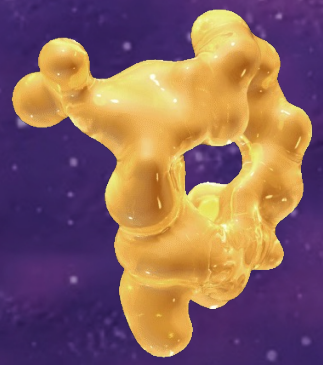
HEPION PHARMACEUTICALS

NASDAQ:**HEPA**

Rencofilstat (CRV431):

A Novel Drug Candidate for NASH, Fibrosis, and HCC



Creating a Therapeutic Ecosystem

February 2023

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Rencofilstat

Anti-Fibrotic Drug Candidate

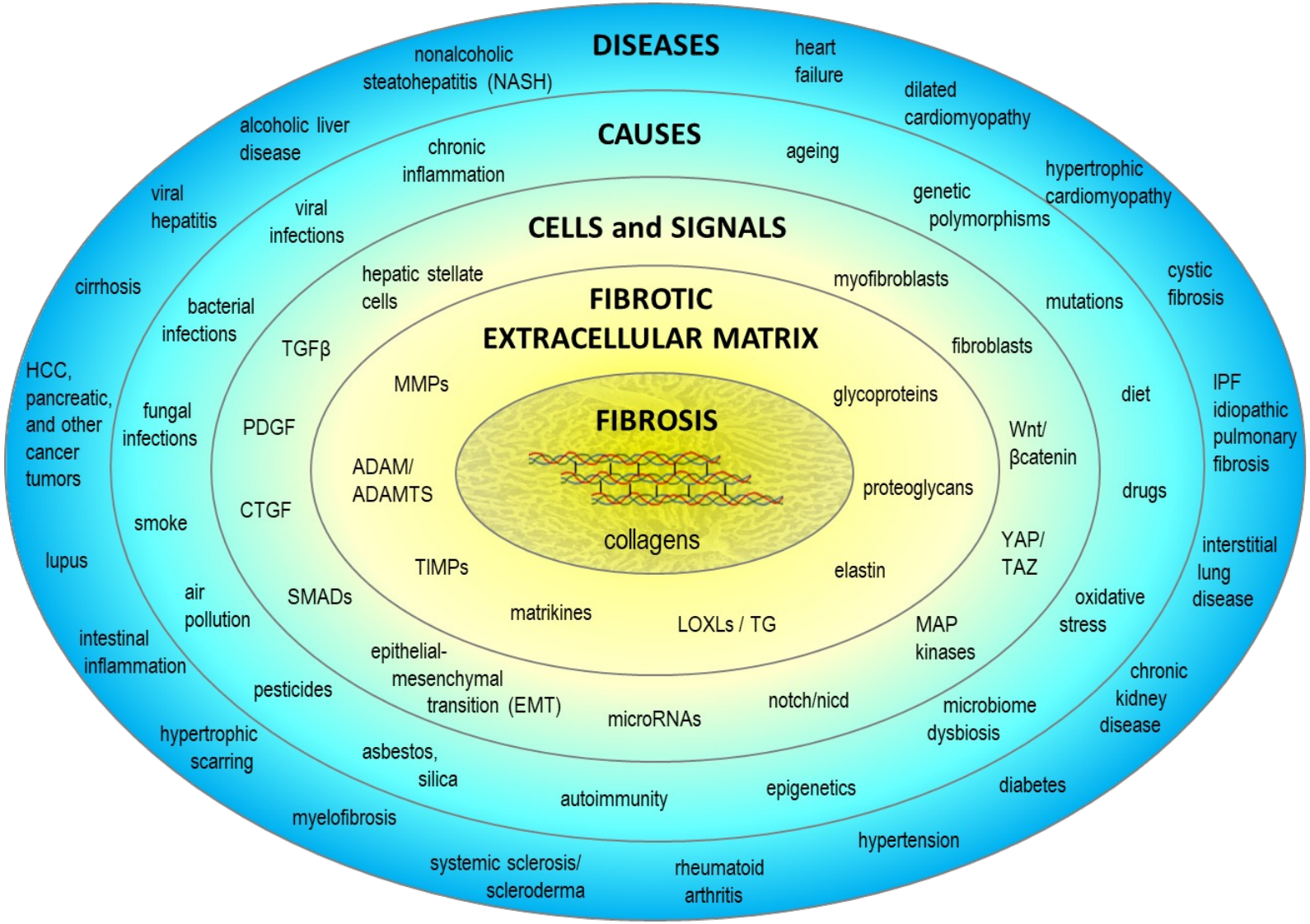
Rencofilstat Highlights

- 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 280 subjects dosed
- Currently undergoing Phase 2 clinical trials

Rencofilstat Mode of Action

Collagen - Core To Fibrotic Diseases

Excessive collagen production – universal to every fibrotic disease

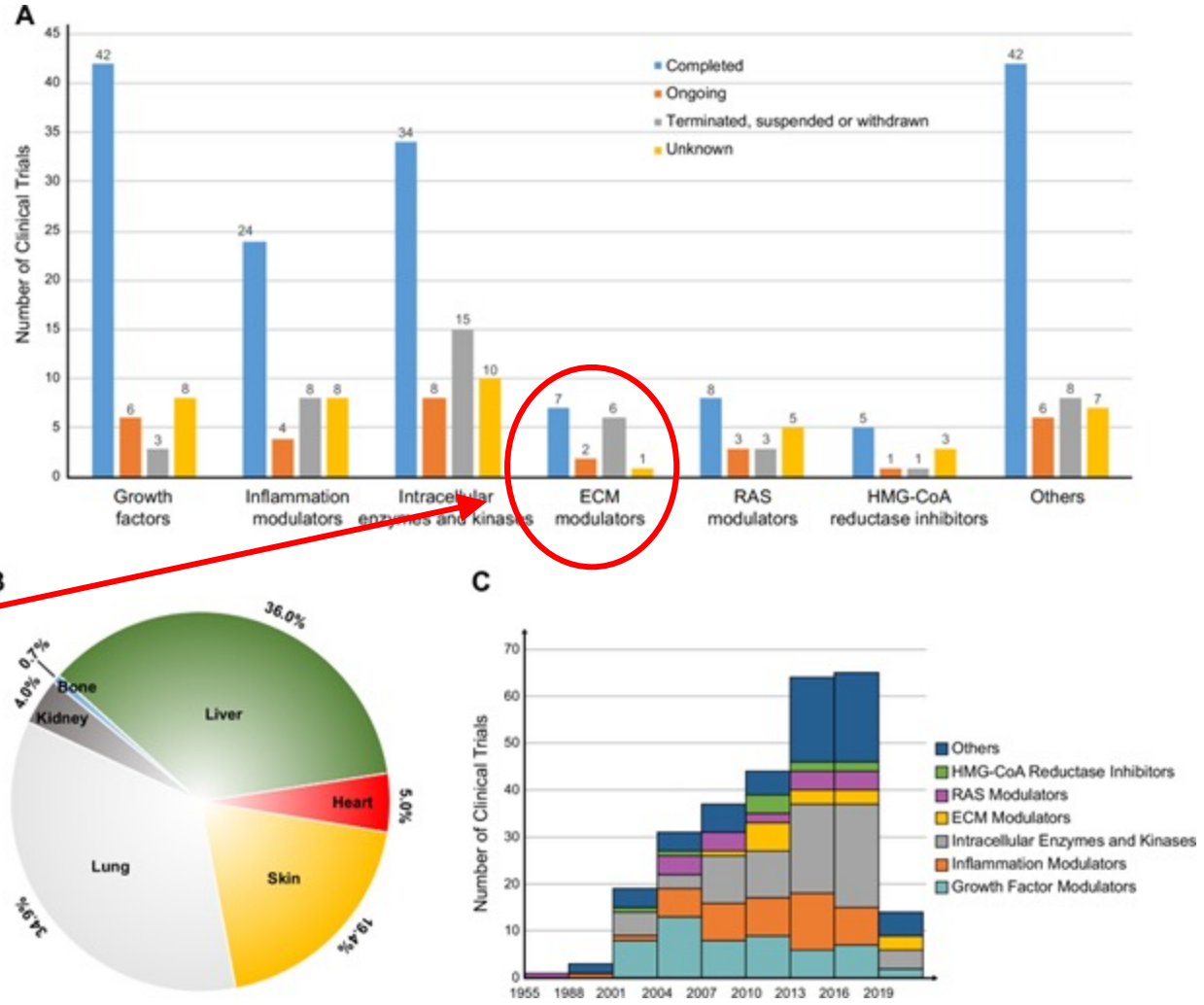


- Fibrosis is an exaggerated “scarring” of tissue in response to many types of cellular injuries, chronic inflammation, & other tissue insults
- Fibrosis impairs normal organ structure & function
- Fibrosis contributes to an estimated 1/3 of deaths worldwide
- Collagen molecules are the primary constituents of fibrotic scars

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 and other extracellular matrix (ECM) molecules common to fibrotic diseases. Therefore, identification of disease-specific fibrogenic stimuli is not necessary for rencofilstat's antifibrotic activity.

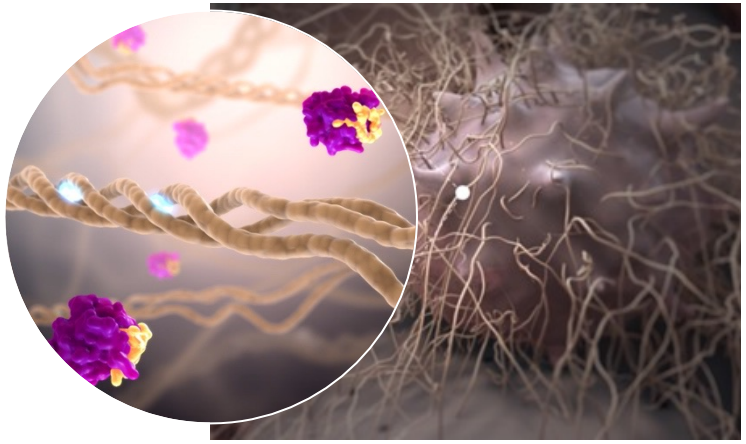


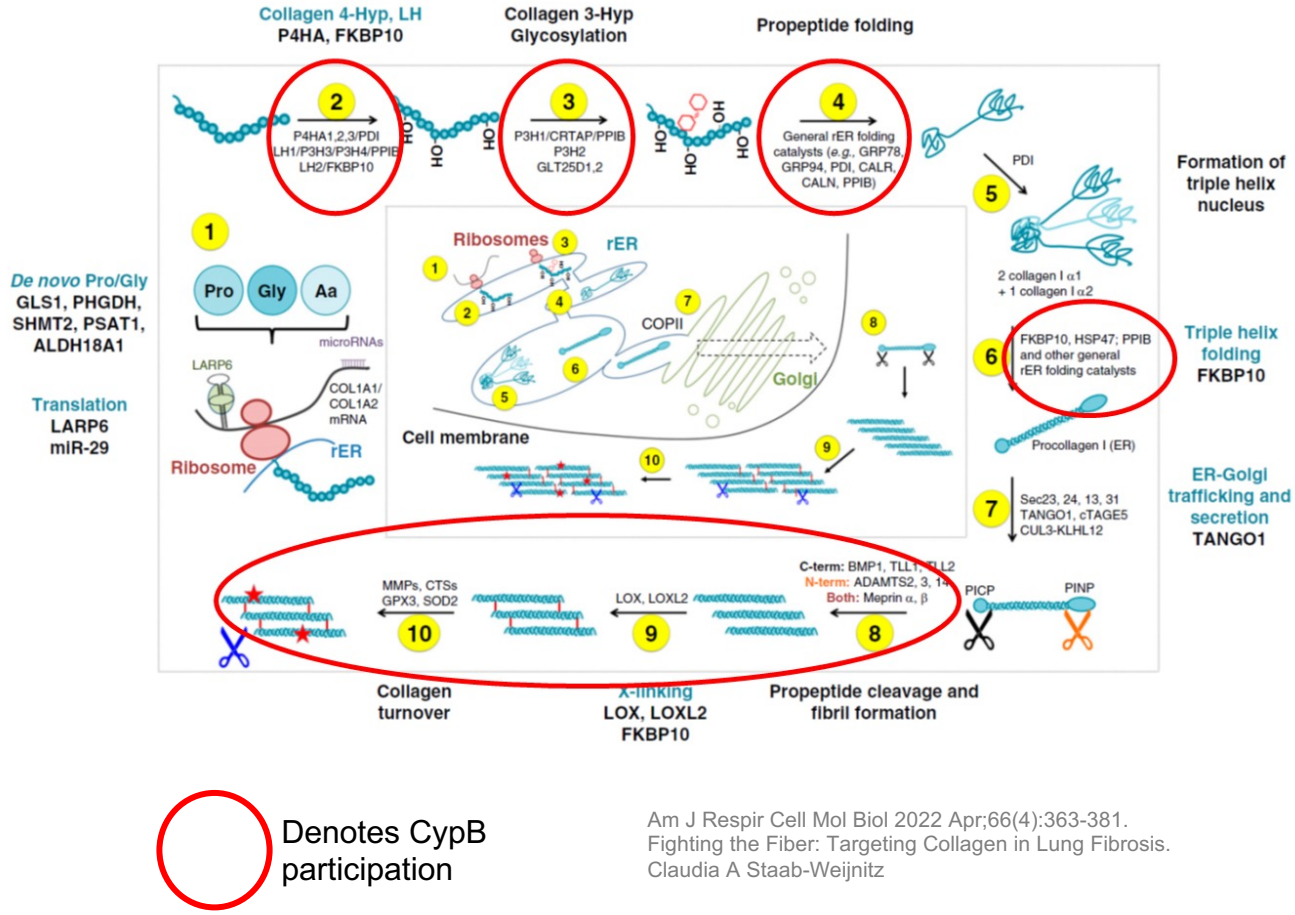
Physiol Rev 2022 Apr 1;102(2):605-652.
Development of antifibrotic therapy for stricturing Crohn's disease: lessons from randomized trials in other fibrotic diseases

Rencofilstat Attenuates Collagen Synthesis by Inhibiting Cyclophilin B Enzyme Activity - "normalizing" disease-associated fibrosis

Cyclophilin B is one of the most active enzymes involved in the proper folding, synthesis, secretion, and eventual crosslinking of collagen that forms the fibrotic matrix.

Rencofilstat potently inhibits cyclophilin B and thereby decreases collagen production and fibrosis.



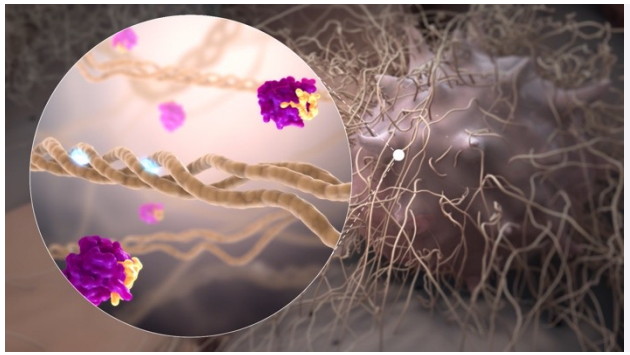


Denotes CypB participation

Am J Respir Cell Mol Biol 2022 Apr;66(4):363-381.
Fighting the Fiber: Targeting Collagen in Lung Fibrosis.
Claudia A Staab-Weijnitz

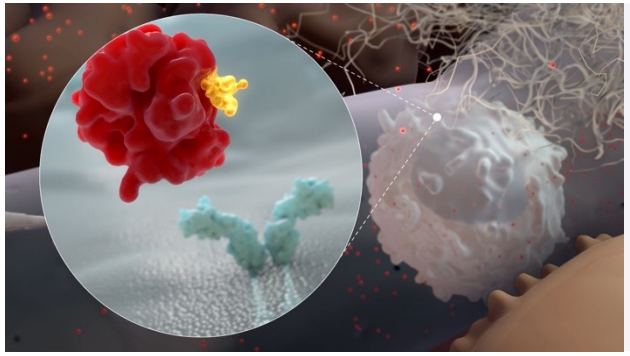
Rencofilstat Inhibits Three Primary Cyclophilins

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



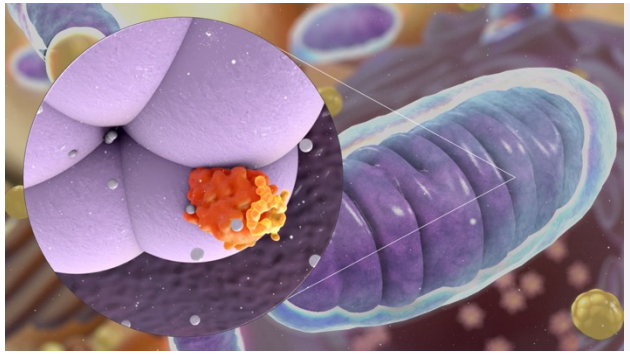
ANTI-FIBROTIC

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: Proof of Concept

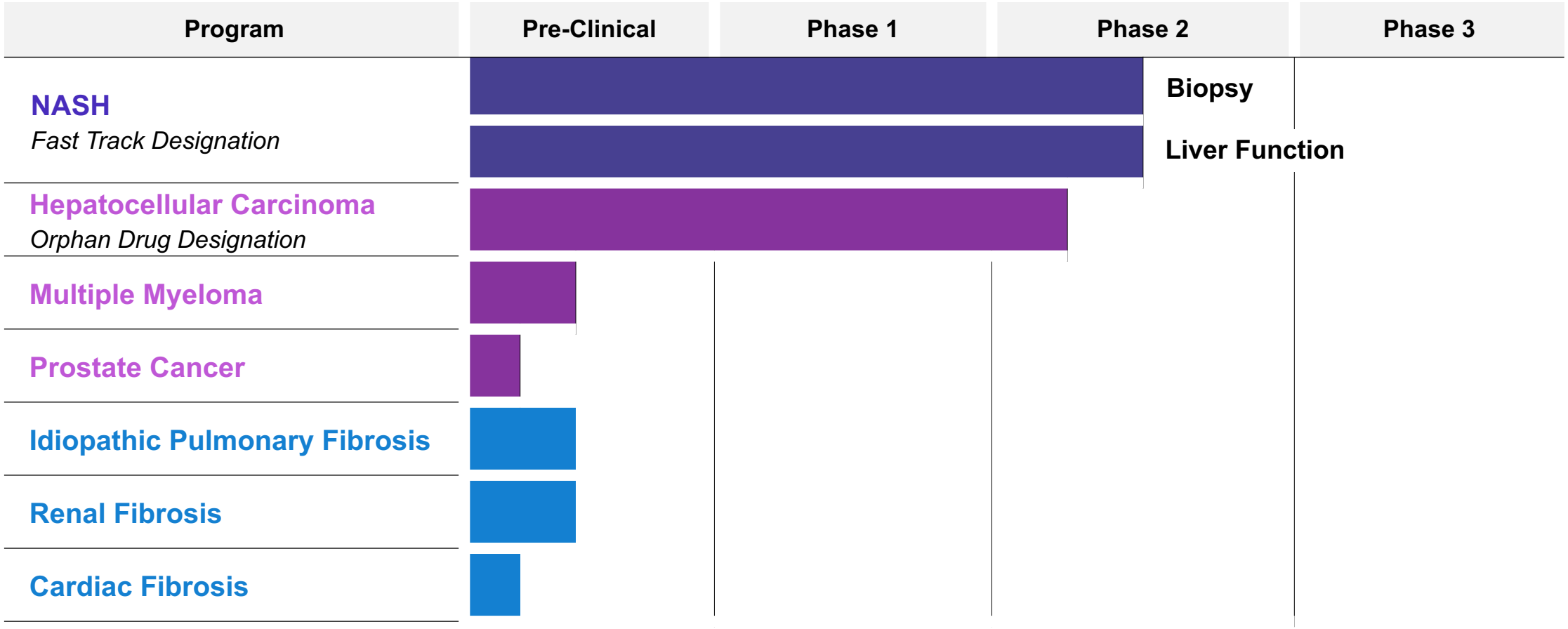
Cyclophilin Inhibition Produces Consistent Antifibrotic Effects

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

NASH
Fibrotic Liver Disease
Leading Indication for Rencofilstat

Summary of Rencofilstat Programs – ‘Pipeline within a Product’



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%****

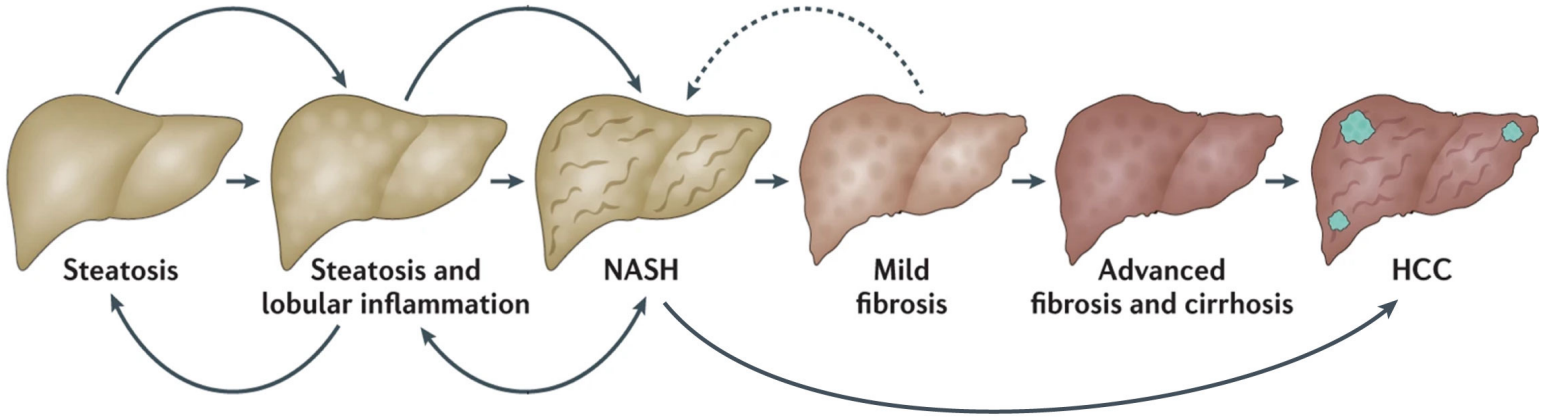


Image adapted from "From NASH to HCC: current concepts and future challenges", Anstee et al. (2019)

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

Why Develop a Drug for NASH?

- No currently approved drugs for the treatment of NASH
- Market for NASH is extremely large (estimated as ~20 million adults in U.S. alone)
- NAFLD/NASH may be asymptomatic with no convenient diagnostic to identify subjects early in disease progression
- Symptoms may only appear when disease has progressed to the point where disease associated fibrosis is well established
- Consequences of NASH may be severe (need for liver transplant, cancer, cardiovascular disease, and death)

NASH Therapeutic Strategies

Multiple therapeutic agents targeting multiple stages of disease likely required

WHY?

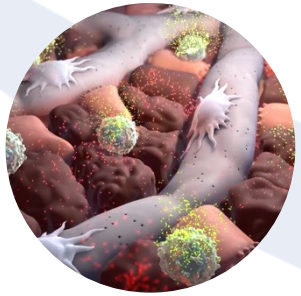
- Generally poor response rates with drugs in development
- Many pathologic mechanisms contribute to disease

normal liver cells

Most failed drugs and drugs in development are "metabolic" drugs
e.g., target liver fat

fatty liver cells

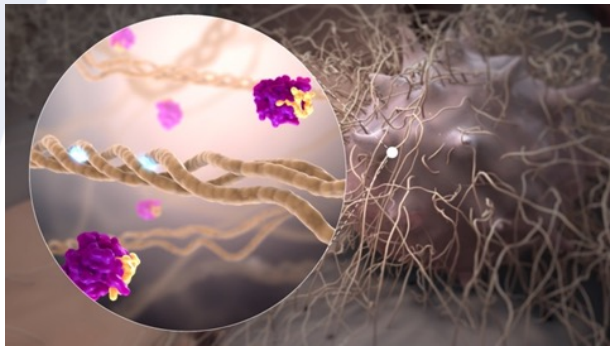
RENCOFILSTAT directly targets fibrosis and inflammation



inflammation, cell injury, and activation of fibrotic cells

production of fibrotic matrix

Rencofilstat inhibits collagen



NASH DISEASE PROGRESSION

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 problematic
- Widely available simple companion diagnostics needed (e.g., Hepion's A.I.)

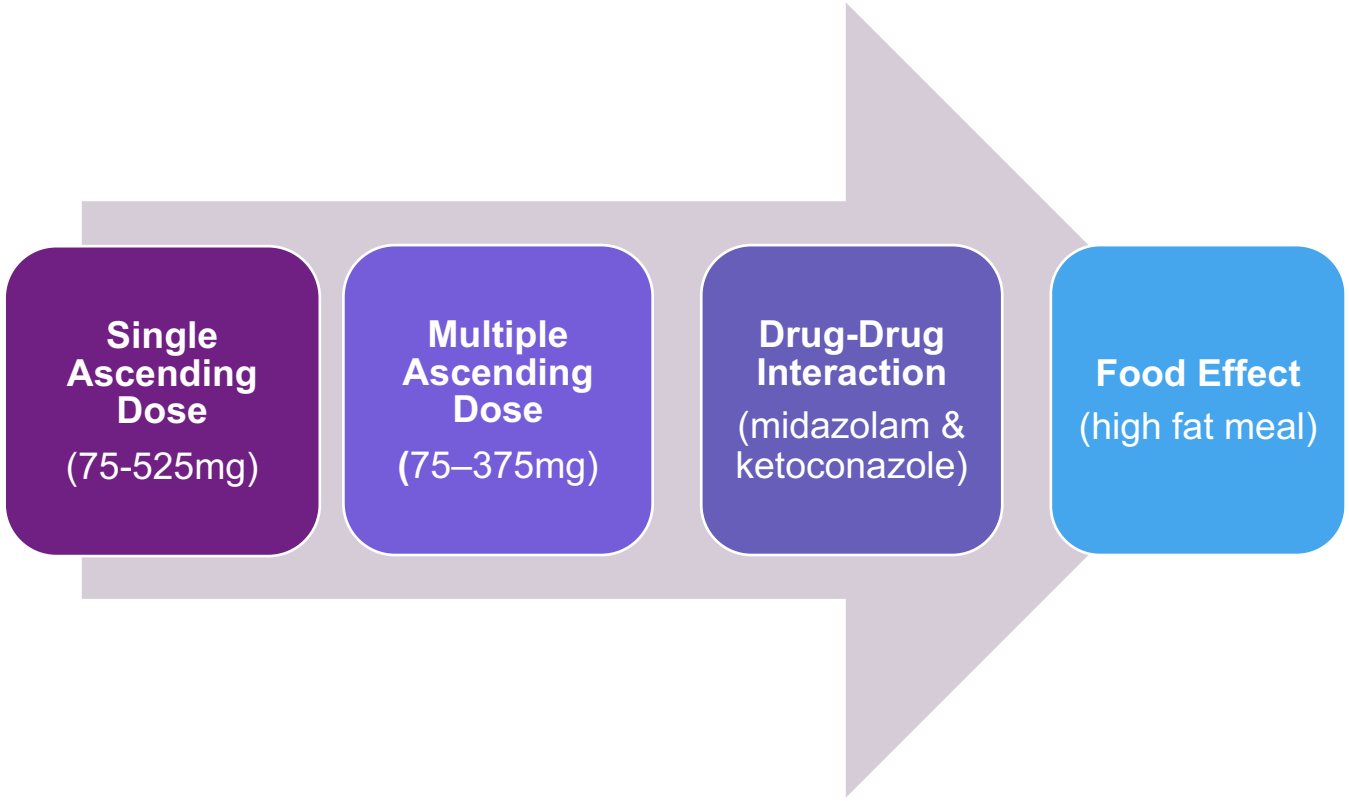
3. Need for Commercial Strategy

- 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



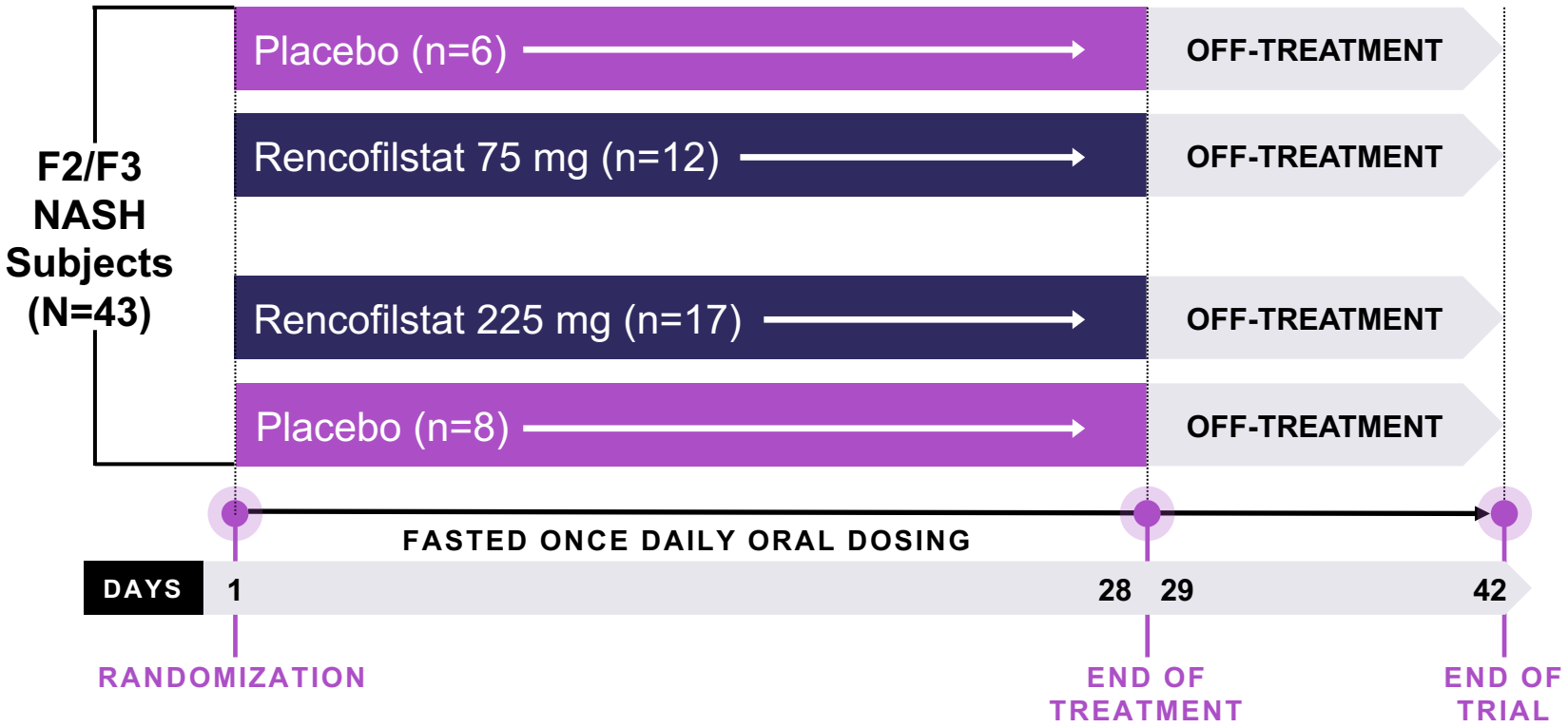
- No serious adverse events
- No adverse events with dose response
- Effective $t_{1/2}$ ~ 30 hours
- $Tmax_{ss}$ ~ 1 – 2 hours
- Ketoconazole increased rencofilstat concentrations ~ 5-fold
- Rencofilstat had no effect on midazolam exposure
- Rencofilstat absorption was not decreased with high fat meal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

Conducted at 10 sites in the US

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

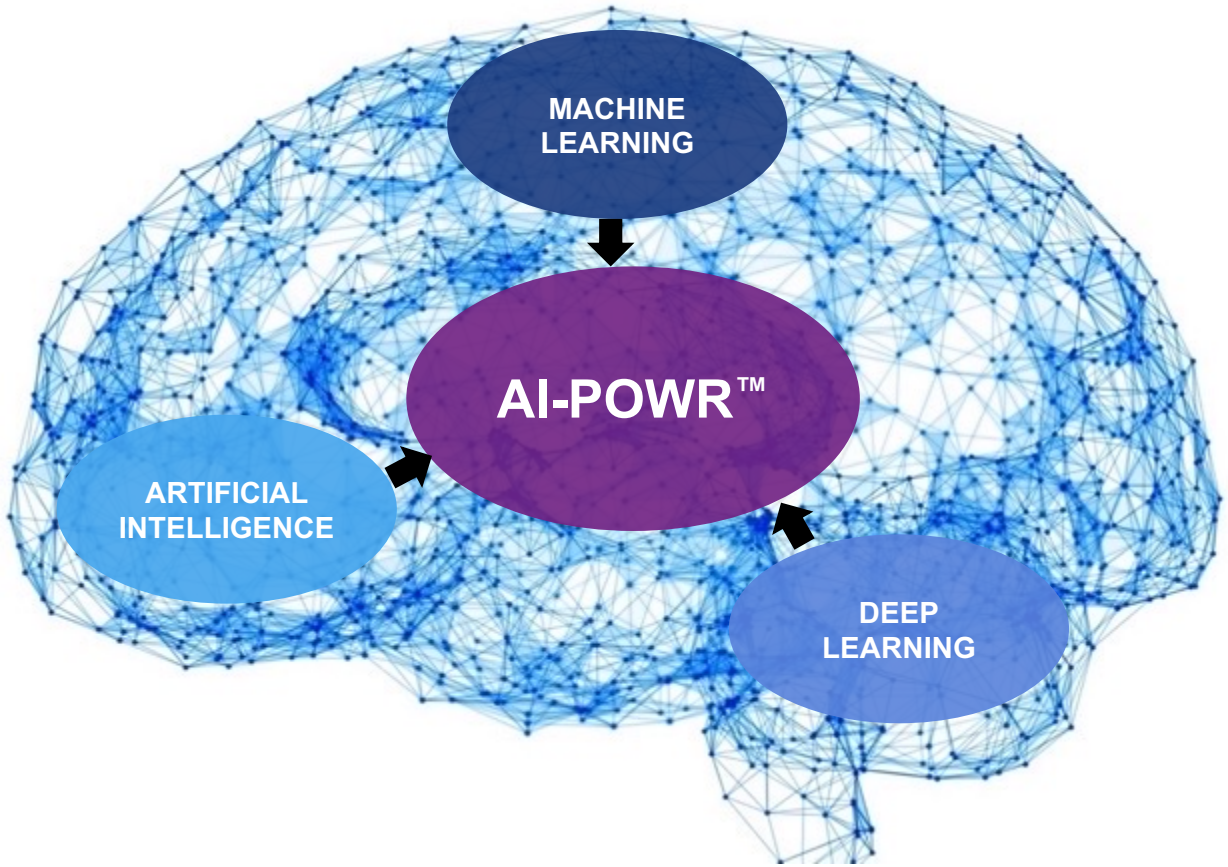
Hepion's Proprietary Artificial Intelligence

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

Developing a Panel for Clinical Development and Commercialization

AI-POWR™

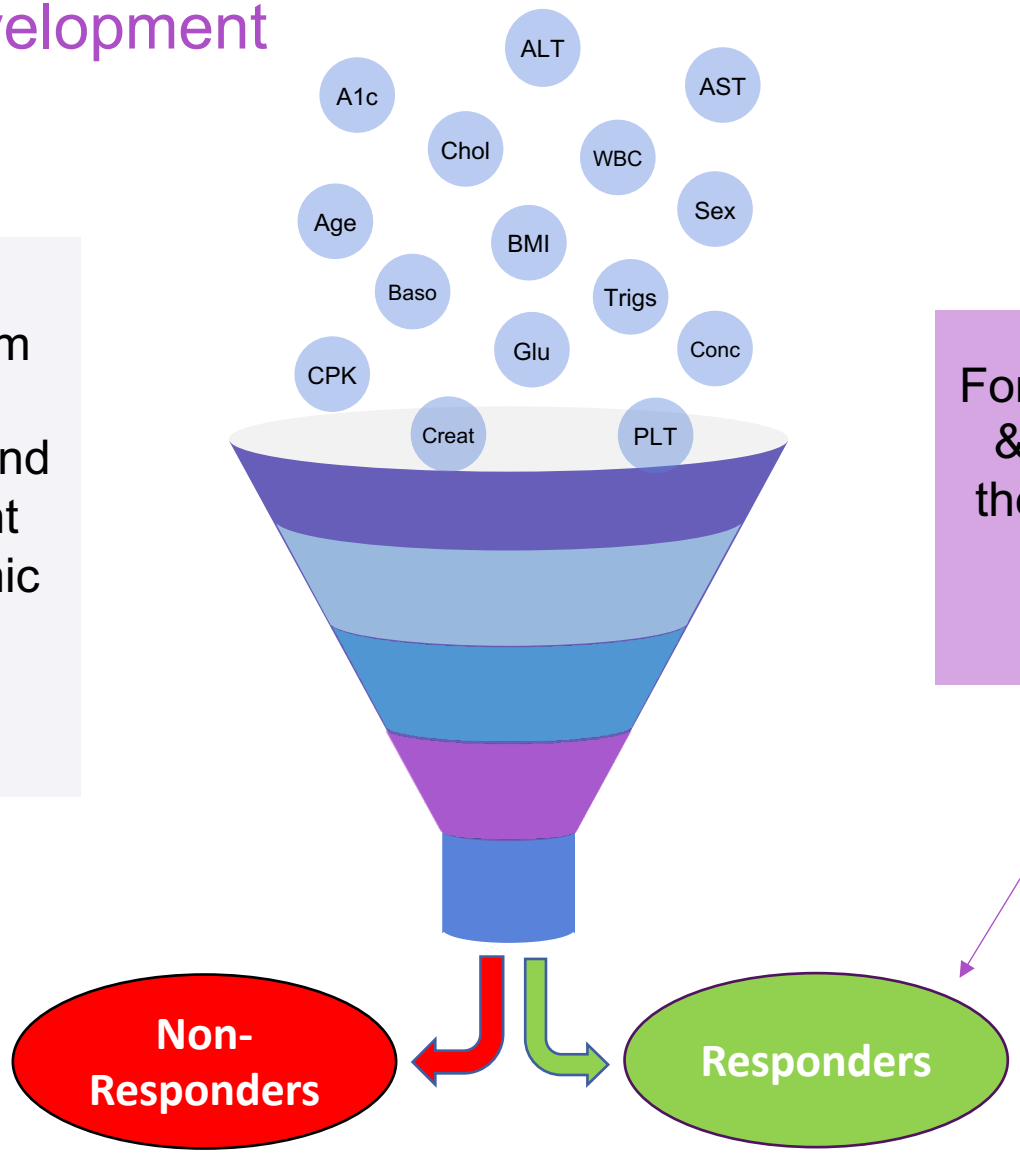
- Facilitates:
  - Improved drug target selection
  - Clinical study design
  - *a priori* responder analysis
- Designed to elucidate both disease and pharmacodynamic biomarkers



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

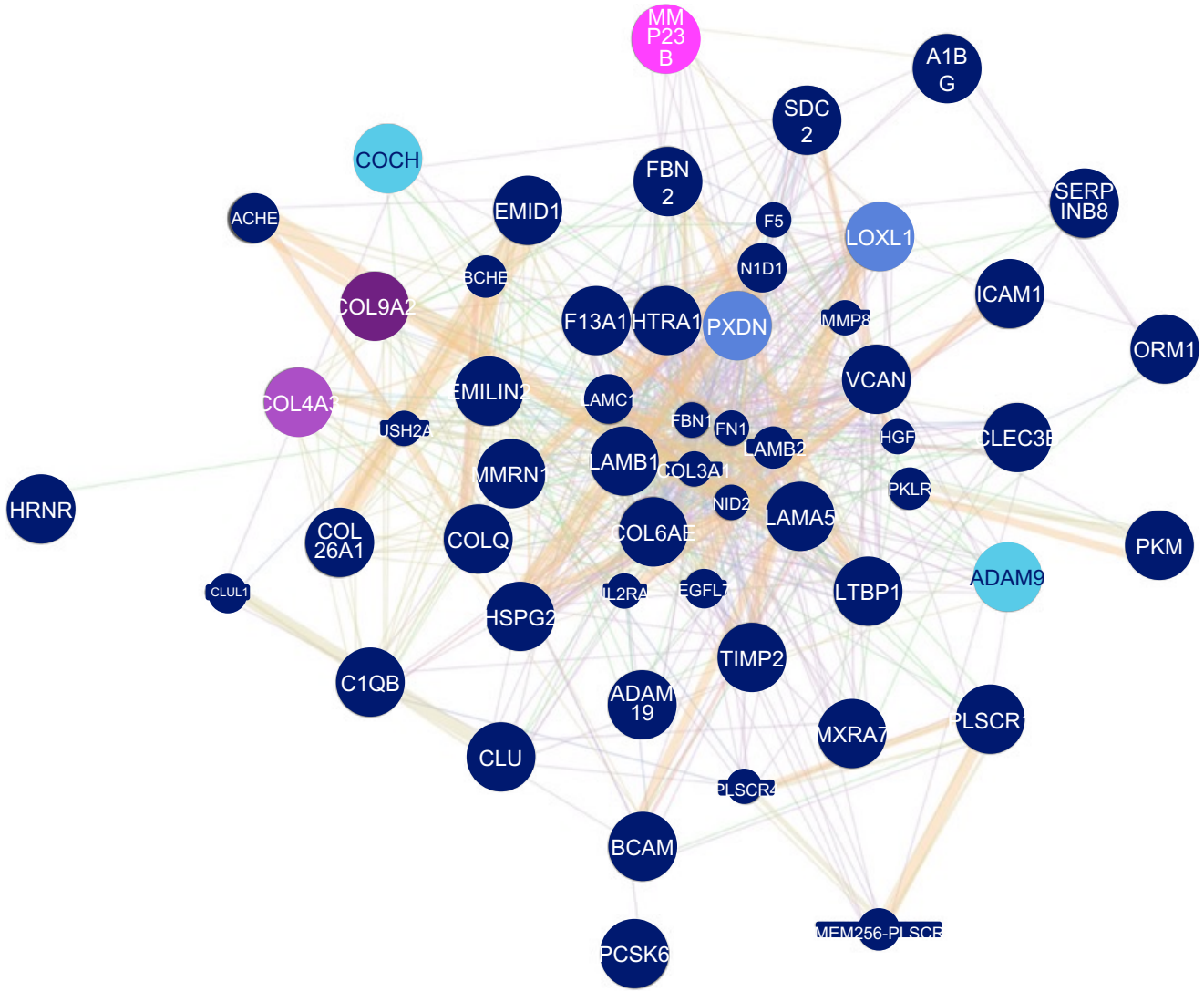


For future Phase 3 trials & commercialization, the appropriate patient population will be targeted

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.

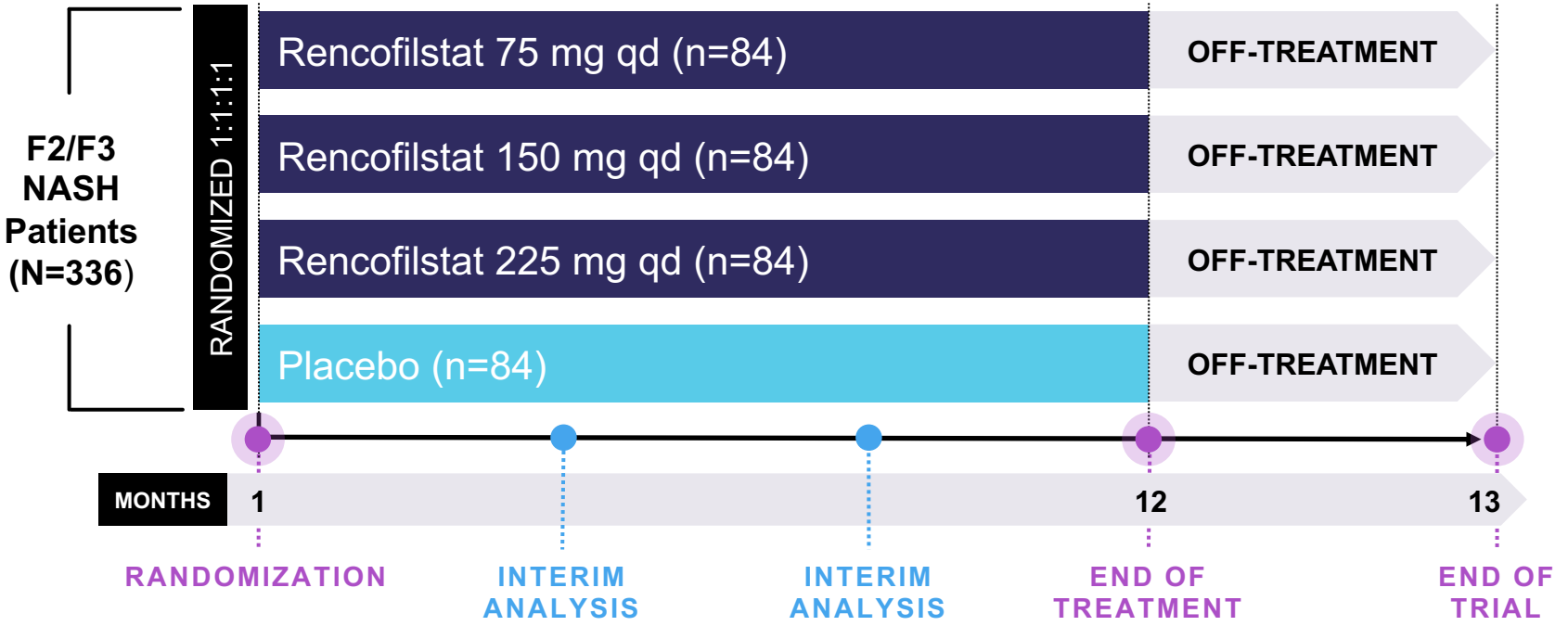


- collagen-containing extracellular matrix
- collagen binding
- collagen type IV trimer
- collagen type IX trimer
- collagen fibril organization
- collagen catabolic process

Phase 2b
‘ASCEND-NASH’ Trial
(Enrolling)

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 34 subjects in each cohort reach day 180 and when 56 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:

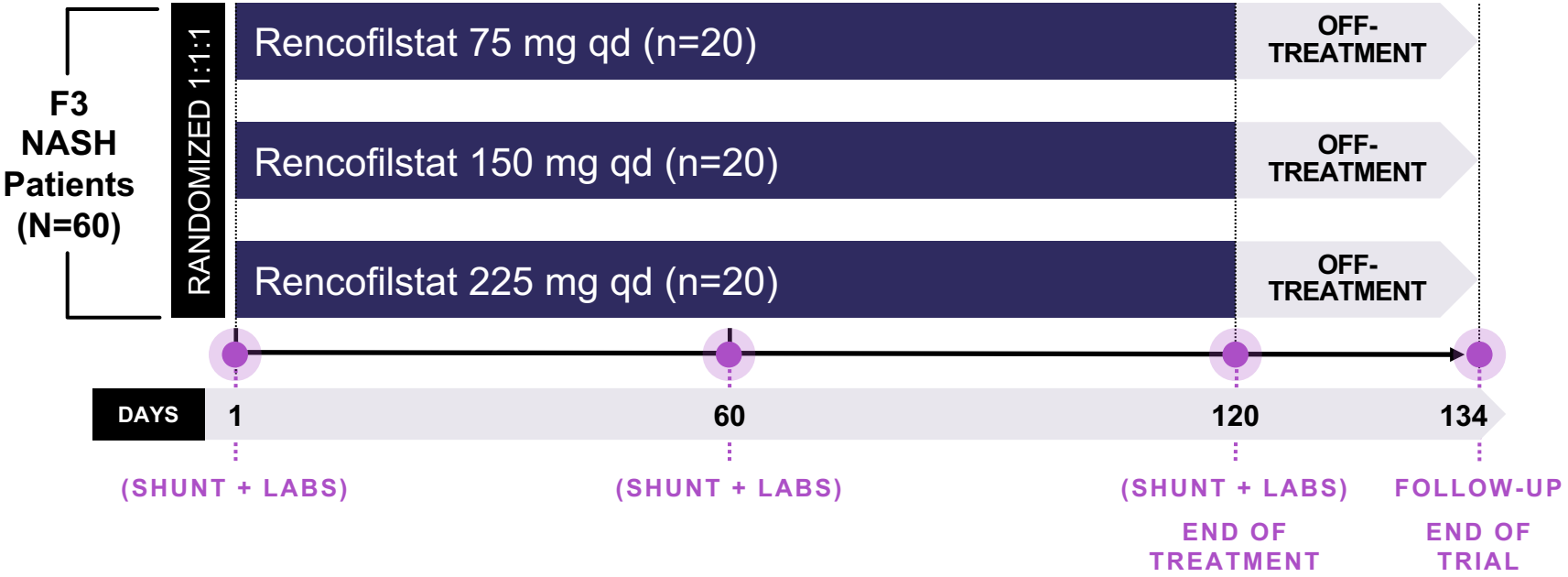
Superiority of rencofilstat compared to placebo on histology at month 12 relative to screening by assessing the proportion of subjects with improvement in fibrosis by:

- 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
(Fully Enrolled)

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:

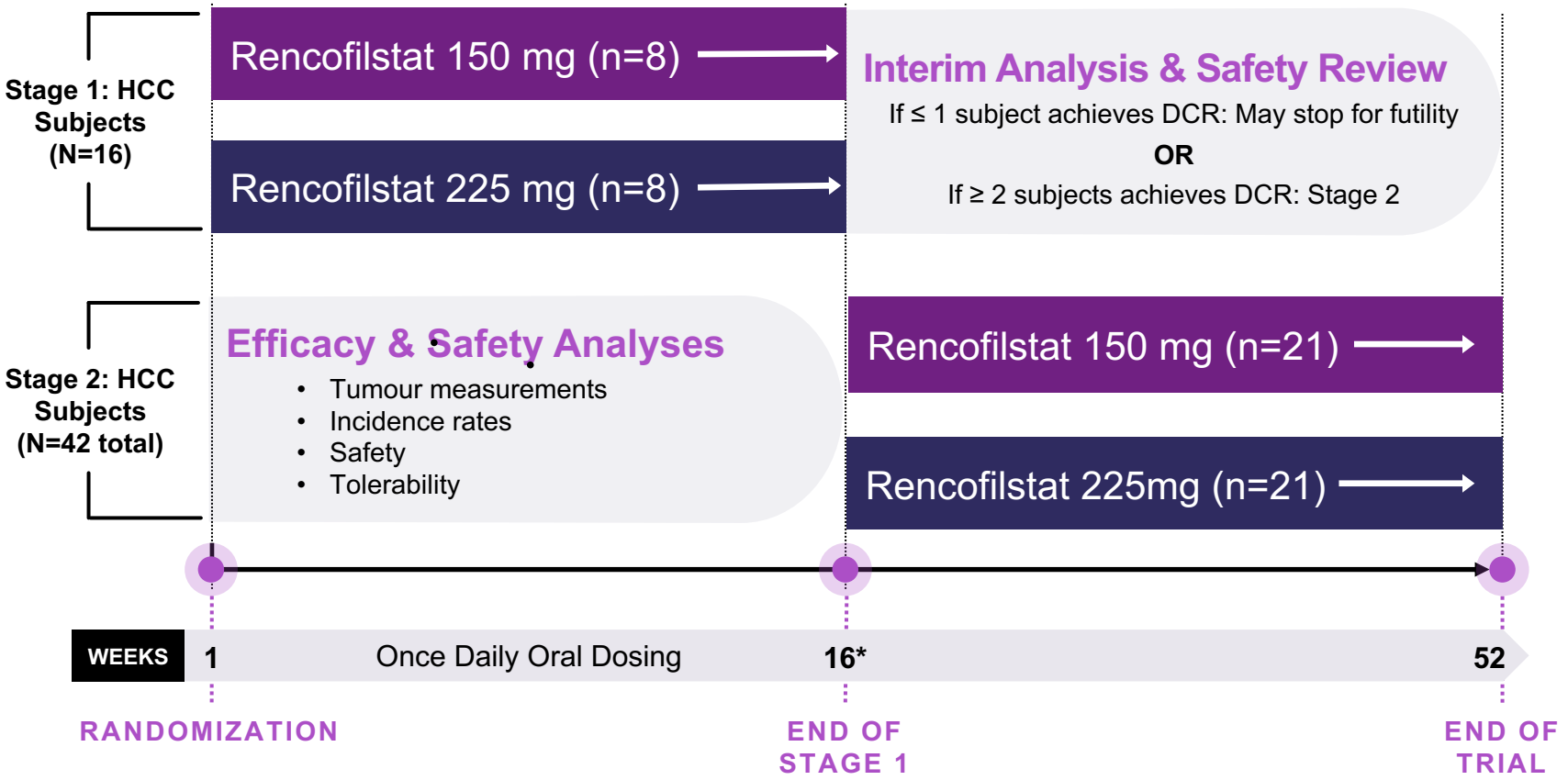
- Percent of subjects with a reduction in DSI score of >2
- Change from baseline in portal and systemic Hepatic Filtration Rate (HFR) using HepQuant SHUNT Test
- Change from baseline in Fibrosis-4 (FIB-4) scores
- Change from baseline in Enhanced Liver Fibrosis (ELF) scores
- Change from baseline in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

Intellectual Property

Intellectual Property Position

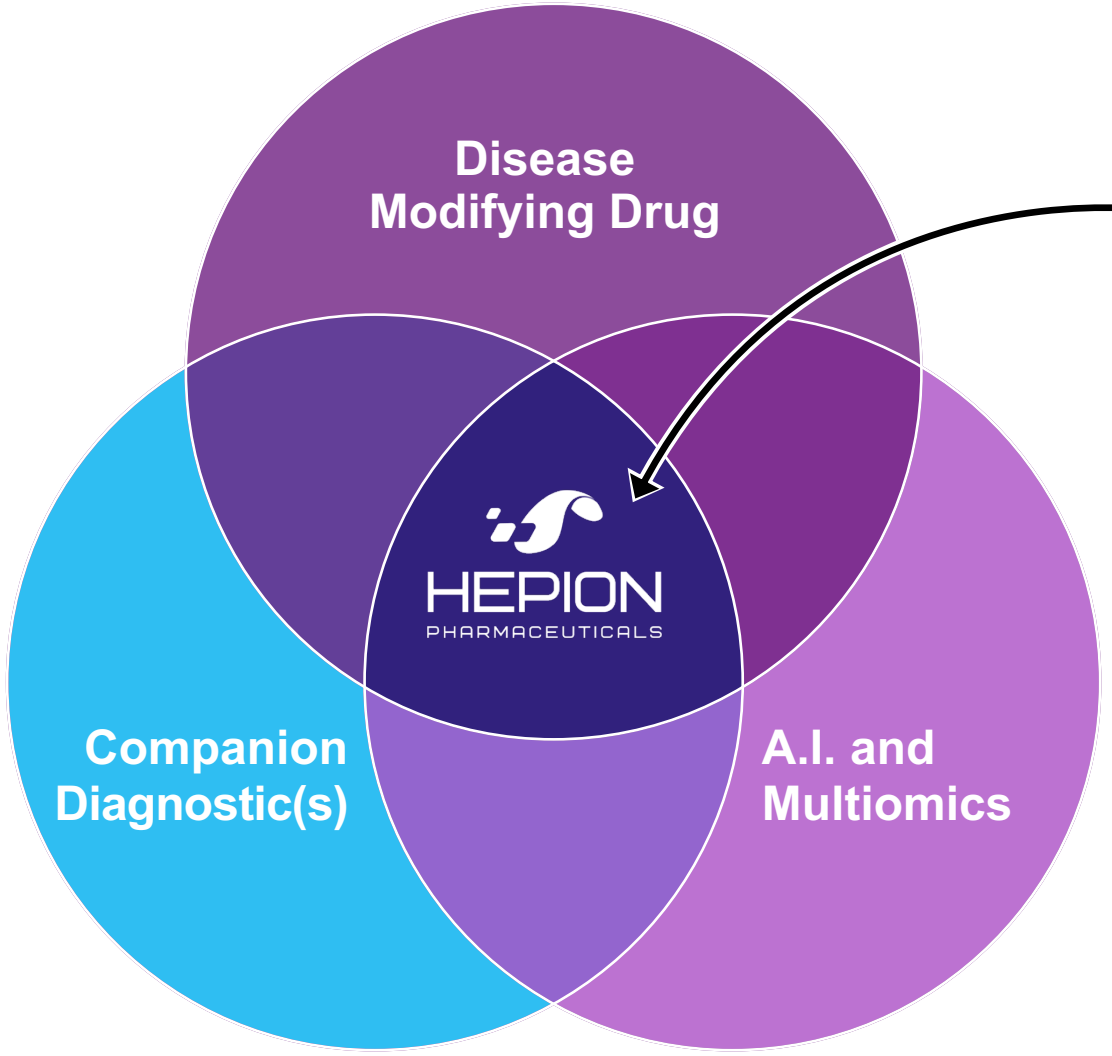
Long Patent Life with Patent Term Extensions (PTE)

Family	Status	Notes
Composition of Matter	54 US & International Issued Patents	December 2031 Expiry (December 2036 Expiry with PTE) Assuming 2028 and 2029 NDA submission and approval
Composition of Matter (optimization)	Provisional	
Formulation	23 US & International Applications Filed; Intent to Grant Received	November 2039 Expiry (May 2043 Expiry with PTE) Assuming 2023 patent grant and 2028 and 2029 NDA submission and approval
Method of Use, Treating Fibrosis	23 US & International Applications Filed	February 2041 Expiry + PTE
Method of Use, Treating Cancer	23 US & International Applications Filed	February 2041 Expiry + PTE
Method of Use, Antithrombotic Agents	US & PCT Applications Filed	December 2041 Expiry + PTE
Manufacturing	Provisional	

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 280 subjects
- Two Phase 2 NASH trials ongoing
- 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

HEPION PHARMACEUTICALS RENCOFILSTAT

HEPION PHARMACEUTICALS AI-POWR™

Financials

$59.1 M
Cash
as of 9/30/22

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.

John Cavan, MBA
CFO

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

Todd Hobbs, MD
CMO

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

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.

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.

Patrick Mayo, PhD
SVP, Clinical Pharmacology and Analytics

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

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