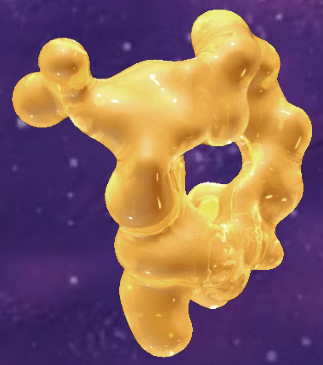
HEPION PHARMACEUTICALS

NASDAQ:**HEPA**

Rencofilstat (CRV431):

A liver-targeting drug candidate for NASH and HCC



Creating a Therapeutic Ecosystem

September 2022

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The Need and Opportunity

NASH and HCC are driving a Healthcare Crisis

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.

HCC
hepatocellular carcinoma

- **Most prevalent type (90%)** of liver cancer & liver cancer is 2 most common cancer-related death*
- **>905,000 new cases and >830,000 deaths globally***
  >30,000 new cases annually in U.S.* with **5-year survival of 18%****

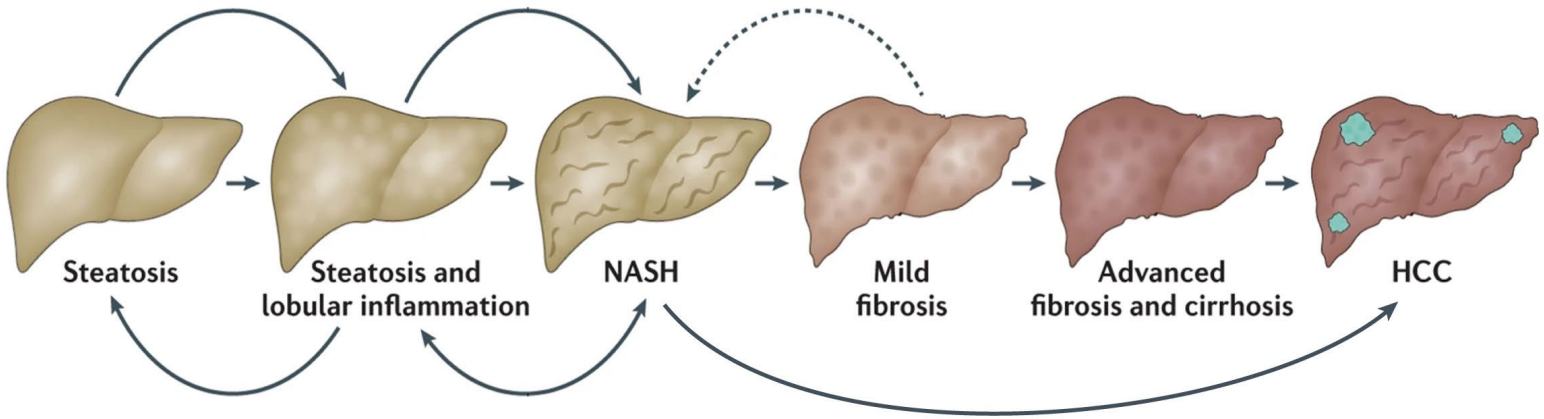


Image adapted from "From NASH to HCC: current concepts and future challenges", Anstee et al. (2019)

*The Global Cancer Observatory (Globocan), December 2020
**UpToDate, February 2022

Challenges to Achieve Development and Commercial Success

A Comprehensive Approach For Solutions

NASH

- No FDA drugs approved
- Traditional metabolism-regulating drugs largely not efficacious
- Multifactorial disease processes – metabolism, inflammation, fibrosis

HCC

- Poor prognosis and rising incidence from NASH
- Tyrosine kinase inhibitors and immune checkpoint inhibitors (ICIs) approved, but outcomes poor
- NASH may restrict responses to ICIs

1. Need for Disease Modifying Drugs

- Many molecules in development, majority targeting metabolic disease (liver fat)
- Need to address advanced fibrosis

2. Need for Companion Diagnostic(s)

- Disease typically asymptomatic
- Biopsies required, with significant drawbacks
- Widely available simple companion diagnostics needed

3. Need for Commercial Strategy

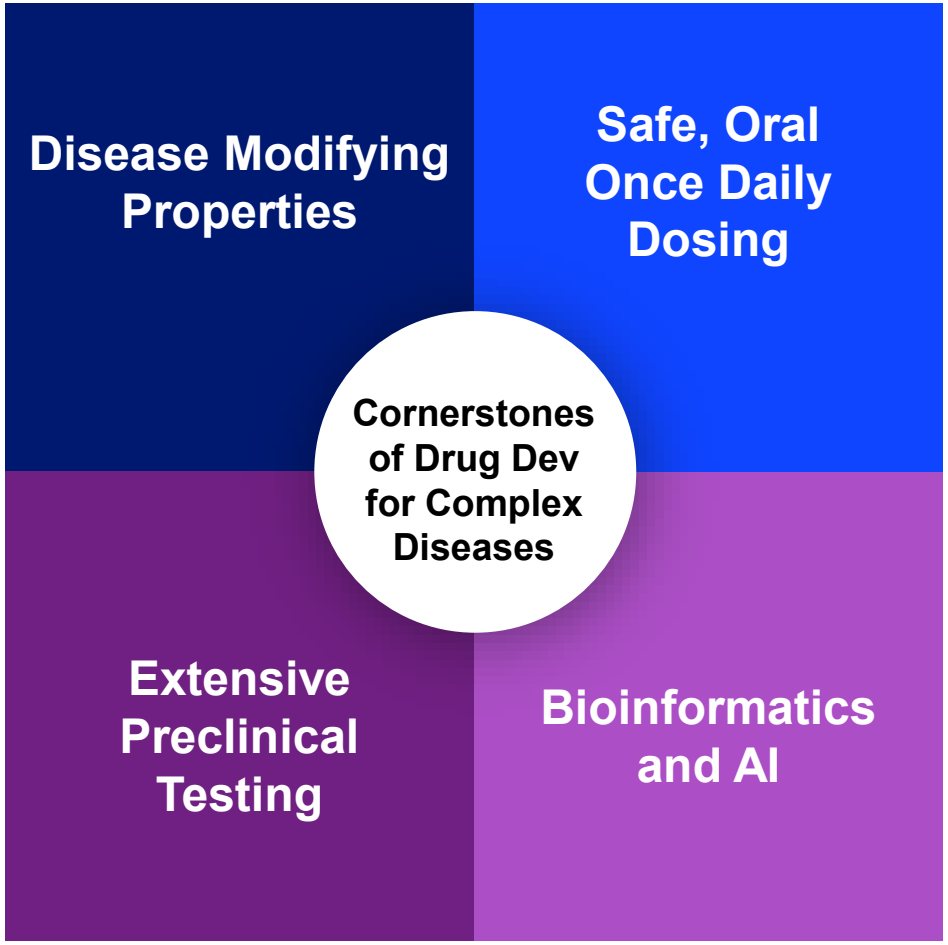
- Identify RESPONDER population to increase clinical success
- Address Market Access considerations

Hepion's Development Strategy

Rencofilstat Characteristics Offer Numerous Opportunities for Success

Targets KEY disease pathologies including fibrosis, inflammation, cell injury & death

Positive outcomes from diverse animal and laboratory studies increase the likelihood of success in the clinic



Oral medication with few side effects derived from proven drug class

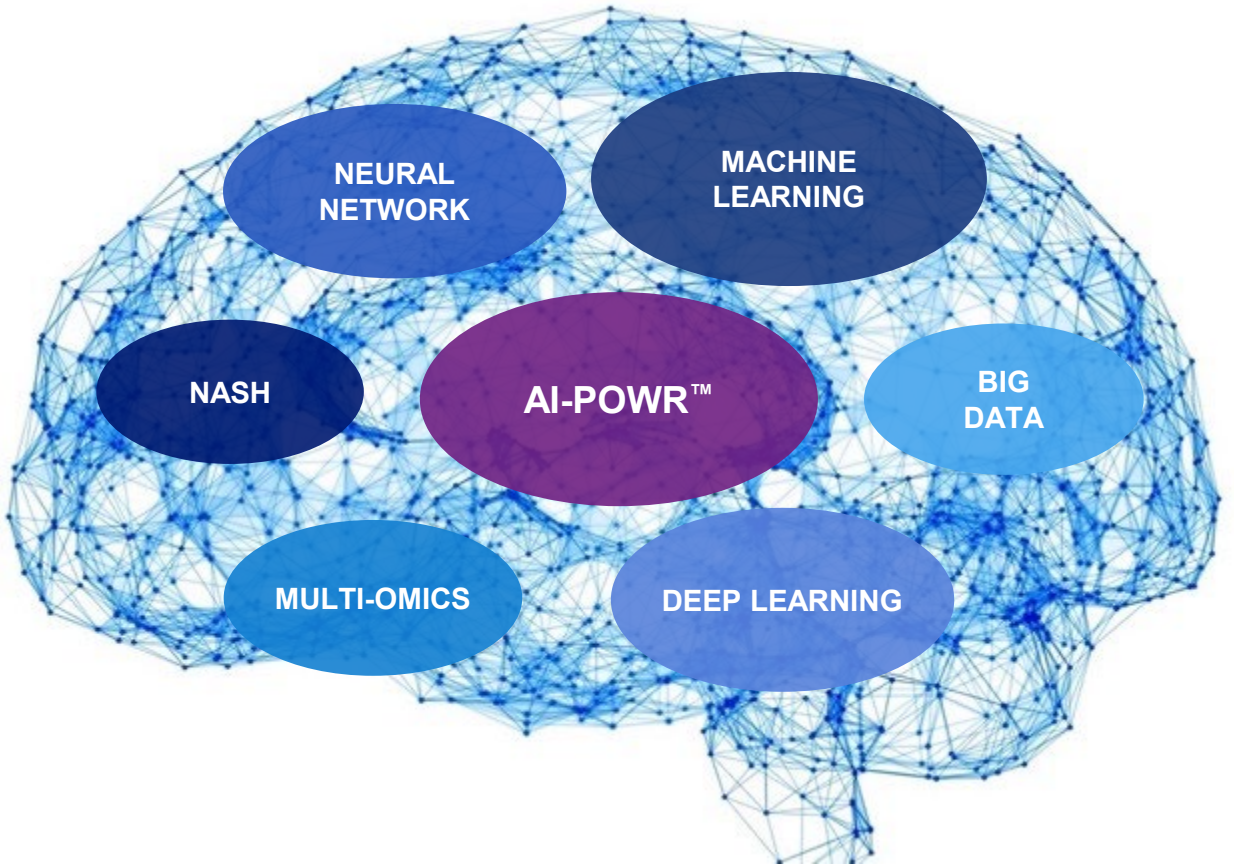
Analysis of large data sets to understand disease processes and identify ideal patients

Hepion's Proprietary State-of-the-Art Artificial Intelligence

Developing a Panel for Clinical Development and Commercialization

AI-POWR™

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



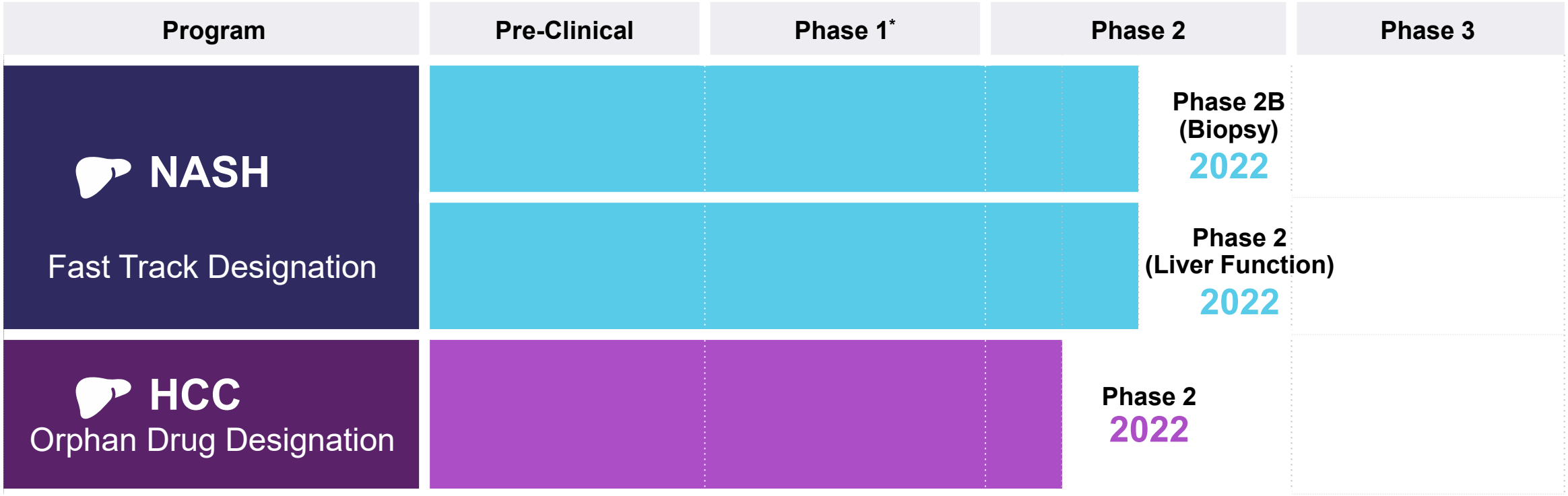
Rencofilstat

Drug Candidate for NASH and HCC

Rencofilstat Snapshot

- Cyclophilin inhibitor – novel approach to treating liver disease
- Once-daily, oral medication – soft gel capsules
- No serious adverse events to date
- Liver targeting: [liver] > [blood]
- Targets key pathologies including fibrosis, inflammation, cell injury
- Clinical Studies – 184 subjects dosed successfully
- *Fast Track Designation* for NASH
- *Orphan Drug Designation* for HCC
- Two separate Phase 2 NASH trials initiated

Rencofilstat Clinical Programs Advancing in 2022



*The Phase 1 program was comprised of Single and Multiple Ascending Doses, a Drug-Drug Interaction, and Food Effect studies.

Cyclophilins –Modulators of Diverse Biological Functions

Participants in Many Disease Processes

Cyclophilins:

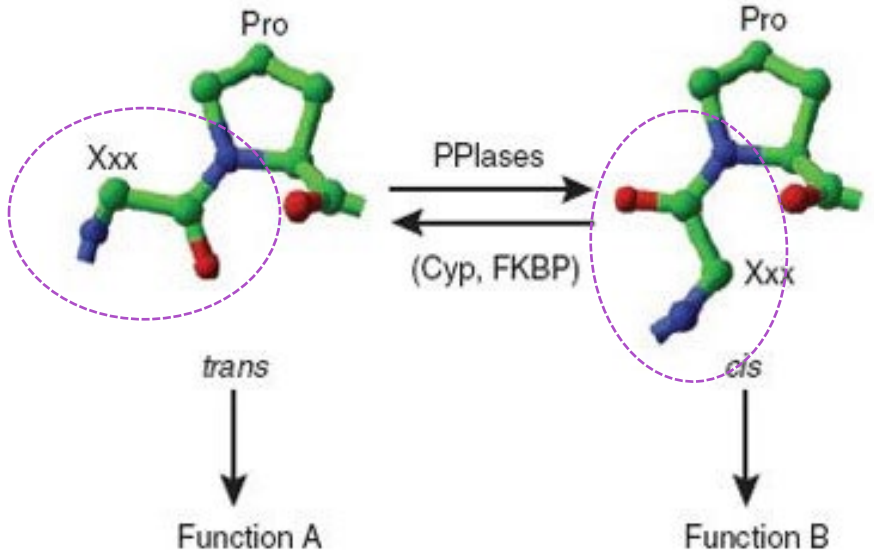
- enzymes that regulate the functions of target proteins through alterations in protein conformation

Cyclophilin Modulatory Roles:

- protein synthesis, folding, and degradation
- intracellular signal transduction
- ligand-receptor interactions
- molecular trafficking and secretion
- RNA splicing

Rencofilstat inhibition of multiple cyclophilin isoforms produces broad therapeutic effects

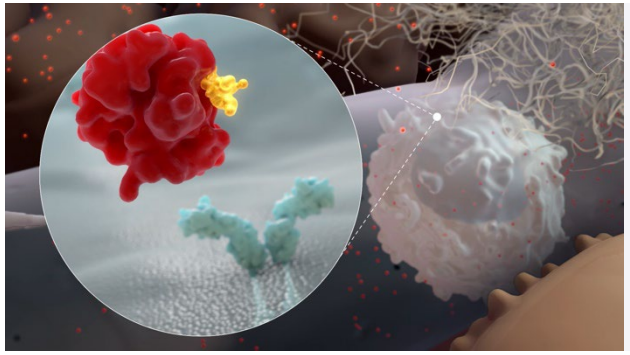
Proline Peptide Bond *cis-trans* Isomerization



Lu et al. (2007) Prolyl cis-trans isomerization as a molecular timer. Nature Chem Biol 3 (10): 619-629.

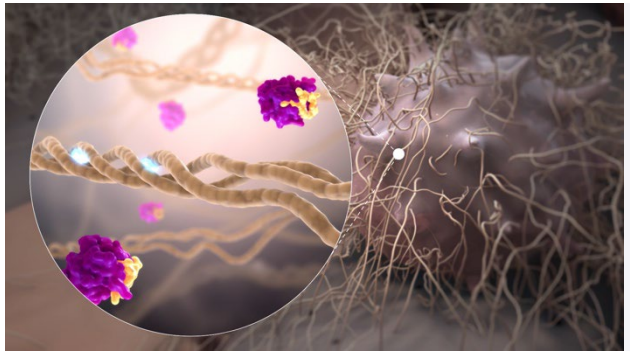
Rencofilstat Inhibits Three Primary Cyclophilins

Hitting the Right Targets – Inflammation, Fibrosis, and Cell Injury/Death



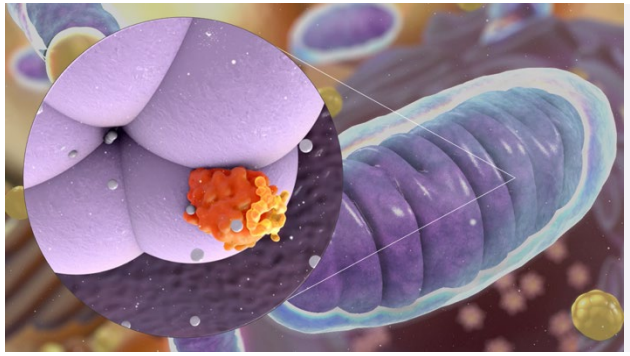
ANTI-INFLAMMATORY

Rencofilstat blocks **Cyclophilin A** binding to CD147 receptors and thereby decreases pro-inflammatory signaling



ANTI-FIBROTIC

Rencofilstat blocks **Cyclophilin B** binding to pro-collagen fibrils and thereby decreases formation and secretion of fibrotic collagen



CYTOPROTECTIVE

Rencofilstat blocks **Cyclophilin D** activation of mitochondrial membrane pores and thereby decreases cell death in injured livers

Preclinical NASH: Antifibrotic and Anti-inflammatory Effects

Extensive Preclinical Testing

ANIMAL MODELS (mice and rats)

- 8 NASH-related studies
  - diet and/or chemical-induced liver disease
- Chronic lung fibrosis study
- Acute lung injury study
- Acute renal injury study
- Cyclophilin knockout studies
- 2 diabetes-related studies

TRANSLATIONAL RESEARCH

- Human LIVER slices (tumor-adjacent fibrosis)
- Human LUNG slices (pulmonary fibrosis)
- Human blood platelets

- Consistent antifibrotic effects up to 80%
- Decreases in weight gain and adiposity
- Decreases in acute lung injury
- Alterations in 'omic' signatures consistent with therapeutic effects
- Anti-thrombotic potential

Preclinical HCC: Multi-modal and Drug Combination Effects

Diverse Experimental Models and Analyses

EXPERIMENTAL MODELS

- Murine syngeneic Hep53.4 transplant into normal and fatty livers
- Murine NASH-induced HCC (STAM)
- 12 human HCC cell lines
- Multiple myeloma cellular studies
- Drug combinations on cancer cell lines

BIOINFORMATICS

- Whole exome sequencing: 36 samples
- RNA-seq: 178 samples
- Metabolomics: 52 samples
- Public databases

- Monotherapy and drug combination anti-tumor effects
- Synergy with anti-PD1 agents in NASH-related HCC model
- Extended survival in animal models
- Immuno-modulatory, proteostatic, oncogenic signaling, metabolic, and chemoresistance mechanisms

Cyclophilins in Cancer

Numerous Cancer Processes Regulated by Cyclophilins

CYCLOPHILIN-REGULATED PROCESSES IN CANCER	Cyp A	Cyp B	Cyp D	Cyp E, G, H, L1, L3
Proteostasis (synthesis, folding, ubiquitin-proteosome)	✓	✓		
Signal transduction				
• MDM2-p53-p21	✓	✓	✓	
• ERK1/2, p38, PI3K/Akt, CrkII, STAT3, Jak2/STAT5	✓	✓	✓	
• Wnt/β-catenin/Myc	✓	✓		
• TGFβ-SMAD2/3	✓	✓		
Cell proliferation, migration, cell death	✓	✓	✓	
Resistance to hypoxia, radiation, and chemotherapy	✓	✓		
Inflammation (neutrophils, cytokines)	✓	✓		
Energy metabolism			✓	
Immunomodulation	✓			
Tumor extracellular matrix		✓		
Transcription and splicing			✓	✓

Overview of Phase 1 Studies (completed)

Phase 1 Studies Completed – Safe and Well Tolerated

Key Findings

Single Ascending Dose: 75 mg – 525 mg

- No SAEs
- No AEs with Dose Response

Multiple Ascending Dose: 75 mg – 375 mg

- No SAEs
- No AEs with Dose Response
- Effective $t_{1/2}$ ~ 30 hours, $Tmax_{ss}$ ~ 1 – 2 hours

Drug-Drug Interaction: Midazolam & Ketoconazole

- 4.9-fold increase in Cmax and 4.4-fold increase in AUC with ketoconazole
- No increase in midazolam exposure

Food Effect: High Fat Meal

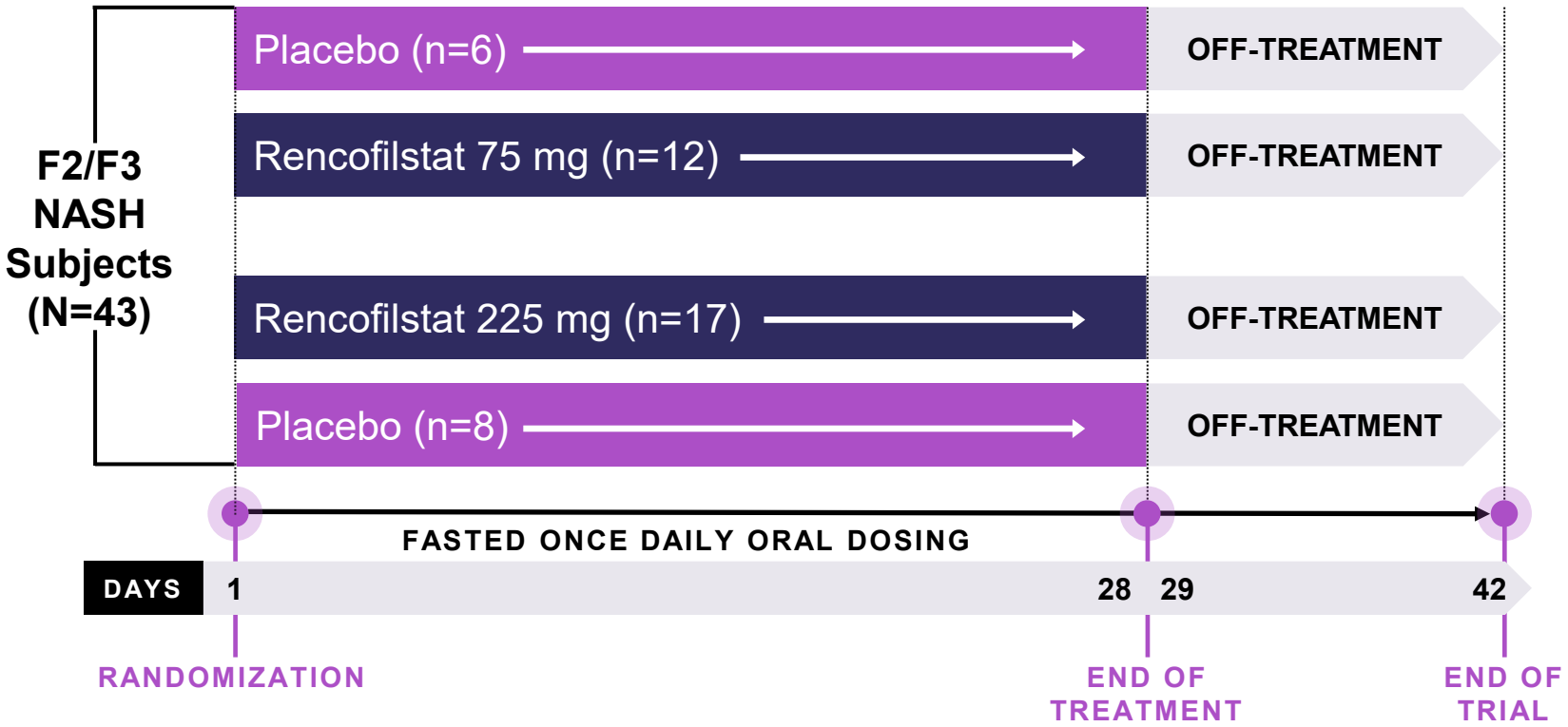
- Cmax Ratio: 102.2 (90.5 - 115.4)
- AUC Ratio: 118.5 (96.1 - 146.0)

Overview of Phase 2a ‘AMBITION’ NASH Trial (completed)

Phase 2a 'AMBITION' NASH Study

Safety, Tolerability, and Pharmacokinetics

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



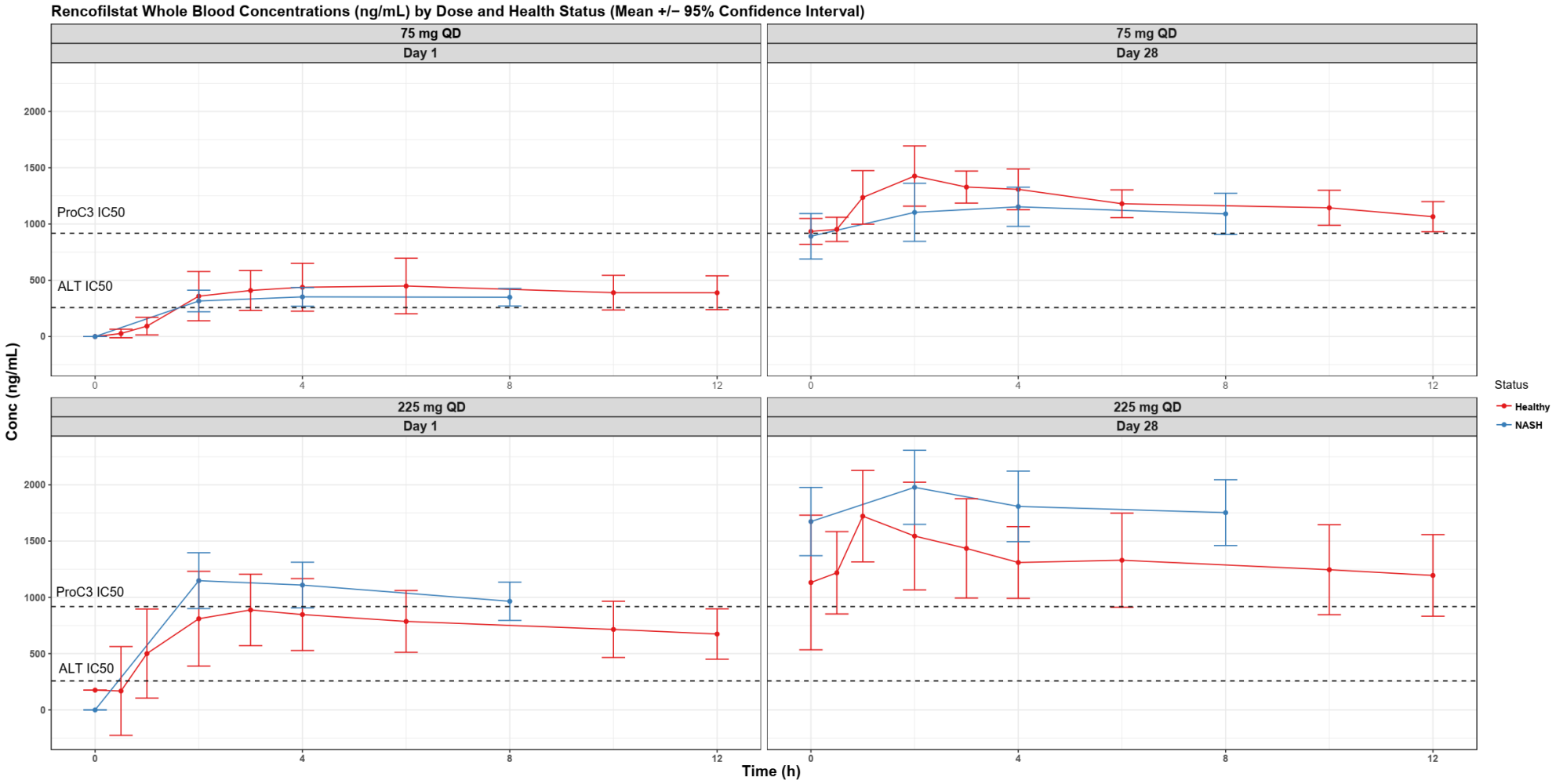
Primary Endpoints:

- Safety
- Tolerability
- Pharmacokinetics

Conducted at 10 sites in the US

Phase 2a: All Primary Endpoints Met

Adequate Exposures Anticipated for Efficacy

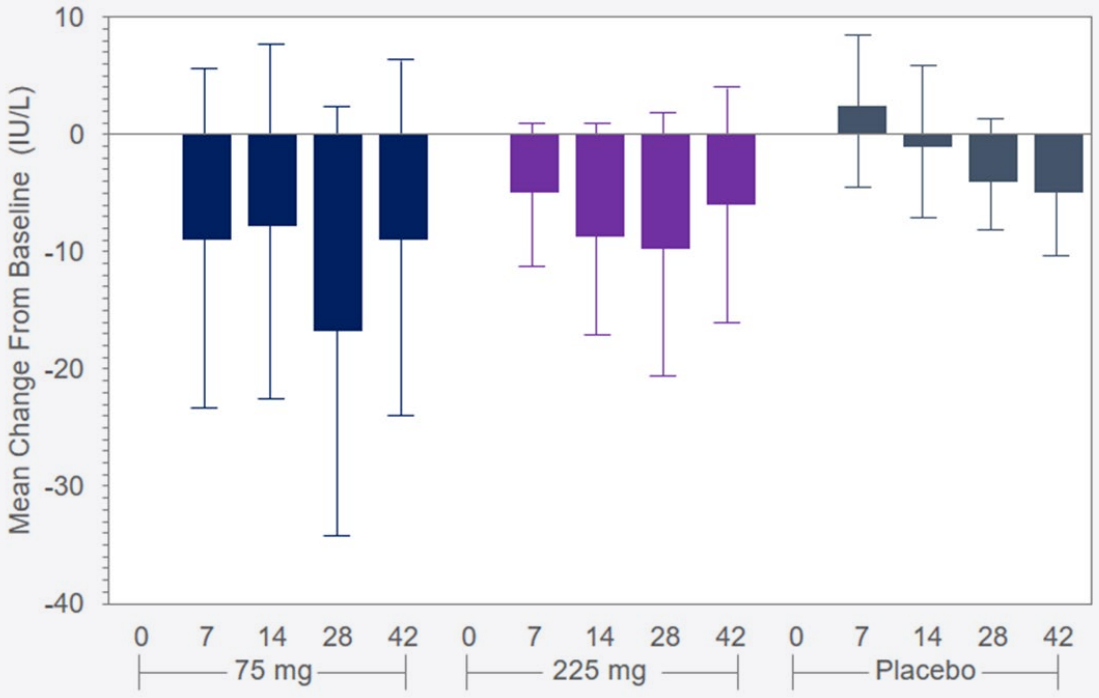


- No Serious Adverse Events
- Rencofilstat concentrations not significantly altered by NASH
- 225 mg QD achieves effective concentrations after the first dose*

***Response analysis** suggests concentrations > 800 ng/mL by Day 14 are associated with clinically relevant reductions in ALT and ProC3 and changes in gene activity and lipids consistent with NASH resolution. This concentration is achieved on Day 1 with a 225 mg QD dose and Day 28 with a 75 mg QD dose.

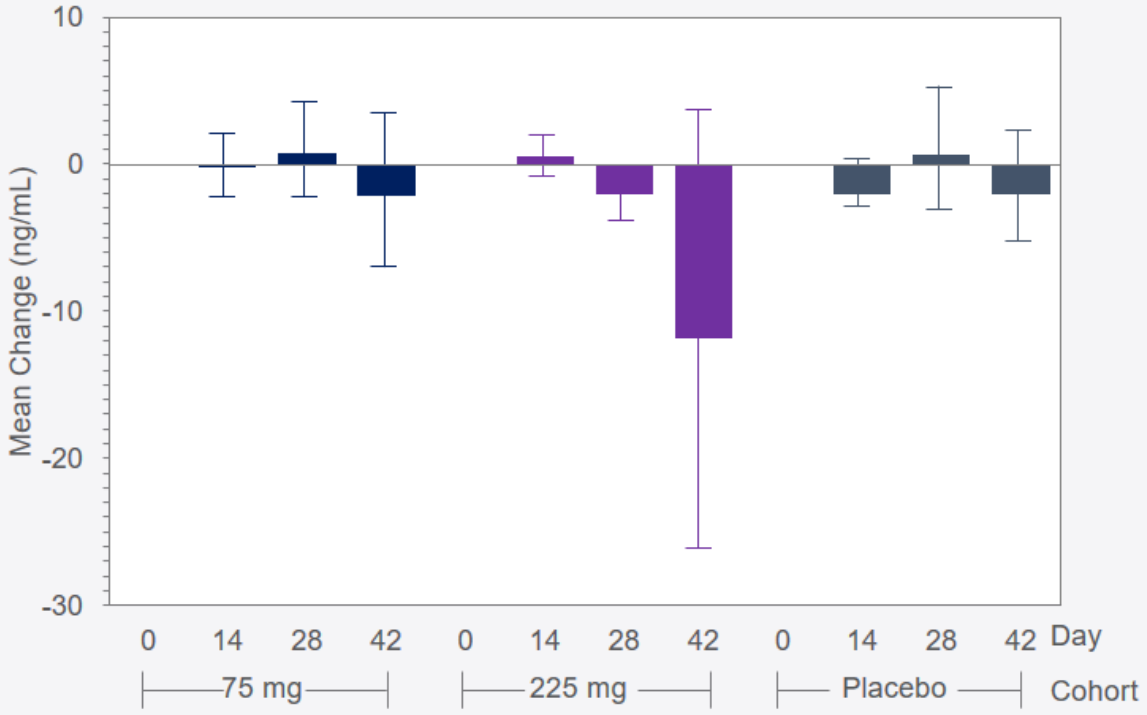
Phase 2a: Clinical Efficacy Biomarkers

ALT Change from Baseline



- ALT has a high efficiency for screening NASH drug effects but low effectiveness as a sole marker for NASH Fibrosis Response[1]

Pro-C3 Change from Baseline ≥ 17.5 ng/mL



- ProC3 emerging as biomarker indicative of fibrosis[2]

[1] Loomba, Rohit. "Serum alanine aminotransferase as a biomarker of treatment response in nonalcoholic steatohepatitis." Clinical Gastroenterology and Hepatology 12.10 (2014): 1731-1732.

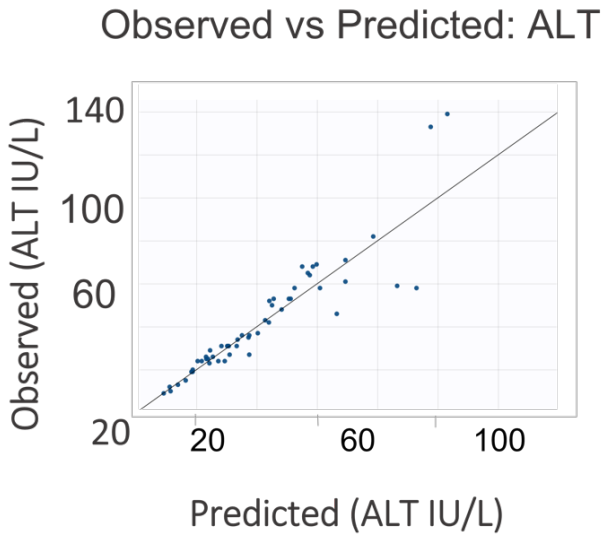
[2] Boyle, Marie, et al. "Performance of the PRO-C3 collagen neo-epitope biomarker in non-alcoholic fatty liver disease." *Jhep Reports* 1.3 (2019): 188-198.

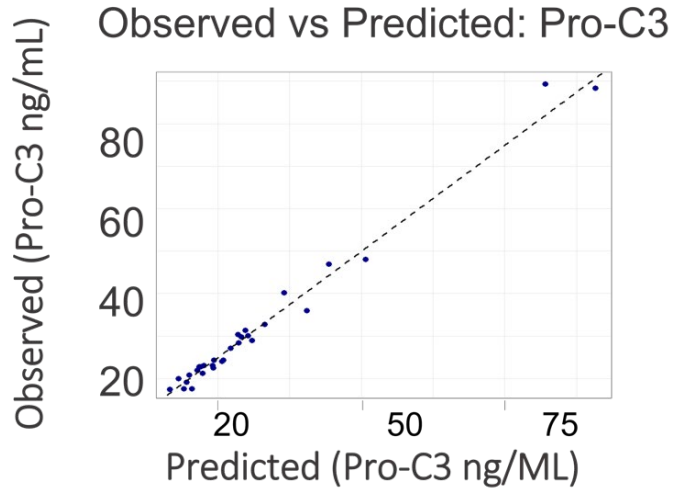
Machine Learning and A.I. Applied to Phase 2a Program

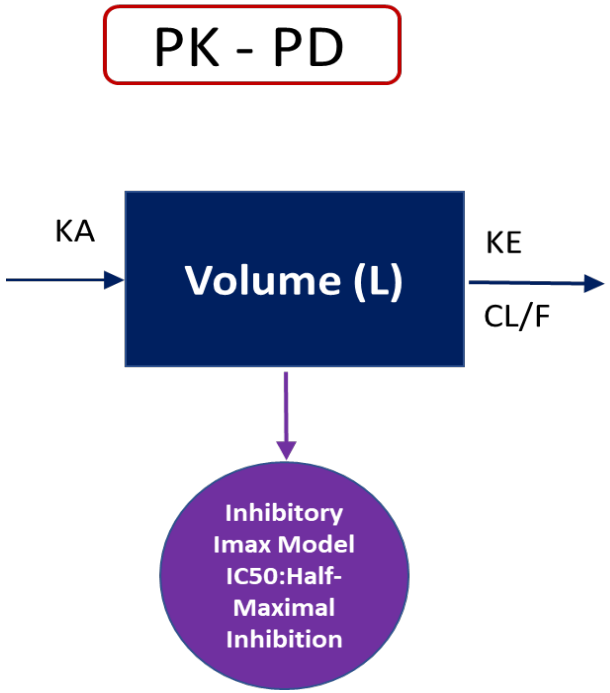
Phase 2a: PK-PD - Changes in ALT and Pro-C3 are Predictable

Early Evidence of a Concentration-effect Relationship

- Higher drug concentrations required to decrease Pro-C3 as compared to ALT
- Forecasting expected efficacy biomarker movements can be made early and accurately







PD	IC50 (ng/mL)	SE	RSE (%)
IC50 - ALT	258.0	70.1	27.2
IC50 - ProC3	918.9	84.3	9.3

- ALT and ProC3 Baseline was used as a covariate
- The effect of rencofilstat concentration in ALT and ProC3 can be predicted at any baseline

Phase 2a: Responder Analysis Illustration Using ALT

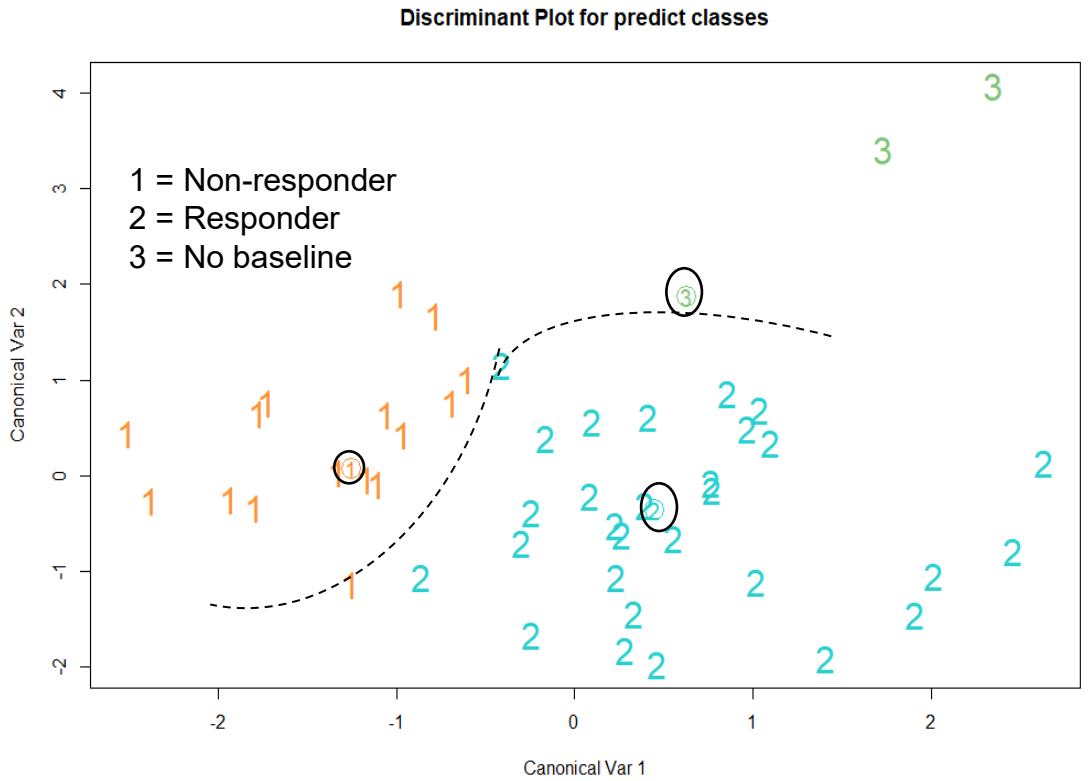
Used to Enrich Future Trials for Greater Success

By using multiple variable machine learning, Hepion can accurately identify patients that are more likely to respond to rencofilstat

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



Circled Numbers denote Group Centroid

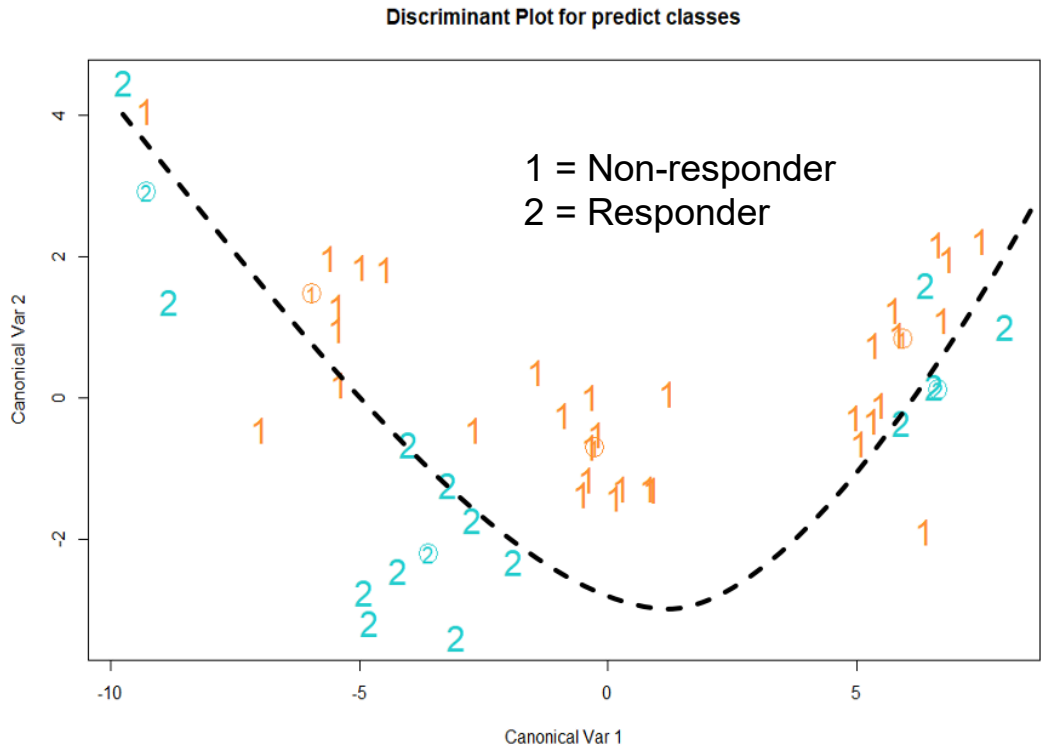
Phase 2a: Responder Analysis Illustration Using Pro-C3

Used to Enrich Future Trials for Greater Success

By using multiple variable machine learning, Hepion can accurately identify patients that are more likely to respond to rencofilstat

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

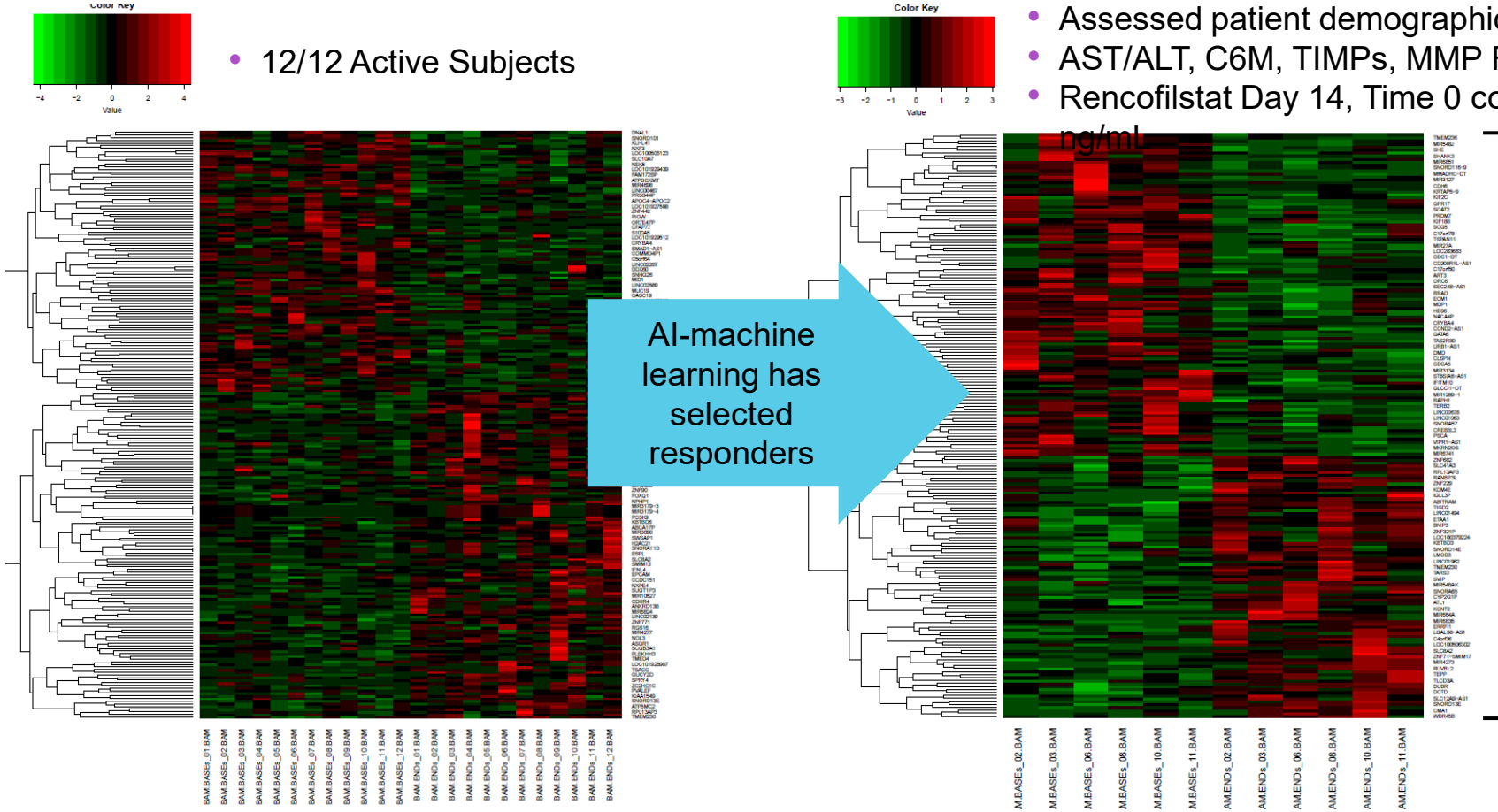
Circled Numbers denote Group Centroids

Phase 2a: Genomic Analysis of Subjects (75mg) Generates a Responder Panel

- 12/12 Active Subjects

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

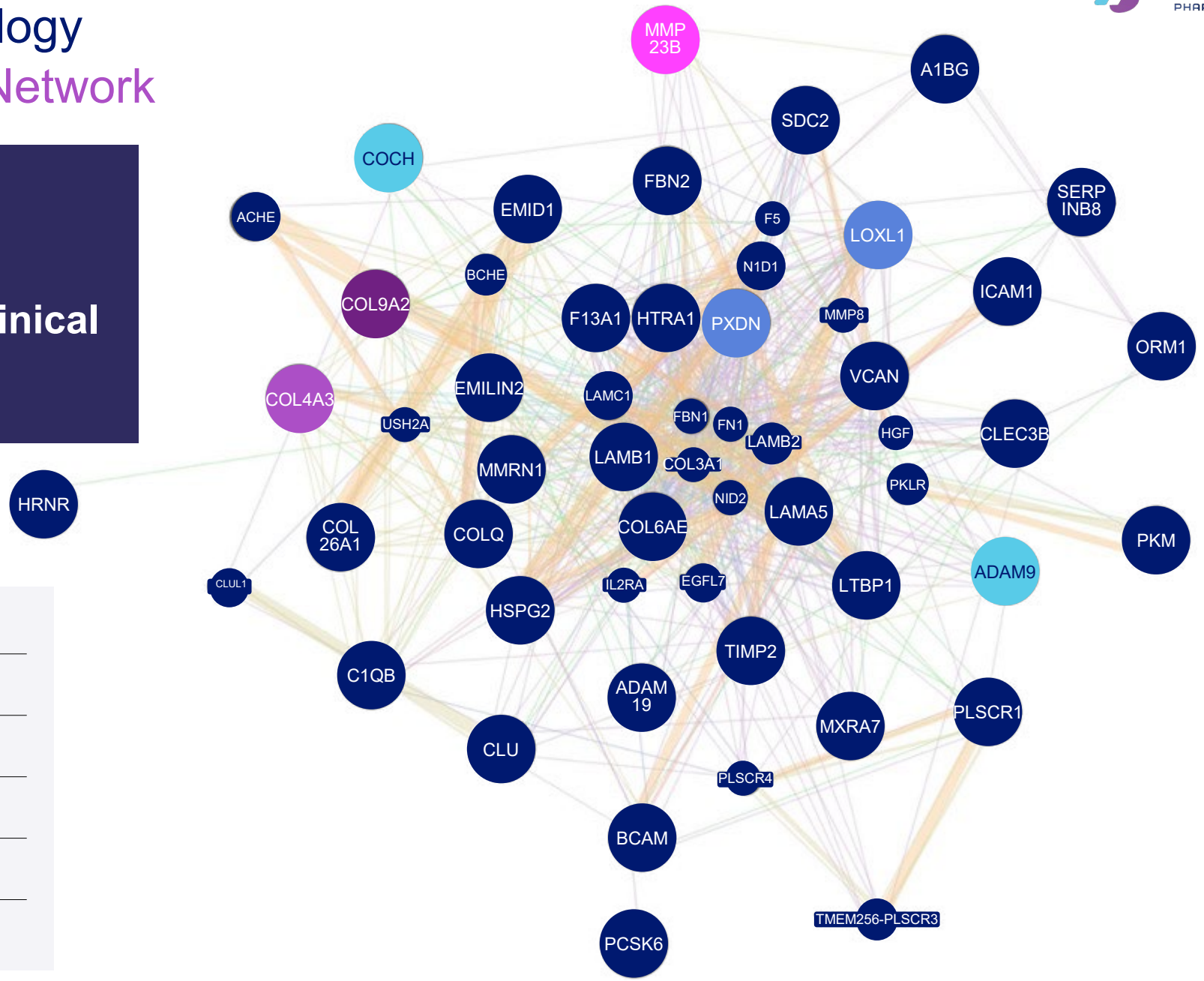
- Assessed patient demographics and baseline labs
- AST/ALT, C6M, TIMPs, MMP Responders
- Rencofilstat Day 14, Time 0 concentration > 800 ng/ml



AI training to decrease heterogeneity and predict *a priori* who will respond to rencofilstat

Phase 2a: Gene Ontology
Collagen Regulatory Network

Consistent antifibrotic effects observed with rencofilstat 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

Phase 2a ‘AMBITION’ NASH Study

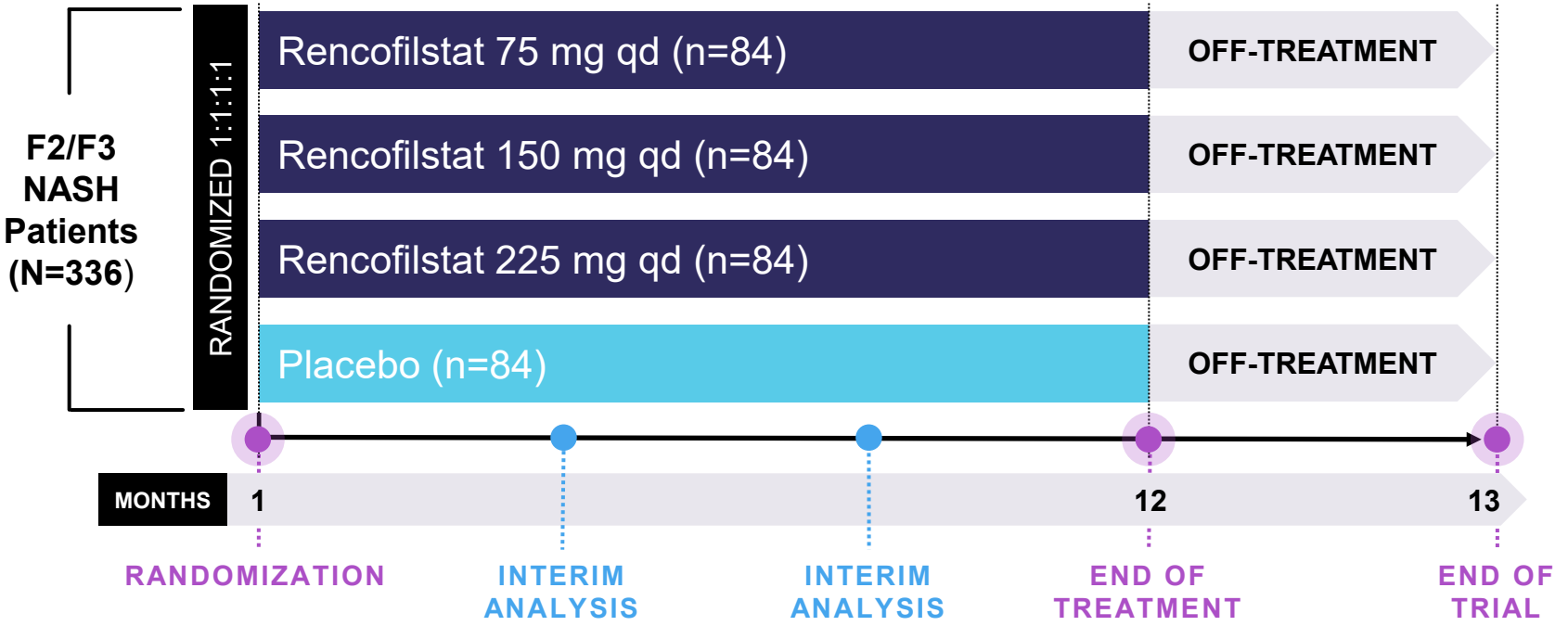
Summary

- Rencofilstat is safe and well-tolerated while showing efficacy signals in only 28 days including:
  - Reduction in ALT (marker of inflammation & fibrosis)
  - Reduction in Pro-C3 (marker of fibrosis)
  - Downregulation of collagen genes
  - Upregulation of genes associated with liver recovery and favorable lipid dynamics
- Blood exposures in subjects with NASH similar to healthy subjects
- Data to support training of AI-POWR and *a priori* prediction of rencofilstat responders
- Data was utilized to support the addition of a 150 mg dose cohort for the Phase 2b protocol and to adjust inclusion criteria (e.g., Pro-C3 > 14 ng/mL)

Phase 2b
‘ASCEND-NASH’ Trial
(in progress)

Phase 2b ASCEND-NASH (Biopsy Trial)

Primary Objective: Evaluate the efficacy and safety of once-daily 75mg, 150 mg, and 225 mg doses of Rencofilstat 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 Rencofilstat response

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

- Power = 90% to distinguish each dose level
- FDA feedback obtained – study design endorsed

Developing a Strategy to Monitor Clinical Outcomes

Exploring Meaningful Diagnostic Value Alongside Rencofilstat (supplemental to biopsy)

Machine Learning & A.I.

- Develop panel of biomarkers
- Refine inclusion & exclusion criteria for trials
- Refine strategy for commercialization and market access
- Pricing and reimbursement

Exploratory Diagnostics

- Require high diagnostic value and accessibility
- **Hepion** and **ENDRA** – Thermo Acoustic Enhanced UltraSound (TAEUS)
- Cost-effective, non-invasive
- Early diagnosis

Other Diagnostics

- Biopsy
- Fibroscan
- Etc.

Phase 2b ASCEND-NASH

Primary Efficacy Endpoint:

Superiority of rencofilstat 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:

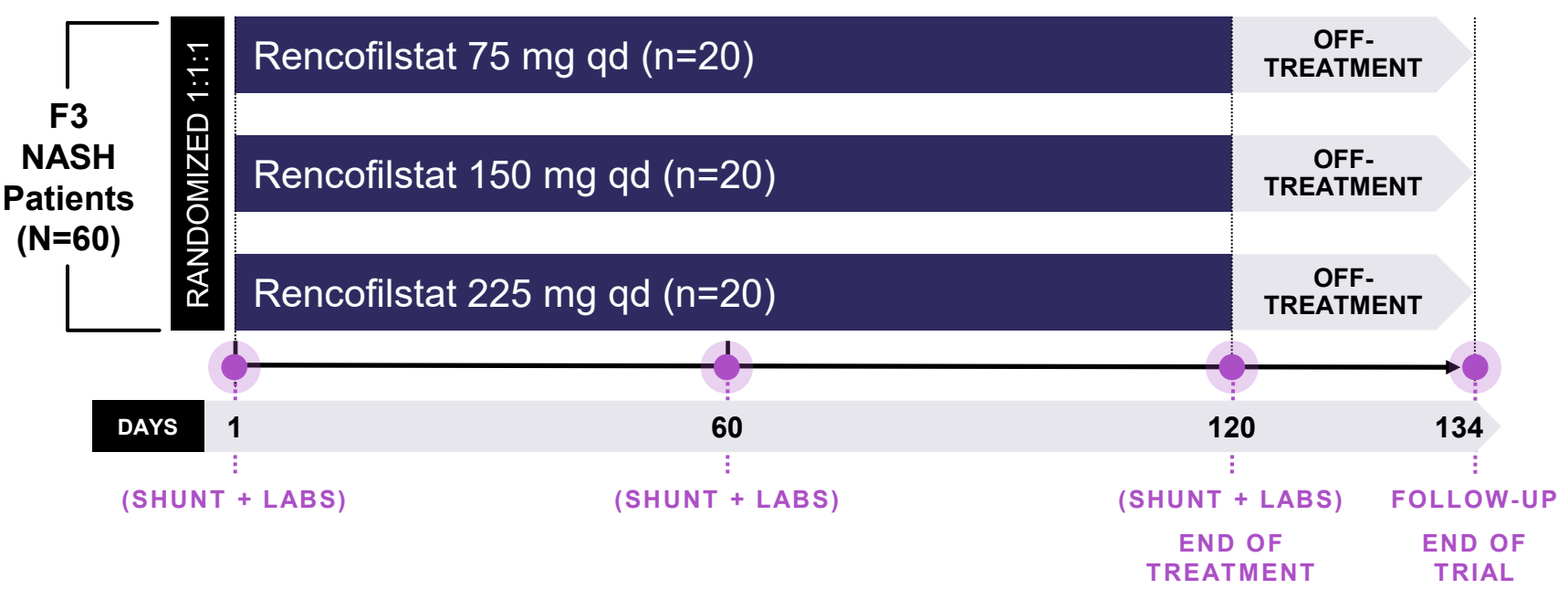
Superiority of rencofilstat compared to placebo on histology at month 12 relative to screening by assessing the proportion of subjects with improvement in fibrosis by:

- At least 1 stage regardless of effect on NASH
- At least 2 stages regardless of effect on NASH
- At least 2 stages AND no worsening of NASH.

Phase 2
‘ALTITUDE-NASH’ Trial
(in progress)

Phase 2 'ALTITUDE-NASH' (Liver Function Trial)

Primary Objective: Evaluate the change in *hepatic function* with once daily (QD) 75 mg, 150 mg, and 225 mg doses of rencofilstat in subjects with NASH F3 fibrosis using the HepQuant SHUNT test.



Endpoints:

- Efficacy:
  - HepQuant SHUNT
  - NASH NIMs
- Safety
- Tolerability
- Pharmacokinetics

- Subjects identified from historical biopsy or by meeting AGILE 3+ criteria for F3
- Subjects who complete study will be considered for enrollment into ASCEND-NASH 2b

Phase 2 ‘ALTITUDE-NASH’ (Liver Function Trial)

Primary Efficacy Endpoint:

Change from baseline in DSI score of subjects taking rencofilstat using HepQuant SHUNT Test, on Day -1, Day 60, and Day 120

Secondary Efficacy Endpoints:

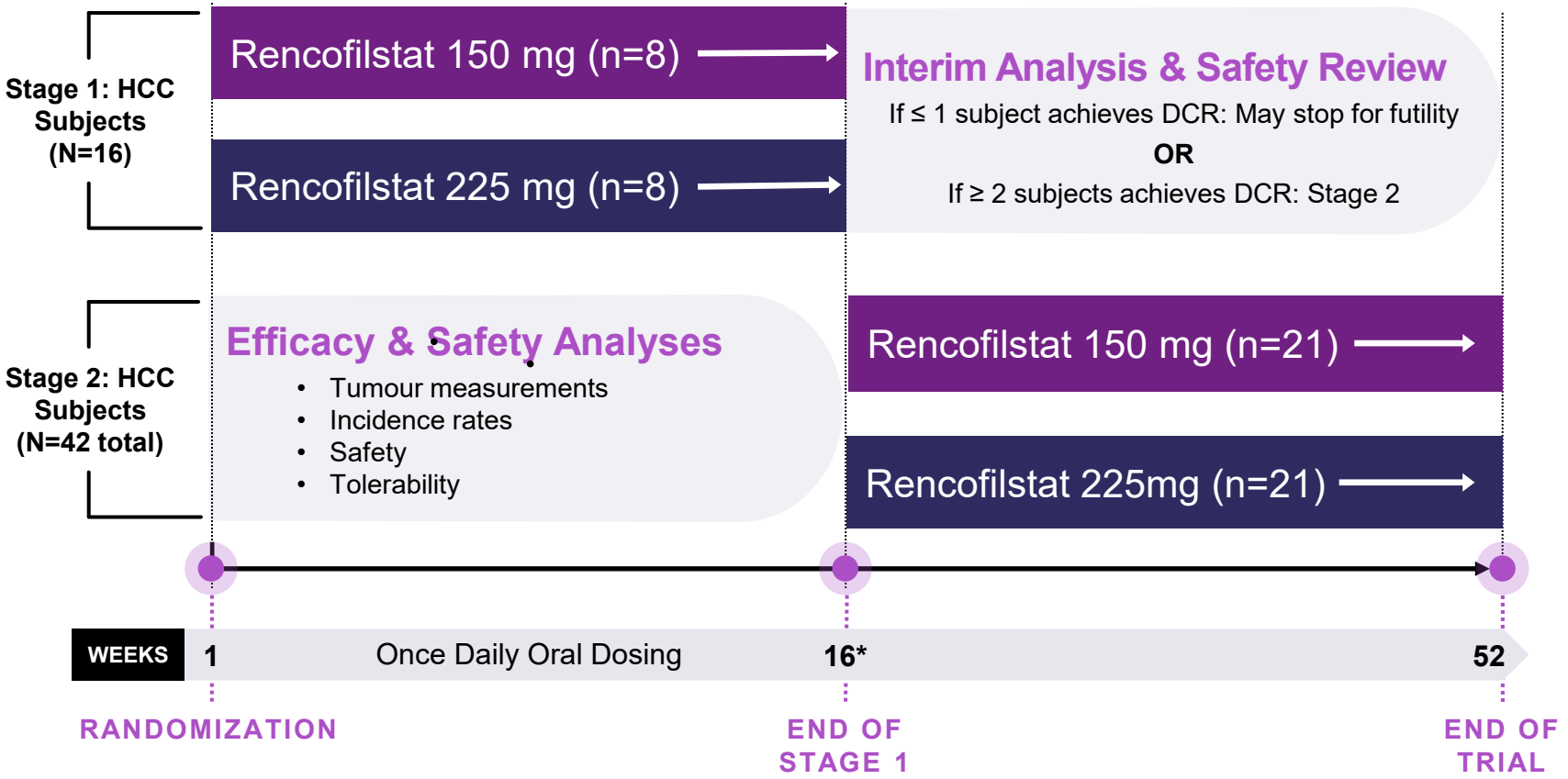
- Percent of subjects with a reduction in DSI score of >2
- Change from baseline in portal and systemic Hepatic Filtration Rate (HFR) using HepQuant SHUNT Test
- Change from baseline in Fibrosis-4 (FIB-4) scores
- Change from baseline in Enhanced Liver Fibrosis (ELF) scores
- Change from baseline in Pro-C3 levels
- To evaluate all HepQuant SHUNT Test parameters in predicting and monitoring response to rencofilstat in subjects with NASH F3 fibrosis.

Phase 2a HCC Trial (upcoming)

PHASE 2a: Advanced Hepatocellular Carcinoma (HCC)

Simon 2 Stage - Safety, Tolerability, Pharmacokinetics, and Efficacy

A Phase 2a, Open-Label, Multi-Center, Simon 2-Stage Clinical Study to Assess the Preliminary Efficacy, Safety, and Pharmacokinetics of 2 Dosage Levels of Rencofilstat in Advanced Metastatic Resistant or Refractory HCC Subjects



Inclusion Criteria:

- Intolerant to at least 1 prior systemic regimen and have at least 1 untreated lesion
- Previous Tx with 1 checkpoint inhibitor in combination with anti-VEGF

Primary Endpoints:

- Safety
- Tolerability
- Pharmacokinetics
- Disease Control Rate

*Administration of Rencofilstat may continue until disease progression according to RECIST version 1.1

Phase 2a HCC: Objectives

Primary Objectives:

- Assess disease control rate (**DCR**)
- Assess the **safety and tolerability** of CRV431

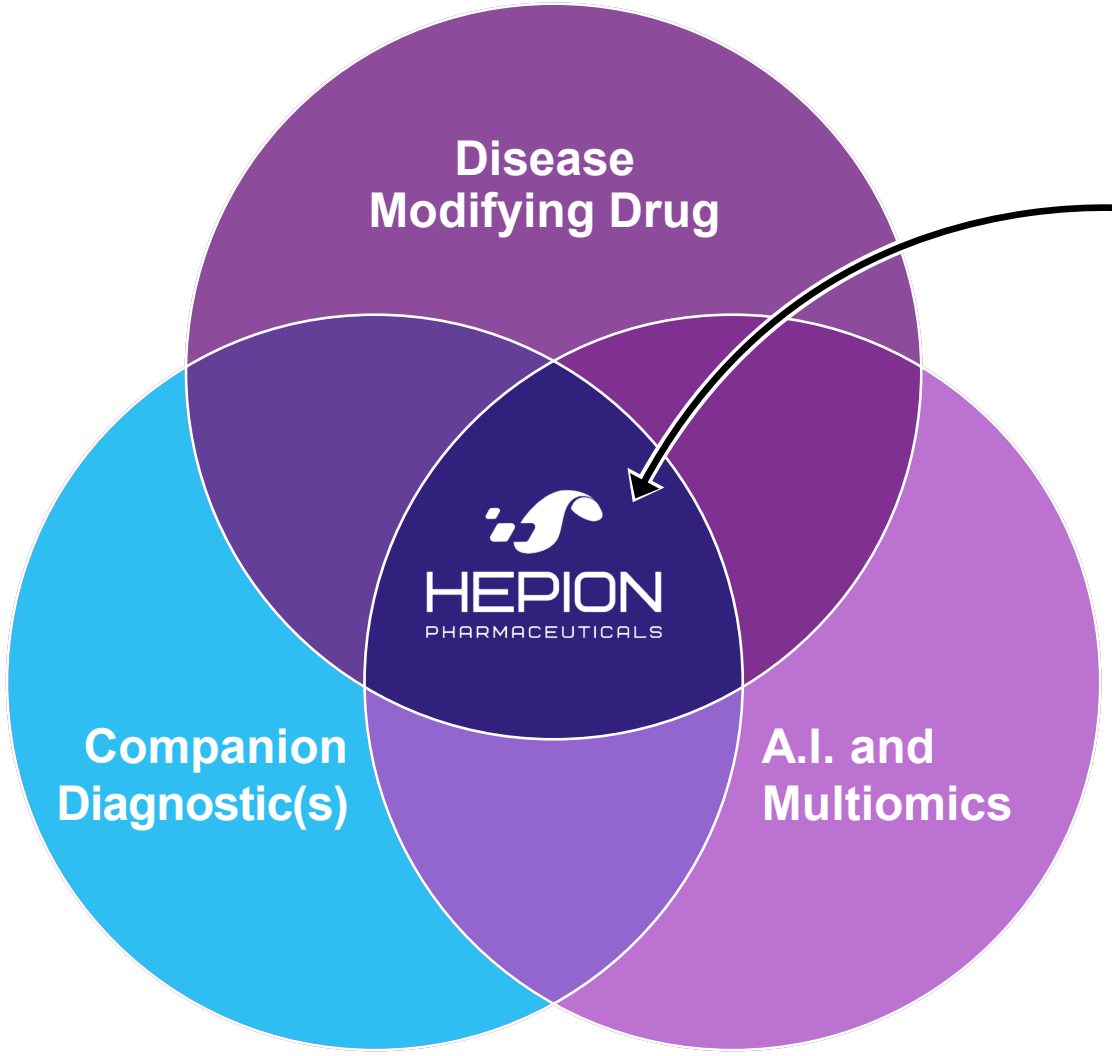
Secondary Objectives:

- Assess the effect of rencofilstat on:
    - Duration of response (**DoR**) measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented.
    - Overall survival (**OS**).
    - Objective response rate (**ORR**) and the individual components of the ORR (i.e., CR alone, PR alone).
    - 4-month progression free survival (**PFS-4**).

Summary

Hepion's Approach to Developing an Ecosystem

Creating a Bundle to Support Rencofilstat's Success



Strategy:

- Rencofilstat (disease modifying), efficacious, safe and well-tolerated
- Companion Point-of-Care Diagnostic (e.g., Blood Panel, TAEUS)
- Identify Responders, Hepion's Proprietary A.I. and Multiomic Analyses (Offering Clinical and Commercial Efficiencies)

Tackling Chronic Liver Disease

- Rencofilstat, once-daily oral, targeting key drivers of pathology
- Two Phase 2b NASH trials underway
- Upcoming Phase 2a for HCC
- Developing companion proprietary A.I. for clinical development and commercialization strategy
- Investigating companion diagnostics (e.g., TAEUS)
- 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 RENCOFILSTAT

A Potential Therapy for NASH and HCC

HEPION PHARMACEUTICALS AI-POWR™

AI-Driven, Bioinformatic Platform

Financials

$71.7 M
Cash
as of 6/30/22

76.2 M
Common Shares Outstanding

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