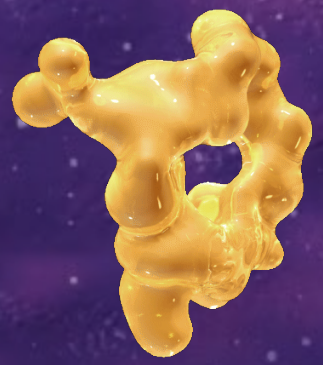
HEPION PHARMACEUTICALS

NASDAQ:**HEPA**

Rencofilstat (CRV431):

Update on NASH Clinical Program



Creating a Therapeutic Ecosystem

March 3, 2023

Todd M. Hobbs MD
CMO

Rencofilstat

Anti-Fibrotic Drug Candidate

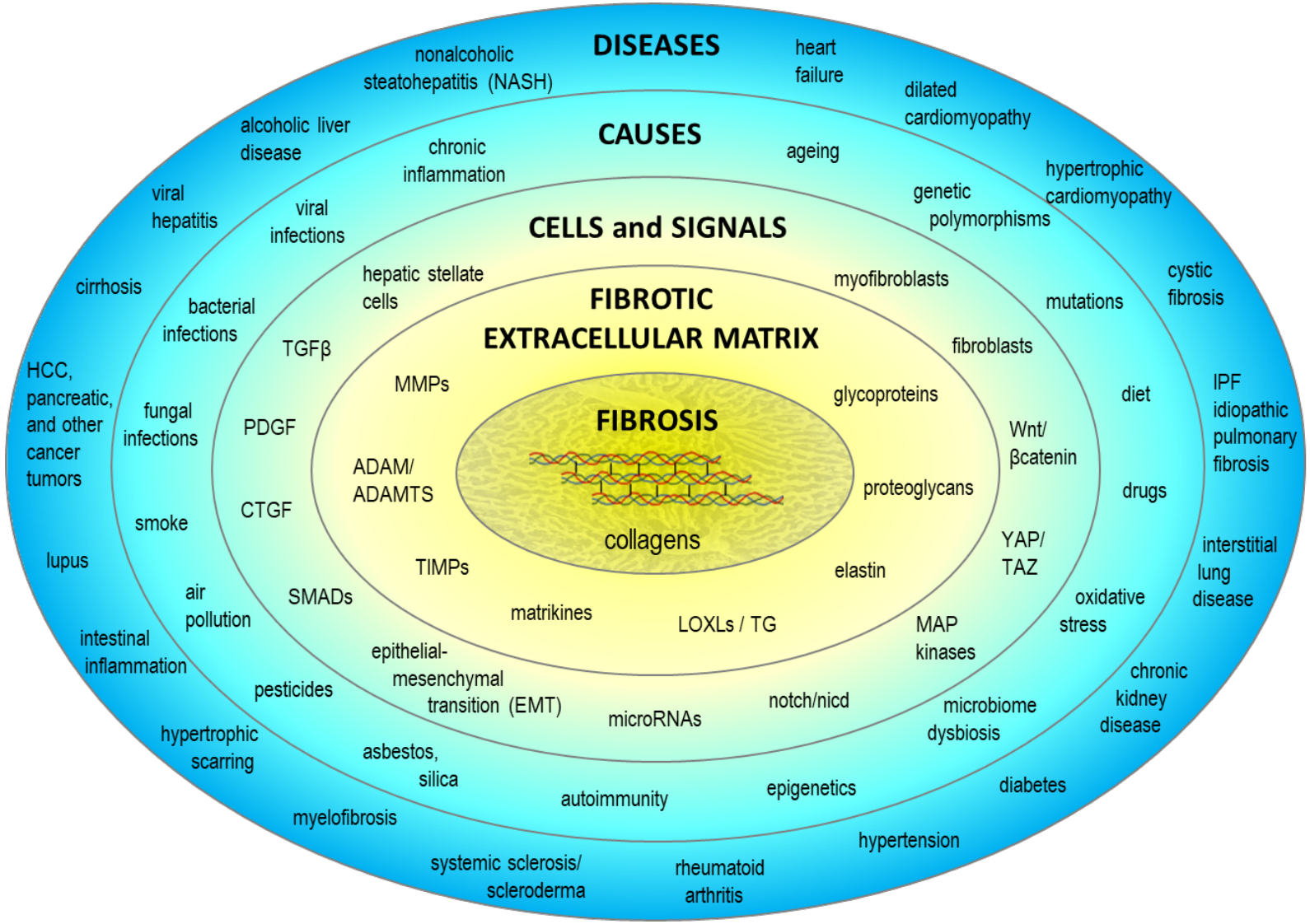
Rencofilstat Highlights

- Novel mechanism - cyclophilin inhibition
- Once-daily, oral medication – soft gel capsules
- Collagen-targeting anti-fibrotic
- Targets key pathologies including fibrosis, inflammation, cell injury
- All clinical trials to date show rencofilstat to be safe and well tolerated – approximately 300 subjects dosed

Rencofilstat Mode of Action

Collagen - Core To Fibrotic Diseases

Excessive collagen production – universal to every fibrotic disease

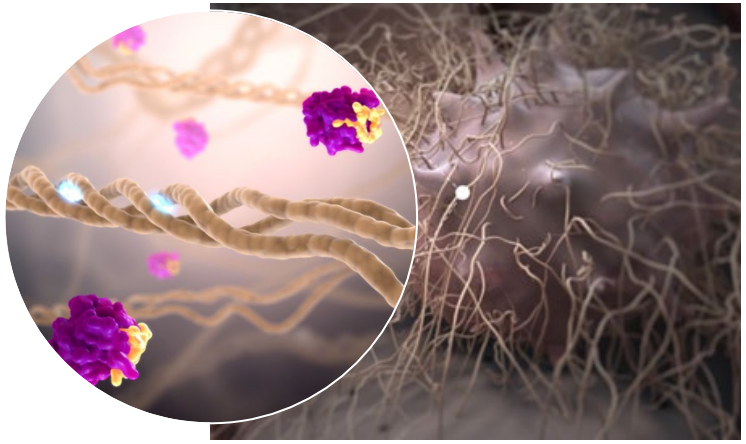


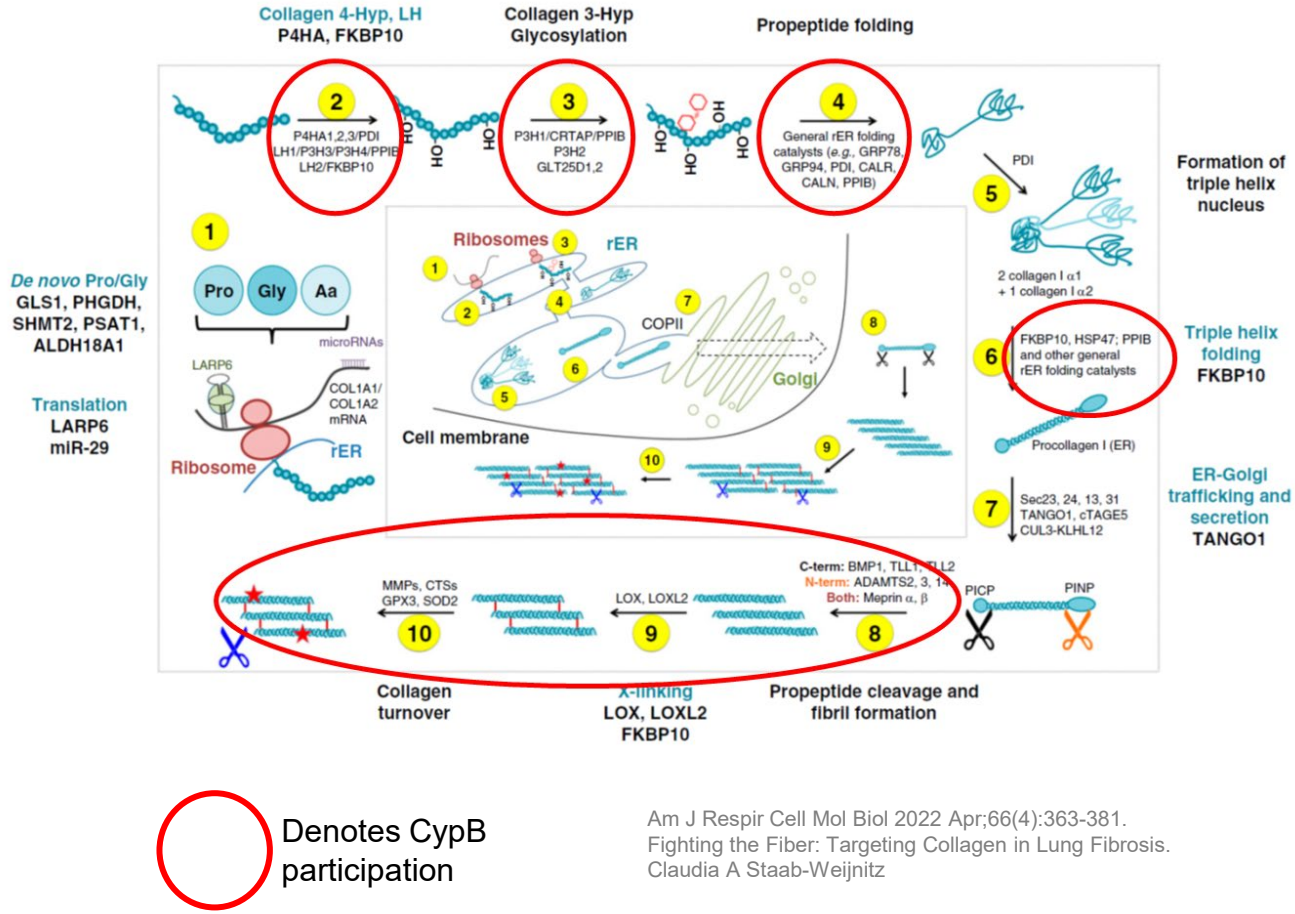
- Fibrosis is an exaggerated “scarring” of tissue in response to many types of cellular injuries, chronic inflammation, & other tissue insults
- Fibrosis impairs normal organ structure & function
- Fibrosis contributes to an estimated 1/3 of deaths worldwide
- Collagen molecules are the primary constituents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

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.



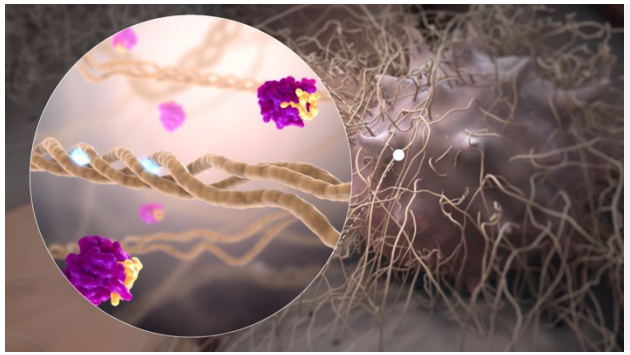


Denotes CypB participation

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

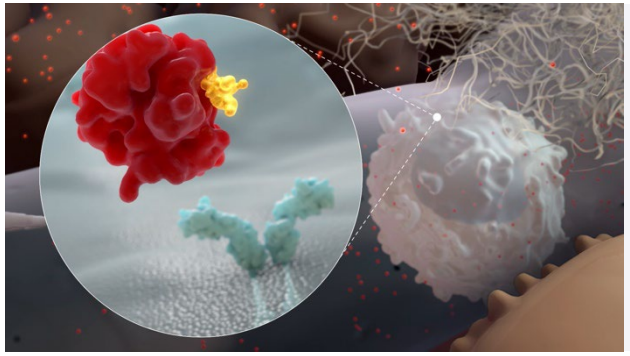
Rencofilstat Inhibits Three Primary Cyclophilins

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



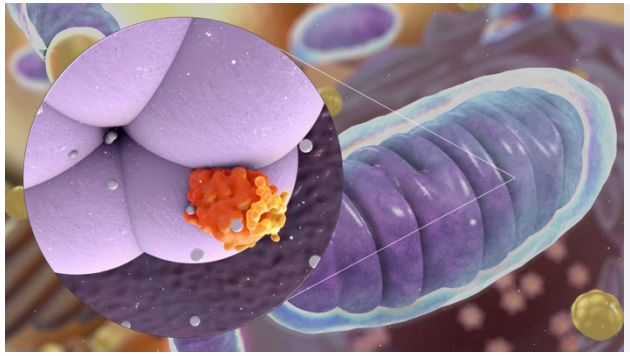
ANTI-FIBROTIC

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

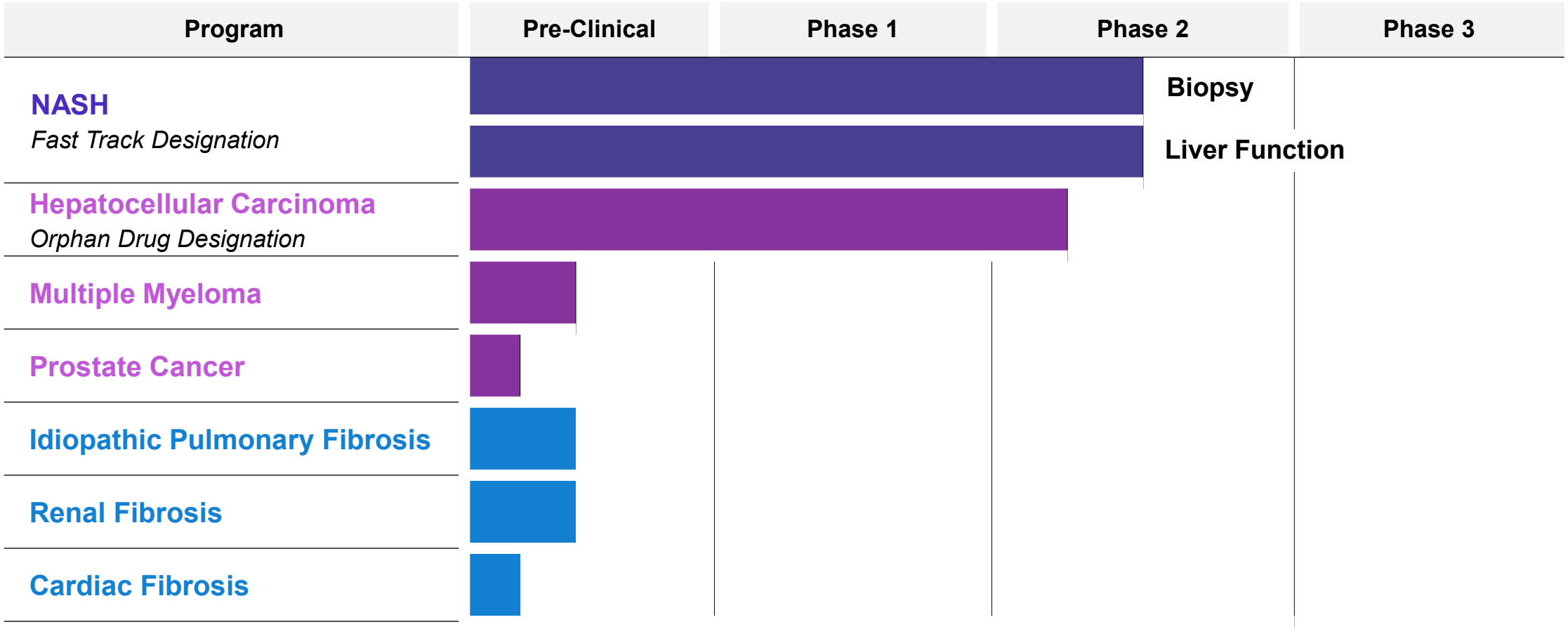
Cyclophilin Inhibition Produces Consistent Antifibrotic Effects

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’



NASH Therapeutic Strategies

Multiple therapeutic agents targeting multiple stages of disease likely required

WHY?

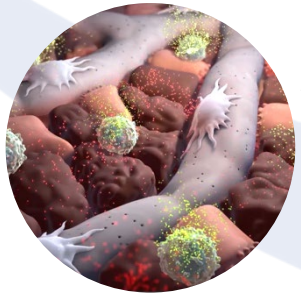
- Generally poor response rates with drugs in development
- Many pathologic mechanisms contribute to disease

normal liver cells

fatty liver cells

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

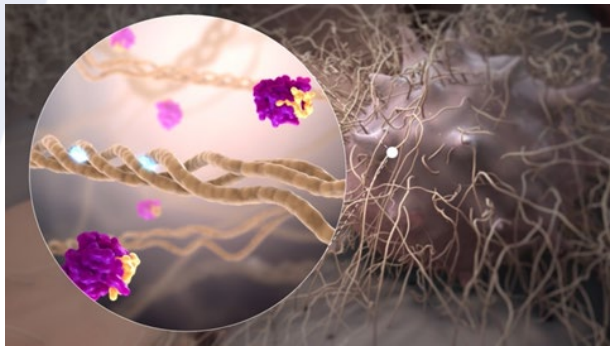
RENCOFILSTAT directly targets fibrosis and inflammation



inflammation, cell injury, and activation of fibrotic cells

production of fibrotic matrix

Rencofilstat inhibits collagen

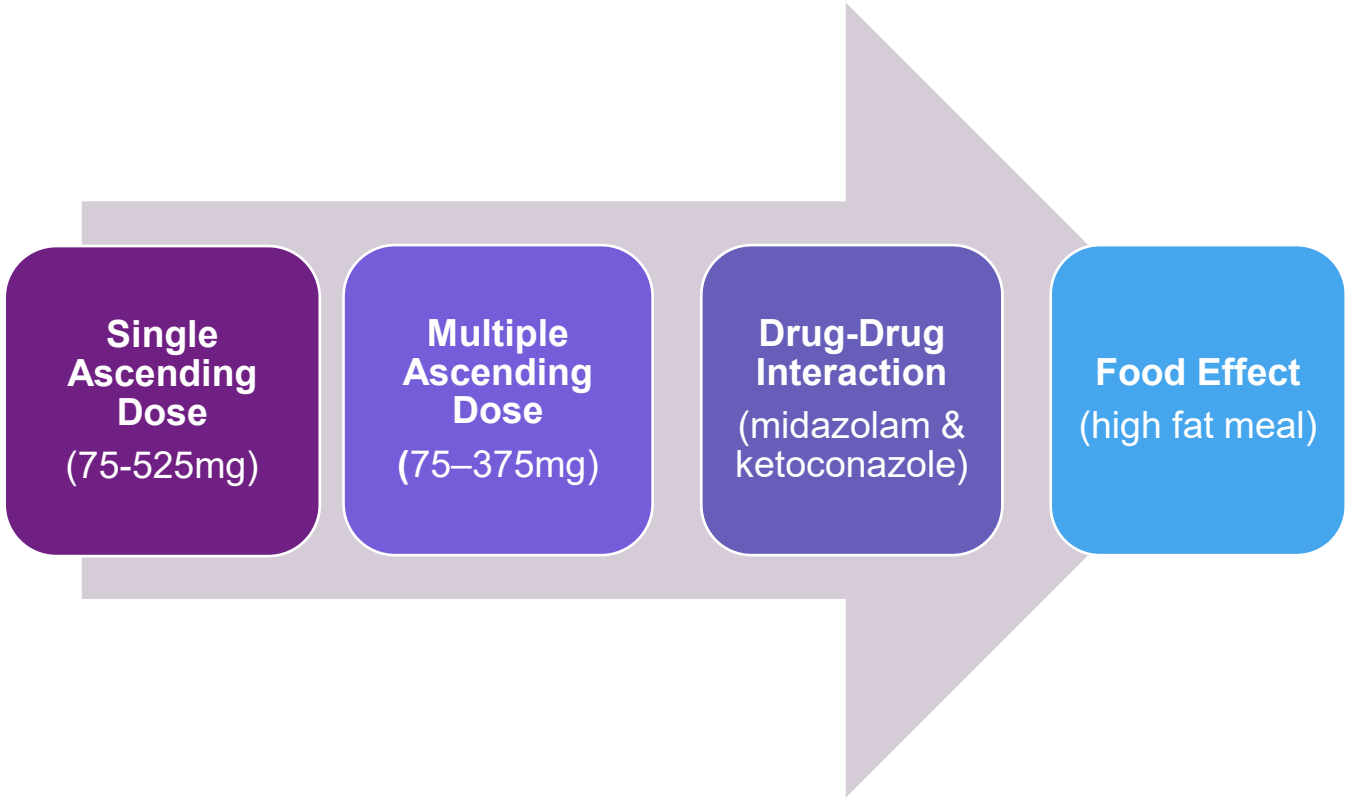


NASH DISEASE PROGRESSION

Overview of Phase 1 Studies (completed)

Phase 1 Studies Completed – Safe and Well Tolerated

Key Findings



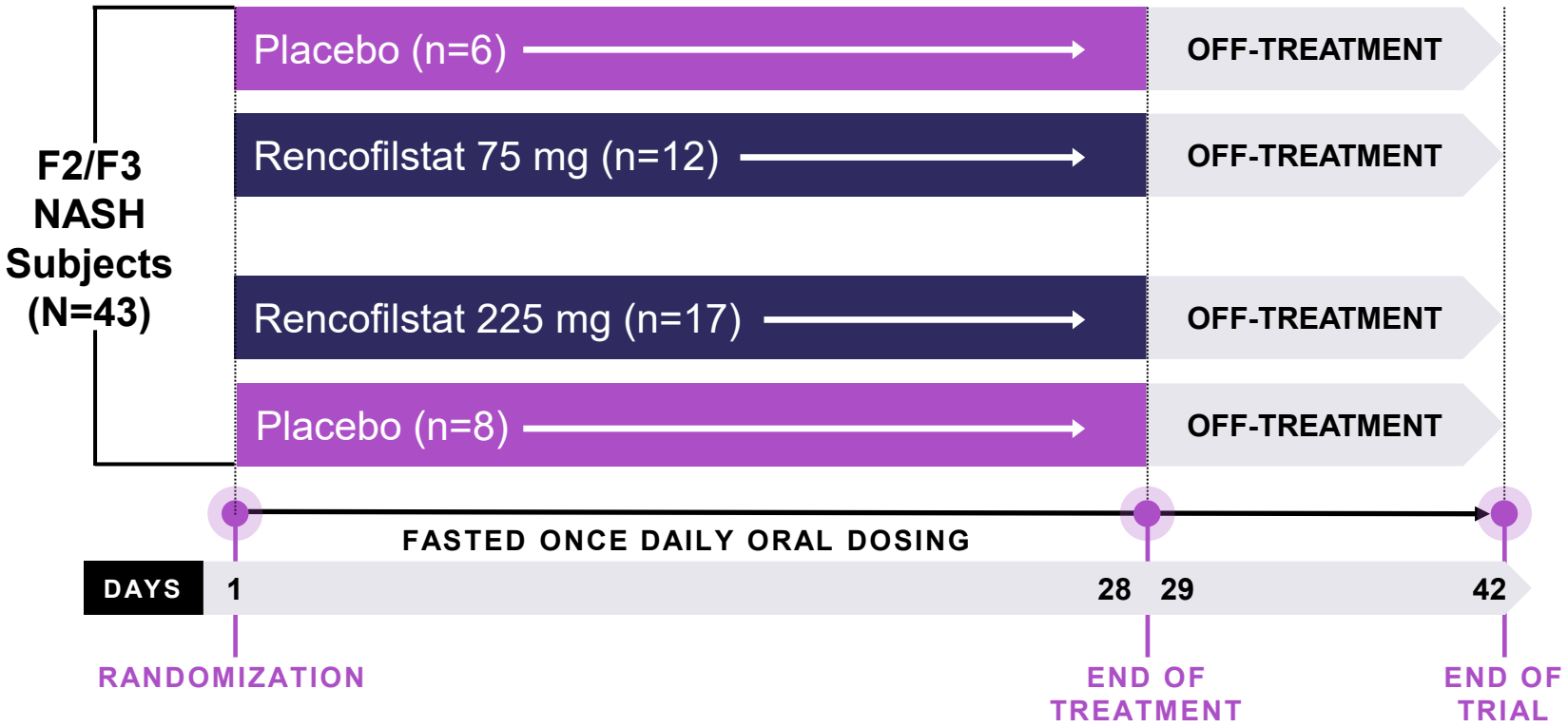
- No serious adverse events
- No adverse events with dose response
- Effective $t_{1/2}$ ~ 30 hours
- $Tmax_{ss}$ ~ 1 – 2 hours
- Ketoconazole increased rencofilstat concentrations ~ 5-fold
- Rencofilstat had no effect on midazolam exposure
- Rencofilstat absorption was not decreased with high fat meal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

- Efficacy signals observed after 28 days:
  - 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 observed with both ALT and Pro-C3

- Rencofilstat concentrations were not significantly altered in NASH subjects

- Rencofilstat concentrations expected to be effective in NASH endpoints (ALT and Pro-C3) were achieved with both 75mg and 225mg doses

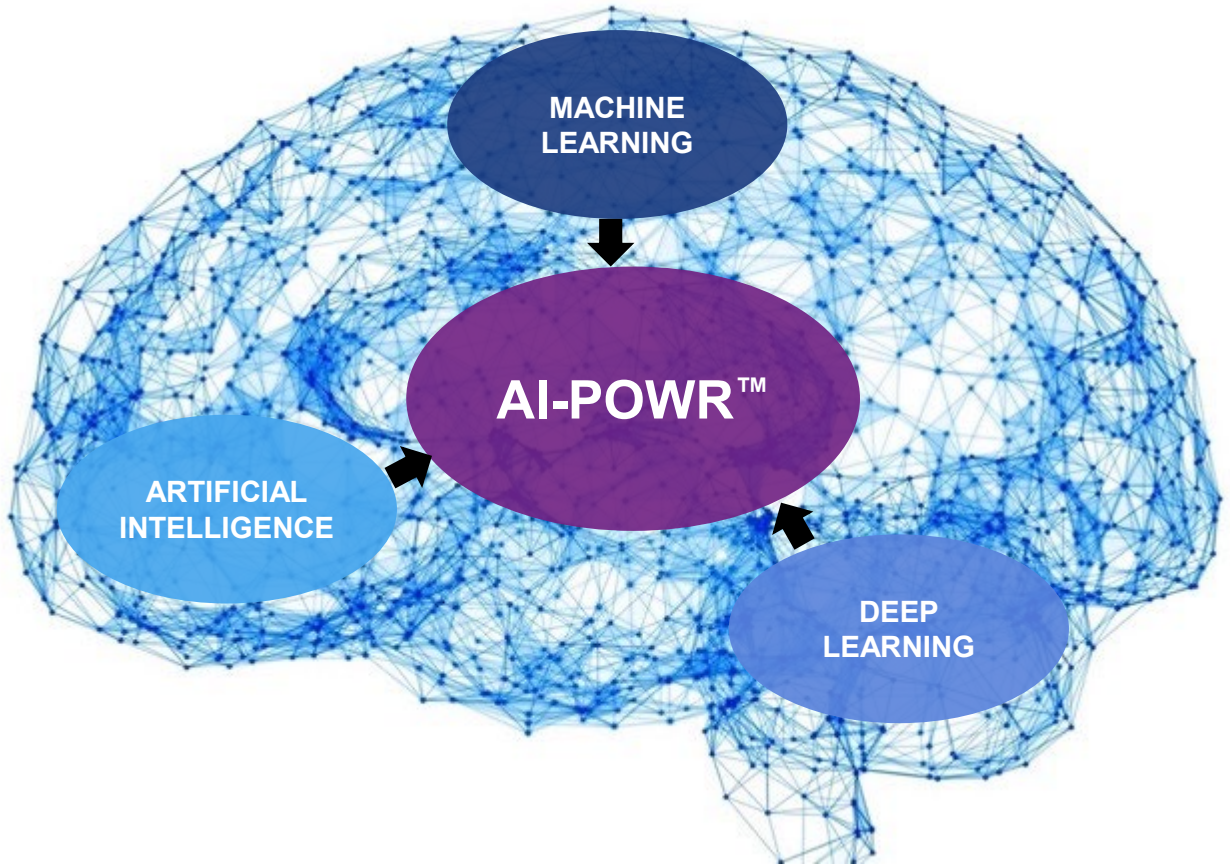
Hepion's Proprietary Artificial Intelligence

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

Developing a Panel for Clinical Development and Commercialization

AI-POWR™

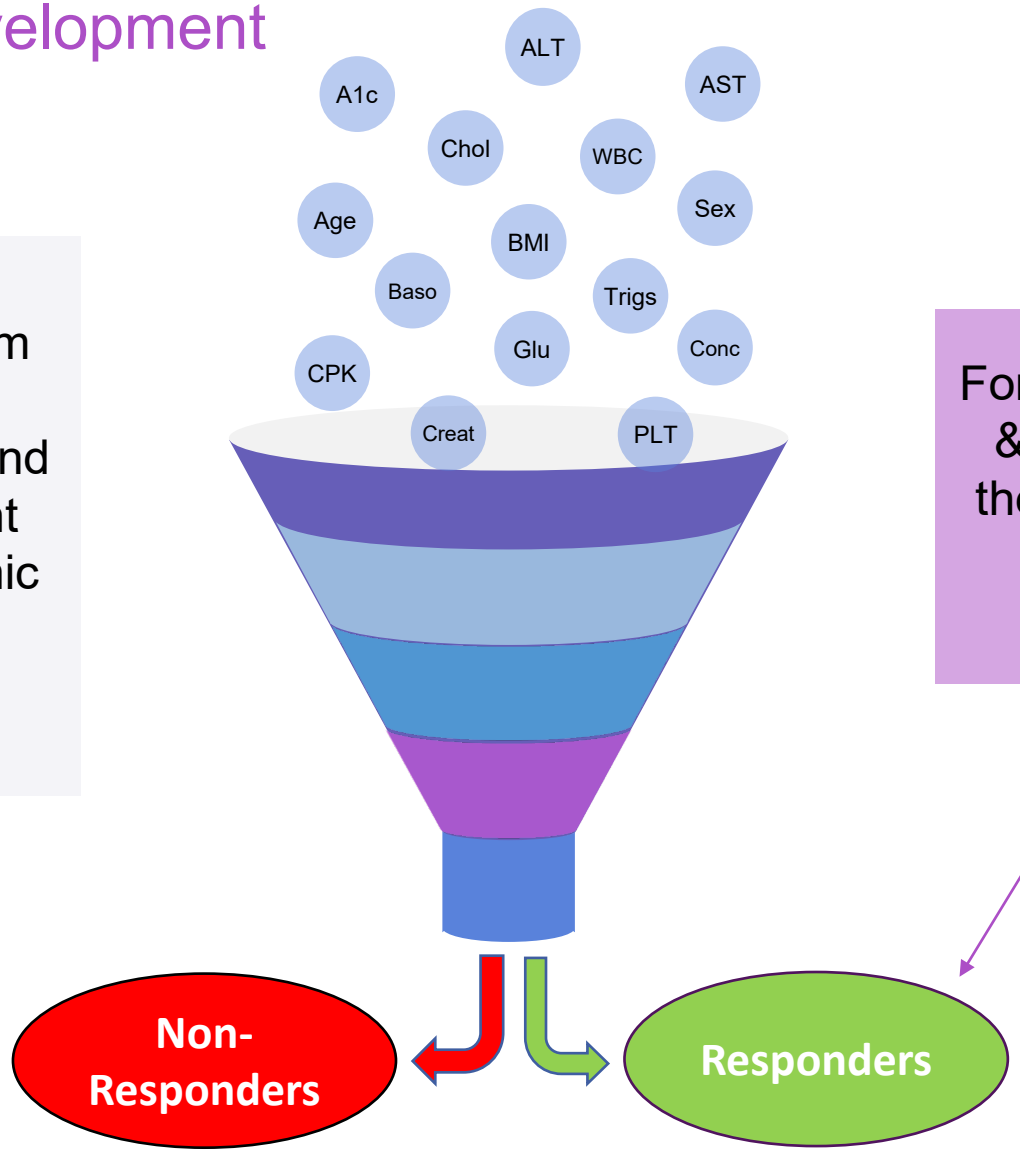
- Facilitates:
  - Improved drug target selection
  - Clinical study design
  - *a priori* responder analysis
- Designed to elucidate both disease and pharmacodynamic biomarkers



AI-POWR™ Applied to the Phase 2a Program

Guiding Hepion's Future Development

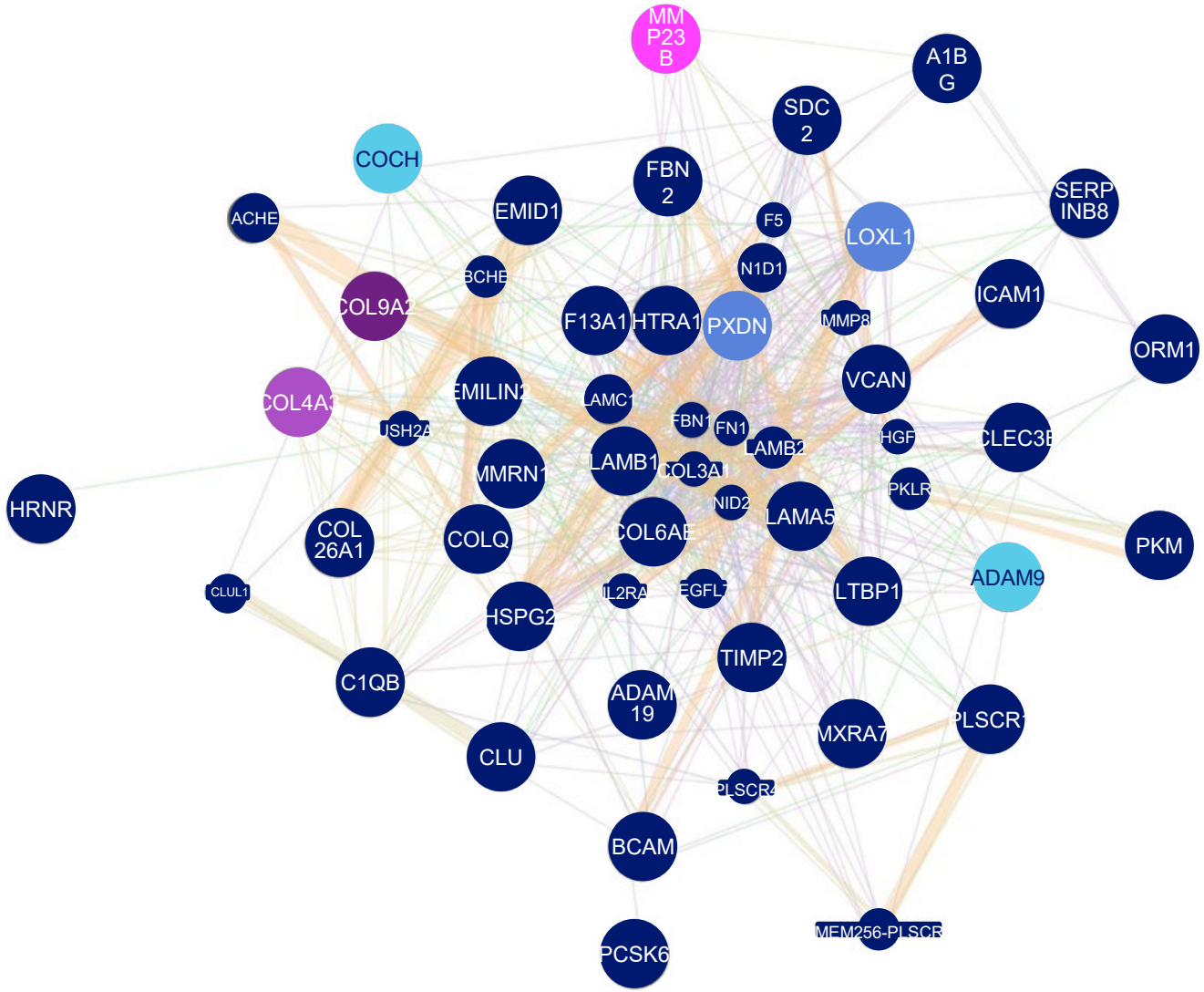
Using machine learning on data from the Phase 2a, Hepion was able to identify subjects more likely to respond to rencofilstat with clinically relevant changes in ALT, Pro-C3, and genomic biomarkers and elucidation of a companion diagnostic panel



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.

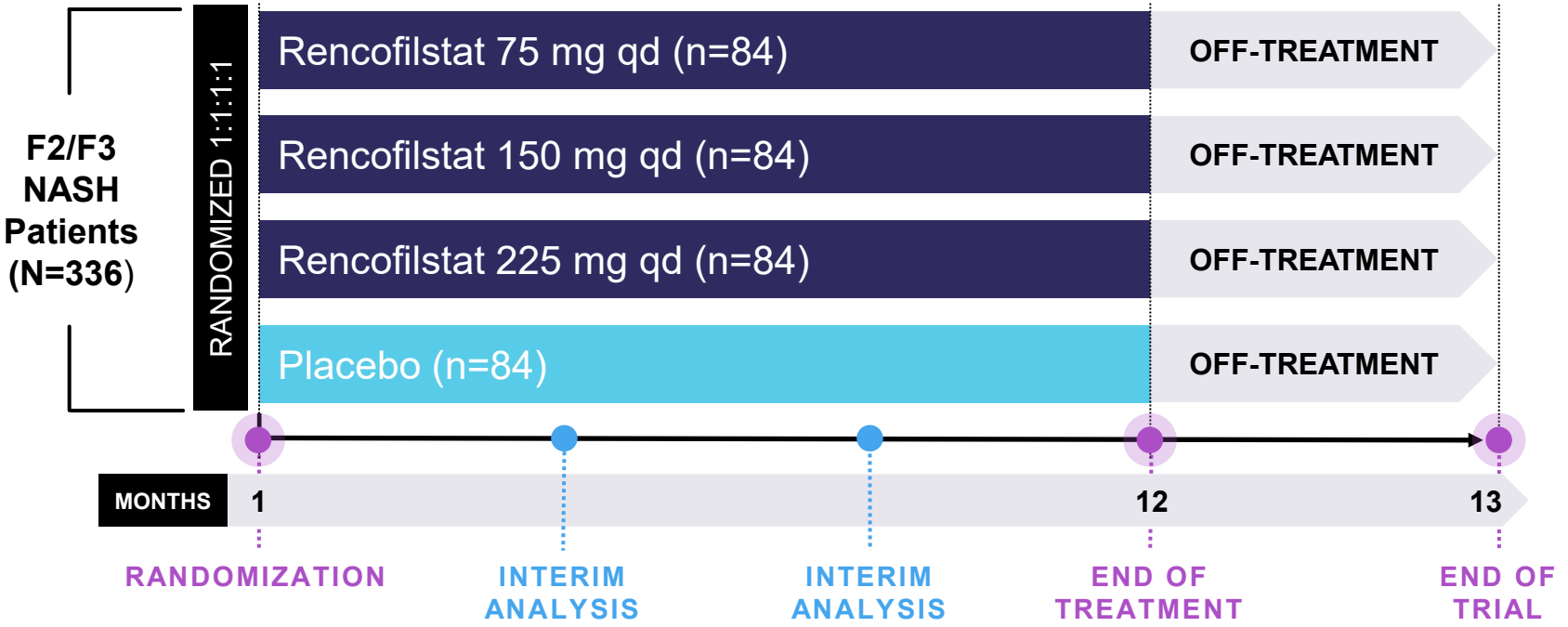


- collagen-containing extracellular matrix
- collagen binding
- collagen type IV trimer
- collagen type IX trimer
- collagen fibril organization
- collagen catabolic process

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 2b – ASCEND-NASH

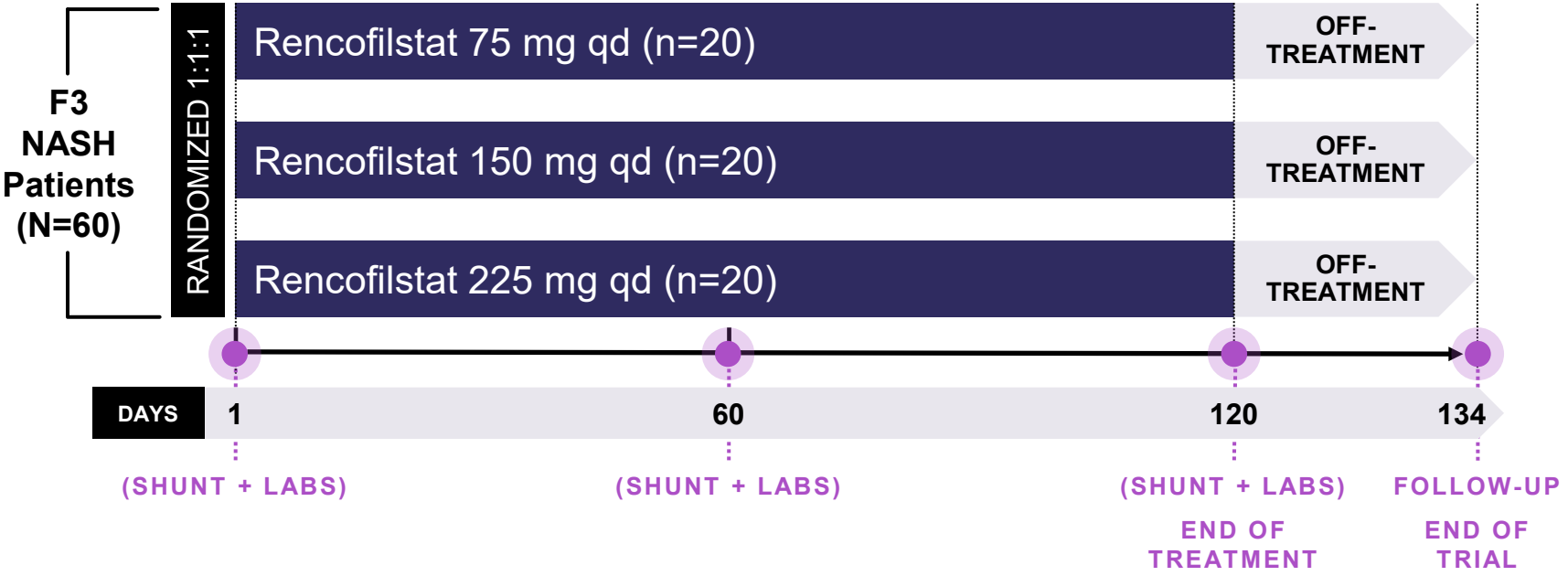
Status as of March 2023

- Site activated and recruiting - up to **90** total sites
  - Elimination of costly sites or those with unproven recruitment success
  - All sites activated and recruiting by end of Q1, 2023
  - Countries include: **US, Mexico, Spain, Germany, France, and Hungary**
  - Anticipated **12-14** months to fully recruit all **336** subjects
- First subject dosed – **Nov 8th**
- Measures in place to reduce screen failure rate
  - Traditionally high biopsy screen fail rates in phase 2b/3a studies
  - Aggressive pre-screening strategy and close follow up with sites
- Interim DSMB meeting to determine efficacy / futility targeted to occur **Q1 2024**

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 can be considered for enrollment into ASCEND-NASH 2b

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

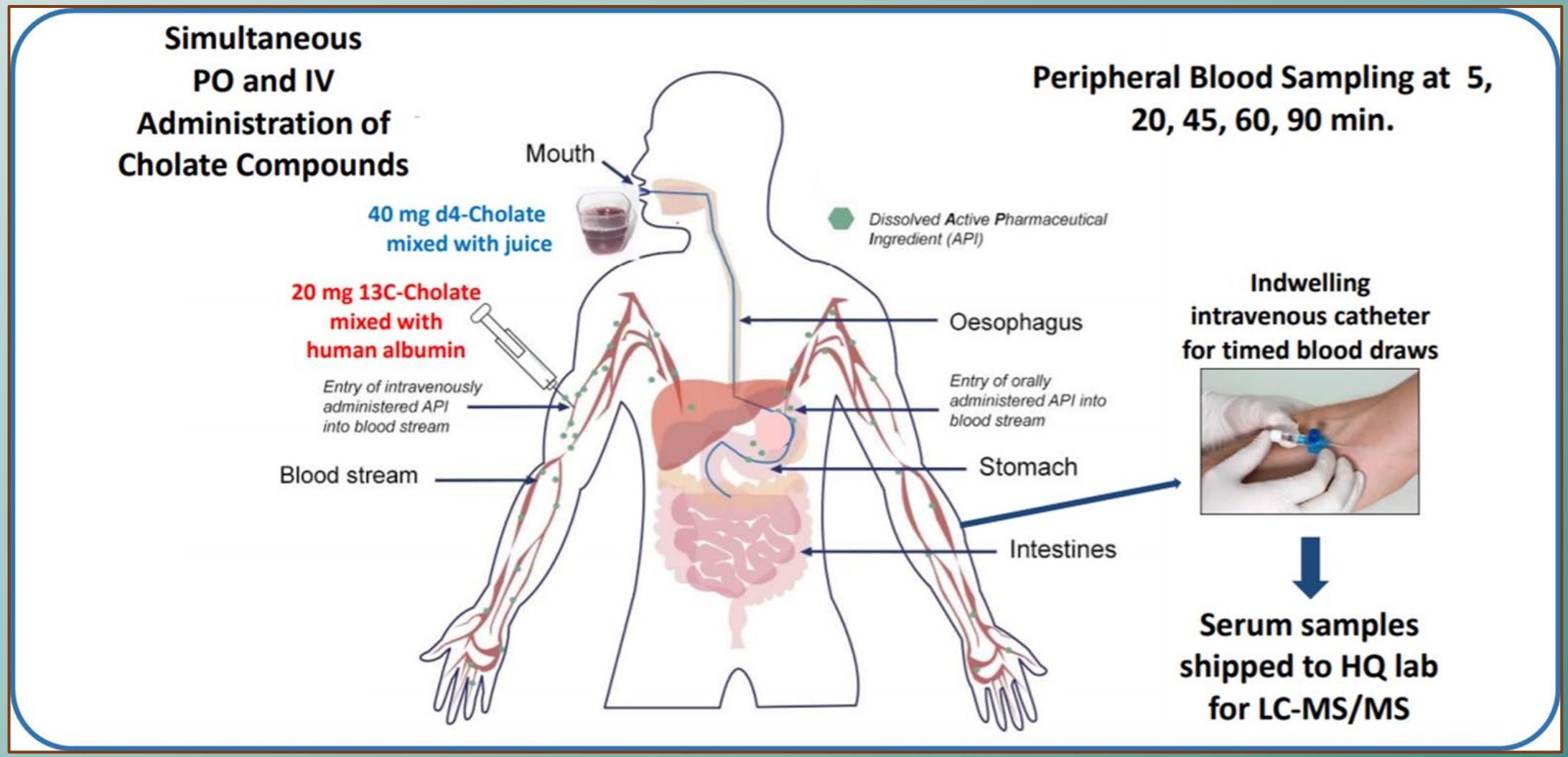
Primary Efficacy Endpoint:

Change from baseline in **Disease Severity Index (DSI) score** of subjects taking rencofilstat using HepQuant SHUNT Test on Day 120

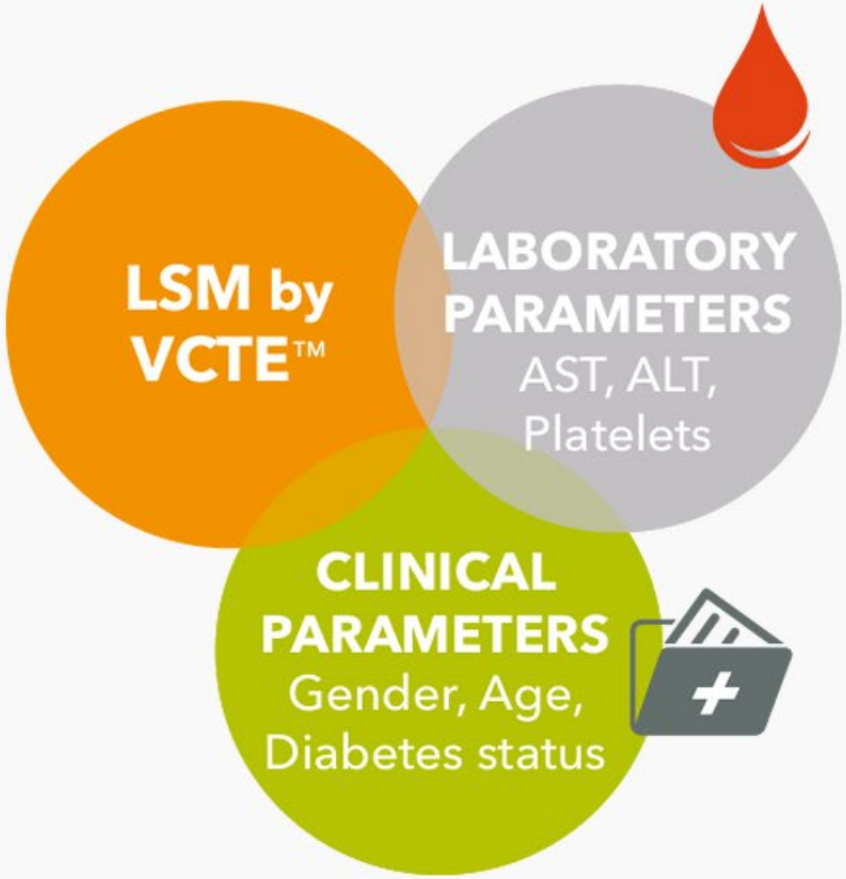
Secondary Efficacy Endpoints:

- 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 Transaminases (**AST/ALT**)
- 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.

HepQuant SHUNT Test



AGILE 3+ to Identify Patients with Fibrosis ≥3



AGILE 3+

AGILE3+ DEVELOPMENT AND VALIDATION: NOVEL FIBROSCAN BASED SCORE TO DIAGNOSE ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE PATIENTS

	Derivation cohort	Internal validation cohort	Muticentric US external validation cohort	Multicentric French external validation cohort
N patients	**1434**	**700**	**585**	**1042**
AUROC [95% CI]	0.90	0.91	0.86	0.87
Rule out cut-off	<0.45			
% patients	44%	42%	54%	53%
Se/Sp	0.85/0.78	0.87/0.76	0.82/0.75	0.83/0.75
NPV	0.90	0.91	0.88	0.87
Indeterminate zone	≥0.45 - <0.68			
% patients	13%	17%	16%	18%
Rule in cut-off	≥0.68			
% patients	17%	16%	10%	8%
Se/Sp	0.71/0.90	0.69/0.91	0.61/0.87	0.61/0.90
PPV	0.81	0.81	0.73	0.79

AGILE 3+ cutoff of ≥0.53 used to determine eligibility based on historical data correlating to biopsy results

Phase 2 – ALTITUDE-NASH
HepQuant Liver Function Study

- 60 subjects (full enrollment) completed 15 weeks earlier than predicted by 20 research sites in U.S.
- 68 total subjects enrolled into 3 dosing groups (75, 150, 225 mg)
- LPLV on track for early Q2 readout
- AGILE3+ as a screening tool well accepted by sites
- Baseline characteristics reveal an advanced fibrosis population
- Data to be available for abstracts at upcoming NASH congresses

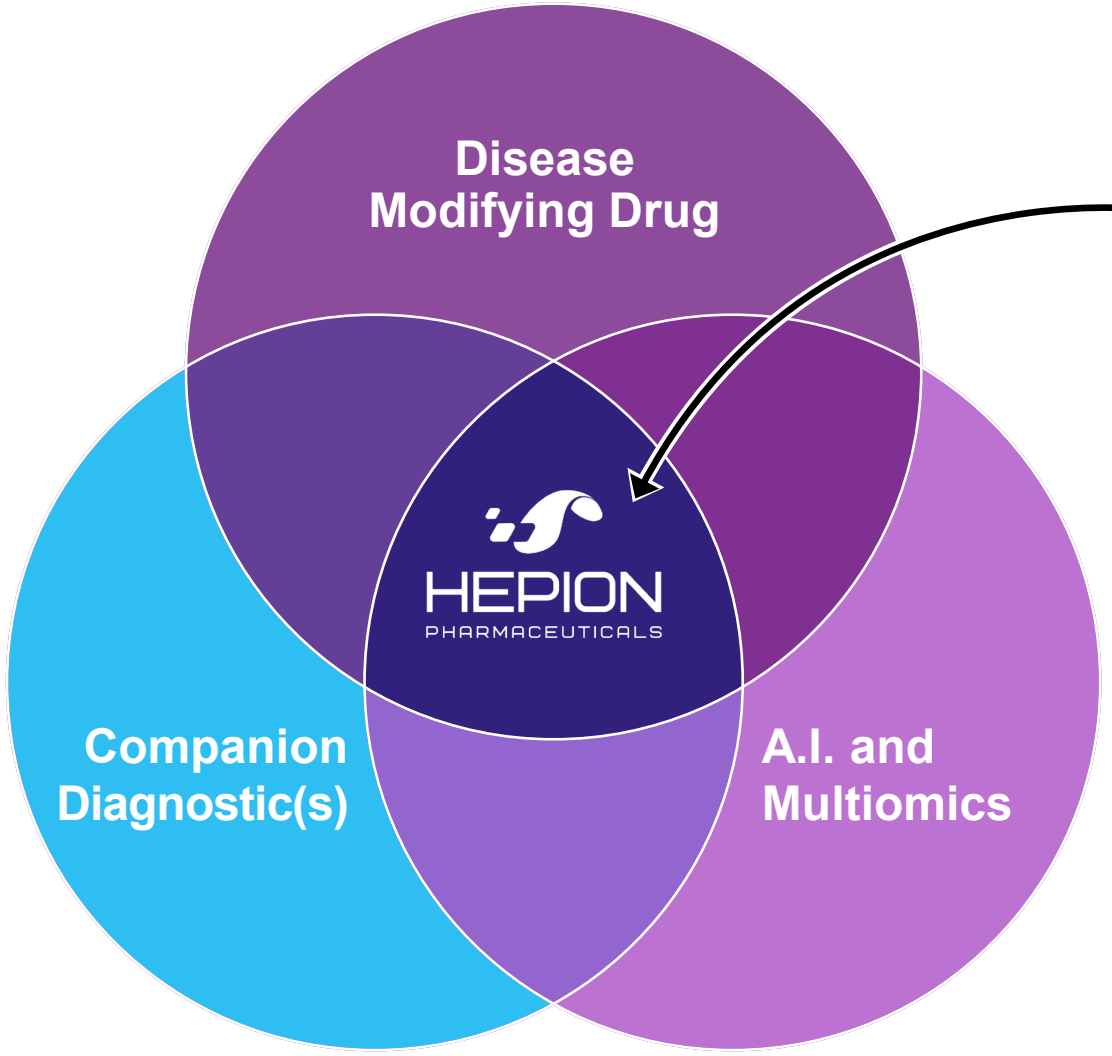
‘ALTITUDE-NASH’ Baseline characteristics

	75 mg (n=24)	150 mg (n=23)	225 mg (n=23)
Age (year)	**61.5** ± 9.6	**57.4** ± 9.9	**61.0** ± 8.9
Sex (% female)	**37.5**	**60.9**	**43.5**
Diabetes (%)	**70.8**	**73.9**	**69.6**
BMI	**36.6** ± 7.4	**39.9** ± 6.2	**37.6** ± 8.1
AGILE3+	**0.753** ± 0.181	**0.733** ± 0.131	**0.704** ± 0.142
AST (U/L)	**45.0** ± 63.2	**24.2** ± 7.8	**31.9** ± 21.3
ALT	**49.6** ± 54.3	**31.9** ± 11.7	**48.2** ± 42.0
ELF	**9.90** ± 1.13	**9.64** ± 1.00	**9.47** ± 0.51
FibroScan LSM, kPa	**16.8** ± 8.3	**13.9** ± 4.8	**14.5** ± 8.5
Pro-C3 (ng/ml)	**46.3** ± 28.6	**36.1** ± 15.6	**32.9** ± 6.7
FIB-4	**1.65** ± 1.12	**1.13** ± 0.53	**1.48** ± 0.72

LSMean ± SD

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)

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