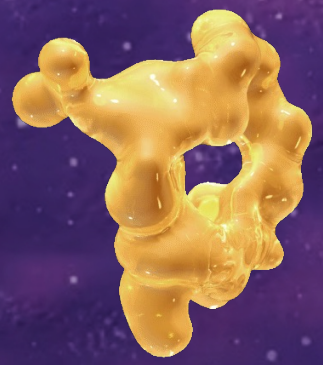
HEPION PHARMACEUTICALS

NASDAQ:**HEPA**

Rencofilstat (CRV431):

A Novel Drug Candidate for NASH, Fibrosis, and HCC



Creating a Therapeutic Ecosystem

July 2023

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Rencofilstat

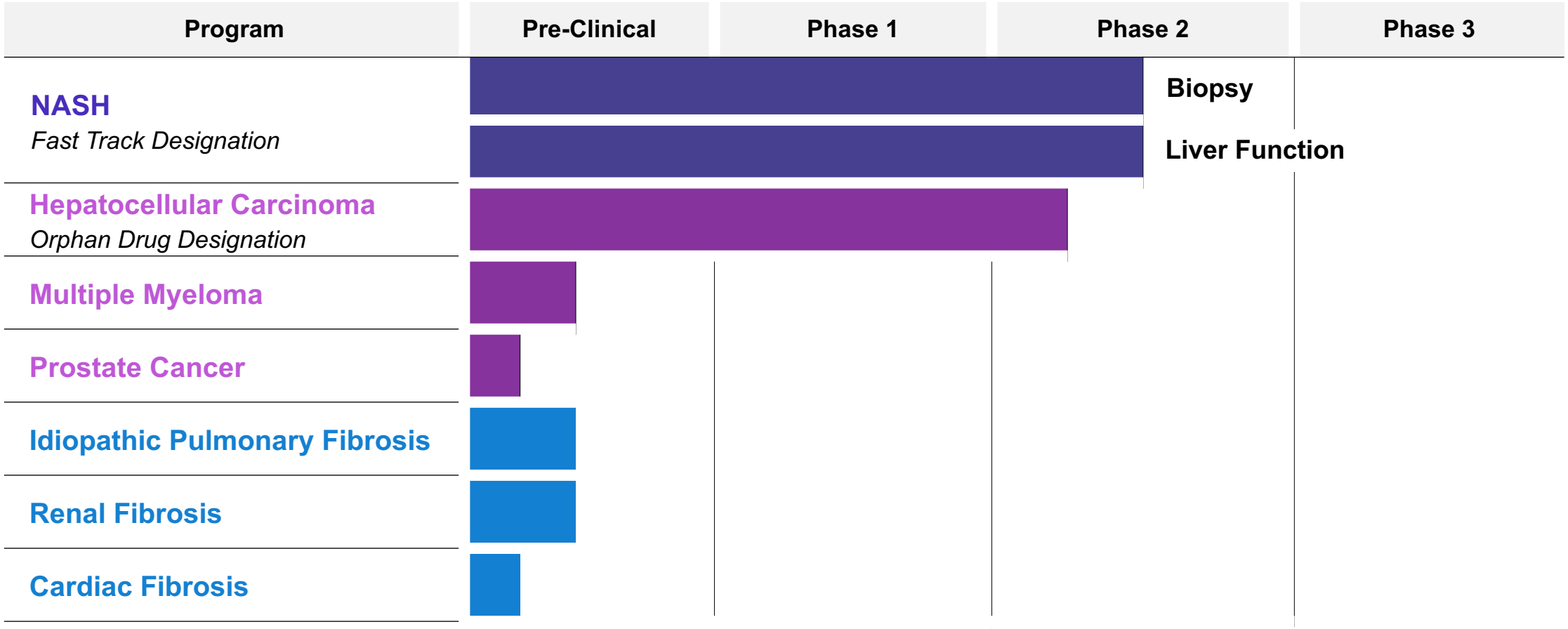
Anti-Fibrotic Drug Candidate

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 well tolerated – over 425 subjects dosed
- Currently undergoing Phase 2 clinical trials

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**
  Approx. 20 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%****

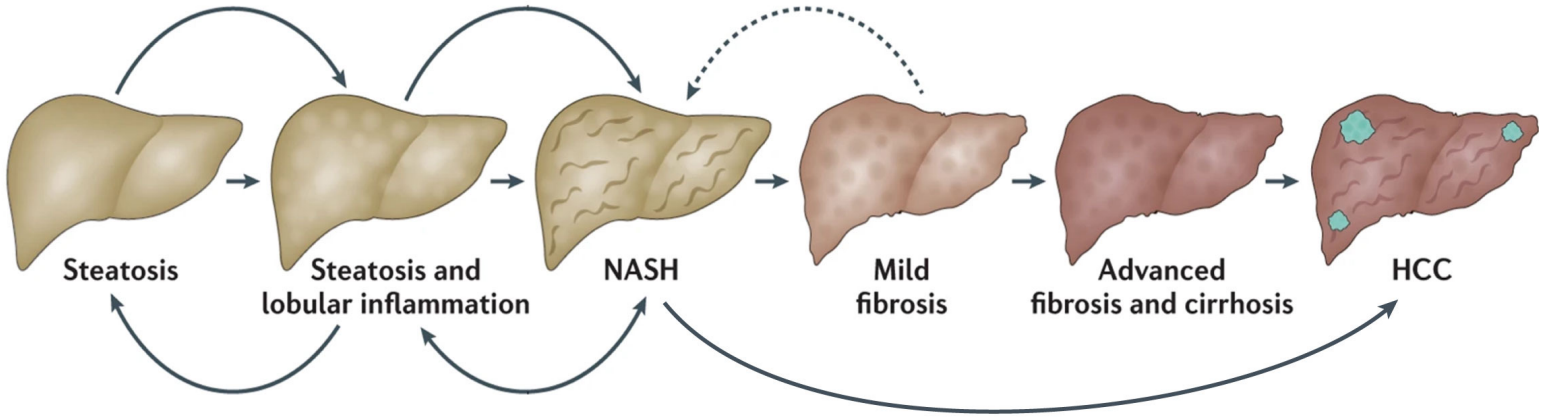


Image adapted from "From NASH to HCC: current concepts and future challenges", Anstee et al. (2019)

*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?

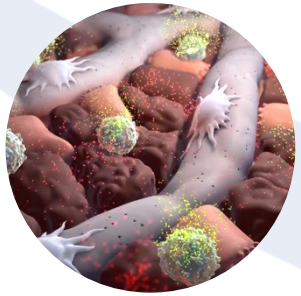
- Generally poor response rates with drugs in development
- Many pathologic mechanisms contribute to disease

normal liver cells

fatty liver cells

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

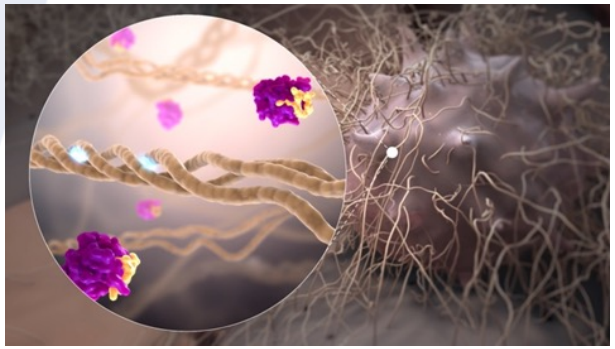
RENCOFILSTAT directly targets fibrosis and inflammation



inflammation, cell injury, and activation of fibrotic cells

production of fibrotic matrix

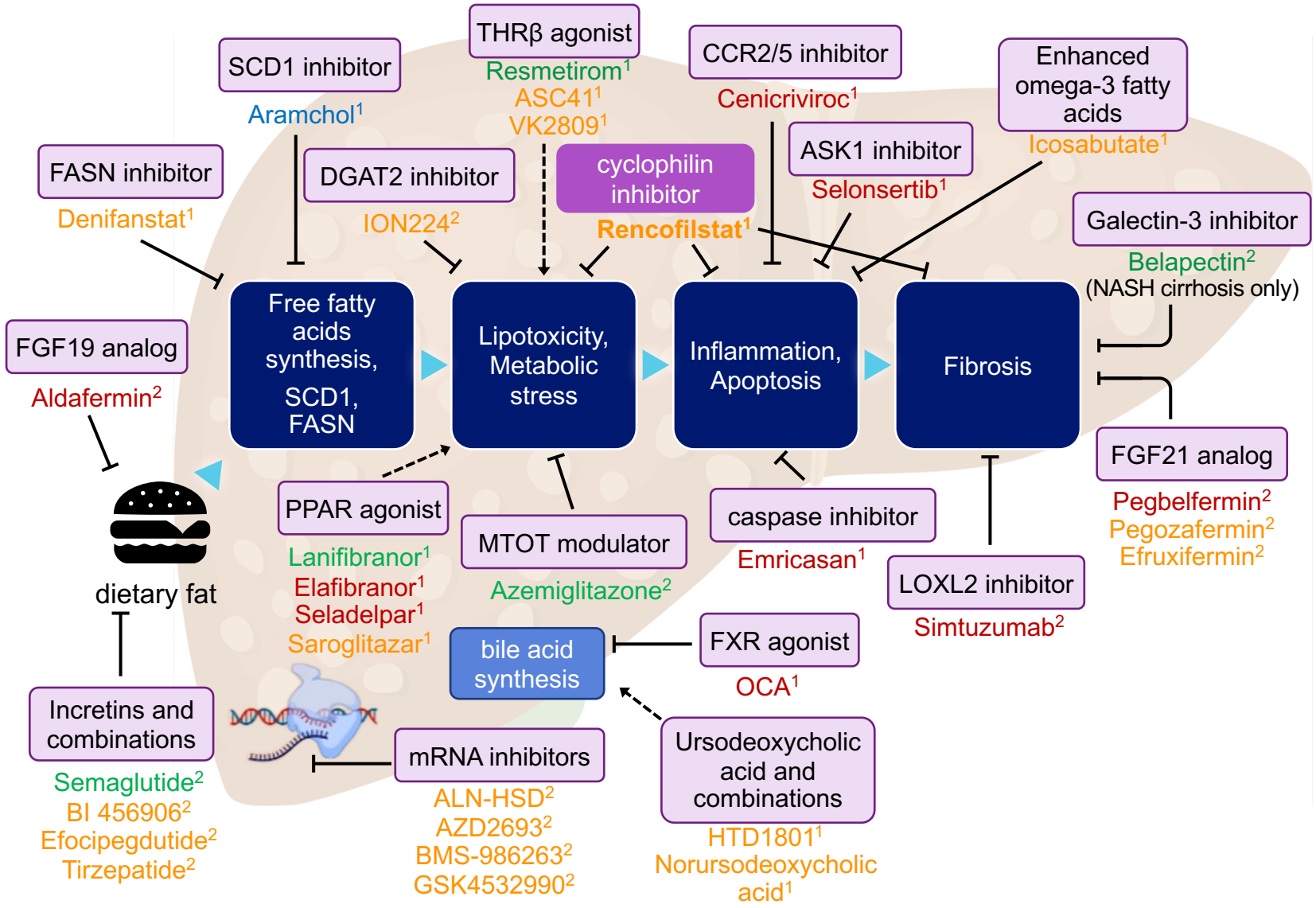
Rencofilstat inhibits collagen



NASH DISEASE PROGRESSION

NASH Drug Development Landscape

Phase 2b and 3

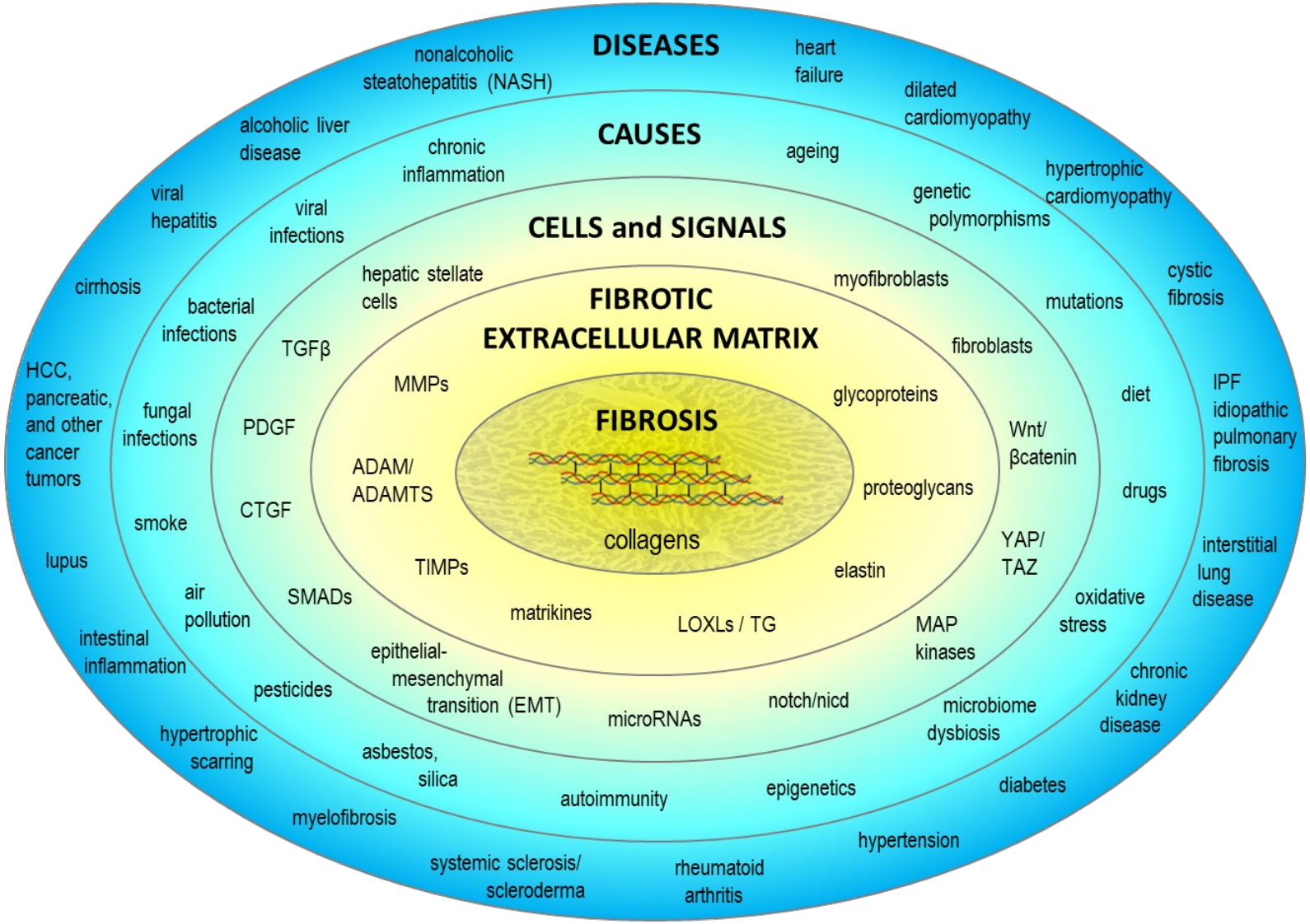


Phase 3
Phase 2b
Discontinued
Suspended
[1] Oral dosing
[2] Injection/infusion
Regulation
Inhibition

Rencofilstat Mode of Action

Collagen - Core To Fibrotic Diseases

Excessive Collagen Production – Universal to Every Fibrotic Disease



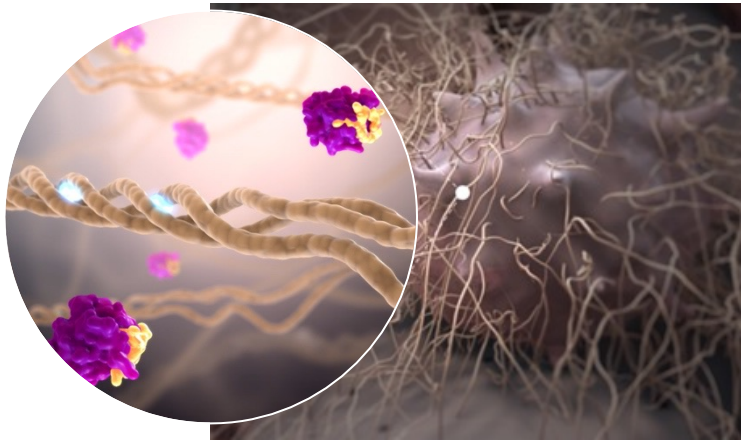
- Fibrosis is an exaggerated “scarring” of tissue in response to many types of cellular injuries, chronic inflammation, & other tissue insults
- Fibrosis impairs normal organ structure & function
- Fibrosis contributes to an estimated 45% of deaths in the developed world*
- Collagen molecules are the primary constituents of fibrotic scars

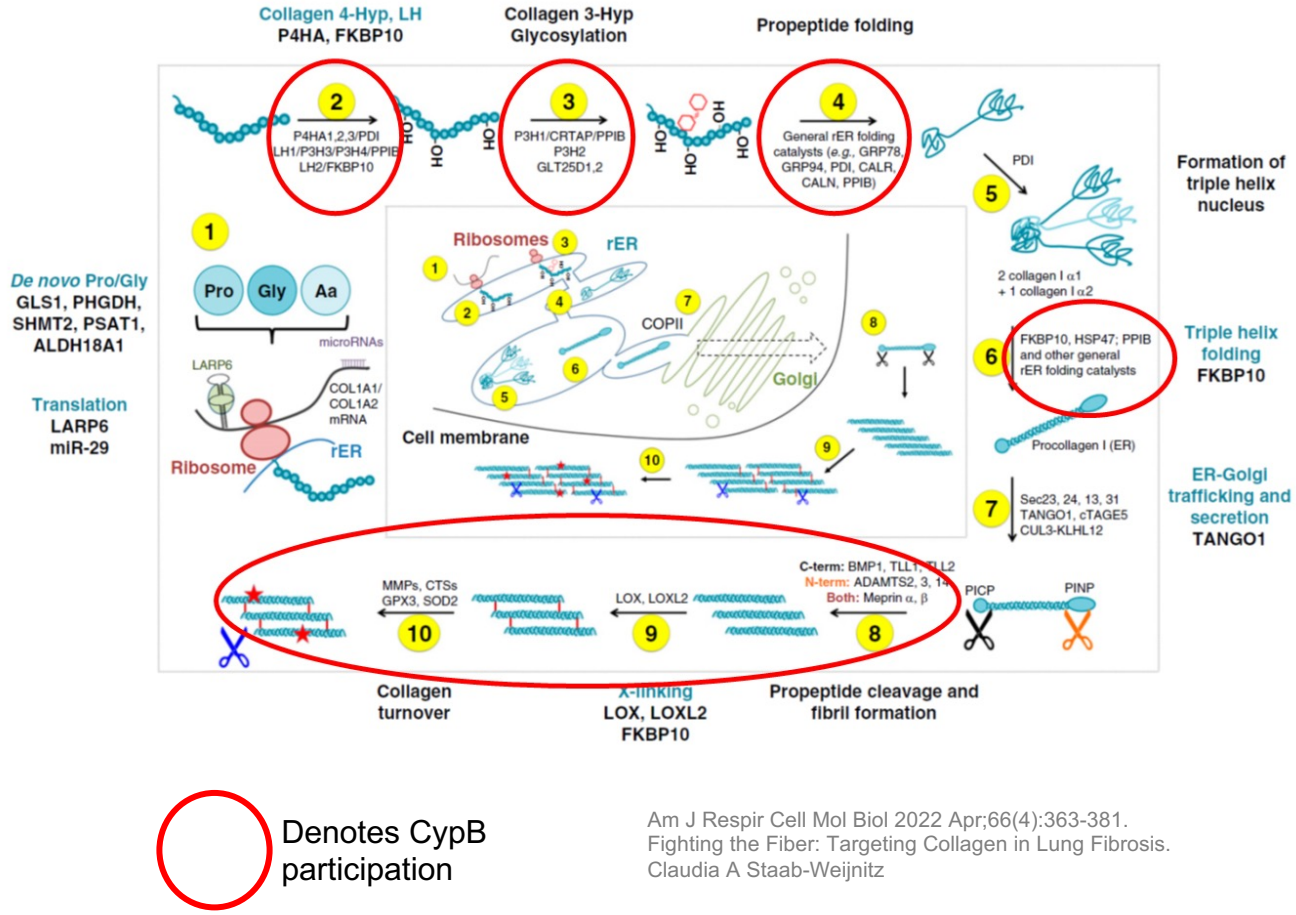
Nature Reviews Drug Discovery 14.10 (2015): 693-720

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

Preclinical Models: Proof of Concept

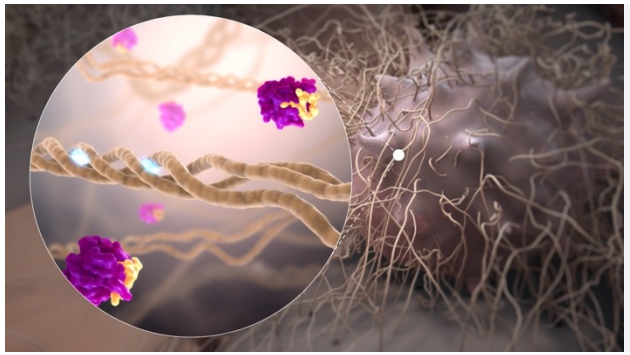
Cyclophilin Inhibition Produces Consistent Antifibrotic Effects

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

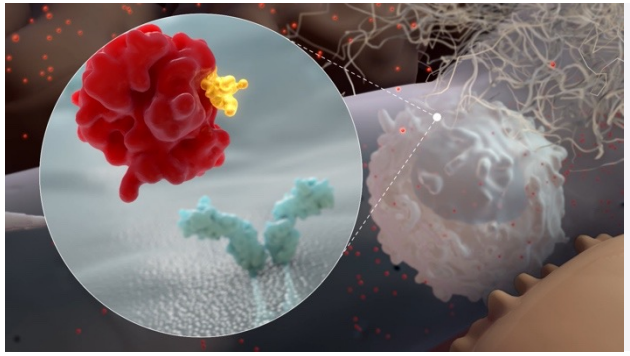
Rencofilstat Inhibits Three Primary Cyclophilins

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



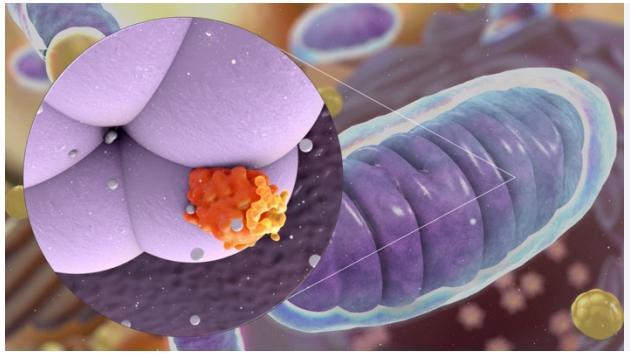
ANTI-FIBROTIC

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



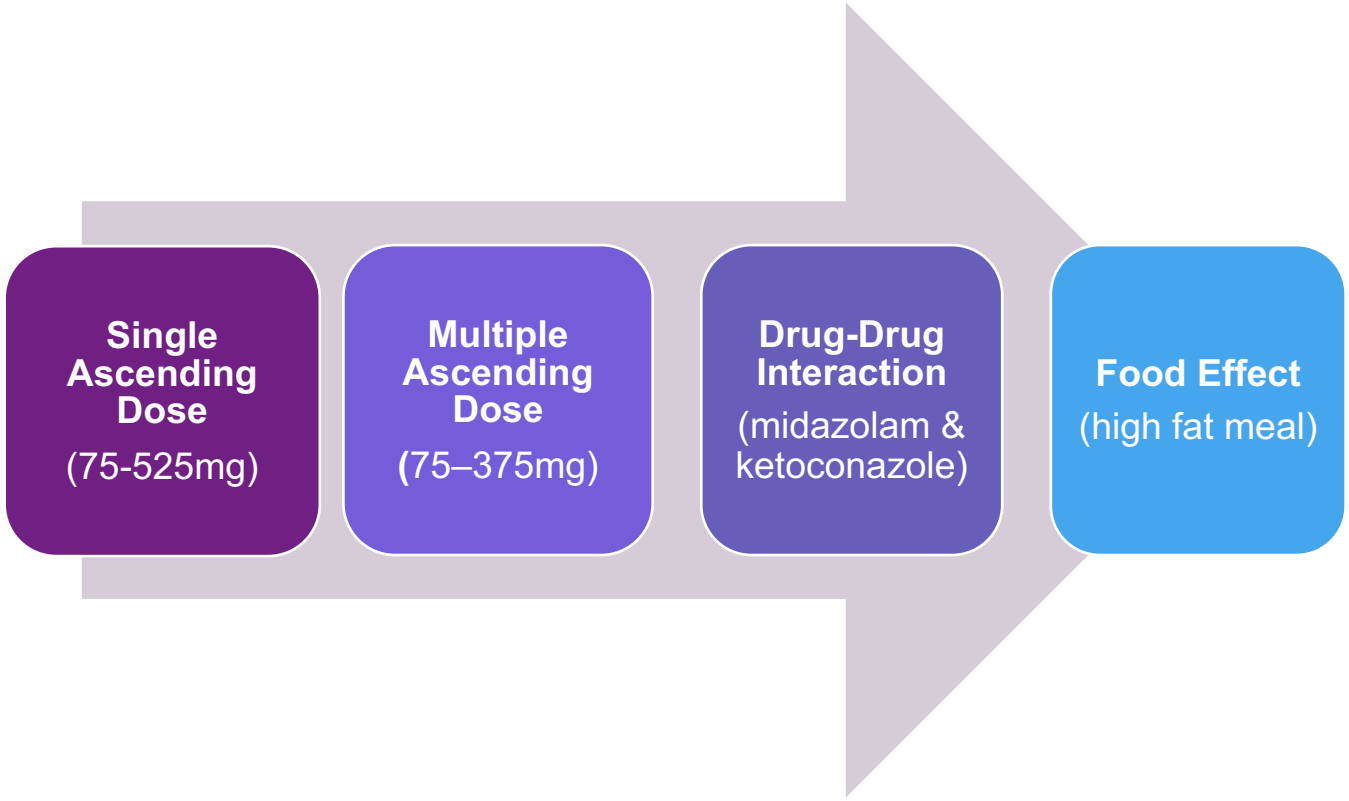
CYTOPROTECTIVE

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

Overview of Phase 1 Studies (Completed)

Phase 1 Studies Completed – Demonstrated a Favorable Safety Profile

Key Findings



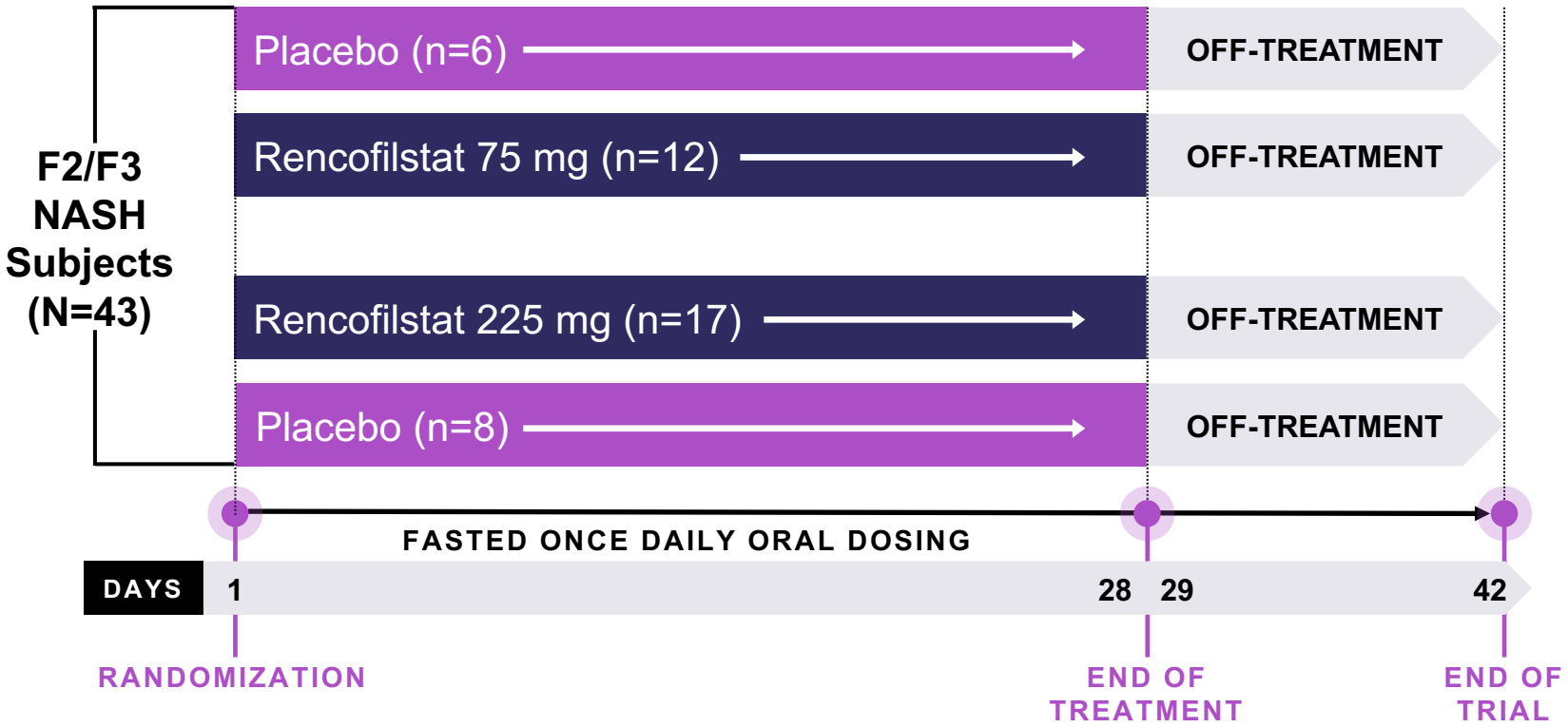
- No serious adverse events
- No adverse events with dose response
- Effective $t_{1/2}$ ~ 30 hours
- $Tmax_{ss}$ ~ 1 – 2 hours
- Ketoconazole increased rencofilstat concentrations ~ 5-fold
- Rencofilstat had no effect on midazolam exposure
- Rencofilstat absorption was not decreased with high fat meal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

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

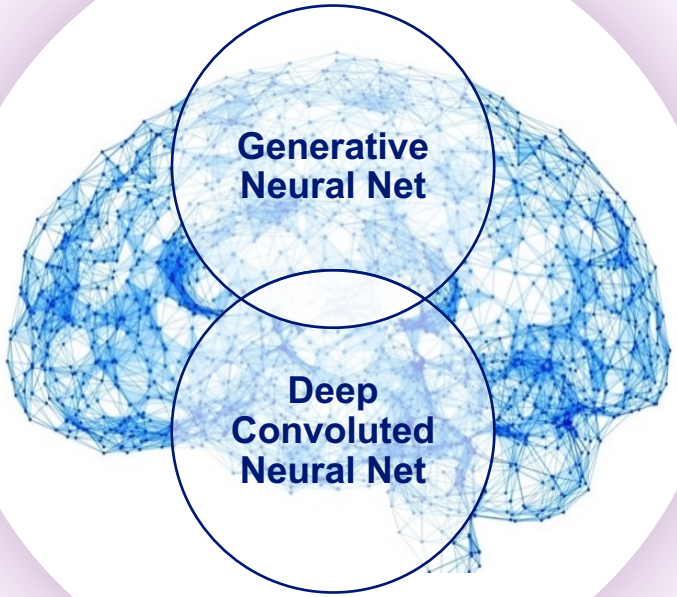
Hepion's Proprietary Artificial Intelligence

The Hepion AI-POWR™ Proprietary Clinical Process

AI-POWR™

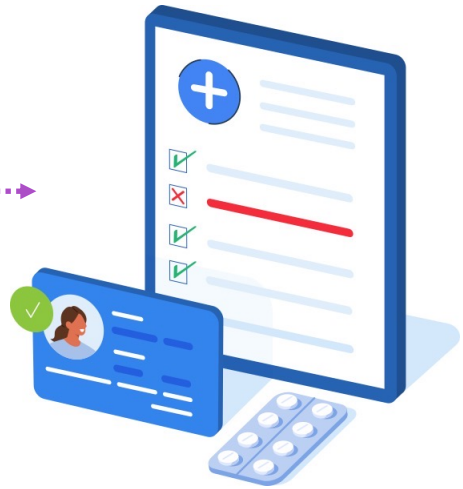
All Data

INPUT



OUTPUT

Right Patient
Right Dose



The Hepion AI-POWR™ Proprietary Clinical Process

AI-POWR™
PKPD/QSP/PBPK
+ Multi-omics
+ QoL
+ Safety
+ Deep Learning AI
= Digital Biomarkers
Responders

Pre-Clinical Data
Informs AI/ML
for Clinical
Development

- Biomarkers
- Patient Selection
- Simulation

1. AI/ML pop PKPD
2. AI/ML QSP
3. AI/ML PBPK

- Responder Identification
- Phase III Enrichment
- **Predict Clinical Outcome**

via AI/ML 1,2,3

Deep Learning Individual Response Model
Drug-Disease Interaction Model

- Digital Biomarkers
- **Eliminate Biopsy**
- Patient Specific Dosing
- Clinical Monitoring
- Reimbursement

AI-POWR™ Allows for Validation Comparisons
1. AI/ML included within developmental processes
2. AI/ML overarching input to outcome

Illustration of Hepion's AI-POWR™ for Rencofilstat (RCF)

*Genes (number)	Predictive Genes (number)	AUROC	Comment
1733 Statistically Significant	25	0.97	Highly Predictive for ProC3 Response

*Key genes identified demonstrate RCF – CypA and B interaction in NASH subjects

Lipids (number)	Predictive Lipids (number)	AUROC	Comment
443 Statistically Significant	25	0.74	Highly Predictive for ProC3 Response

Clinical Labs	AUROC	Comment
443 Statistically Significant	0.56	Poorly Predictive for ProC3 Response

ProC3 reduction (analogous to Fibrosis Score Response) associated with RCF blood concentrations of:

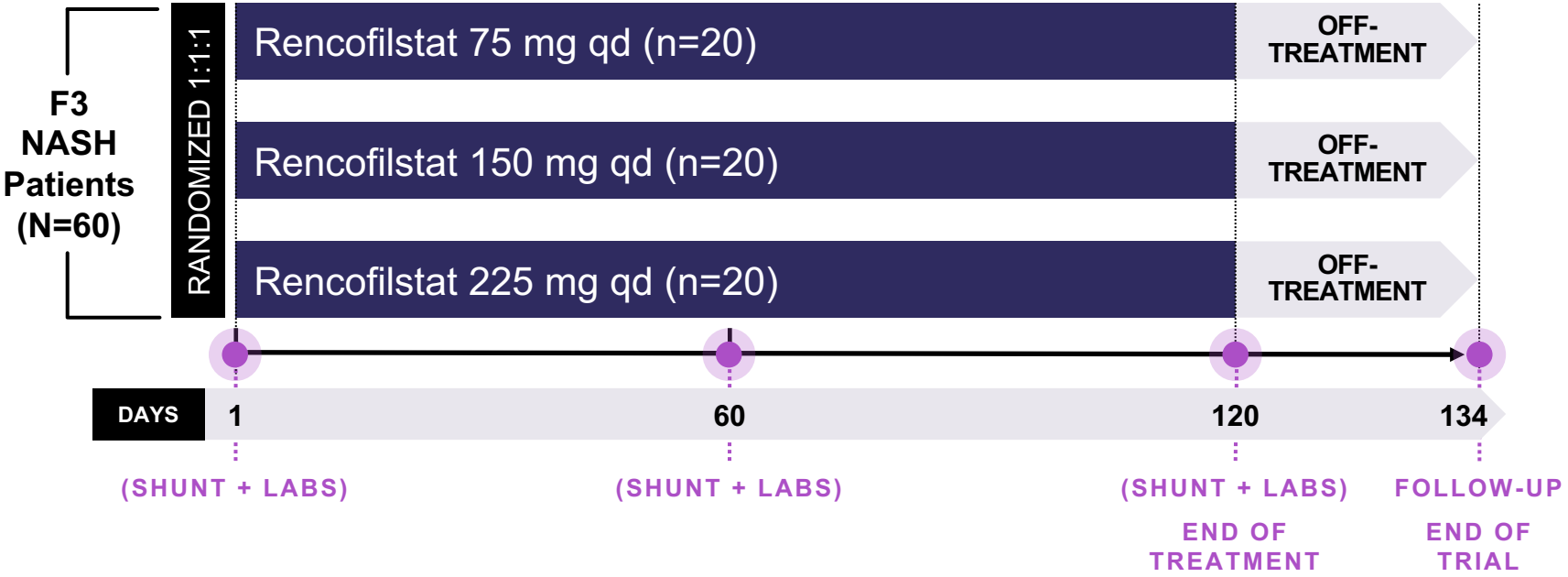
- 964.2 ng/mL (trough)
- 1160 ng/mL (2-hour)

Efficacious blood concentrations attained by day 14 and day 1 for 75 and 225 mg RCF, respectively, suggesting a third dosing cohort of 150 mg in future trials

Phase 2
‘ALTITUDE-NASH’ Trial
(Clinically Complete)

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'

HepQuant SHUNT Test Results

All Subjects with Paired Data (n=61)

	All Doses	75 mg	150 mg	225 mg
	% of Subjects with a greater than 2-point Decrease in DSI			
	32.8 (20/61)	26.1 (6/23)	15.0 (3/20)	61.1 (11/18)•
	Absolute Change from Baseline to Day 120			
BMI (kg.m^{-2})	-0.04	0.21	-0.09	-0.31
DSI (score)	-0.55	-0.41	0.24	-1.62*
SHUNT (%)	-1.7%*	-2.1	-0.2	-2.8*
HR (%)	1.3	1.4	-1.1	3.9**
RISK ACE (Events per 100 pt-yrs)	-1.2***	-1.5	-0.8***	-1.2***

Functionally Impaired Subjects# with Paired Data (n=34)

	All Doses	75 mg	150 mg	225 mg
	% of Subjects with a greater than 2-point Decrease in DSI			
	41.2 (14/34)	50.0 (6/12)	16.7 (2/12)	60.0 (6/10)
	Absolute Change from Baseline to Day 120			
BMI (kg m^{-2})	0.17	0.16	0.35	0.00
DSI (score)	-1.30*	-2.05	-0.17	-1.76*
SHUNT (%)	-3.4%**	-5.8%*	-1.0	-3.4
HR (%)	2.9%*	4.6	-0.4	5.0*
RISK ACE (Events per 100 pt-yrs)	-1.6**	-2.3	-1.0**	-1.5***

In subjects with the most advanced functional impairment, 4 measures of liver impairment significantly improved compared to baseline with rencofilstat treatment for 4 months, independent of dose

*p < 0.05; **p < 0.01; ***p < 0.001; paired t-test, no correction for multiple comparisons
•Chi-Square p < 0.05; #DSI>17 or SHUNT%>25%

DSI – Disease Severity Index
BMI – Body Mass Index
HR – Hepatic Reserve
RISK ACE - annual risk of a patient developing an adverse clinical outcome

Phase 2 'ALTITUDE-NASH'

Key NASH Non-Invasive Markers (NIMs) Results

	All Subjects % Change From Baseline			Subjects with Baseline ProC3 ≥ 37.5 ng/ml % Change From Baseline		
	75 mg rencofilstat n=23	150 mg rencofilstat n=21	225 mg rencofilstat n=21	75 mg rencofilstat n=10	150 mg rencofilstat n=7	225 mg rencofilstat n=6
ALT	-3.37*,****	-13.01*,**	-21.63*,**	-13.24*,***	-32.24*	-37.78*,**
AST	4.54*,**	-8.64*,**	4.68*	6.73*,****	-30.72****	-11.34*,**
ProC3	-6.47	-11.12*	-9.58*,****	-3.39****	-17.05****	-16.23*,****
PIIINP	2.75	-0.47*	-5.6*	-1.22****	-7.36*,**	-21.48*,**
TIMP1	3.76	30.5	-3.9	2.4	-6.69*	-4.77*
Hyaluronic acid	11.67	-13.18*	-10.67*	-4.56*,****	6.99*,**	-19.66*,**
ELF score	1.03****	3.85*,**	-2.51*,**	-0.95*,****	-1.64*,**	-5.31*,**

Rencofilstat 225 mg after 4 months of treatment in the high-risk population led to the greatest improvements in NASH biomarkers

*Different from Baseline p < 0.001, Friedman ANOVA;
**Different from 75 mg Dose p< 0.01; ***Different from 150 mg Dose; ****All Doses p < 0.001.

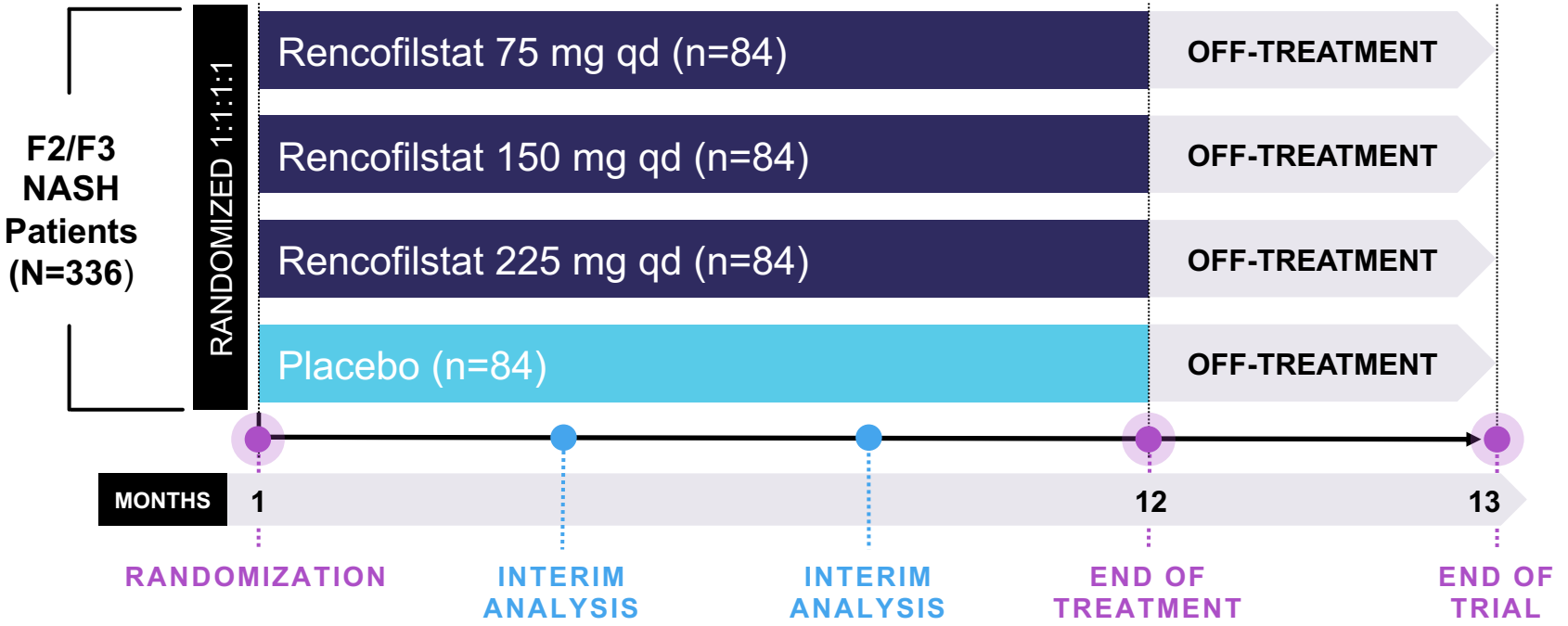
ALT – alanine transferase
ProC3 – procollagen 3 C-terminal peptide
TIMP1 – tissue inhibitor of metalloproteinase – 1

AST – aspartate transaminase
PIIINP – procollagen 3 N-terminal peptide
ELF – enhanced liver fibrosis

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:

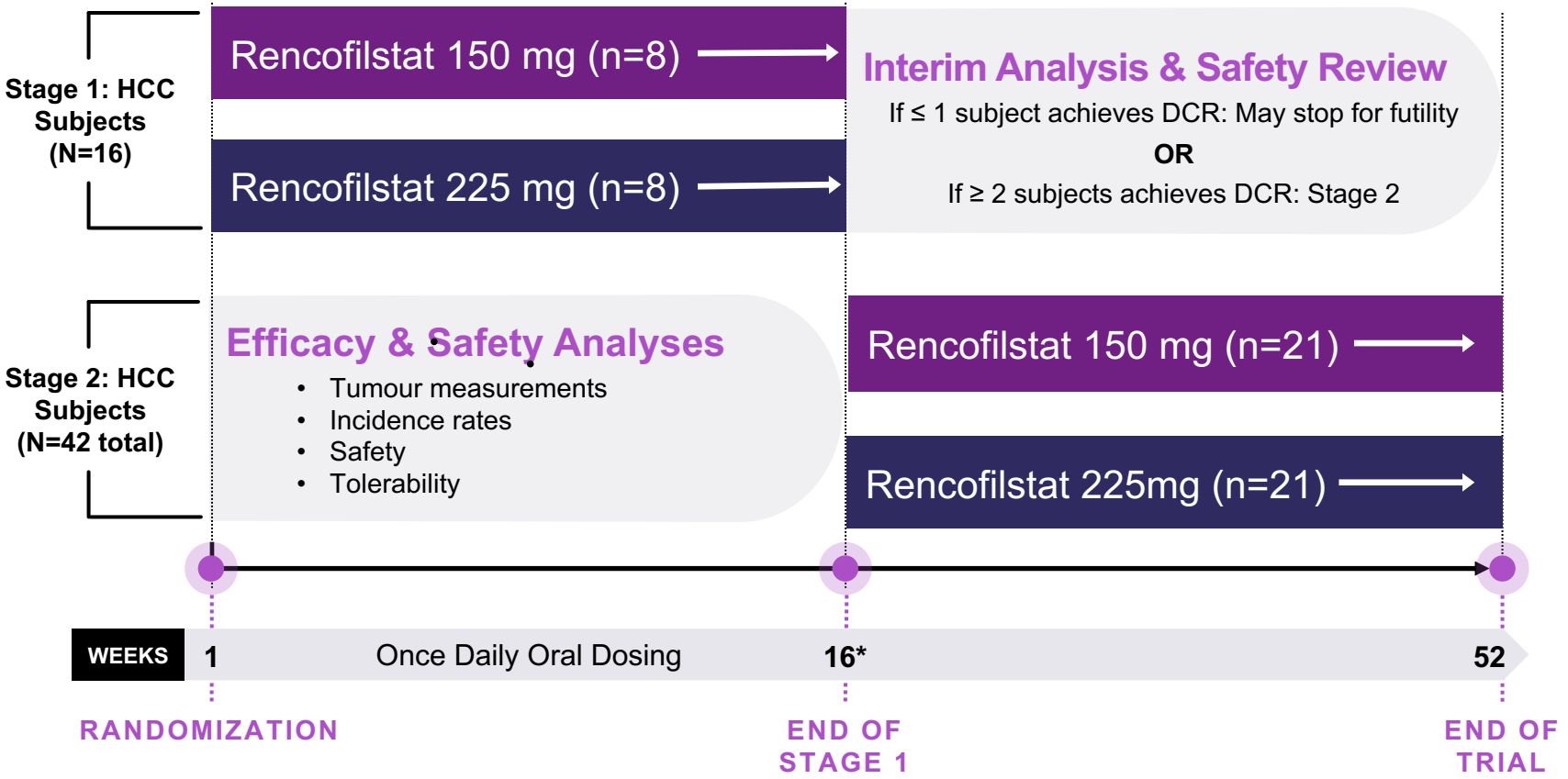
- At least 1 stage regardless of effect on NASH
- At least 2 stages regardless of effect on NASH
- At least 2 stages AND no worsening of NASH.

Phase 2a HCC Trial (Pending)

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 (Solid State)	Filed	
Formulation	23 US & International Applications Filed; EU Granted (28 countries)	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	Filed	

Summary

Tackling Fibrotic Diseases

- Rencofilstat, once-daily oral, targeting key drivers of pathology, tested in over 425 subjects
- Two Phase 2 NASH trials:
  - ALTITUDE-NASH – Clinically Complete
  - ASCEND-NASH Phase 2b – Recruiting
- 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

$43.0 M
Cash
as of 03/31/23

3.8 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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