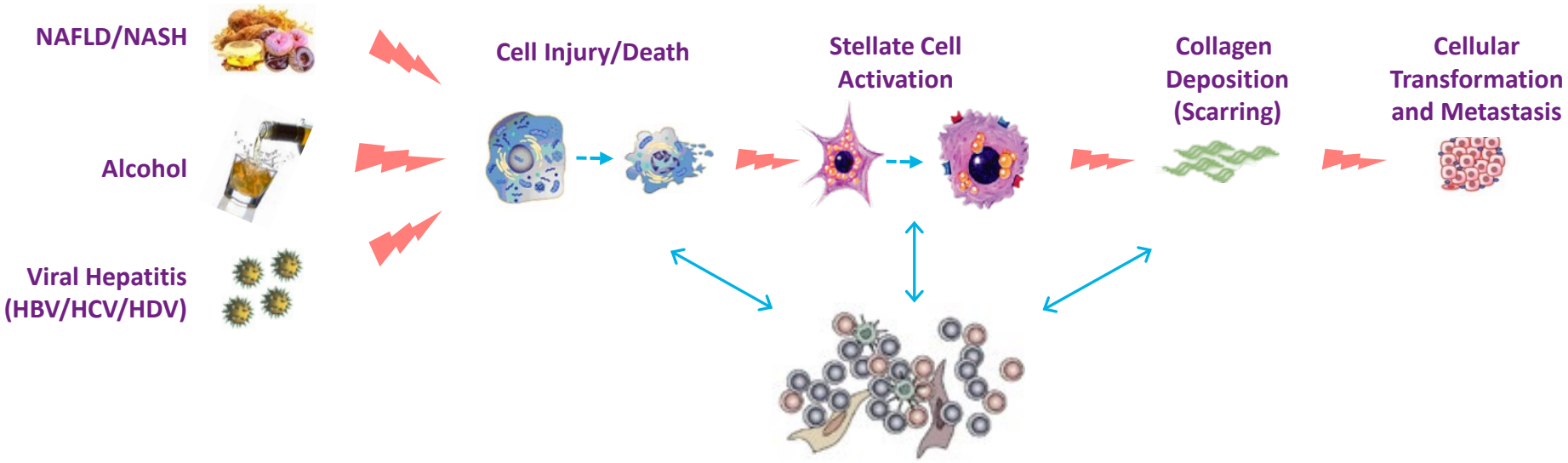
Cirrhosis/Cancer

Block cancer cell adaptation to hypoxia

Suppress metastasis-related gene expression

Suppress cell proliferation

Sensitize to cell death



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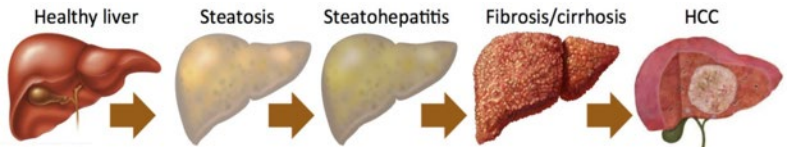
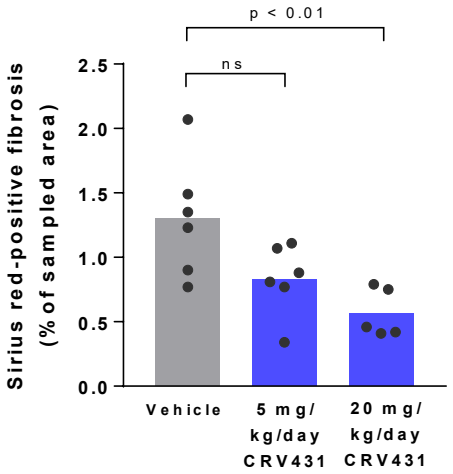
Anti-Fibrotic Activity in NASH Models

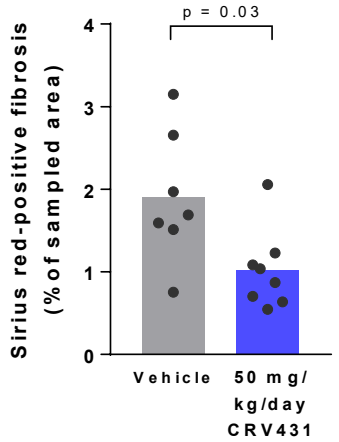
STAM Mouse Model
(High fat diet + streptozotocin)



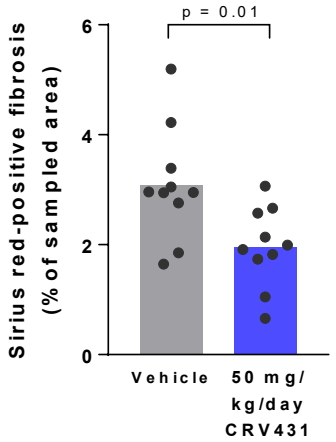
3 - 11 weeks oral CRV431 treatment



3 weeks treatment
57% reduction in fibrosis

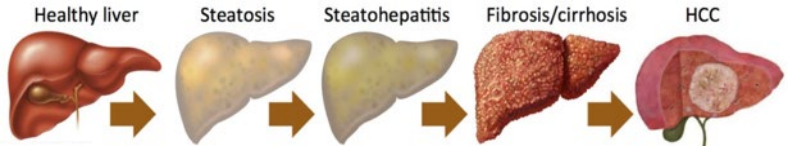


6 weeks treatment
46% reduction in fibrosis

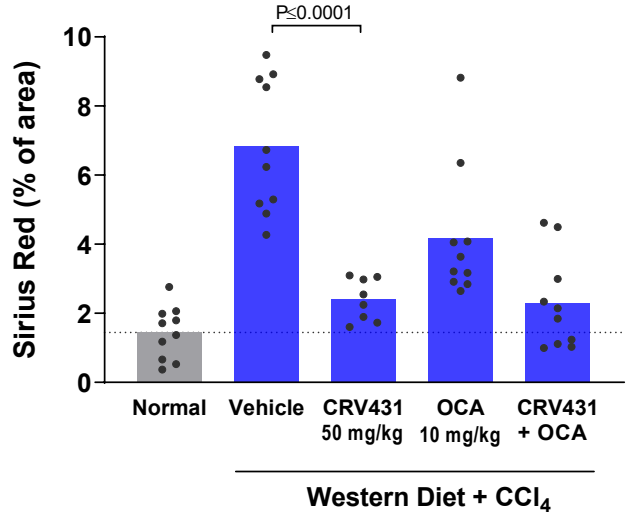


11 weeks treatment
37% reduction in fibrosis

"Friedman" Mouse Model
(Western diet + CCl_4)



6 weeks oral CRV431 treatment



6 weeks treatment:
82% reduction in fibrosis

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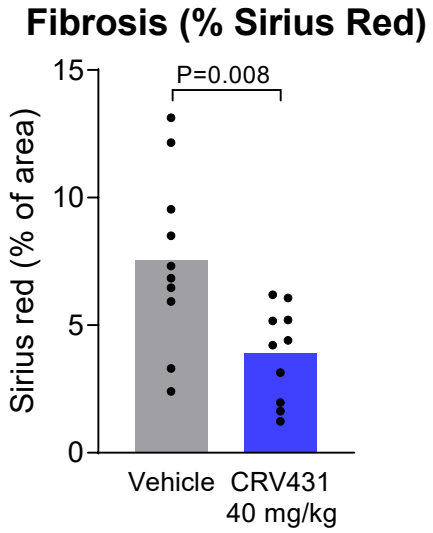
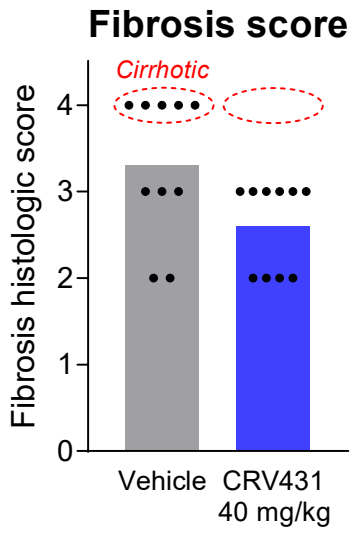
Anti-Fibrotic Activity in Liver Toxin Models

Rat Thioacetamide Model

9 weeks thioacetamide

9 weeks vehicle or CRV431





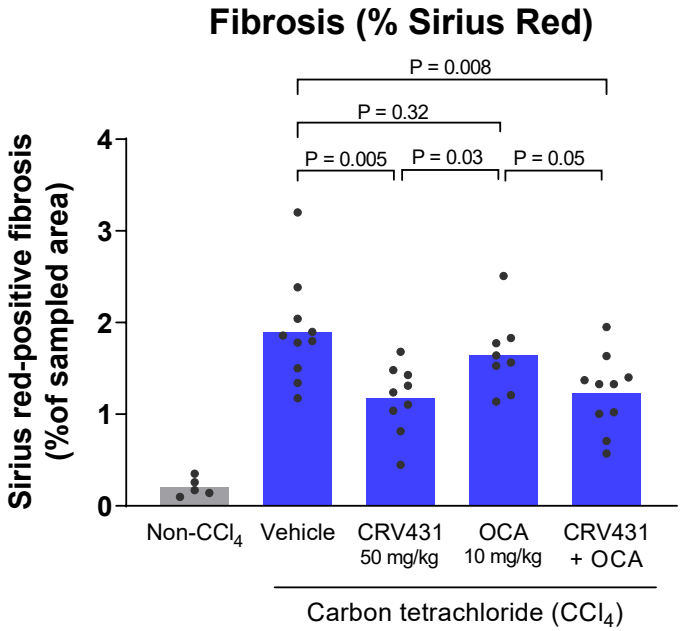
9 weeks treatment
48% reduction in fibrosis

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:
43% reduction in fibrosis

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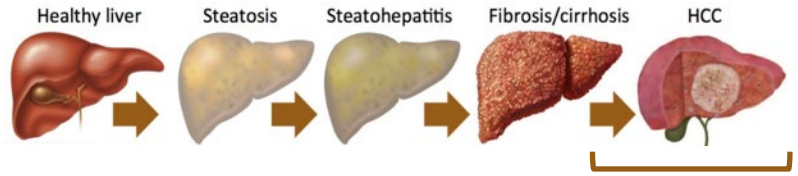
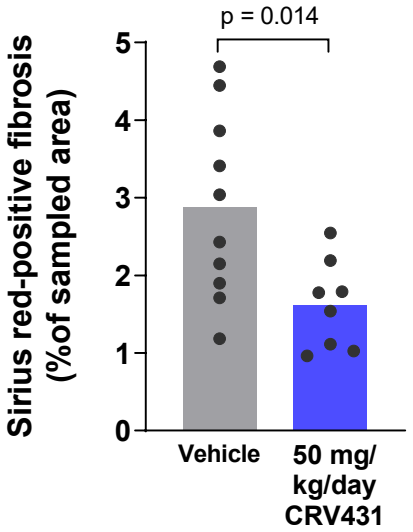
Anti-Cancer Activity in Late-Stage NASH Model

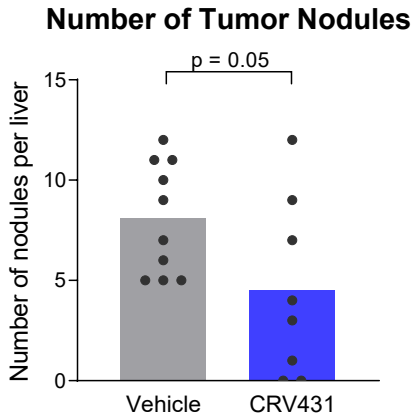
STAM Mouse Model
(Streptozotocin + High Fat Diet)



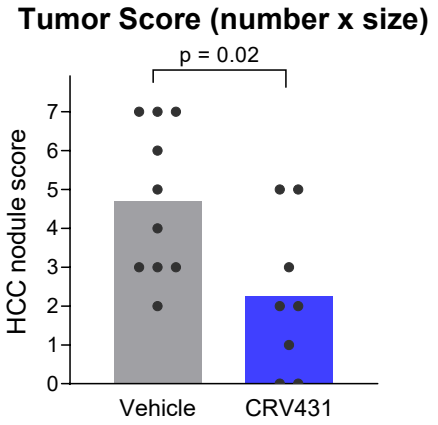
10 weeks oral CRV431 treatment



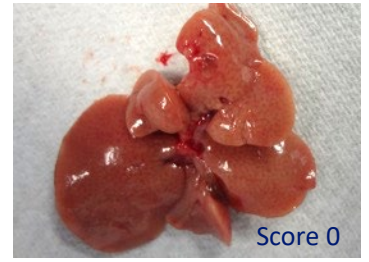
10 weeks treatment
44% reduction in fibrosis

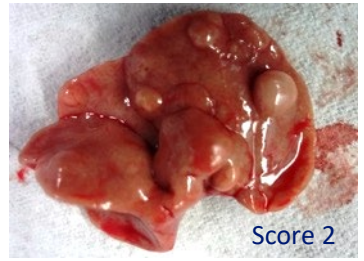


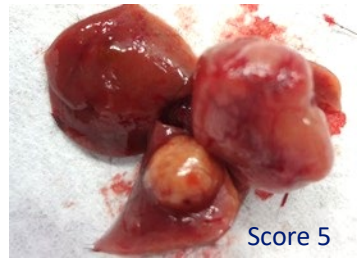
44% reduction in tumor number

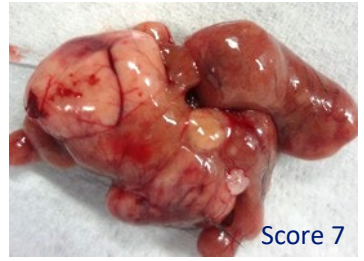


52% reduction in tumor composite score

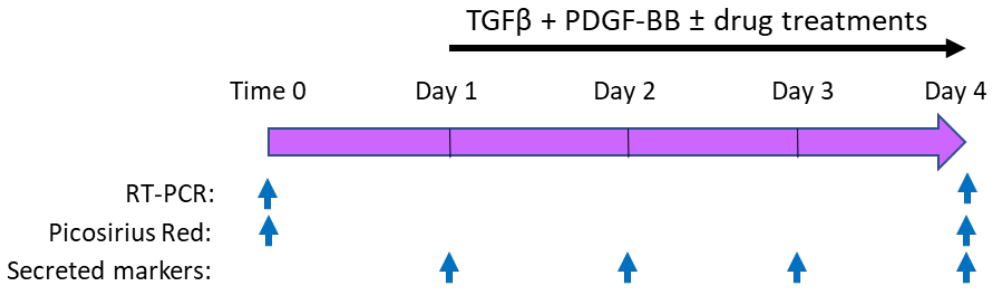






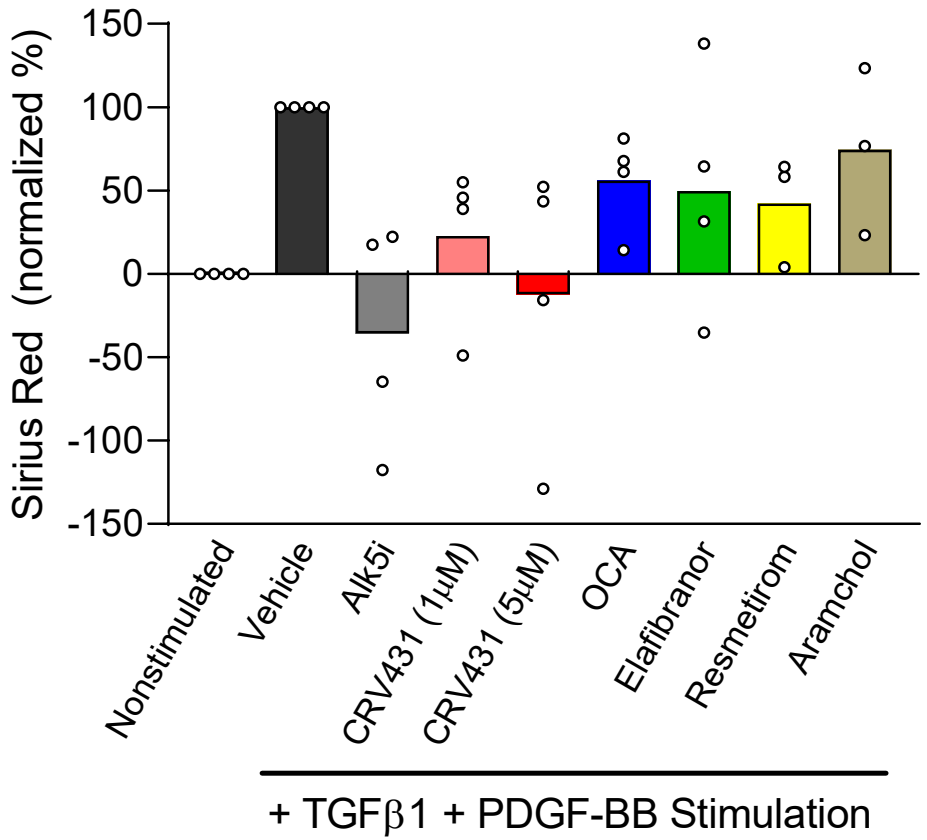


Anti-Fibrotic Activity in Human Liver Explant Tissue (FibroFind, UK)



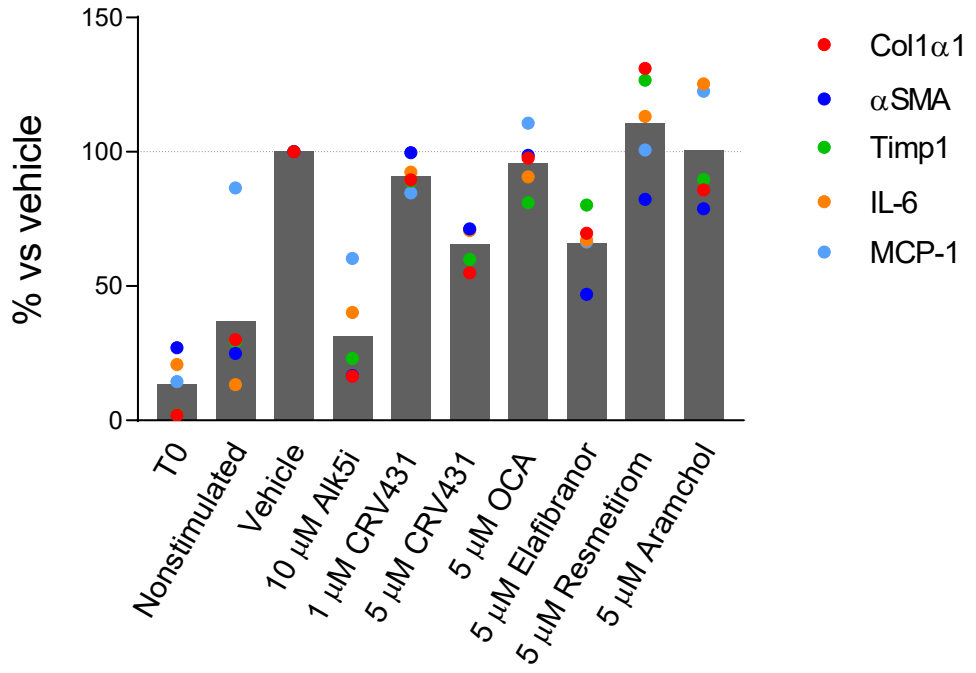
- Precision cut liver slices (PCLS), 4 human donors
- 3 days pro-fibrotic stimulation (TGFβ + PDGF-BB) ± CRV431 (1 and 5 µM) or NASH drug candidates (5 – 20 µM)
- Baseline fibrosis = 6.2% Sirius red staining (range 1.3 - 9.5%), which increased 1.5-fold to 9.6% (range 6.6 - 11.5%) after 3 days stimulation
- Alk5i (10 µM; inhibitor of TGFβ receptor kinase) served as positive control to block stimulation
- CRV431 (5 µM) was most effective of five NASH drug candidates at preventing TGFβ + PDGF-BB-induced fibrosis

Picrosirius Red Staining of Fibrotic Collagen

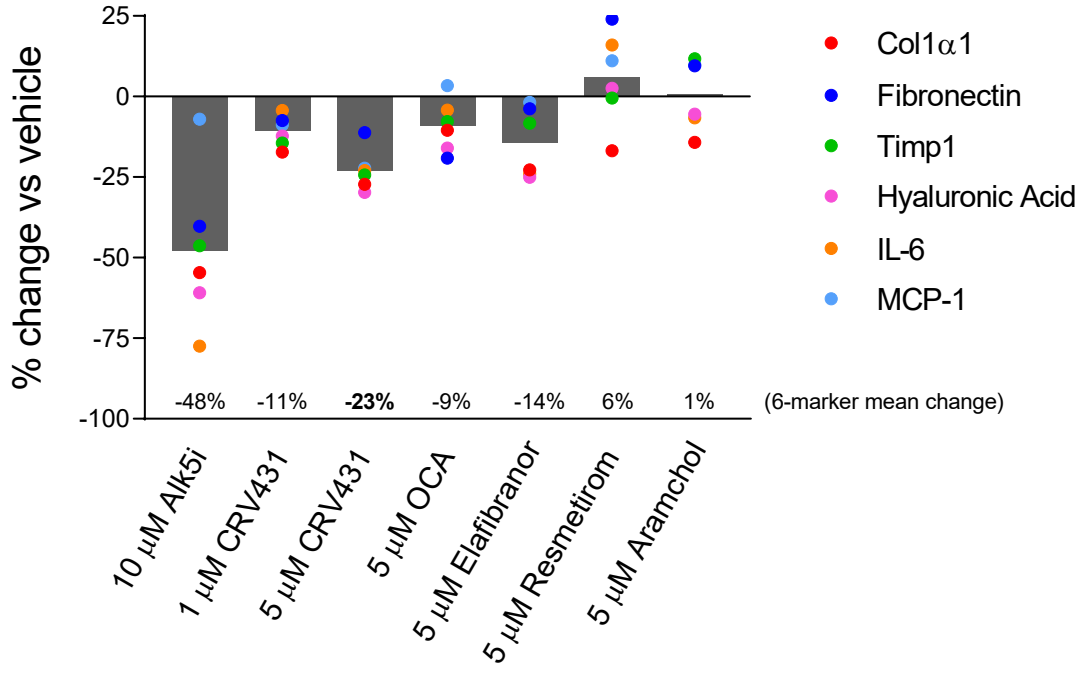


Anti-Fibrotic Activity in Human Liver Explant Tissue (FibroFind, UK)

Gene Expression



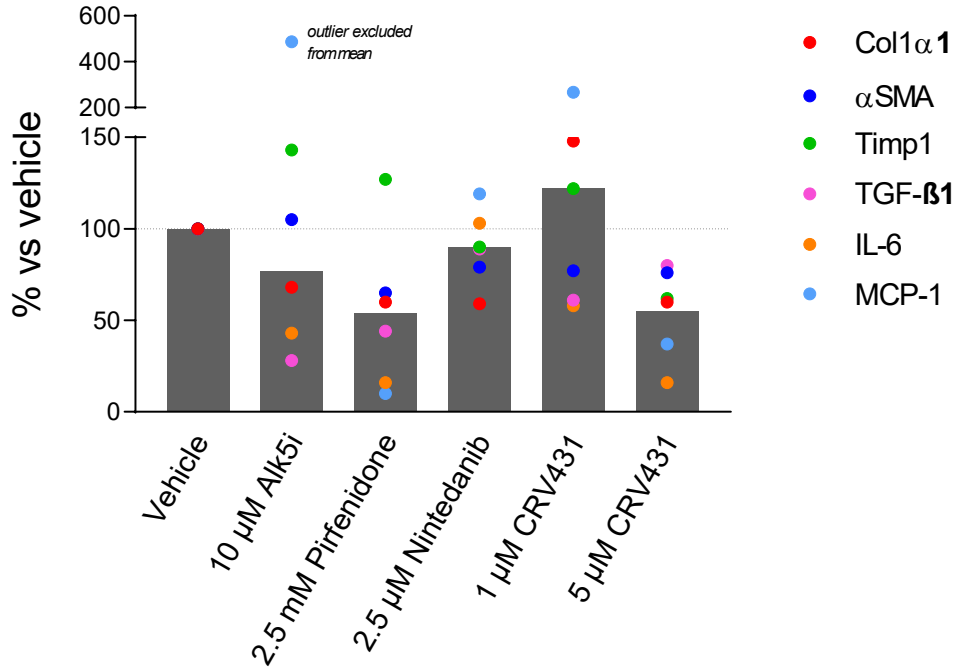
Secreted Protein Markers (Daily Average Change)



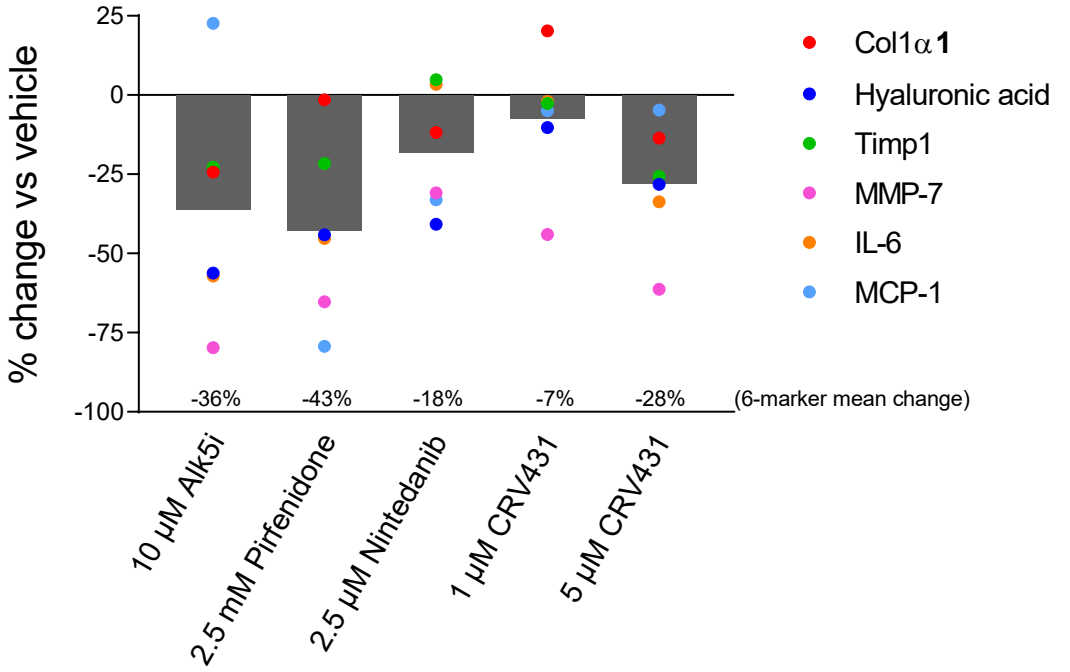
- CRV431 (5 µM) decreased gene expression and production of all secreted protein markers of inflammation and fibrosis after stimulation
- CRV431 was the most effective of all NASH drug candidates compared at 5 µM

Anti-Fibrotic Activity in Human IPF Lung Explant Tissue (FibroFind, UK)

Gene Expression



Secreted Protein Markers (Daily Average Change)



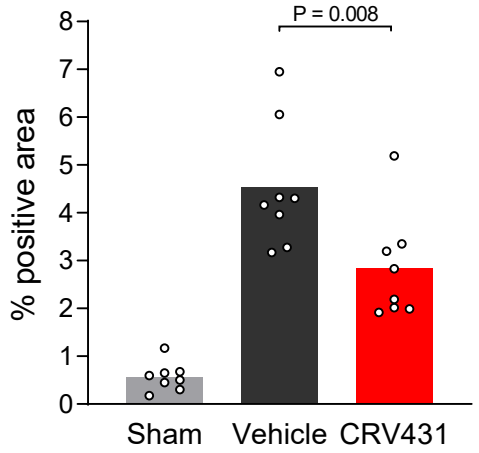
- Precision cut lung slices from idiopathic pulmonary fibrosis (IPF) patient, in culture for 6 days
- CRV431 (5 µM) decreased gene expression and secretion of all markers of inflammation and fibrosis (similar or greater magnitude than pirfenidone and nintedanib)

Renal Fibrosis Model in Mice (SMC Labs, Japan)

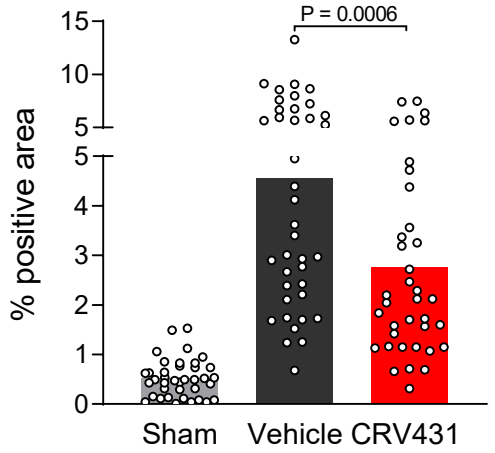
Unilateral ureter obstruction (UUO)

- 14 days of treatment (n = 8 per group)
- Vehicle or CRV431 50 mg/kg/day
- Left ureter ligation

Sirius red per mouse
(5 sections per mouse x 8 mice)



Sirius red per histological section
(5 sections per mouse x 8 mice)



Day 14 Analyses	Vehicle vs SHAM	CRV431 vs Vehicle
Kidney weight	3-fold increase (ligated kidney)	No difference
PAS-histology	tubular dilation, atrophy, inflammation, and casts	No difference
BUN	No difference	No difference
αSMA-IHC	No difference	No difference
Fibronectin-IHC	No difference	No difference
Hydroxyproline	3-fold increase	No difference
Sirius red-histology	**9-fold increase**	**42% reduction**

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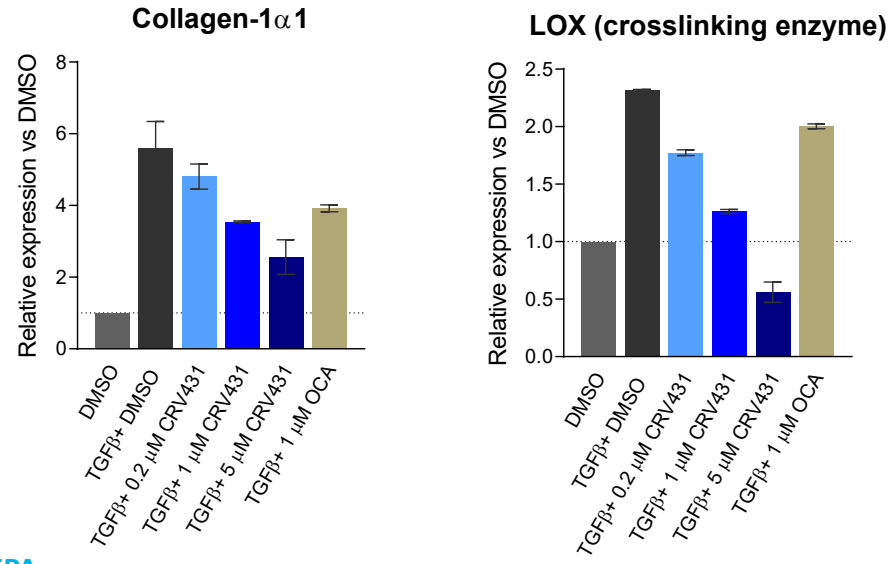
Anti-Fibrotic Mechanisms of Action

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

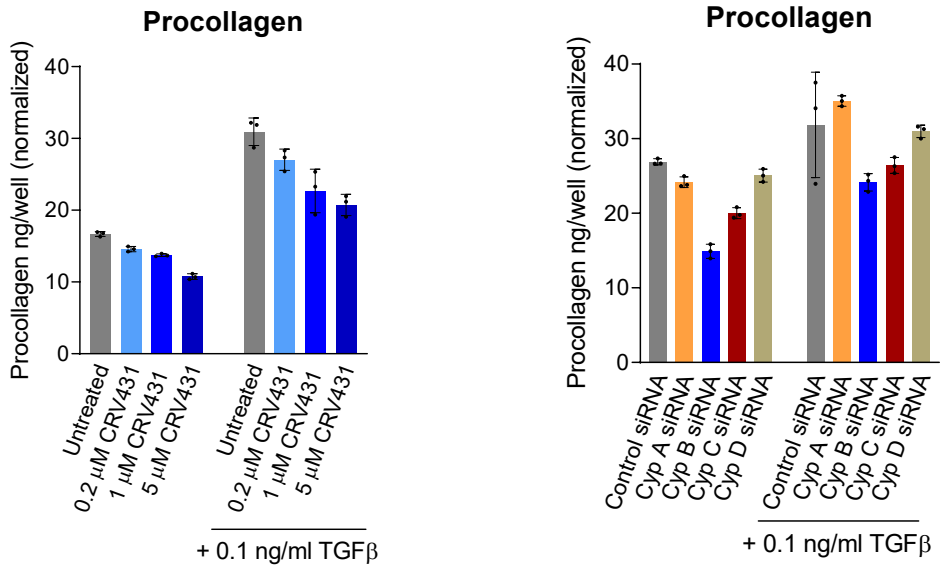
- decrease expression of fibrosis-related genes
- decrease cyclophilin B-dependent collagen synthesis and secretion

Representative Experiments on LX-2 Hepatic Stellate Cells

Fibrosis-Related Gene Expression Reduced by CRV431



Procollagen Secretion Reduced by CRV431 or Cyp B Knockdown



Consistent Nonclinical Anti-Fibrotic Activities

Species	Model	Location	CRV431	Fibrosis Reduction*	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
Mice	Renal ureter obstruction	SMC Laboratories (Japan)	2 weeks	42% ↓	None
Human	LX-2 hepatic stellate cell cultures	Hepion	1-2 days	30-50% ↓ collagen secretion	Fibronectin secretion ↓ Fibrotic gene expression ↓
Human	Human liver explant cultures	FibroFind (UK)	4 days	100% ↓	RNA levels and secretion of inflammatory/fibrotic proteins ↓
Human	IPF human lung explant cultures	FibroFind (UK)	6 days	n/a	RNA levels and secretion of inflammatory/fibrotic proteins ↓

* % Sirius red relative to baseline

Clinical Pharmacology

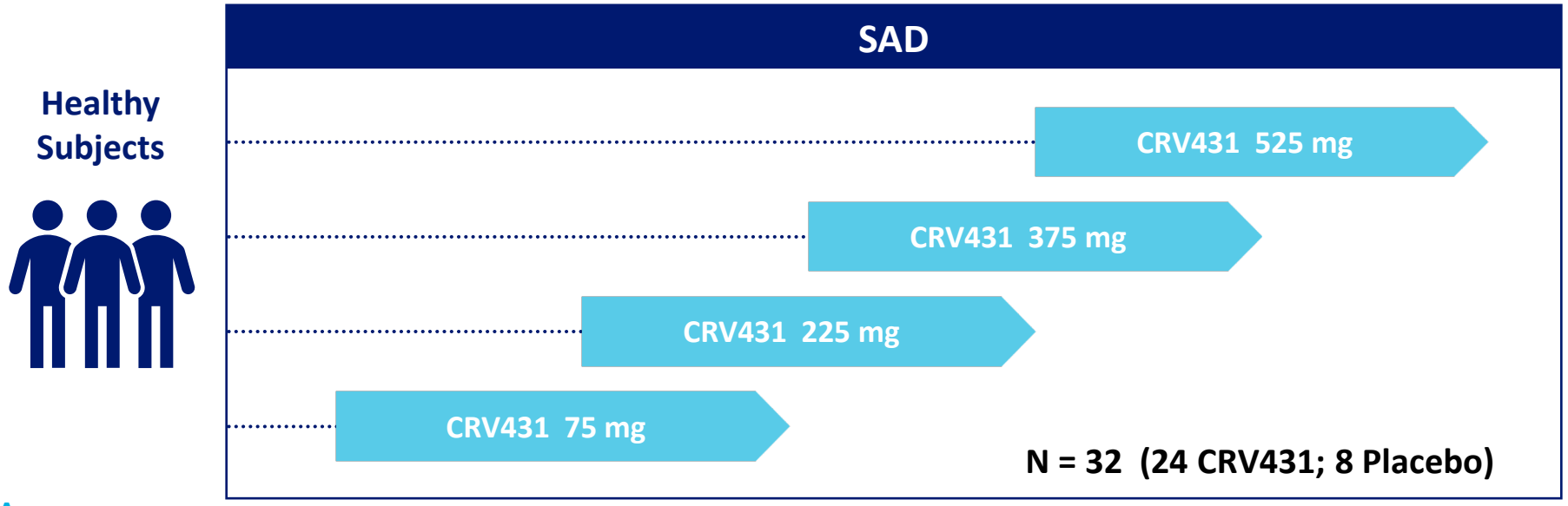
Single Ascending Dose (SAD) Study: (CRV431-101)

Objectives

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

Design

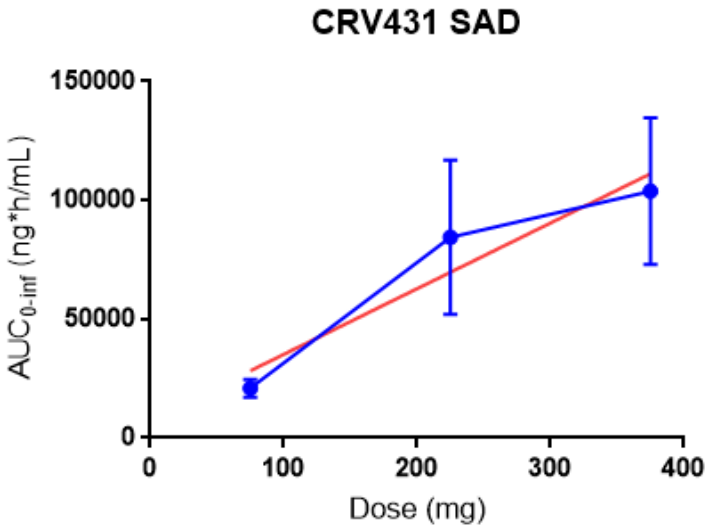
- → Randomized, Partially blinded, Placebo-controlled, sequential SAD Study in healthy volunteers



Clinical Pharmacology: CRV431

Mean Pharmacokinetic Parameters: Non-Compartment Model

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



Goodness of Fit	
R square	0.914

- Drug Exposure Is Linear Up To 375mg (r^2=0.914)
- Pharmacokinetic Profile Supports Once Daily Dosing
- Long Terminal Elimination Half-life Is Related To Drug Distribution Into Deep Tissue Or Peripheral Compartments

Clinical Pharmacology

Safety Profile and Conclusions: SAD Study

Safety Profile

- No SAEs
- AEs were mild to moderate, and mostly unrelated to study drug
- No Grade 3 or Grade 4 laboratory abnormalities
- Vital signs and ECGs were unremarkable

Conclusions

- Doses were tested up to 525 mg with no concerns
- The collective data demonstrated a favorable pharmacological, pharmacokinetic, and safety profile for CRV431 with acceptable safety margins
- Supportive of continuing the proposed clinical development programs

Clinical Pharmacology

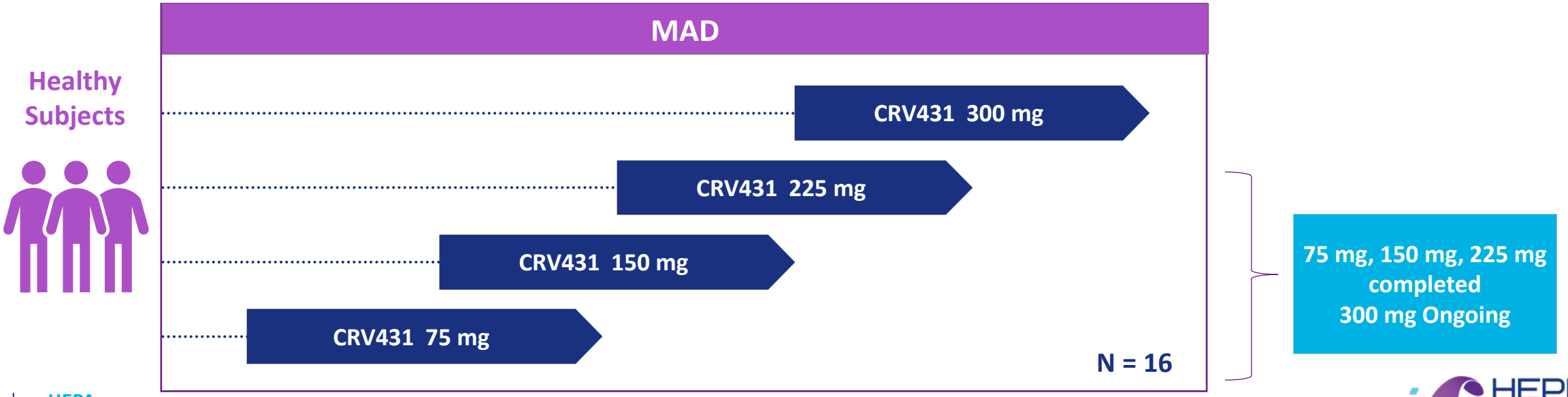
Multiple Ascending Dose (MAD) Study (CRV431-101)

Objectives

- To evaluate the safety and tolerability of multiple oral doses of CRV431 at increasing dose levels over 28 days
- To evaluate maximum tolerated dose
- To evaluate the pharmacokinetics of CRV431 at steady state

Design

- Randomized, sequential MAD study in healthy volunteers



Clinical Pharmacology

Phase 2A Pilot Study (CRV431-201, the 'AMBITION' Trial)

Objectives

- To evaluate the safety and tolerability of once daily (qd) 75 mg dose of CRV431 in presumed nonalcoholic steatohepatitis (NASH) fibrosis stage 2 (F2)/fibrosis stage 3 (F3) subjects compared to placebo control over 28 days of dosing
- To evaluate antifibrotic activity of CRV431
- To generate exploratory antifibrotic biomarker data: collagen biomarkers, matrix metalloproteinases, lipidomics, and genomics

Design

- Multi-center, single-blind, placebo-controlled study
- Univariate Endpoints: AST, Pro-C3, ELF Score, Fibroscan

F2/F3 NASH Patients (n=18)

Cohort*	Fibrosis Stage	N	Day 1 – 28, fasted oral dosing	Day 29 - 42
A	F2/F3	12	CRV431 75 mg	Observation/Follow-up
B		6	Placebo	

*randomized assignment; 2:1 – CRV431:placebo

Multivariate multi-omics analysis to elucidate CRV431 activity biomarkers in F2/F3 NASH

The Bioinformatics of CRV431 in NASH/NAFLD Human Liver Slices

Early Analysis of Key NASH Genetics After 3-Days CRV431

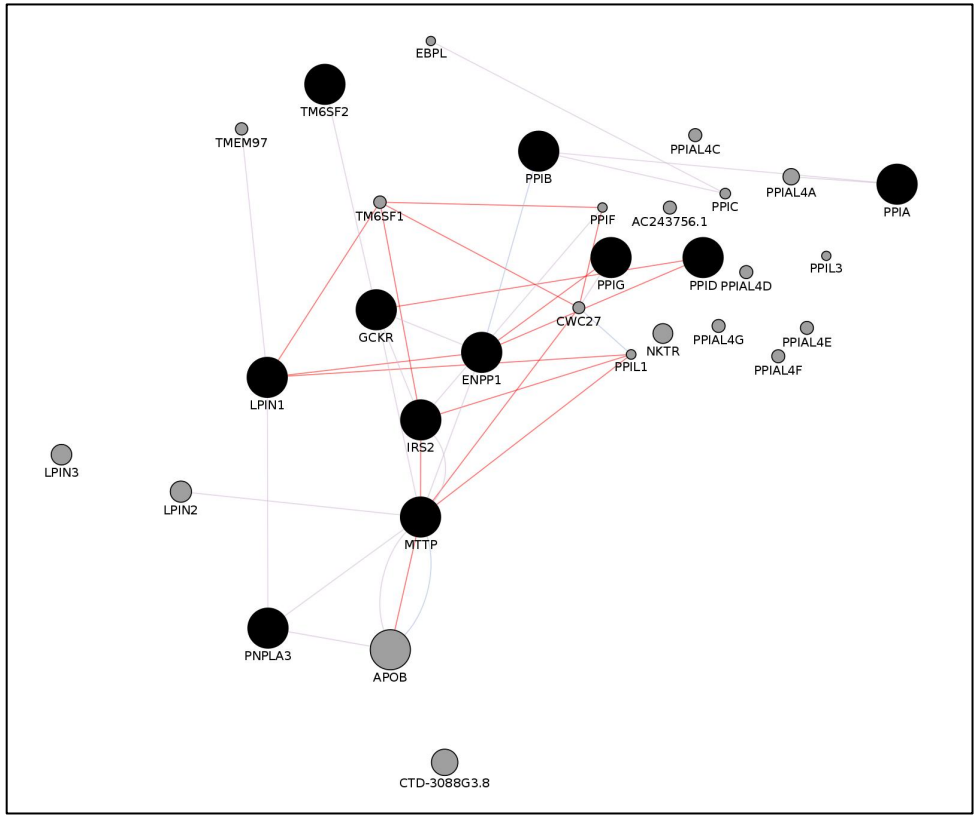
- NASH/NAFLD is heterogenous
- Genetic analysis of the effects of CRV431 on 28,278 genes, gene-variants, non-encoding microRNA and long RNA
- A study of genes and environmental interactions (epigenetics) may suggest specific genetic risk factors or specific genetic types of NASH.
- Decreased function of these genes is associated with NASH/NAFLD and fibrosis
- Bioinformatics will help guide clinical development of CRV431, and optimize for success

Gene	Implications for NASH (Down-regulation, loss-of-function, polymorphism)	Fold Change	p-value
TM6SF2	Linked to NASH and fibrosis	4.2	0.0007
PNPLA3	Triacylglycerol hydrolysis: linked to NASH and fibrosis	1.6	0.046
ApoB	Apolipoprotein of chylomicrons and LDL, ligand for LDL, linked to dyslipidemia, NASH and fibrosis	10.9	0.0001
MTTP	Lipoprotein assembly: linked to NASH and fibrosis	5.5	0.0003
GCKR	Linked to maturity-onset type 2 diabetes and NASH	2.7	0.0036
LPIN1	Mutations associated with metabolic syndrome: linked to NASH and fibrosis	1.9	0.01

Eslam, Mohammed, Luca Valenti, and Stefano Romeo. "Genetics and Epigenetics of NAFLD and NASH: clinical impact." Journal of Hepatology 68.2 (2018): 268-279

Clinical Pharmacology: CRV431 and the Genetics of NASH

Bioinformatics: Gene-Gene Network Interactions



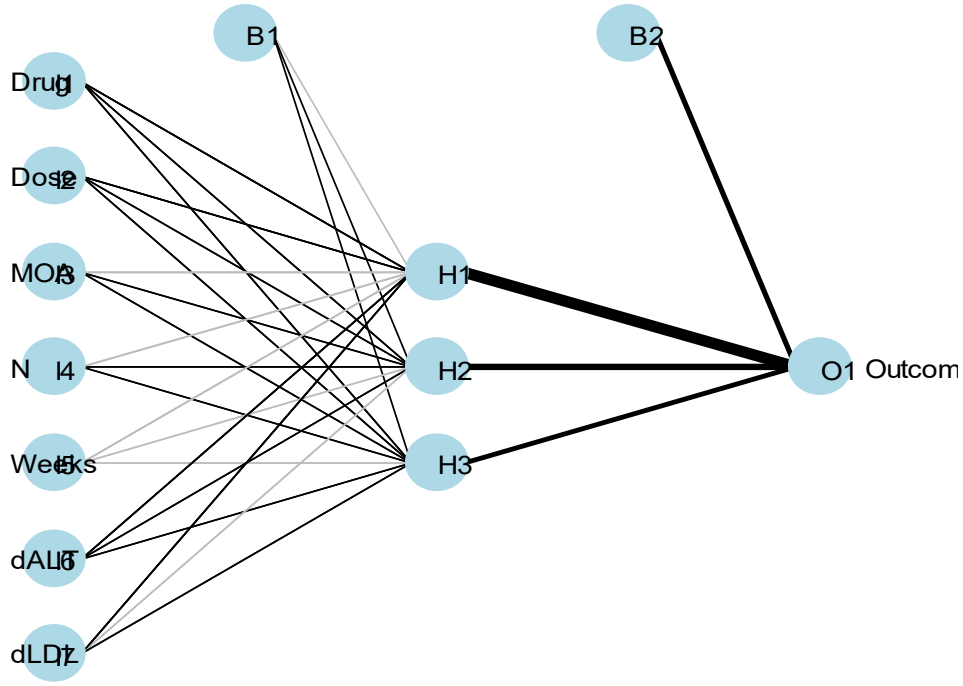
Red line = gene-gene interactions.

- CRV431 inhibits all cyclophilins
- Cyclophilin B (PPIB) and G (PPIG) have direct regulatory effects on NAFLD/NASH genes
- Network analysis demonstrates the genetic role of CRV431 in NASH
- Prospective genomic analysis allows for specific selection of patients/end-points or precision medicine to ensure clinical success

Bioinformatics: Artificial Intelligence (AI) Predicting Clinical Outcomes

STEP 1: Create Shallow Neural Net

STEP 2: Create Deep Neural Net: In-Training with Enhanced Proprietary Methods



Assess CRV431 in NASH and increase probability of success

Neural Network Architecture

- ✓ Inputs: Drug Type, Drug Dose, Mechanism of Action, Number of Patients in Clinical Trial, Weeks Duration, Change in ALT, LDL: Outcome was %Decrease in Primary Measure
- ✓ First layer receives input variables (I1 through I7), each connected to all nodes in hidden layers (H1 through H3)
- ✓ Black lines = positive weights
- ✓ Grey lines = negative weights
- ✓ Line thickness is proportional to relative magnitude of each weight

Clinical Timelines

2020

H1

- Initiate Phase 2 NASH biomarker pilot trial ('AMBITION'), 28-day CRV431 once daily dosing

Q3

- Data from Clinical 28-day study, oral CRV431 Multiple Ascending Dose (MAD), once daily dosing*
- Bioinformatic biomarker analysis, genomic analysis: NASH + CRV431
- AI Analysis: NASH + CRV431

Q4

- Data from Phase 2 NASH pilot trial ('AMBITION'), 28-day CRV431 75 mg once daily oral dosing

2021

Q2

- Initiate Phase 2b NASH, approx. 200 patients, CRV431 orally, once daily for 24 weeks

* This was previously scheduled to be completed at end of H1 but has been pushed out a quarter because one higher dosing cohort is likely needed, as CRV431 has not yet demonstrated any dose limiting adverse events.

Non-Clinical Events

2020

Q1

- Initiate chronic toxicology in rat and monkey √
- Continue fibrosis studies √

Q2

- Data from kidney fibrosis model √
- Bioinformatic analyses of previous animal models

H2

- Data from Diamond NASH mice
- Data from cyclophilin knockouts

2021

H1

- Data from chronic toxicology, rat and monkey

Financial Summary

Cash

- $13.9 MM as of 12/31/2019
- $11.3 MM raised in 2020 via At The Market (ATM) facility

Shares outstanding

- 3.8 MM shares outstanding as of 12/31/2019
- 5.2 MM shares issued via ATM facility
- 9.0 MM shares currently outstanding

Research coverage

- Yasmeen Rahimi, Ph.D. – Roth Capital
- Kumar Raja, Ph.D. – Brookline Capital
- Nathaniel Calloway, Ph.D. – Edison Group

THANK YOU

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