Efruxifermin Drives Multidimensional Histologic Improvement in Compensated Cirrhosis: An AI-Based Analysis from the SYMMETRY Randomized Controlled Trial

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See efruxifermin publications at AASLD here:

Disclosures

- **Advisory Board/Consulting:** Akero, Altimmune, AstraZeneca, Boehringer Ingelheim, Boston Pharmaceuticals, CIMA, Curve Biosciences, Daiichi Sankyo, Enveda, Echosens, GSK, Hepanova, HistoIndex, Kriya, Lilly, Madrigal, Merck, Neuraly, Novo Nordisk, OPKO, Perspectum, Regeneron, Rivus, Roche, Sidera Bio, Takeda
- **Principal Investigator for a Drug Study:** Akero, Allergan, Altimmune, Boehringer Ingelheim, Bristol Myers Squibb, Boston Pharmaceuticals, Conatus, Corcept, Enanta, Galectin, Genfit, Gilead, GSK, Kowa, Lilly, Madrigal, Merck, Novartis, Novo Nordisk, Rivus, Shire, Takeda, Terns, Viking, Zydus
- **Stockholder:** OPKO, Altimmune
- **Speaking Bureau:** Madrigal, Boehringer Ingelheim, Novo Nordisk
- **NIH Funding:** 1R01DK143254-01 (PI)

Efruxifermin Bivalent Structure Optimized for MASH Efficacy with Convenient Once-Weekly Dosing

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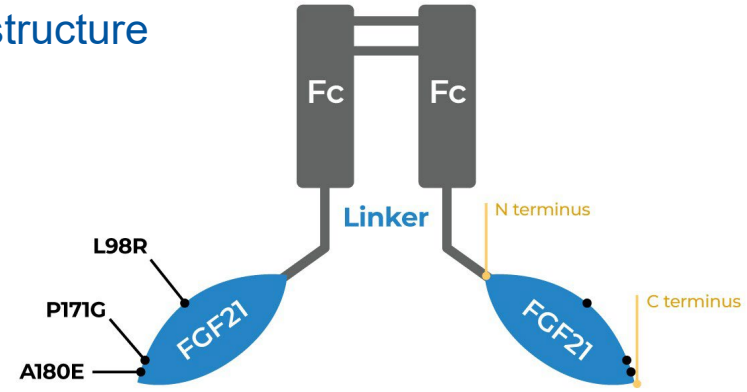
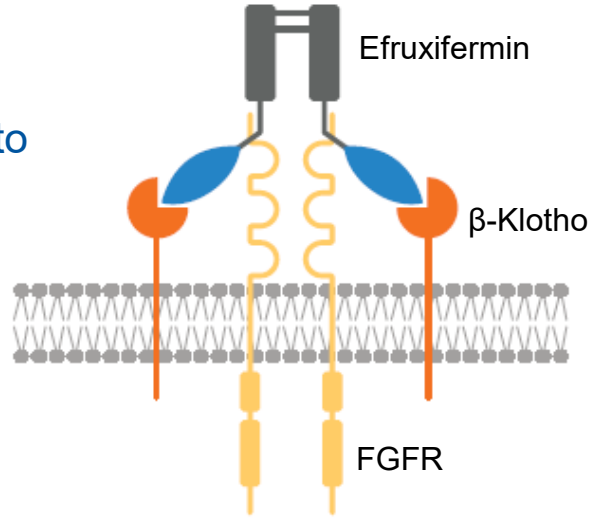
Efruxifermin structure



Bivalent structure enhances binding to target cells



Efruxifermin is a long-acting bivalent Fc-FGF21 fusion protein designed to mimic native FGF21

- High affinity for target cells that express FGFR1c/2c/3c and β-Klotho[1,2]
- Prolonged half-life enables weekly dosing[3]
- Balanced and sustained agonism of target receptors (FGFR1c/2c/3c) across weekly dosing interval, no FGFR4 activity[3]
- Pharmacodynamic effect sustained through Week 96 in clinical trials[4,5]

[1] Stanislaus et al. Endocrinology. 2017;158(5):1314-27; [2] Tillman et al. Efruxifermin, a bivalent Fc-FGF21 analog, demonstrates improved biophysical and pharmacological engagement with live cells compared to monovalent FGF21 analogs. AASLD The Liver Meeting 2022; Washington DC; [3] Kaufman et al. Cell Rep Med. 2020;Jul 21;1(4):100057; [4] Noureddin et al. Lancet 2025;405(10504):719-730; [5] Noureddin et al. N Engl J Med 2025;392(24):2413-2424.
FGF21, fibroblast growth factor 21; FGFR, fibroblast growth factor receptor; MASH, metabolic dysfunction-associated steatohepatitis.

Efruxifermin Clinical Program Covers the Spectrum of MASLD / MASH

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MASH Clinical Trials

MASLD / MASH Progression



PHASE 2a
complete

BALANCED
Efruxifermin vs placebo for 16 weeks[1] (N=80)

Cohort C
(expansion of BALANCED)
Efruxifermin vs placebo for 16 weeks[2] (N=30)

PHASE 2b
complete

HARMONY
Efruxifermin vs placebo for 96 weeks[4,5] (N=128)

symmetry FOR CIRRHOTIC NASH
Efruxifermin vs placebo for 96 weeks[6] (N=182)

Cohort D
(expansion of SYMMETRY)
Efruxifermin vs placebo in GLP-1 users with T2D for 12 weeks[3] (N=31)

PHASE 3
ongoing

synchrony HISTOLOGY
Efruxifermin vs placebo for 240 weeks (N≈1650)

synchrony OUTCOMES
Efruxifermin vs placebo; event-driven duration (N≈2150)

synchrony REAL-WORLD
Efruxifermin vs placebo for 52 weeks; N≈700 (Enrollment complete)

[1] Harrison et al. Nat Med. 2021 Jul;27(7):1262-1271; [2] Harrison et al. JHEP Rep. 2022 Aug 23;5(1):100563; [3] Harrison et al. Clin Gastro Hep 2025;23(1):103-113; [4] Noureddin et al. Lancet 2025;405(10504):719-730; [5] Noureddin et al. N Engl J Med 2025;392:2413-2424. [6] Harrison et al. Clin Gastro Hep 2025;23(1):103-113.
F4c, compensated cirrhosis; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

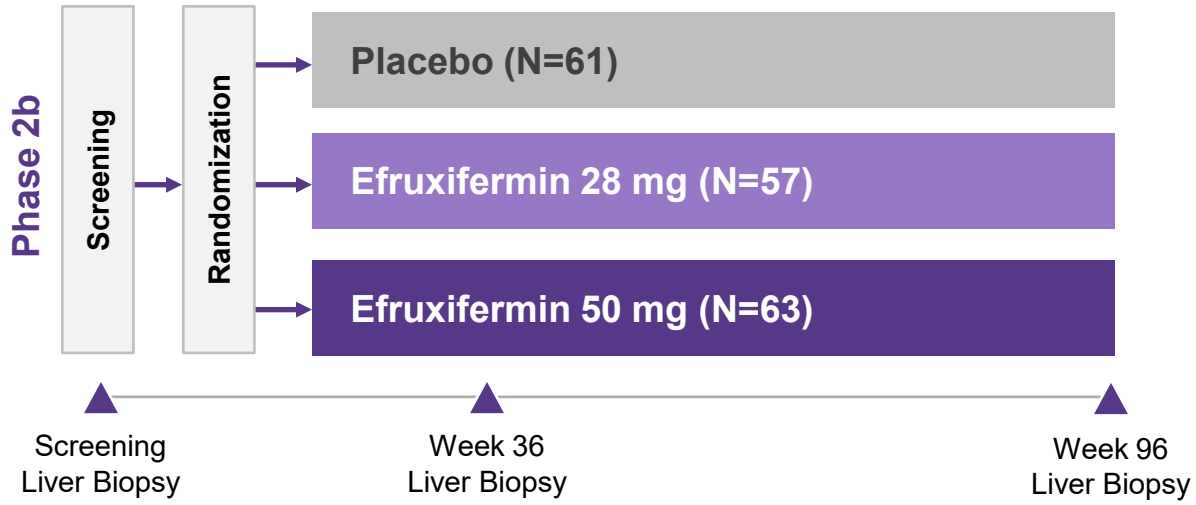
SYMMETRY: Efruxifermin in Compensated Cirrhosis (F4c) due to MASH

Study Design
- Efruxifermin vs placebo for 96 weeks

Population
- Biopsy-defined F4c MASH
- 181 randomized and dosed
- 134 with Week 96 liver biopsy

Primary Histology Endpoint
- ≥1-stage fibrosis improvement without MASH worsening

Key Secondary Endpoints
- MASH resolution
- Noninvasive tests of fibrosis, liver injury, metabolic markers



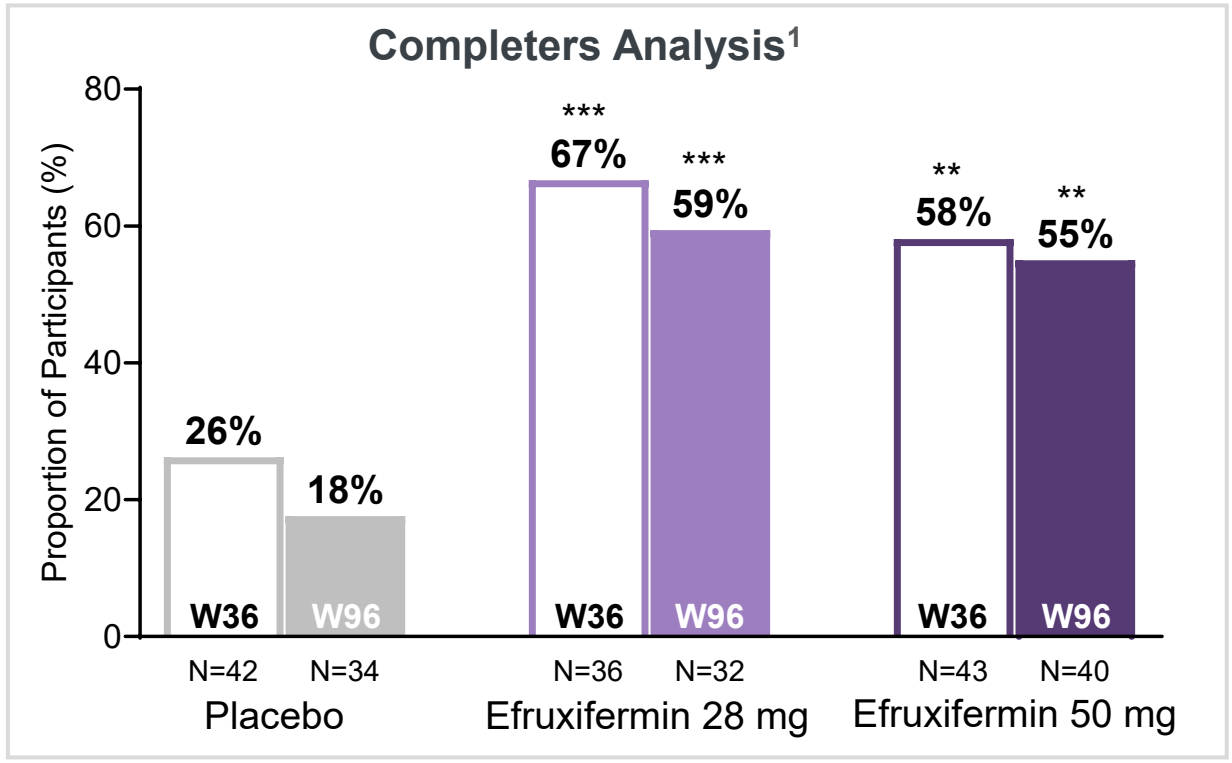
Baseline Characteristics	N=181
Age, years	61
% Female	67%
% with T2D	80%
ELF score	10.5
Liver Stiffness by VCTE, kPa	24
ALT, U/L	40
AST, U/L	37
HbA1c, %	6.7
HOMA-IR	11.7
Weight, kg	99
GLP-1 RA use, %	27%
Statin use, %	47%
Triglycerides, mg/dL	151

[1] Noureddin et al. N Engl J Med 2025;392:2413-2424. Registration: NCT05039450

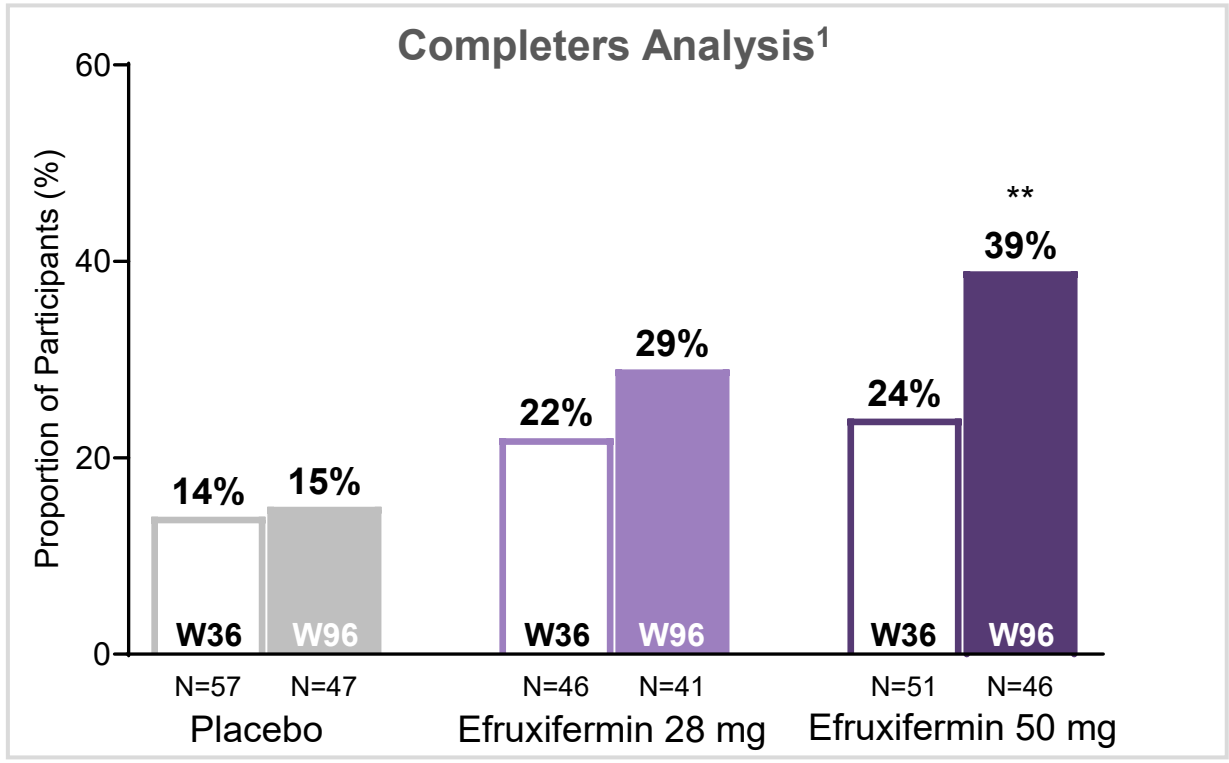
Baseline data are for all randomized participants that received at least one dose of study drug. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis test; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1C, glycated hemoglobin A1C; HOMA-IR, homeostasis model of insulin resistance; MASH, metabolic dysfunction-associated steatohepatitis; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography (FibroScan).

Statistically Significant Improvements in MASH Resolution and Fibrosis with Efruxifermin 50 mg at Week 96

MASH Resolution at Week 36 and 96 by NASH CRN



≥1-Stage Fibrosis Improvement & No Worsening of MASH at Week 36 and 96 by NASH CRN



[1] Data are for participants with liver biopsies available at baseline and specified timepoints and are results of central reading based on NASH CRN criteria. **p<0.01, ***p<0.001 vs placebo (Cochran-Mantel-Haenszel test). MASH resolution data are for participants with biopsy-defined MASH at baseline. MASH, metabolic dysfunction-associated steatohepatitis.

Aim

Evaluate the change in liver histology with efruxifermin in the SYMMETRY trial that enrolled patients with F4c MASH using AI-powered digital pathology:

1. **AIM-MASH+ continuous NAS and fibrosis scores**[1]
2. LiverExplore quantification of fibrosis and cellular composition, including fibrosis, tissue, and cellular changes[2]

[1]Iyer, J.S., Juyal, D., Le, Q. et al. *Nat Med* **30**, 2914–2923 (2024). [2]Gerardin, Y., Stanford-Moore, A., Patel, N. et al. *medRxiv* 2025.06.12.25328580 (2025).

AIM-MASH+ and LiverExplore are For Research Use Only. Not for use in diagnostic procedures.

AIM-MASH algorithms yield automated CRN scores from paired H&E- and trichrome-stained biopsy whole slide images

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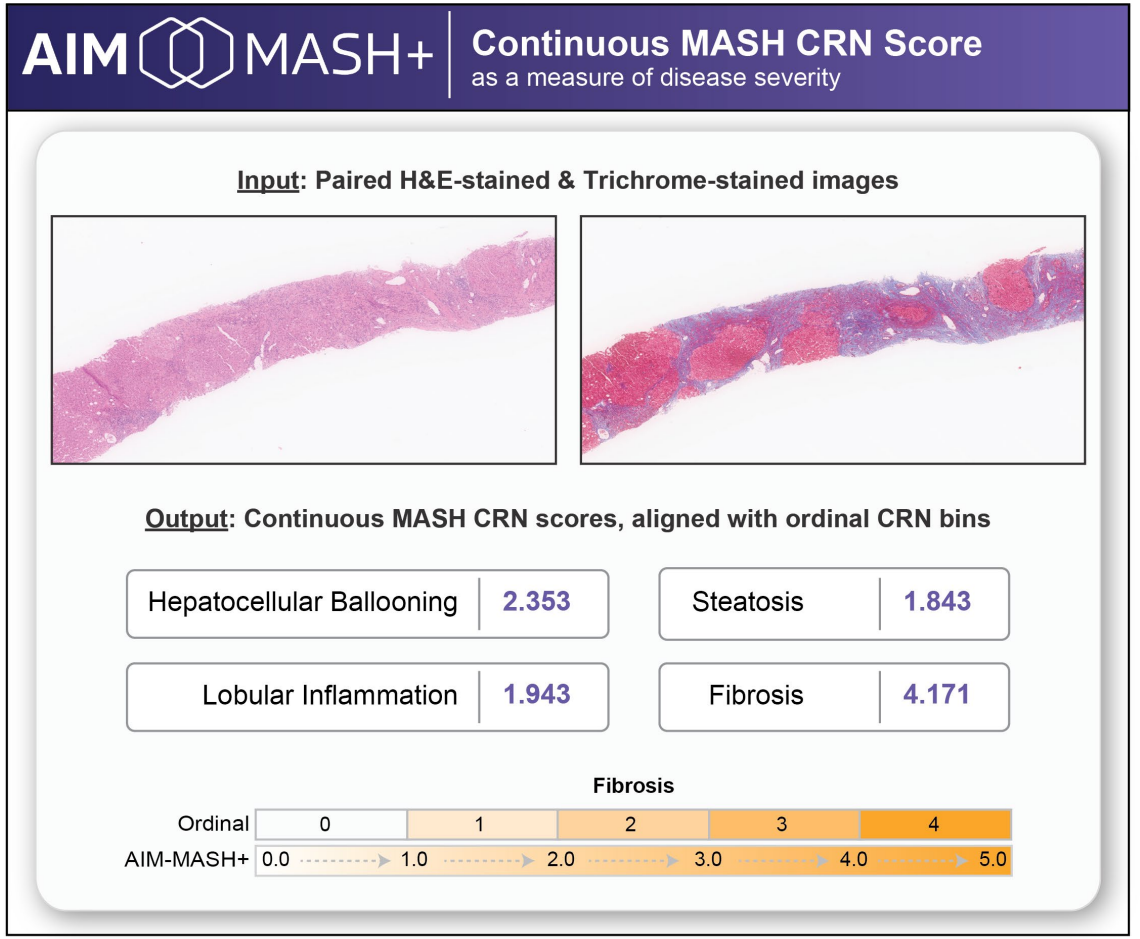
- **AIM-MASH AI Assist**
  - Generates automated, ordinal MASH CRN scores that are adjudicated by pathologist[1]
  - FDA and EMA qualified for use for enrollment and primary endpoint assessment in prospective MASH clinical trials

- **AIM-MASH+**
  - Generates continuous MASH CRN scores, aligned with ordinal scores [2]
  - Research Use Only tool for exploratory endpoints and analysis



[1]Pulaski, H., Harrison, S.A., Mehta, S.S. et al. *Nat Med* **31**, 315–322 (2024);[2]Iyer, J.S., Juyal, D., Le, Q. et al. *Nat Med* **30**, 2914–2923 (2024).

AIM-MASH AI Assist is qualified as a tool in the EU and as a drug development tool (DDT) in the US for use in MASH clinical trials.
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Statistically significant improvement in continuous NASH CRN scores with efruxifermin

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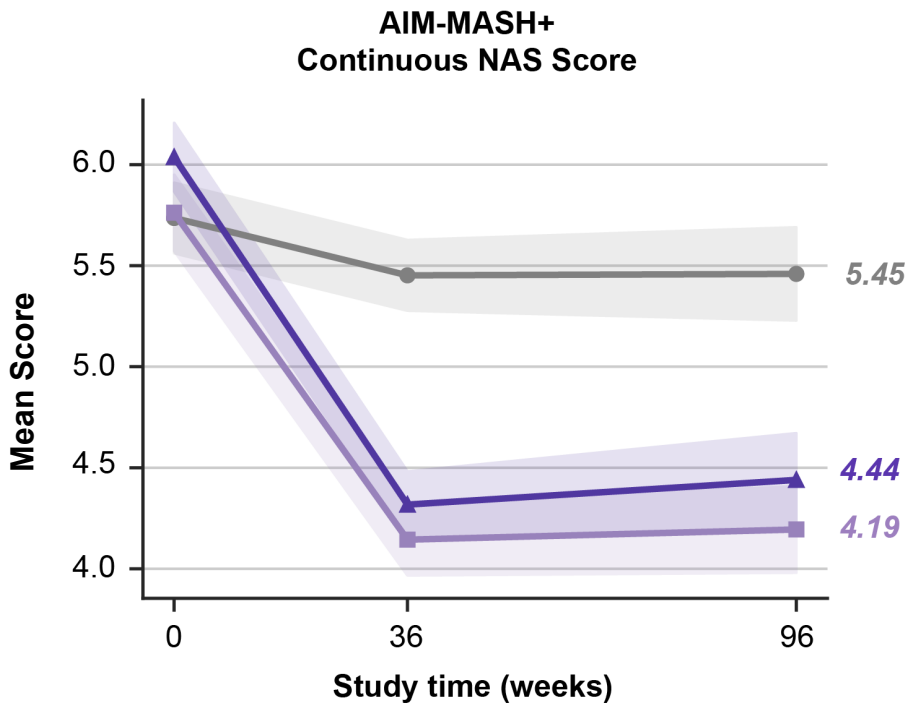

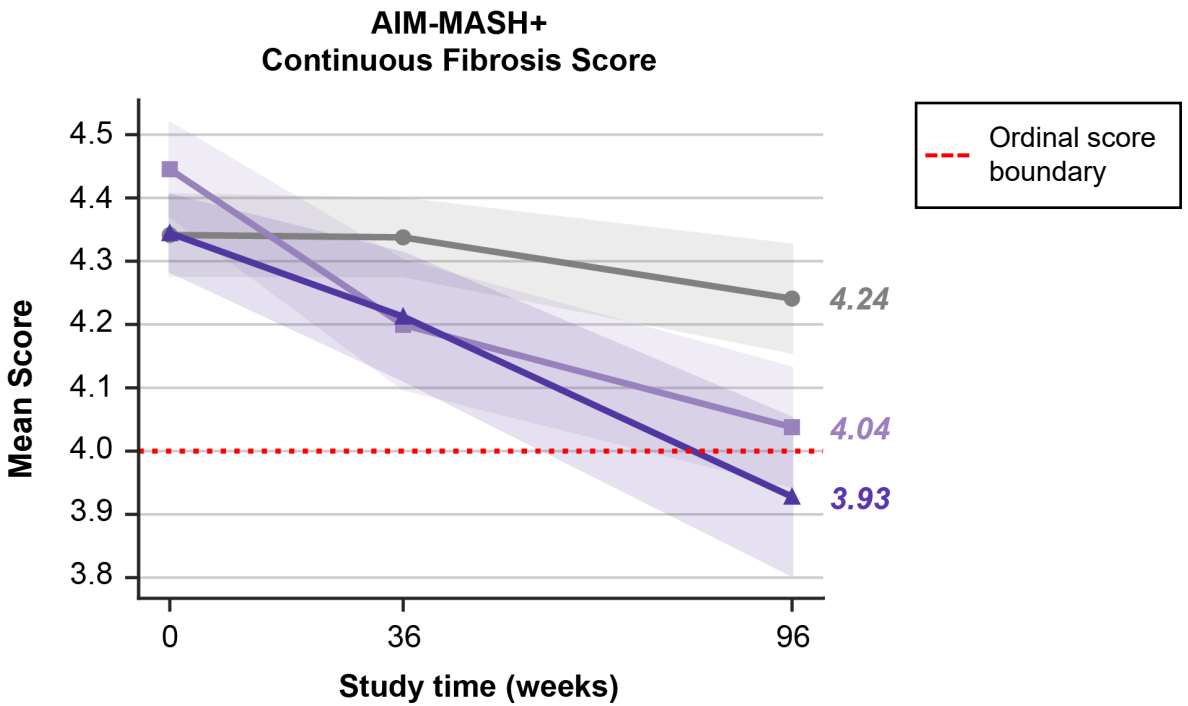

Comparison to Placebo	Week 36	Week 96
28 mg	*** p<0.001	*** p<0.0001
50 mg	*** p<0.001	*** p<0.0001

Comparison to Placebo	Week 36	Week 96
28 mg	n.s. p=0.062	* p=0.011
50 mg	n.s. p=0.247	** p=0.002

Shaded regions represent standard error.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (ANCOVA)
AIM-MASH+ is For Research Use Only. Not for use in diagnostic procedures.

PathAI AIM MASH+

Aim

Evaluate the change in liver histology with efruxifermin in the SYMMETRY trial that enrolled patients with F4c MASH using AI-powered digital pathology:

1. AIM-MASH+ continuous NAS and fibrosis scores[1]
2. **LiverExplore quantification of fibrosis and cellular composition, including fibrosis, tissue, and cellular changes[2]**

[1]Iyer, J.S., Juyal, D., Le, Q. et al. *Nat Med* **30**, 2914–2923 (2024). [2]Gerardin, Y., Stanford-Moore, A., Patel, N. et al. *medRxiv* 2025.06.12.25328580 (2025).

AIM-MASH+ and LiverExplore are For Research Use Only. Not for use in diagnostic procedures.

LiverExplore Provides AI-Powered Cell, Tissue, and Fibrosis Classification and Quantification from H&E-stained Tissue

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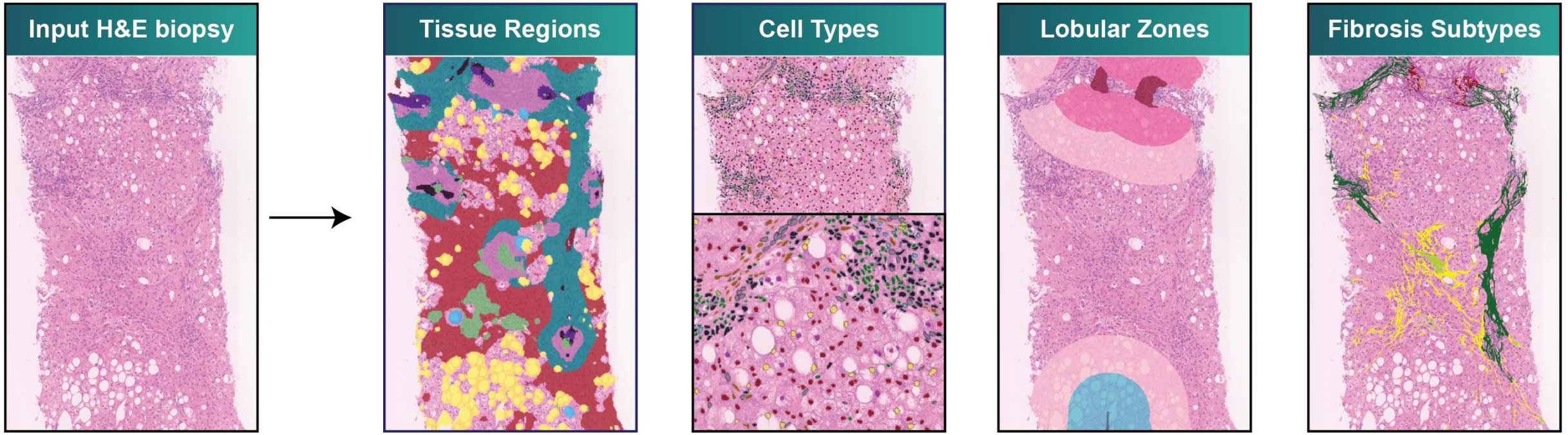


Tissue Regions

- Hepatocellular ballooning
- Lobular inflammation
- Portal inflammation
- Interface hepatitis
- Normal hepatocyte region
- Steatosis
- Bile duct
- Blood vessel
- Normal interface

Cell Types

- Plasma cell
- Neutrophil
- Macrophage
- Lymphocyte
- Eosinophil
- Fibroblast
- Steatotic hepatocyte
- Normal hepatocyte
- Ballooned hepatocyte
- Other hepatocyte
- Other cell

Lobular Zones

- Zone 1
- Zone 2
- Zone 3
- Portal tract
- Central vein

Fibrosis Subtypes

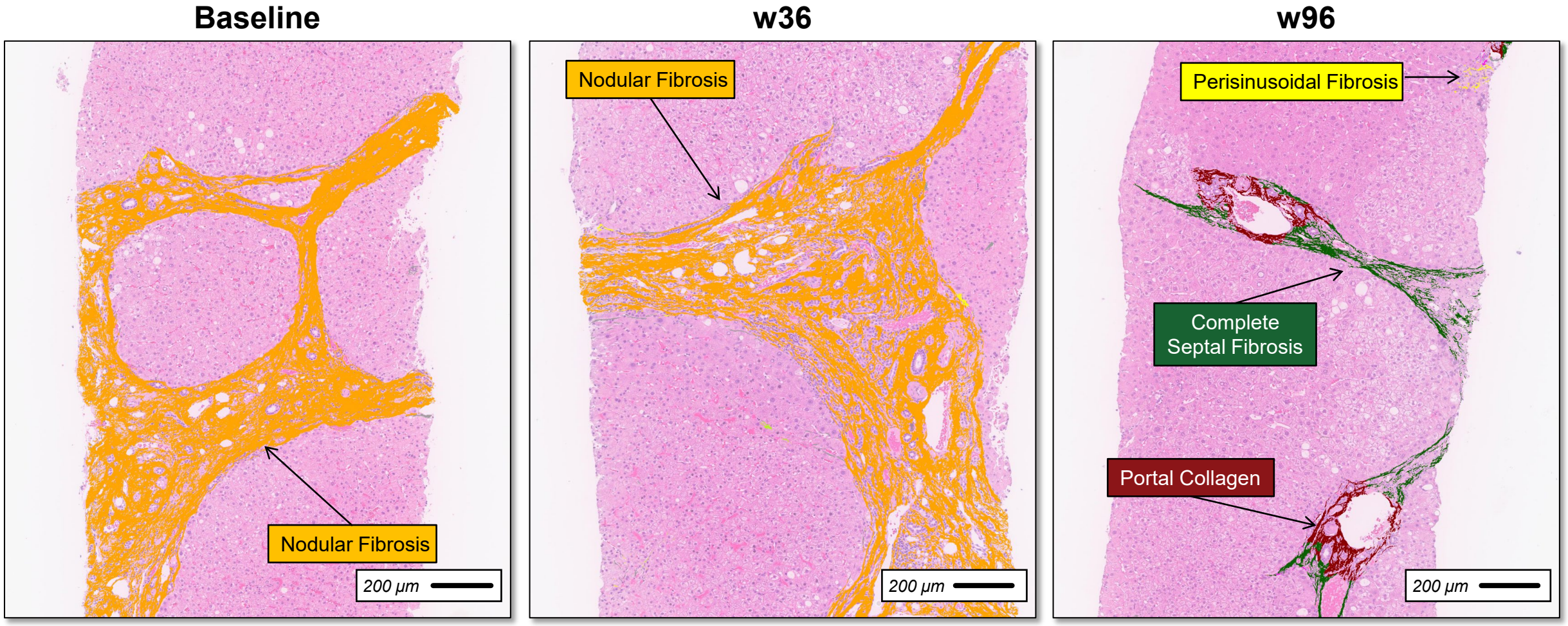
- Structural collagen
- Portal collagen
- Perivenular fibrosis
- Periportal fibrosis
- Perisinusoidal fibrosis
- Incomplete septal fibrosis
- Complete septal fibrosis
- Nodular fibrosis

Gerardin, Y., Stanford-Moore, A., Patel, N. et al. *medRxiv* 2025.06.12.25328580 (2025).

LiverExplore is For Research Use Only. Not for use in diagnostic procedures.

PathAI LiverExplore™

Efruxifermin associated with time and dose dependent improvements in total, early, and advanced fibrosis



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Efruxifermin associated with time and dose dependent improvements in total, early, and advanced fibrosis

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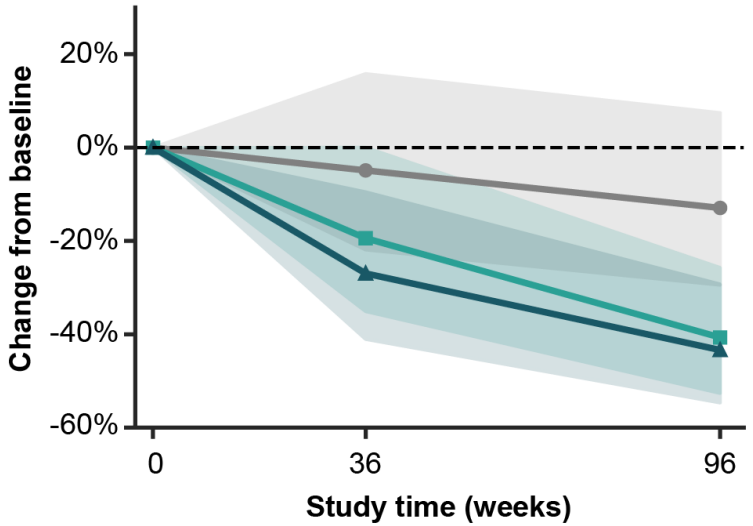
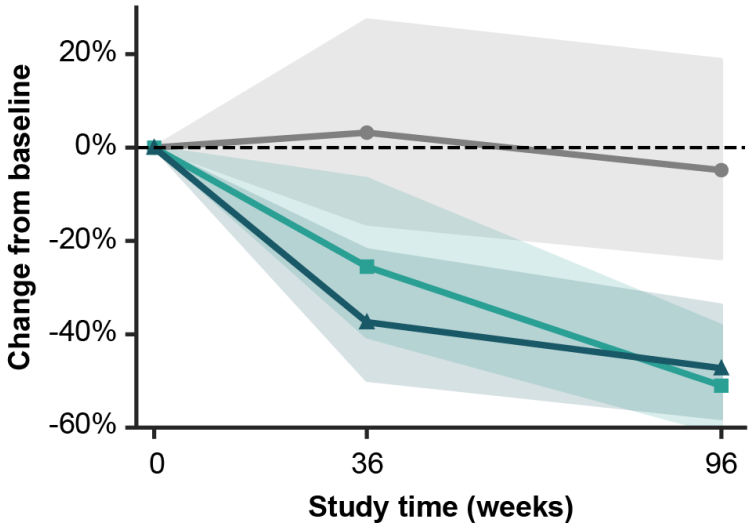
Total Fibrosis
(Periportal, Perisinusoidal, Incomplete Septal, Complete Septal, and Nodular Fibrosis)



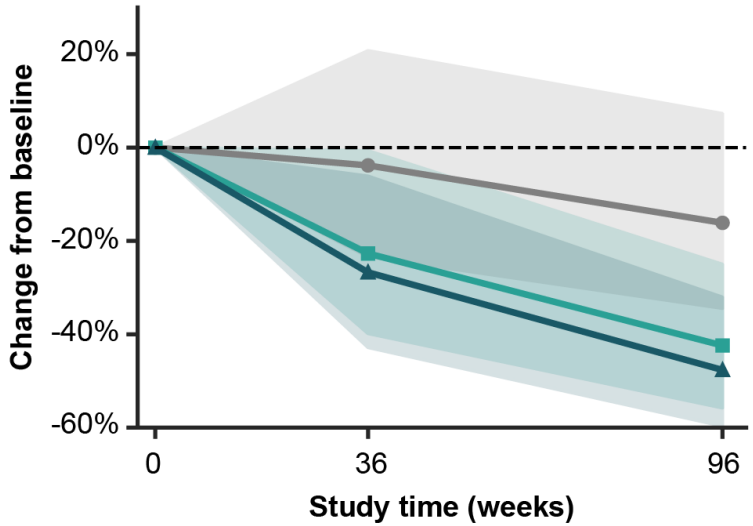
Comparison to Placebo	
28 mg	n.s. p=0.204
50 mg	* p=0.040

Early-Stage Fibrosis
(Periportal and Perisinusoidal Fibrosis)



Comparison to Placebo		
28 mg	* p=0.016	*** p<0.001
50 mg	*** p<0.001	*** p<0.001

Advanced Fibrosis
(Complete Septal and Nodular Fibrosis)



Comparison to Placebo		
28 mg	n.s. p=0.149	*** p=0.021
50 mg	n.s. p=0.067	*** p=0.003

Fibrosis subtypes are measured as areas relative to the area of evaluable tissue. Shaded regions represent 95% confidence intervals.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (ANCOVA)

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Efruxifermin associated with improvement in hepatocyte phenotype

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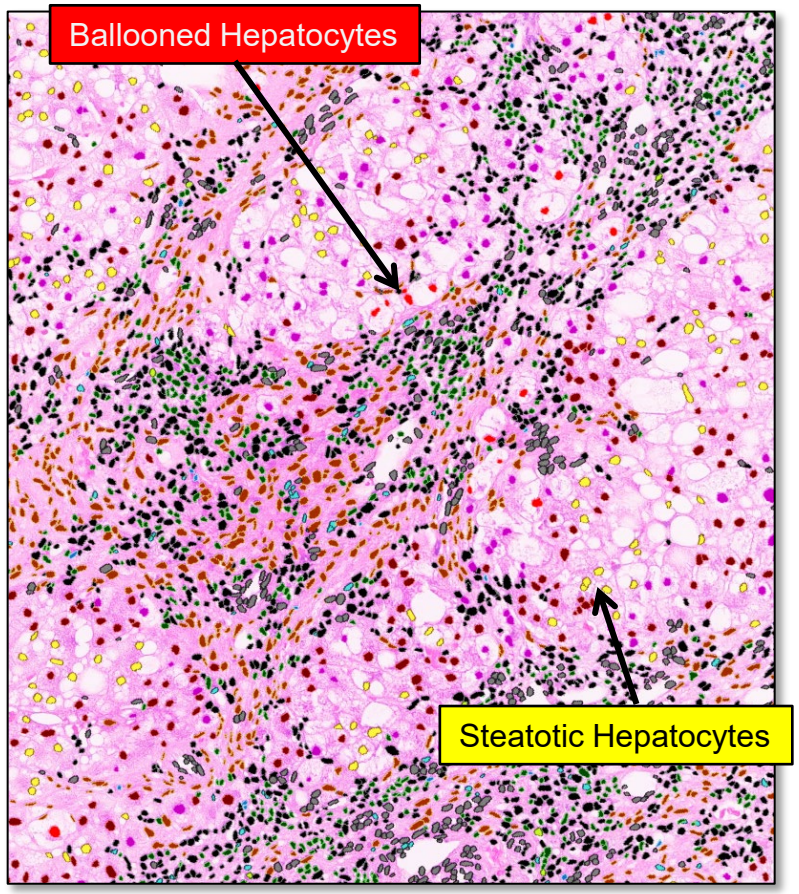
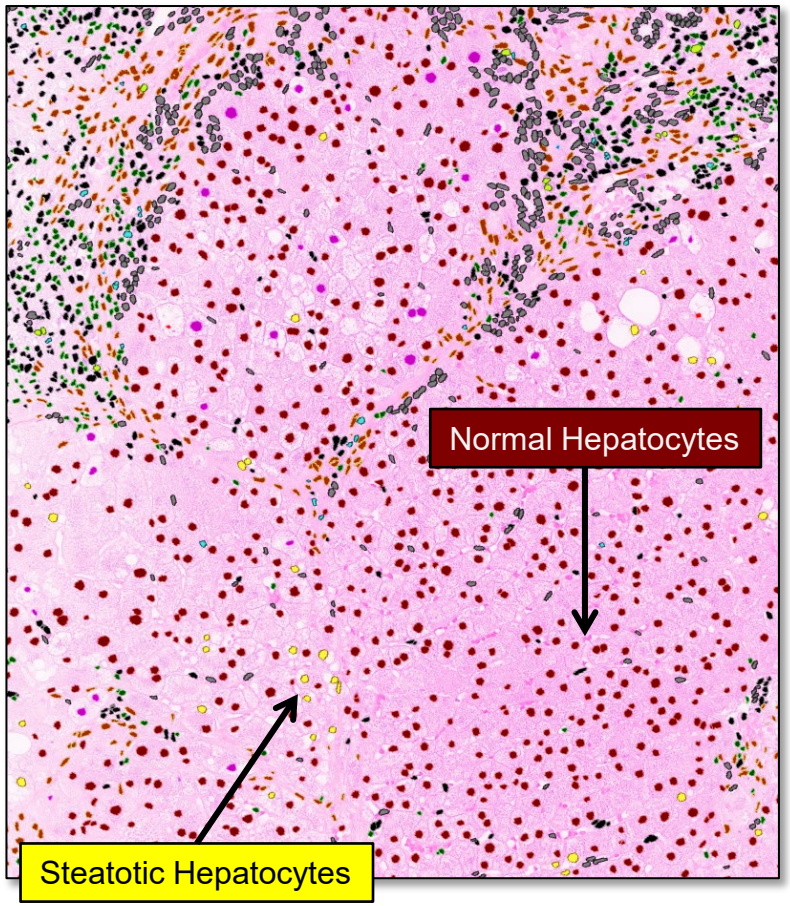
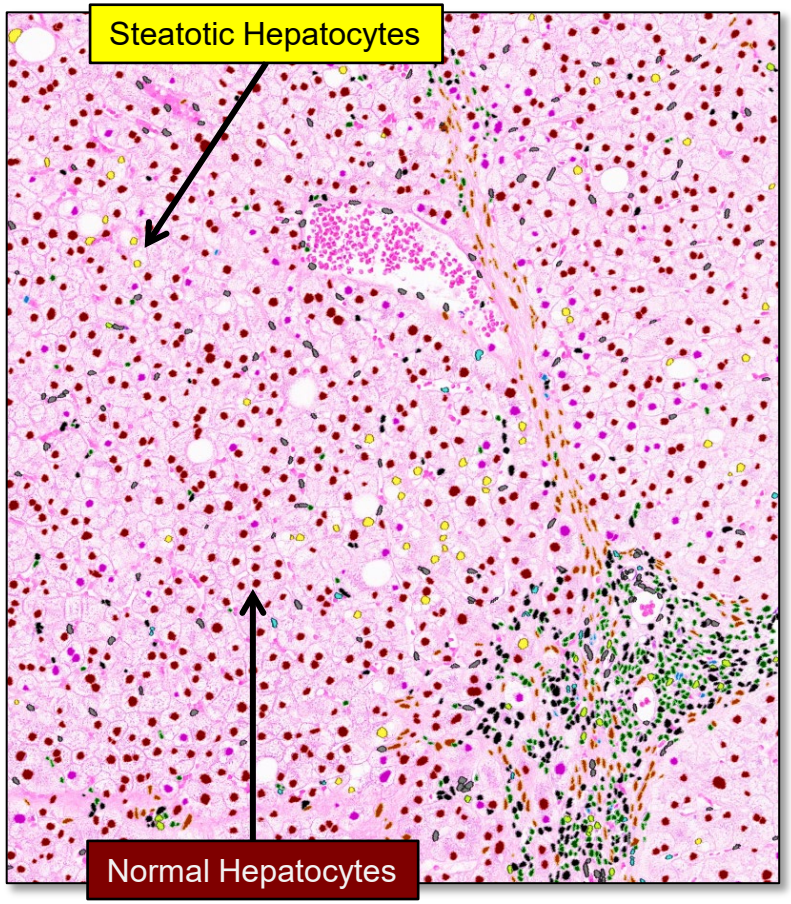
Baseline



w36



w96



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Efruxifermin associated with improvement in hepatocyte phenotype

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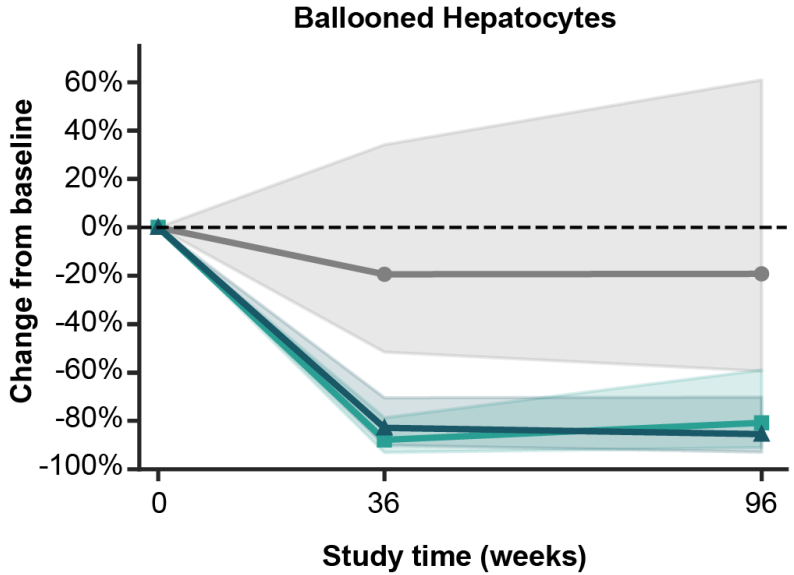

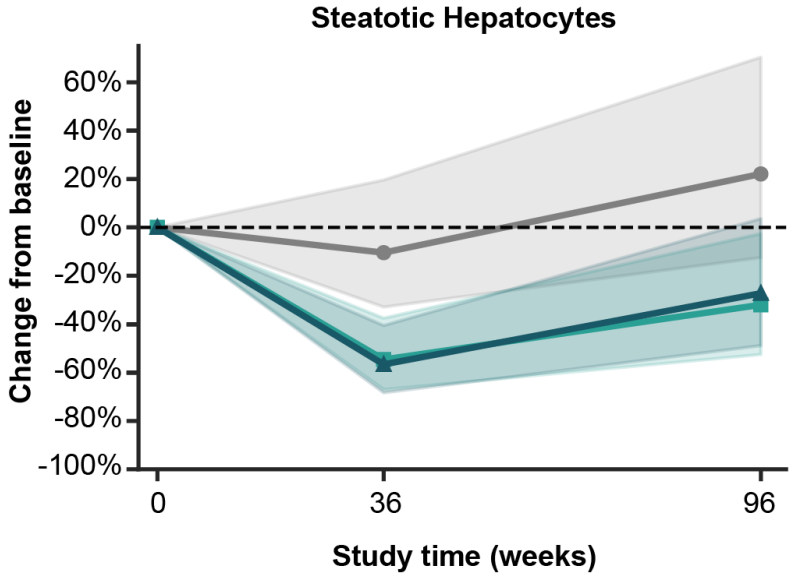

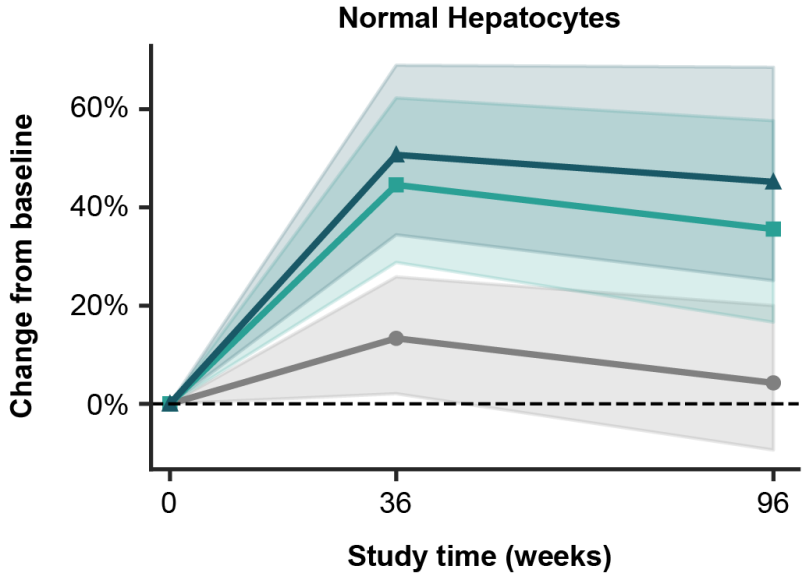

Comparison to Placebo				
28 mg	***	p<0.001	**	p=0.001
50 mg	***	p<0.001	***	p<0.001

Comparison to Placebo				
28 mg	***	p<0.001	**	p=0.008
50 mg	***	p<0.001	*	p=0.017

Comparison to Placebo				
28 mg	***	p<0.001	**	p=0.004
50 mg	***	p<0.001	***	p<0.001

Cell types are quantified as counts relative to the number of total cells. Shaded regions represent 95% confidence intervals.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (ANCOVA)

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Efruxifermin associated with improvement in immune cell phenotype

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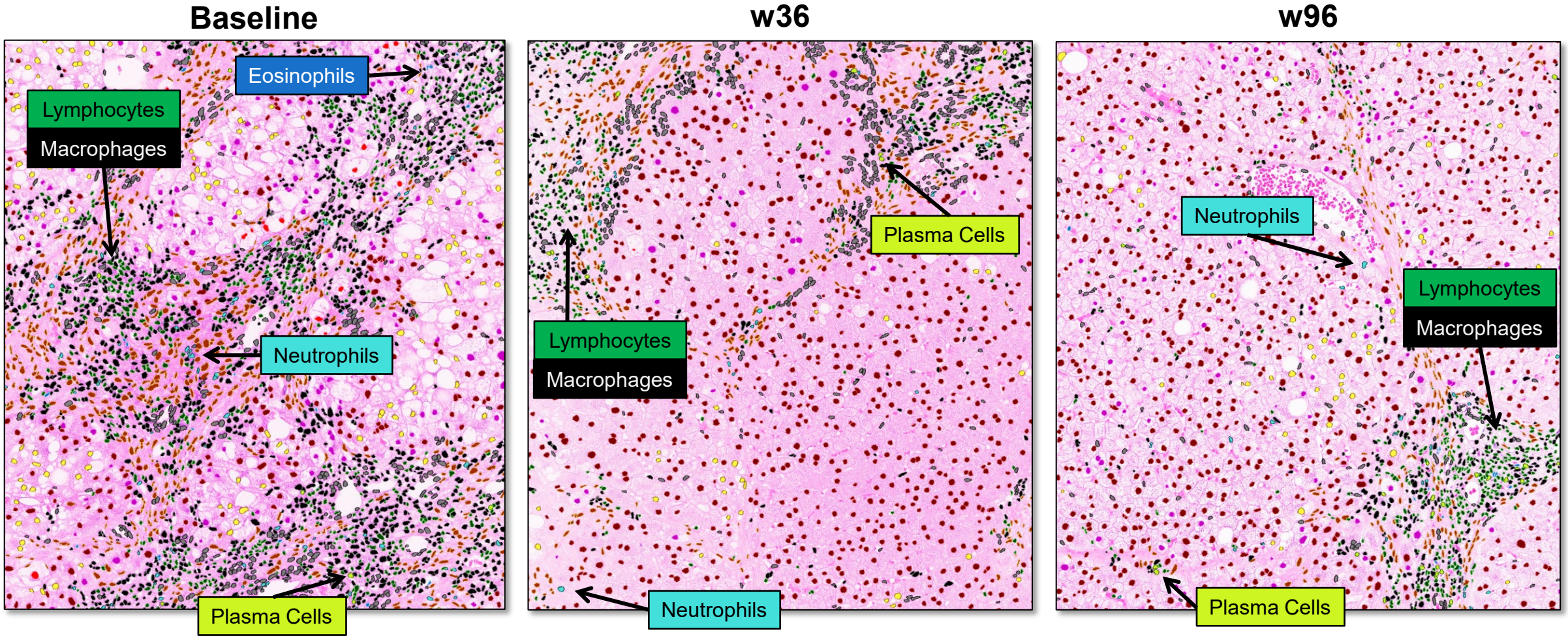

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Efruxifermin associated with improvement in immune cell phenotype

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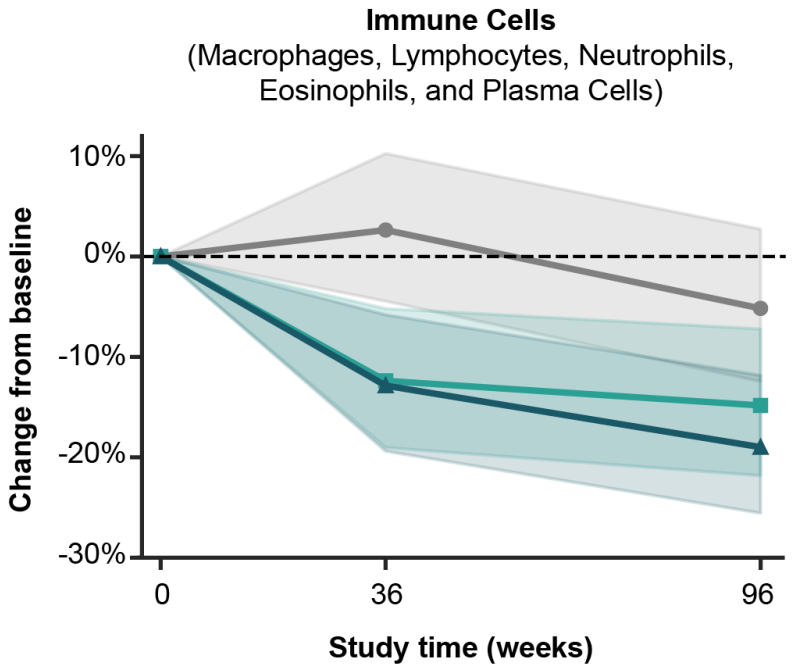

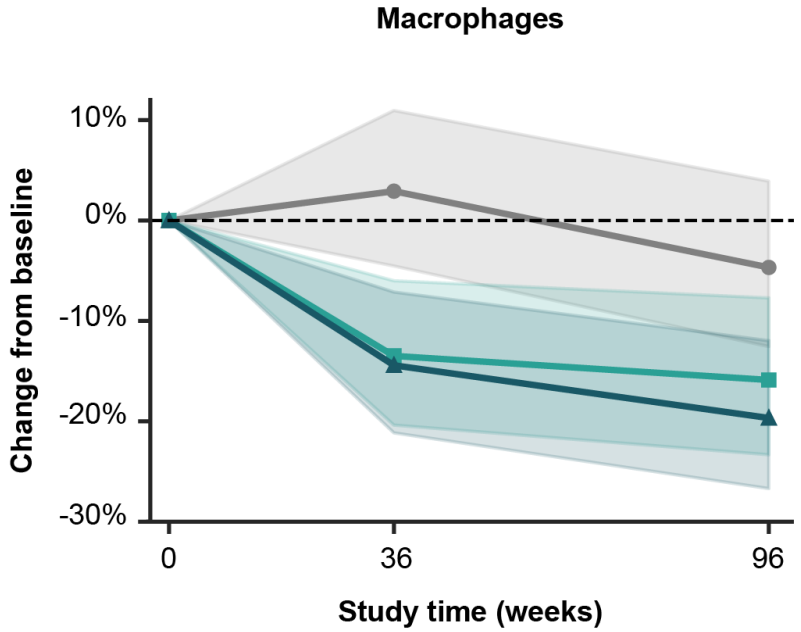

Comparison to Placebo		
28 mg	** p=0.001	* p=0.041
50 mg	*** p<0.001	** p=0.003

Comparison to Placebo		
28 mg	*** p<0.001	* p=0.028
50 mg	*** p<0.001	** p=0.002

Cell types are quantified as counts relative to the number of total cells. Shaded regions represent 95% confidence intervals.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (ANCOVA)

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Summary

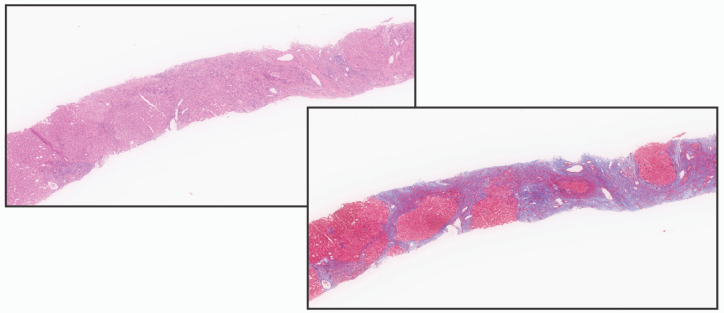
- We conducted a post hoc analysis of the SYMMETRY trial that enrolled participants with MASH and compensated cirrhosis (F4c) using AI-powered digital pathology.
- Efruxifermin was associated with improvements in:
  - continuous fibrosis and steatohepatitis scores (**AIM-MASH+**)
  - total, early, and late-stage fibrosis (**LiverExplore**)
  - hepatocyte phenotype: reduced steatotic and ballooned hepatocytes, and increased normal hepatocytes (**LiverExplore**)
- Results are consistent with the robust antifibrotic effects of efruxifermin previously observed with conventional histology and noninvasive measures.
- Results indicate a potential beneficial effect of efruxifermin on liver function.
- The phase 3 clinical trial of efruxifermin in individuals with compensated cirrhosis is currently enrolling.
  - SYNCHRONY Outcomes: NCT06528314

Summary

- Digital pathology algorithms allow more granular study of anti-MASH therapeutics.
  - **AIM-MASH+** allows more precise measurement of disease severity through continuous CRN scores
  - **LiverExplore** quantifies components of the liver microenvironment, yielding cellular-level resolution of drug-induced effects

AIM MASH+ | Continuous MASH CRN Score
as a measure of disease severity[1]

Input:
Paired H&E-stained & Trichrome-stained images

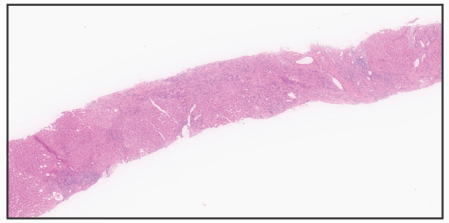


Output:
Continuous MASH CRN scores

Steatosis	1.843
Lobular Inflammation	1.943
Ballooning	2.353
Fibrosis	4.171

LiverExplore™ | Spatially-respolved liver composition
for deeper biological insights[2]

Input:
Single H&E-stained image



Output:
Quantitative histologic features

Proportion of steatotic hepatocytes to all cells in evaluable tissue	0.0436
Proportion of steatosis tissue area to evaluable tissue area	0.128
Proportion of advanced fibrosis area to evaluable tissue area	0.086
Proportion of early-stage fibrosis area to evaluable tissue area	0.008

[1]Iyer, J.S., Juyal, D., Le, Q. et al. *Nat Med* **30**, 2914–2923 (2024).; [2]Gerardin, Y., Stanford-Moore, A., Patel, N. et al. *medRxiv* 2025.06.12.25328580 (2025).

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PathAI **Booth #1158**

Thank you!

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