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)

Daren R. Ure, Daniel J. Trepanier, Patrick R. Mayo and Robert T. Foster

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).

ARTICLE HISTORY
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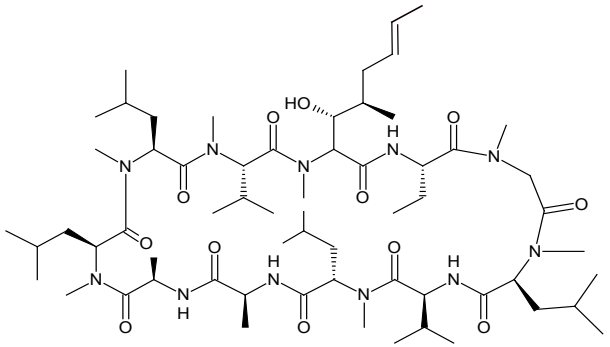
KEYWORDS
Cyclophilin; cyclosporine;

The Genesis of CRV431: From Calcineurin to Cyclophilin

Theory	Prediction and Experimentation	Findings
Modifying Cyclosporine A can greatly increase its immunosuppressive benefits	Modifications of Cyclosporine A can either eliminate or enhance immunosuppression. Our team's past discovery, voclosporin, was chemically modified to enhance immunosuppression	Inhibition of each cyclophilin isoform produces distinct therapeutic effects

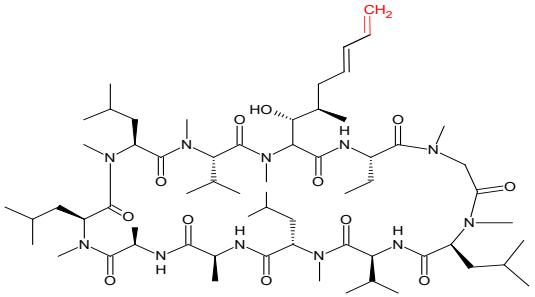
Cyclosporine A



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

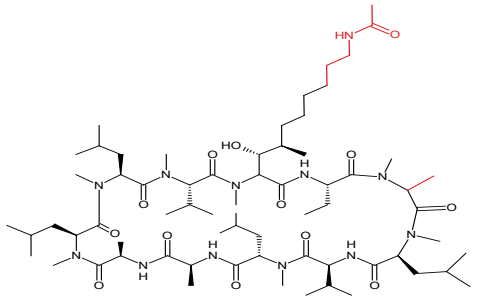
Voclosporin

Aurinia Pharma

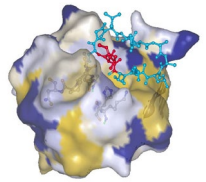


Modifications increase affinity for calcineurin and **increase immunosuppression potency**

CRV431



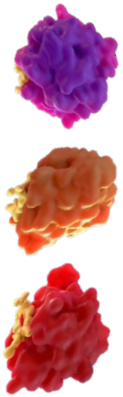
Modifications increase affinity for cyclophilins (13-fold) and **eliminate immunosuppression**



CRV431 binds potently (Ki≈1 nM) to around 10 of 17 cyclophilin isoforms in the human body

CRV431 Multiple Benefits Through Cyclophilin Antagonism

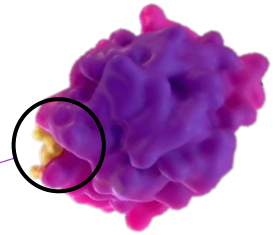
Cyclophilin enzymes regulate the structure and activity of many proteins throughout the body



Regulatory roles of cyclophilins in many disease pathways make them good candidates as drug targets

CRV431
Pan-Cyclophilin Inhibitor

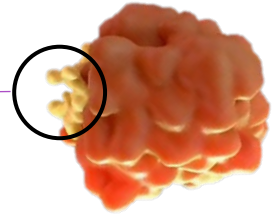
Binds to Cyclophilin A to reduce inflammation



Cyclophilin A (cytosol and secreted)

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

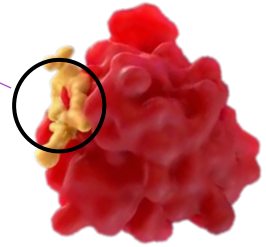
Binds to Cyclophilin B to reduce fibrosis



Cyclophilin B (endoplasmic reticulum)

Promotes fibrotic scarring by controlling collagen production

Binds to Cyclophilin D to mitigate mitochondrial damage



Cyclophilin D (mitochondria)

Promotes mitochondrial pore opening leading to mitochondrial and necrotic cell death

Regulates mitochondrial metabolism

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 ▼ tissue fibrosis
IPF lung explants (1 donor)	Endogenous stimulation	

Animal Models (8 independent 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
Rats (liver fibrosis)	Thioacetamide	48%▼ fibrosis; prevented cirrhosis

- Decreases in inflammation and fibrosis consistently observed in pre-clinical models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Phase 1: LEARN

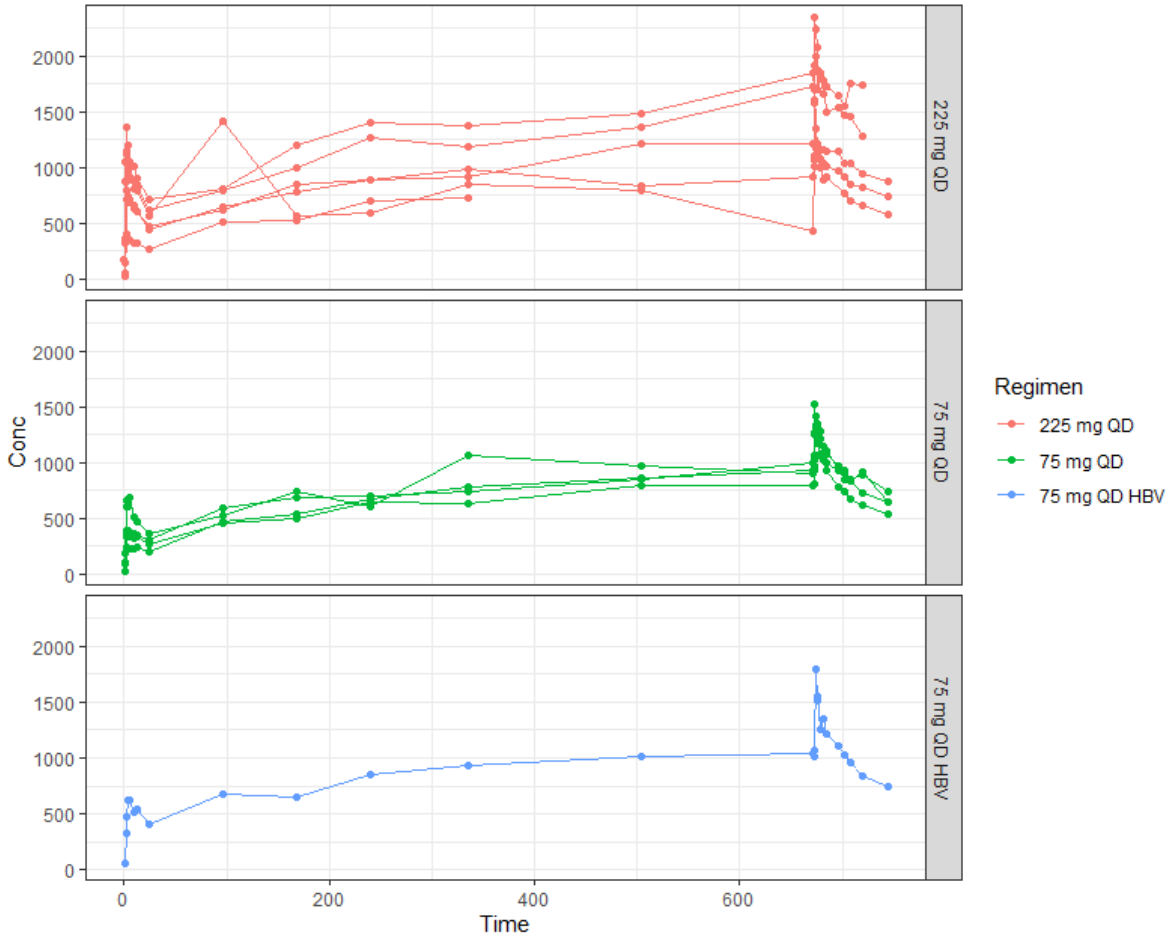
HEPA-CRV431-101:Multiple Ascending Dose Baseline Demographics

		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/m^2)							
	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

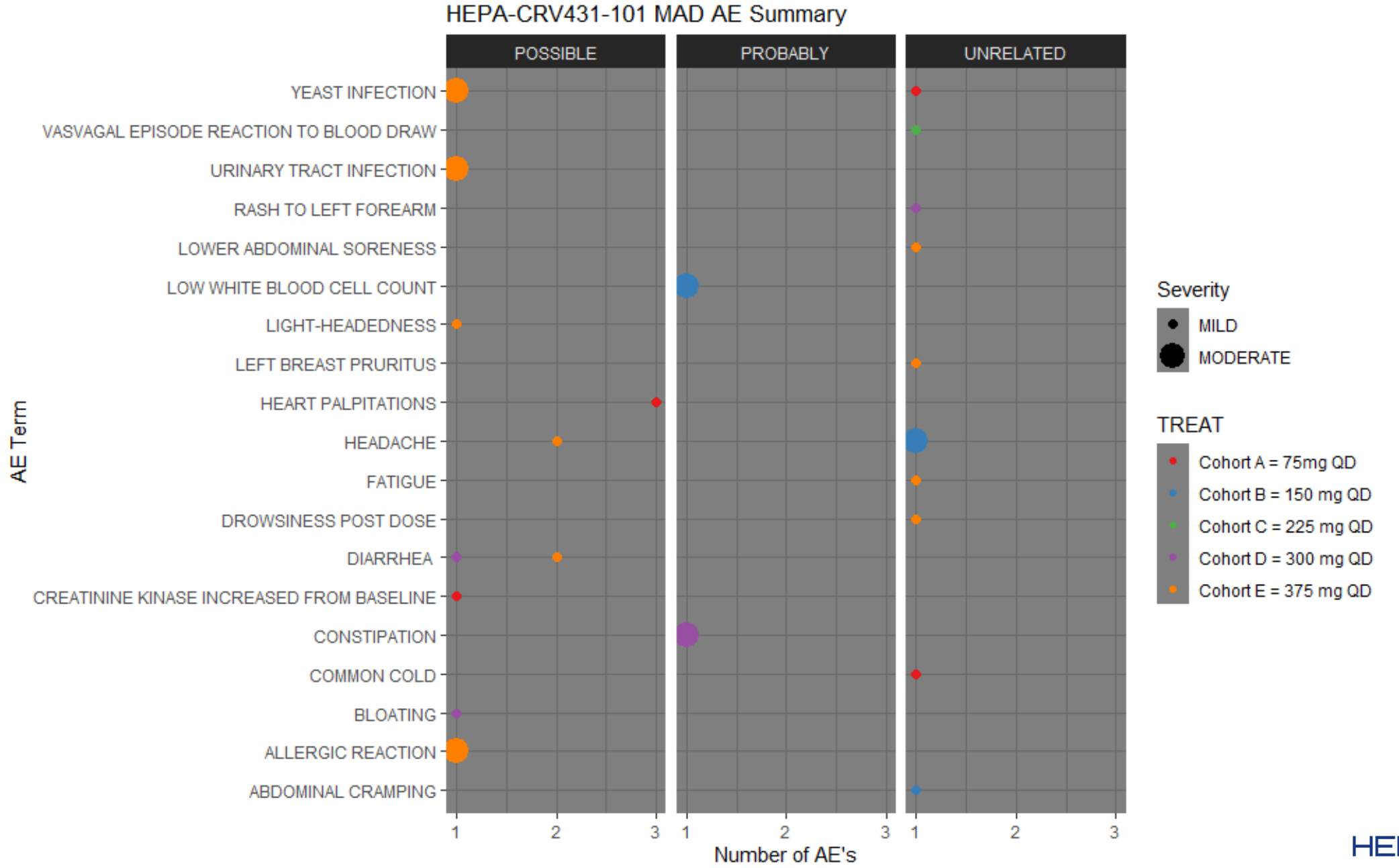
HEPA-CRV431-101: Multiple Ascending Dose PK Summary

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)

- ✓ 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.

Drug-Drug Interaction (DDI)

- ✓ 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.

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

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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

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	

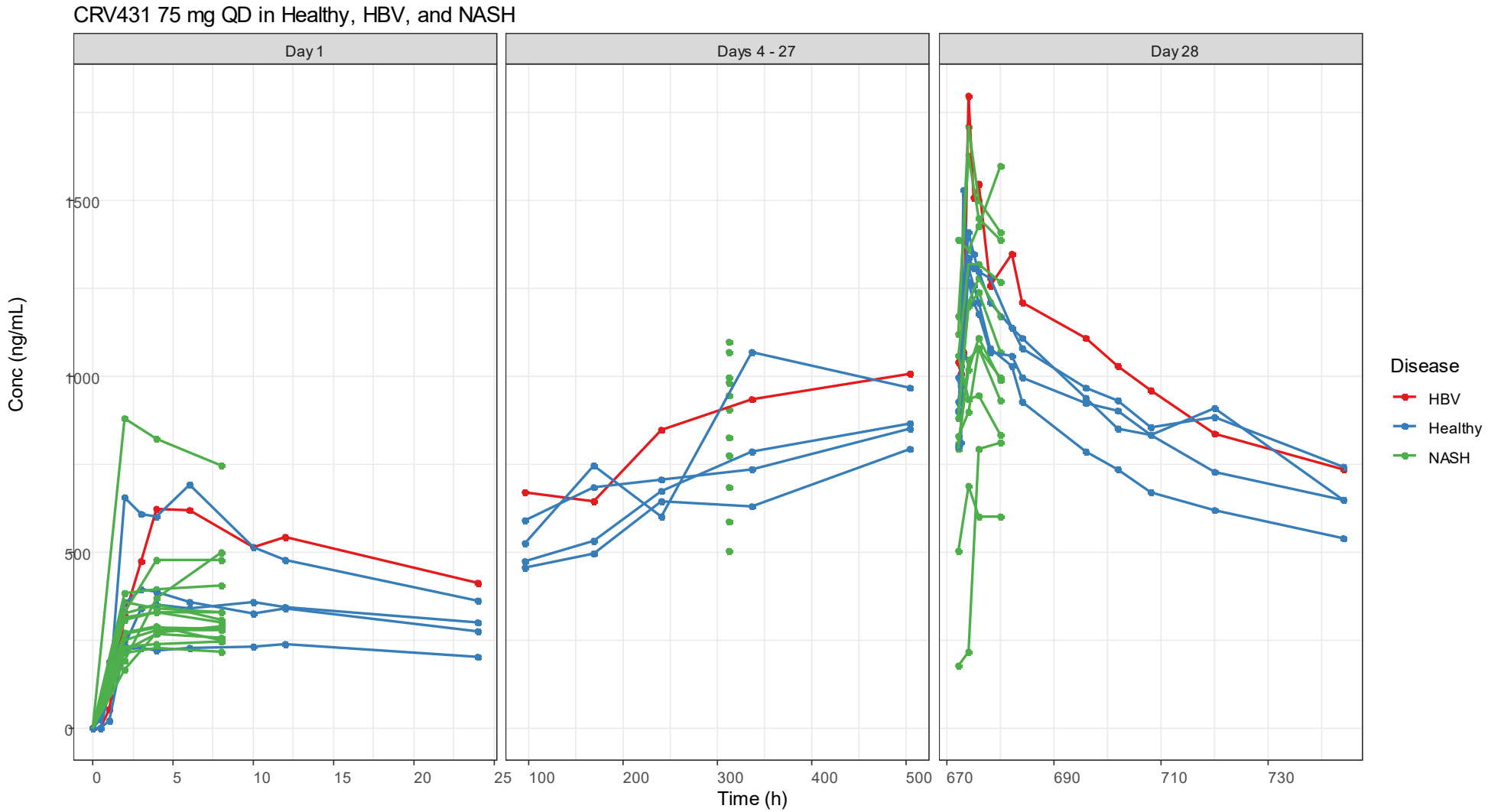
*randomized assignment; 2:1 – CRV431:placebo

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

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

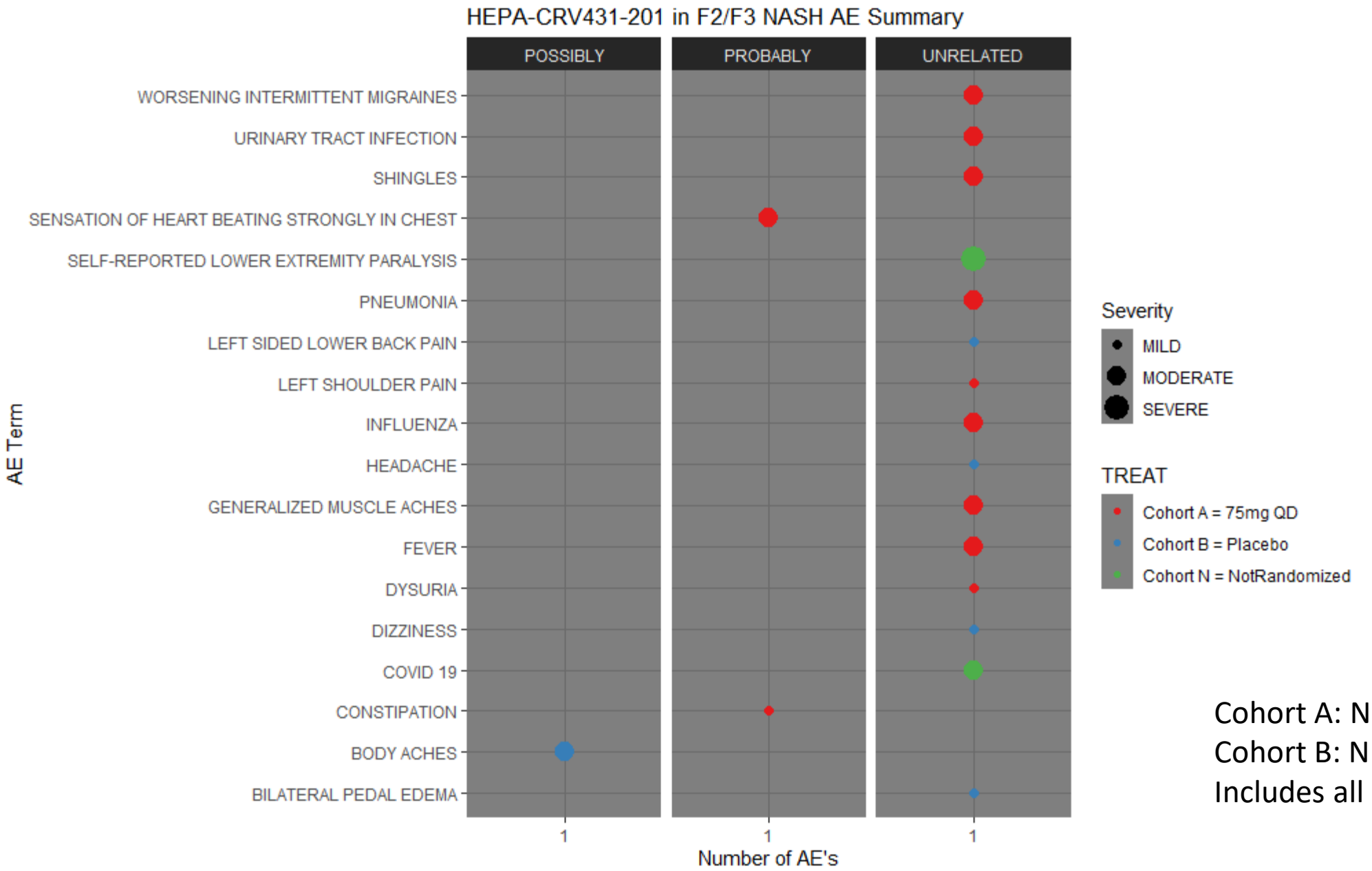
	CRV431 75MG	CRV431 225MG	POOLED PLACEBO	TOTAL
	(N= 15)	(N=5)	(N=8)	(N=28)
AGE				
MEAN (SD)	59.1 (9.6)	62.2 (5.3)	63.0 (7.2)	60.8 (8.48)
MEDIAN	61	59	64.5	62
MIN, MAX	39, 72	56, 69	51, 72	39, 72
SEX				
MALE	7 (47%)	3 (60%)	5 (62%)	15 (54%)
FEMALE	8 (53%)	2 (40%)	3 (38%)	13 (46%)
HEIGHT AT SCREENING (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



- 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



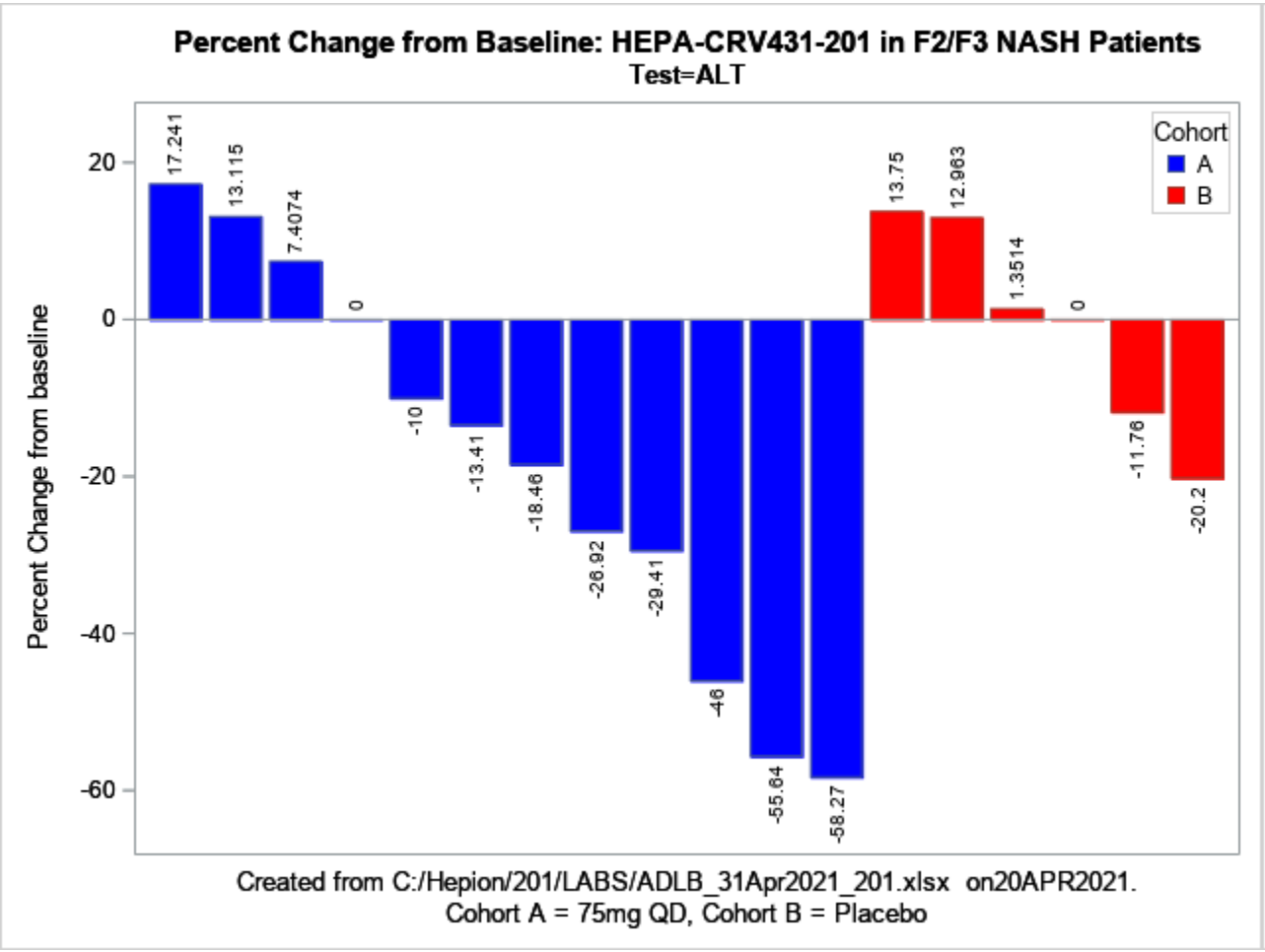
Cohort A: N=15
Cohort B: N = 6
Includes all randomized

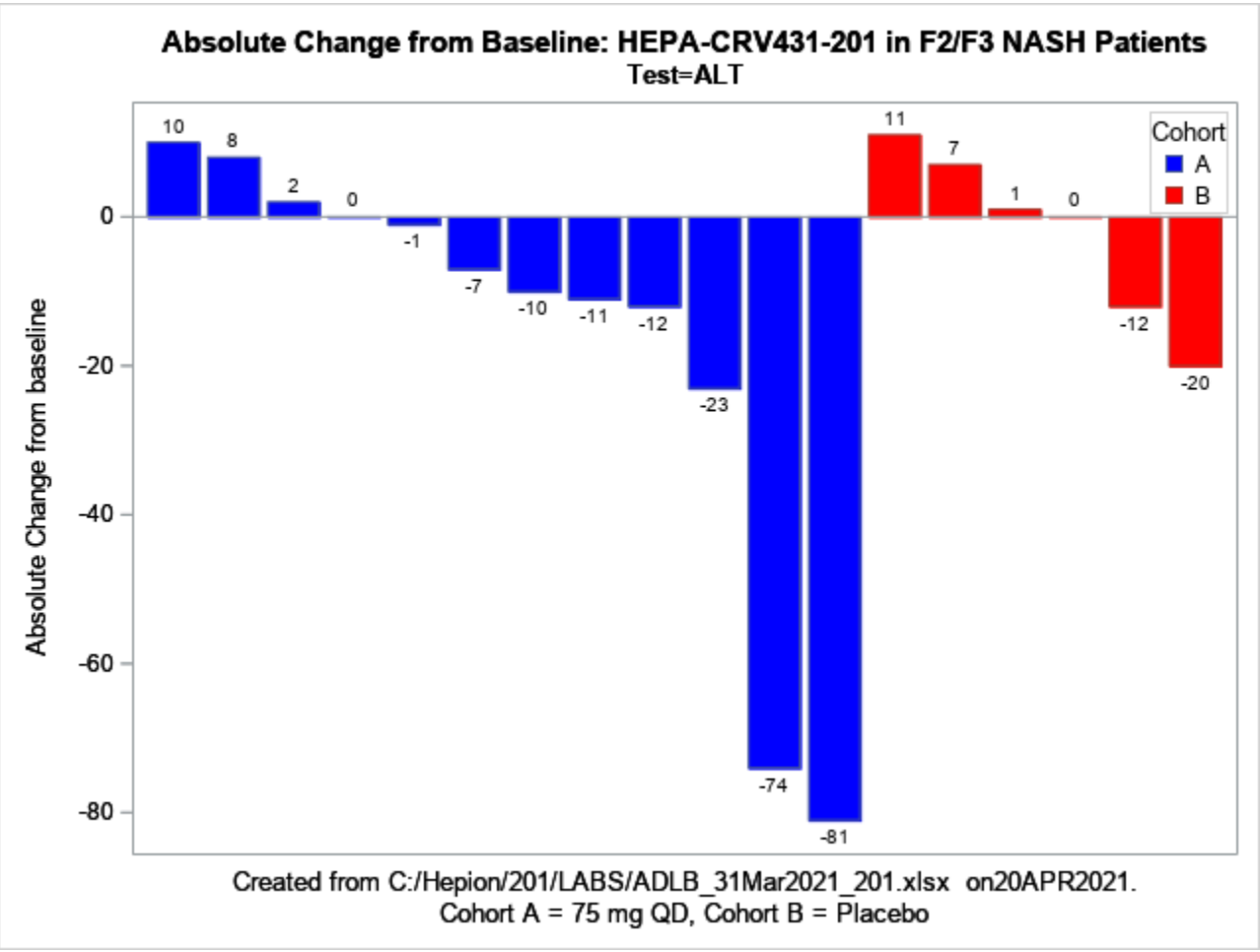
Exploratory Efficacy: Transaminases

Cohort A = 75 mg QD x 28 Days

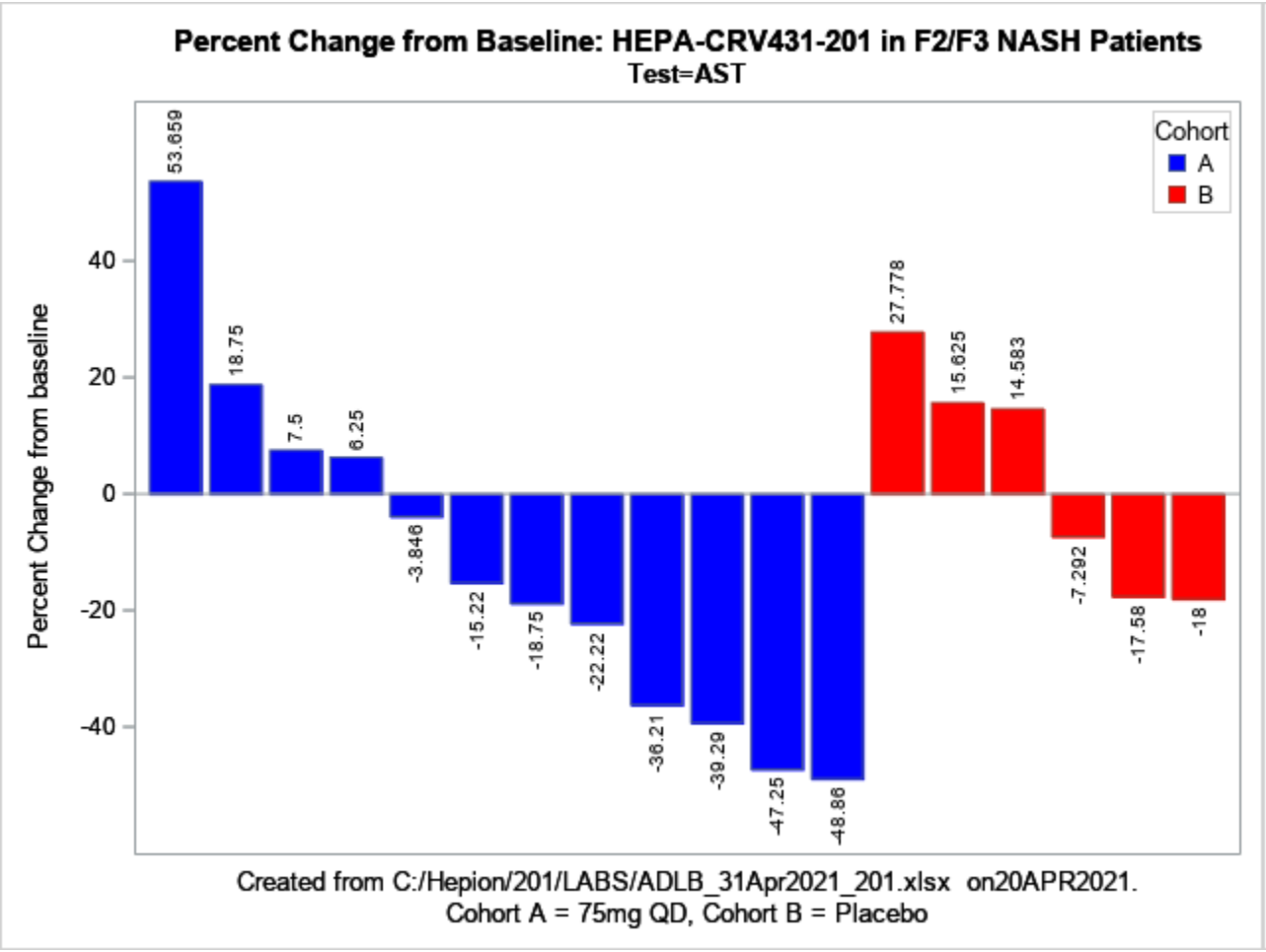
Cohort B = Placebo QD x 28 Days

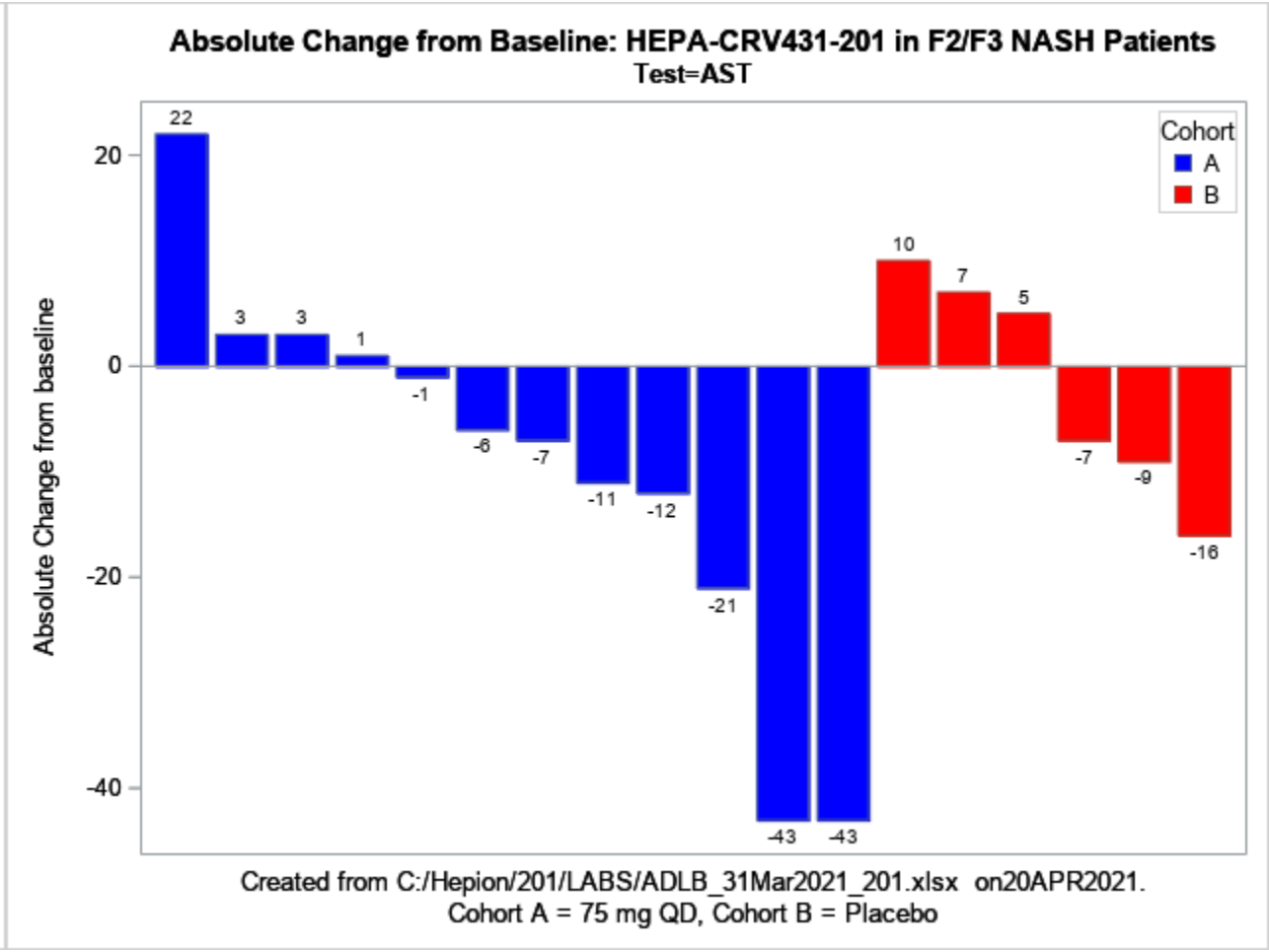
Exploratory Efficacy 75 mg Cohort: Alanine Transaminase at Day 28

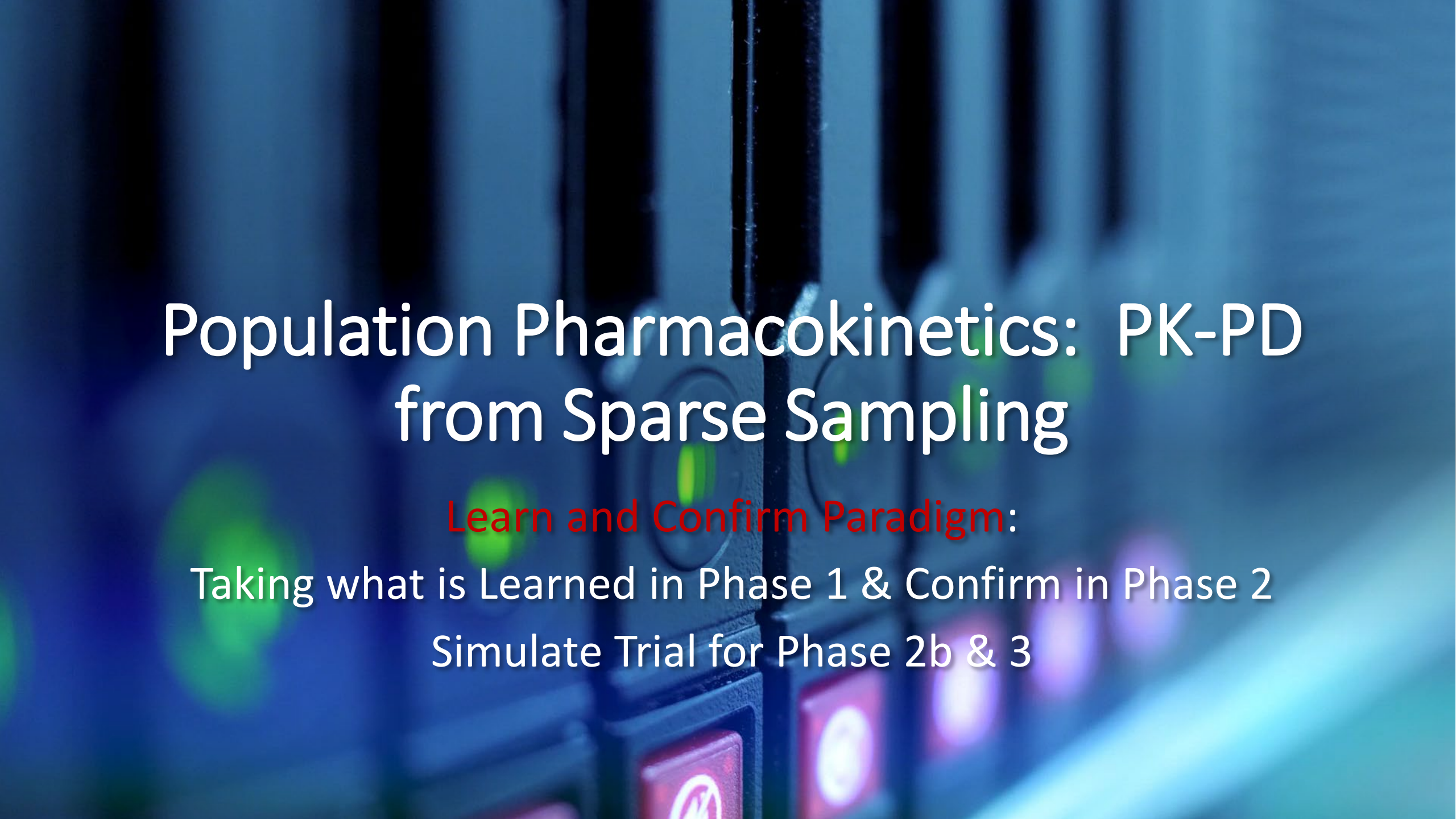




Exploratory Efficacy 75 mg Cohort: Aspartate Transaminase at Day 28







Population Pharmacokinetics: PK-PD from Sparse Sampling

Learn and Confirm Paradigm:

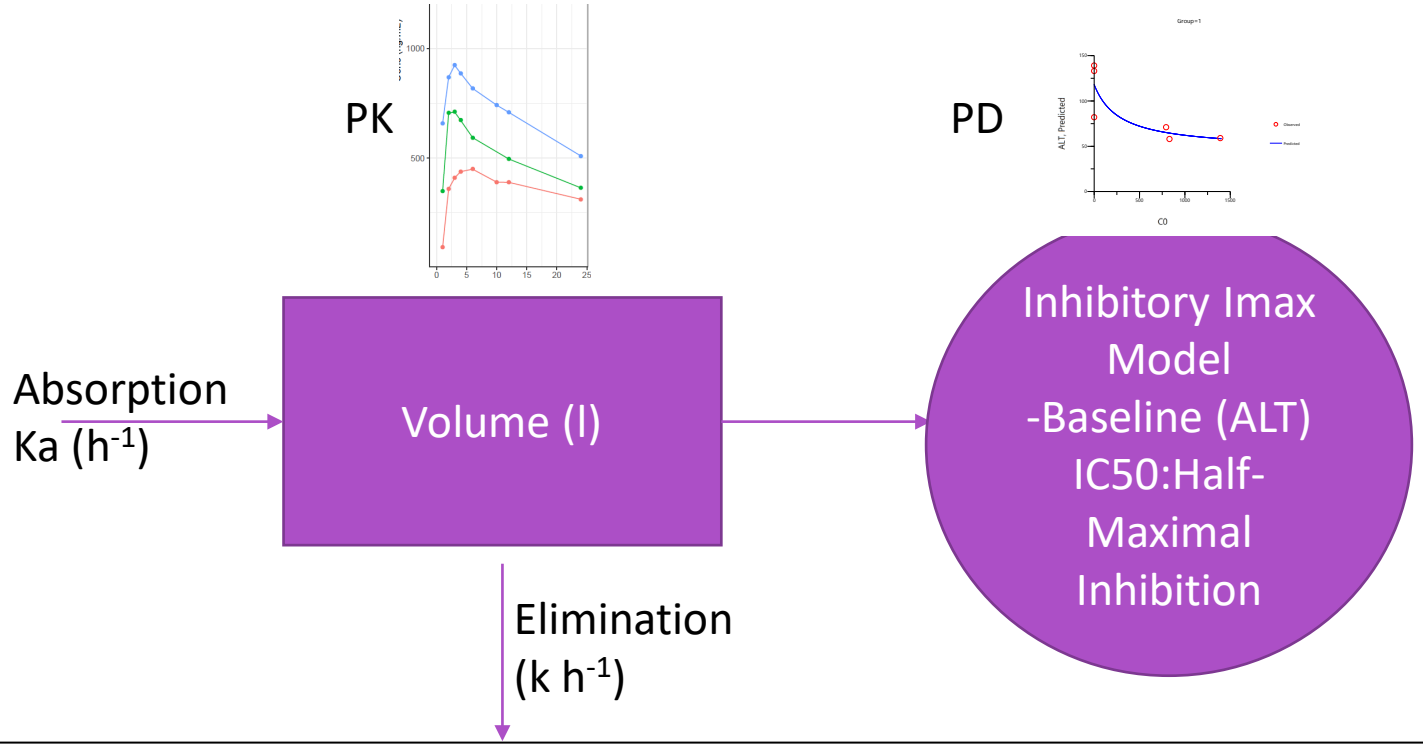
Taking what is Learned in Phase 1 & Confirm in Phase 2

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: ↑Cholesterol ~ ↓Absorption
  ↑Baseline AST ~ ↑Effect
  ↑Lean Body Weight ~ ↓ IC50

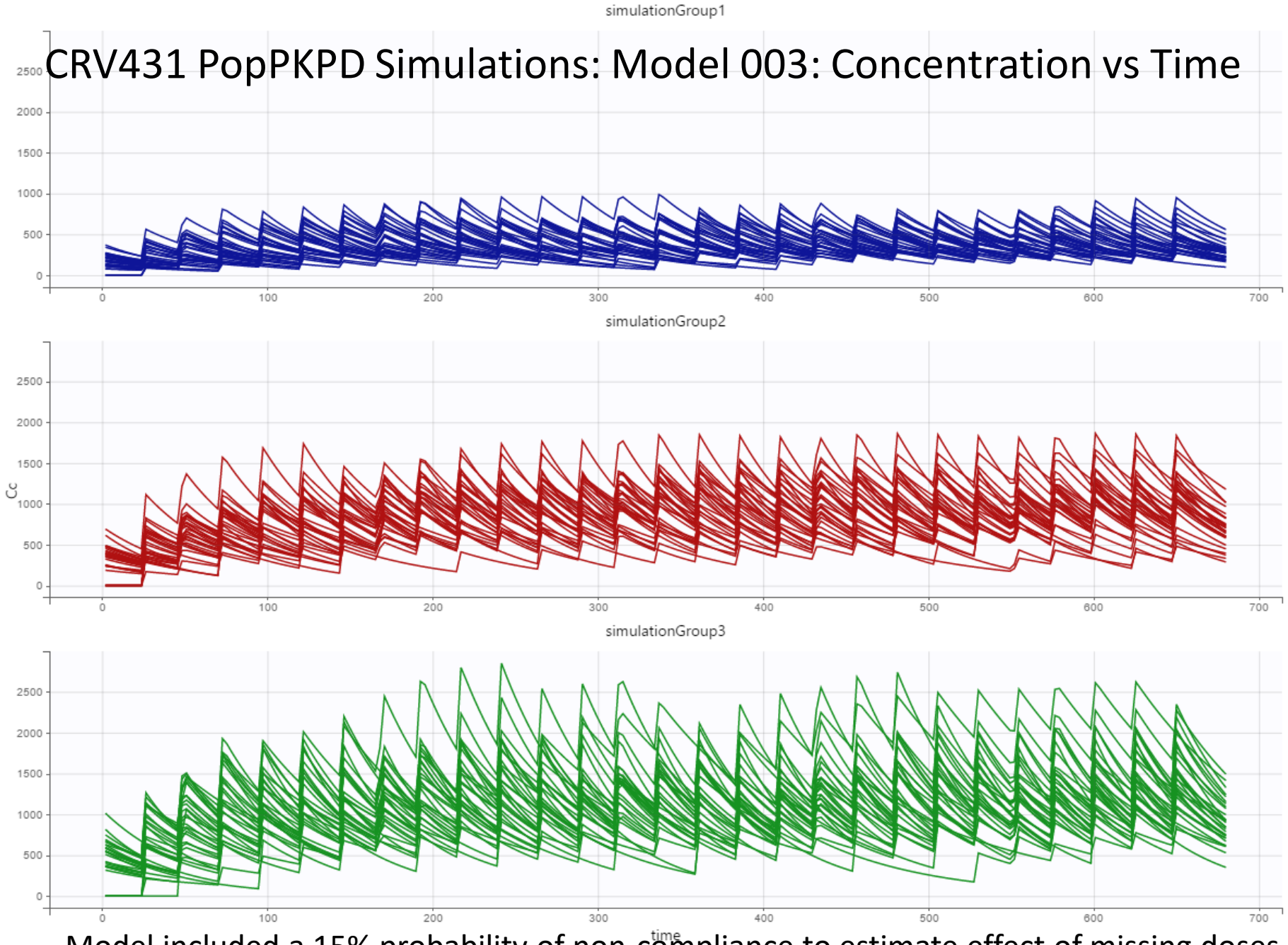
Trial Simulation PK

75 mg QD ->

150 mg QD ->

225 mg QD ->

CRV431 PopPKPD Simulations: Model 003: Concentration vs Time



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

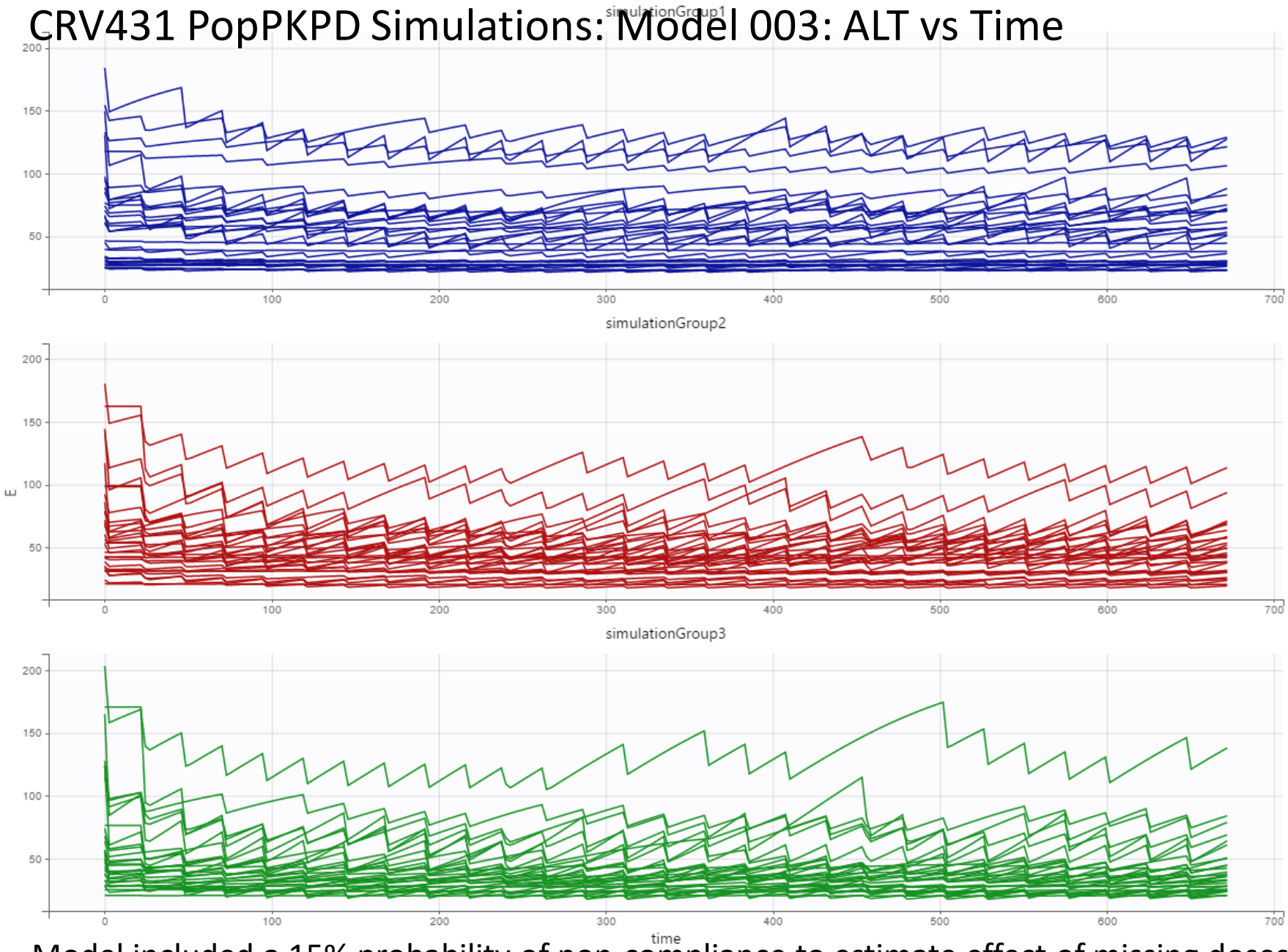
Trial Simulation PD

75 mg QD ->

150 mg QD ->

225 mg QD ->

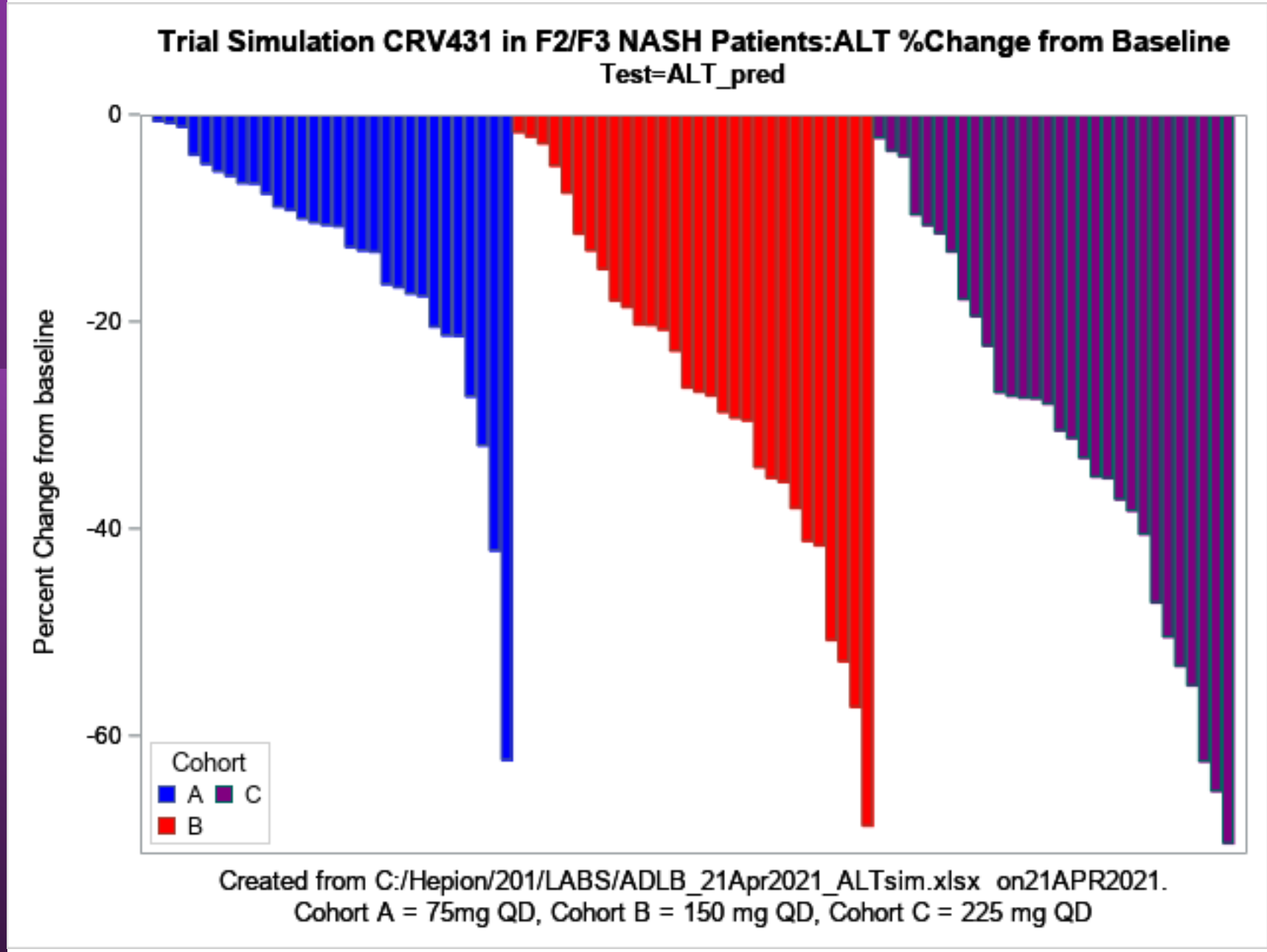
CRV431 PopPKPD Simulations: Model 003: ALT vs Time



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

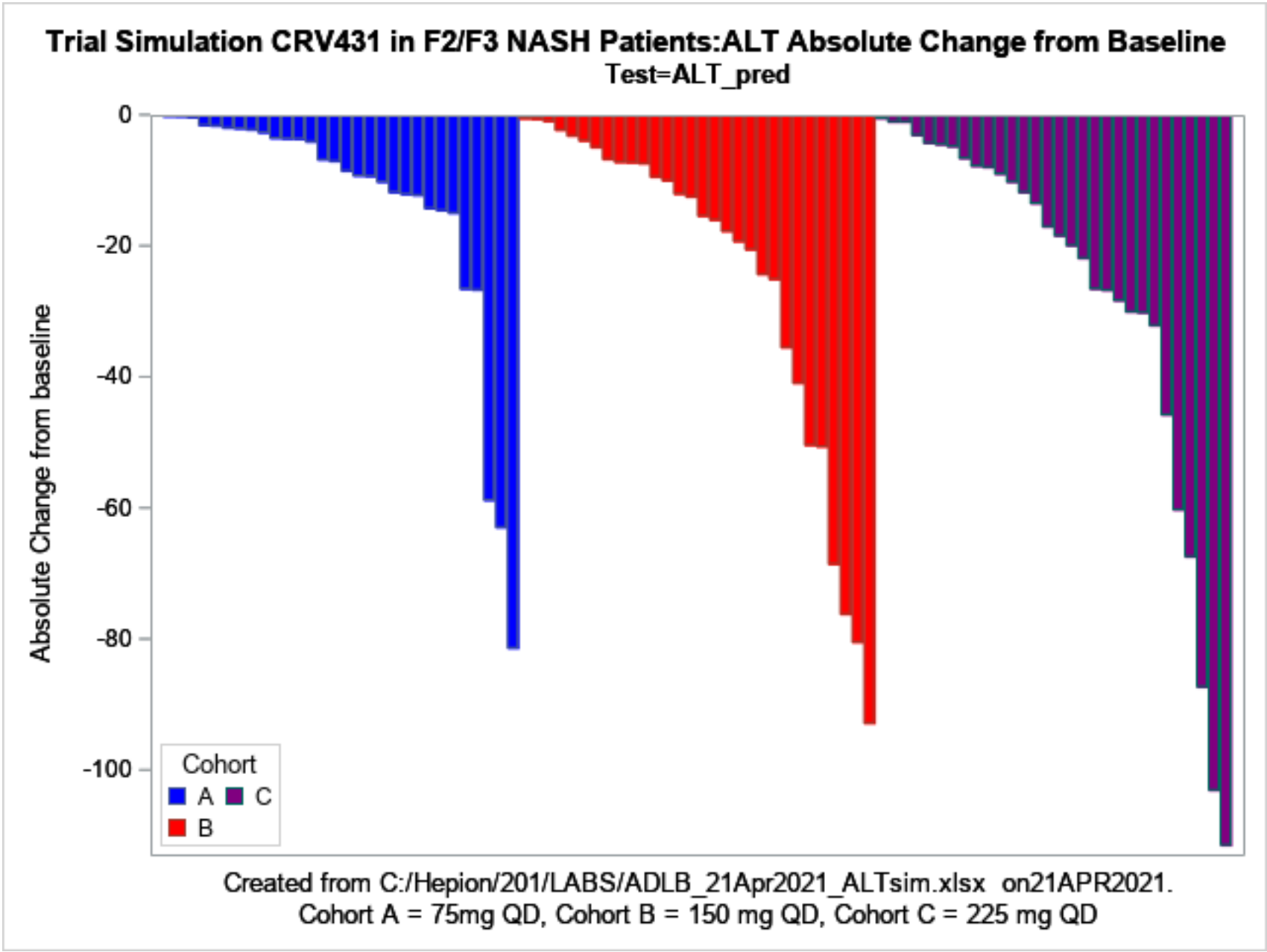
Trial Simulation %Change Day 28

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



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

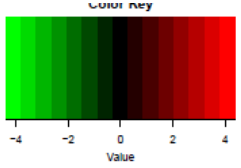
Exploratory Analysis

Gene Ontology using GeneWalk

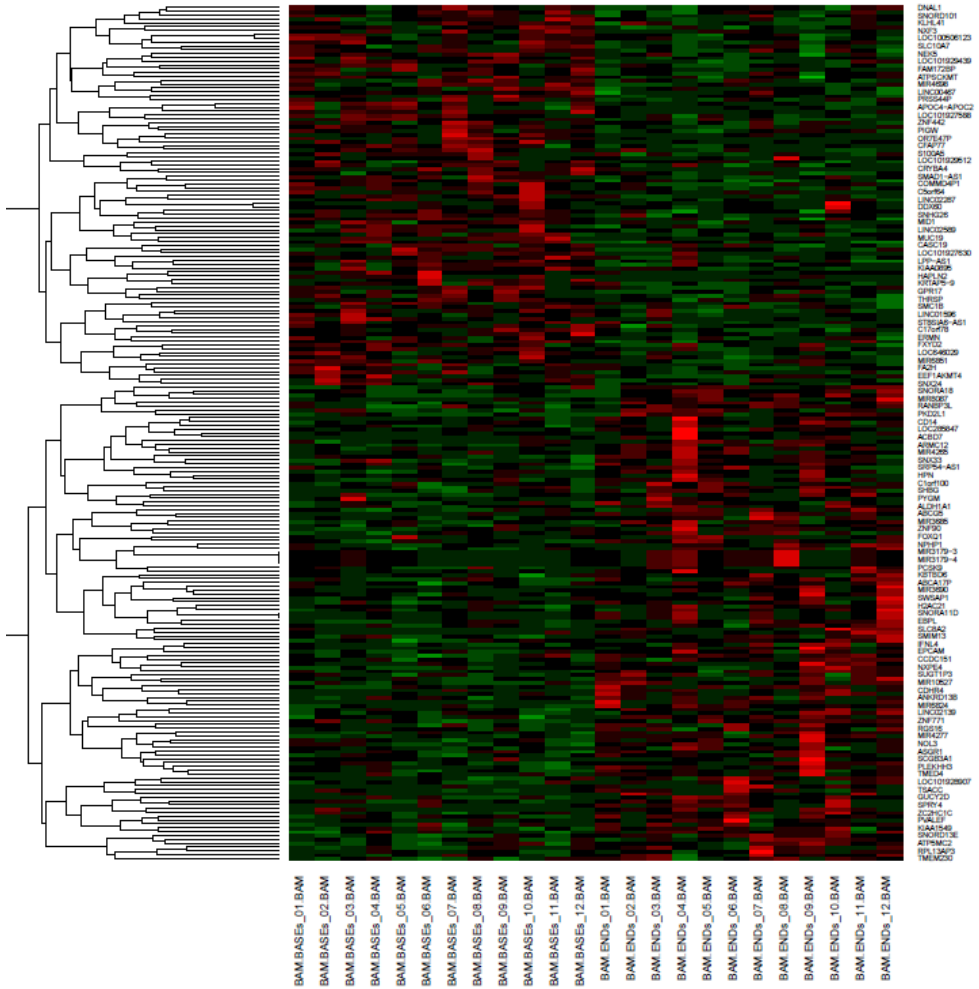
DESeq2, rrvgo

Phase2a: Bioinformatics & AI

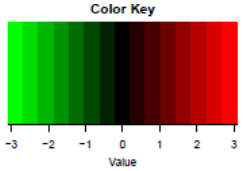
Standard Differentially Expressed Genes - DESEq2(Median Ratios): Day 1 v Day 28



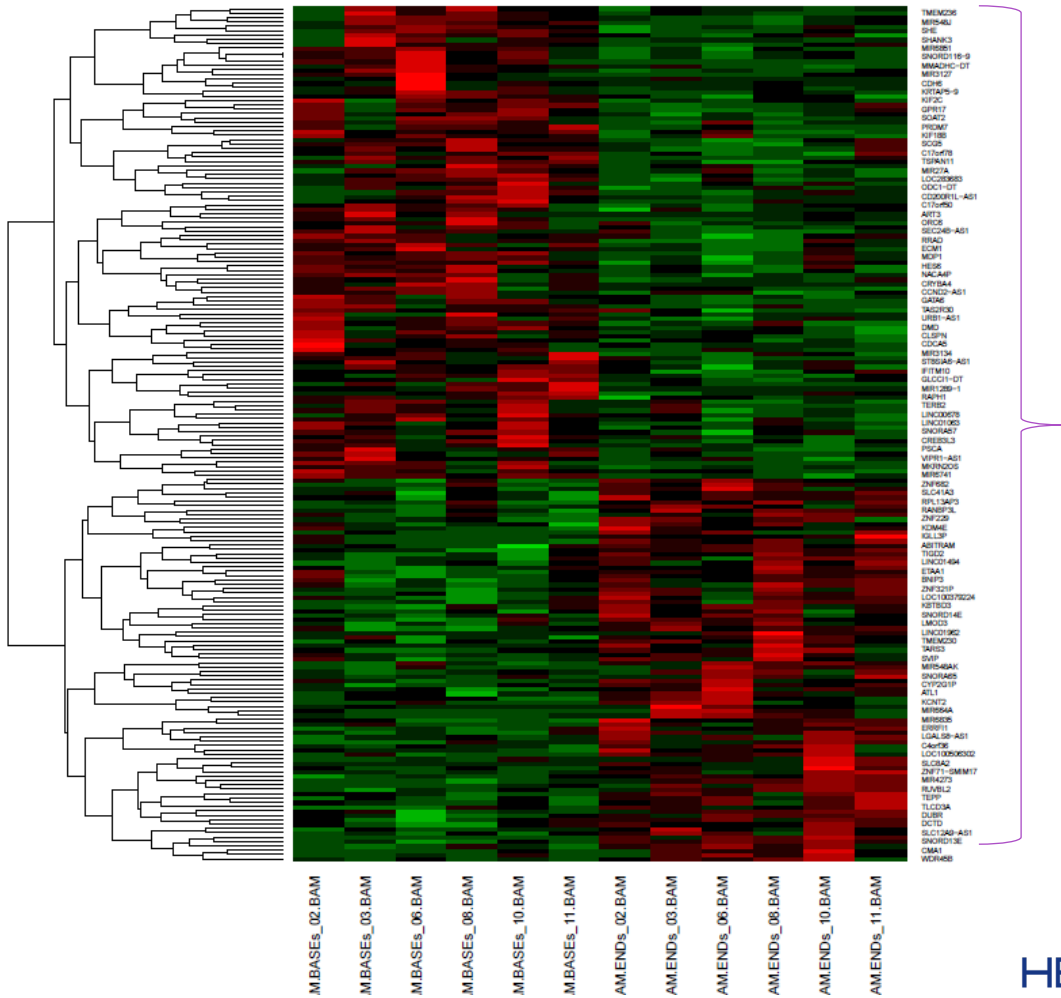
- RNA Seq Blood
- 12/12 Active Subjects



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

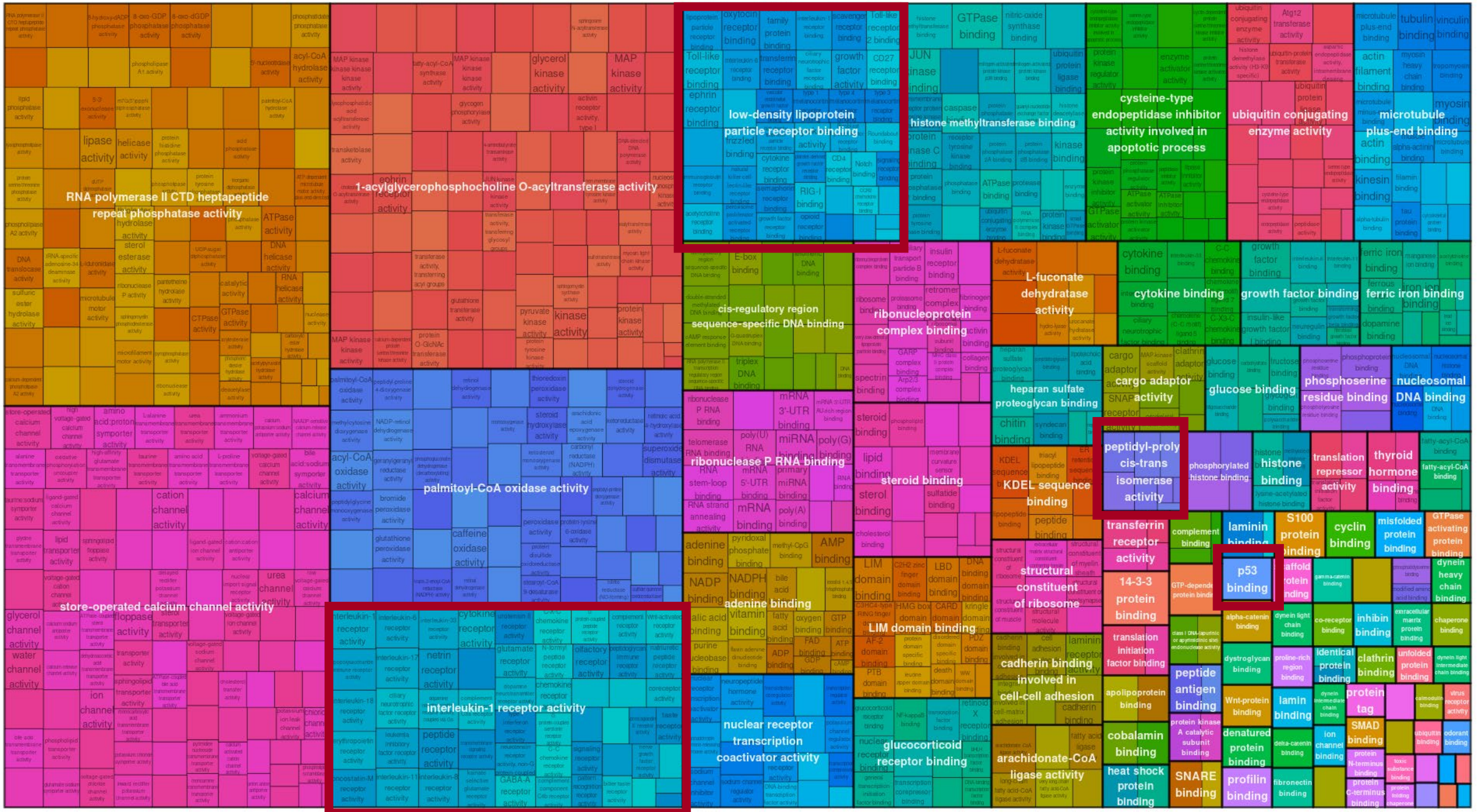


- Assessed patient demographics
- ALL Baseline labs
- Drug Concentration
- 6/12 Subjects

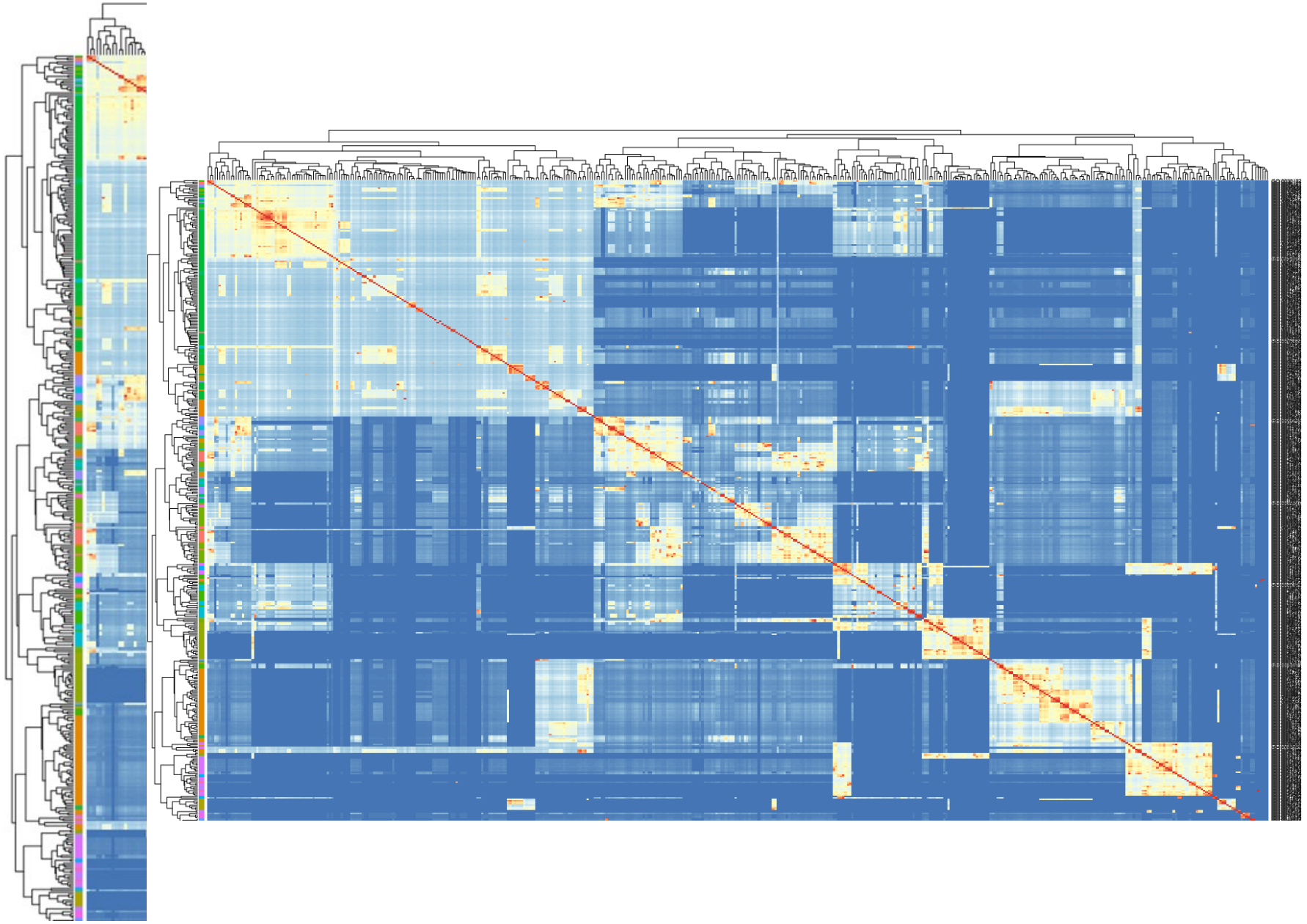


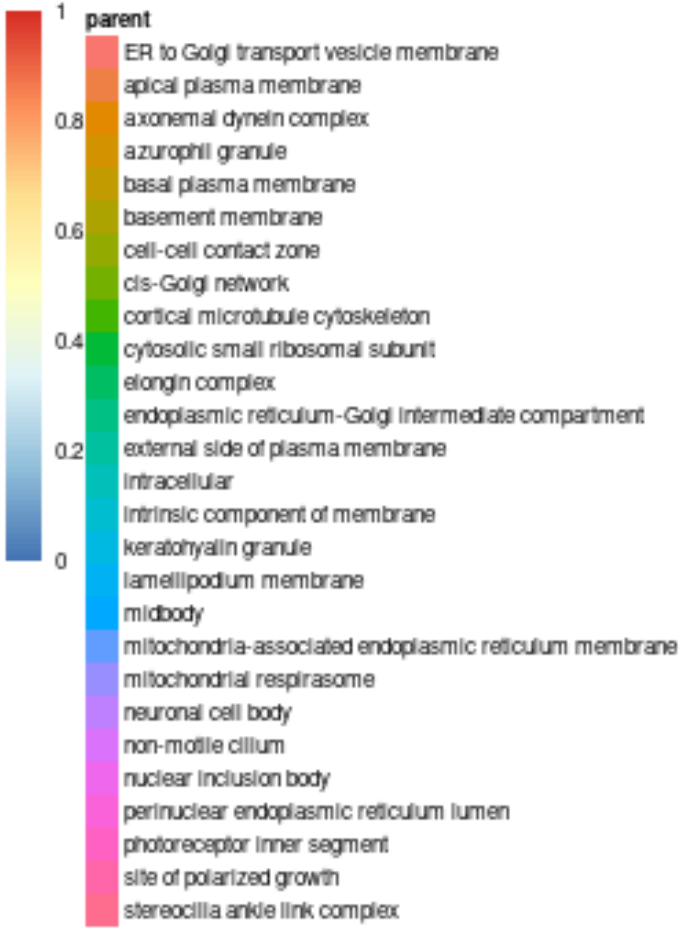
Potential Genomic Biomarker Responder Panel

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



Cellular Component Heat Map

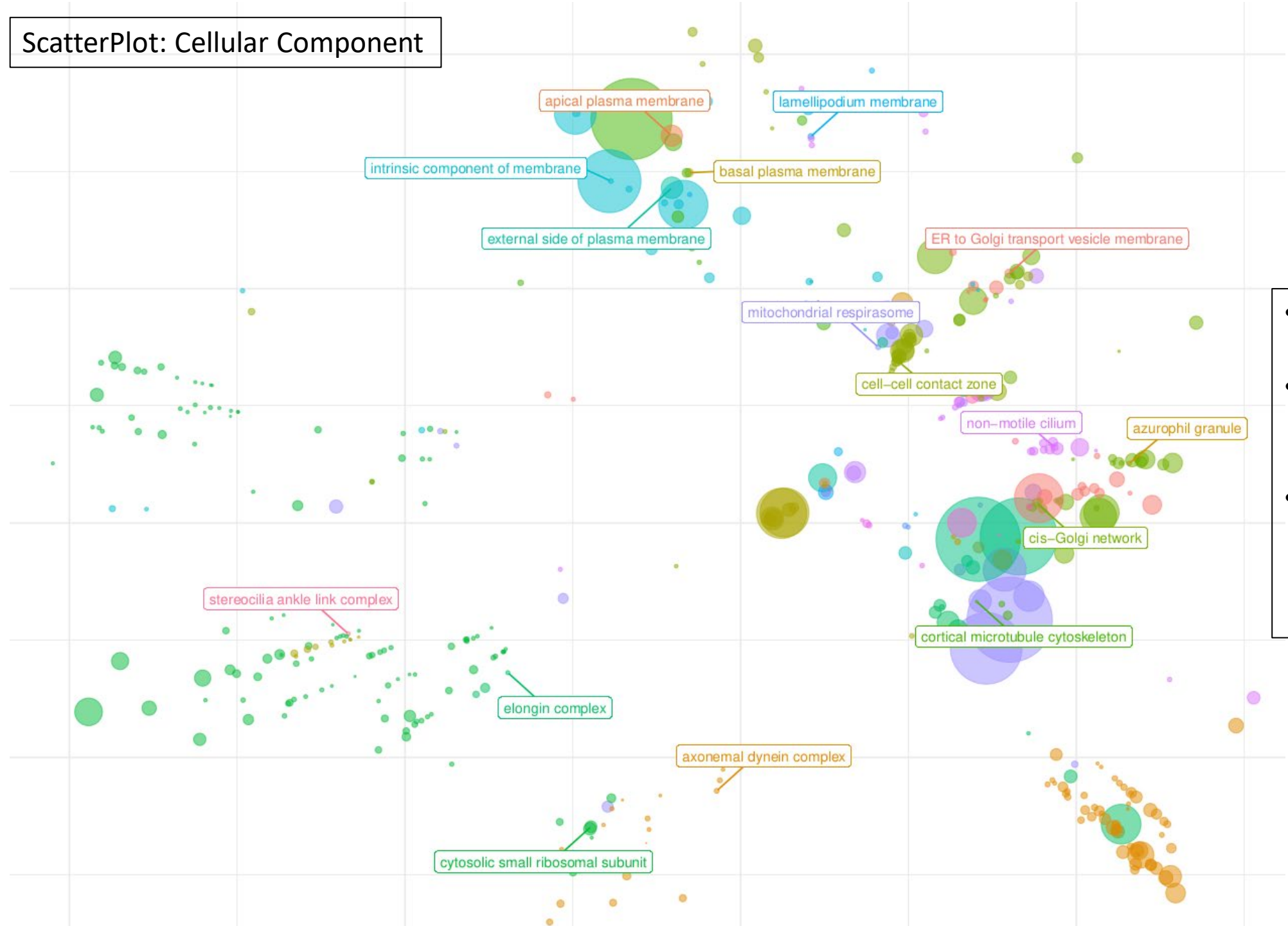




Expanded

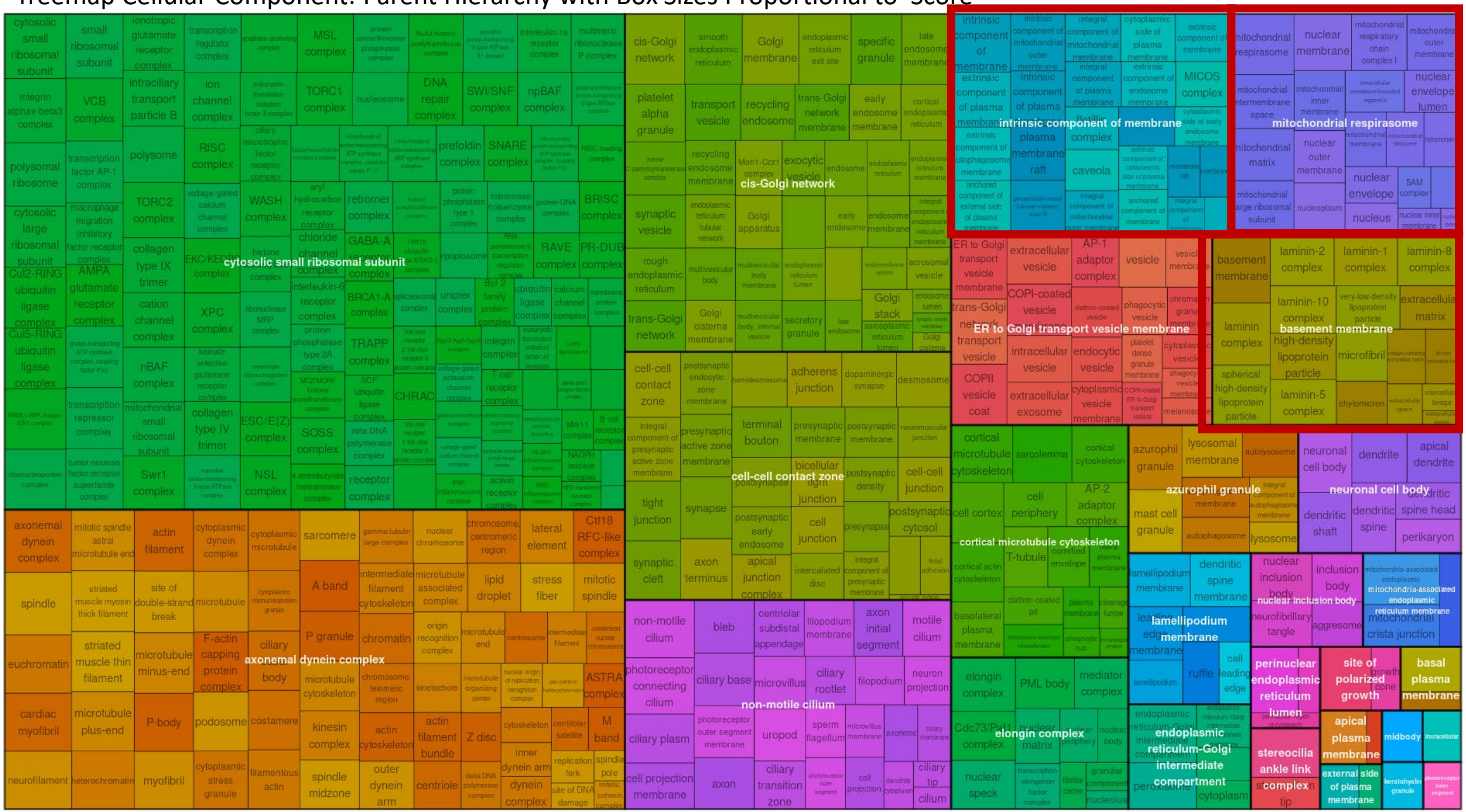
Expanded

ScatterPlot: Cellular Component



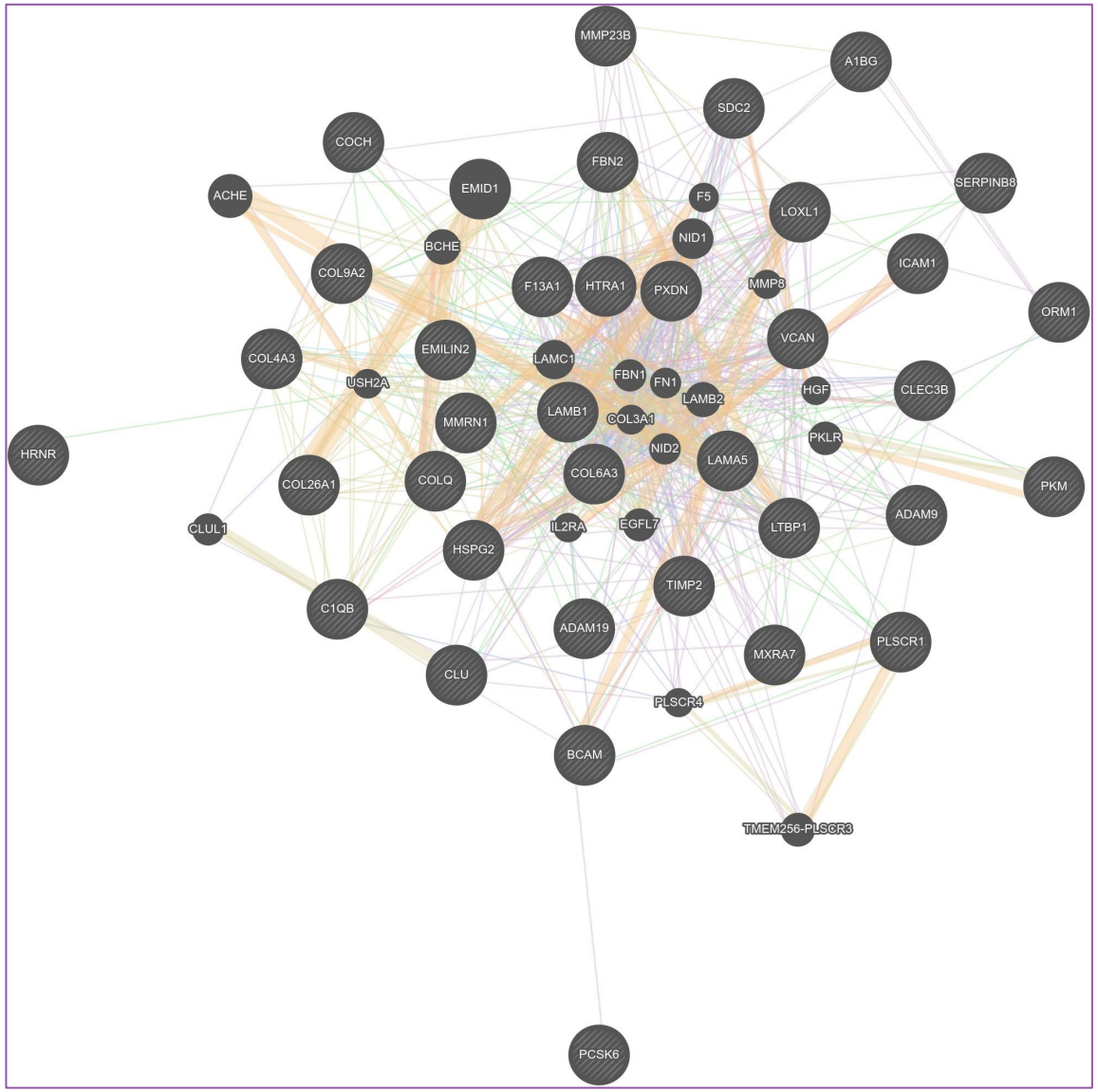
- GO terms as scatter points
- Distance between represents similarity between terms
- Size of point (bubble) provides scores (or number of genes) in the GO term

Treemap Cellular Component: Parent Hierarchy with Box Sizes Proportional to Score



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
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



- 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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