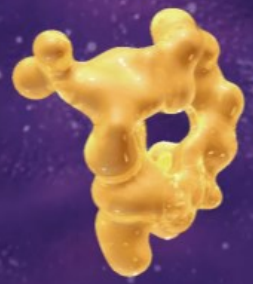
HEPION PHARMACEUTICALS

Rencofilstat (CRV431):

A liver-targeting drug candidate for NASH and HCC

Todd M. Hobbs MD – CMO
May 27, 2022



smart drug
smart technology
smart development

The Challenges

Complex and Associated Diseases

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 still poor
- NASH restricts responses to ICIs

New approaches to developing NASH and HCC therapeutics are needed

Hepion's Strategy

Cornerstones of Drug Development For Complex Diseases

Targeting multiple disease mechanisms maximizes the opportunity to reverse complex diseases such as NASH and HCC

Oral medications with few side effects and derived from proven drug classes offer several advantages as stand-alone and combination therapies

PLEIOTROPIC DRUG ACTIONS	SAFE, ORAL ONCE DAILY DOSING
EXTENSIVE PRECLINICAL TESTING	BIOINFORMATICS / AI

Positive outcomes from diverse preclinical animal and laboratory studies increases the likelihood of translating success to clinical trials

Analysis of large data sets – transcriptomics, lipidomics, proteomics – to understand disease processes and develop personalized medicine strategies

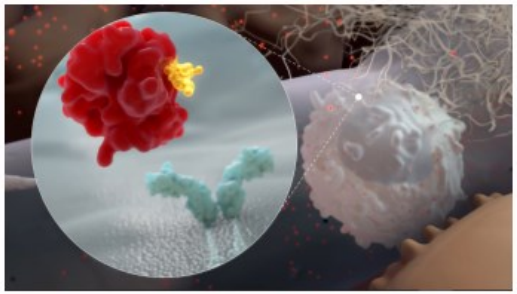
Rencofilstat

Drug Candidate for NASH and HCC

Rencofilstat

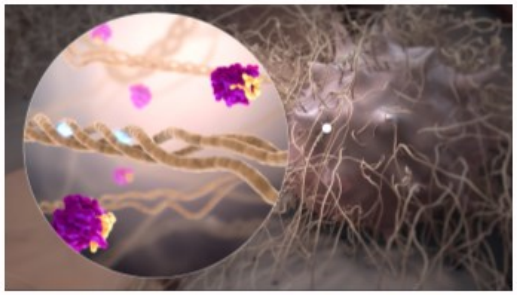
- Non-Immunosuppressive Cyclophilin inhibitor – new drug class
- Once-daily, oral medication – soft gel capsules
- No serious adverse effects
- Liver targeting: [liver] > [blood]
- Pleiotropic activities in preclinical models of NASH, liver fibrosis, and hepatocellular carcinoma (HCC)
- Clinical Studies – 159 subjects dosed successfully
- Phase 2 NASH and HCC programs – to be initiated, Q3, 2022

Rencofilstat Inhibition of Three Primary Cyclophilins in NASH



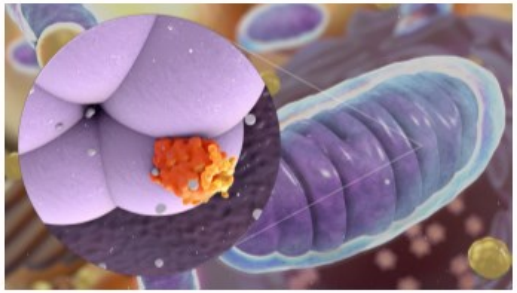
ANTI-INFLAMMATORY

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 Studies

Extensive Testing in Disease Models

ANIMAL MODELS (mice and rats)

- 8 NASH-related studies
  - diet and/or chemical-induced liver disease
- 4 HCC-related studies
  - spontaneous tumors and transplant tumor models
- 2 diabetes-related studies
- 1 acute renal injury study
- 1 acute lung injury study
- 1 chronic lung fibrosis study

TRANSLATIONAL RESEARCH

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

RENCOFILSTAT EFFECTS

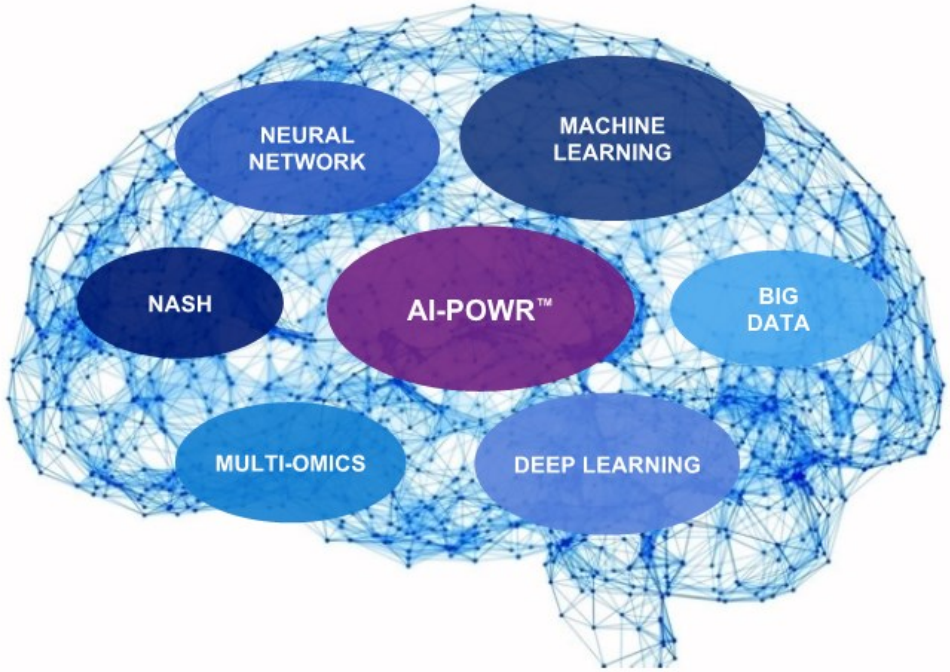
- Anti-inflammatory and anti-fibrotic effects across all animal and translational models
- Consistent reductions in liver fibrosis by up to 80%
- Decreases in liver tumour number and size
- Decreases in weight gain and adiposity
- Decreases in acute lung injury
- Decreases in platelet activation
- Alterations in lipidomic, metabolomic, proteomic, and transcriptomic signatures consistent with therapeutic effects

Hepion's Artificial Intelligence

Rencofilstat: Multiple Beneficial Properties and State-of-the-Art Artificial Intelligence

AI-POWR™

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



Rencofilstat Clinical Programs Advancing in 2022

Program	Pre-Clinical	Phase 1*	Phase 2	Phase 3
NASH (biopsy)	IND 142904		Phase 2B 2022	
HCC	IND 158432		Phase 2 2022	
NASH (liver function)	IND 142904		Phase 2 2022	

- **HBV and COVID-19 INDs open to partnerships**

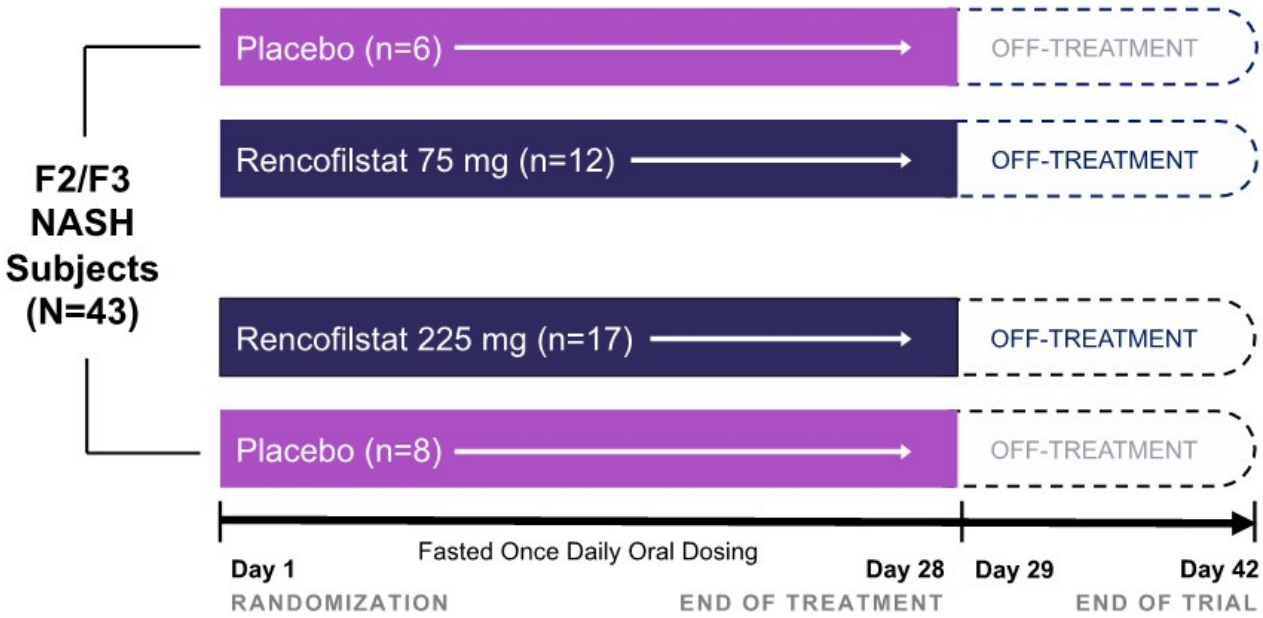
*The Phase 1 program was comprised of Single and Multiple Ascending Doses, and a Drug-Drug Interaction study.

PHASE 2A
‘AMBITION’ NASH TRIAL
(completed)

PHASE 2a 'AMBITION' NASH Study

NASH Subjects - 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

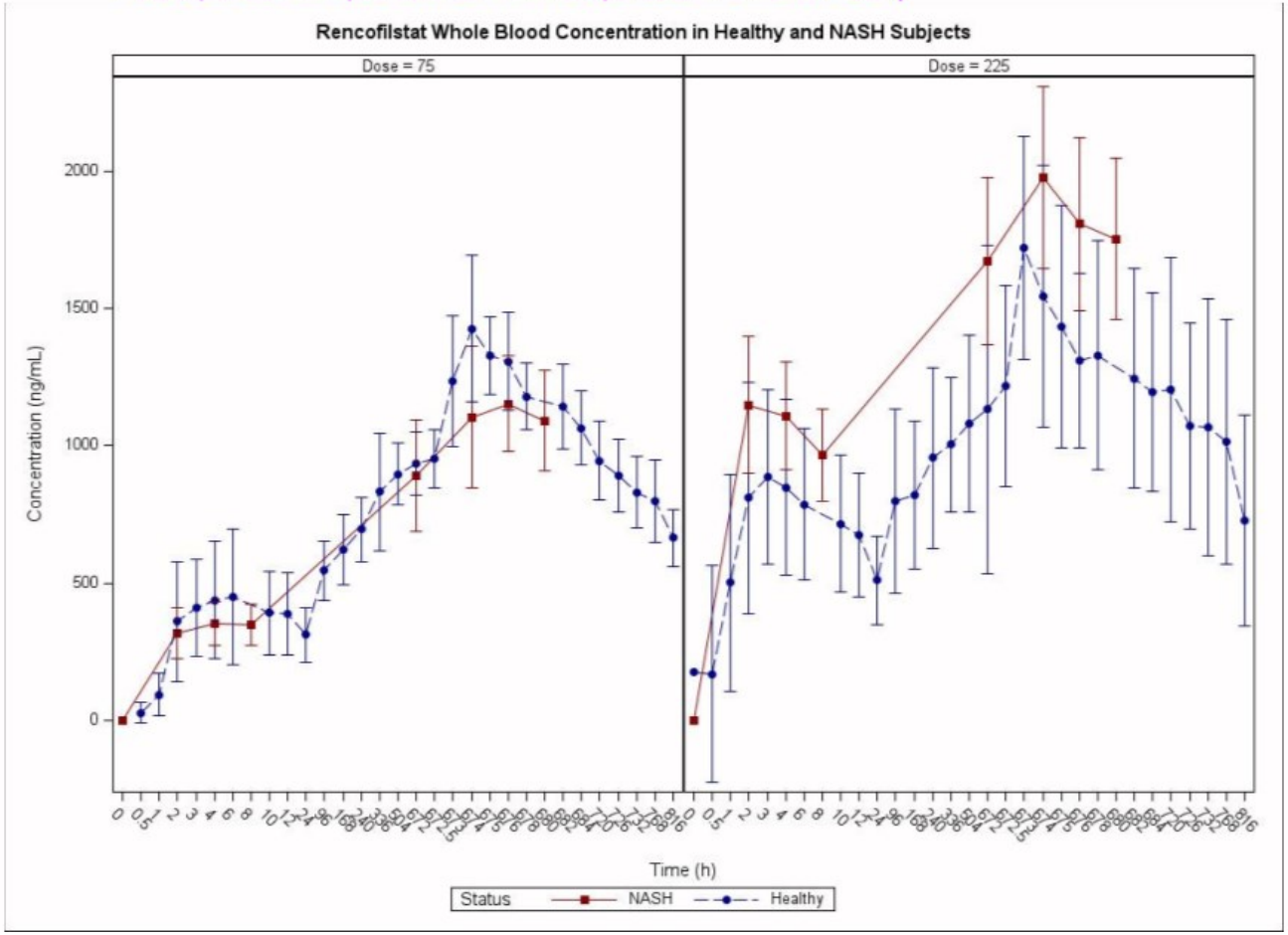
PHASE 2a 'AMBITION' NASH Study

Baseline Characteristics

Treatment		75mg	Placebo	225mg	Placebo	All subjects
N		15	6	17	9	**47**
Age, years		59.1 (9.9)	61.8 (8.7)	54 (13.3)	61.1 (13.8)	**58.0 (11.94)**
Sex	Female	8 53.33%	3 50%	10 58.82%	2 22.22%	**23** **48.94%**
	Male	7 46.67%	3 50%	7 41.18%	7 77.78%	**24** **51.06%**
Ethnicity	Hispanic or Latino	6 40%	3 50%	10 58.82%	6 66.67%	**25** **53.19%**
	Not Hispanic or Latino	9 60%	3 50%	7 41.18%	3 33.33%	**22** **46.81%**
Race	White	14 93.33%	5 83.33%	17 100%	9 100%	**45** **95.74%**
	Unknown or Not Reported	1 6.67%	1 16.67%	0 0%	0 0%	**2** **4.26%**
BMI, (SD) kg/m2		37.1 (8.5)	36.1 (6.5)	37.7 (6.4)	39.2 (10.6)	**37.57 (7.82)**
ALT, (SD) IU/L		62.5 (42.1)	75.8 (36.8)	39.3 (18.4)	52.9 (35.6)	**51.46 (32.18)**
AST, (SD) IU/L		51.9 (35.3)	70.2 (40.1)	33.1 (14.3)	44.7 (36)	**43.83 (27.71)**
Pro-C3, (SD) ng/mL		23.15 (6.88)	23.19 (10.55)	19.94 (9.07)	18.56 (5.84)	**22.70 (12.44)**
ELF Score, (SD)		10.3 (0.8)	10.1 (0.4)	9.8 (0.9)	9.7 (1.0)	**10.0 (0.74)**
Fibroscan Fibrosis, (SD) kPa		21.8 (20.6)	18.8 (16.1)	23.0 (20.7)	13.6 (5.4)	

All Primary Endpoints Met – Safety, Tolerability, & Pharmacokinetics ('PK')

Adequate Exposures Anticipated for Efficacy



No Serious Adverse Events

NASH does not significantly alter Rencofilstat Concentrations

75 mg QD achieves maximum concentrations > 1000 ng/mL on Day 28

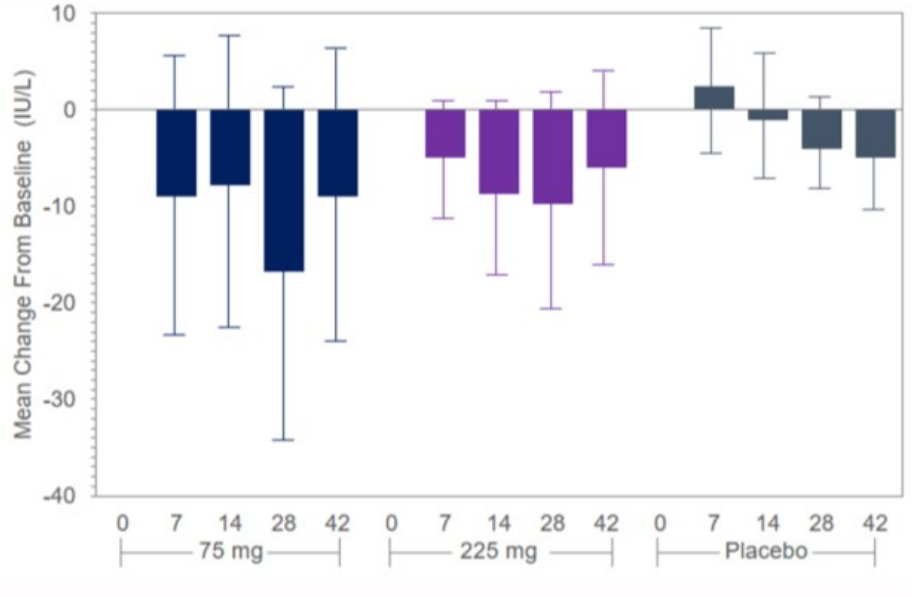
225 mg QD achieves maximum concentrations > 1000 ng/mL on Day 1

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.

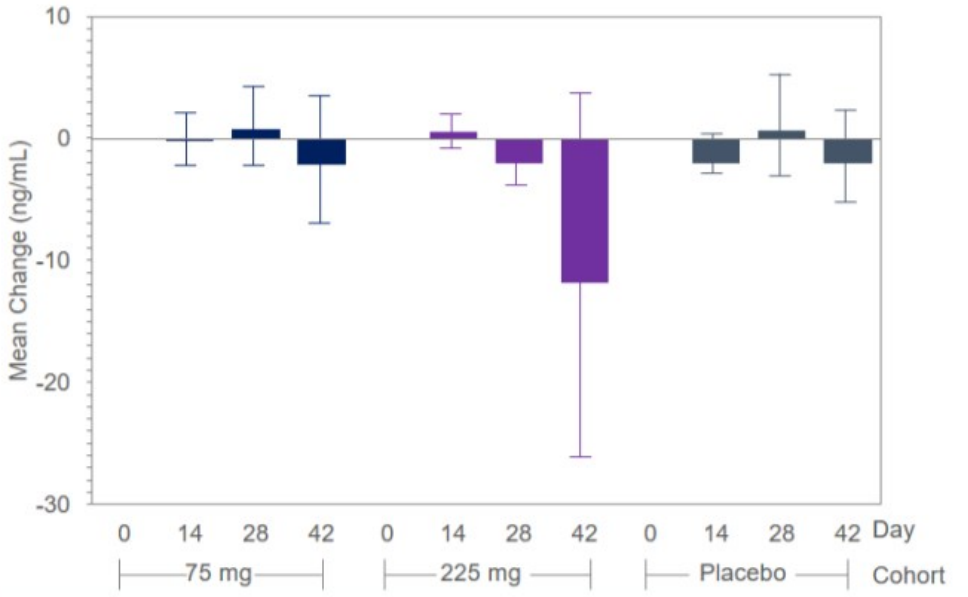
225 mg QD achieves effective concentrations after the first dose.

Clinical Efficacy Endpoints

ALT Change from Baseline



Pro-C3 Change from Baseline ≥ 17.5 ng/mL



-Changes in ALT may indicate drug activity but alone not linked to fibrosis response

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

-ProC3 emerging as biomarker indicative of fibrosis

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.

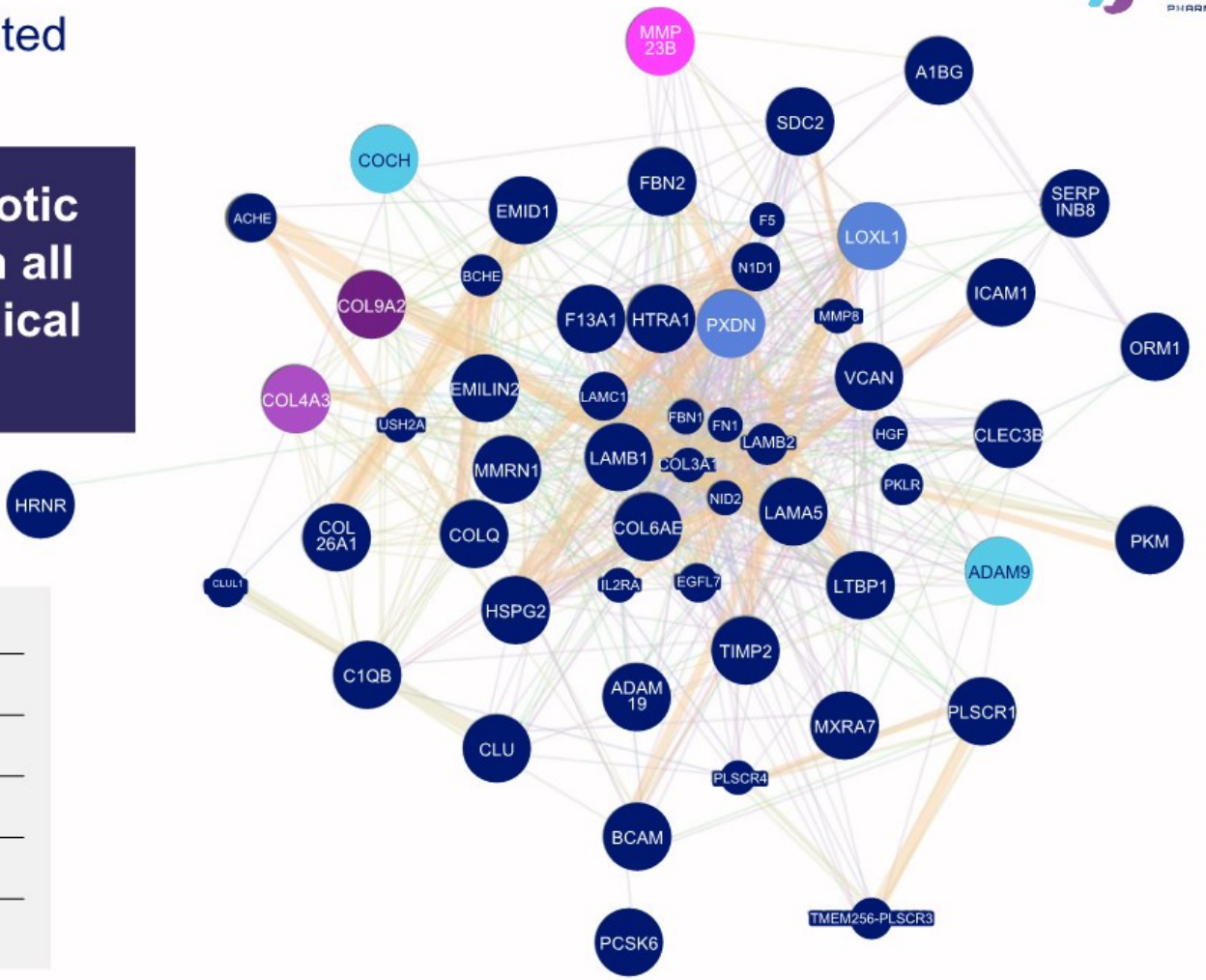
Addition Exploratory Endpoints Collected:

- Analysis limited by study duration and number of subjects

- **ELF Score**
  - No significant changes over 28 days
- **Fibroscan**
  - Small reductions in both Fibrosis (kPa) and Steatosis (dB/m) endpoints for all groups over 28 days – not significant vs. placebo
- **AST**
  - Reductions over 28 days for 75mg cohort
  - No change in 225mg cohort from lower baseline of 32 IU/L
- **Collagen Biomarkers** (C1M, C3M, C4M, C6M, C7M and Pro-C8)
  - Reductions from baseline when stratified by Pro-C3 >15.0 ng/mL
  - Significant reduction seen in C6M for 225mg cohort

Clinical Collagen-Related
Gene Regulatory Network

Consistent antifibrotic effects observed in all preclinical and clinical models

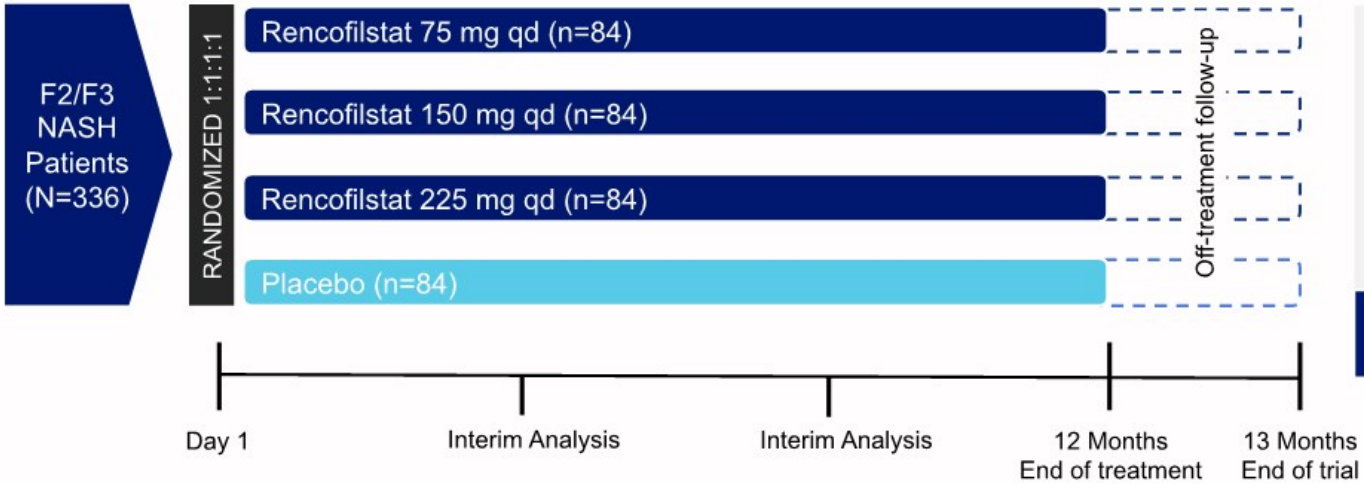


- collagen-containing extracellular matrix
- collagen binding
- collagen type IV trimer
- collagen type IX trimer
- collagen fibril organization
- collagen catabolic process

PHASE 2B ‘ASCEND-NASH’ TRIAL (Q3 2022)

Phase 2b ASCEND-NASH

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 – design is accepted

Phase 2b ASCEND-NASH

Endpoints

Primary Efficacy Endpoint:

Superiority of Rencofilstat (75mg, 150 mg, 225 mg) 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 (75mg, 150 mg, 225 mg) compared to placebo on histology at month 12 relative to screening by assessing:

Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system), regardless of effect on NASH

- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system), regardless of effect on NASH
- Proportion of subjects with improvement in fibrosis by at least 2 stages (NASH CRN system) AND no worsening of NASH. By at least 1 stage regardless of the effect on NASH

ASCEND-NASH

Many Ongoing Activities Occurring Ahead of FPFV

- **CRO** selected with deep NASH experience
- Design finalized with **336 subjects**
- Three rencofilstat doses and matched placebo arm (84 subjects/arm)
- **125 sites** selected to target a **12-14 month** recruitment
- **Final country selection**: US, Germany, France, Italy, Spain, Mexico, Hungary
- **F4** cohort will be studied in a separate trial
- Robust liver biopsy process in place
- Numerous CMC challenges overcome

ASCEND-NASH

Interim Analysis plans

- **DSMB** with extensive NASH experience in place
- Hepion blinded from results until DBL
- Safety review for any signals and at each of two planned interim analyses
  - First Efficacy Interim Analysis – After 34 subjects in each cohort (136) pass day 180 visit and have Non-invasive Measures (NIM) available
    - NIM include: **MRE, Fibroscan, ALT/AST, Pro-C3, ELF score, CK-18, APRI, NFS, FIB-4**
    - Each dose evaluated separately using NIM for efficacy in order to proceed
  - Second Interim Analysis – After 56 subjects in each cohort (224) complete day 365 (biopsy) –
    - Will allow for earlier look at histopathology

Key Considerations Addressed in Phase 2B design

Learnings from FDA and other programs applied

Number of Subjects:

- Larger subject numbers allow for higher power for all three doses to better inform selection of a single dose in phase 3

Trial Length:

- For fibrosis endpoint, minimum of 12 months is required by FDA
- Shorter study may not allow enough time to observe drug effect on fibrosis endpoint
- Shorter trials further confounded by placebo effect seen in first 4-6 weeks of trial

Endpoints:

- For phase 2, desire to keep both fibrosis and steatosis endpoints as options
- May refine the primary endpoint for phase 3 based on these results
- For EMA submission, both endpoints currently required

Dose Selection:

- Adding a middle dose (150 mg) will enable Hepion to take the lowest effective dose into phase 3, which improves overall supply costs

Key Considerations Addressed in Phase 2B design (cont.)

Learnings from FDA and other programs applied

Biopsy Procedures:

- Numerous trials impacted by high placebo rates and inconsistent reads from single pathologist
- Hepion will employ a 2 pathologist read with a 3rd pathologist to resolve any differences
- Additional H & E stained slides will be obtained to allow for increased review of tissue for ballooning, etc.

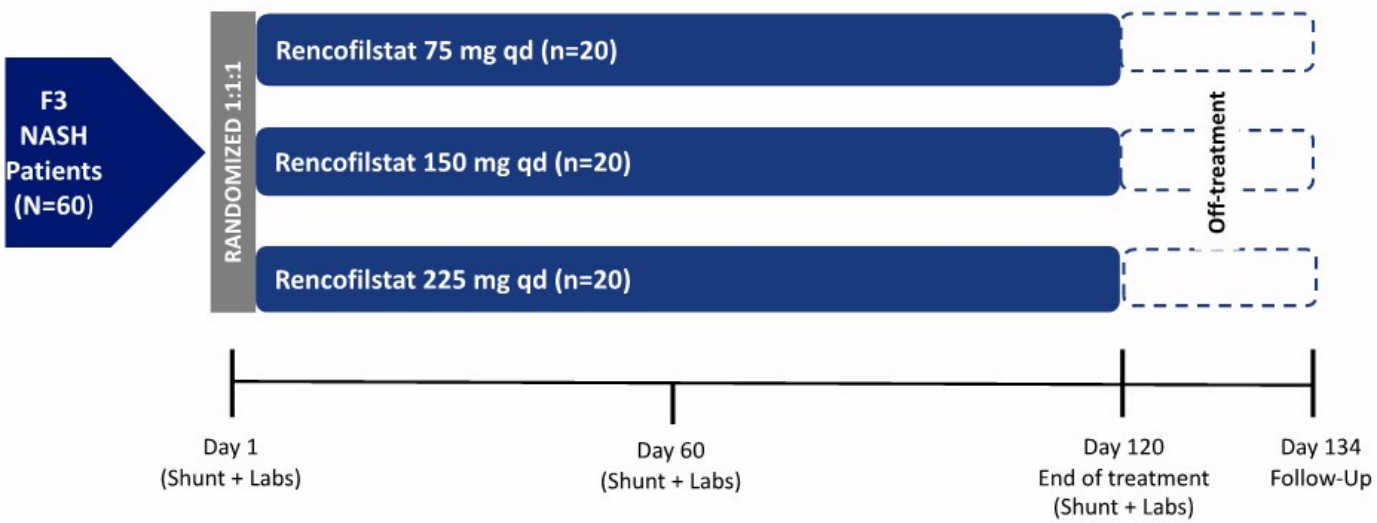
Other Considerations:

- With long recruitment and trial conduct for biopsy readout, interim analysis will add significant guidance to overall efficacy assessment at an earlier timepoint
- AI Power™ will be used to analyze results providing for a deeply enriched phase 3 program
- Open labeled 'ALTITUDE-NASH' study to add additional information on rencofilstat's impact on hepatic function

PHASE 2 ‘ALTITUDE-NASH’ TRIAL (Q3 2022)

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.



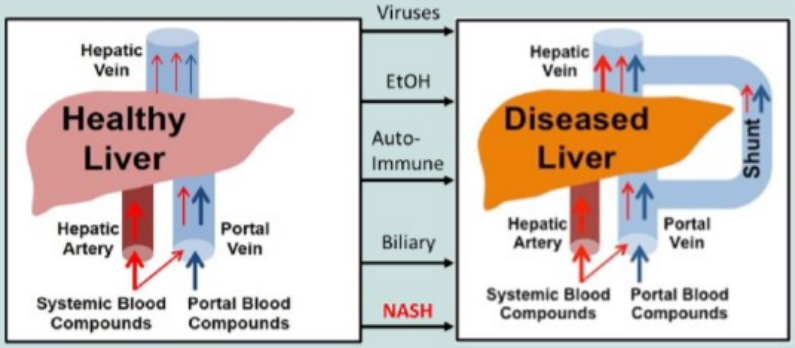
Endpoints:

- Efficacy:
  - HepQuant
  - NASH NIMs
- Safety/Tolerability
- Pk

- 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

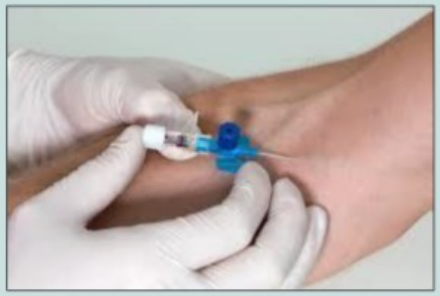
HepQuant Shunt Test: An Accurate Measure of Liver Function

HepQuant SHUNT Test



- Liver cell function – cholate uptake via specific hepatic transporters
- Dual blood inflows – portal and systemic (HFRs)
- Portal-systemic shunting (SHUNT%)

- Disease Severity Index (DSI) - global liver function



- Cholate is an endogenous primary bile acid in man.
- D4- and 13C-cholates are labeled with stable non-radioactive isotopes. NO RADIATION OR XENOBIOTIC.
- D4-cholate is delivered to the liver via portal vein and 13C-cholate via systemic circulation.
- D4-cholate, 40 mg, is taken orally and 13C-cholate, 20 mg, is administered intravenously.
- Blood is sampled at t = 5, 20, 45, 60 and 90 min via an indwelling intravenous catheter.

HepQuant DSI Links Liver Dysfunction to Risk for Clinical Outcome

DSI, HepQuant's proprietary disease severity index

HepQuant Research suggests that As Liver Function decreases And the DSI Increases

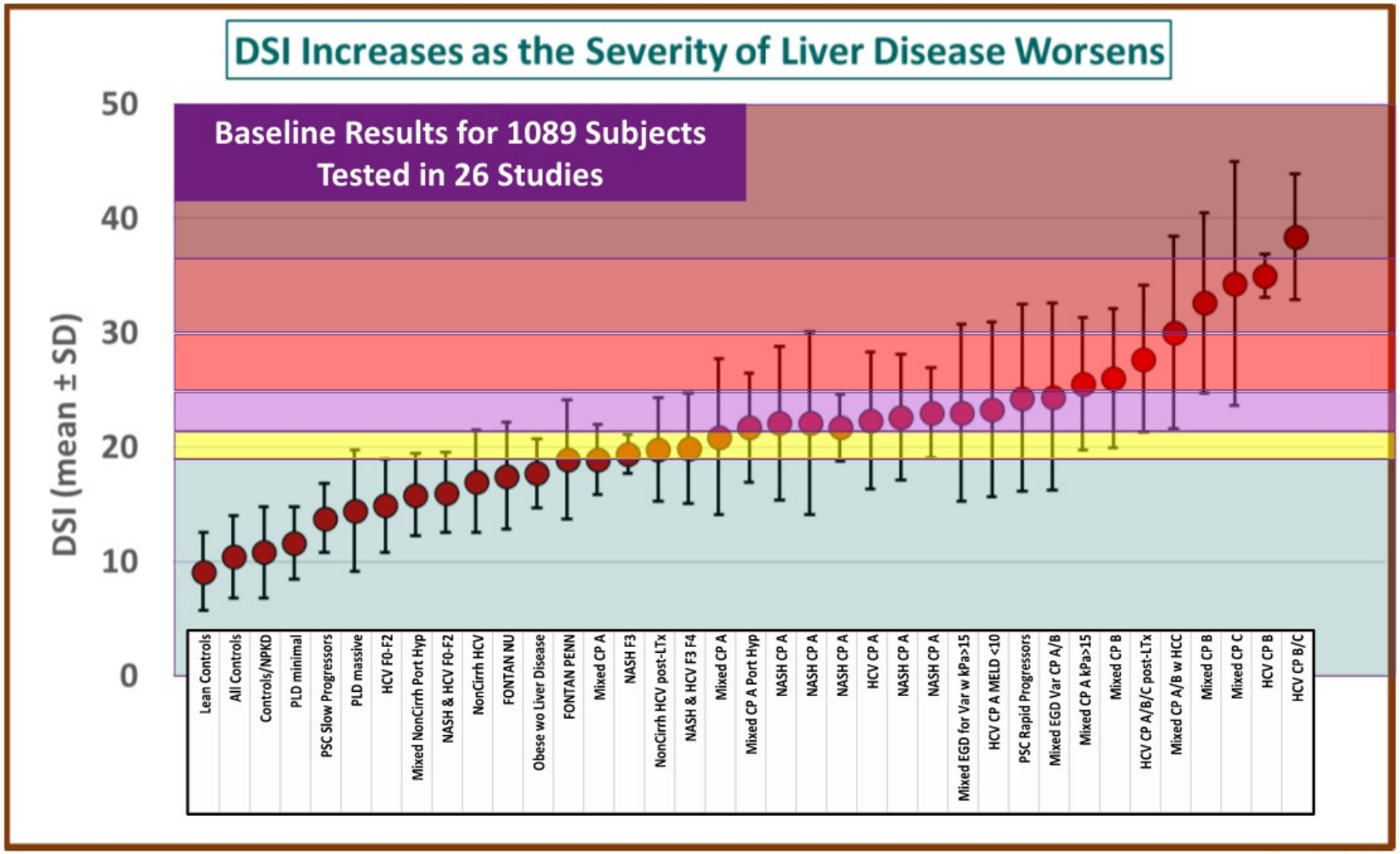
The Risk for Complications and Negative Outcomes Increases

Studies Completed in:

Hep C | NAFLD/NASH | Advanced CLD/Cirrhosis | PSC | HCC | Polycystic Liver Disease
SVR in HCV | Liver Transplant | MELD Scores | Portal Hypertension | Varices
Liver Disease as a Consequence of Congenital Heart Disease (FONTAN)

DSI Increases as the Severity of Liver Disease Worsens

DSI
HepQuant's Proprietary Disease Severity Index



DSI 18.3

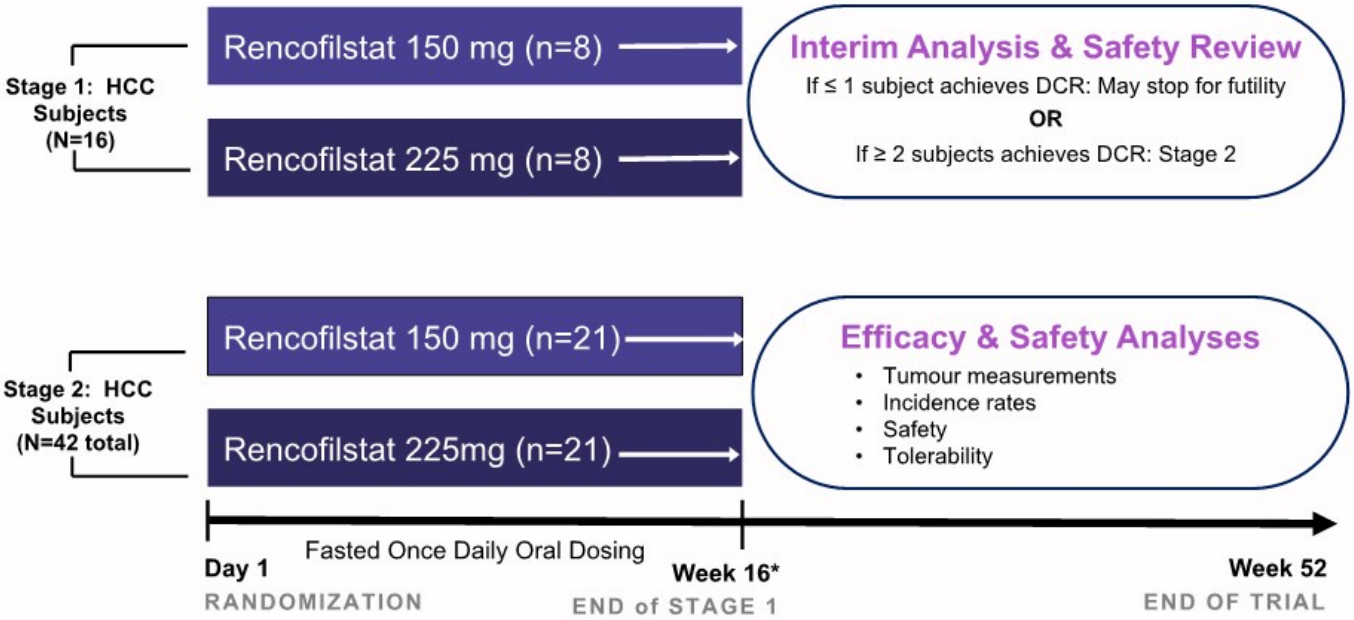
Each Bar / Whisker represents a set or subset of study subjects – spanning most common etiologies and stages of Chronic Liver Disease. (Data on File with HepQuant) – In every clinically-defined set or subset of subjects those with DSI above the mean would be at greater risk for complications or clinical outcome.

PHASE 2A HCC TRIAL (Q2 2022)

PHASE 2a: HEPA-CRV431-209, Simon 2 Stage Design

Advanced HCC Subjects - Safety, Tolerability, Pharmacokinetics, and Efficacy

HEPA-CRV431-209: 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 Hepatocellular Carcinoma Subjects



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

Inclusion Criteria:

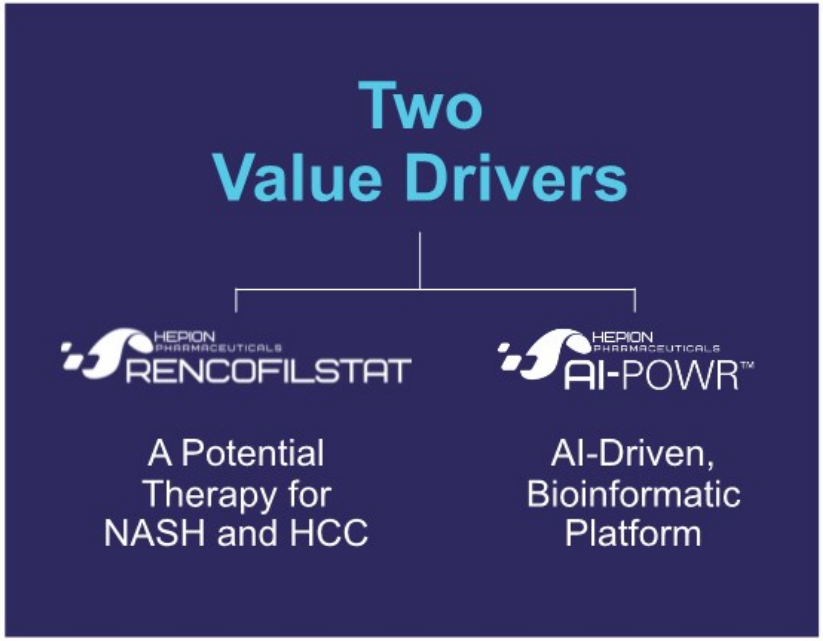
- Failure of standard first- or second-line systemic treatment(s) to include: disease progression and at least 1 untreated lesion

Primary Endpoints:

- Safety
- Tolerability
- Pharmacokinetics
- Disease Control Rate

Summary

- Rencofilstat, once-daily oral, multi-modal
- Phase 2a NASH trial completed with success
- Phase 2 activities initiated for NASH
  - 12 - month paired biopsy 2B study
  - 4 - month hepatic function study
- Phase 2a activities initiated for HCC
- Hepion's Proprietary Artificial Intelligence Platform (AI-POWR™)
- Core scientific team with >100 years collective cyclophilin expertise
- Core scientific team discovered and developed voclosporin (currently marketed)
- Robust IP



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