Hydronidone (F351) Phase 3 Trial in CHB-Associated Liver Fibrosis

- Topline Data Review

May 22, 2025

NASDAQ: GYRE

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Summary of Topline Results

1. Primary Endpoint Met with High Statistical Significance

- ≥1-stage fibrosis regression at Week 52:
  Hydronidone: 52.85% vs. Placebo: 29.84%
  *(**P = 0.0002**; ITT[1] analysis with central blinded pathology review)*

2. Key Secondary Endpoint Achieved

- ≥1-grade inflammation improvement without fibrosis progression at Week 52:
  Hydronidone: 49.57% vs. Placebo: 34.82%
  (P = 0.0246)

3. Favorable Safety Profile

- Serious Adverse Events: 4.88% (6/123, Hydronidone) vs. 6.45% (8/124, Placebo)
- **No discontinuations due to adverse events**

4. Clinical and Regulatory Pathways

- **Breakthrough Therapy Designation** (China NMPA[2], 2021), potentially first-in-class approval
- **New Drug Application (NDA)** to NMPA expected in **Q3 2025,** with **accelerated approval** to be sought
- U.S. IND filing for Phase 2 trial in **MASH fibrosis** expected in 3Q 2025; trial initiation planned for 2H 2025

1. ITT = Intent-To-Treat. 2. NMPA = National Medical Products Administration of China

Phase 3 Clinical Trial Overview

Objective: To evaluate the efficacy and safety of Hydronidone (270 mg/day) - the most effective dose identified in the Phase 2 study - in combination with Entecavir for the treatment of liver fibrosis associated with chronic hepatitis B (CHB)

Key Inclusion Criteria	• Age: 18–65, CHB with significant fibrosis (Ishak ≥3) • Positive HBV-DNA; ALT < 8× ULN • No antiviral, antifibrotic herbal meds within 3 months
Key Exclusion Criteria	• Decompensated cirrhosis, liver cancer suspicion, BMI > 30 • GI bleeding, high bilirubin/AFP, platelet ≤60×10^9/L • Hepatitis C or non-viral hepatitis, serious comorbidities • Pregnancy or recent participation in other trials
Statistical Method	• Sample size: 248 patients (124[1] per arm) • Efficacy evaluated in ITT and PPS population using χ^2 test, Wilcoxon rank-sum test, and ANCOVA.

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1. One patient in the Hydronidone treatment group did not receive any dose of the study medication and was therefore excluded from the final analysis.

Phase 3 Trial Design: CHB-Associated Liver Fibrosis

Primary Endpoint:

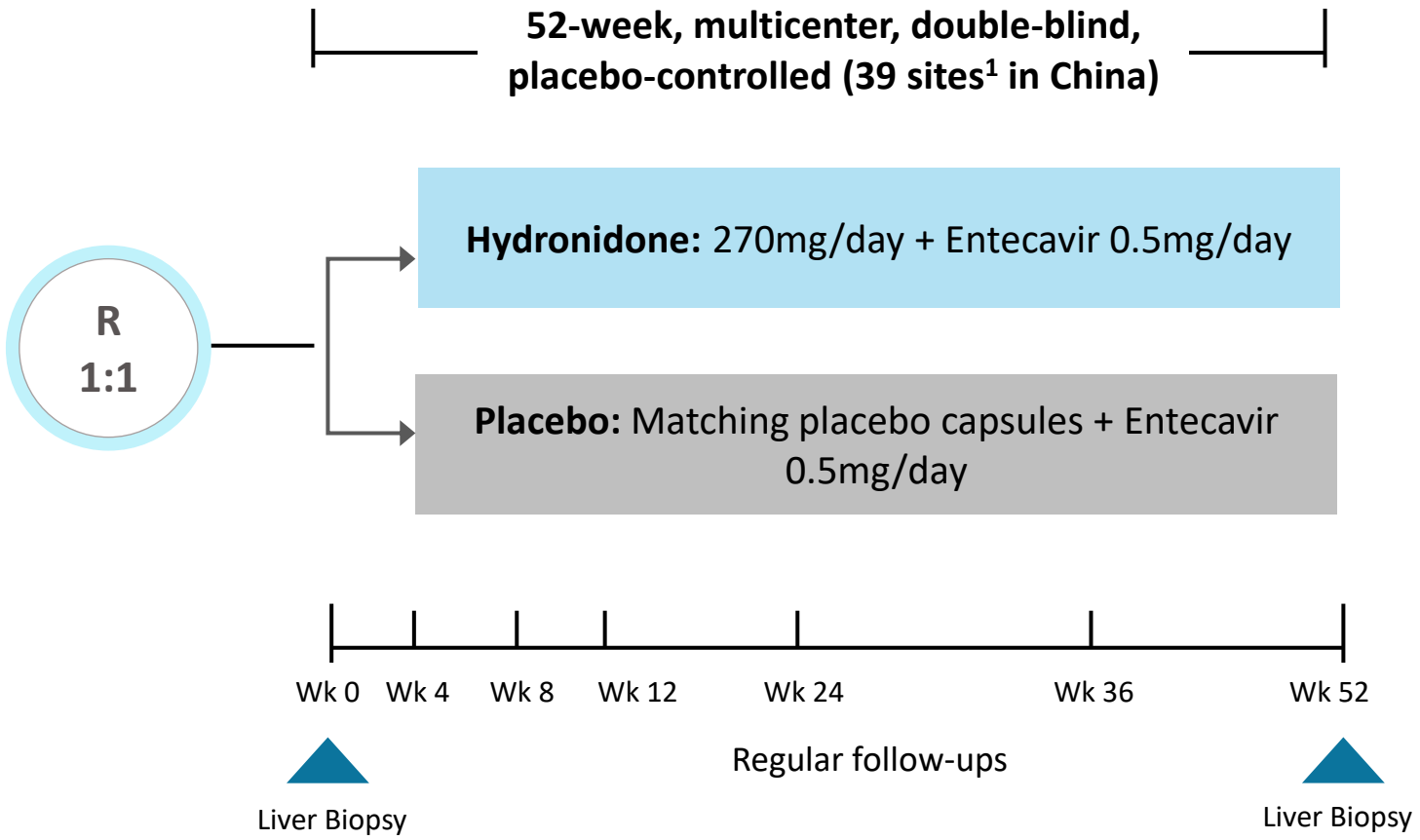
Efficacy of fibrosis reversal, defined as a decrease in the Ishak stage score of liver fibrosis ≥ 1 after 52 weeks of treatment compared to baseline.

Key Secondary Endpoint:

A decrease in liver inflammation grade by ≥1 after 52 weeks of treatment relative to baseline, without progression of fibrosis (Scheuer score).

Assessment:

Liver biopsies at baseline and week 52; read independently by **three blinded expert pathologists.**



1. The trial initially planned for 44 hospital centers. 39 were activated, and 35 ultimately enrolled patients, reflecting common variability in multicenter trial execution.

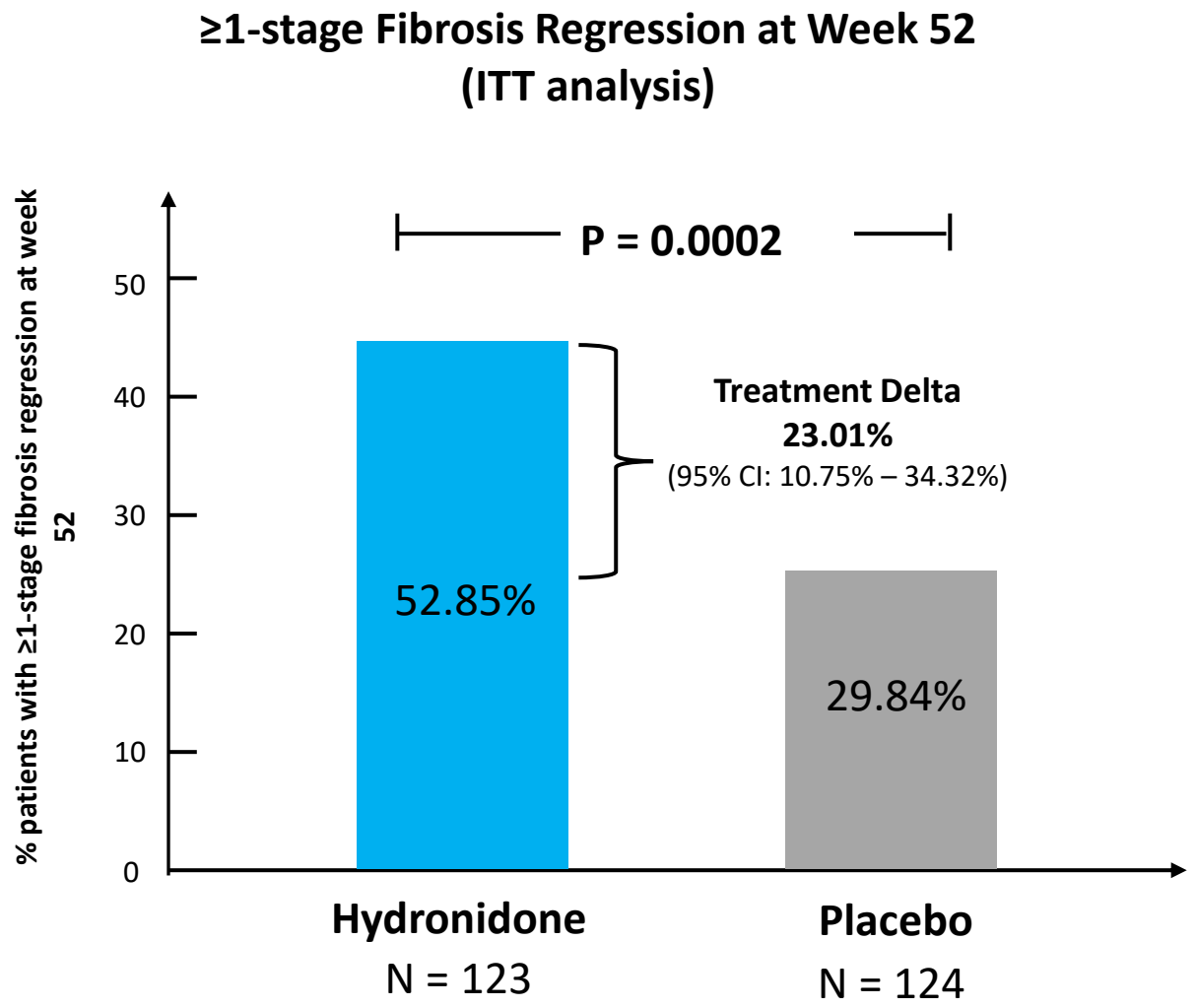
Baseline Demographics

Baseline Characteristic	Hydronidone (N=123)	Placebo (N=124)
Age, mean (SD), years	44.24 (10.30)	44.25 (10.24)
Male, n (%)	87 (70.7)	98 (79.03)
Female, n (%)	36 (29.27)	26 (20.97)
BMI, mean (SD), kg/m^2	24.05 (3.01)	23.58 (3.06)
ALT, mean (SD), U/L	59.37 (55.74)	68.43 (62.43)
AST, mean (SD), U/L	48.74 (35.03)	54.76 (44.32)
Total Bilirubin (TBIL), mean (SD), µmol/L	15.66 (6.20)	16.39 (7.72)
HBV DNA, log10 IU/mL, mean (SD)	4.82 (1.94)	5.24 (1.92)
HBeAg Positive, n (%)	42 (34.15)	49 (39.52)
FibroScan LSM, mean (SD), kPa	12.87 (6.19)	12.85 (6.51)
On Entecavir at Baseline, n (%)	123 (100%)	124 (100%)

Patient Disposition

Patient Status	Hydronidone (N=123)	Placebo (N=124)
Randomized	124	124
Received at least 1 dose	123	124
Completed 52 weeks of treatment	118	116
Discontinued early	6	8
– Due to AE	0	0
– Lost to follow-up	1	1
– Withdrew consent	4	7
– Other (e.g., protocol deviation)	1	0
Included in ITT analysis	123	124
Included in PPS (per-protocol)	115	112

Primary Endpoint Met with Statistically Significant Fibrosis Regression



- Primary endpoint achieved
- **+23.0% treatment delta** vs. placebo
- Highly statistically significant (**p=0.0002**)
- Consistent with fibrosis regression rates observed in Phase 2

Note: P = 0.0002 (Cochran-Mantel-Haenszel test). 95% CI based on Newcombe-Wilson method. Trial was designed to detect ≥20% absolute delta in fibrosis regression at 52 weeks.

Safety Profile

Safety Event	Hydronidone (N=123)	Placebo (N=124)
Any TEAE	98 (79.67%)	103 (83.06%)
Grade 1 AEs	27.64%	33.06%
Grade 2 AEs	43.90%	43.55%
Grade ≥3 AEs	8.13%	6.45%
Drug-related AEs (ADRs)	32.52%	33.87%
Grade ≥3 ADRs	1.63%	1.61%
Discontinuation due to AE	0	0
Temporary interruption due to AE	0	0.81%
Dose reduction due to AE	0	0
Any SAE	6 (4.88%)	8 (6.45%)
Due to Investigational Drug:		
Possibly unrelated	2	3
Unrelated	4	5
Death	0	0

Summary of all Serious Adverse Events (SAEs)

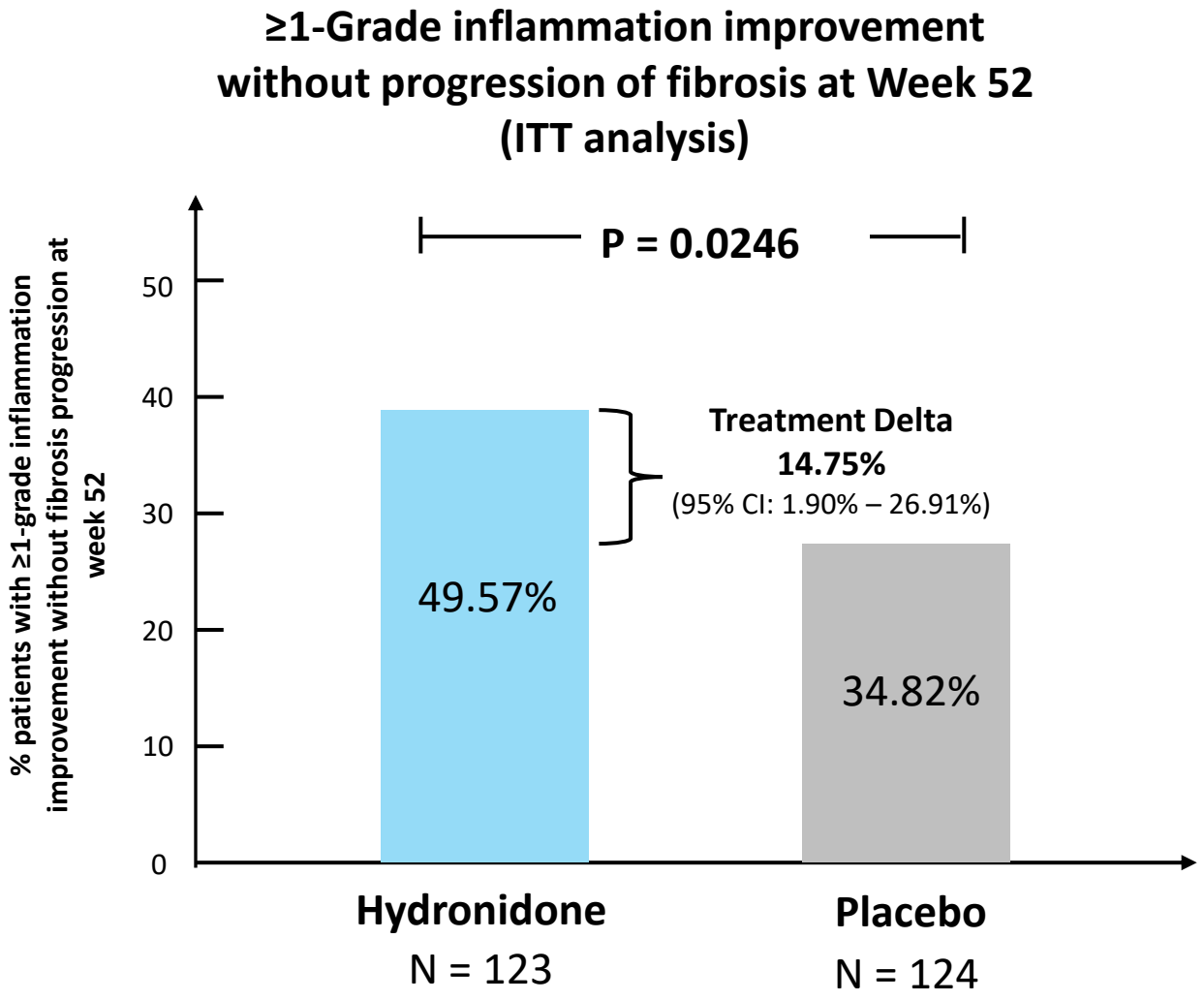
- All SAEs were assessed to be **unrelated to the investigational drug (Hydronidone).**
- **No discontinuations** due to SAEs across either treatment arm.

System Organ Class	Preferred Term	Hydronidone (N=123)	Placebo (N=124)
All SAEs		**6 (4.88%) / 9 cases**	**8 (6.45%) / 8 cases**
1. Gastrointestinal Disorders	Ascites	2	0
	Hemorrhoids	1	0
	Inguinal Hernia	0	1
2. Musculoskeletal Disorders	Carpal Tunnel Syndrome	1	0
	Disc Herniation	1	0
	Spondyloarthritis	0	1
3. Injury/poisoning/complications	Radius Fracture	1	0
	Humerus Fracture	1	0
4. Infections and Infestations	Infectious Pneumonia	1	0
	Upper Respiratory Infection	0	1

Summary of all Serious Adverse Events (SAEs cont'd)

System Organ Class	Preferred Term	Hydronidone (N=123)	Placebo (N=124)
5. Renal and Urinary Disorders	Nephrolithiasis	0	1
	Renal Cyst	0	1
6. Respiratory, Thoracic and Mediastinal Disorders	Pulmonary Mass	1	0
7. Hepatobiliary Disorders	Cholestatic jaundice	0	1
8. Neoplasms benign, malignant and unspecified (including cysts and polyps)	Benign Epididymal Neoplasm	0	1
9. Cardiac disorders	Arrhythmia	0	1
TOTAL		**9**	**8**

Key Secondary Endpoint Met: Significant Reduction in Liver Inflammation

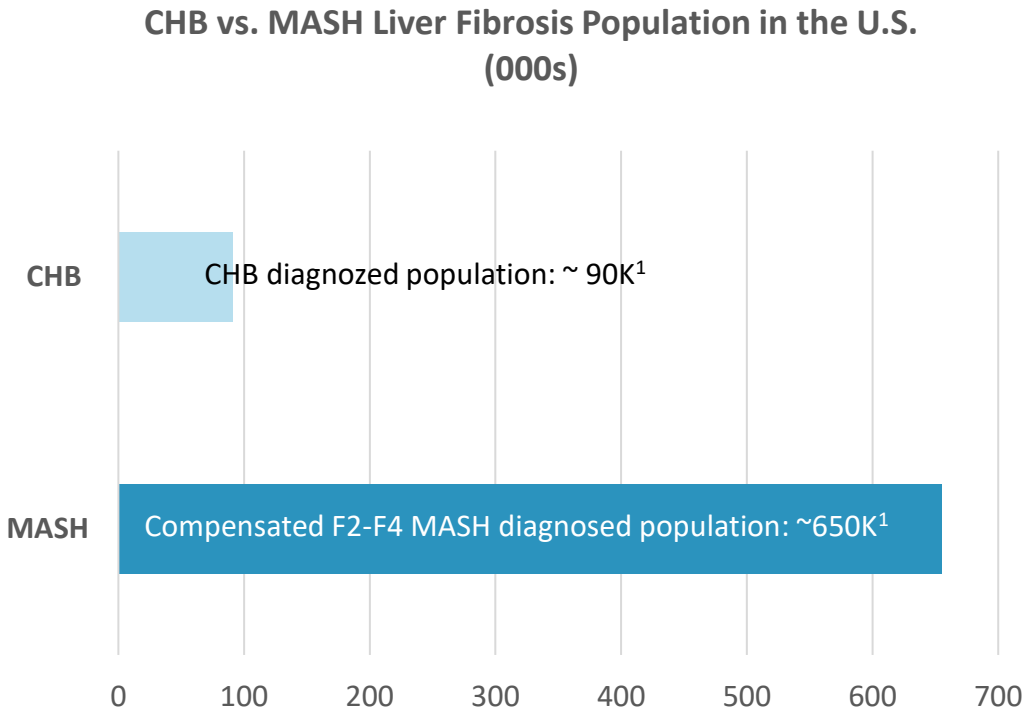


- Statistically significant (p=0.0246)
- +14.75% treatment delta vs placebo
- Reinforces **anti-inflammatory** activity

Note: Additional secondary endpoints were evaluated but are not shown here as they were not the focus of this topline announcement.

Note: P = 0.0246 (Cochran-Mantel-Haenszel test). 95% CI based on Newcombe-Wilson method. This was a secondary endpoint without pre-specified power; interpretation is exploratory.

Expanding Hydronidone's Potential: From CHB Fibrosis in China to MASH in the U.S.



Market Opportunity

In the U.S., the MASH fibrosis market is approximately **7.2 times larger** than the CHB fibrosis market.

Clinical Rationale

Hydronidone modulates TGF-β / p38γ / Smad7 signaling pathway — directly targeting fibrosis progression and **offering a differentiated approach from metabolic agents**.

Regulatory Pathway

Hydronidone's CHB data **helps to reduce risks in MASH development** and potentially supports *accelerated regulatory review and fast track*.

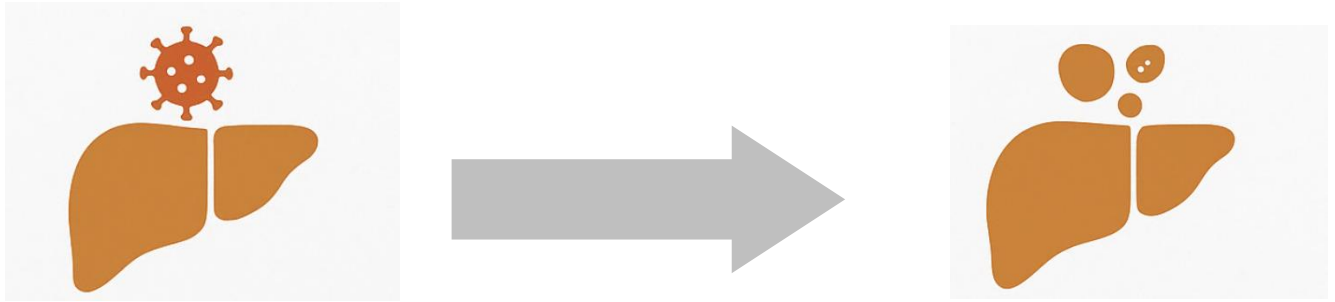
Competitive Differentiation

Hydronidone's unique anti-fibrotic approach positions it as a **complementary therapy** — not a competitor — to metabolic agents like THR-β, GLP-1s, and FGF21.

1. Based on analysis of third-party epidemiological research, published academic studies, and internal modeling.

CHB and MASH Share Common Fibrotic Signaling Pathway

Rationale for MASH expansion: Hydronidone targets the same core fibrotic biology - TGF-β, p38γ, and Smad7 - underlying both CHB and MASH, providing a mechanistically de-risked path into MASH.



	CHB- Associated Liver Fibrosis	**MASH- Associated Liver Fibrosis**
Etiology	Viral (HBV)	Metabolic (Obesity, T2 diabetes)
Fibrosis Driver	TGF-β / p38γ / Smad7	
Target Cell Type	Hepatic Stellate Cells	
F351 Mechanism	Anti-fibrotic via TGF-β, p38γ & Smad7	

Hydronidone is Purpose-Built on Pirfenidone's Foundation - with Enhanced Potency and Safety

Pirfenidone → [Structural Analog + Hydroxyl Group] → Hydronidone

↓ ↓

Modest Liver Activity ↑ Hepatotoxicity

Enhanced Smad7 Upregulation + Phase II Metabolism [1] → ↓ *Hepatotoxicity* + ↑ Anti-fibrotic Potency

Attribute	Pirfenidone	Hydronidone	Benefit
Structure	Parent compound	Analog with –OH group	↑ Smad7
MoA	TGF-β	TGF-β + p38γ + Smad7	↑ Potency
Metabolism	Phase I (oxidation)	Phase II (conjugation)	↓ Toxicity
Hepatic Safety	Known liver risk	Improved	↑ Tolerability
MASH Evidence	Some benefit (PROMETEO, model)[2]	Strong effect in a validated preclinical model	↑ Rationale

- Hydronidone enhances pirfenidone's anti-fibrotic effect by also inhibiting p38γ and upregulating Smad7, improving hepatic safety and supporting its expansion into metabolic liver diseases like MASH.

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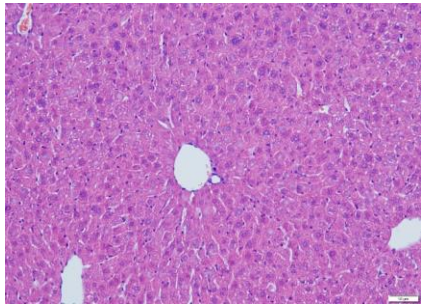
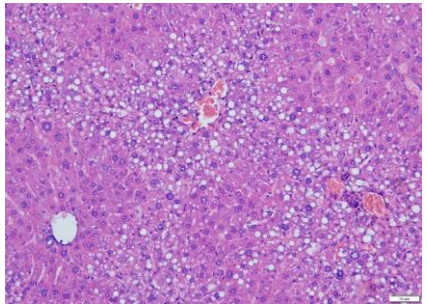
1. Phase II metabolism is associated with improved hepatic safety due to faster detoxification. 2. González-Huezo M, et al. Real-life proof-of-concept trial of prolonged-release pirfenidone in advanced liver fibrosis (PROMETEO study). Hepatol Int. 2021;15(2):377–388.

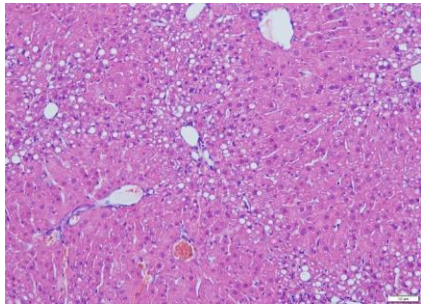
Hydronidone Demonstrates Dose-Dependent Anti-Fibrotic Efficacy in Preclinical MASH Model



Vehicle



Hydronidone-15mpk



Hydronidone-50mpk

Endpoint	Vehicle	Hydronidone (15 mpk)	Hydronidone (50 mpk)
Fibrosis	Extensive fibrosis	Moderate reduction in fibrosis	Marked reduction in fibrosis
Ballooning	Prominent ballooning	Mild improvement	Moderate to marked improvement
NASH Score	Elevated NAS score	Partial improvement in NAS score	Substantial improvement in NAS score

- Hydronidone reduced **fibrosis and ballooning** in a dose-dependent manner.
- **Outperformed Pirfenidone** in the model, demonstrating superior potency in fibrosis reversal.
- Validates anti-fibrotic activity in a **metabolic disease setting**, supporting MASH expansion.

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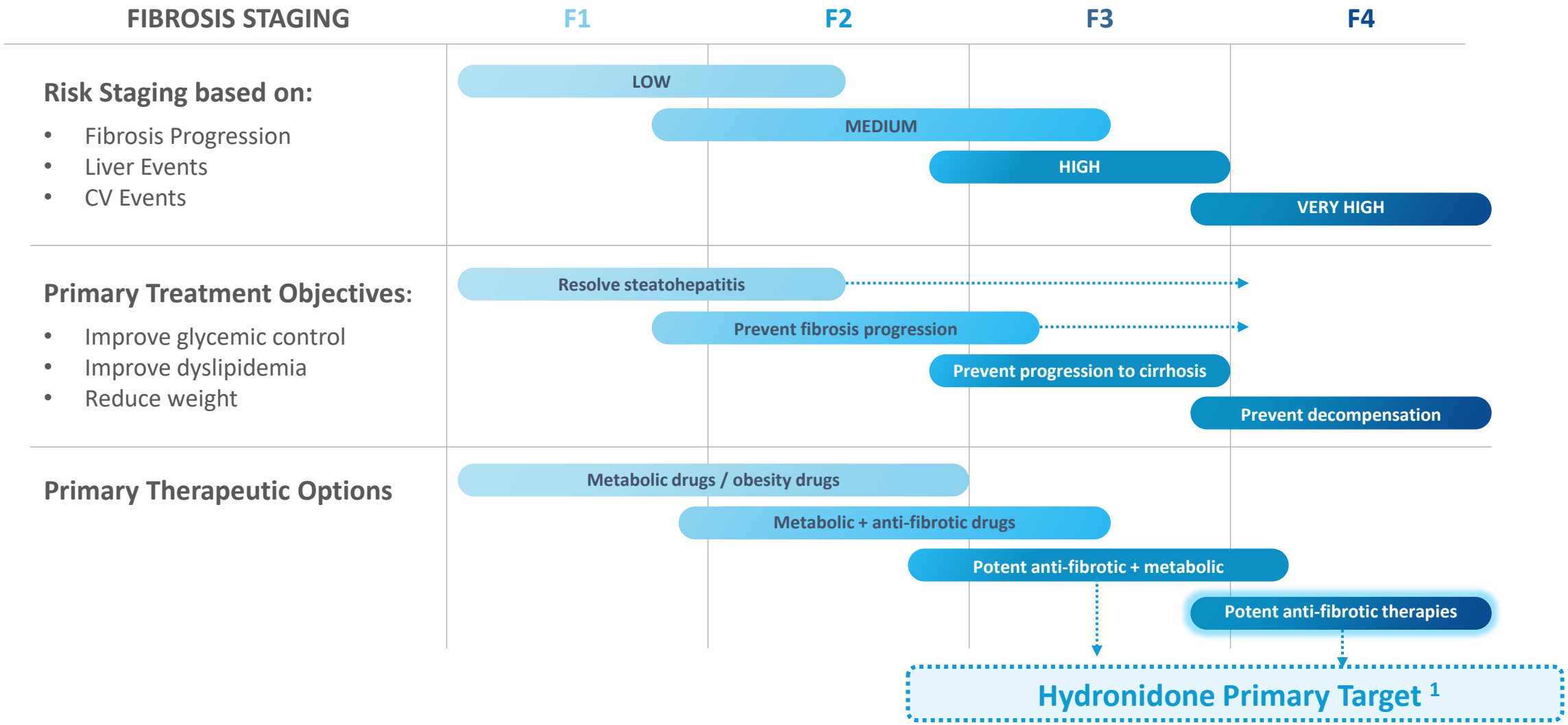
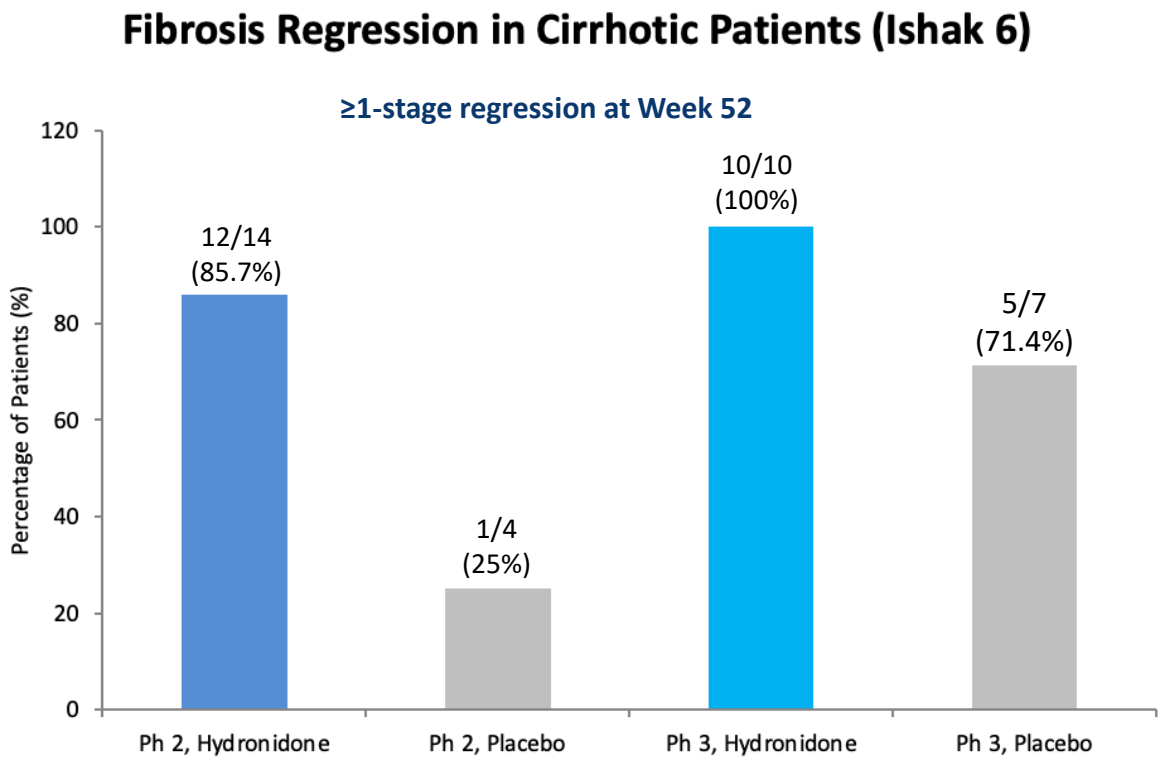
Note: 100 mpk not shown due to plateaued efficacy or potential toxicity. **Study conducted in a CCl_4 + HFD-induced NASH model** using histology-based endpoints (fibrosis, ballooning, NAS). Full scientific package available upon request.

Hydronidone Targets Fibrosis Specifically for Advanced MASH



1. We estimate ~650K compensated F2–F4 MASH patients in the U.S., based on market data and internal modeling. F351 is expected to target the full group, with a **core focus of ~450K patients**, excluding low-risk F2s and prioritizing the top 15–20% of F2s with progressive fibrosis.

Meaningful Fibrosis Regression Observed in Ishak 6 (F4) Patients in Two Independent Trials



Subgroup-based analysis; not powered for statistical significance.
(Biopsy-confirmed results from 52-week, randomized, double-blind trials with blinded reads by independent pathologists)

Phase 2:

- **36% (5/14)** of cirrhotic patients (Ishak 6) achieved **≥2-stage regression** and were considered **no longer cirrhotic** at Week 52.
- **12/14 (86%)** showed **≥1-stage improvement**, indicating broad antifibrotic activity.
- In the placebo arm, only **1 patient improved**, which happened to be a **≥2-stage regression**.

Phase 3:

- **100% (10/10)** of cirrhotic patients (Ishak 6) in the treatment group had **≥1-stage regression** at Week 52.
- **Mean improvement** was **−1.5** vs. **−1.0** in placebo.
- Placebo response: **5/7 patients (71.4%)** showed ≥1-stage regression, but **mean score change** remained lower than Hydronidone.

While exploratory and observed in CHB-associated cirrhosis, the consistent ≥2-stage regression seen in Phase 2/3 suggests Hydronidone may have the potential to reverse cirrhosis.

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Note: Phase 2 and Phase 3 used different methods to assess fibrosis regression. Phase 2 reported categorical outcomes (including ≥2-stage regression), while Phase 3 focused on ≥1-stage improvement and mean Ishak score change. In both studies, analyses were limited to biopsy-confirmed cirrhotic patients (Ishak 6 at baseline) and evaluated fibrosis improvement at Week 52 separately from non-cirrhotic patients.

Positioning Hydronidone In The Evolving MASH Treatment Landscape

	ORAL			INJECTABLE					
	Gyre THERAPEUTICS	Madrigal Pharmaceuticals	VIKING THERAPEUTICS	akero	89bio	Lilly	novo nordisk	Boehringer Ingelheim	
	Hydronidone	**Rezdiffra**	**VK2809**	**EFX**		**Pegozafermin**	**Tirzepatide**	**Semaglutide**	**Survodutide**
Indication	CHB	MASH	MASH	MASH		MASH	MASH	MASH	MASH
Study Phase	**Phase 3**	Approved	Phase 2b	Phase 2b		Phase 2b	Phase 2b	Phase 2	Phase 2
MOA	TGF-β	THR-β	THR-β	FGF21		FGF21	GIP/GLP-1	GLP-1	GLP-1/glucagon
Population	ITT	ITT	ITT	ITT	ITT	ITT	ITT	Modified ITT	ITT
N (Active/ Placebo)	123/124	~319/~309	44/41	43/43	63/61	81/45	219/219	80/80	77/77
Total ITT	248	966	181	126	181	192	659	320	295
Focus	**F2 - F4**	F2 - F3	F2 - F3	F2 - F3	F4	F2 - F3	F2 - F3	F2 - F3	F2 - F3
Duration	52 wks	52 wks	52 wks	96 wks		24 wks	52 wks	72 weeks	46 weeks
Fibrosis Improvement	52.9%	~26%	56.8%	49%	29%	27%	54.9%	43%	36%
Placebo	29.8%	~10%	34.1%	19%	12%	7%	29.7%	33%	22%
Placebo-Adjusted	**+23.0%**	+16%	+22.7%	+30%	+17%	+20%	+25.2%	+10%	+14%

Note: This illustrative comparison includes data from distinct disease settings (CHB and MASH). While fibrosis is a shared endpoint, differences in etiology, pathophysiology, and trial design limit direct comparability. Cross-indication interpretation is hypothetical and does not imply therapeutic equivalence.

- **Rezdiffra (Madrigal) sets the benchmark** as the first FDA-approved therapy for MASH.
- Hydronidone offers a **fibrosis-first approach**, acting directly on fibrotic tissue, and is the only agent with **a demonstrated focus on F4 (cirrhotic)** patients.
- **Hydronidone is designed to be complementary,** not competitive — potentially used as an add-on alongside metabolic agents.
- **Our regulatory aim** is to establish a new standard for direct fibrosis reversal in MASH patients.

Comparator data sourced from published studies and company press releases (e.g., Madrigal, Viking, Akero, 89bio, Lilly, Novo Nordisk, Boehringer Ingelheim). Differences in disease, design, and population limit direct comparison.

Key Takeaways and Next Steps

Primary Endpoint Met with High Statistical Significance

- ≥1-stage fibrosis regression at Week 52:
  Hydronidone: 52.85% vs. Placebo: 29.84% *(P = 0.0002)*
- Consistent with fibrosis regression rates observed in Phase 2

Key Secondary Endpoint Achieved

- ≥1-grade inflammation improvement without fibrosis progression: Hydronidone: 49.57% vs. Placebo: 34.82% *(P = 0.0246)*

Favorable Safety Profile

- Serious Adverse Events: 4.88% (6/123, Hydronidone) vs. 6.45% (8/124, Placebo)
- No discontinuations due to adverse events; All SAEs were assessed to be unrelated to Hydronidone

Key Next Steps

- Received Breakthrough Therapy Designation from China NMPA in 2021; potential **first-in-class** approval - **Gyre's second**, following Pirfenidone in 2011.
- NDA submission to NMPA expected in Q3 2025, seeking **accelerated approval** based on positive Phase 3 results.
- IND filing for **MASH-associated liver fibrosis** planned for Q3 2025; pending FDA clearance, Phase 2 trial **expected to begin in 2H 2025**.

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APPENDIX: Clinical Trial - Common Adverse Events Detail & F351 - Mechanism of Action

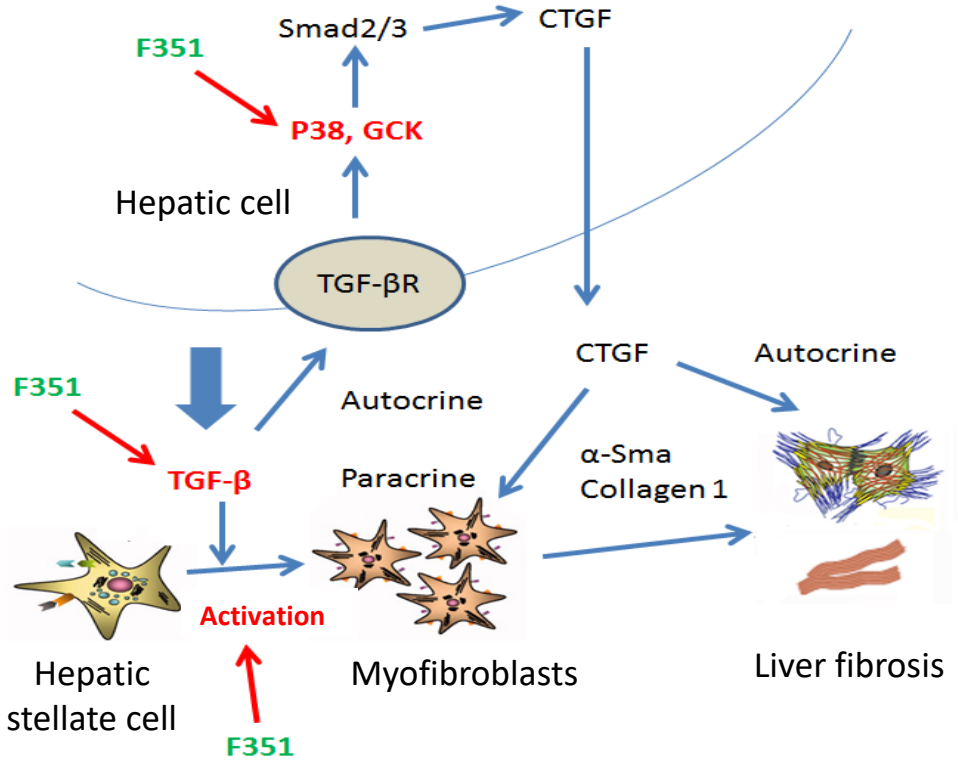
Most common adverse events (≥5% Incidence)

Preferred Term	Hydronidone (%)	Placebo (%)
Upper Respiratory Tract Infection	25 (20.33)	21 (16.94)
COVID-19	14 (11.38)	8 (6.45)
Urinary Tract Infection	10 (8.13)	7 (5.65)
Hyperlipidemia	12 (9.76)	13 (10.48)
Hepatic Steatosis	8 (6.50)	12 (9.68)
Liver pain	8 (6.50)	8 (6.45)

- No major safety signal emerged throughout the 52-week treatment period.
- Adverse events were balanced between Hydronidone and placebo groups.
- Most events were mild and not treatment-limiting.
- No increases in pruritus, hepatotoxicity, or lipid-related abnormalities.

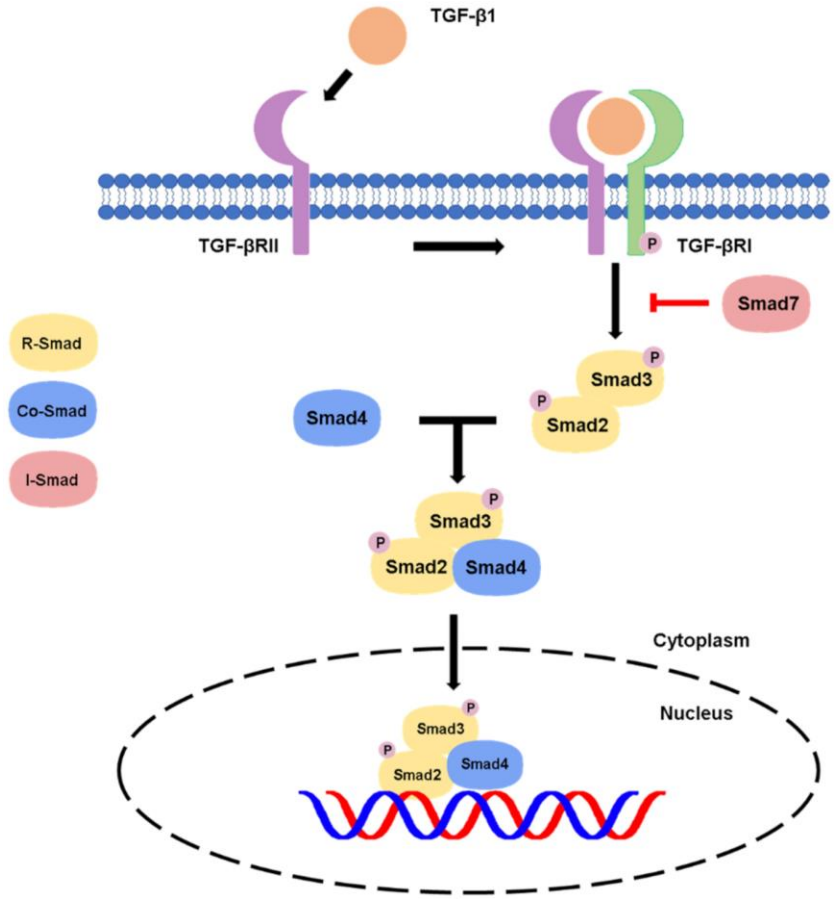
Comparison of Hydronidone and Pirfenidone metabolism

Liver Injury → TGF-β ↑ triggers multiple fibrosis pathways:
1. → p38γ → HSC Activation → α-SMA ↑ → ECM Accumulation → Fibrosis
2. → Smad2/3 (phosphorylation) → Fibrosis
3. ⊣ Smad7 (inhibitory) → Upregulation of TGF-beta signaling → Activation of both p38gamma and SMAD2/3 cascades



- As a key profibrotic cytokine, TGF-β drives hepatic stellate cell (HSC) activation, promotes extracellular matrix (ECM) deposition, and triggers fibrogenesis.
- The p38γ isoform plays a pivotal role in TGF-β-stimulated collagen production. F351 attenuates fibrosis, at least in part, by targeting the p38 MAPK transduction pathway.
- During hepatic injury, TGF-β upregulation triggers hepatic stellate cell (HSC) activation and differentiation into myofibroblasts. This phenotypic transformation is characterized by cytoskeletal remodeling, including α-smooth muscle actin (α-SMA) expression, which serves as a specific marker for myofibroblasts and the onset of fibrogenesis.
- Extensive preclinical and clinical studies indicate that activated myofibroblasts with elevated α-smooth muscle actin (α-SMA) expression serve as the dominant producers of fibrillar collagen and key ECM proteins, thereby driving hepatic fibrogenesis.

TGF-β plays important role in liver fibrosis by activating HSCs

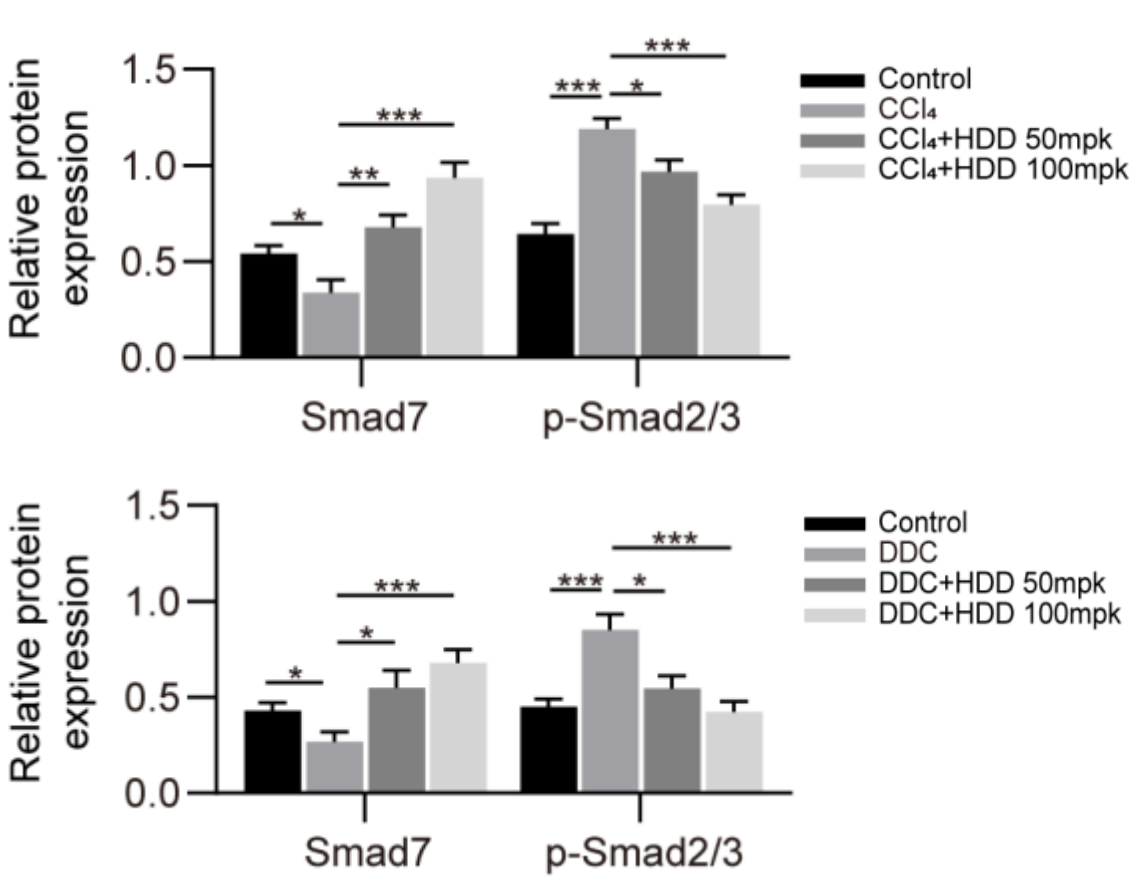


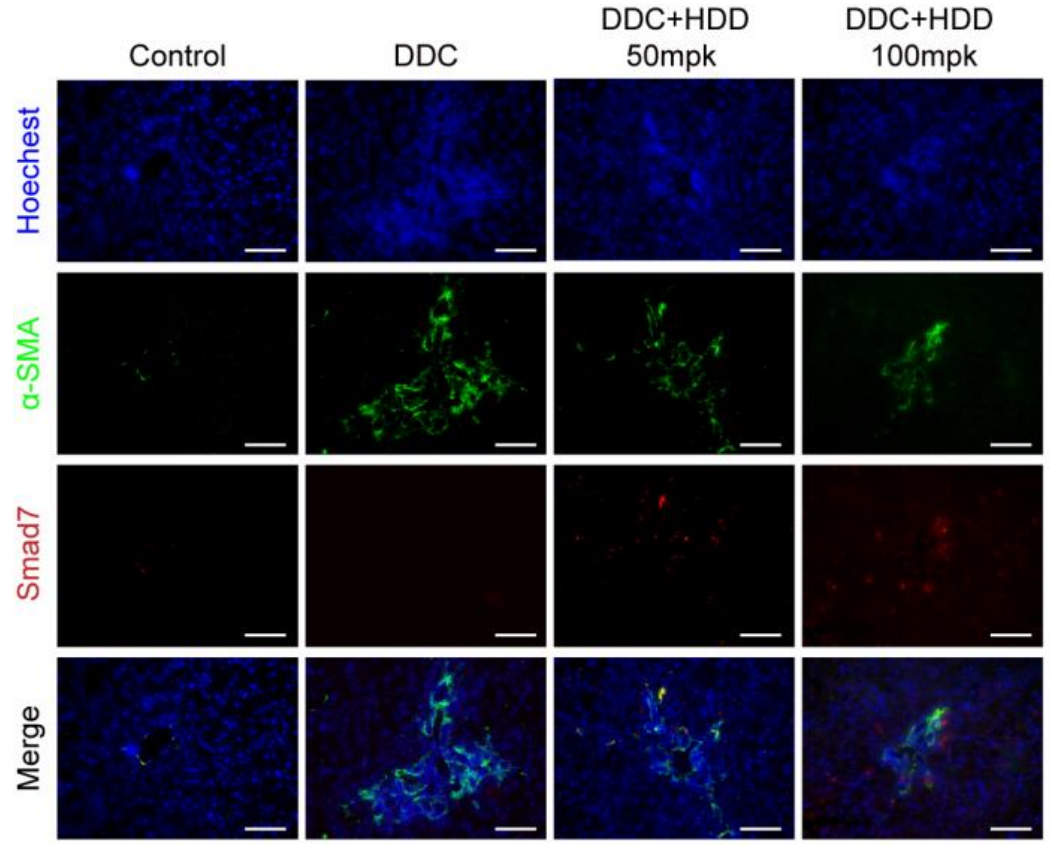
- Smad7 is a negative regulator of TGF-β signaling.
- Smad7 knockdown can promote HSC activation and liver fibrosis.
- Smad7 overexpression can prevent liver fibrosis.
- **Hydronidone is believed to effectively target this pathway.**

Inhibiting HSC activation is believed to be one of the most effective therapeutic strategies to fight liver fibrosis

1. Xu, Xianjun et al. "Hydronidone ameliorates liver fibrosis by inhibiting activation of hepatic stellate cells via Smad7-mediated degradation of TGFβRI." *Liver international : official journal of the International Association for the Study of the Liver* vol. 43,11 (2023): 2523-2537. doi:10.1111/liv.15715

Animal studies demonstrated Hydronidone upregulated the expression of Smad7 and inhibited phosphorylation of Smad2/3



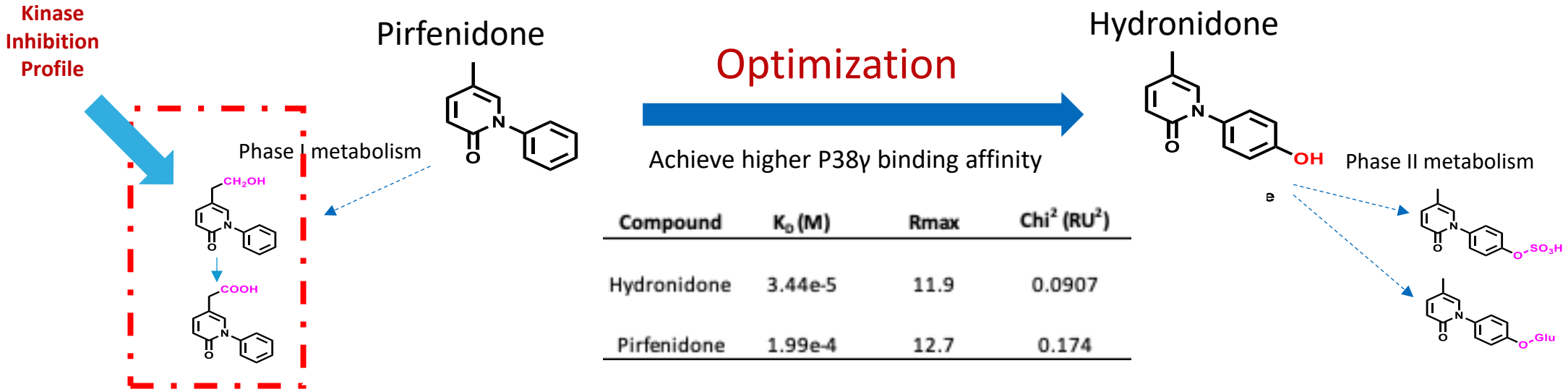


Smad7 is a known negative regulator of liver fibrosis, suggesting clinical potential in a recognized cascade

Note: Statistical significance: *p < .05, **p < .01, *p < .001 (one-way ANOVA with post hoc tests). Data from Xu et al., Liver International (2023), 43(11): 2523–2537. doi:10.1111/liv.15715.

Hydronidone vs. Pirfenidone: Mechanistic and safety advantages

- The introduction of a hydroxyl group shifts its metabolic profile from Pirfenidone's dominant Phase I oxidation to preferential Phase II conjugation (M3/M4 metabolites). Phase II metabolism, known as "detoxification metabolism," can prevent the formation of active metabolites and covalent binding to proteins, suggesting a mechanistic basis for hydronidone's improved hepatic safety profile compared with Pirfenidone.



Compound	K_D (M)	Rmax	Chi^2 (RU^2)
Hydronidone	3.44e-5	11.9	0.0907
Pirfenidone	1.99e-4	12.7	0.174

- In vitro kinase assay shows that both hydronidone and Pirfenidone effectively inhibit p38γ activity, with hydronidone exhibiting a higher inhibition potency than Pirfenidone.
- These findings indicate that hydronidone exhibits stronger inhibition of the p38γ pathway, potentially contributing to its enhanced antifibrotic activity.

Hydronidone shaping up to be Pirfenidone 2.0

Feature	Hydronidone	Pirfenidone
Mechanism of Action	Tri-pathway mechanism: inhibits p38γ, upregulates Smad7, and suppresses TGF-β/Smad2/3 signaling	Broadly downregulates TGF-β levels, with less defined pathway specificity
Metabolism	Undergoes Phase II metabolism, known for safer detoxification and fewer reactive byproducts	Primarily metabolized through Phase I oxidation (CYP1A2), which can generate reactive metabolites
Liver Safety	Designed to reduce hepatotoxicity; favorable liver safety profile in trials	Observed increases in liver enzymes in some patients; rare hepatic events documented
Fibrosis Efficacy (in humans)	Shown to reverse fibrosis in 55% of patients with CHB (270 mg group)[1]	Exploratory clinical data in liver fibrosis; not approved for fibrotic liver disease

1. Cai et al. Clin Gastroenterol Hepatol. 2023;21(7):1893–1901. doi:10.1016/j.cgh.2022.05.056

Thank you

Contact:

David Zhang
David.Zhang@Gyretx.com