HEPION PHARMACEUTICALS

NASH-TAG 2021

Park City, Utah

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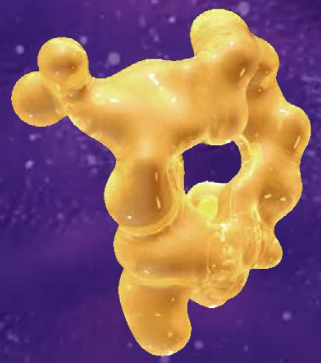
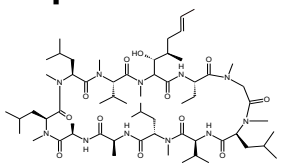
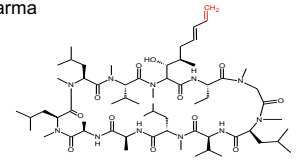
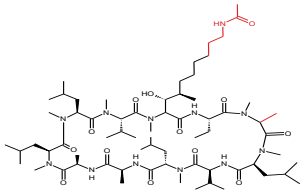
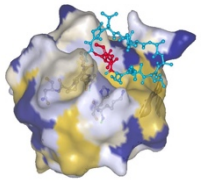
Robert Foster, PharmD, PhD, CEO



smart drug
smart technology
smart development

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 produces 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 around 10 of 17 cyclophilin isoforms in the human body

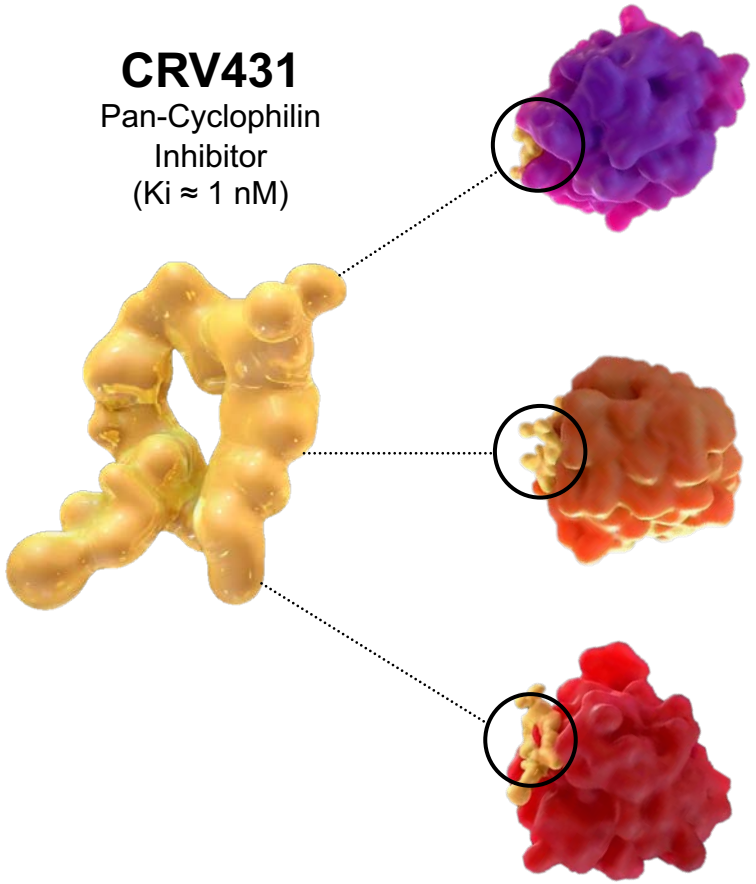
Why Target Cyclophilins?

Cyclophilins shown to play deleterious roles in:

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

MULTIPLE THERAPEUTIC ACTIONS
THROUGH CYCLOPHILIN INHIBITION

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

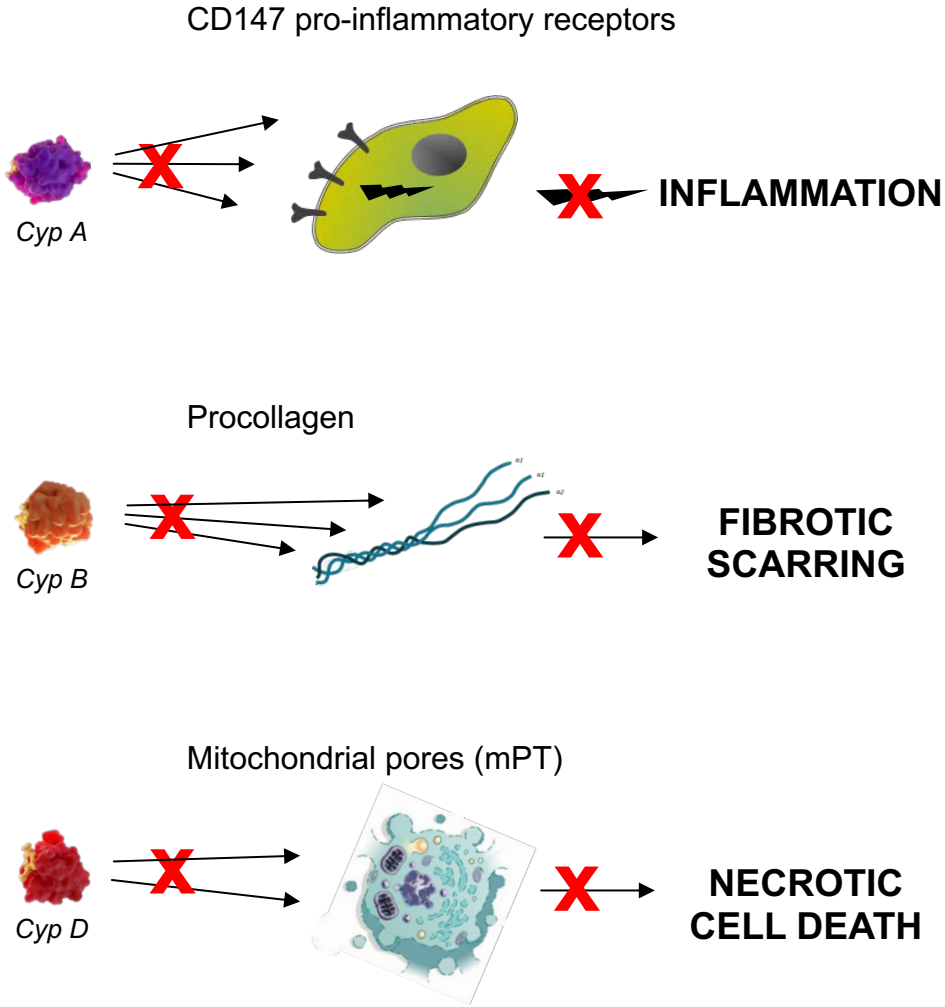
Cyclophilin B
(endoplasmic reticulum)

Promotes fibrotic scarring by controlling collagen production

Cyclophilin D
(mitochondria)

Regulates mitochondrial metabolism

Promotes mitochondrial pore opening leading to mitochondrial and necrotic cell death



ANTIFIBROTIC AND OTHER PRECLINICAL ACTIVITIES

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

NASH
CLINICAL PROGRAM

- ☑ **Phase 1** completed
- ➡ **Phase 2a** ongoing – completion Q2 2021
- ➡ **Phase 2b** in planning – starting Q3 2021

PHASE 1
HEALTHY SUBJECTS - SAFETY, TOLERABILITY AND PK

Single Ascending Dose (SAD)

- ✓ N = 32 (24 CRV431; 8 Placebo)
- ✓ Doses: 75 mg, 225 mg, 375mg, 525 mg (single doses)
- ✓ Drug Exposure is in the range in which efficacy was demonstrated in pre-clinical models
- ✓ Pharmacokinetics are first order and support once daily dosing
- ✓ No SAE's, Mild AE's, No dose response in AE's or changes in clinical labs
- ✓ No changes in vital signs or ECG

Multiple Ascending Dose (MAD)

- ✓ N = 25 (All CRV431)
- ✓ Doses: 75 mg, 150 mg, 225 mg, 300 mg, 375 mg QD x 28 Days
- ✓ Drug Exposure starting at 75 mg QD is in the range in which efficacy was demonstrated in pre-clinical models
- ✓ Pharmacokinetics are first order and support once daily dosing
- ✓ No SAE's, Mild AE's, No dose response in AE's or changes in clinical labs
- ✓ No changes in vital signs or ECG
- ✓ Data supported initiation of Phase 2a NASH Trial

Drug-Drug Interaction (DDI)

- ✓ N= 18
- ✓ Single CRV431 Drug Interaction Study with tenofovir

PHASE 2A
NASH SUBJECTS - SAFETY, TOLERABILITY AND PK

OBJECTIVES

- Safety and tolerability of once daily (qd) 75 mg and 225 mg doses of CRV431 in presumed NASH fibrosis stage 2 (F2)/fibrosis stage 3 (F3) patients compared to placebo control for 28 days
- Exploratory biomarkers of fibrosis and lipid metabolism: collagens, matrix metalloproteinases, lipidomics, and genomics
- Multi-omic/trait data analysis by AI-POWR™

STUDY DESIGN

- Multi-center (10 Sites), single-blind, placebo-controlled study
- Univariate Endpoints: AST, Pro-C3, ELF Score, Fibroscan

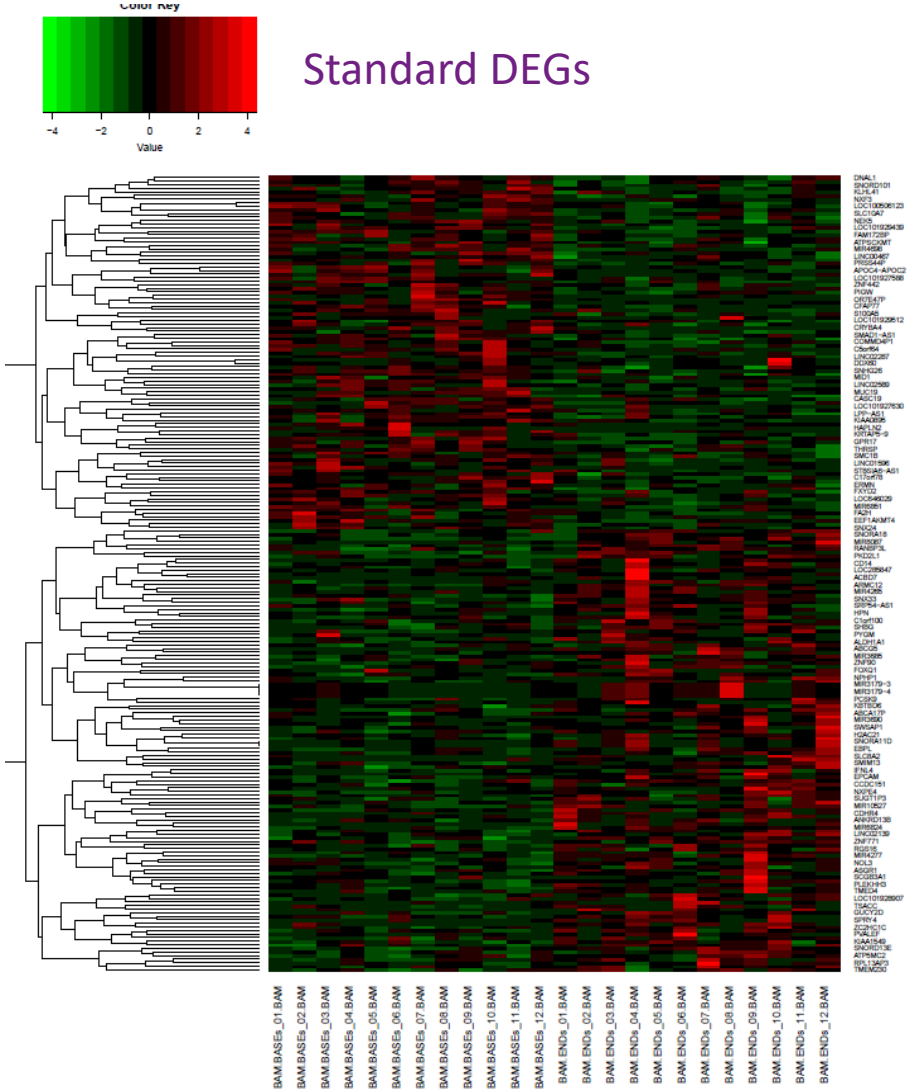
F2/F3 NASH Patients (n=36)

Cohort*	Fibrosis Stage	N	Day 1 – 28, faster oral dosing	Day 29 – 42
A	F2/F3	12	CRV431 75 mg	
B		6	Placebo	Observation/Follow-up
C	F2/F3	12	CRV431 225 mg	
D		6	Placebo	

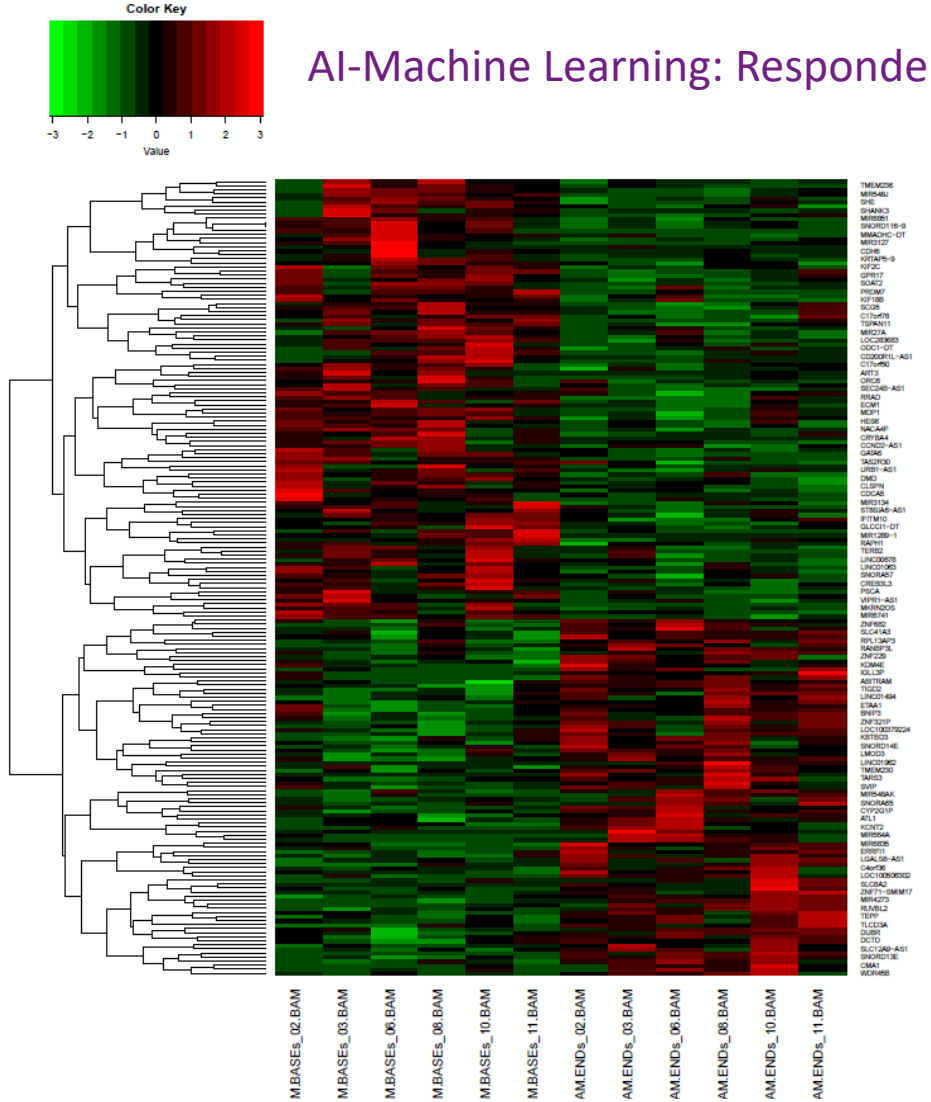
*randomized assignment; 2:1 – CRV431:placebo

Multivariate multi-omics-trait AI-POWR™ analysis to elucidate CRV431 activity biomarkers in F2/F3 NASH for Phase 2b Patient/Biomarker Selection

PHASE 2A
BIOINFORMATICS & AI

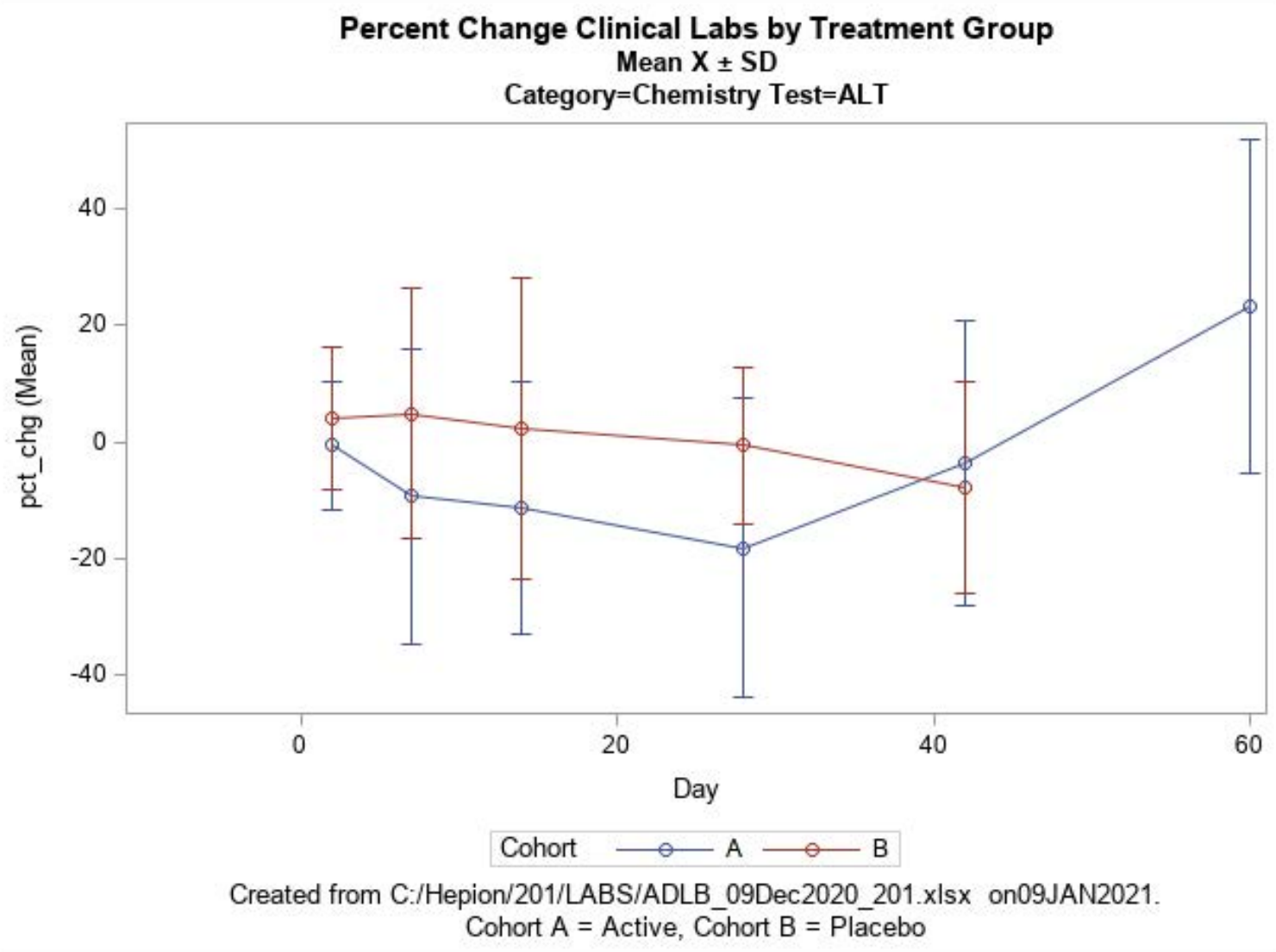


Standard DEGs

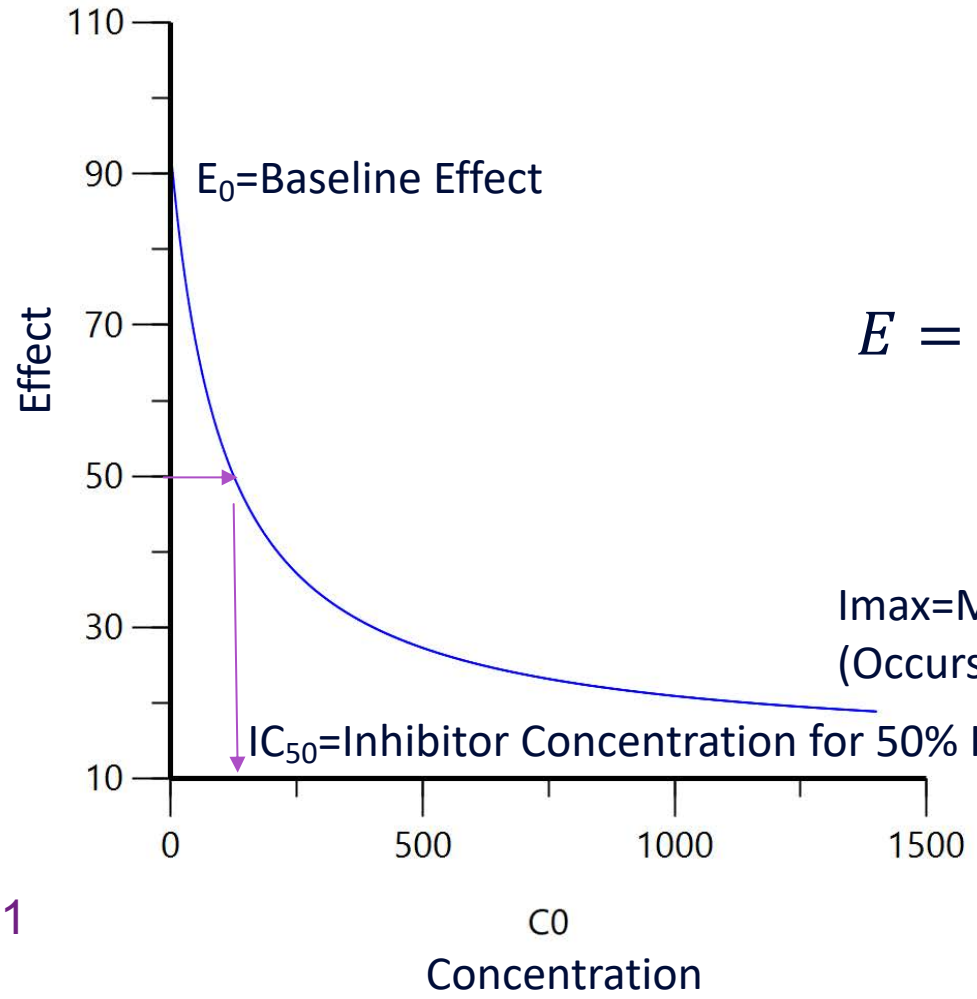


AI-Machine Learning: Responder Analysis

PHASE 2A
CRV431 75 MG QD PO, ALT %CHANGE FROM BASELINE



PD NOMENCLATURE
DIRECT INHIBITORY IMAX MODEL WITH BASELINE EFFECT

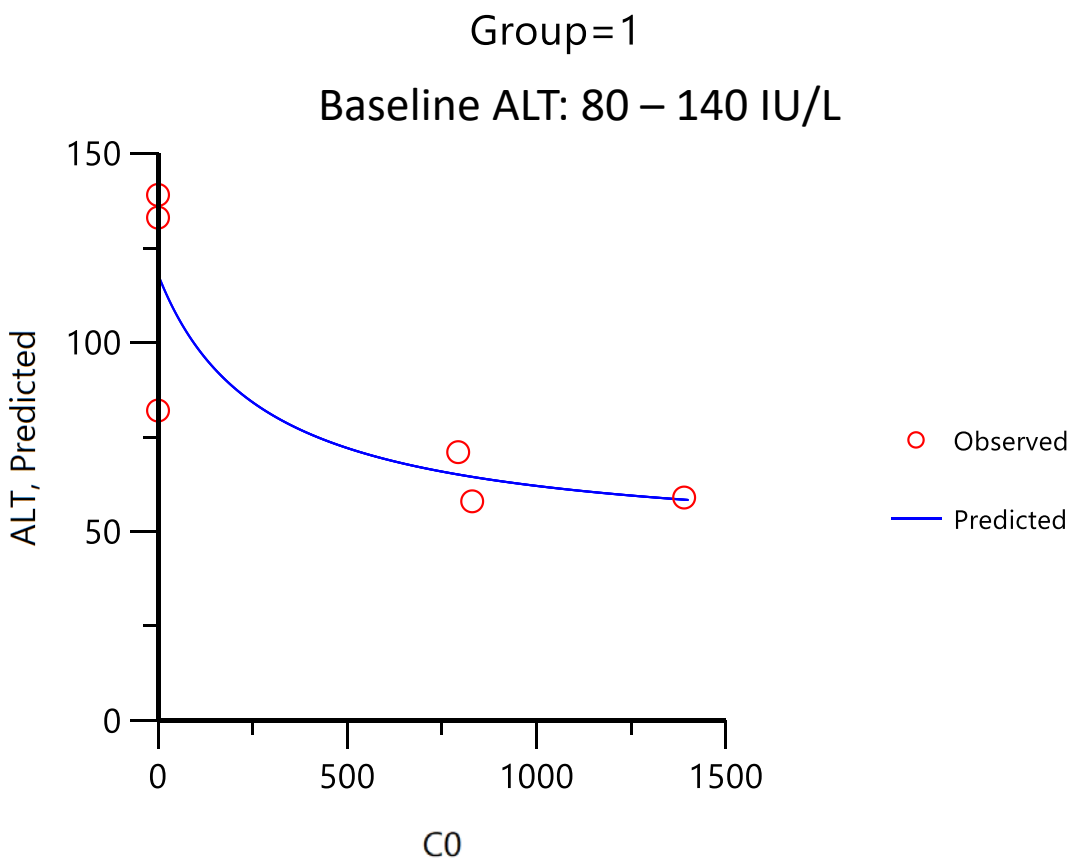


$$E = E_0 - {(Imax * C)}/{(C + IC50)}$$

Imax=Maximum Inhibitory Effect
(Occurs asymptotically x -> ∞)

Baseline: Day 1
Effect: Day 28

PHASE 2A
EARLY PK-PD RESULTS



Group 1: ALT E_0 118.0 -> Imax 71.5 = 60.6% Reduction
IC50 = 278.6 ng/mL at Time 0 (Trough)

Group	PD	Mean	SD	r
1	Imax	71.5	102.3	
1	IC50	278.6	**1752.4***	
1	E0	118.0	15.1	0.9

*Note: High Variability

- Early signs of a concentration-effect relationship after lowest dose of CRV431 and only 28 days treatment
- IC50 is achieved even by 75 mg QD, but variability is high and requires HIGHER concentrations to confirm
- Data are pending with a 225 mg QD cohort

PHASE 2B
NASH SUBJECTS - EFFICACY

OBJECTIVES

- Efficacy of once daily (qd) 75 mg and 225 mg doses of CRV431 in biopsy proven NASH F2 and F3 patients compared to placebo over 6 months of dosing
- 1-point reduction in fibrosis score in liver biopsies (pathologist and AI read)
- AI-POWR™ identification of biomarkers of CRV431 response from multi-omics, clinical labs, and other trait data

STUDY DESIGN

- Multi-Center (28 US Sites), triple-blind, placebo-controlled (2:1), study
- Liver biopsies, MRE scans, Fibroscan, ALT, AST, Pro-C3, ELF-Score, fibrosis biomarkers, lipidomics, genomics, proteomics

F2/F3 NASH Patients (n=300)

Cohort*	Fibrosis Stage	N	6 Months	3 Month
A	F2/F3	100	CRV431 75 mg	
B		50	Placebo	Observation/Follow-up
C	F2/F3	100	CRV431 225 mg	
D		50	Placebo	

*randomized assignment; 2:1 – CRV431:placebo

Multivariate multi-omics-trait AI-POWR™ analysis to update CRV431 activity biomarkers in F2/F3 NASH for Phase 3 Patient/Biomarker Selection

CONTACT US

Robert T. Foster, PharmD, Ph.D.
Chief Executive Officer

Hepion Pharmaceuticals Inc.
399 Thornall Street, First Floor
Edison, New Jersey, USA, 08837
Email: rfoster@hepionpharma.com

www.hepionpharma.com