



HEPION
PHARMACEUTICALS

CRV431

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>



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REVIEW



OPEN ACCESS



Check for updates

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

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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).

ARTICLE HISTORY

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KEYWORDS

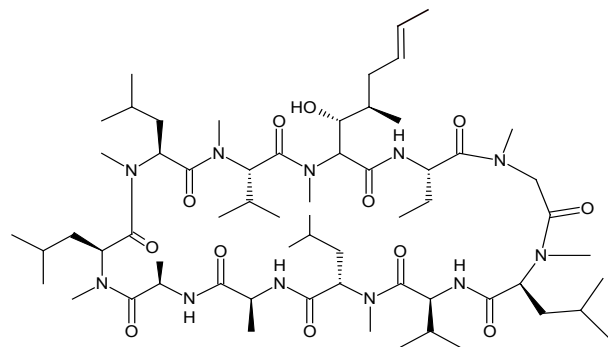
Cyclophilin; cyclosporine

The Genesis of CRV431: From Calcineurin to Cyclophilin

Theory

Modifying Cyclosporine A can greatly increase its immunosuppressive benefits

Cyclosporine A



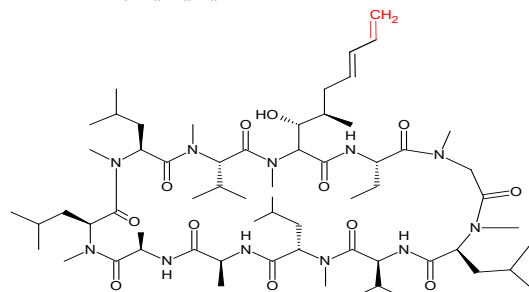
Nearly 40 years of clinical use as immunosuppressive drug for organ transplantation and autoimmune diseases.

Prediction and Experimentation

Modifications of Cyclosporine A can either eliminate or enhance immunosuppression. Our team's past discovery, voclosporin, was chemically modified to enhance immunosuppression

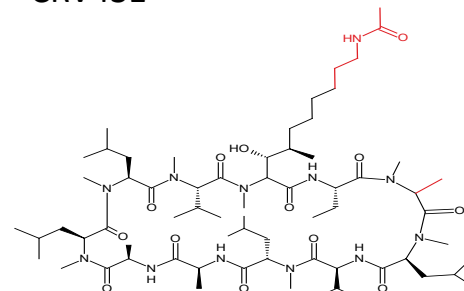
Voclosporin

Aurinia Pharma



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

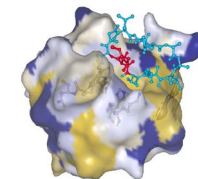
CRV431



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

Findings

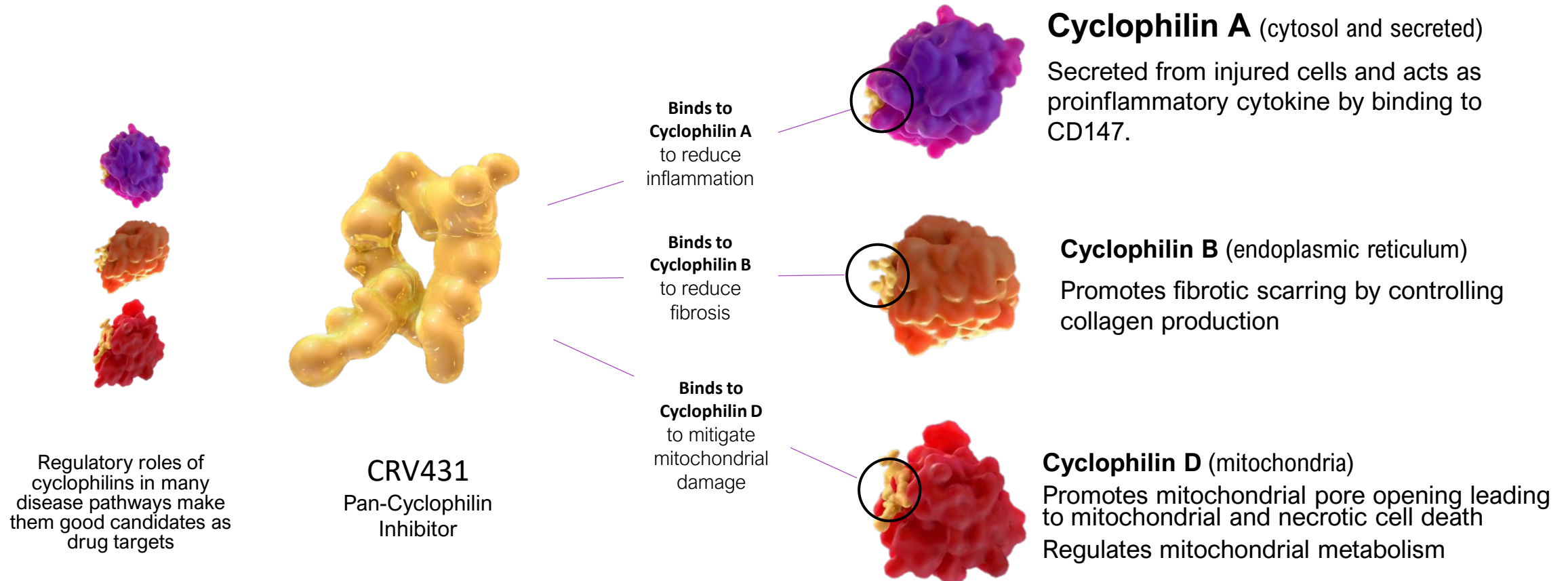
Inhibition of each cyclophilin isoform produces distinct therapeutic effects



CRV431 binds potently ($K_i \approx 1$ nM) to around 10 of 17 cyclophilin isoforms in the human body

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

Hepatic stellate cells, fibroblasts
(multiple organs)

TGFβ or endogenous stimulation

CRV431 Effects

▼ fibrotic gene expression
▼ procollagen and fibronectin secretion

Human Tissue Explants

Liver explants (4 donors)

(Precision Cut Slice Cultures)

TGFβ+PDGF-BB or endogenous stimulation

IPF lung explants (1 donor)

Endogenous stimulation

CRV431 Effects

▼ inflammatory/fibrotic gene expression
▼ inflammatory/fibrotic protein secretion
▼ tissue fibrosis

Animal Models (8 independent studies)

Mice (liver fibrosis)

Western diet + carbon tetrachloride

Mice (liver fibrosis)

High fat diet + streptozotocin (4 studies)

Mice (liver fibrosis)

Carbon tetrachloride

Mice (kidney fibrosis)

Unilateral ureter obstruction

Rats (liver fibrosis)

Thioacetamide

CRV431 Effects

82% ▼ fibrosis; ▼ weight gain
37-57% ▼ fibrosis; ▼ weight gain; 50% ▼ liver tumors
44% ▼ fibrosis
42% ▼ fibrosis
48% ▼ fibrosis; prevented cirrhosis

- Decreases in inflammation and fibrosis consistently observed in pre-clinical models



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Phase 1: LEARN

HEPA-CRV431-101: Multiple Ascending Dose Baseline Demographics

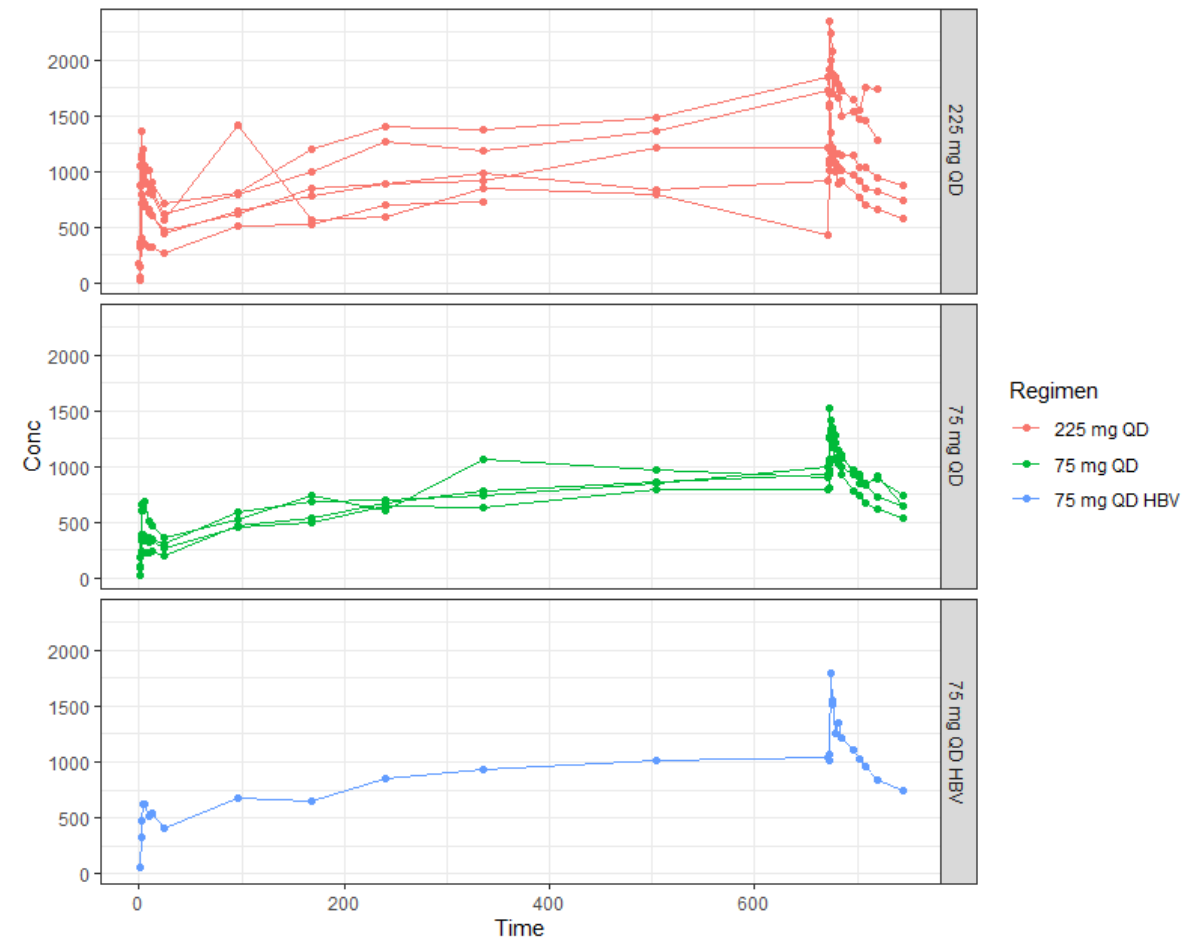


		75mg	150mg	225mg	300mg	375mg	Overall
Sex	Female	6 (60%)	1 (25%)	1 (17%)	2 (50%)	5 (56%)	15 (45%)
	Male	4 (40%)	3 (75%)	5 (83%)	2 (50%)	4 (44%)	18 (55%)
Age (y)	n	10	4	6	4	9	33
	Mean	35.6	34.8	42	50.3	48.6	42
	SD	11.3	6.45	11.4	6.8	12.3	11.9
	Minimum	20	27	28	41	22	20
	Median	36	35.5	41.5	51.5	49	41
	Maximum	54	41	55	57	61	61
Weight (kg)	n	9	4	6	4	9	32
	Mean	84.2	81.45	87.4	79.1	77.2	81.8
	SD	17.6	8.036	12.5	24.2	11.3	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)	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

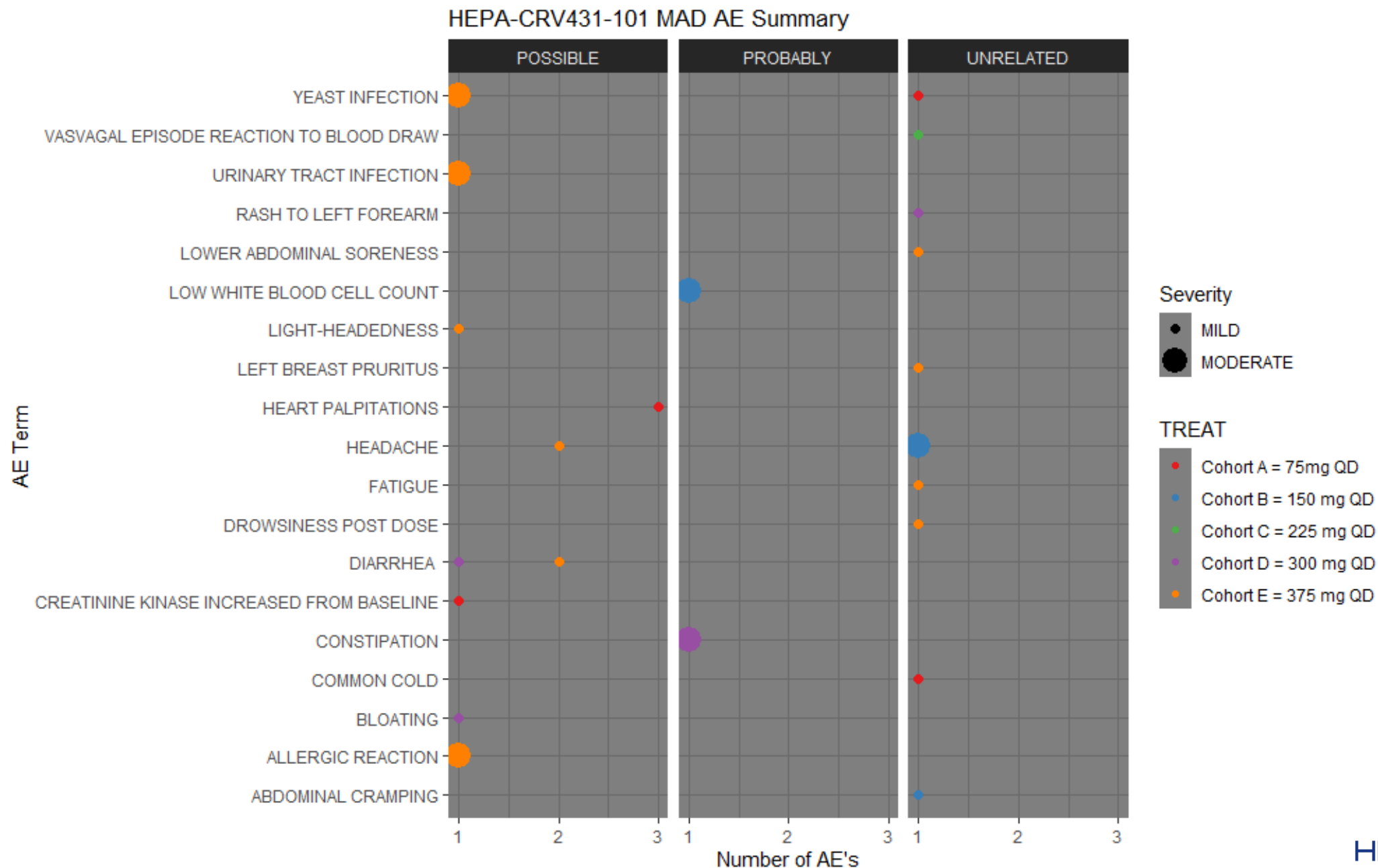
HEPA-CRV431-101: Multiple Ascending Dose PK Summary

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-Term Terminal Elimination Half-Life ($t_{1/2Lz}$) = 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)
<ul style="list-style-type: none">✓ 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.	<ul style="list-style-type: none">✓ N= 18✓ Single CRV431 Drug Interaction Study with tenofovir✓ No SAE's, mild AE's or changes in clinical labs✓ No changes in vital signs of ECG.	<ul style="list-style-type: none">✓ 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



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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 \geq 20 IU/L, Pro-C3 \geq 15.5 ng/mL OR ELF Score \geq 9.8 Score Fibroscan \geq 8.5 kPa



F2/F3
NASH
Patients
(n=36)

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	COMPLETE
C	F2/F3	12	CRV431 225 mg	LAST PATIENT Randomized 4/27
D		6	Placebo	

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

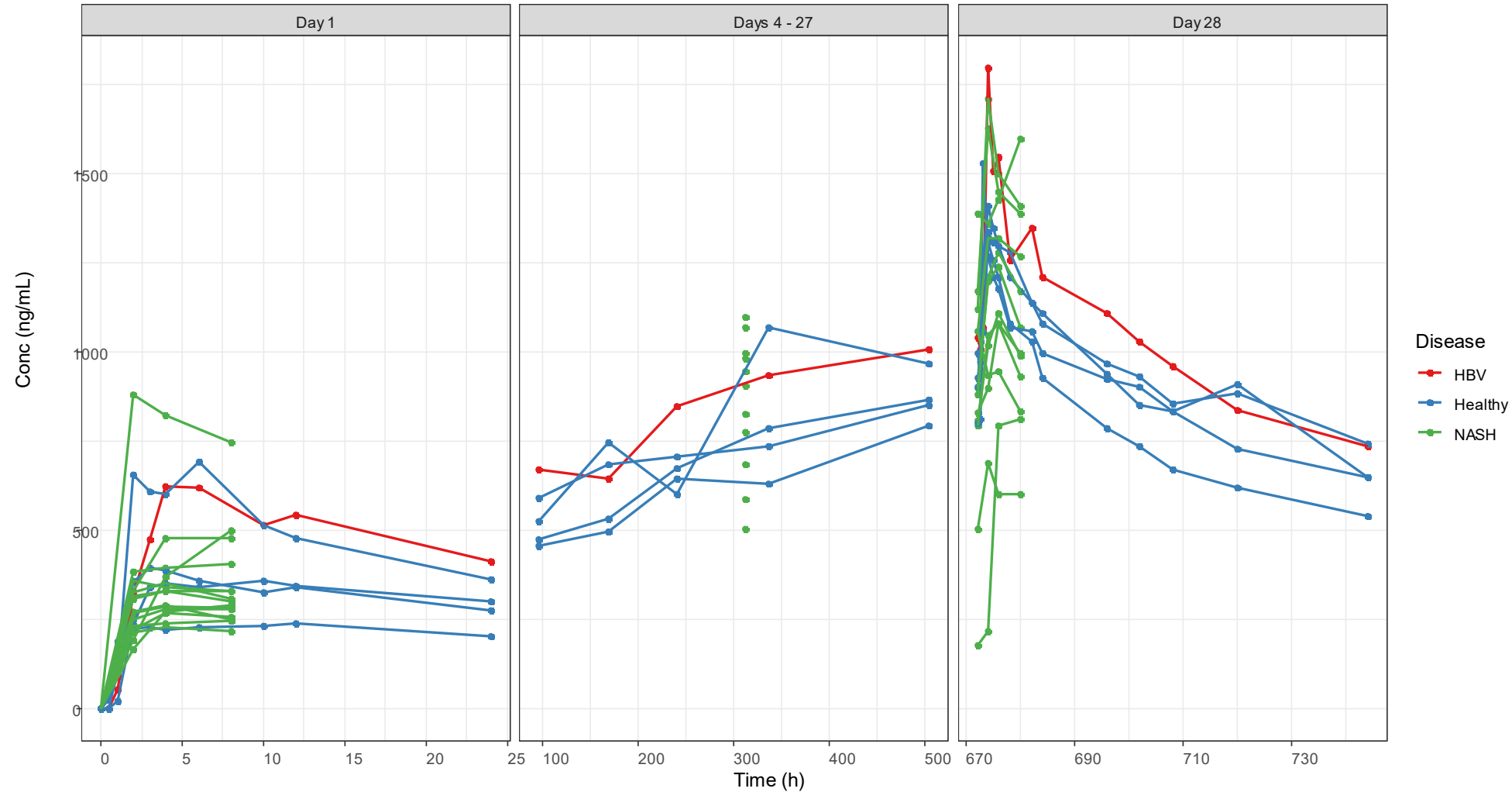
*randomized assignment; 2:1 – CRV431:placebo

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

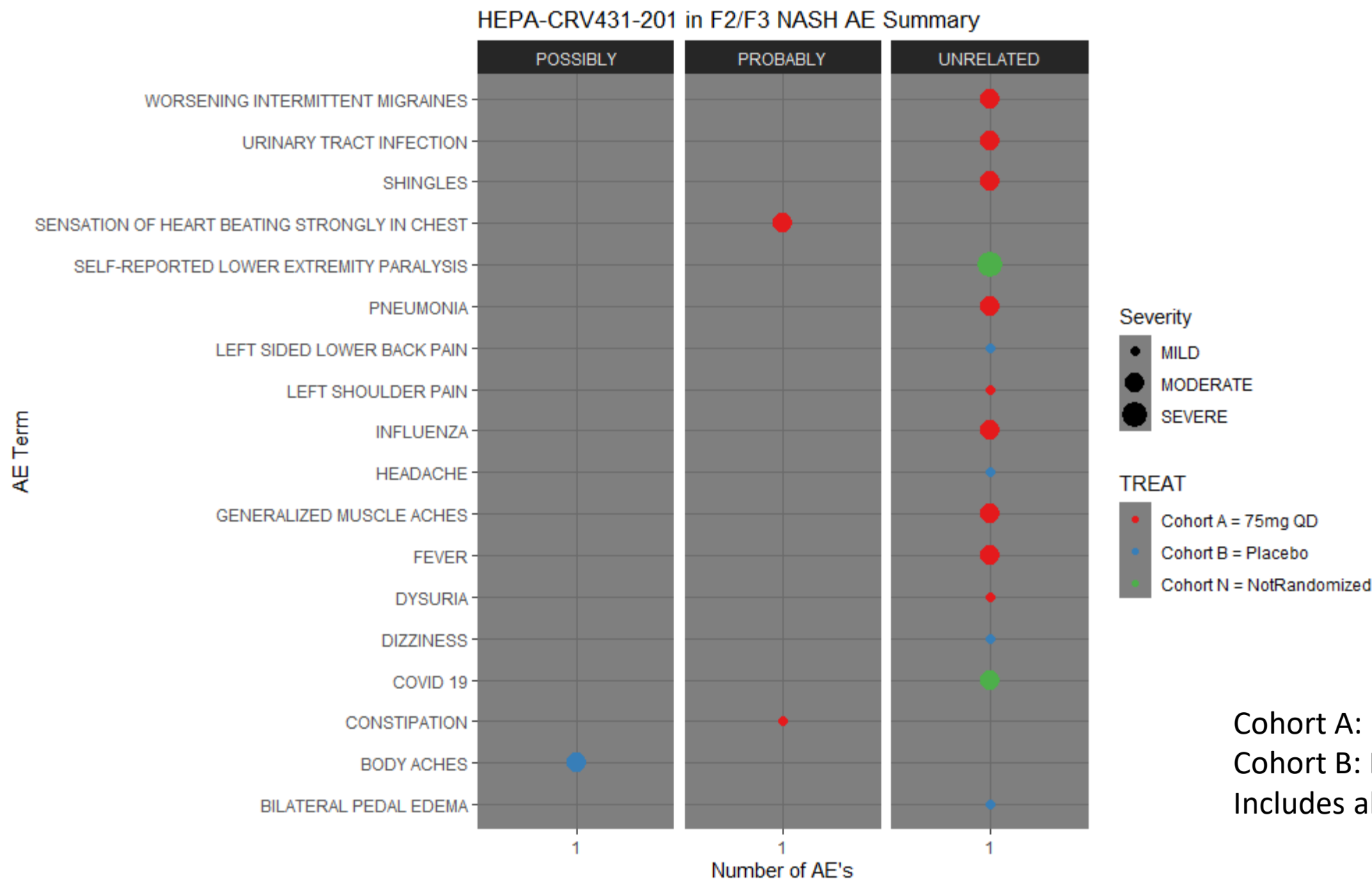
CRV431 75 mg QD in Healthy, HBV and F2/F3 NASH Patients

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



Cohort A: N=15
Cohort B: N = 6
Includes all randomized



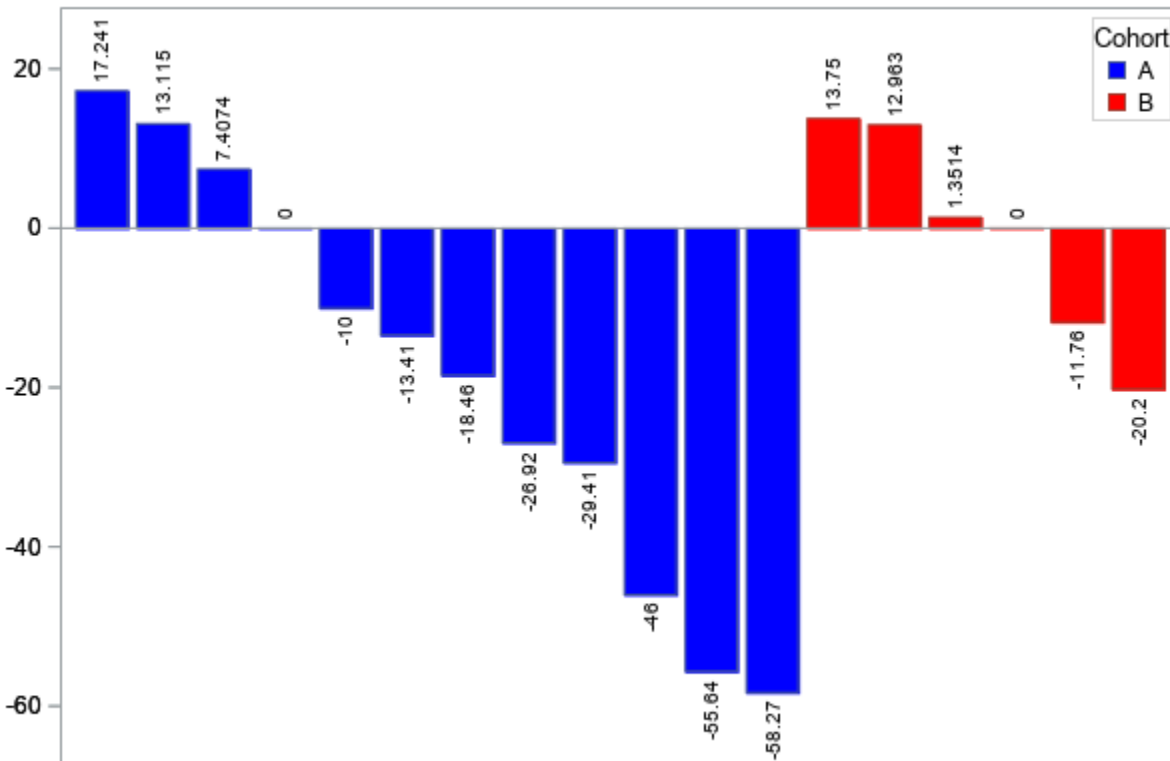
Exploratory Efficacy: Transaminases

Cohort A = 75 mg QD x 28 Days

Cohort B = Placebo QD x 28 Days

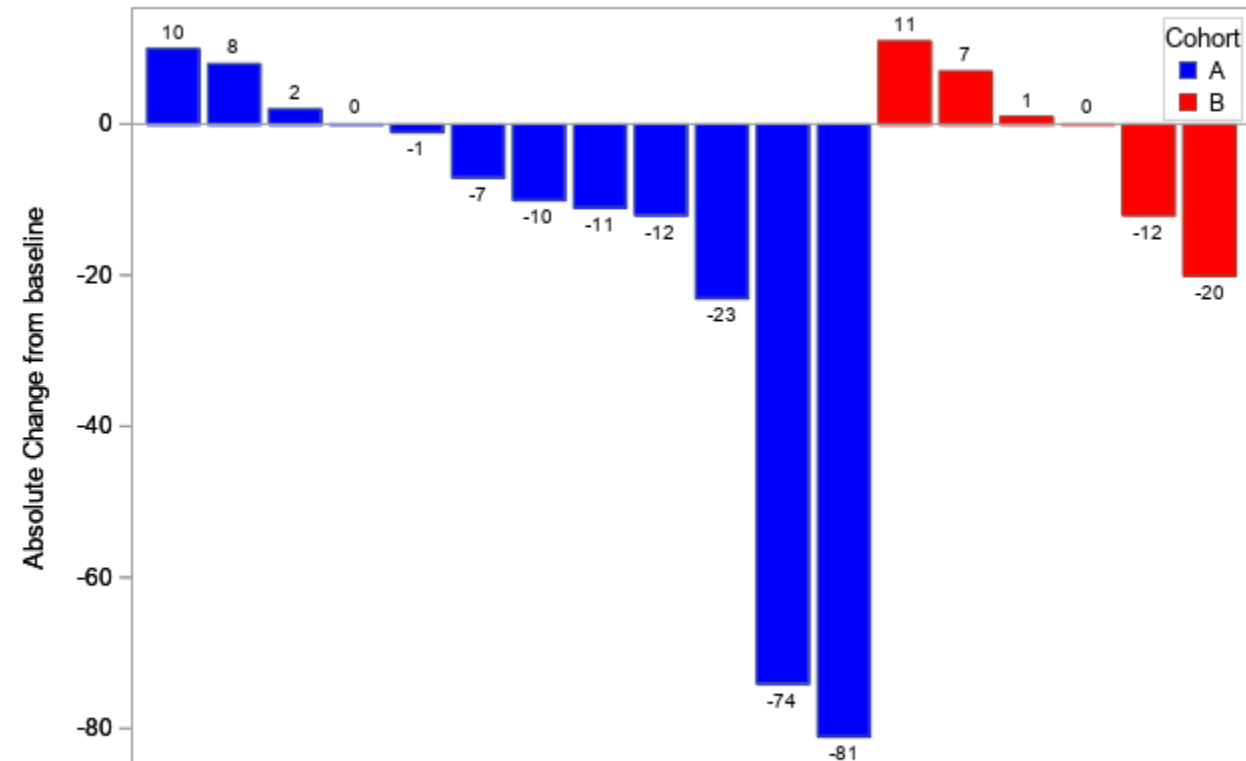
Exploratory Efficacy 75 mg Cohort: Alanine Transaminase at Day 28

Percent Change from Baseline: HEPA-CRV431-201 in F2/F3 NASH Patients
Test=ALT



Created from C:/Hepion/201/LABS/ADLB_31Apr2021_201.xlsx on20APR2021.
Cohort A = 75mg QD, Cohort B = Placebo

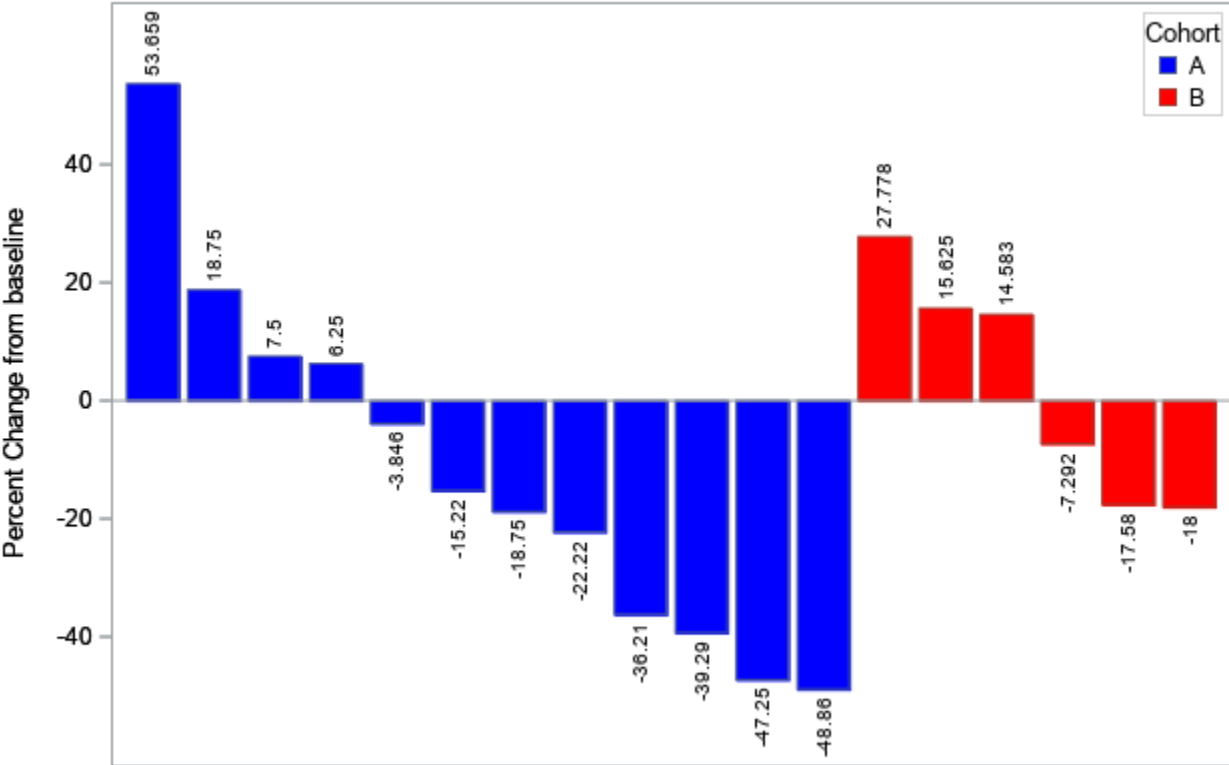
Absolute Change from Baseline: HEPA-CRV431-201 in F2/F3 NASH Patients
Test=ALT



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Cohort A = 75 mg QD, Cohort B = Placebo

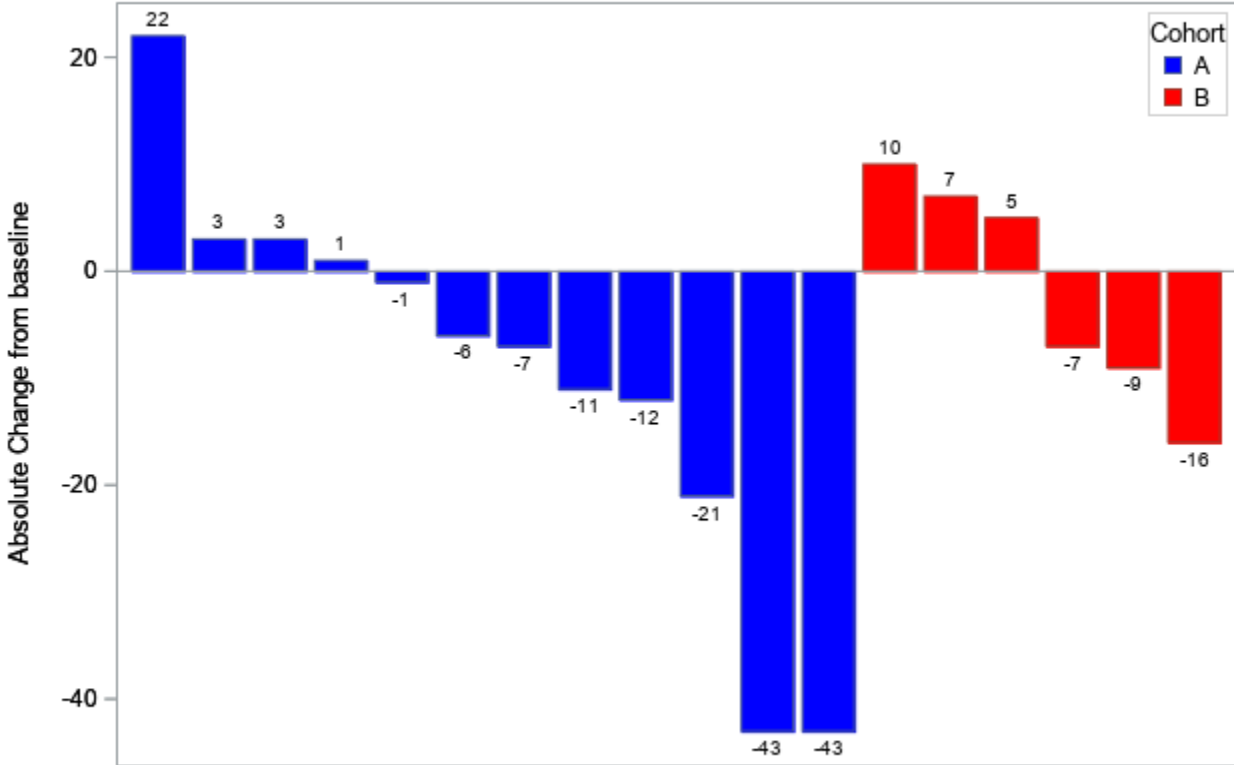
Exploratory Efficacy 75 mg Cohort: Aspartate Transaminase at Day 28

Percent Change from Baseline: HEPA-CRV431-201 in F2/F3 NASH Patients
Test=AST



Created from C:/Hepion/201/LABS/ADLB_31Apr2021_201.xlsx on20APR2021.
Cohort A = 75mg QD, Cohort B = Placebo

Absolute Change from Baseline: HEPA-CRV431-201 in F2/F3 NASH Patients
Test=AST



Created from C:/Hepion/201/LABS/ADLB_31Mar2021_201.xlsx on20APR2021.
Cohort A = 75 mg QD, Cohort B = Placebo

Population Pharmacokinetics: PK-PD from Sparse Sampling

Learn and Confirm Paradigm:

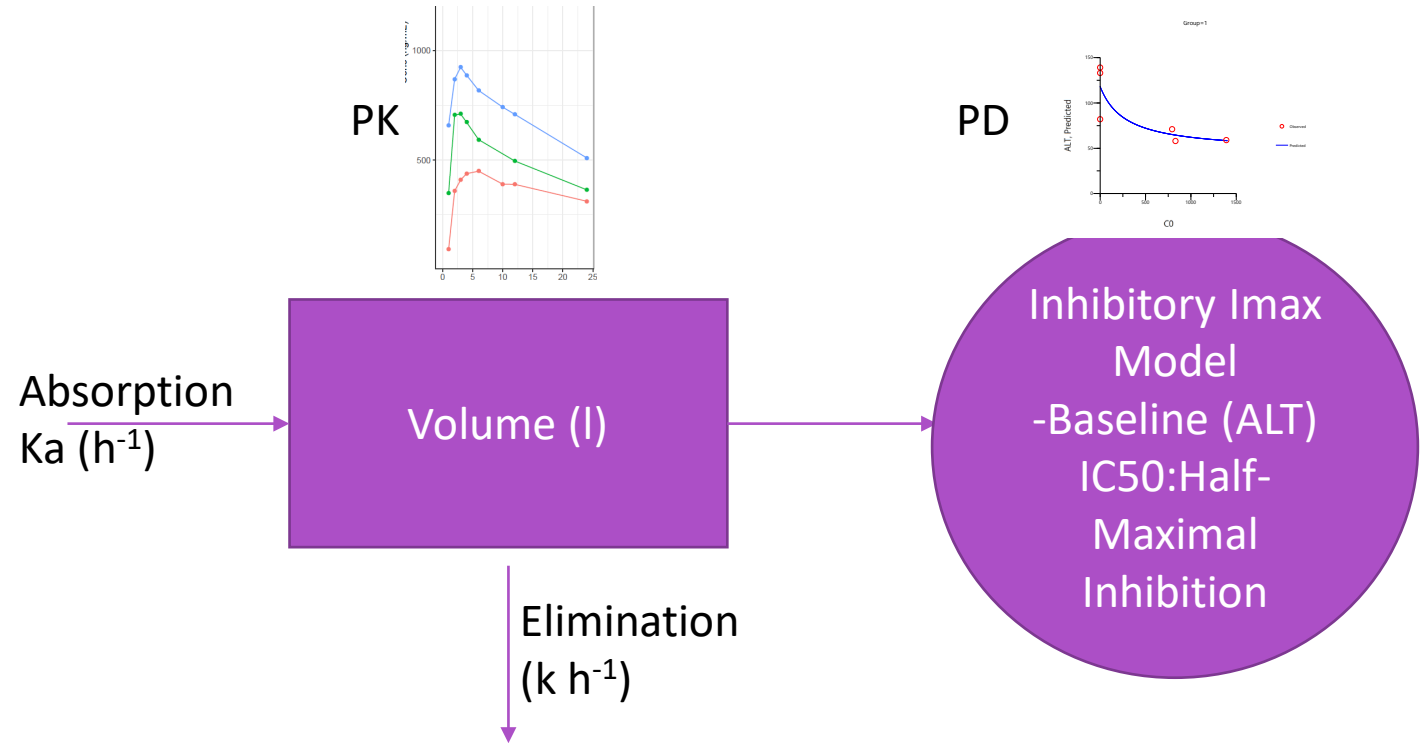
Taking what is Learned in Phase 1 & Confirm in Phase 2

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 I_{max} Model -> Predict Serum ALT

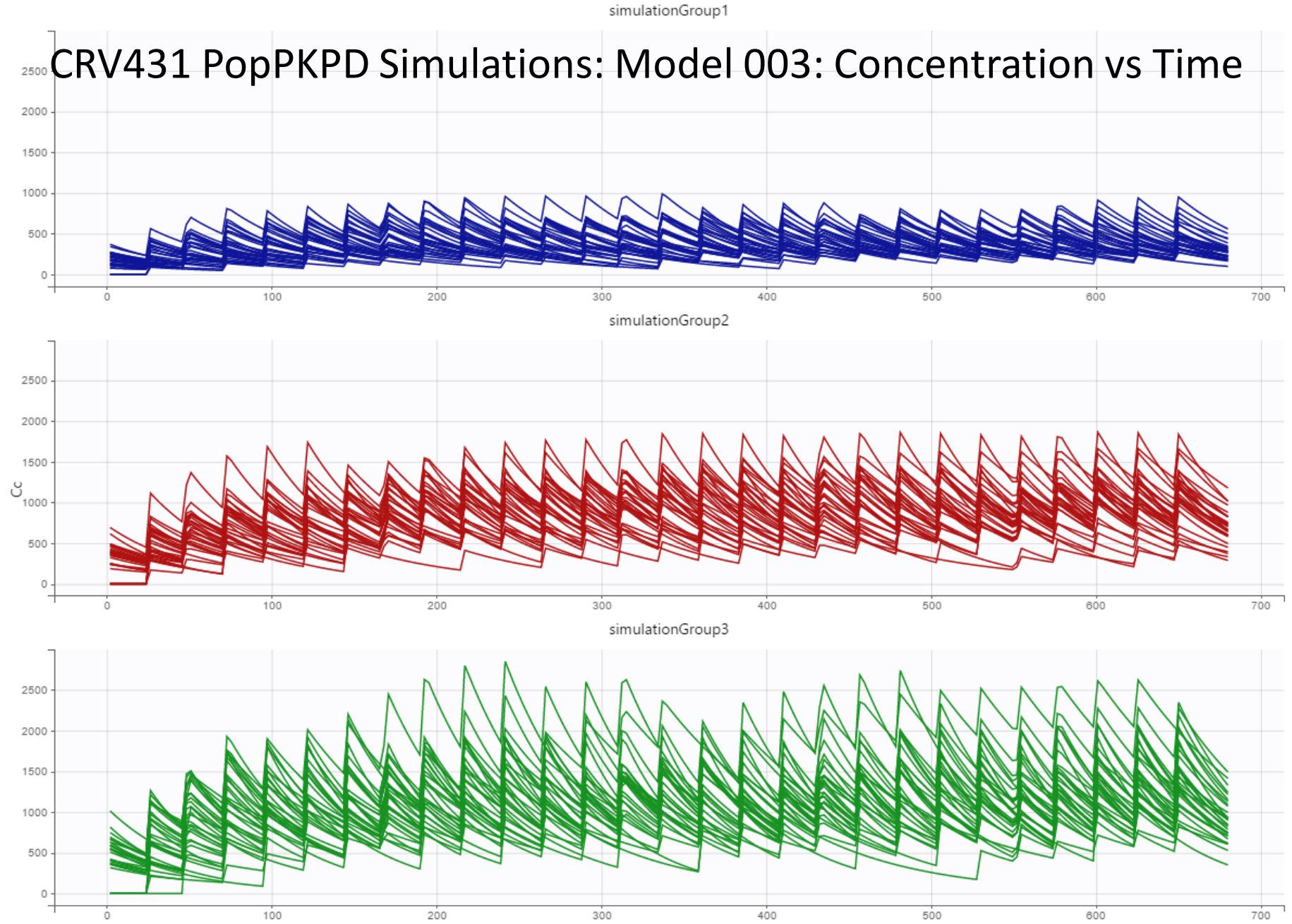


- Assess patient characteristics (COVARIATES) that help refine prediction of both PK and PD.
- Final Covariate Model: \uparrow Cholesterol \sim \downarrow Absorption
 \uparrow Baseline AST \sim \uparrow Effect
 \uparrow Lean Body Weight \sim \downarrow IC50

Trial Simulation
PK
75 mg QD ->

150 mg QD ->

225 mg QD ->



Model included a 15% probability of non-compliance to estimate effect of missing doses

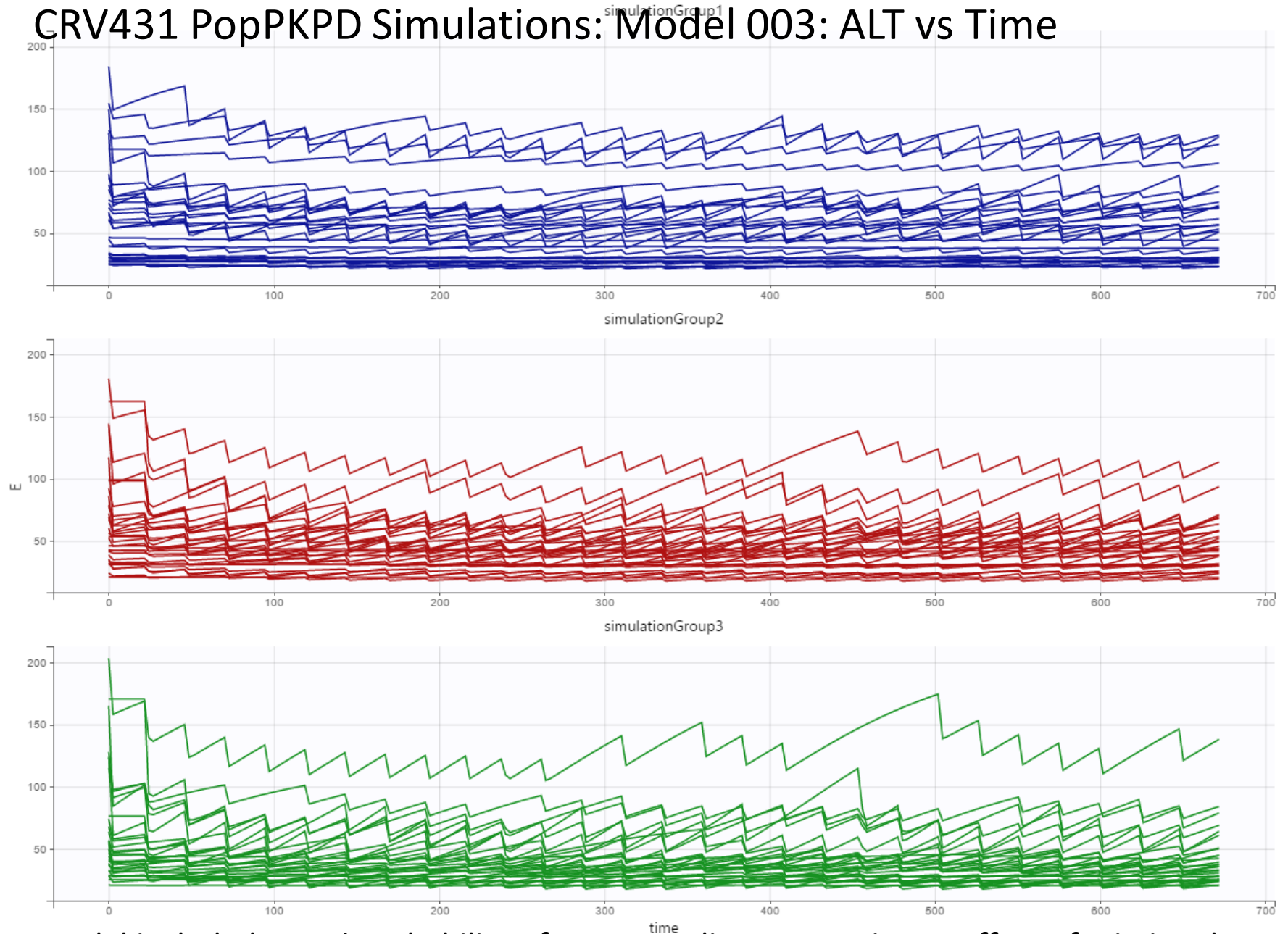
Trial Simulation PD

75 mg QD ->

150 mg QD ->

225 mg QD ->

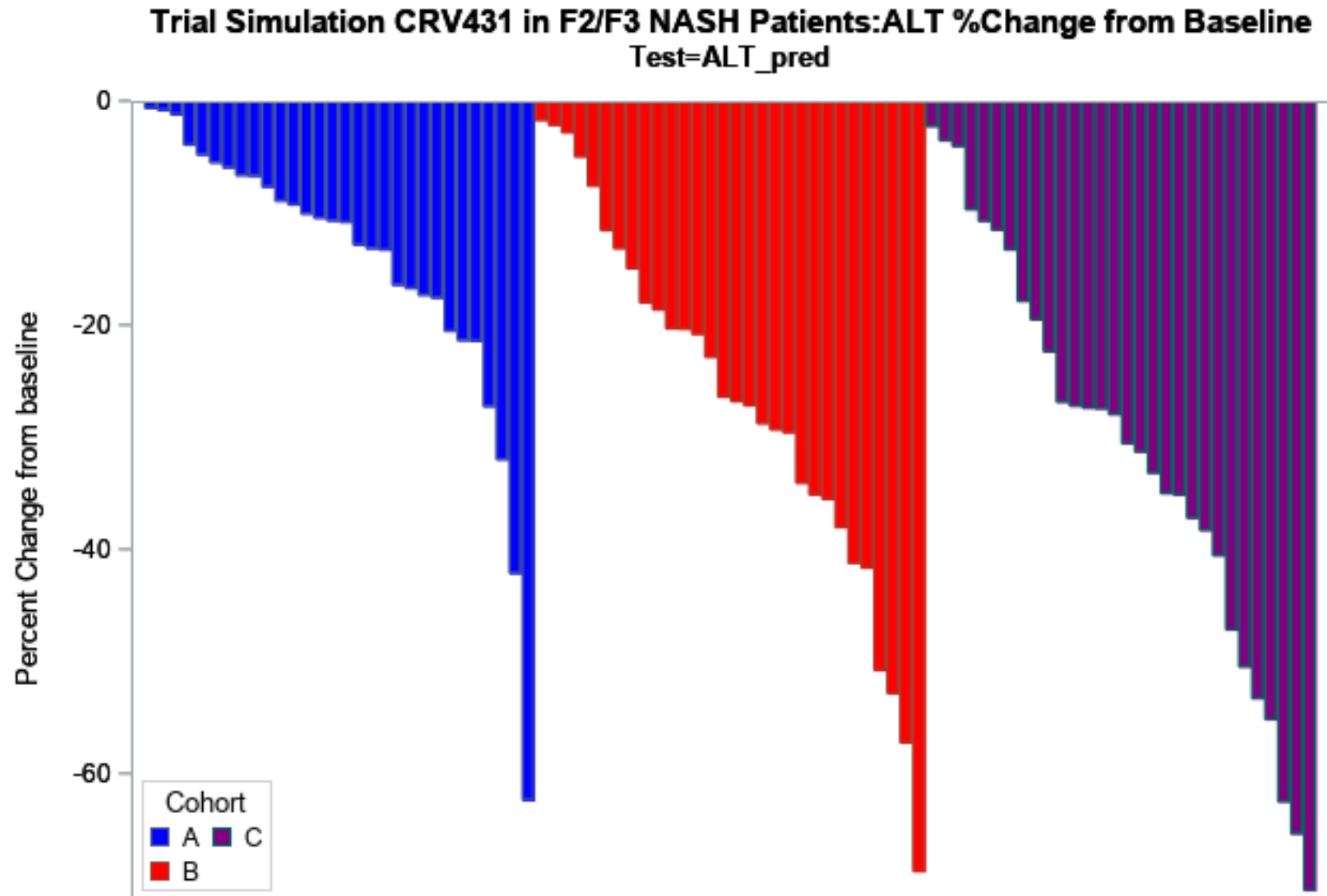
CRV431 PopPKPD Simulations: Model 003: ALT vs Time



Model included a 15% probability of non-compliance to estimate effect of missing doses

Trial Simulation %Change Day 28

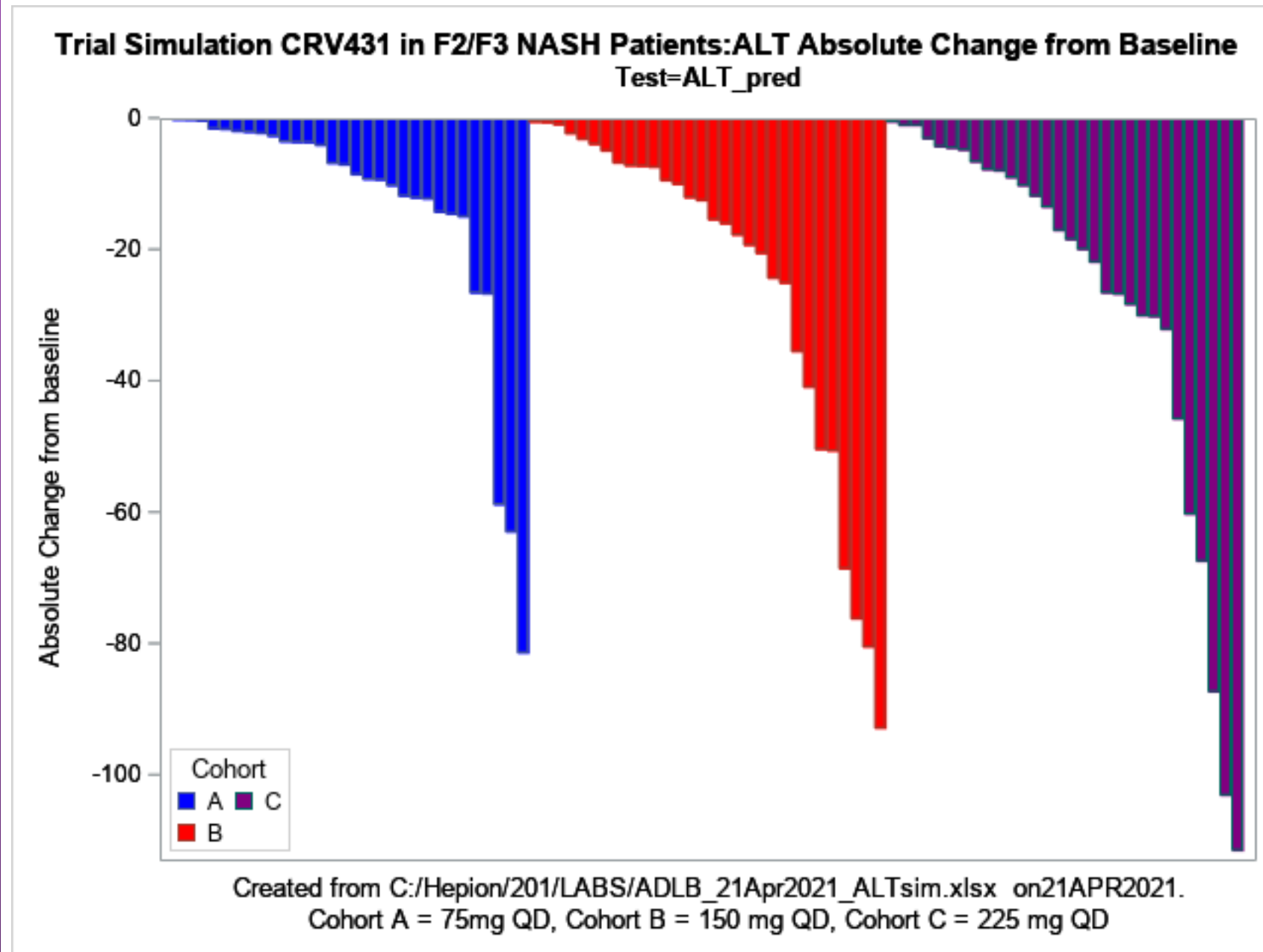
Cohort	N	Mean	Std Dev	Min	Max
75mg Observed	12	-18.0	25.8	-58.3	17.2
A=75mg	30	-14.6	13.0	-62.3	-0.6
B=150mg	30	-26.7	16.8	-68.7	-1.7
C=225mg	30	-31.2	18.5	-70.5	-2.2



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

Trial Simulation Absolute Change from Baseline Day 28

Cohort	N	Mean	Std Dev	Min	Max
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



Bioinformatics

Exploratory Analysis

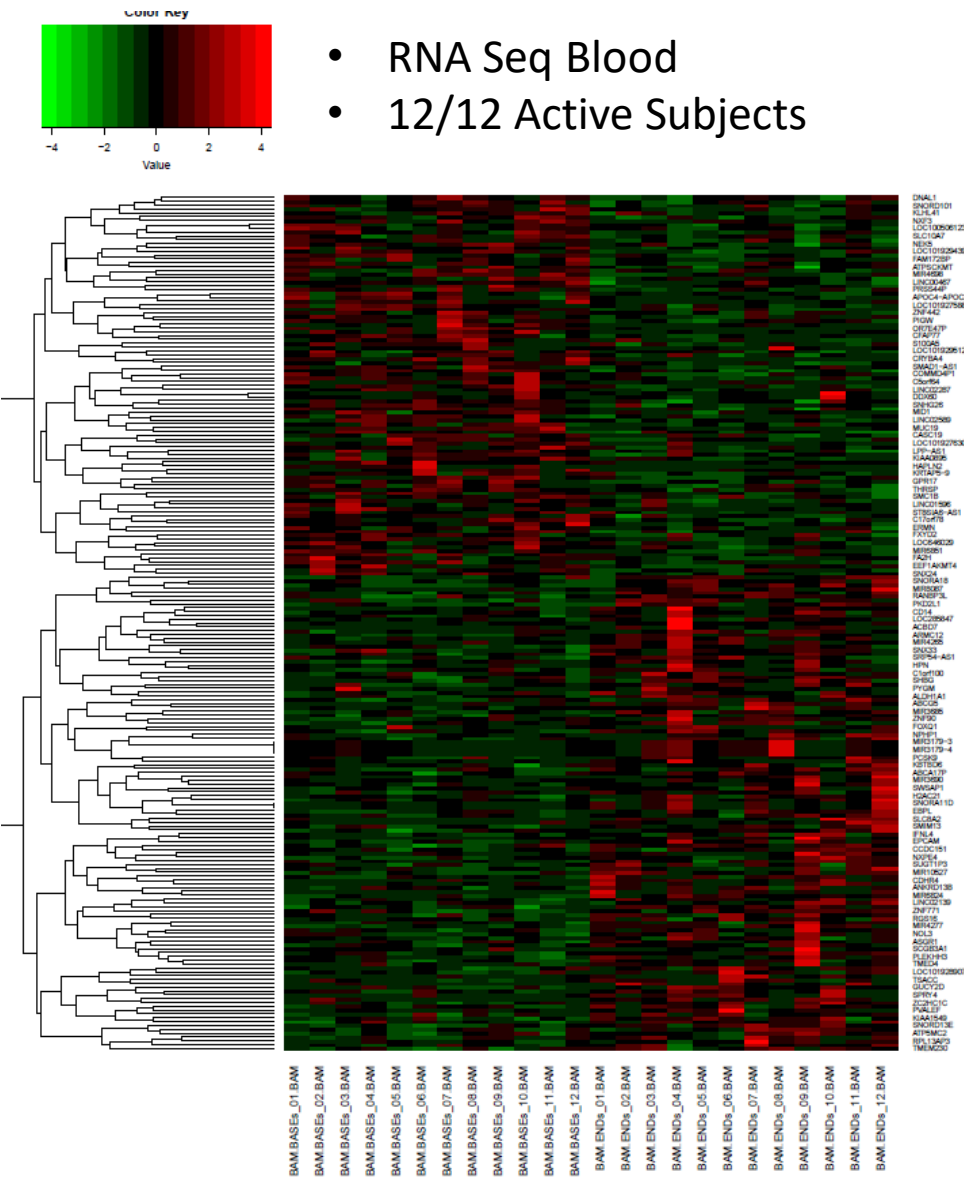
Gene Ontology using GeneWalk

DESeq2, rrvgo

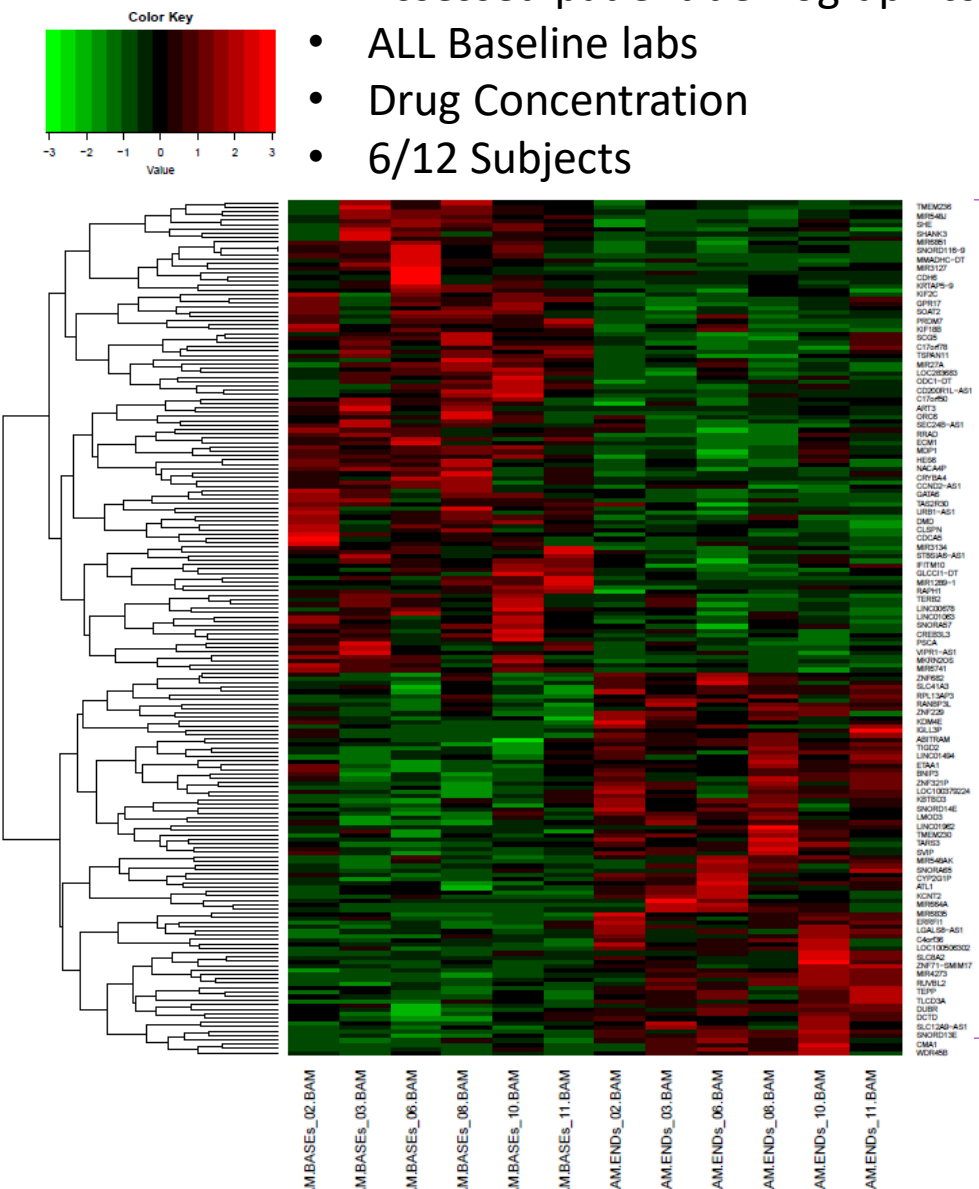


Phase2a: Bioinformatics & AI

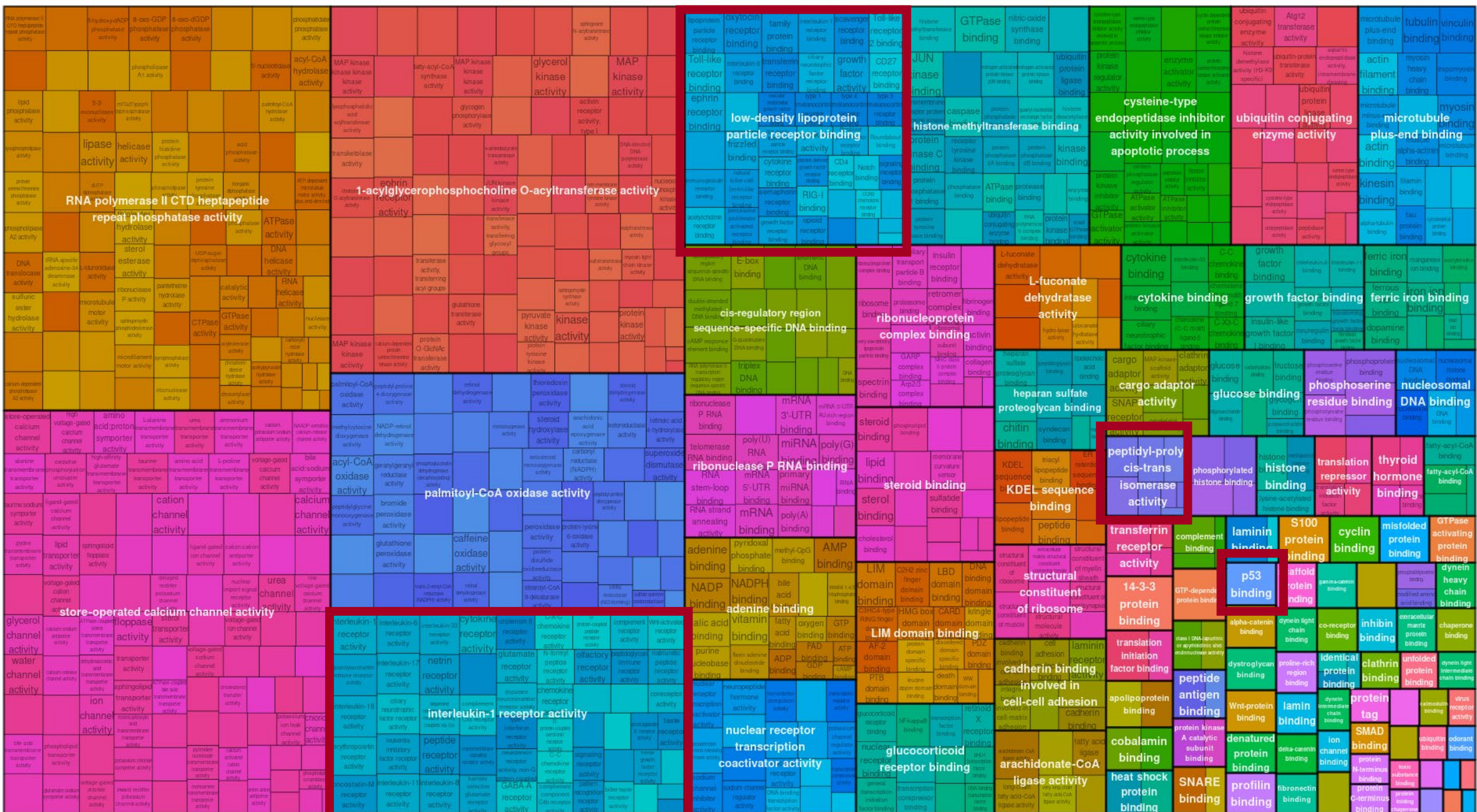
Standard Differentially Expressed Genes - DESeq2(Median Ratios): Day 1 v Day 28



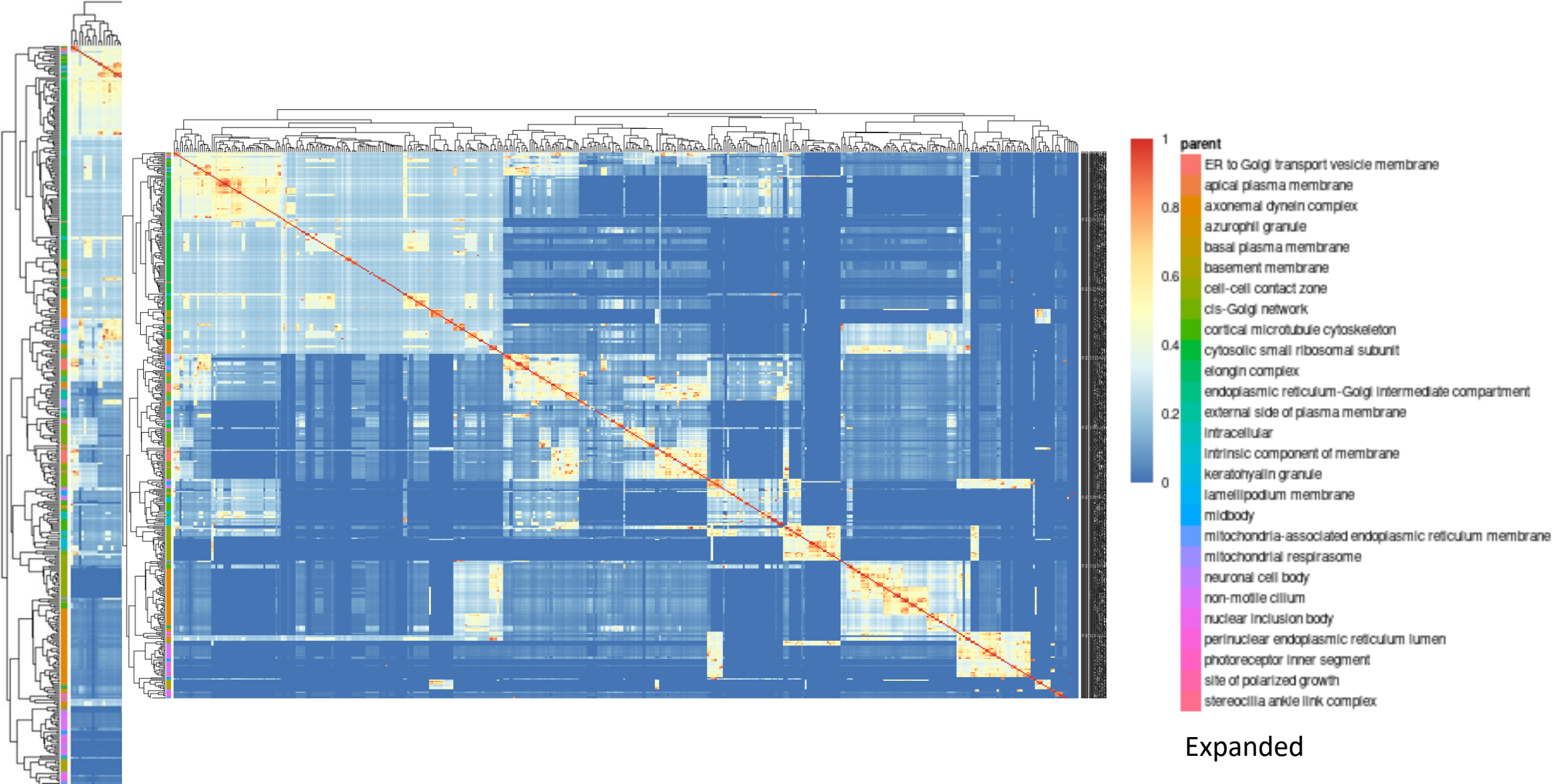
AI-Machine Learning: Responder Analysis (AI-POWR™)



Potential
Genomic
Biomarker
Responder
Panel



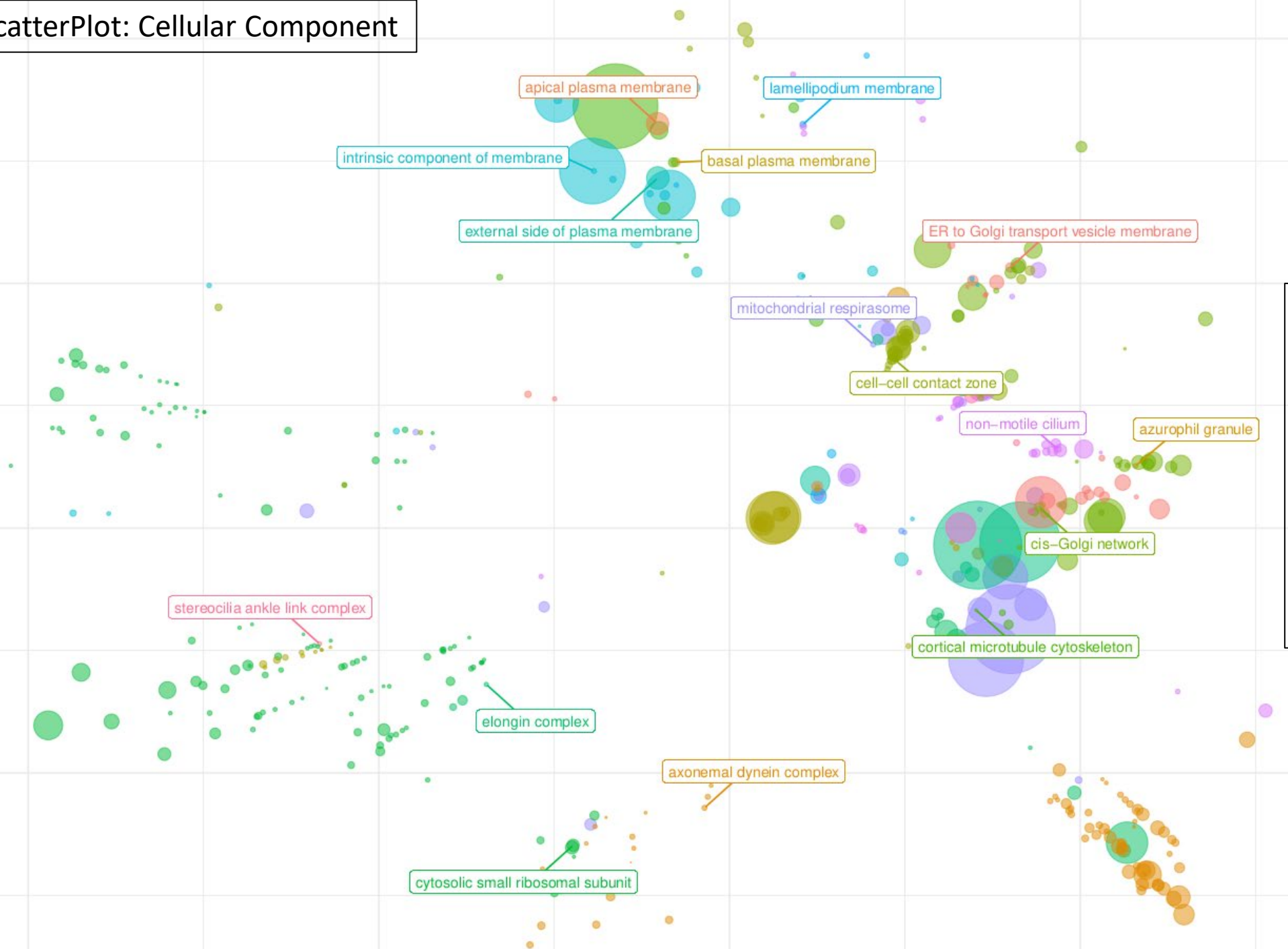
Cellular Component Heat Map



Expanded

Expanded

ScatterPlot: Cellular Component

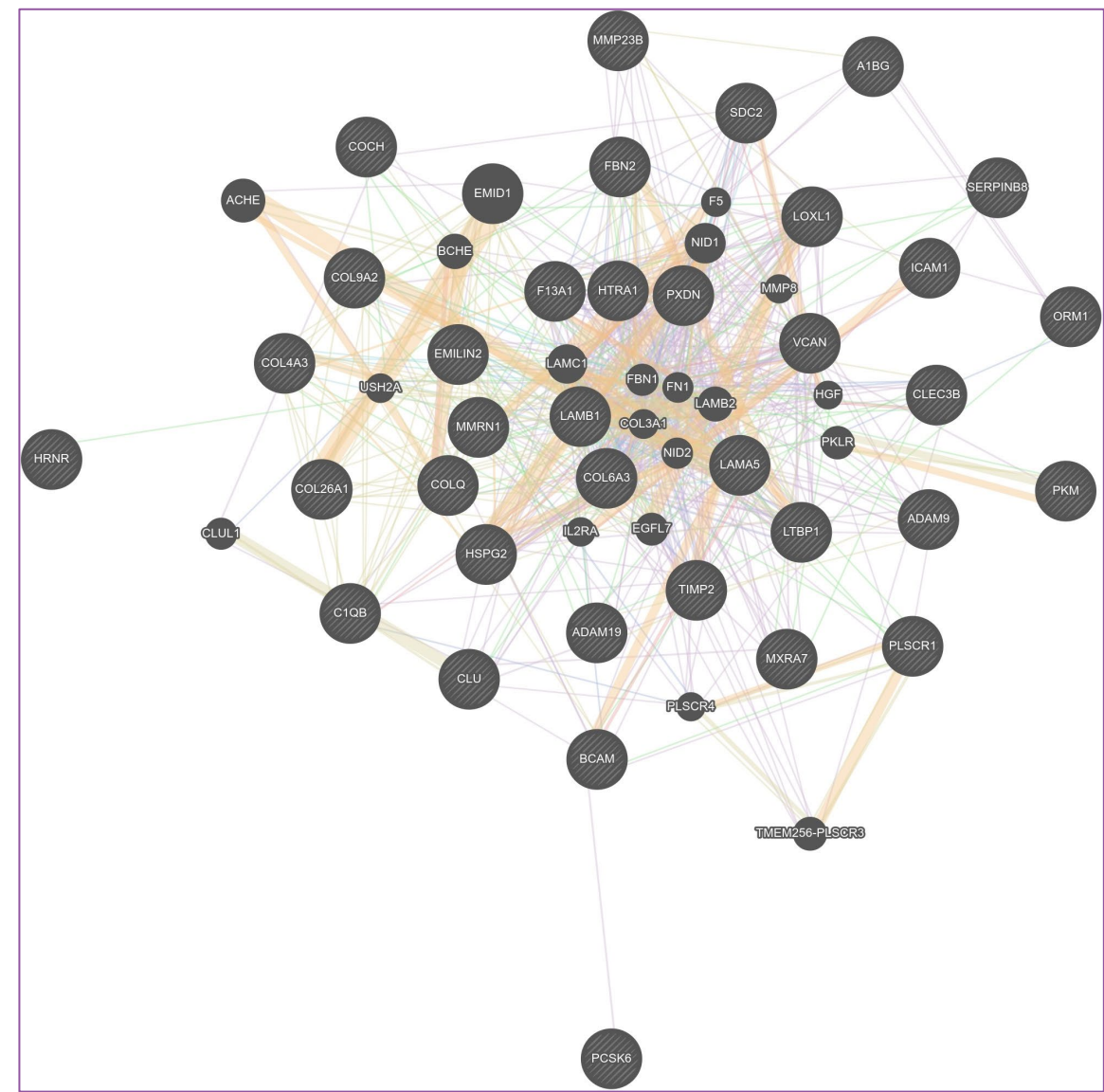


- GO terms as scatter points
- Distance between represents similarity between terms
- Size of point (bubble) provides scores (or number of genes) in the GO term

cytosolic small ribosomal subunit	small ribosomal subunit	ionotropic glutamate receptor complex	transcription regulator complex	apoptase-protecting complex	MSL complex	protein serine/threonine phosphatase complex	NUA4 histone acetyltransferase complex	secobarbital protein transporting V-type ATPase, V1 domain	interleukin-18 receptor complex	multimeric ribonuclease P complex	cis-Golgi network	smooth endoplasmic reticulum	Golgi membrane	endoplasmic reticulum exit site	specific granule	late endosome membrane	intrinsic component of membrane	intrinsic component of mitochondrial outer membrane	integral component of mitochondrial membrane	cytoplasmic side of plasma membrane	extrinsic component of membrane	mitochondrial respirasome	nuclear membrane	mitochondrial respiratory chain complex I	mitochondrial outer membrane						
integrin alpha-v-beta3 complex	VCB complex	intracellular transport particle B	ion channel complex	eukaryotic translation initiation factor 3 complex	TORC1 complex	nucleosome	DNA repair complex	SWI/SNF complex	npBAF complex	plasma membrane protein transporting V-type ATPase complex	platelet alpha granule	transport vesicle	recycling endosome	trans-Golgi network membrane	early endosome membrane	cortical endoplasmic reticulum	extrinsic component of plasma membrane	intrinsic component of plasma membrane	integral component of plasma membrane	component of endosome membrane	MICOS complex	mitochondrial intermembrane space	mitochondrial inner membrane	mitochondrial membrane-bounded organelle	nuclear envelope lumen						
polysomal ribosome	transcription factor AP-1 complex	polysome	RISC complex	ciliary neurotrophic factor receptor complex	synapsin II-associated receptor complex	mitochondrial protein transporting ATP synthase complex, catalytic sector F1F1	mitochondrial protein transporting ATP synthase complex	prefoldin complex	SNARE complex	mitochondrial protein transporting ADP synthase complex, coupling factor 1	RISC-loading complex	synaptic vesicle	recycling endosome membrane	Mon1-Ccz1 complex	exocytic vesicle	endosome	endoplasmic reticulum membrane	anchored component of external side of plasma membrane	intrinsic component of plasma membrane	plasma membrane caveola	cytoplasmic side of early endosome membrane	mitochondrial matrix	nuclear outer membrane	mitochondrial membrane	nuclear ribosome	mitochondrial outer membrane					
cytosolic large ribosomal subunit	macrophage migration inhibitory factor receptor complex	TORC2 complex	voltage-gated calcium channel complex	WASH complex	hydrocarbon receptor complex	retromer complex	histone acetyltransferase complex	protein phosphatase type 1 complex	telomerase complex	protein-DNA complex	BRISC complex	synaptic vesicle	endoplasmic reticulum tubular network	Golgi apparatus	early endosome	endosome membrane	integral component of endoplasmic reticulum membrane	phosphatidylinositol 3-kinase complex, class III	integral component of mitochondrial outer membrane	anchored component of membrane	integral component of membrane	mitochondrial large ribosomal subunit	nucleoplasm	nuclear envelope	nucleus	nuclear inner membrane					
Cul2-RING ubiquitin ligase complex	AMPA receptor complex	EKC/KECK complex	histone channel complex	GABA-A receptor complex	chloride channel complex	GABA-A receptor complex	Hrd1 p. ubiquitin ligase ERAD-L complex	proteasome	RNA polymerase II transcription regulator complex	polymerase II transcription initiation factor 4F complex	RAVE complex	PR-DUB complex	multivesicular body	multivesicular body membrane	endoplasmic reticulum lumen	endomembrane system	acrosomal vesicle	trans-Golgi network	vesicle	vesicle membrane	basement membrane	laminin-2 complex	laminin-1 complex	laminin-8 complex							
Cul5-RING ubiquitin ligase complex	glutamate receptor complex	cation channel complex	XPC complex	ribonuclease MRP complex	interleukin-6 receptor complex	BRCA1-A complex	spliceosomal complex	uniplex complex	Bcl-2 family protein complex	ubiquitin ligase complex	calcium channel complex	membrane protein complex	trans-Golgi network	Golgi cisterna membrane	multivesicular body, internal vesicle	secretory granule	late endosome	Golgi stack	trans-Golgi network	vesicle	intracellular vesicle	endocytic vesicle	platelet dense granule membrane	cytoplasmic vesicle	COPII-coated vesicle	dalphin-coated vesicle	phagocytic vesicle	chromatin granule	very-low-density lipoprotein particle	extracellular matrix	
ML-1-25P/14-3-3/14-3-3/14-3-3 complex	transcription repressor complex	nBAF complex	selective glutamate receptor complex	messenger ribonucleoprotein complex	mitochondrial small ribosomal subunit	collagen type IV trimer	ESC/E(Z) complex	SOSS complex	zeta DNA polymerase complex	TRAPP complex	T cell receptor complex	Integrin complex	cell-cell contact zone	postsynaptic endocytic zone membrane	hemidesmosome	adherens junction	dopaminergic synapse	desmosome	COPII vesicle coat	extracellular exosome	cytoplasmic vesicle membrane	COPI-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle
ribonucleoprotein complex	tumor necrosis factor receptor superfamily complex	mitochondrial small ribosomal subunit	collagen type IV trimer	ESC/E(Z) complex	SOSS complex	zeta DNA polymerase complex	TRAPP complex	T cell receptor complex	Integrin complex	cell-cell contact zone	postsynaptic endocytic zone membrane	hemidesmosome	adherens junction	dopaminergic synapse	desmosome	COPII vesicle coat	extracellular exosome	cytoplasmic vesicle membrane	COPI-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	COPII-coated vesicle	
axonal dynein complex	mitotic spindle astral microtubule end	actin filament	cytoplasmic dynein complex	cytoplasmic microtubule	sarcomere	gamma-tubulin large complex	nuclear chromosome	chromosome centromeric region	lateral element	Ctf18 RFC-like complex	cell-cell contact zone	postsynaptic active zone membrane	terminal bouton	presynaptic active zone membrane	postsynaptic active zone membrane	neurovascular junction	cell-cell junction	cortical microtubule cytoskeleton	sarcolemma	cortical cytoskeleton	azurophil granule	lysosomal membrane	autolysosome	neuronal cell body	dendrite	apical dendrite					
spindle	striated muscle myosin thick filament	site of double-strand break	microtubule	cytoplasmic ribonucleoprotein granule	A band	intermediate filament cytoskeleton	microtubule associated complex	lipid droplet	stress fiber	mitotic spindle	cell-cell contact zone	postsynaptic active zone membrane	terminal bouton	presynaptic active zone membrane	postsynaptic active zone membrane	neurovascular junction	cell-cell junction	cortical microtubule cytoskeleton	sarcolemma	cortical cytoskeleton	azurophil granule	lysosomal membrane	autolysosome	neuronal cell body	dendrite	apical dendrite					
euchromatin	striated muscle thin filament	microtubule minus-end	F-actin capping protein complex	ciliary body	P granule	chromatin	microtubule end	centrosome	intermediate filament	condensed nuclear chromosome	cell-cell contact zone	postsynaptic active zone membrane	terminal bouton	presynaptic active zone membrane	postsynaptic active zone membrane	neurovascular junction	cell-cell junction	cortical microtubule cytoskeleton	sarcolemma	cortical cytoskeleton	azurophil granule	lysosomal membrane	autolysosome	neuronal cell body	dendrite	apical dendrite					
cardiac myofibril	microtubule plus-end	P-body	podosome	costamere	kinesin complex	actin cytoskeleton	actin filament bundle	Z disc	cytoskeleton	centriolar satellite	M band	cell-cell contact zone	postsynaptic active zone membrane	terminal bouton	presynaptic active zone membrane	postsynaptic active zone membrane	neurovascular junction	cell-cell junction	cortical microtubule cytoskeleton	sarcolemma	cortical cytoskeleton	azurophil granule	lysosomal membrane	autolysosome	neuronal cell body	dendrite	apical dendrite				
neurofilament	heterochromatin	myofibril	cytoplasmic stress granule	filamentous actin	spindle midzone	outer dynein arm	centriole	cella DNA polymerase complex	dynein complex	dynein complex	cell-cell contact zone	postsynaptic active zone membrane	terminal bouton	presynaptic active zone membrane	postsynaptic active zone membrane	neurovascular junction	cell-cell junction	cortical microtubule cytoskeleton	sarcolemma	cortical cytoskeleton	azurophil granule	lysosomal membrane	autolysosome	neuronal cell body	dendrite	apical dendrite					

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
COCH	collagen binding	GO:0005518	molecular function
COCH	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
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



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

CRV431 in NASH Phase 2a Preliminary Conclusions

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.



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