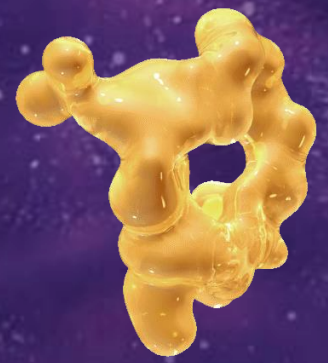
HEPION PHARMACEUTICALS

A BETTER APPROACH TO DRUG DEVELOPMENT FOR LIVER DISEASES

December 2021 | INVESTOR PRESENTATION



smart drug
smart technology
smart development

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The Need and Opportunity

NASH is a Healthcare Crisis

1. **NASH leads to cirrhosis, liver cancer (HCC), end stage liver disease, and death**
2. **Soon to be lead reason for liver transplantation**
3. **Large cost to healthcare system**

No drugs are approved for treating NASH

NAFLD

non-alcoholic fatty liver disease

"Fatty liver" disease associated with obesity, diabetes, hypertension, etc.

Approx. 25% of global population

Up to 100 million in U.S.

NASH

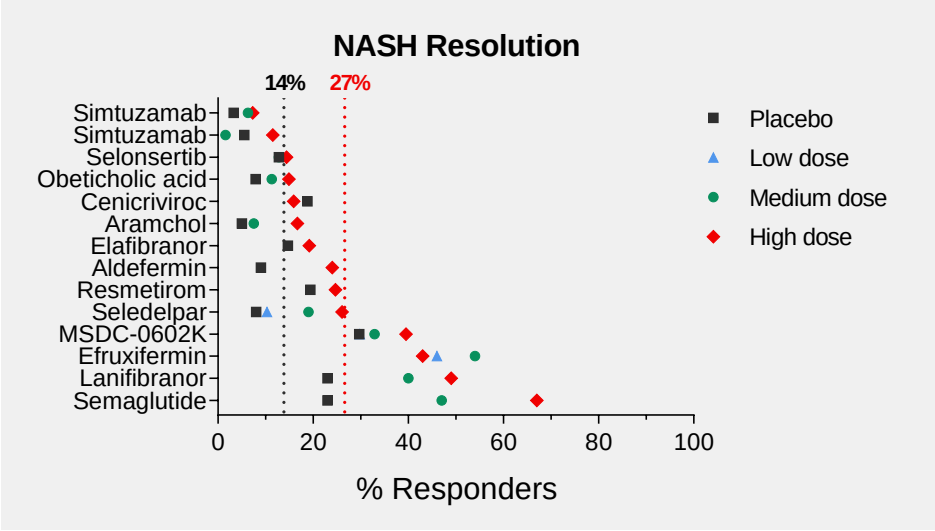
non-alcoholic steatohepatitis

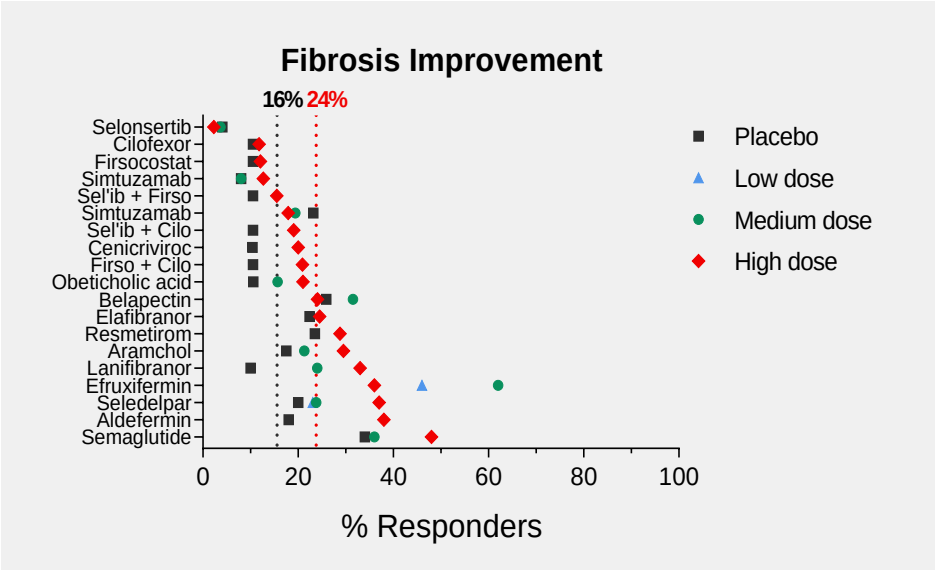
A more severe form of NAFLD, with inflammation and liver scarring (fibrosis)

1.5 – 6.5% globally

Up to 17 million in U.S.

The Challenges
Nash Drug Development





Regulatory agencies require improvement in several indices of NASH by analysis of liver biopsies:

- Fatty deposits, cell death, inflammation and/or liver scarring (fibrosis)

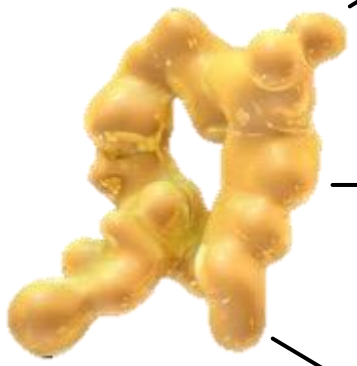
Most study outcomes have been disappointing:

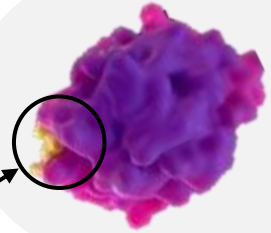
- High placebo responses
- Low responses on histologic endpoints from most candidate drugs
- Several drug candidates discontinued

+ New approaches to developing NASH therapeutics are needed

Multiple Therapeutic Actions
Through Cyclophilin Inhibition – A Novel Class

CRV431
Pan-Cyclophilin Inhibitor
(Ki ≈ 1 nM)

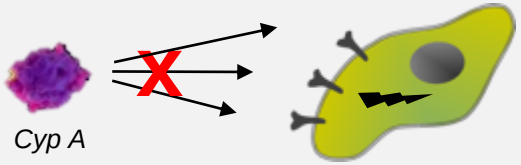


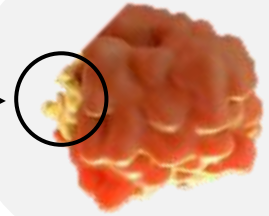


Cyclophilin A
(cytosol and secreted)

Secreted from injured cells and acts as proinflammatory cytokine by binding to CD147

CD147 pro-inflammatory receptors

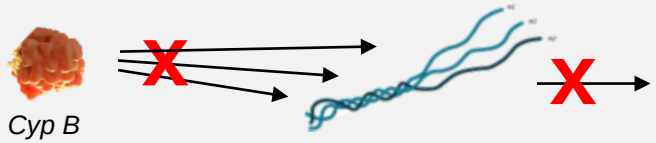


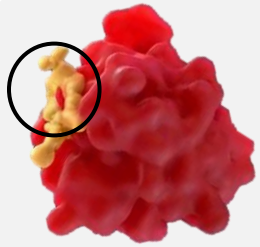


Cyclophilin B
(endoplasmic reticulum)

Promotes fibrotic scarring by controlling collagen production

Procollagen



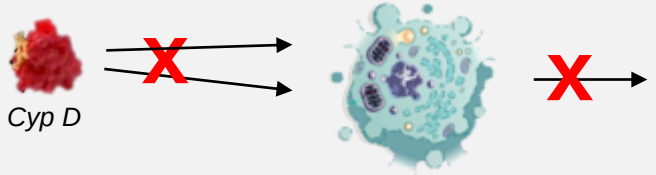


Cyclophilin D
(mitochondria)

Regulates mitochondrial metabolism

Promotes mitochondrial pore opening leading to mitochondrial and necrotic cell death

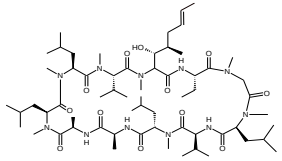
Mitochondrial pores (mPT)



Genesis of HEPION PHARMACEUTICALS CRV431

Theory	Prediction and Experimentation	Findings
Modifying Cyclosporine A can greatly change its binding and functional properties	Modifications that increase calcineurin binding and immunosuppression (voclosporin) Modifications that decrease calcineurin binding and immunosuppression, and increase cyclophilin binding and inhibition (CRV431)	Inhibition of each cyclophilin isoform may produce distinct therapeutic effects

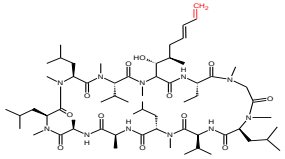
Cyclosporine A



Nearly 40 years of clinical use as immunosuppressive drug for organ transplantation and autoimmune diseases

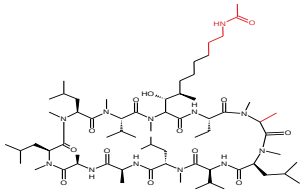
Voclosporin

Aurinia Pharma

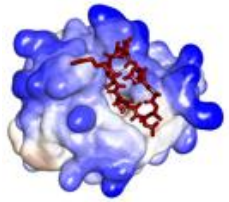


Modifications increase affinity for calcineurin and **increase immunosuppression potency**

CRV431



Modifications increase affinity for cyclophilins (13-fold) and **eliminate immunosuppression**



CRV431 binds potently (Ki≈1 nM) to at least10 of 17 known cyclophilin isoforms

Why Target Cyclophilins?

Cyclophilins shown to play deleterious roles in many acute and chronic disease processes:

Viral Hepatitis • Cancers • Acute And Chronic Lung Injury • Myocardial Infarction • Stroke • Arthritis • Atherosclerosis • Thrombosis • Aortic Aneurysm • Coronary Artery Disease • Pulmonary Arterial Hypertension • ALS • Alzheimer's Disease • Multiple Sclerosis • Muscular Dystrophies • Traumatic CNS Injury

IND Approvals

Program	Pre-Clinical	Phase 1*	Phase 2	Phase 3	NDA Submission
NASH	IND 142904 →	→	Phase 2B Initiation **Q1 2022**		Projected NDA filing **2028**
COVID-19	IND 151344 →	→	**Will not proceed unless externally funded/licensed**		
HBV	IND 1376787 →	→	**Open to partnerships**		

*Separate Phase 1 programs were not conducted for each separate indication. The Phase 1 program was comprised of Single and Multiple Ascending Doses, and a Drug-Drug Interaction study.

Non-clinical
Evidence of Strong and Consistent Beneficial Activities for CRV431

Human Cell Cultures		CRV431 Effects
Hepatic stellate cells, fibroblasts (multiple organs)	TGFβ or endogenous stimulation	▼fibrotic gene expression ▼procollagen and fibronectin secretion
Blood platelets	Collagen and thrombin stimulation	▼procoagulant platelet formation

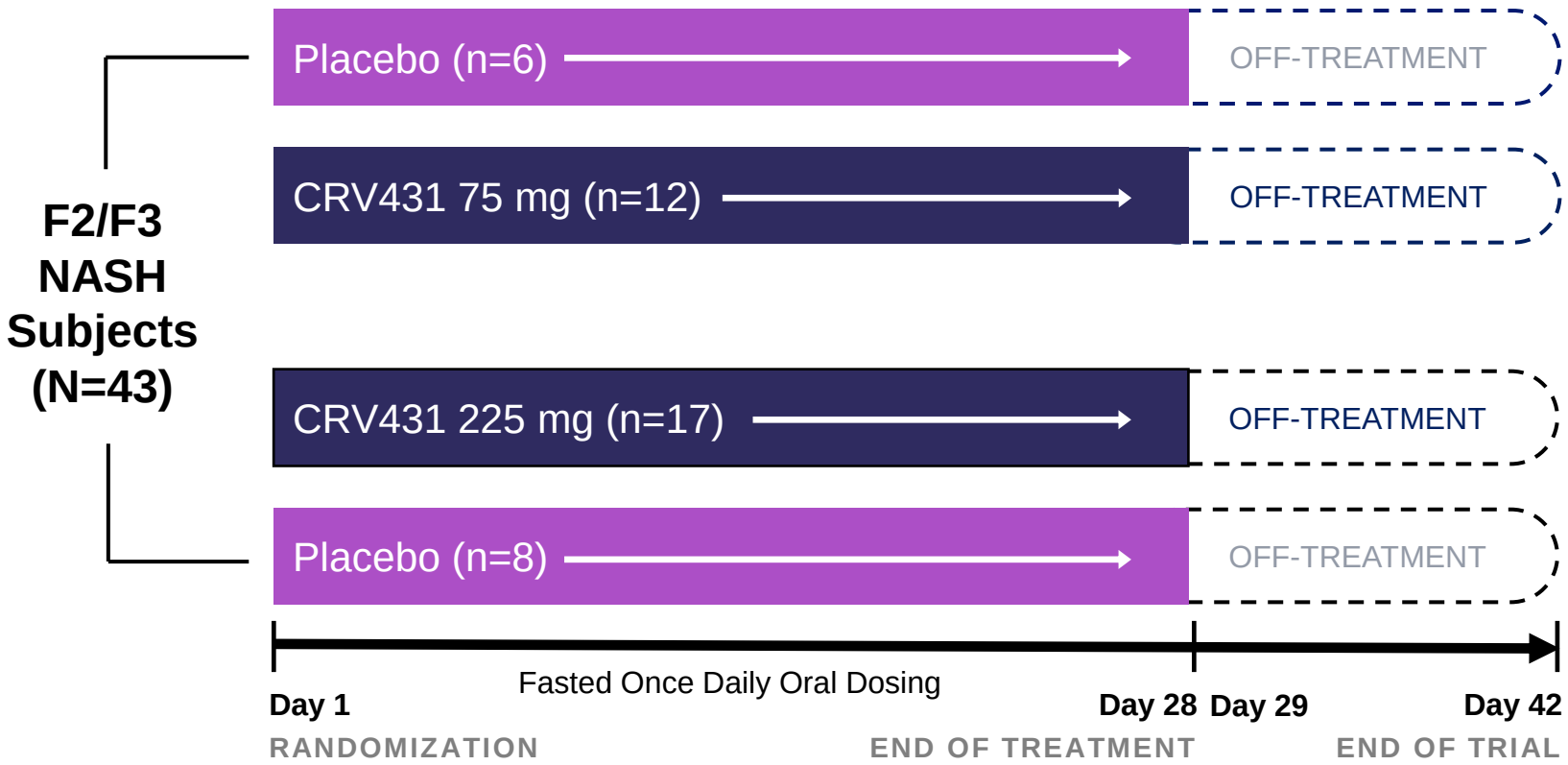
Human Tissue Explants (Precision Cut Slice Cultures)		CRV431 Effects
Liver explants (4 donors)	TGFβ+PDGF-BB or endogenous stimulation	▼ inflammatory/fibrotic gene expression ▼ inflammatory/fibrotic protein secretion ▼ tissue fibrosis
IPF lung explants (1 donor)	Endogenous stimulation	

Animal Models		CRV431 Effects
Mice (NASH)	Western diet + carbon tetrachloride	82%▼ fibrosis; ▼weight gain
Mice (NASH)	High fat diet + early STZ (4 studies)	37-57%▼fibrosis; ▼weight gain; 50%▼liver tumors
Mice (liver fibrosis)	Carbon tetrachloride	44%▼ fibrosis
Mice (kidney fibrosis)	Unilateral ureter obstruction	42%▼ fibrosis
Rats (liver fibrosis)	Thioacetamide	48%▼ fibrosis; prevented cirrhosis
Mice (acute lung injury)	Lipopolysaccharide inhalation	▼BAL fluid inflammatory cytokines, neutrophils
Mice (diabetes)	High fat diet + late STZ	▼adiposity; ▼weight gain

Overview of PHASE 2A ‘AMBITION’ TRIAL

PHASE 2a 'AMBITION' Study
NASH Subjects - Safety, Tolerability, and Pharmacokinetics

AMBITION: A Phase 2a, Multi-center, Single-Blind, Placebo-Controlled, Proof of Concept Study
to Evaluate the Safety & Tolerability of CRV431 Dosed Once Daily in NASH Induced F2 & F3 Subjects



Primary Endpoints:

- Safety
- Tolerability
- Pharmacokinetics

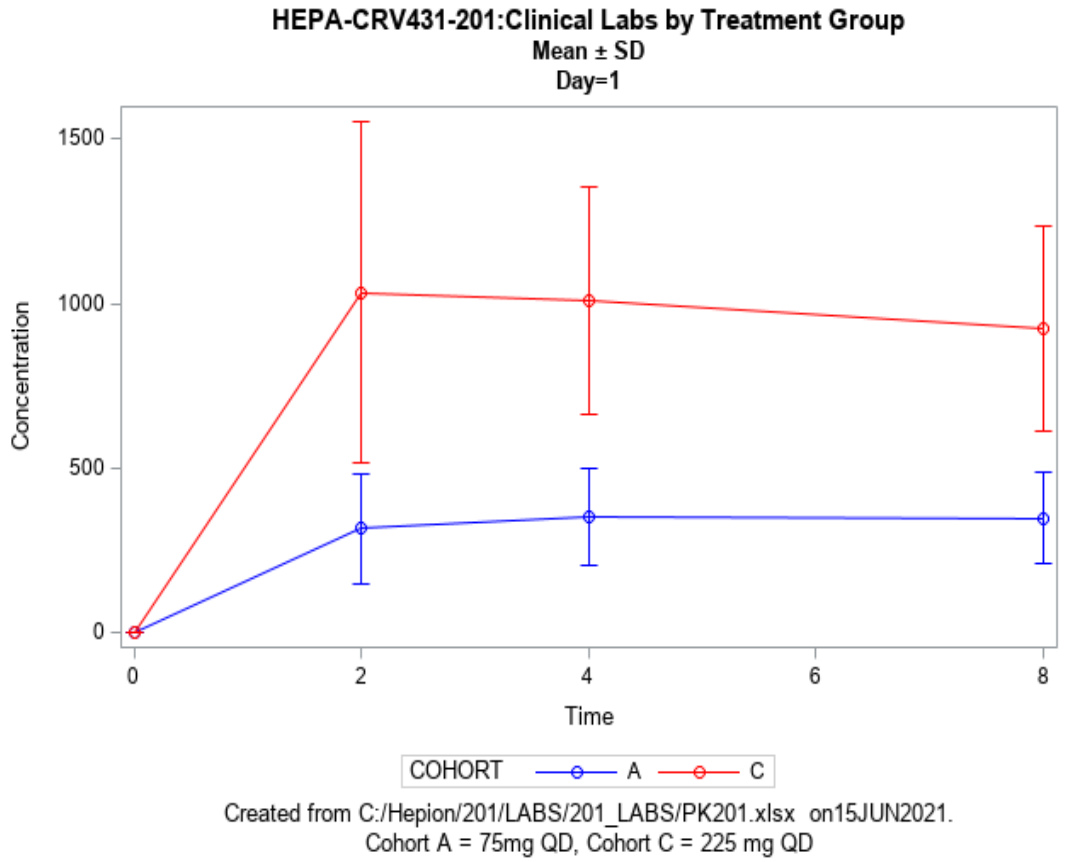
Phase 2a: 'AMBITION' Study
Baseline Demographics

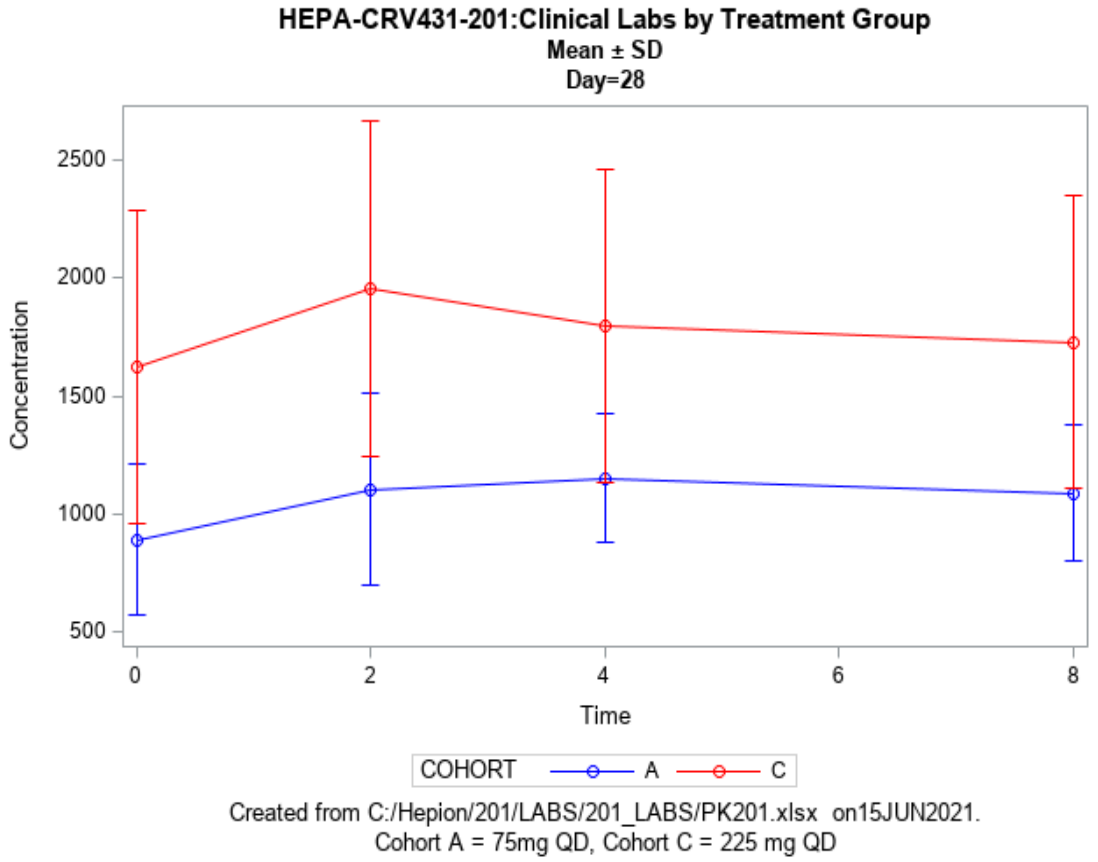
	CRV431 75 mg **(n = 12)**	CRV431 225 mg **(n = 17)***	Pooled Placebo **(n = 14)**
Age (**years**)			
Mean (SD)	61.9 (8.0)	54.0 (13.3)	61.1 (12.0)
Range	48-72	27-71	27-72
Gender			
Male n (%)	7 (58.3)	7 (41.2)	9 (64.3)
Female n (%)	5 (41.7)	10 (58.8)	5 (35.7)
Race			
White n (%)	11 (91.7)	17 (100)	13 (92.9)
Hispanic n (%)	1 (8.3)	1 (7.1)	2 (4.7)
BMI (**kg/m^2**)			
Mean (SD)	35.0 (8.0)	37.7 (6.4)	38.9 (8.8)
Range	25-53	28-53	29-57

*1- Subject with Active Covid

All Primary Endpoints Met – Safety, Tolerability, & Pharmacokinetics ('PK')

Adequate Exposures Anticipated for Efficacy





Slides demonstrate accumulation of drug to steady state

Cohort C (225 mg) achieves maximum concentrations > 1000 ng/mL on Day 1

Cohort A (75 mg) achieves maximum concentrations ~ 1000 ng/mL on Day 28

Biomarker response analysis suggests 225 mg QD achieves effective concentrations early

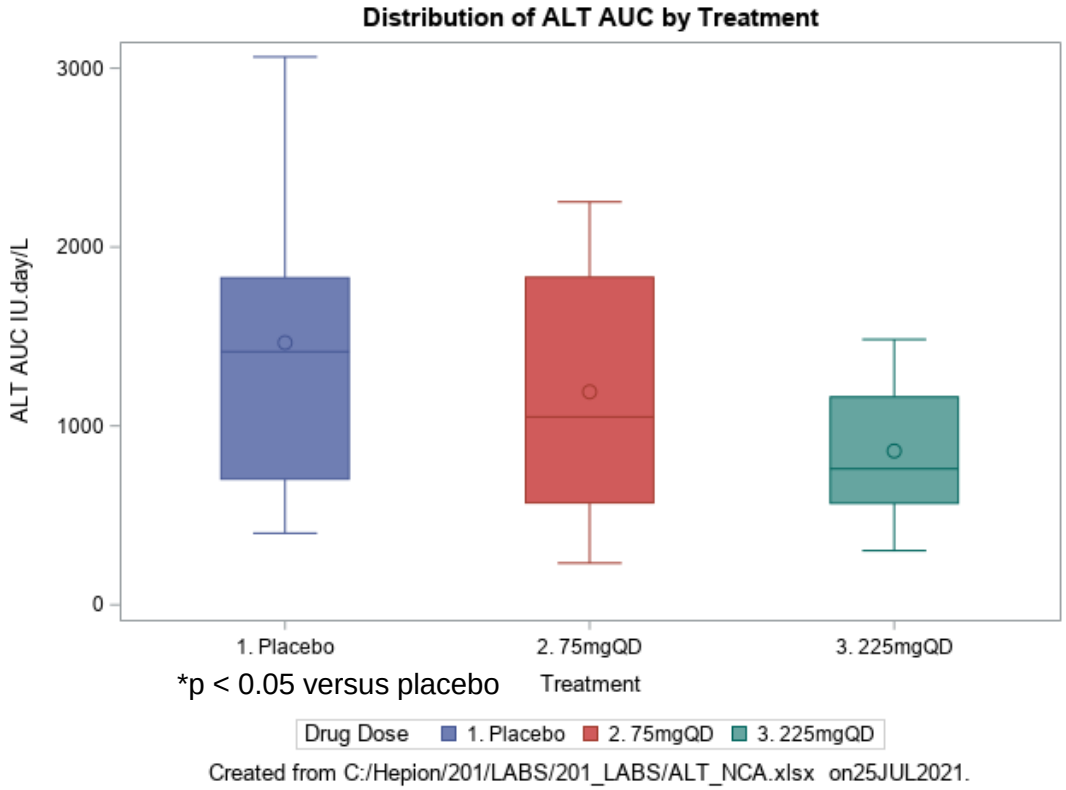
No Serious Adverse Events

ALT, Area Under the Curve (AUC) – Pharmacodynamics ('PD')

Change From Baseline (FOUR Weeks)

	Placebo	75 mg	225 mg
Mean ± SD (%)	-6.1 ± 13.3	**-18.4** ± 25.8	**-21.1** ± 21.0
Median (%) (Range)	-5.2 (-23.8 – 13.8)	-15.9 (-58.3 – 17.2)	-20.0 (-81.5 – 11.1)
N (%) Reduction ALT	7/14 (50%)	8/12 (67%)	13/15 (87%)
AUC of ALT (IU*D/L)	1465.1 ± 810.9	1190.5 ± 712.1	859.9 ± 387.0*

*p = 0.0493 ANOVA

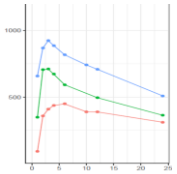


- Mean % change demonstrates dose response
- Variability suggests presence of responders & non-responders at each dose level
- Responder: Reduction in ALT demonstrates dose response

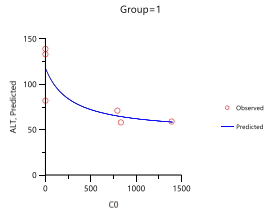
- Area-Under-the-ALT Curve follows changes from Baseline to Day 28
- The decrease in AUC demonstrated a dose response that was statistically significant by ANOVA and Bonferroni post-hoc test

‘PK-PD’ Model Successfully Predicts ALT Effects (Responder & Non-Responder)

PK



PD



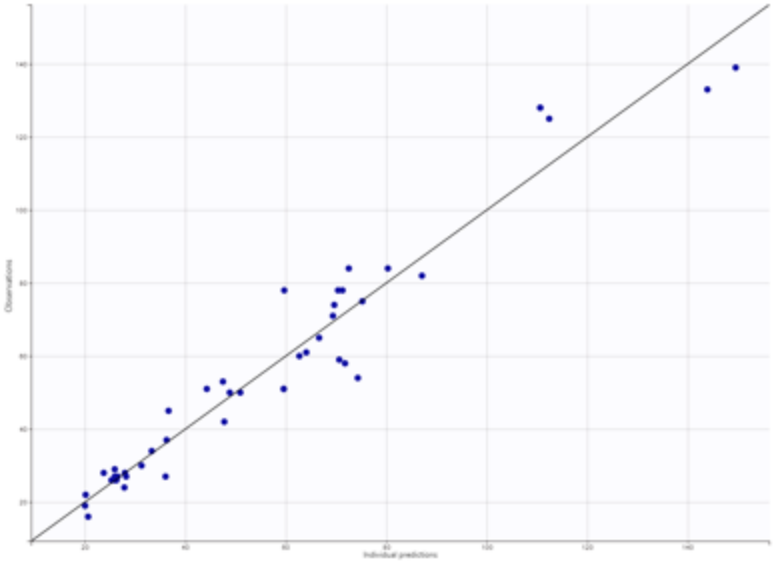
Absorption
Ka (h^{-1}) →

Volume (L)

→ Inhibitory Imax Model
-Baseline (ALT)
IC50:Half-Maximal Inhibition

↓ Elimination
(k h^{-1})

Observed vs Predicted: ALT



Assess patient characteristics (Covariates) that help refine prediction of both PK and PD

Final Covariate Model:

↑Cholesterol ~ ↓Absorption

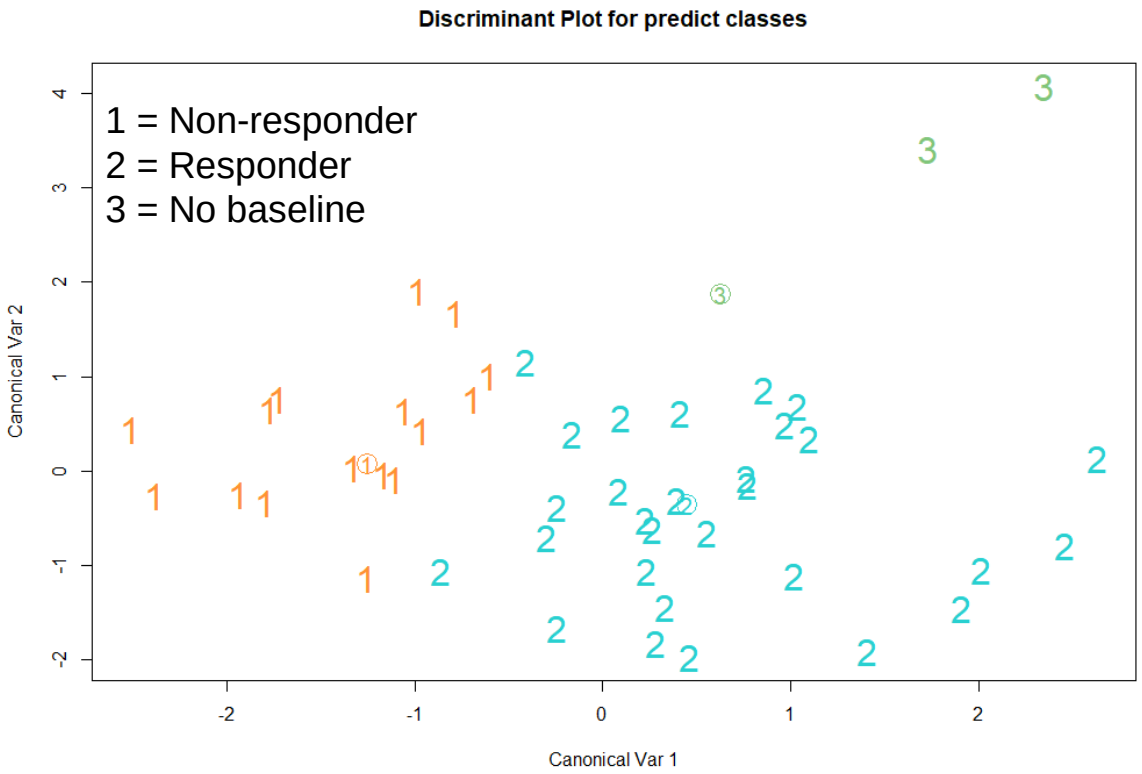
↑Baseline AST ~ ↑Effect

↑Lean Body Weight ~ ↓ IC50

Confirms Concentration-Effect for ALT

Allows simulations for Phase 2b and Phase 3

ALT Responder Analysis



ALT Responder Analysis

ALT	Non-Responder	Responder	Unknown
Age	61.6	57.2	60.6
BMI	40.2	36.1	36.1
Sex	> Male	> Female	2.0
Day 1, 2h	284.2	596.5	264.8
Day 14, 0h	483.4	882.5	667.9
Day 28, 0h	557.9	1040.7	706.0
Day 28, 2h	724.0	1243.0	870.1
BASO	0.0677	0.0741	0.0540
CPK	128.8	100.0	114.4
CREAT	0.700	0.683	0.700
GLUCOSE	117.3	134.8	109.4
PLT	228.5	235.7	237.8
TRIGs	164.5	174.6	169.0
WBC	7.2	7.6	6.5
CHOL	160.5	176.5	188.2
AST	42.8	50.4	75.6
ALT	51.8	59.8	79.6
A1C	6.7	6.9	6.5

By Flexible Discriminate Analysis: Misclassification Error = 0.04255

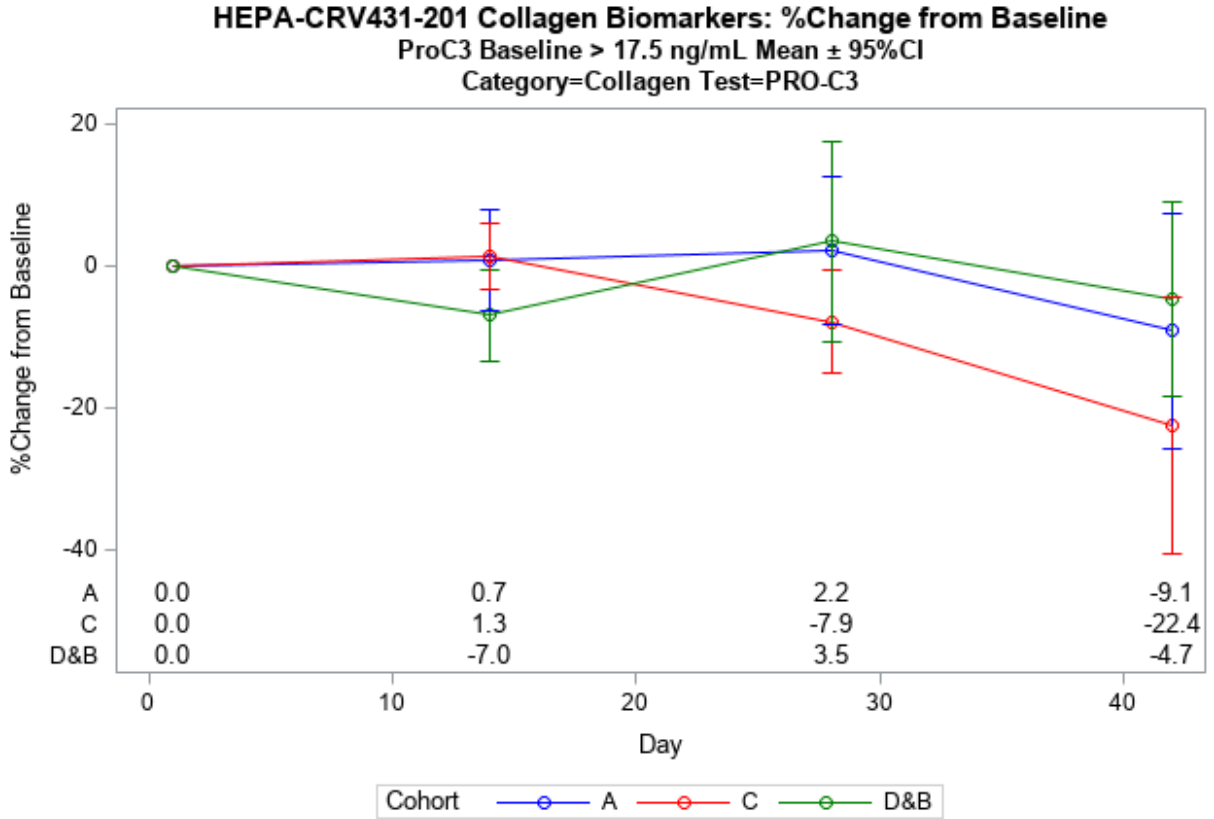
Discriminant analysis evaluates the ability of multiple variables to correctly classify individuals: Responders/Non-Responders

Step 1: Identify Responders vs Non-Responders: Means of Non-Responders vs Responders (and Unknown) are shown in the table

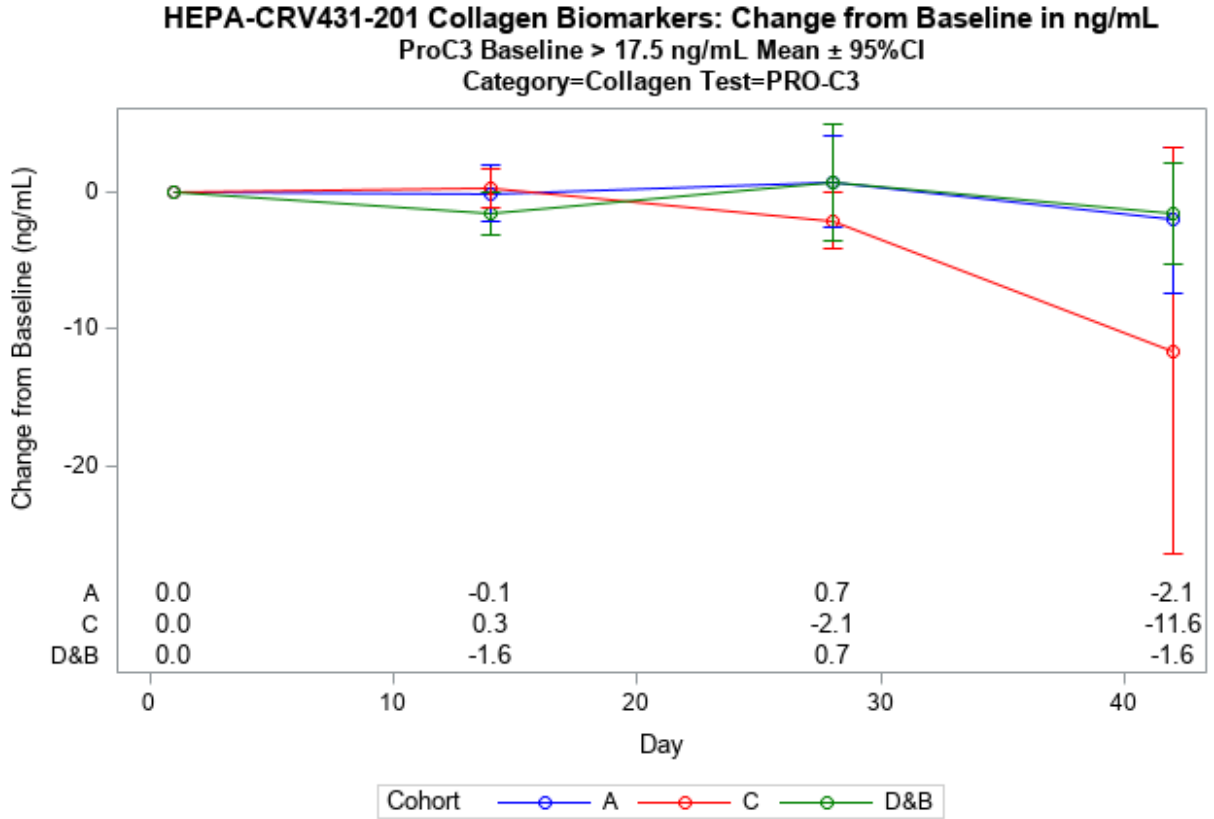
Step 2: Evaluate if Multiple Variables correctly identify responder class with minimal error and good separation (Figure)

Pro-C3: Collagen Formation – Pharmacodynamics (’PD’)

Released N-terminal Pro-Peptide of Type III Collagen



Created from C:\Hepion\201\FInalDataSets\ProC3.xlsx on27AUG2021.
Cohort A = 75mg QD, Cohort C = 225 mg QD, Cohort D&B = Placebo



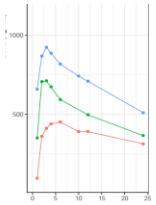
Created from C:\Hepion\201\FInalDataSets\ProC3.xlsx on27AUG2021.
Cohort A = 75mg QD, Cohort C = 225 mg QD, Cohort D&B = Placebo

ProC3 indicates ACTIVE FIBROSIS

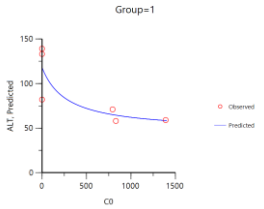
Source: HEPA:CRV431-201: Phase2A Trial on NASH

PK-PD Model Successfully Predicts Pro-C3

PK



PD



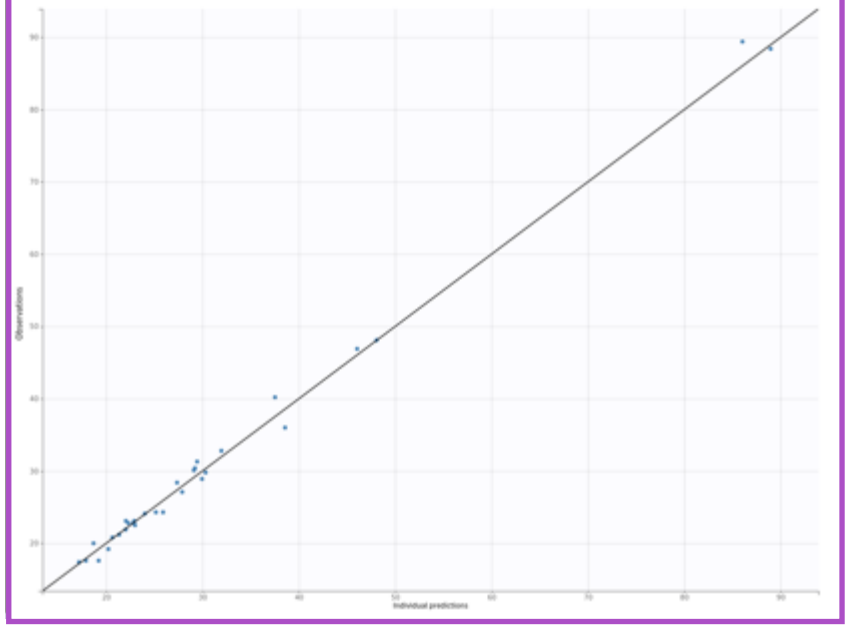
Absorption
Ka (h^{-1}) →

Volume (L)

→ Inhibitory Imax Model
-Baseline (Pro-C3)
IC50:Half-Maximal Inhibition

↓ Elimination
(k h^{-1})

Observed vs Predicted: Pro-C3



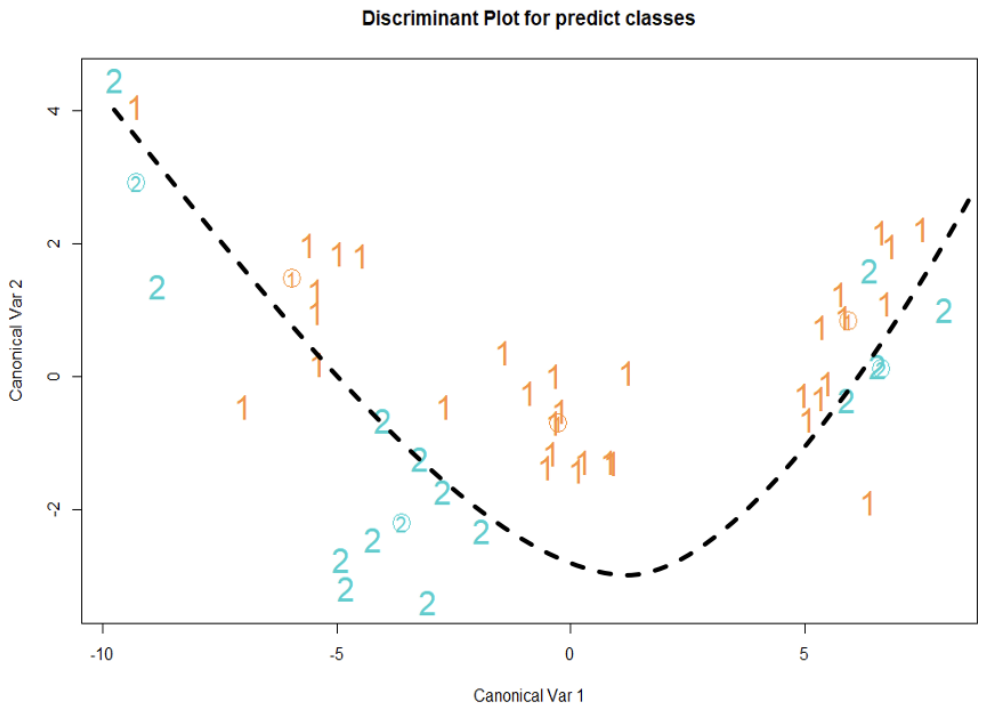
No Covariates were required to predict both PK and PD

Final Covariate Model:
- PK 1-Compartment
- PD: Inhibitory Imax Model with Baseline Pro-C3

Quantitative Concentration-Effect for Pro-C3

Allows simulation of Phase 2b and Phase 3 trials

Pro-C3 CRV431 Responder Analysis



1 = Non-responder
2 = Responder

Pro-C3 Responder Analysis

Pro-C3	Non-Responder	Responder
Sex	>Male	>Female
Age	60.4	55.4
BMI	36.3	39.1
CHOL	177.9	163.5
TRIGs	181.0	150.1
AST	45.6	62.5
ALT	55.3	69.0
PLT	239.8	221.3
Day 1, 2h	449.8	528.2
Day 14, 0h	732.3	785.5
Day 28, 0h	828.1	964.2
Day 28, 2h	1012.8	1160.0
BASO	0.0697	0.0713
WBC	7.6	7.1
GLUCOSE	128.3	124.9
A1C	6.9	6.5
CPK	105.5	118.1
CREAT	0.666	0.740

By Mixture Discriminate Analysis: Misclassification Error = 0.02128

Discriminant analysis evaluates the ability of multiple variables to correctly classify individuals: Responders/Non-Responders

Step 1: Identify Responders vs Non-Responders: Means of Non-Responders vs Responders are shown in the table

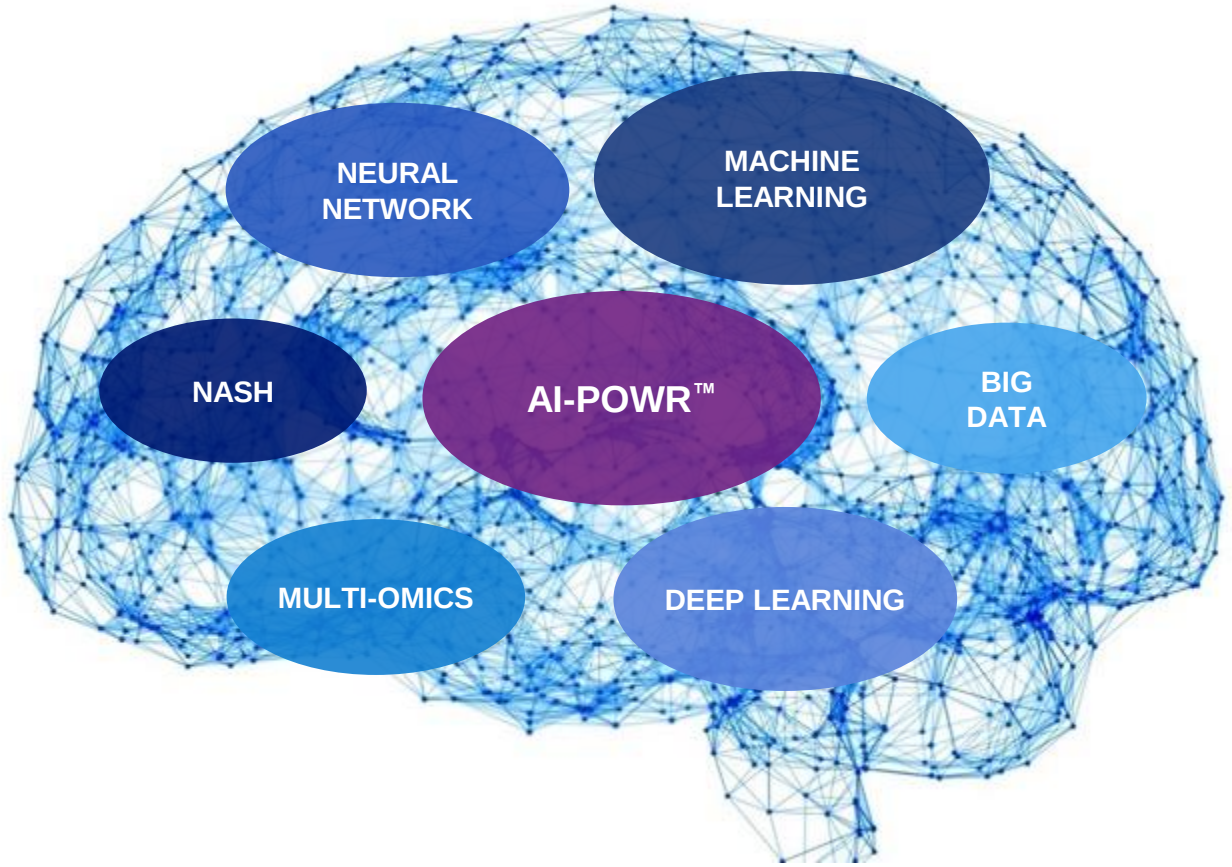
Step 2: Evaluate if Multiple Variables correctly identify responder class with minimal error and good separation (Figure)

Hepion's Artificial Intelligence

CRV431: Multiple Beneficial Properties and State-of-the-Art Artificial Intelligence

AI-POWR™

- Understand disease mechanisms
- Identify biomarkers
- Track disease progression and regression
- Predict drug responders
- Precision medicine



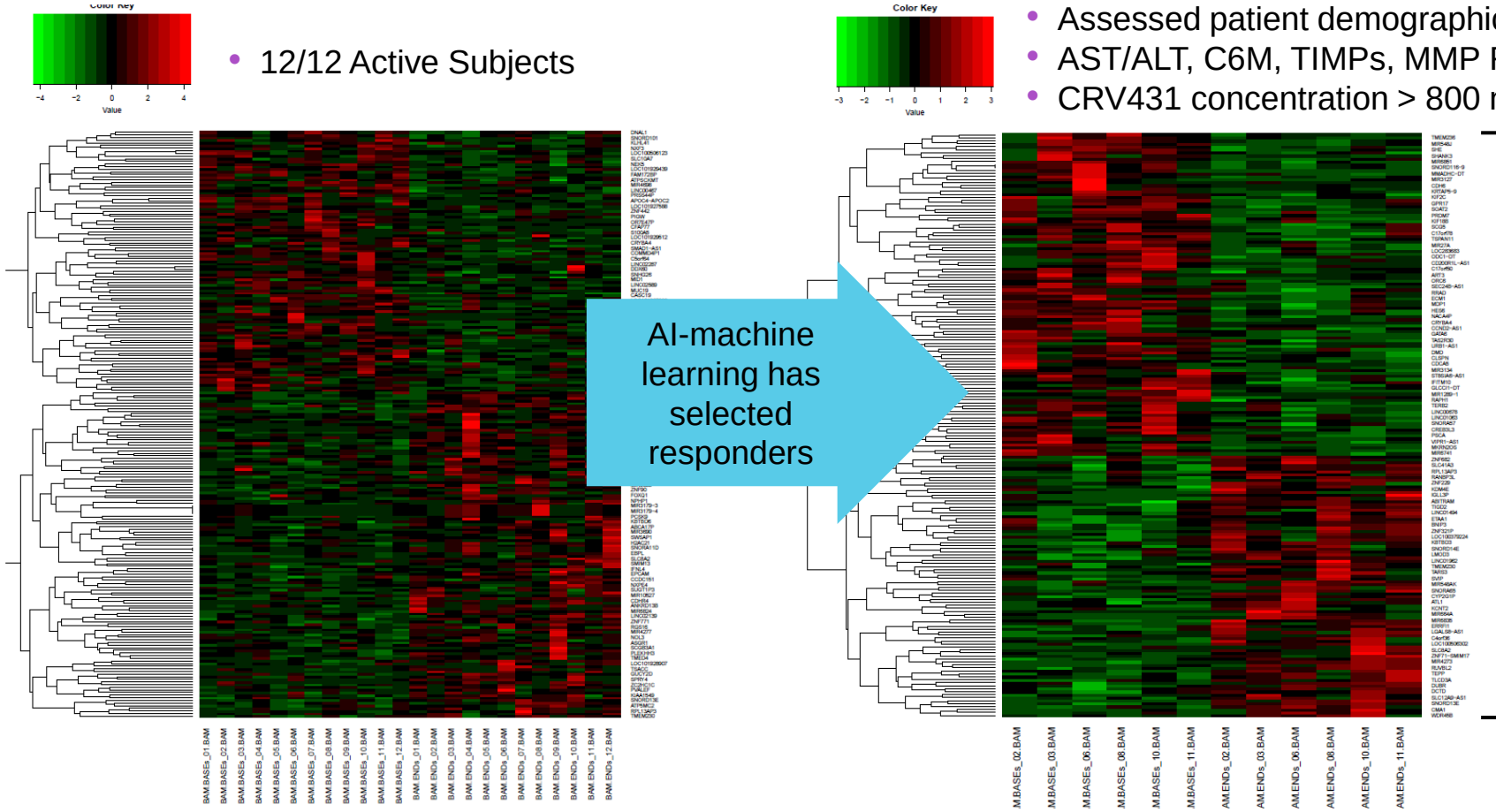
Phase 2a: Transcriptomics & AI

Standard Differentially Expressed Genes - DESEq2

- 12/12 Active Subjects

AI-POWR™
(n=6 out of 12 total subjects)

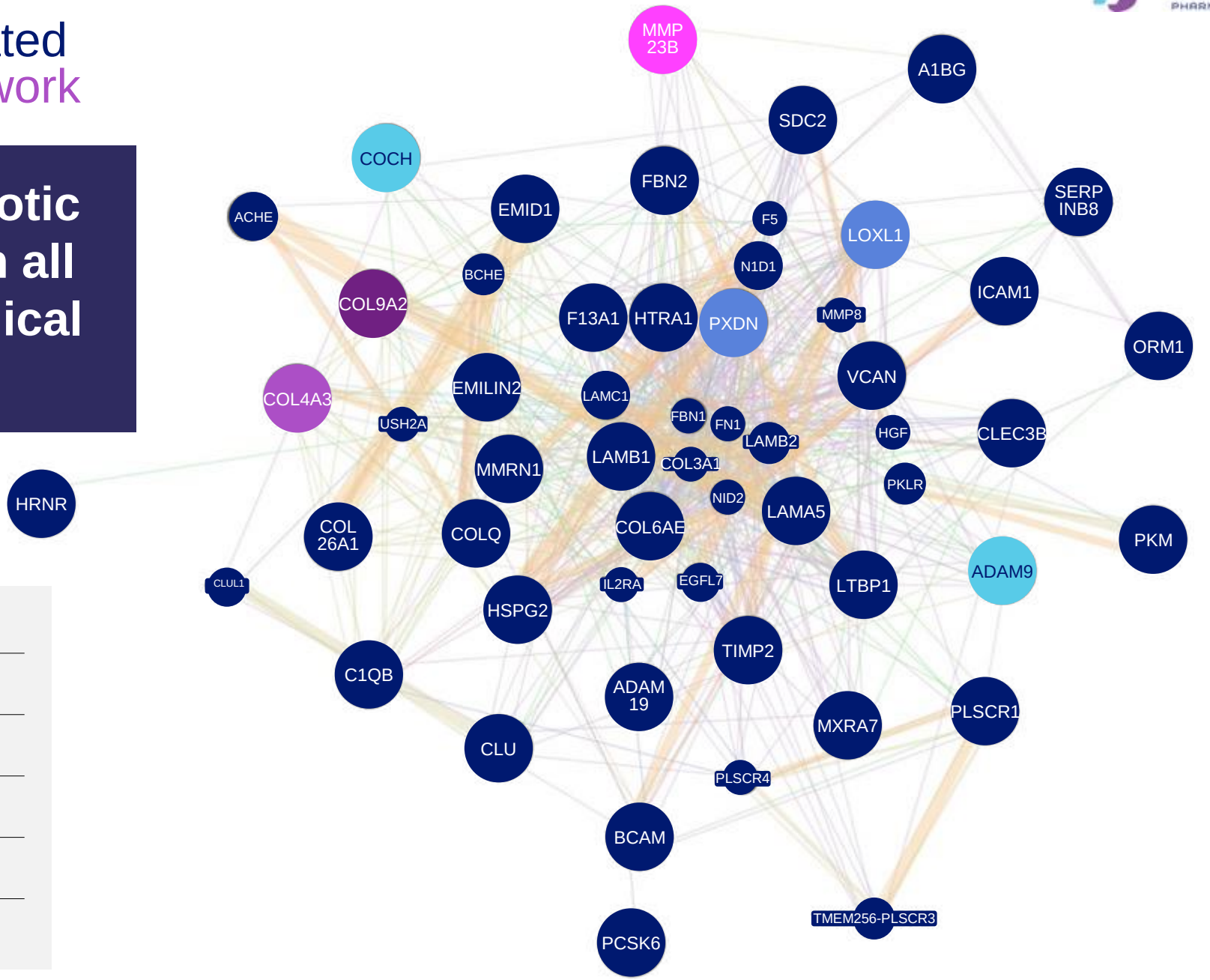
- Assessed patient demographics and baseline labs
- AST/ALT, C6M, TIMPs, MMP Responders
- CRV431 concentration > 800 ng/mL



The AI is training to decrease heterogeneity and predict *a priori* who will respond to CRV431

Clinical Collagen-Related Gene Regulatory Network

Consistent antifibrotic effects observed in all preclinical and clinical models



- collagen-containing extracellular matrix
- collagen binding
- collagen type IV trimer
- collagen type IX trimer
- collagen fibril organization
- collagen catabolic process

Conclusions
Phase 2a Study

Phase 2a study provided safety and exposure data in NASH subjects

Phase 2a study demonstrated signals of efficacy (reduced inflammation and fibrosis) within 4 weeks

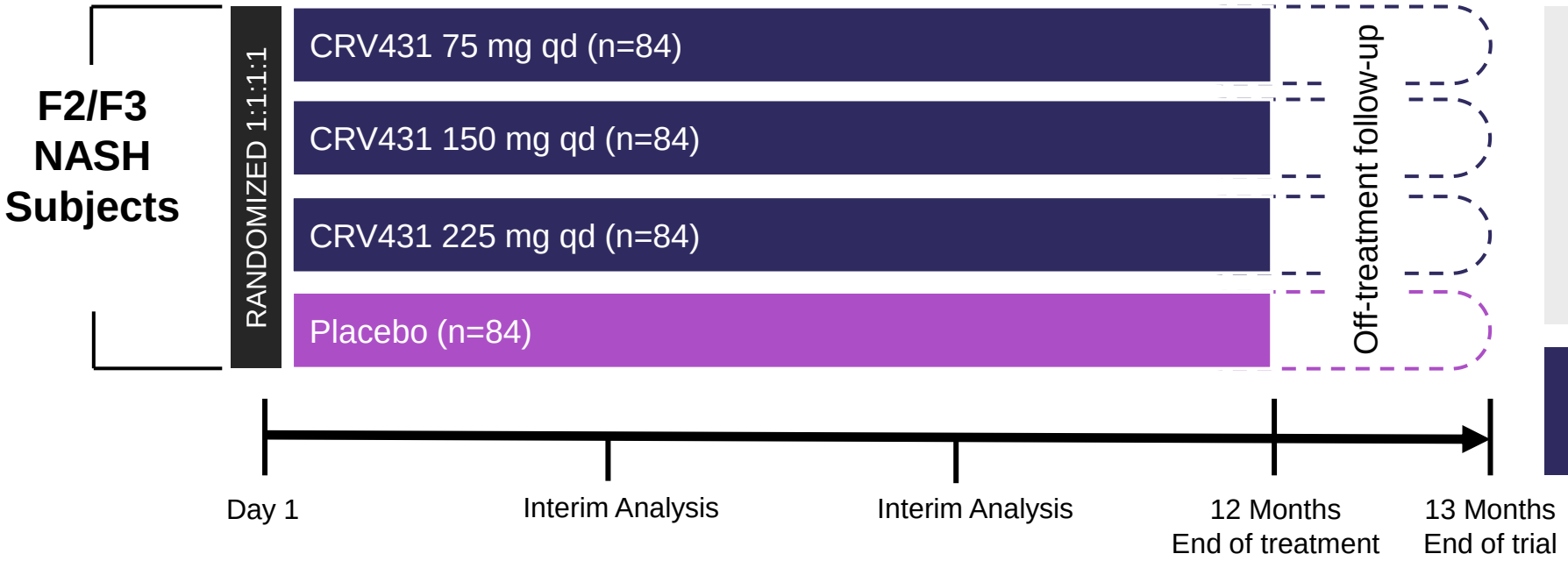
Phase 2a study provided *post-hoc* responder analysis data to further train AI-POWR™ for *a priori* responder analysis

Data from the Phase 2a was utilized to add a 150 mg dose cohort for the Phase 2b protocol and to adjust inclusion criteria (Pro-C3 > 14 ng/mL)

PHASE 2B ‘ASCEND-NASH’ TRIAL

Phase 2b ‘ASCEND-NASH’

Primary Objective: Evaluate the efficacy and safety of once-daily 75mg, 150 mg, and 225 mg doses of CRV431 compared to placebo in subjects with biopsy proven NASH and stage 2 liver fibrosis (F2) / stage 3 liver fibrosis (F3)



AI-POWR™
identification of biomarkers of CRV431 response

Data to inform phase 3 trial patient selection and biomarkers for analysis.

Phase 2b Endpoints

Primary Efficacy Endpoint:

Superiority of CRV431 (75mg, 150 mg, 225 mg) compared to placebo on liver histology at month 12 relative to the screening biopsy, by assessing the proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) OR NASH resolution without worsening of fibrosis

Secondary Efficacy Endpoints:

Superiority of CRV431 (75mg, 150 mg, 225 mg) compared to placebo on histology at month 12 relative to screening by assessing:

- Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on NASH
- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on NASH
- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of NASH, by at least 1 stage regardless of the effect on NASH

2021 ANTICIPATED EVENTS

CRV431

- ☑ Complete Ongoing Phase 2a NASH program by Q1-Q2, 2021
- ☑ Complete long-term animal toxicology (Q2, 2021)
- ➡ Continue to optimize and scale-up chemistry and manufacturing
- ☑ Complete additional clinical Drug-Drug Interaction study (Q2, 2021)
- ✎ NASH Phase 2b preparation (H2, 2021)

AI-POWR™

- ➡ Continue to refine and extend AI-POWR™ for NASH and possible other indications
- ➡ Continue to develop IP for additional indications and business development strategies

Summary

- CRV431, once-daily oral, multi-modal
- Cyclophilin inhibition allows for several benefits, including anti-fibrotic, anti-inflammatory, cytoprotective
- Phase 2a NASH trial completed with success
  - Safe, well-tolerated, PK defined
  - Efficacy signals in only 4 weeks
  - Phase 2b activities initiated
- Hepion's Proprietary Artificial Intelligence Platform (AI-POWR™)
- Core scientific team with >100 years collective cyclophilin expertise
- Core scientific team discovered and developed voclosporin (currently marketed)
- Robust IP

Two Value Drivers

HEPION PHARMACEUTICALS CRV431

A Therapy for NASH with indications for several other conditions

HEPION PHARMACEUTICALS AI-POWR™

AI-Driven, Bioinformatic Platform

Financials

$98.7 M
Cash
as of 9/30/21

76.2 M
Common Shares Outstanding

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