HEPION PHARMACEUTICALS

From Benchtop to Bedside Clinical Development

4th Global NASH Congress

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Why Target Cyclophilins?

Cyclophilins shown to play negative 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

EXPERT OPINION ON INVESTIGATIONAL DRUGS https://doi.org/10.1080/13543784.2020.1703948

REVIEW

OPEN ACCESS Check for updates

Cyclophilin inhibition as a potential treatment for nonalcoholic steatohepatitis (NASH)

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Hepion Pharmaceuticals Inc, Edmonton, AB, Canada

ABSTRACT

Introduction: Cyclophilins are a family of diverse regulatory enzymes that have been studied for over 30 years; they participate in many pathophysiological processes. Genetic deletion or pharmacologic inhibition of cyclophilins has shown therapeutic effects in a wide spectrum of disease models, including liver disorders, and hence may be beneficial in treating nonalcoholic steatohepatitis (NASH).

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Taylor & Francis

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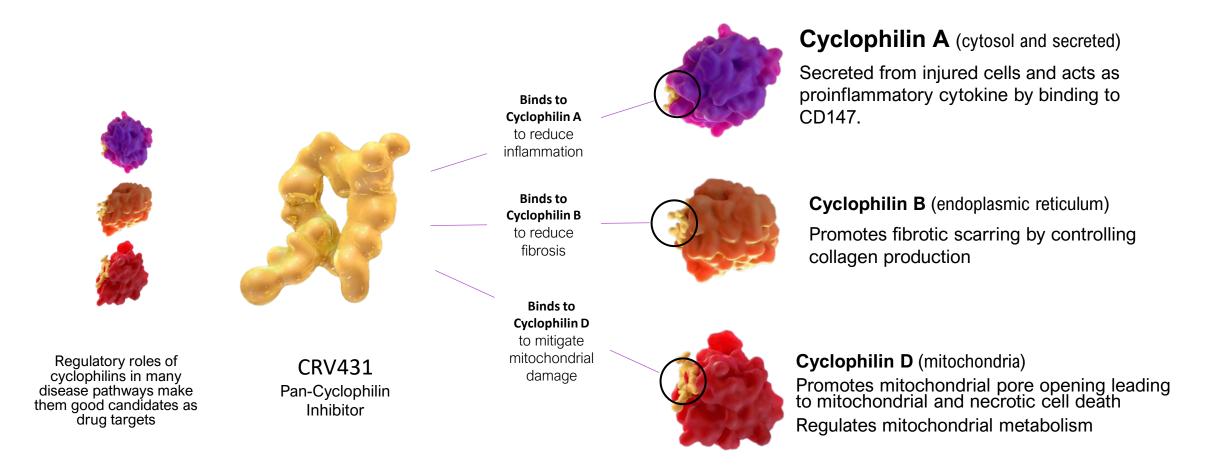
KEYWORDS

The Genesis of CRV431: From Calcineurin to Cyclophilin

Theory	Prediction and Expe	erimentation	Findings	
Modifying Cyclosporine A can greatly increase its immunosuppressive benefits	Modifications of Cyclosporine A can immunosuppression. Our team's pas chemically modified to enhanc	Inhibition of each cyclophilir isoform produces distinc therapeutic effects		
Cyclosporine A \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow	Voclosporin Aurinia Pharma $\downarrow \downarrow $	CRV431 \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow	CRV431 binds potently (Ki≈1 nM) to around 10 of 17 cyclophilin isoforms in the human body	
Nearly 40 years of clinical use as immunosuppressive drug for organ transplantation and autoimmune diseases.	Modifications increase affinity for calcineurin and increase immunosuppression potency	Modifications increase affinity for <u>cyclophilins</u> (13-fold) and eliminate immunosuppression		

CRV431 Multiple Benefits Through Cyclophilin Antagonism

Cyclophilin enzymes regulate the structure and activity of many proteins throughout the body



Preclinical Antifibrotic Efficacy

FIBROSIS – a response to chronic injury – is a major cause of organ dysfunction and its reduction is the primary goal in the treatment of NASH

Human Cell Cultures		CRV431 Effects
Hepatic stellate cells, fibroblasts (multiple organs)	TGFβ or endogenous stimulation	 ▼ fibrotic gene expression ▼ procollagen and fibronectin secretion
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
IPF lung explants (1 donor)	Endogenous stimulation	 ▼ Inflatin factory/fibrotic protein secretion ▼ tissue fibrosis
Animal Models (8 indeper	ndent studies)	CRV431 Effects
Mice (liver fibrosis)	Western diet + carbon tetrachloride	82%▼ fibrosis; ▼ weight gain
Mice (liver fibrosis)	High fat diet + streptozotocin (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

 Decreases in inflammation and fibrosis consistently observed in pre-clinical models
 HEPION p. 5

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Phase 1: LEARN

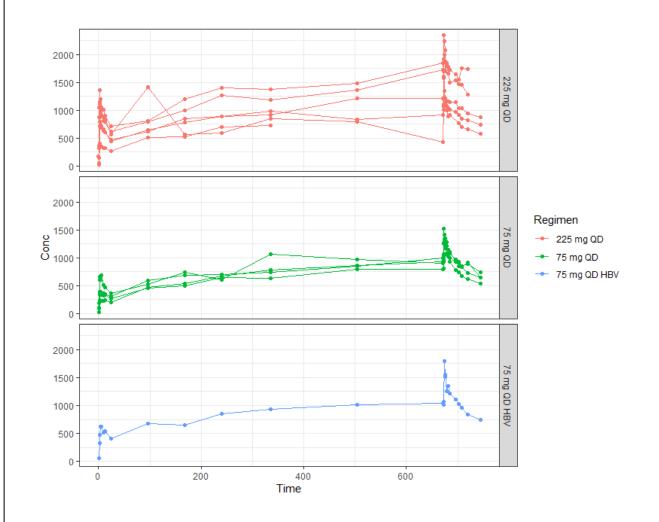
HEPA-CRV431-101:Multiple Ascending Dose Baseline Demographics

0000			75mg	150mg	225mg	300mg	375mg	Overall
<u>Å</u> ŪÅŬ	Sex	Female Male	6 (60%) 4 (40%)	1(25%) 3(75%)	1(17%) 5(83%)	2 (50%) 2 (50%)	5(56%) 4(44%)	15 (45%) 18 (55%)
	Age (y)	n	10	4	6	4	9	33
		Mean	35.6	34.8	42	50.3	48.6	42
		SD	11.3	6.45	11.4	6.8	12.3	11.9
		Minimum	20	27	28	41	22	20
		Median	36	35.5	41.5	51.5	49	41
		Maximum	54	41	55	57	61	61
			0	A	c		0	22
	Weight (kg)	n Maan	9 84.2	4 81.45	6 87.4	4 79.1	9 77.2	32 81.8
		Mean SD	84.2 17.6	81.45	87.4 12.5	24.2	11.3	81.8 14.7
		Minimum	63.1	71.9	76.9	58.7	51.7	51.7
		Median	80.7	81.7	81.6	75.5	79.9	80.6
		Maximum	113.9	90.5	107.3	106.6	89.6	113.9
	Height (cm)	n	9	4	6	4	9	32
		Mean	167.4	174.4	171.3	165.6	164.9	168.1
		SD	8.68	7.73	4.63	12.1	8.45	8.49
		Minimum	154	167	167	150	153	150
		Median	170.2	173	170.5	167.8	163	170.1
		Maximum	178	185	180	177	178	185
	BMI (kg/m²)							
	2 (8/ /	n	9	4	6	4	9	32
		Mean	29.9	26.8	29.7	28.3	28.3	28.8
		SD	4.8	2.1	3.4	5.2	3.4	3.9
		Minimum	25	23.9	27.6	22.2	20.7	20.7
		Median	28.9	27.4	28.1	28.4	28.3	^{28.3} ⊢
		Maximum	38.9	28.5	36.3	34.0	32.7	39.0

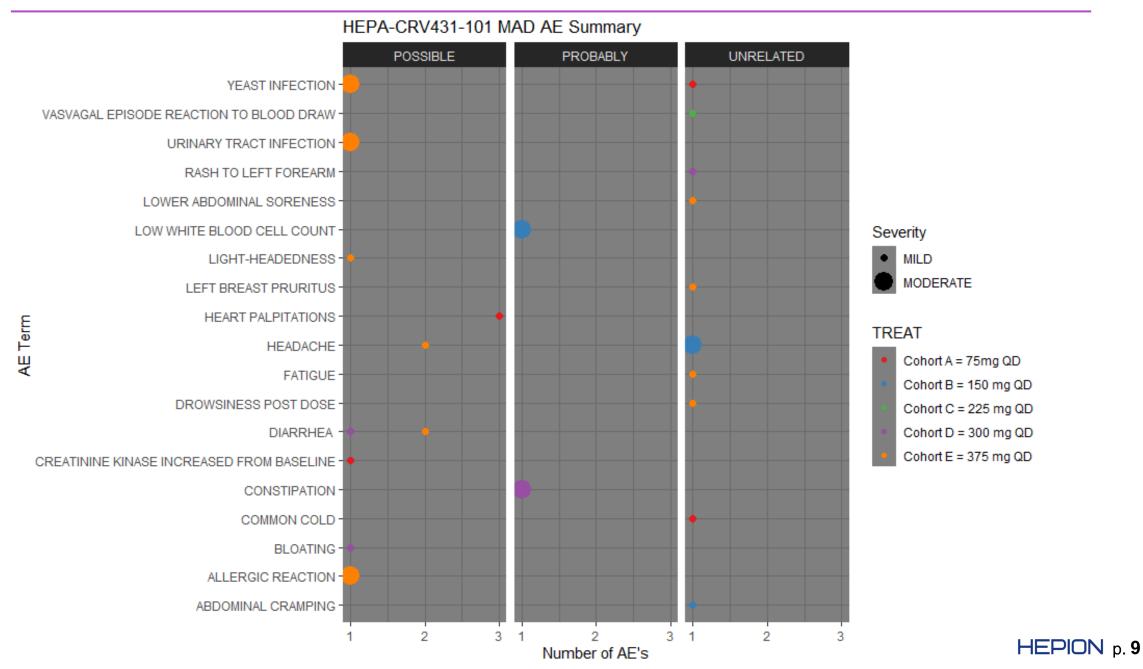
HEPA-CRV431-101: Multiple Ascending Dose PK Summary

Learn PK in Phase 1: Confirm in Phase 2: Model Based Drug Development

- Pharmacokinetics are first order best described by a 1-Compartment Model
- Exposures occur in the anticipated effective range from 75 mg to 225 mg QD
- Drug reaches peak concentration within 2 hours
- Long-Terminal Elimination Half-Life (t1/2Lz) = 90.9 ± 45.4 h, but this does not determine accumulation.
- Effective Half-Life = 30.2 ± 11.8 h determines accumulation and supports once daily dosing
- Accumulation Factor from Day 1 to Day 28: 2.4 ± 0.7
- Dose Proportionality: 1.0 ± 0.2 over effective dose range
- Bioavailability decreases with Doses > 300 mg QD
- Maximum exposure is achieved at 225 mg QD



HEPA-CRV431-101: Multiple Ascending Dose Safety: Adverse Events



PHASE 1 STUDIES – Safety, tolerability and pharmacokinetics (PK)

CRV431 Once Daily in Healthy Subjects

Single Ascending Dose (SAD)	Drug-Drug Interaction (DDI)	Multiple Ascending Dose (MAD)
✓ N = 32 (24 CRV431; 8	✓ N= 18	✓ N = 25 (All CRV431).
Placebo).	✓ Single CRV431 Drug Interaction	 Doses: 75 mg, 150 mg, 225
✓ Doses: 75 mg, 225 mg, 375mg,	Study with tenofovir	mg, 300 mg, 375 mg QD x 28
525 mg (single doses)	✓ No SAE's, mild AE's or changes	Days.
✓ Drug Exposure is in the range in	in clinical labs	 Drug Exposure starting at 75
which efficacy was	 No changes in vital signs of 	mg QD is in the range in which
demonstrated in pre-clinical	ECG.	efficacy was demonstrated in
models.	2001	pre-clinical models.
✓ Pharmacokinetics are first order		 Pharmacokinetics are first order
and support once daily dosing.		and support once daily dosing.
✓ No SAE's, Mild AE's, No dose		 No SAE's, Mild AE's, No dose
response in AE's or changes in		response in AE's or changes in
clinical labs.		clinical labs.

✓ No changes in vital signs or ECG.

- clinical labs.
- ✓ No changes in vital signs or ECG.
- ✓ Data supported initiation of Phase 2a NASH Trial

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HEPA-CRV431-201: Phase 2a - F2/F3 NASH LEARN & CONFIRM

HEPA-CRV431-201: Phase 2a Study in F2/F3 NASH Patients

- **OBJECTIVES** Evaluate the safety and tolerability of once daily (qd) 75 mg and 225 mg dose of CRV431 in presumed nonalcoholic steatohepatitis (NASH) fibrosis stage 2 (F2)/fibrosis stage 3 (F3) patients compared to placebo control over 28 days of dosing
 - Confirm PK in NASH patients
 - Explore antifibrotic activity of CRV431
 - Produce exploratory antifibrotic biomarker data: collagen biomarkers, matrix metalloproteinases, lipidomics, and genomics: Multi-Omic/Trait Data for use in AI-POWR™ Algorithm
- **STUDY DESIGN** Multi-center (10 Sites), single-blind, placebo-controlled study
 - Univariate Endpoints: AST ≥ 20 IU/L, Pro-C3 ≥ 15.5 ng/mL OR ELF Score ≥ 9.8 Score Fibroscan ≥ 8.5 kPa

	Cohort*	Fibrosis Stage	Ν	Day 1 – 28, fasted oral dosing	Day 29 - 42	
in	А	F0/F0	12	CRV431 75 mg	Observation/Follow-up	NAultiveriete multi encies trait Al
	В	F2/F3	6	Placebo	COMPLETE	Multivariate multi-omics-trait Al- POWR™ analysis to elucidate
F2/F3 NASH Patients (n=36)	С	F2/F3	12	CRV431 225 mg	LAST PATIENT Randomized 4/27	CRV431 activity biomarkers in F2/F3 NASH for Phase 2b Patient/Biomarker Selection
	D		6	Placebo		

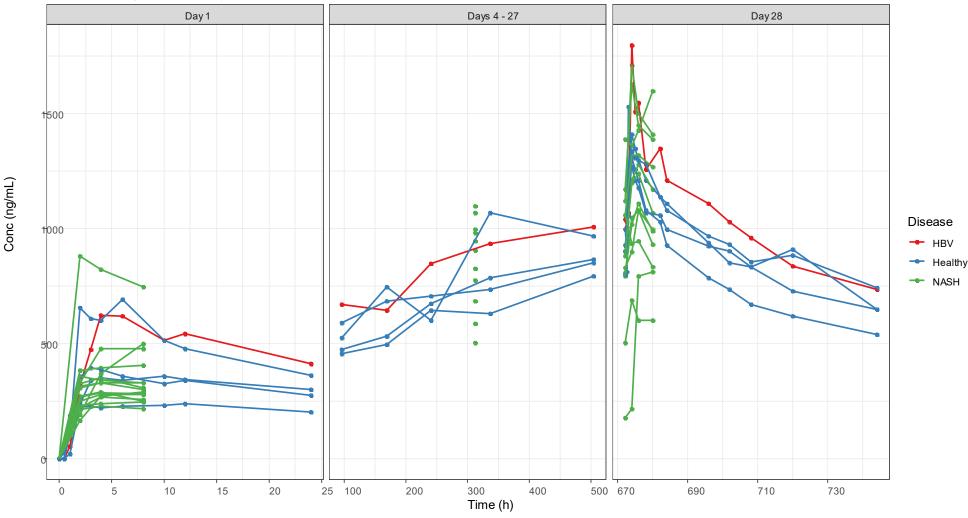
*randomized assignment; 2:1 – CRV431:placebo

HEPA-CRV431-201: Baseline Demographics 75 mg and Placebo Cohorts

	CRV431 75MG	CRV431 225MG	POOLED PLACEBO	TOTAL
	(N= 15)	(N=5)	(N=8)	(N=28)
AGE				
MEAN (SD)	59.1 (9.6)	62.2 (5.3)	63.0 (7.2)	60.8 (8.48)
MEDIAN	61	59	64.5	62
MIN, MAX	39, 72	56, 69	51, 72	39, 72
SEX				
MALE	7 (47%)	3 (60%)	5 (62%)	15 (54%)
FEMALE	8 (53%)	2 (40%)	3 (38%)	13 (46%)
HEIGHT AT SCREENING (CM)				
MEAN (SD)	168.4 (8.6)	172.0 (11.5)	169.3 (9.3)	169.3 (9.5)
MEDIAN	170	175	170	171
MIN, MAX	150, 185	154, 188	155, 180	150, 188
WEIGHT AT SCREENING (KG)				
MEAN (SD)	104.5 (21.9)	112.4 (25.5)	101.9 (21.8)	105.1 (22.8)
MEDIAN	97.1	122.1	100.3	97.5
MIN, MAX	77, 152	64, 135	73, 137	64, 152
BMI AT SCREENING (KG/M ²)				
MEAN (SD)	37.1 (8.2)	37.6 (7.0)	35.4 (6.3)	36.7 (7.5)
MEDIAN	34.4	36.9	35.6	36.7
MIN, MAX	25, 53	27, 49	27, 46	25, 53

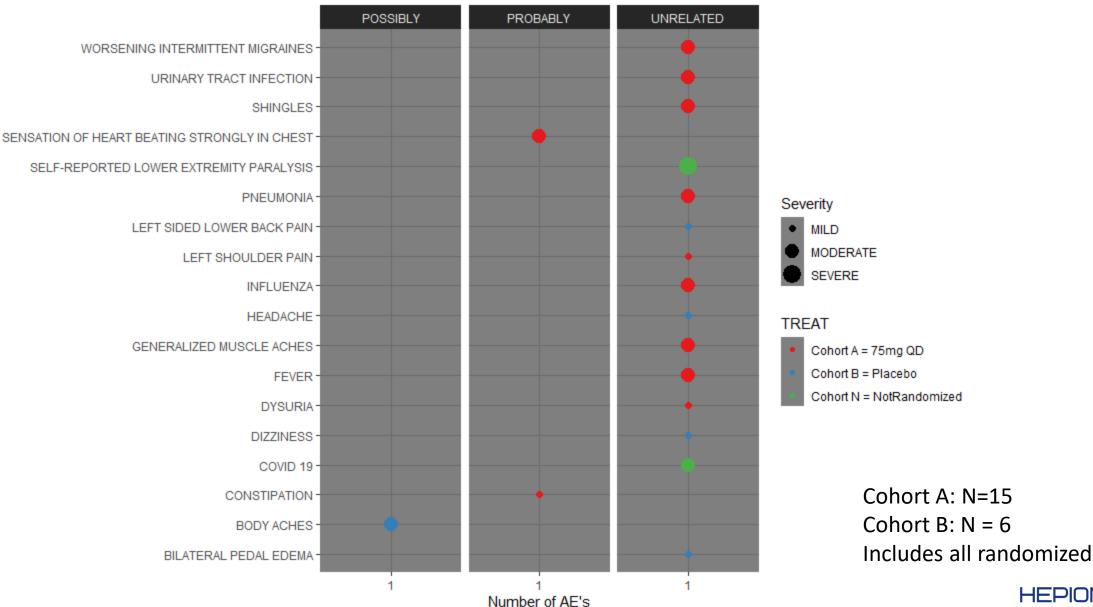
CRV431 75 mg QD in Healthy, HBV and F2/F3 NASH Patients

CRV431 75 mg QD in Healthy, HBV, and NASH



- Exposures in NASH patients are similar to healthy subjects and HBV patients
- No disease-related alterations in PK in this 75mg Cohort

HEPA-CRV431-201: Phase 2a in F2/F3 NASH Patients – AE Summary



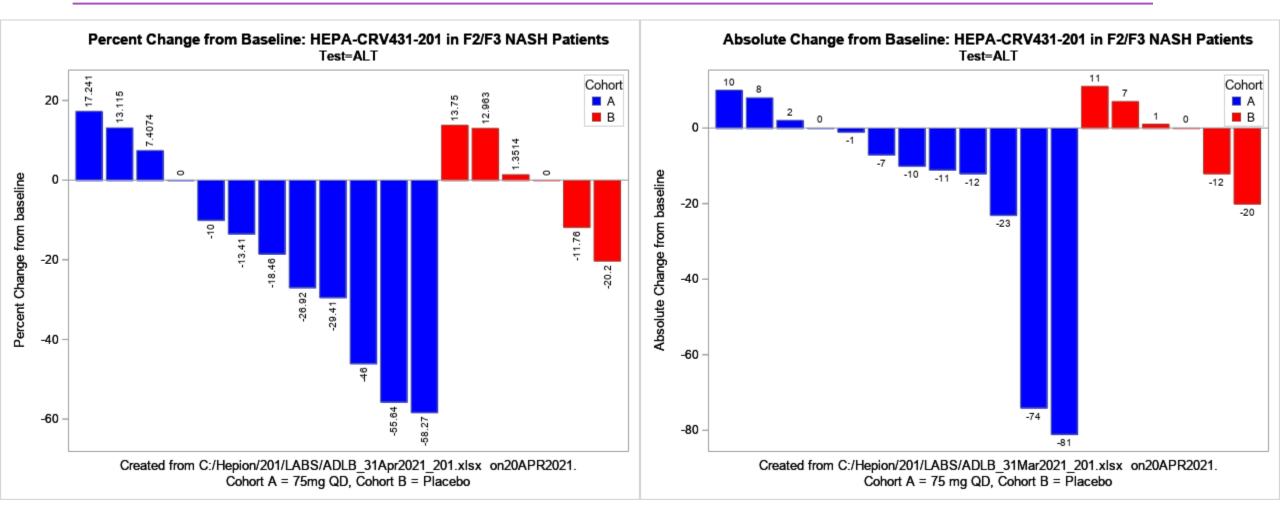
HEPA-CRV431-201 in F2/F3 NASH AE Summary

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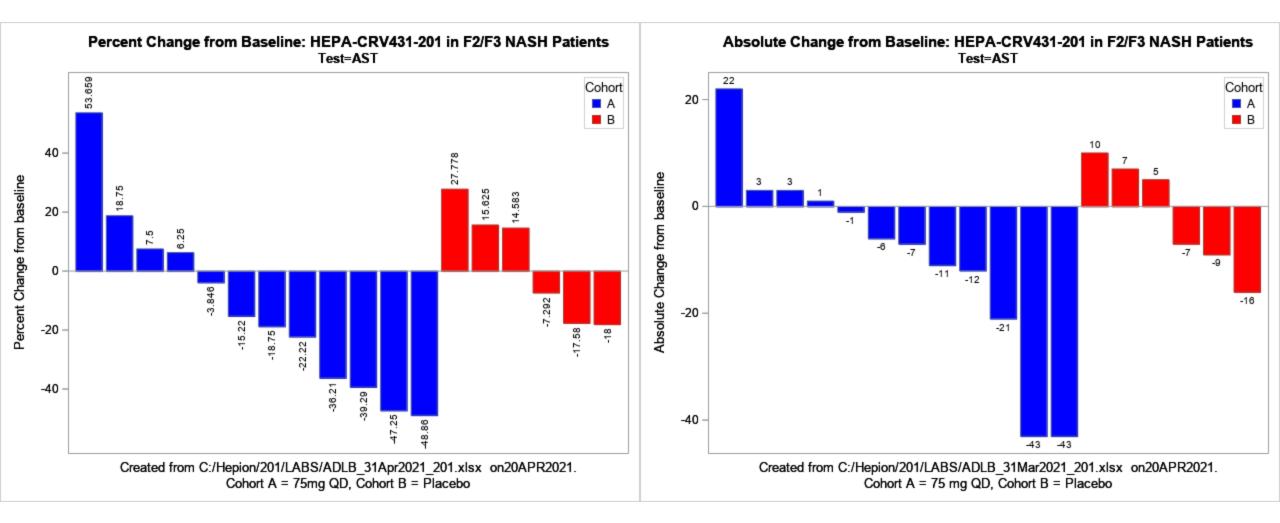
Exploratory Efficacy: Transaminases

Cohort A = 75 mg QD x 28 Days Cohort B = Placebo QD x 28 Days

Exploratory Efficacy 75 mg Cohort: Alanine Transaminase at Day 28



Exploratory Efficacy 75 mg Cohort: Aspartate Transaminase at Day 28

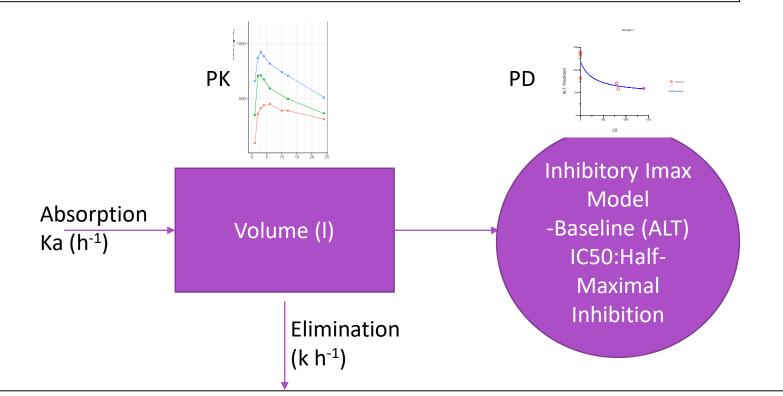


Population Pharmacokinetics: PK-PD from Sparse Sampling Learn and Confirm Paradigm: Taking what is Learned in Phase 1 & Confirm in Phase 2 Simulate Trial for Phase 2b & 3

Population PKPD Model

Use entire data set
Predict PD outcomes
Use for trial simulation

- Nonlinear Mixed Effects Model
- 1-Compartment: First Order absorption and Elimination
- Clinical Effect: Inhibitory Imax Model -> Predict Serum ALT



- Assess patient characteristics (COVARIATES) that help refine prediction of both PK and PD.
- Final Covariate Model: 个Cholesterol ~ ↓Absorption 个Baseline AST ~ 个Effect

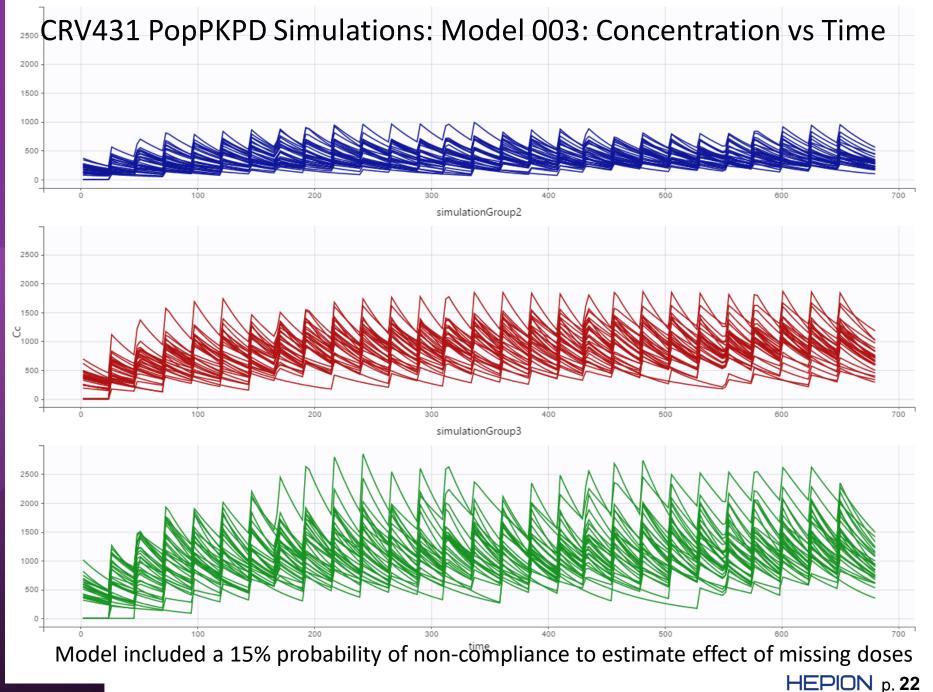
↑Lean Body Weight ~ ↓ IC50

simulationGroup1

Trial Simulation PK 75 mg QD ->

150 mg QD ->

225 mg QD ->

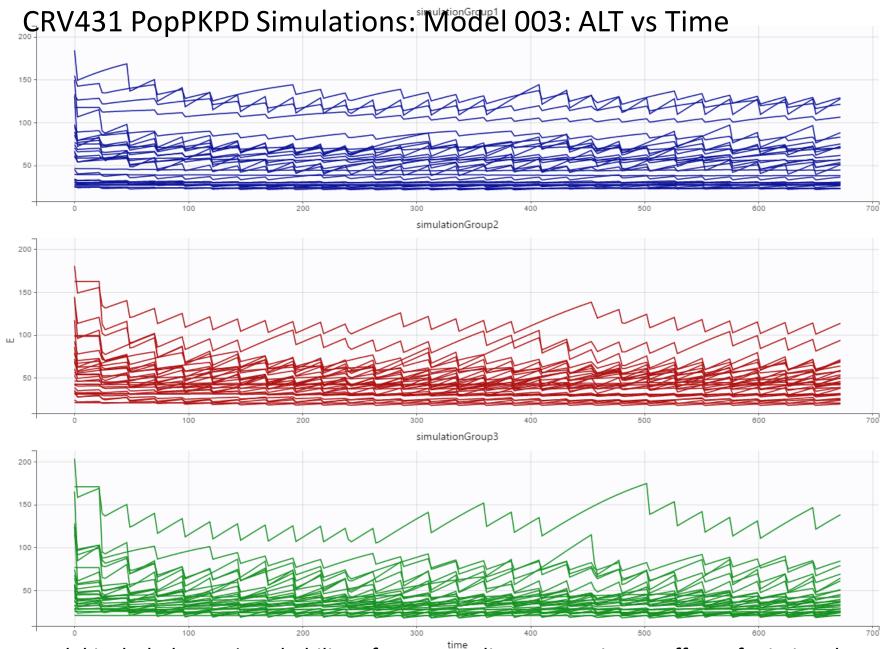


Trial Simulation PD

75 mg QD ->

150 mg QD ->

225 mg QD ->

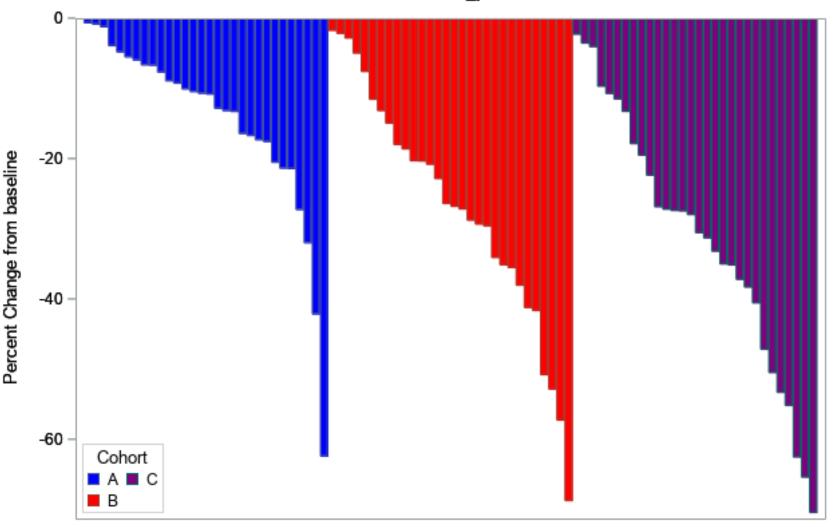


Model included a 15% probability of non-compliance to estimate effect of missing doses HEPION p. 23

Trial Simulation %Change Day 28

Cohort	N	Mean	Std Dev	Min	Мах
75mg Observed	12	-18.0	25.8	-58.3	17.2
A=75mg	30	-14.6	13.0	-62.3	-0.6
B=150mg	30	-26.7	16.8	-68.7	-1.7
C=225mg	30	-31.2	18.5	-70.5	-2.2

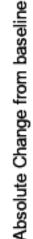
Trial Simulation CRV431 in F2/F3 NASH Patients:ALT %Change from Baseline Test=ALT_pred

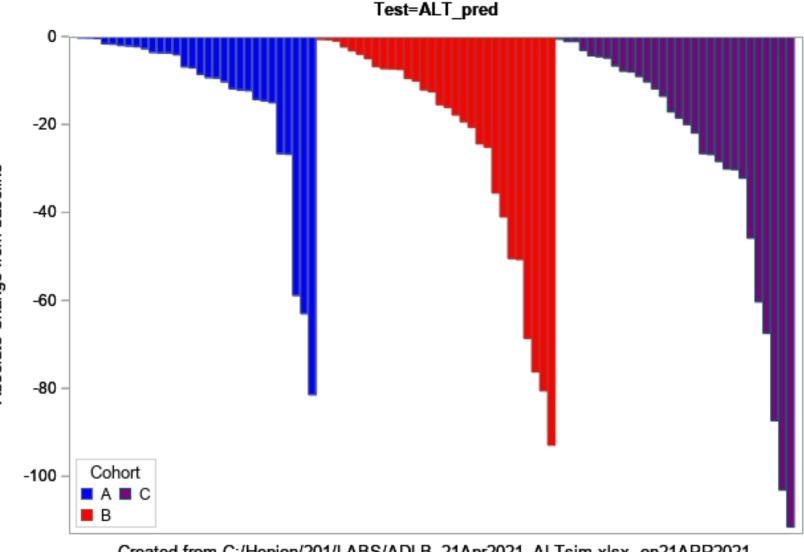


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Trial Simulation Absolute Change from Baseline Day 28

Cohort	Ν	Mean	Std Dev	Min	Мах
75 mg Observed	12	-16.5	29.9	-81.0	10.0
A=75mg	30	-13.8	19.7	-81.3	-0.2
B=150mg	30	-24.1	26.1	-92.7	-0.5
C=225mg	30	-27.1	30.1	-111.4	-0.5





Trial Simulation CRV431 in F2/F3 NASH Patients:ALT Absolute Change from Baseline

Created from C:/Hepion/201/LABS/ADLB_21Apr2021_ALTsim.xlsx on21APR2021. Cohort A = 75mg QD, Cohort B = 150 mg QD, Cohort C = 225 mg QD

Bioinformatics

Exploratory Analysis

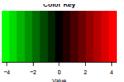
Gene Ontology using GeneWalk

DESeq2, rrvgo

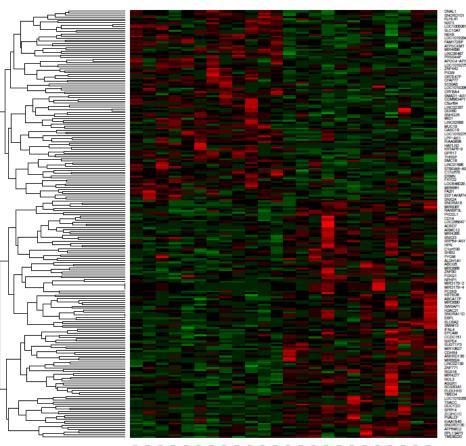


Phase2a: Bioinformatics & AI

Standard Differentially Expressed Genes - DESEq2(Median Ratios): Day 1 v Day 28



- **RNA Seq Blood** ٠
- 12/12 Active Subjects



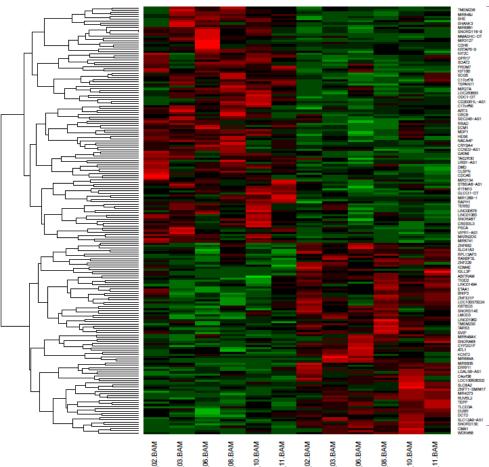
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AI-Machine Learning: Responder Analysis (AI-POWR[™])

- Assessed patient demographics
- **ALL Baseline labs**
- **Drug Concentration**
- 6/12 Subjects

Color Key

-2 -1 0 1 2 3



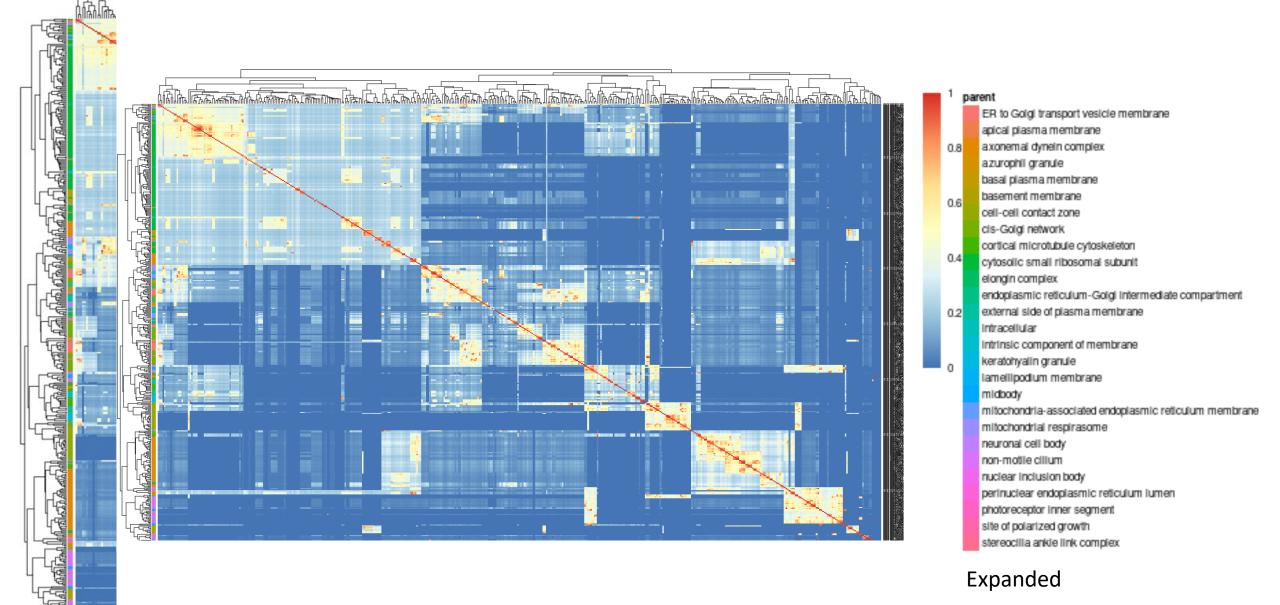
RASEs .

Potential Genomic Biomarker Responder Panel

What is CRV431's Molecular Function: Parent Hierarchy with Box Sizes Proportional to Score

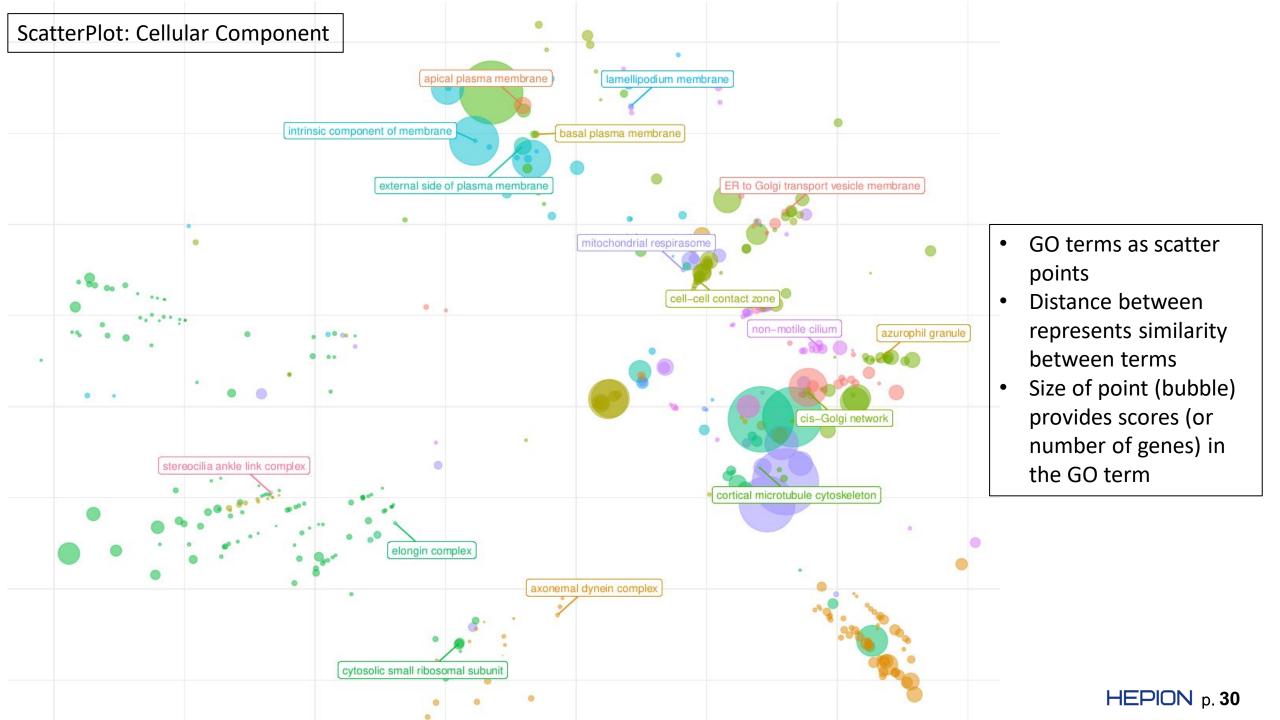
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Cellular Component Heat Map



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Expanded



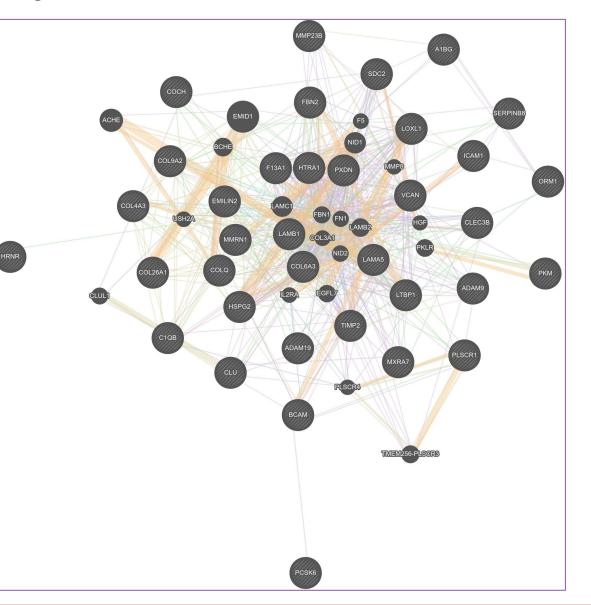
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hgnc_symbol	go_name	go_id	go_domain
A1BG	collagen-containing extracellular matrix	GO:0062023	cellular component
ADAM19	collagen-containing extracellular matrix	GO:0062023	cellular component
ADAM9	collagen binding	GO:0005518	molecular function
BCAM	collagen-containing extracellular matrix	GO:0062023	cellular component
C1QB	collagen-containing extracellular matrix	GO:0062023	cellular component
CLEC3B	collagen-containing extracellular matrix	GO:0062023	cellular component
CLU	collagen-containing extracellular matrix	GO:0062023	cellular component
СОСН	collagen binding	GO:0005518	molecular function
СОСН	collagen-containing extracellular matrix	GO:0062023	cellular component
COL26A1	collagen-containing extracellular matrix	GO:0062023	cellular component
COL4A3	collagen type IV trimer	GO:0005587	cellular component
COL4A3	collagen-containing extracellular matrix	GO:0062023	cellular component
COL6A3	collagen-containing extracellular matrix	GO:0062023	cellular component
COL9A2	collagen type IX trimer	GO:0005594	cellular component
COL9A2	collagen-containing extracellular matrix	GO:0062023	cellular component
COLQ	collagen-containing extracellular matrix	GO:0062023	cellular component
EMILIN2	collagen-containing extracellular matrix	GO:0062023	cellular component
F13A1	collagen-containing extracellular matrix	GO:0062023	cellular component
FBN2	collagen-containing extracellular matrix	GO:0062023	cellular component
HRNR	collagen-containing extracellular matrix	GO:0062023	cellular component
HSPG2	collagen-containing extracellular matrix	GO:0062023	cellular component
HTRA1	collagen-containing extracellular matrix	GO:0062023	cellular component
ICAM1	collagen-containing extracellular matrix	GO:0062023	cellular component
LAMA5	collagen-containing extracellular matrix	GO:0062023	cellular component
LAMB1	collagen-containing extracellular matrix	GO:0062023	cellular component
LOXL1	collagen fibril organization	GO:0030199	biological process
LOXL1	collagen-containing extracellular matrix	GO:0062023	cellular component
LTBP1	collagen-containing extracellular matrix	GO:0062023	cellular component
MMP23B	collagen catabolic process	GO:0030574	biological process
MMP23B	collagen-containing extracellular matrix	GO:0062023	cellular component
MMRN1	collagen-containing extracellular matrix	GO:0062023	cellular component
MXRA7	collagen-containing extracellular matrix	GO:0062023	cellular component
ORM1	collagen-containing extracellular matrix	GO:0062023	cellular component
PCSK6	collagen-containing extracellular matrix	GO:0062023	cellular component
PKM	collagen-containing extracellular matrix	GO:0062023	cellular component
PLSCR1	collagen-containing extracellular matrix	GO:0062023	cellular component
PXDN	collagen fibril organization	GO:0030199	biological process
PXDN	collagen-containing extracellular matrix	GO:0062023	cellular component
SDC2	collagen-containing extracellular matrix	GO:0062023	cellular component
SERPINB8	collagen-containing extracellular matrix	GO:0062023	cellular component
TIMP2	collagen-containing extracellular matrix	GO:0062023	cellular component
VCAN	collagen-containing extracellular matrix	GO:0062023	cellular component

Collagen-Related Gene Network

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Supports anti-fibrotic effects observed in all pre-clinical models

Reduction in transaminases at 28 days signals early efficacy in F2/F3 NASH subjects

CRV431 concentration predicts reductions in serum alanine transaminase

Trial Simulations suggest greater expected efficacy at 150 mg and 225 mg dose levels

Bioinformatics with AI-POWR[™] reveal significant interactions with collagen regulating genes

Confirmation of these effects will be fully evaluated using the 225 mg cohort and the final genomic, lipidomic, and biomarker data for a full simulation of the Phase 2b Trial.





CONTACT US

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