

Rencofilstat (CRV431):

A Novel Drug Candidate for Fibrotic Diseases, including NASH and HCC



Creating a Therapeutic Ecosystem

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Rencofilstat Highlights

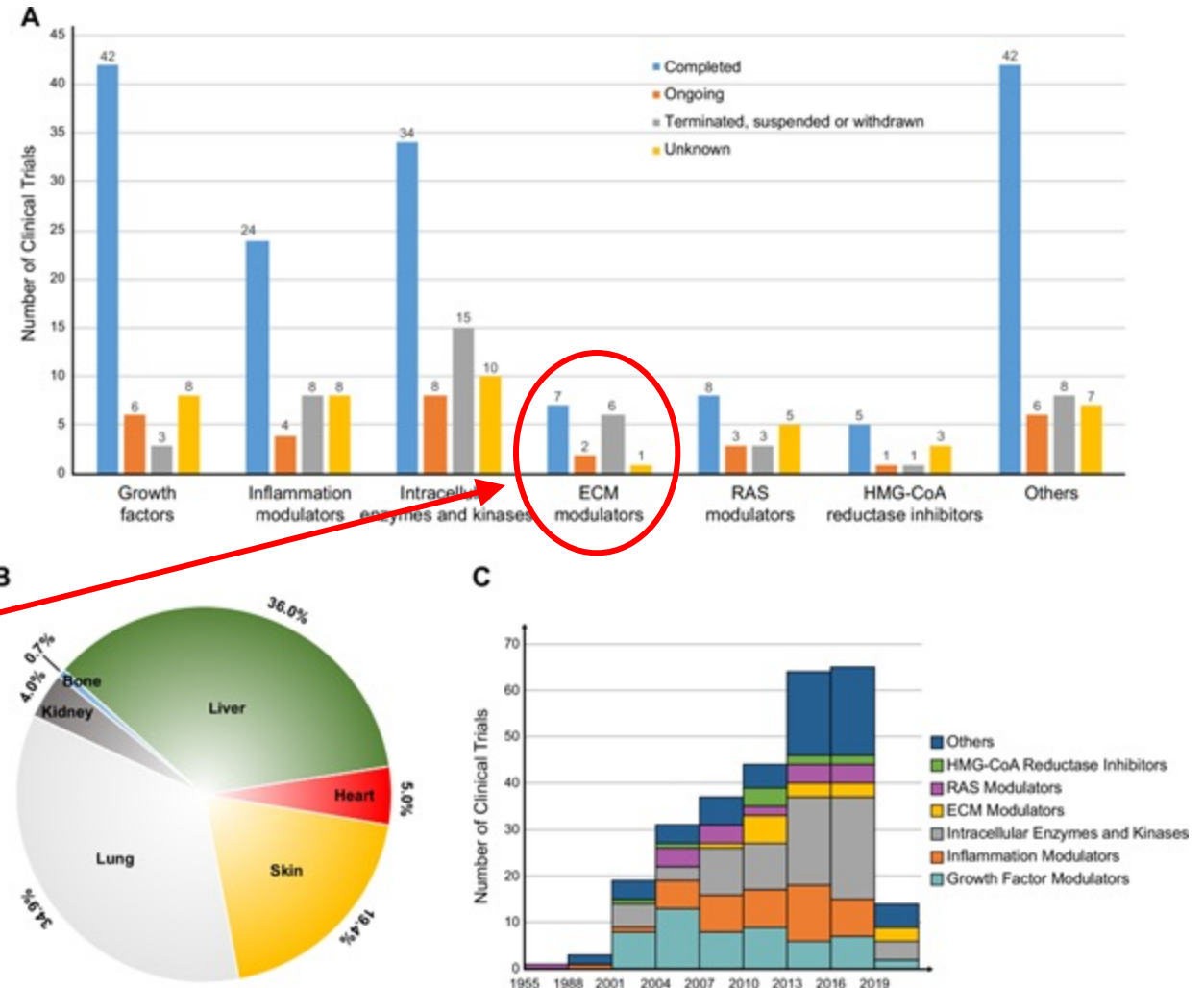
Rencofilstat Anti-Fibrotic Drug Candidate

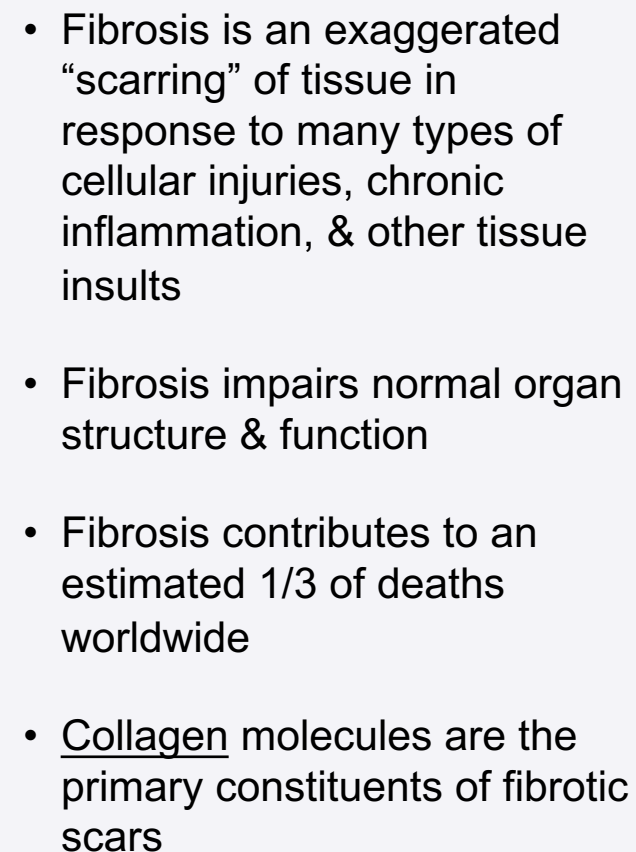
- Novel mechanism - cyclophilin inhibition
- Once-daily, oral medication – soft gel capsules
- Collagen-specific anti-fibrotic
- Targets key pathologies including fibrosis, inflammation, cell injury
- All clinical trials to date show rencofilstat to be safe and well tolerated – over 200 subjects dosed
- Currently undergoing Phase 2 clinical trials

Landscape of Clinical Antifibrotic Drug Development

Opportunity for Collagen-Targeting Therapeutics

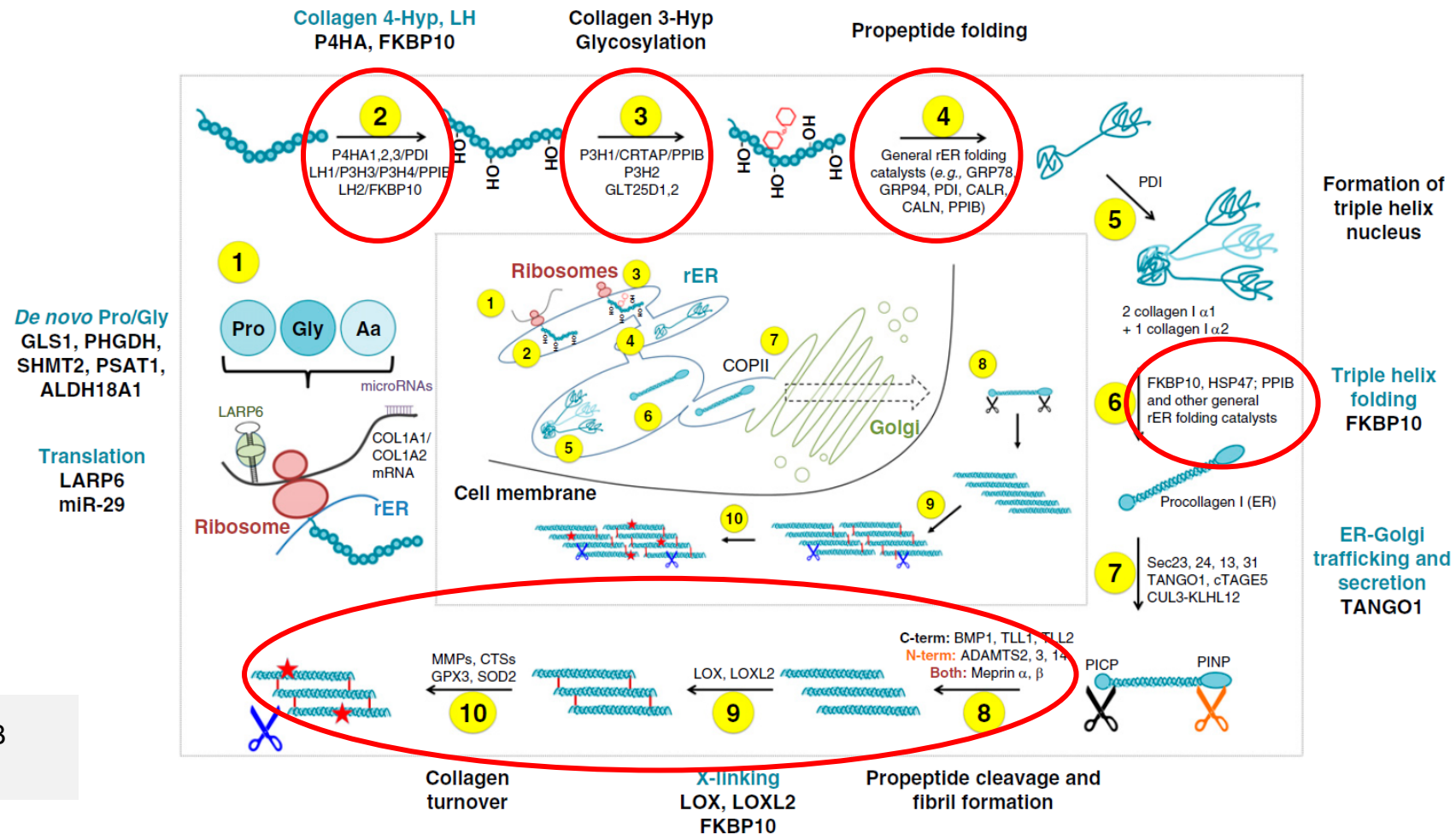
- Despite ≈300 clinical trials, the only approved antifibrotic drugs are pirfenidone and nintedanib
- Most anti-fibrotic agents have targeted upstream drivers of fibrogenesis (e.g., TGFβ) or disease-specific signaling in fibrogenic cells
- *Rencofilstat* directly targets collagen synthesis or other extracellular matrix (ECM) modulators common to fibrotic diseases





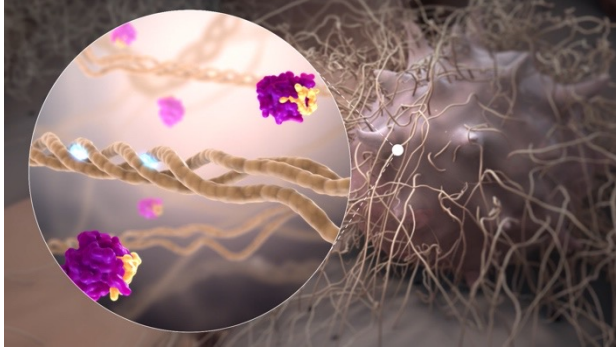
Fibrotic Collagen Production

Cyclophilin B (Cyp B; PPIB) – Participant in several stages of collagen synthesis and fibrotic scar formation



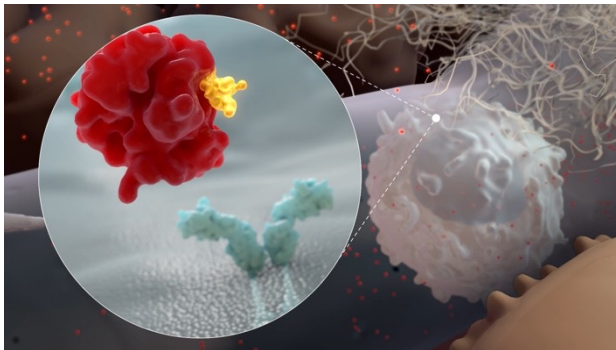
Rencofilstat Inhibits Three Primary Cyclophilins

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



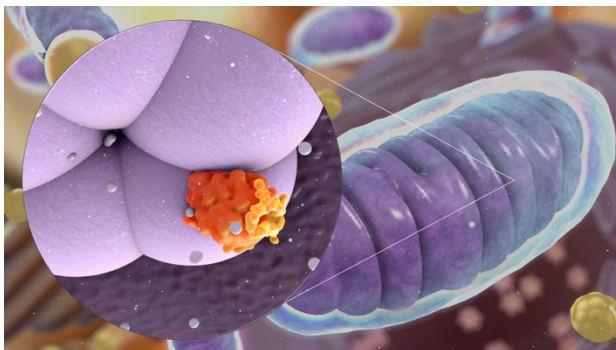
ANTI-FIBROTIC

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



ANTI-INFLAMMATORY

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



CYTOPROTECTIVE

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

Preclinical Models

Consistent Antifibrotic Findings

**Antifibrotic
Activity
Observed in
Every Preclinical
Model**



Liver

- 8 NASH-related models
 - Human liver slices
-



Lung

- Chronic fibrosis
 - Acute injury
 - Human lung slices
-



Kidney

- Acute injury
-



Heart



Skin

Summary of Rencofilstat Programs – ‘Pipeline within a Product’

Program	Pre-Clinical	Phase 1*	Phase 2	Phase 3
NASH <i>Fast Track Designation</i>			Biopsy	
			Liver Function	
Hepatocellular Carcinoma <i>Orphan Drug Designation</i>				
Multiple Myeloma				
Idiopathic Pulmonary Fibrosis				
Renal Fibrosis				
Cardiac Fibrosis				

NASH

Fibrotic Liver Disease

The Need and Opportunity

NASH is 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%**

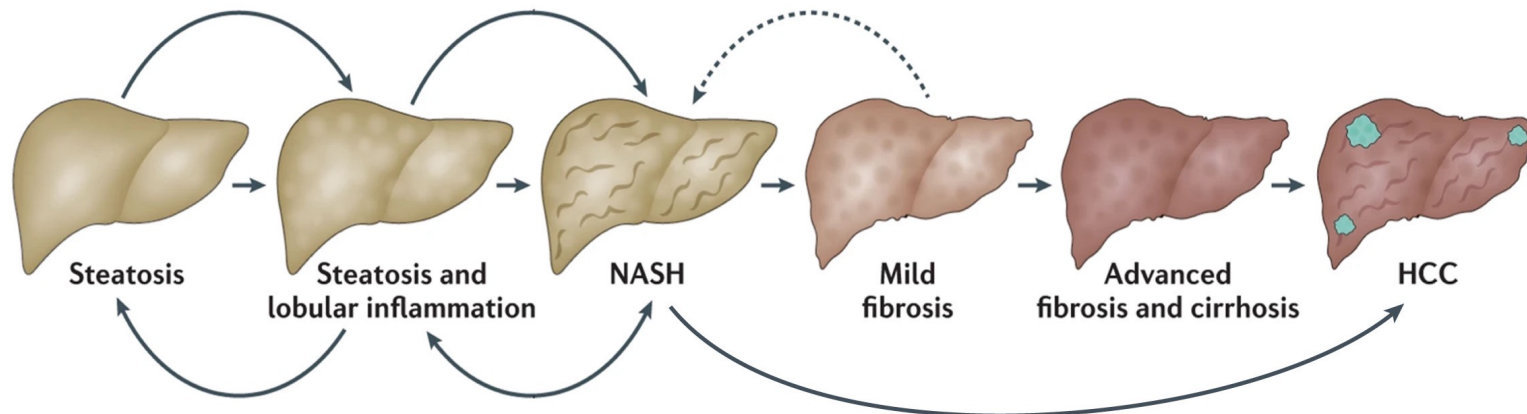


Image adapted from “From NASH to HCC: current concepts and future challenges”, Anstee et al. (2019)

*The Global Cancer Observatory (Globocan), December 2020

**UpToDate, February 2022

Challenges to Achieve Development and Commercial Success

A Comprehensive Approach to Provide Solutions

NASH

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



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

Overview of Phase 1 Studies (completed)

Phase 1 Studies Completed – Safe and Well Tolerated

Key Findings

**Single
Ascending
Dose**
(75-525mg)

**Multiple
Ascending
Dose**
(75–375mg)

**Drug-Drug
Interaction**
(midazolam &
ketoconazole)

Food Effect
(high fat meal)

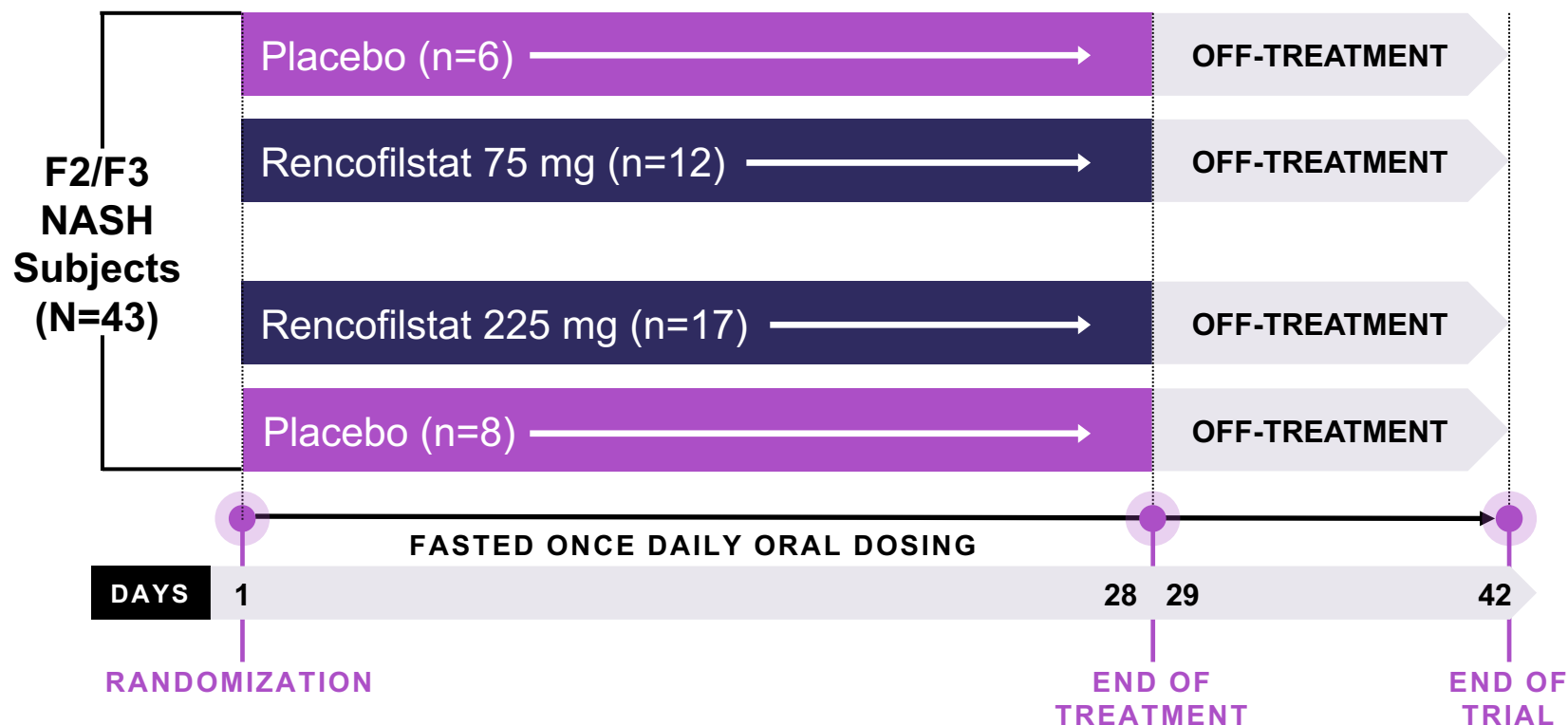
- No serious adverse events
- No adverse events with dose response
- Effective $t_{1/2}$ ~ 30 hours
- $T_{max_{ss}}$ ~ 1 – 2 hours
- Ketoconazole increased rencofilstat concentrations ~ 5-fold
- Rencofilstat had no effect on midazolam exposure
- Rencofilstat absorption was not decreased with high fat meal (AUC increased 18%)

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

Phase 2a 'AMBITION' NASH Study

All Primary Endpoints Met

Rencofilstat is safe and well-tolerated

Efficacy signals were observed 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

Early evidence of a concentration-effect relationship was observed with both ALT and Pro-C3

Rencofilstat concentrations are not significantly altered by NASH

Rencofilstat concentrations expected to be effective in NASH endpoints (ALT and Pro-C3) were achieved

Hepion's Proprietary Artificial Intelligence

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

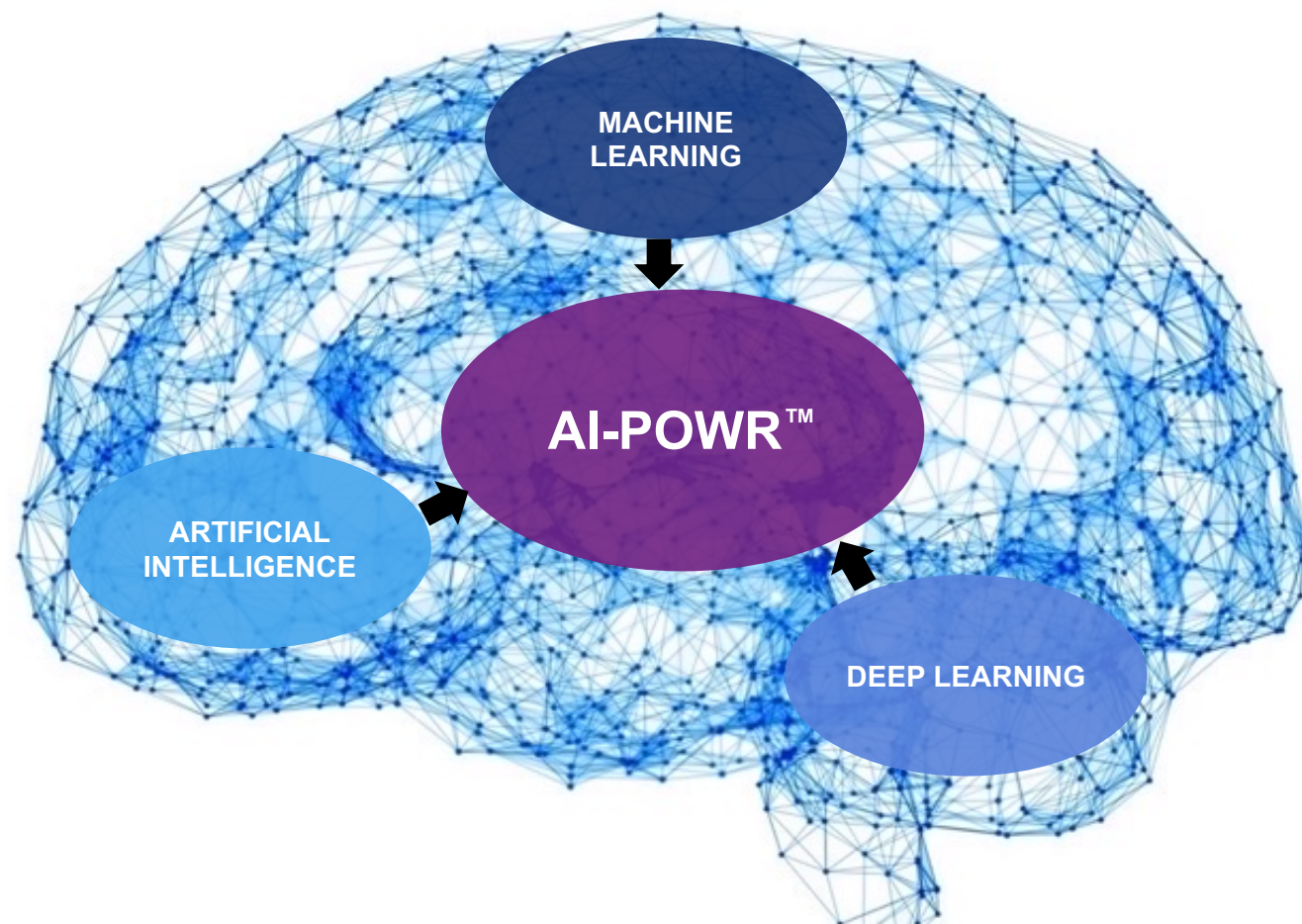
Developing a Panel for Clinical Development and Commercialization

AI-POWR™

Facilitates:

- Improved drug target selection
- Clinical study design
- *a priori* responder analysis

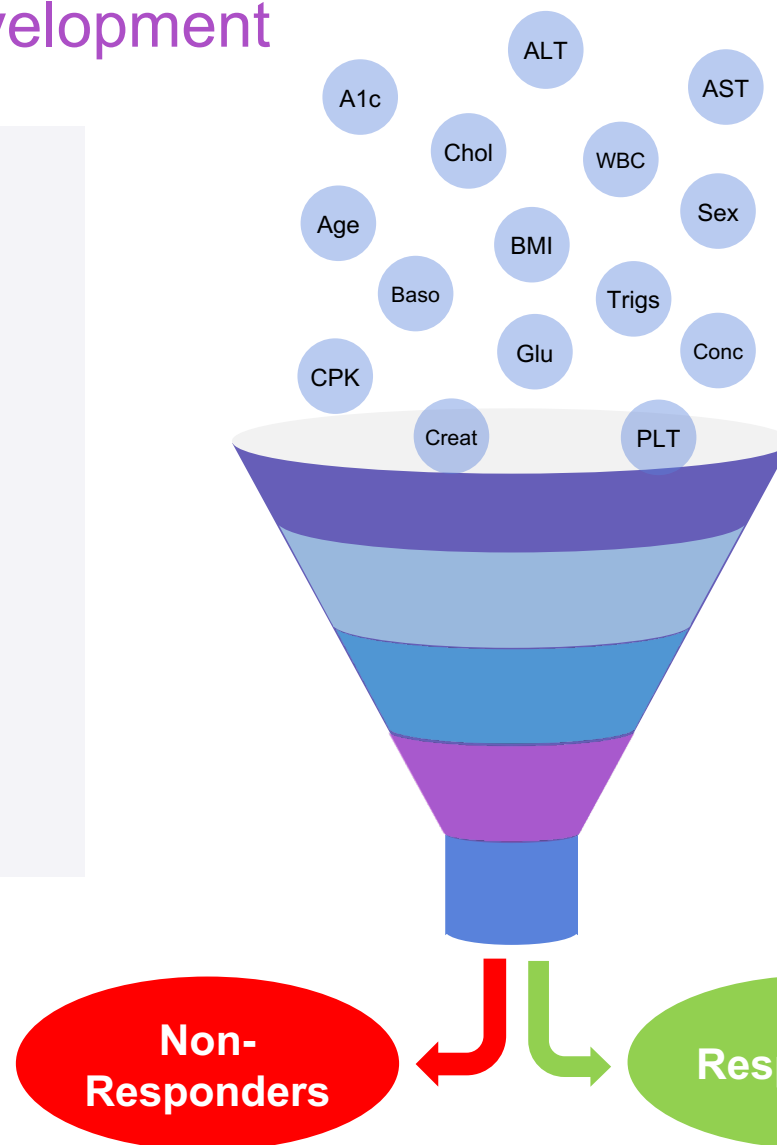
Designed to elucidate both disease and pharmacodynamic biomarkers



AI-POWR™ Applied to the Phase 2a Program

Guiding Hepion's Future Development

Using machine learning on data from the Phase 2a, Hepion was able to identify subjects more likely to respond to rencofilstat with clinically relevant changes in ALT, Pro-C3, and genomic biomarkers and elucidation of a companion diagnostic panel

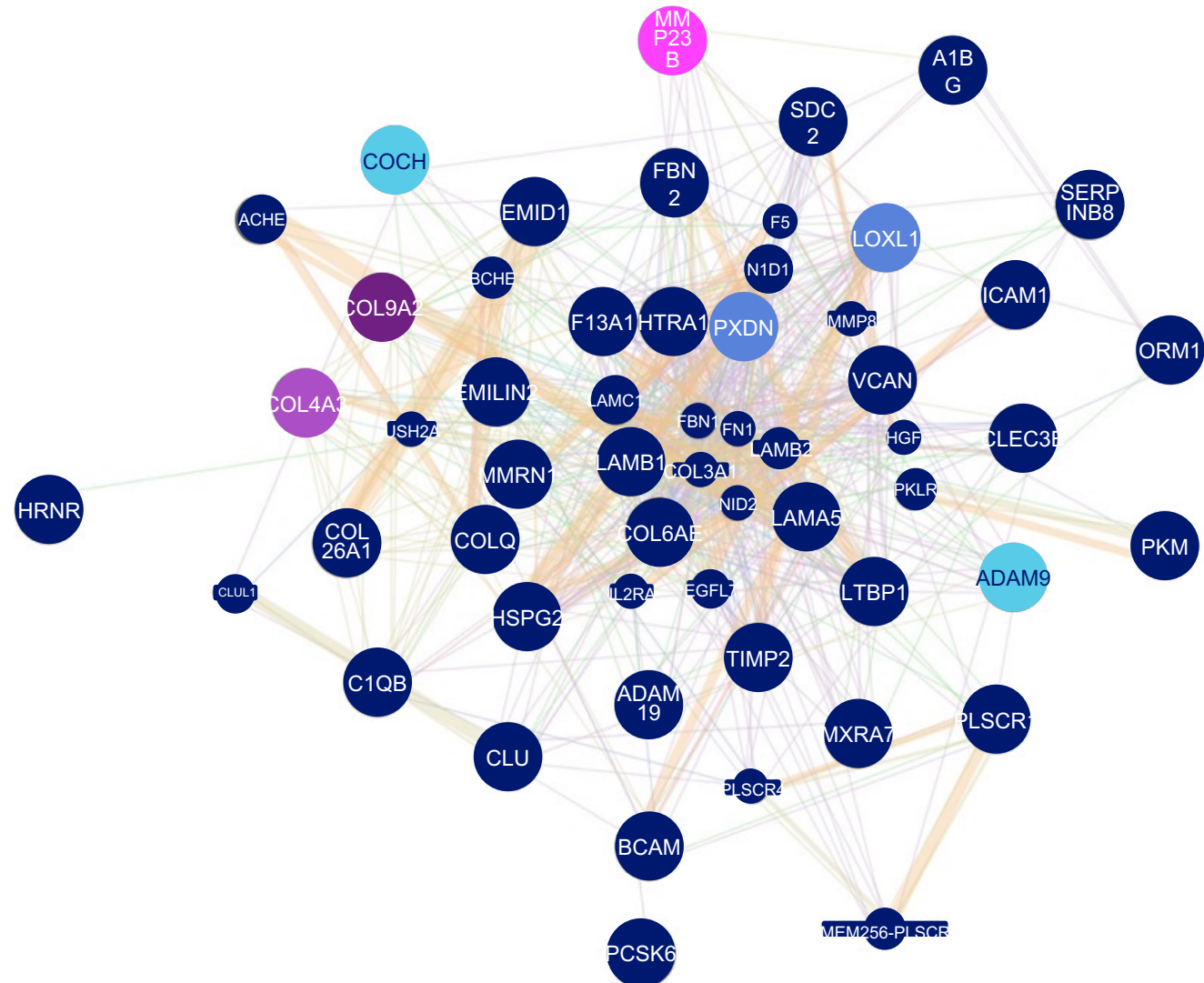


For future Phase 3 trials & commercialization, the appropriate patient population will be targeted

Fibrosis-Associated Gene Network Observed in Phase 2a Blood Samples Supports Rencofilstat Antifibrotic Efficacy in 28-Day Study

Rencofilstat impacted gene expression related to biosynthesis, remodeling, and degradation of collagens.

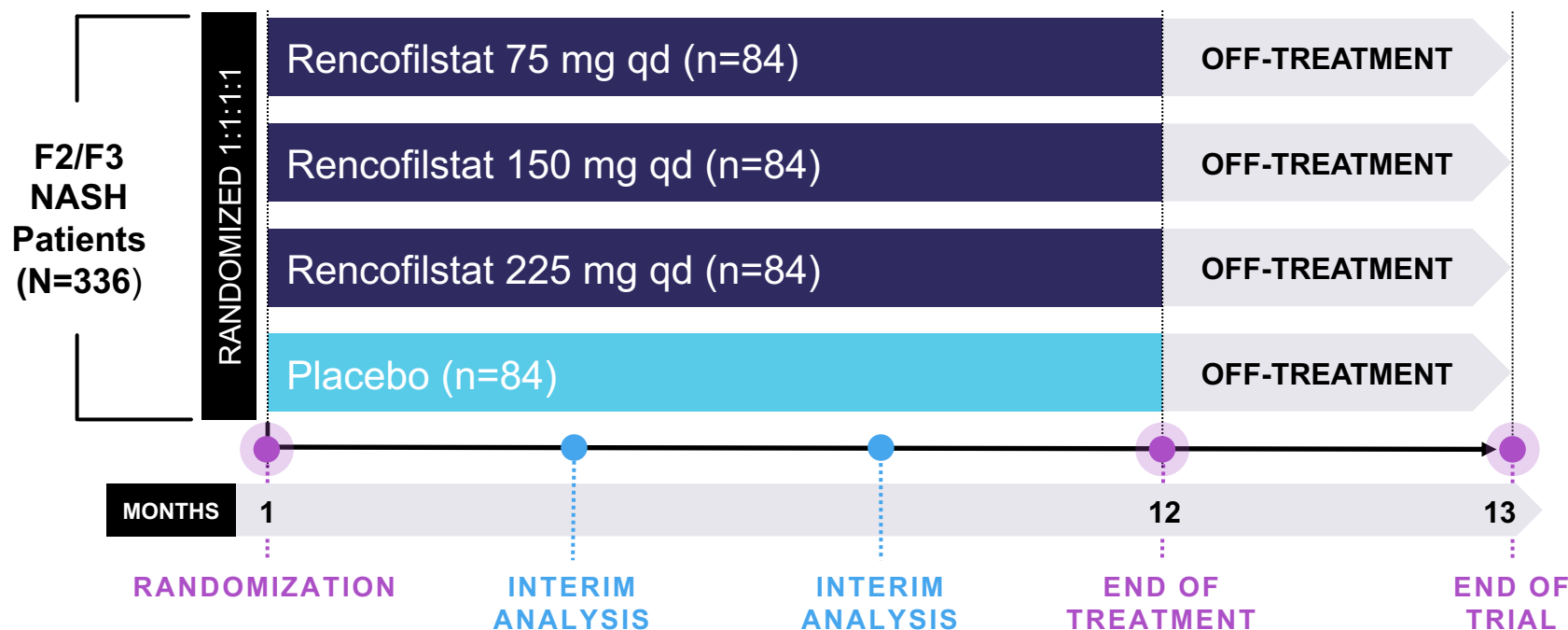
- collagen-containing extracellular matrix
- collagen binding
- collagen type IV trimer
- collagen type IX trimer
- collagen fibril organization
- collagen catabolic process



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 outcomes at each dosing level
- FDA feedback obtained – study design endorsed
- Blinded interim analyses when 1/3 of subjects in each cohort reach day 180 and when 2/3 of subjects in each cohort reach day 365

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:

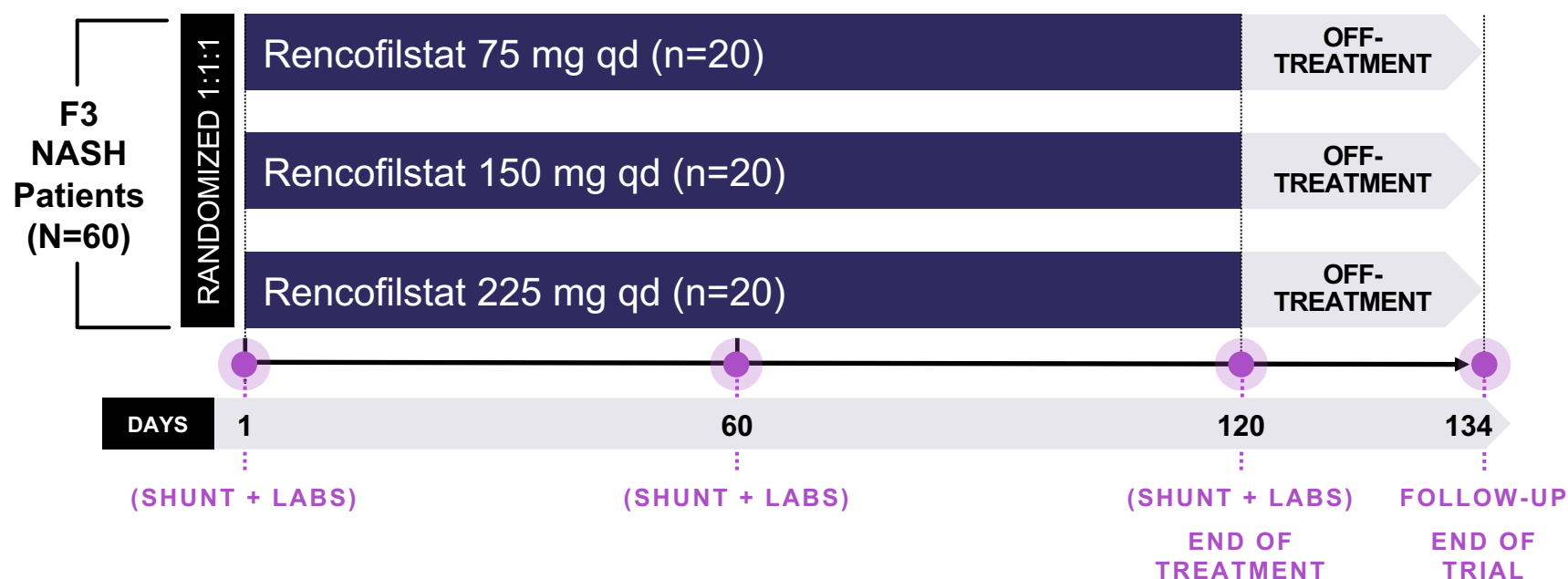
Superiority of rencofilstat compared to placebo on histology at month 12 relative to screening by assessing the proportion of subjects with improvement in fibrosis by:

- 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:

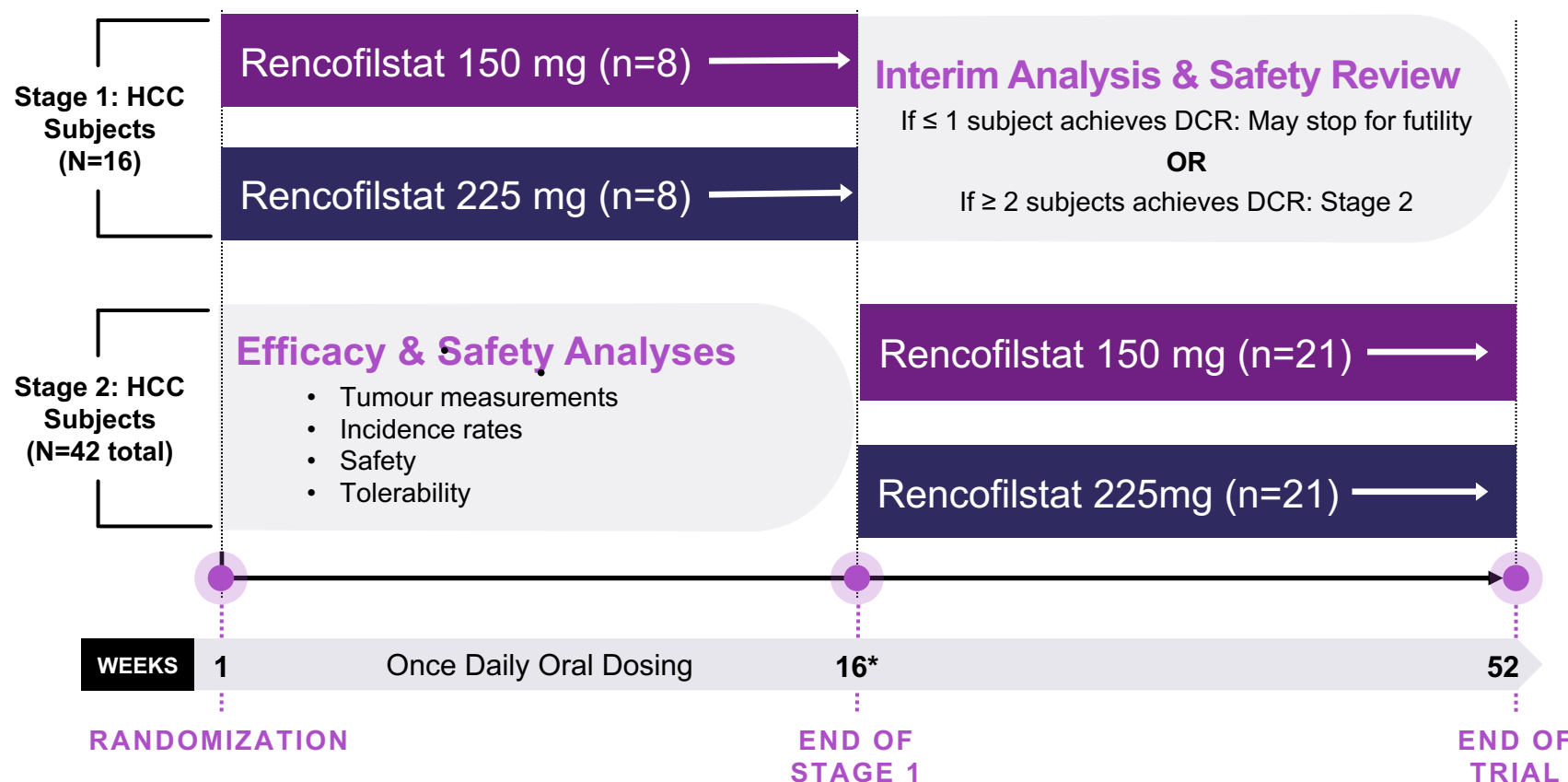
- Percent of subjects with a reduction in DSI score of >2
- Change from baseline in portal and systemic Hepatic Filtration Rate (HFR) using HepQuant SHUNT Test
- Change from baseline in Fibrosis-4 (FIB-4) scores
- Change from baseline in Enhanced Liver Fibrosis (ELF) scores
- Change from baseline in 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)

Safety, Tolerability, Pharmacokinetics, and Efficacy

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



Objectives:

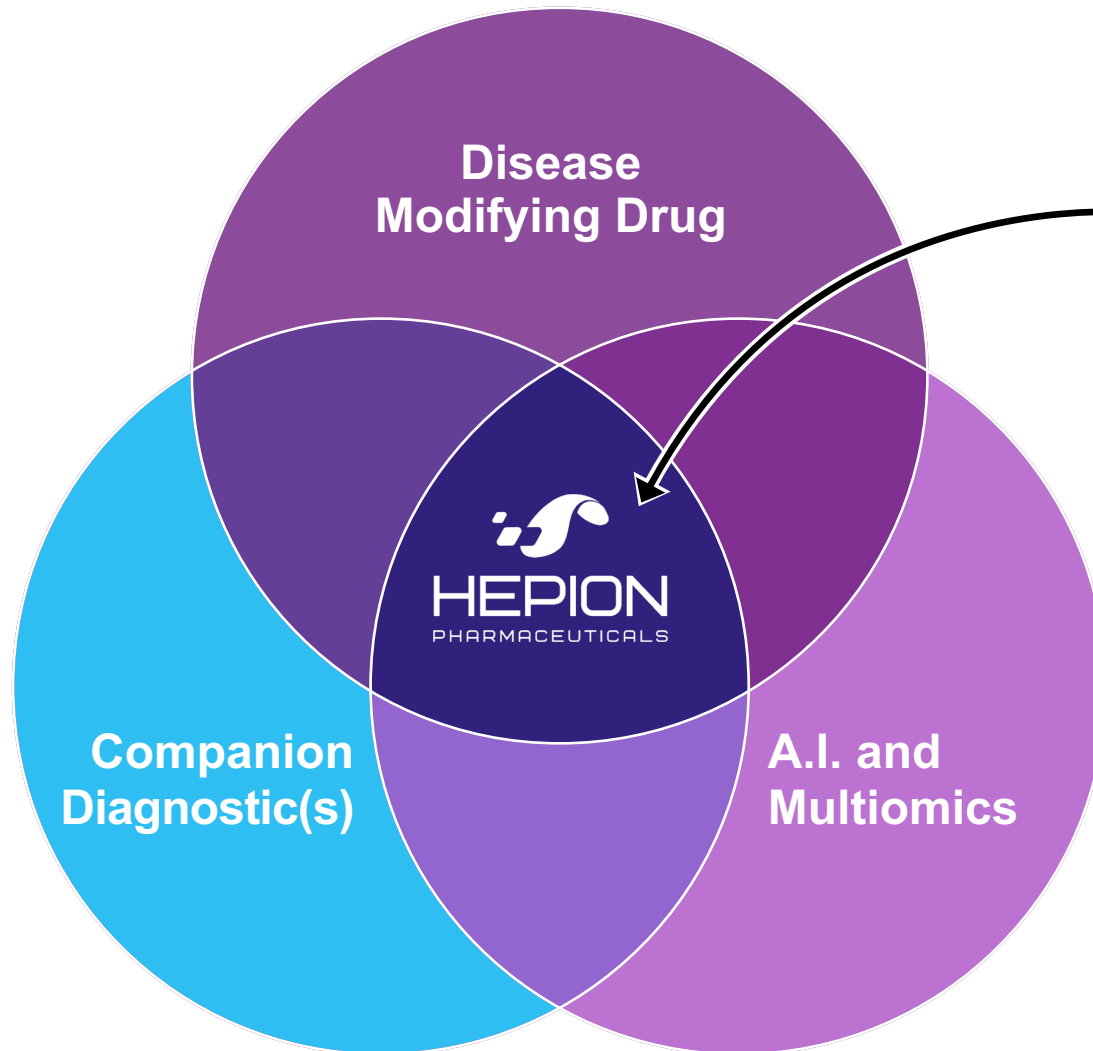
- Safety & tolerability
- Efficacy:
 - Disease Control Rate
 - Duration of response
 - Overall survival
 - Objective response rate
 - 4-month progression free survival
- Pharmacokinetics

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

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)
- A.I. and Multiomic Analyses Identify Responders (Offering Clinical and Commercial Efficiencies)

Tackling Fibrotic Diseases

- Rencofilstat, once-daily oral, targeting key drivers of pathology, tested in over 200 subjects
- Two Phase 2 NASH trials underway
- Upcoming Phase 2 for HCC
- Developing companion A.I. for clinical development and commercialization strategy
- Core scientific team discovered and developed voclosporin (currently marketed)
- Robust IP

Two Value Drivers



Financials

\$71.7 M
Cash
as of 6/30/22

76.2 M
Common Shares
Outstanding

Experienced Team

Core R&D team has collectively > 120 yrs of experience with cyclophilin inhibition drug development, most notably voclosporin (Lupkynis®) for lupus nephritis while at Isotechnika (Aurinia, NASDAQ:AUPH)



Robert Foster, PharmD, PhD
CEO

Founded Isotechnika (Aurinia) in 1993, and served mostly as CEO & Chairman, until 2014. Joined HEPA in 2016 as CSO and became CEO in 2018.



Launa Aspeslet, PhD
COO

Formerly COO of Isotechnika (Aurinia) from 1996-2013. Was CEO of an oncology CRO from 2013 until joining HEPA in 2022.



John Cavan, MBA
CFO

Formerly of Pine Hill, Stemline, Aegerion, AlgoRx, Alharma, Sony, American Express and International Specialty Products, joined HEPA in 2016.



Daren Ure, PhD
CSO

Joined Isotechnika (Aurinia) in 2003 and joined HEPA in 2016.



Daniel Trepanier, PhD
SVP, Drug Development

Joined Isotechnika (Aurinia) in 1997 and joined HEPA in 2016.



Todd Hobbs, MD
CMO

Formerly Chief Medical Officer of Novo Nordisk, joined HEPA in 2021.



Patrick Mayo, PhD
SVP, Clinical Pharmacology and Analytics

Joined Isotechnika (Aurinia) in 2002 and joined HEPA in 2019.

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