This activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA).

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

CMEO Snack

The FGF21 Frontier in Clinically Significant MASH

This activity is supported by an educational grant from Novo Nordisk Inc.

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LEARNING OBJECTIVE 1

Evaluate the biology of FGF21 within metabolic and fibrotic pathways

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LEARNING OBJECTIVE 2

Assess emerging clinical evidence for FGF21 analogues in clinically significant MASH

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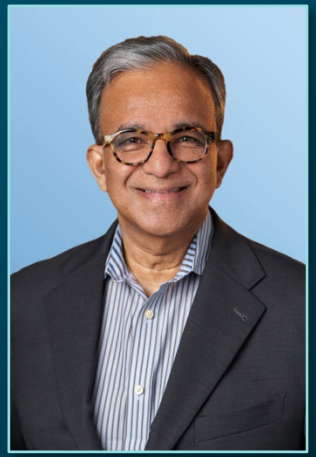
LEARNING OBJECTIVE 3

Appraise the rationale for FGF21-pathway therapy in compensated cirrhosis due to MASH



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Where the Unmet Need Sits in MASH

FIBROSIS STAGE AND MORTALITY RISK

Mortality rises as fibrosis advances

F0-F2:
~0.3 deaths per 100 person-years

→

F3:
~0.9 deaths per 100 person-years

→

F4:
~1.8 deaths per 100 person-years

TREATMENT AVAILABILITY

F2-F3 noncirrhotic MASH

FDA-approved **for noncirrhotic F2–F3 MASH:**
Resmetirom and semaglutide injection
Both indications are approved under the FDA-accelerated approval pathway

F4 compensated cirrhosis

No FDA-approved
pharmacotherapy for MASH-related compensated cirrhosis

Why this matters: Disease risk increases with advancing fibrosis, yet the highest-risk stage (compensated cirrhosis) remains without an approved pharmacologic option.

F2–F4 = fibrosis stages 2–4; MASH = metabolic dysfunction-associated steatohepatitis.
Resmetirom [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/217785s006lbl.pdf. Rinella ME, et al. *Hepatology*. 2023;77(5):1797-1835. Sanyal AJ, et al. *N Engl J Med*. 2021;385(17):1559-1569. Semaglutide [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s031lbl218316s003lbl.pdf.

CME OUTFITTERS



Which statement best describes the biology of FGF21 relevant to its investigation as a therapeutic target in MASH?

A. FGF21 acts primarily in the liver to reduce hepatic inflammation and directly limit fibrotic activity

B. FGF21 signals through FGFR1c/β-klotho to coordinate metabolic effects across the liver, adipose tissue, and other tissues

C. FGF21 acts primarily in the intestine to reduce lipid absorption and thereby decrease hepatic fat accumulation

D. FGF21 signals primarily through hepatic inflammatory pathways to reduce liver injury without substantial systemic metabolic effects

E. I don’t know

Please select your answer now.

CME OUTFITTERS



Which statement best describes the biology of FGF21 relevant to its investigation as a therapeutic target in MASH?

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Please select your answer now.

CME OUTFITTERS

What Is FGF21?

FGF21	FGFR1c + β-klotho	Tissue-specific signaling
Stress-responsive endocrine hormone	Signals through c-isoform FGF receptors, predominantly FGFR1c, with β-klotho as an obligate co-receptor	β-klotho distribution helps define where FGF21 can act: liver, adipose tissue, pancreas, and CNS

Key point:
FGF21 is a multisystem endocrine regulator; its therapeutic rationale in MASH reflects coordinated metabolic and fibrotic pathway effects.

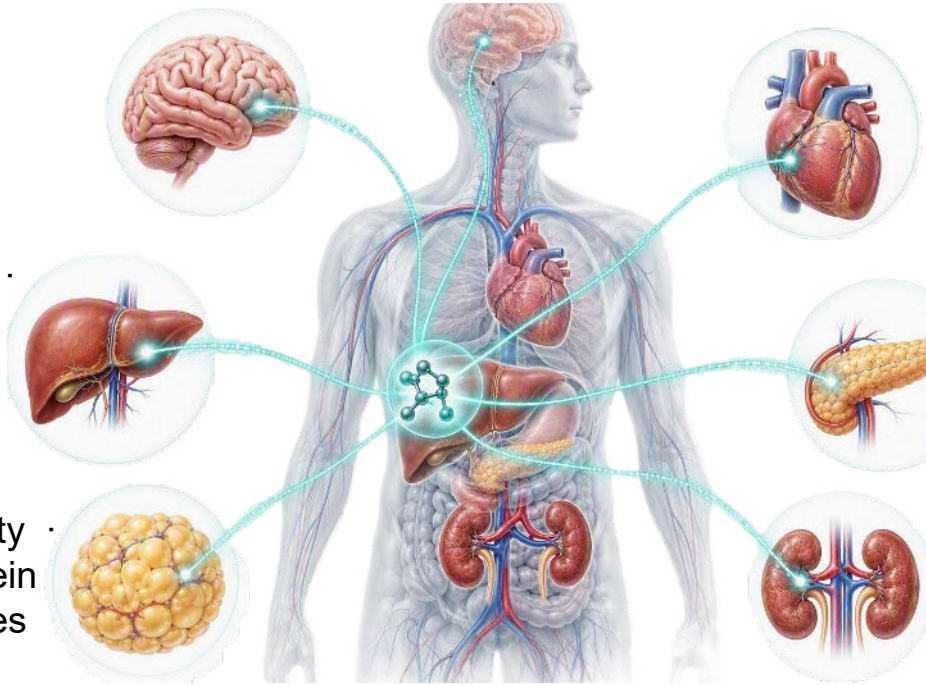
CNS = central nervous system; FGF21 = fibroblast growth factor 21; FGFR1c = fibroblast growth factor receptor 1c.
Geng L, et al. *Nat Rev Endocrinol*. 2020;16(11):654-667. Harrison SA, et al. *J Hepatol*. 2024;81(3):562-576.

CME OUTFITTERS

Pleiotropic Actions of FGF21 Analogues

Native Actions by Tissue

CNS: energy balance and metabolic regulation



Heart: cardioprotective signals (preclinical)

Liver: ↓ de novo lipogenesis · ↓ inflammation · ↑ fatty-acid oxidation

Pancreas: energy balance and metabolic regulation

Adipose: ↑ insulin sensitivity · ↑ adiponectin · ↑ lipoprotein catabolism → ↓ triglycerides

Kidney: renoprotective signals (preclinical)

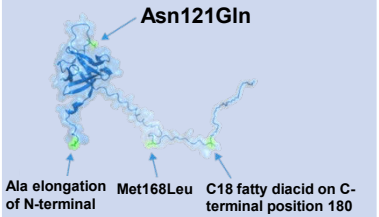
Native FGF21 Couples metabolic improvement with a direct anti-inflammatory/anti-fibrotic effect

Conceptual illustration; scientific context from Harrison SA, et al. *J Hepatol.* 2024;81(3):562-576 and Tan H, et al. *Int J Biol Sci.* 2023;19(1):66-88.

CME OUTFITTERS

Why FGF21 Analogues Rather Than Native FGF21?

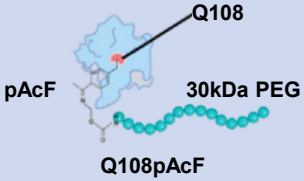
Fatty-diacid conjugation



Zalfermin

$t_{½}$ 5 days
QW

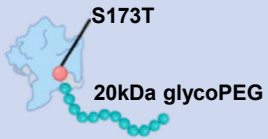
Pegylation



Q108pAcF

Pegbelfermin

$t_{½}$ 1 day
QW

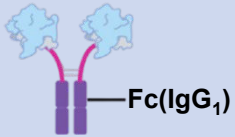


1insM, S173T, R176A

Pegozafermin

$t_{½}$ 3.5 - 4 days
QW or Q2W

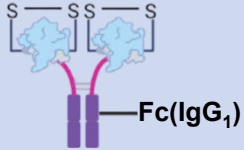
Fc-Fusion



L98R, P171G, A180E

Efruxifermin

$t_{½}$ 3 - 3.5 days
QW



Q27C, G120C

Efimosfermin alfa

$t_{½}$ 21 days
Q4W

MASH Clinical Development Terminated

All FGF21 analogues shown are investigational and are not FDA-approved for MASH.
1insM = insulinoma-associated protein 1; 20kDa = 20 kilodalton; Asn = asparagine; Fc = fragment crystallizable; Gln = glutamine; glycoPEG = glycosylated polyethylene glycol; IgG1 = immunoglobulin G subclass 1; Leu = leucine; Met = methionine; pAcF = partial autocorrelation function; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; t½ = half-life.

Chui ZSW, et al. *Trends Endocrinol Metab*. 2024;35(5):371-384. Harrison SA, et al. *J Hepatol*. 2024;81(3):562-576. Sass-Ørum K, et al. *J Med Chem*. 2024;67(14):11769-11788.

CME OUTFITTERS

How to Interpret the Emerging FGF21 Evidence

Evidence remains investigational

Current efficacy evidence is derived primarily from Phase II/IIb trials; Phase III programs are ongoing.

Do not compare results across trials

Studies differ in design, populations, endpoints, analysis sets, and follow-up duration.

Timing matters

Histologic response may differ depending on when it is assessed; longer-term findings should not be assumed from shorter-duration studies.

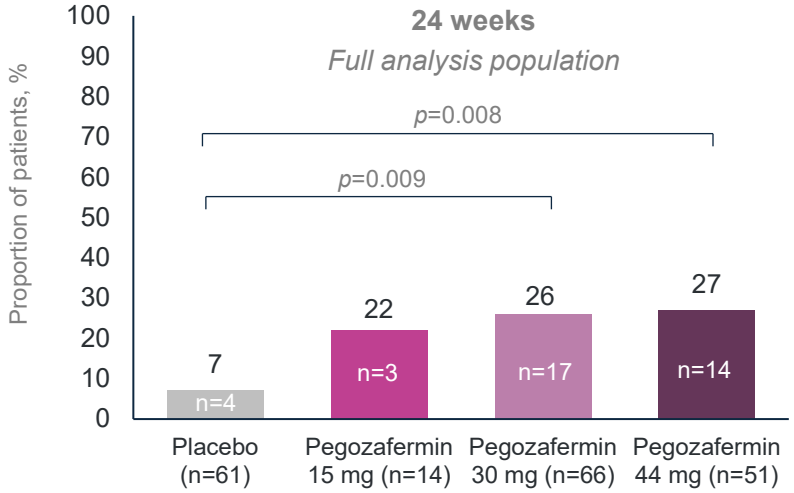
Harrison SA, et al. *J Hepatol*. 2024;81(3):562-576. Loomba R, et al. *Clin Gastroenterol Hepatol*. 2024;22(1):102-112.e9. Noureddin M, et al. *Lancet*. 2026;407(10530):794-804.

CME OUTFITTERS

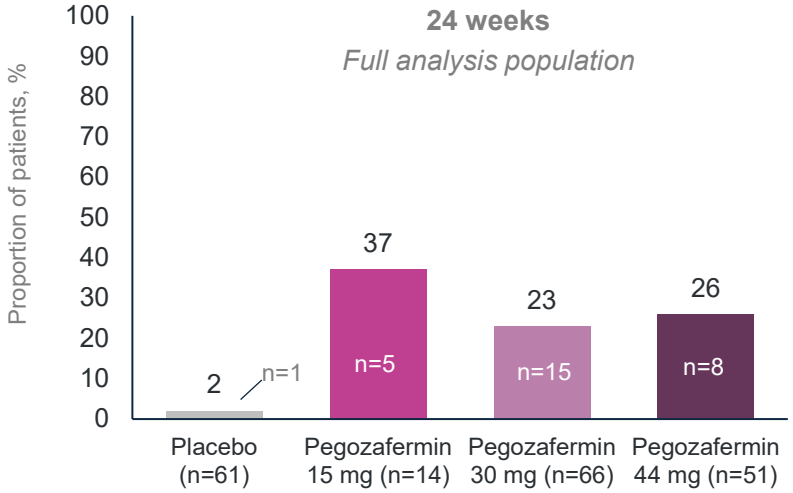
ENLIVEN: Pegozafermin Histologic Outcomes at Week 24 in F2–F3 MASH

Pegozafermin is under clinical investigation and not FDA approved for the treatment of MASH.

Co-primary endpoint: ≥1-stage fibrosis improvement without worsening MASH*



Co-primary endpoint: MASH resolution†,‡



Safety: The most common AEs were GI-related and injection-site erythema. SAEs occurred in 5, 4, 11 and 4% of patients in the pegozafermin 15, 30, 44 mg and placebo groups, respectively. One SAE in the pegozafermin 44 mg group considered drug-related (acute pancreatitis).

Patients were randomized to pegozafermin 15 mg QW, 30 mg QW, 44 mg Q2W, or placebo. *Worsening MASH defined as increase in ballooning, inflammation or steatosis; †Defined as total absence of ballooning and absent or mild inflammation; ‡ Data not statistically analysed for significance in line with established protocol.
AE = adverse event; F = fibrosis; GI = gastrointestinal; SAE = serious adverse event.

Loomba R et al. *N Engl J Med* 2023;389:998-1008.

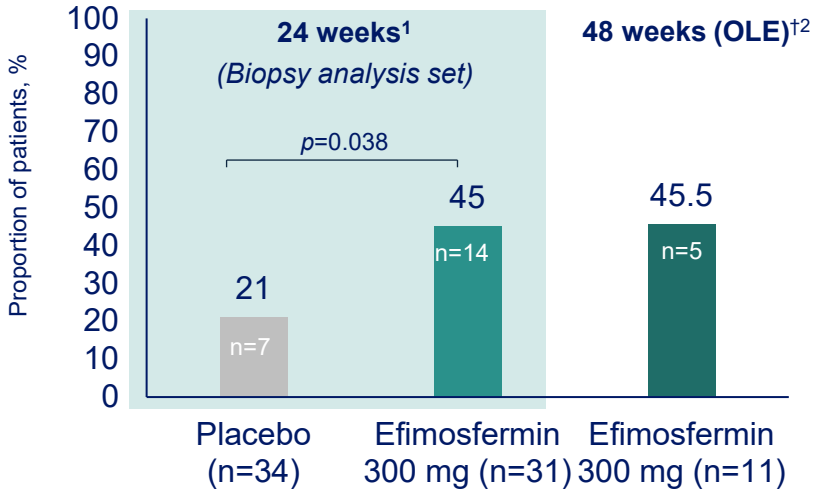
CME OUTFITTERS

Efimosfermin alfa in F2–F3 MASH

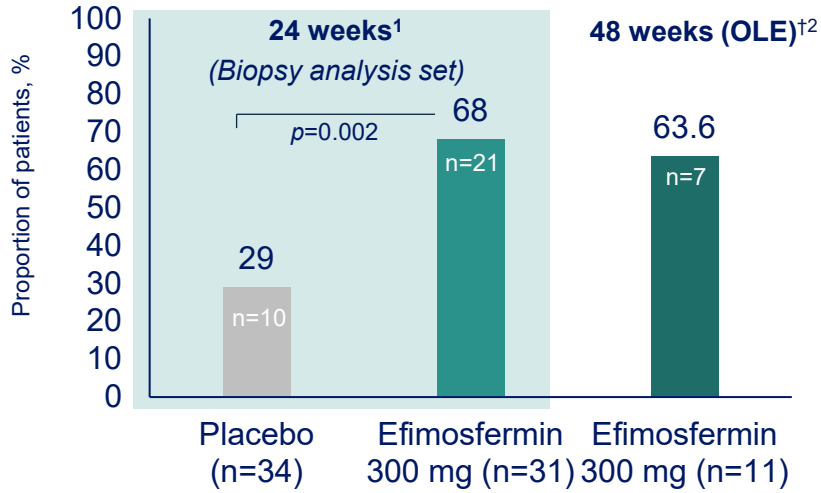
Phase II trial; N=84; primary endpoint: safety and tolerability

Efimosfermin is under clinical investigation and not FDA approved for the treatment of MASH

Exploratory histologic outcome: ≥1-stage fibrosis improvement* without worsening MASH[1,2]



Exploratory histologic outcome: MASH resolution without worsening fibrosis[1,2]



Primary safety endpoint: Most AEs were mild-to-moderate in severity with the most frequent events being GI-related. Two SAEs occurred in the efimosfermin group with one determined as treatment-related‡[1]

Patients were randomized to efimosfermin 300 mg or placebo Q4W.[1,2] *Defined as no increase in NAS for ballooning or lobular inflammation; †Patients who completed the main 24-week study were eligible for the OLE; ‡Grade 3 biliary colic (recurrent disease). This event was most likely due to pre-existing chronic cholelithiasis. NAS = Non-alcoholic Fatty Liver Disease Activity Score; OLE = open-label extension; TEAE = treatment-emergent adverse event.

1. Noureddin M et al. *Lancet* 2026;407(10530):794–804. 2. Noureddin M et al. *Hepatology*. 2026;83(1):E22-E70.

CME OUTFITTERS

Across the Phase II/IIb trials of FGF21 analogues in F2–F3 MASH, placebo fibrosis improvement rates ranged from about 7% to 21%. What does that variability most directly affect?

A. The absolute response rate in treated patients
B. Nothing, because the endpoints were prespecified
C. The apparent size of the treatment effect
D. The safety profile of the class
E. I don’t know

Please select your answer now.

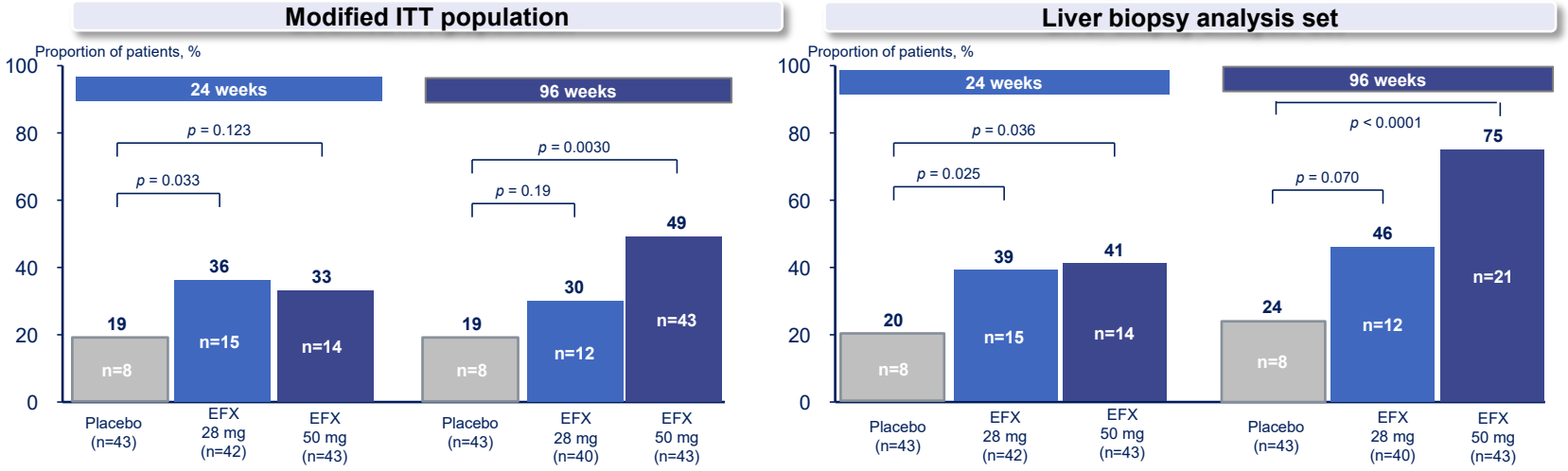
Across the Phase II/IIb trials of FGF21 analogues in F2–F3 MASH, placebo fibrosis improvement rates ranged from about 7% to 21%. What does that variability most directly affect?

A. The absolute response rate in treated patients
B. Nothing, because the endpoints were prespecified
C. The apparent size of the treatment effect
D. The safety profile of the class
E. I don't know

Please select your answer now.

HARMONY: Efruxifermin Histologic Outcomes Through 96 Weeks in F2–F3 MASH

Primary endpoint: ≥1-stage fibrosis improvement without worsening MASH



Safety: Mild-to-moderate GI AEs were more common in efruxifermin groups vs placebo. SAEs occurred in 10%, 16%, and 9% of patients in the efruxifermin 28 mg, efruxifermin 50 mg, and placebo groups, respectively.

Efruxifermin is under clinical investigation and not FDA approved for the treatment of MASH.
EFX = efruxifermin; ITT = intention-to-treat.
Harrison SA, et al. *Lancet Gastroenterol Hepatol*. 2023;8:1080-1093. Noureddin M, et al. *Lancet*. 2025;406:719-730.

CME OUTFITTERS

Why F4 Is Harder to Study

Defining compensated cirrhosis

- Child-Pugh A with no history of a decompensating event
- Not a homogeneous population
- Portal-hypertension severity and hepatic reserve can vary substantially

Why trials are difficult at F4

- Heterogeneity complicates patient enrichment and stratification
- Mature scar may remodel more slowly than pre-cirrhotic fibrosis
- Endpoint selection remains unsettled: histology, noninvasive tests, or clinical decompensation
- Longer follow-up and larger sample sizes may be required

F4 = fibrosis stage 4.

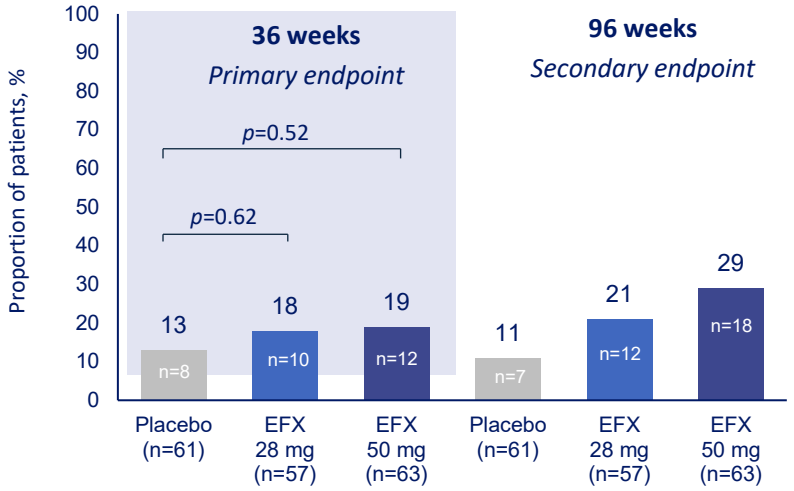
Harrison SA, et al. *Nat Med*. 2023;29(3):562-573. Pericas JM, et al. *Nat Rev Gastroenterol Hepatol*. 2024;21(11):809-823.

CME OUTFITTERS

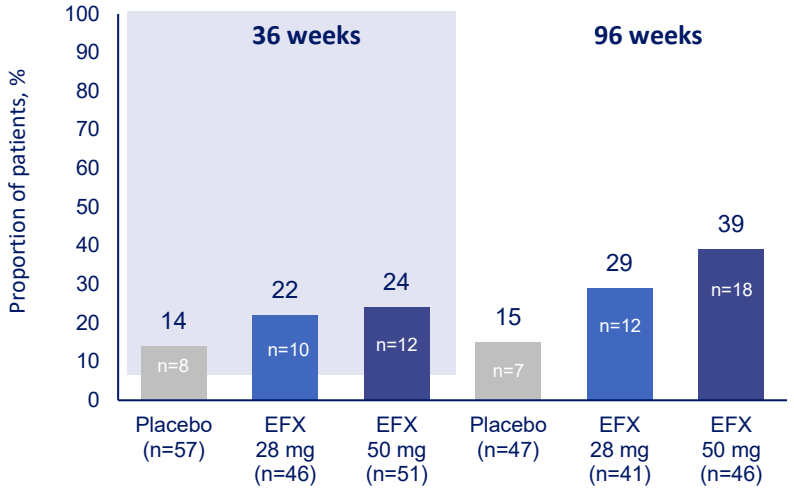
SYMMETRY: Week 36 Primary and Week 96 Secondary Histologic Findings in F4 MASH

Efruxifermin is under clinical investigation and not FDA approved for the treatment of MASH

≥1-stage fibrosis improvement without worsening MASH* (ITT analysis)



≥1-stage fibrosis improvement without worsening MASH* (histology completers)



Safety: Mild-to-moderate GI AEs and administration site reactions were more common in efruxifermin groups vs placebo.
SAEs occurred in 25 and 18% of patients in the efruxifermin and placebo groups, respectively.

Patients were randomized to efruxifermin 28, 50 mg or placebo QW. *Defined as an increase from baseline in any of the NAS sub-scores of ballooning, inflammation, or steatosis.
EFX = efruxifermin. Noureddin M et al. *N Engl J Med* 2025;392:2413–2424.

CME OUTFITTERS



SYMMETRY did not meet its week-36 primary endpoint but showed a fibrosis-improvement signal at week 96. Which interpretation is most defensible?

A. Efruxifermin is ineffective in compensated cirrhosis
B. The trial was underpowered at both time points
C. The week-96 result establishes clinical benefit in compensated cirrhosis
D. The later week-96 signal supports continued study over longer timelines but does not establish clinical benefit
E. I don’t know

Please select your answer now.

CME OUTFITTERS



SYMMETRY did not meet its week-36 primary endpoint but showed a fibrosis-improvement signal at week 96. Which interpretation is most defensible?

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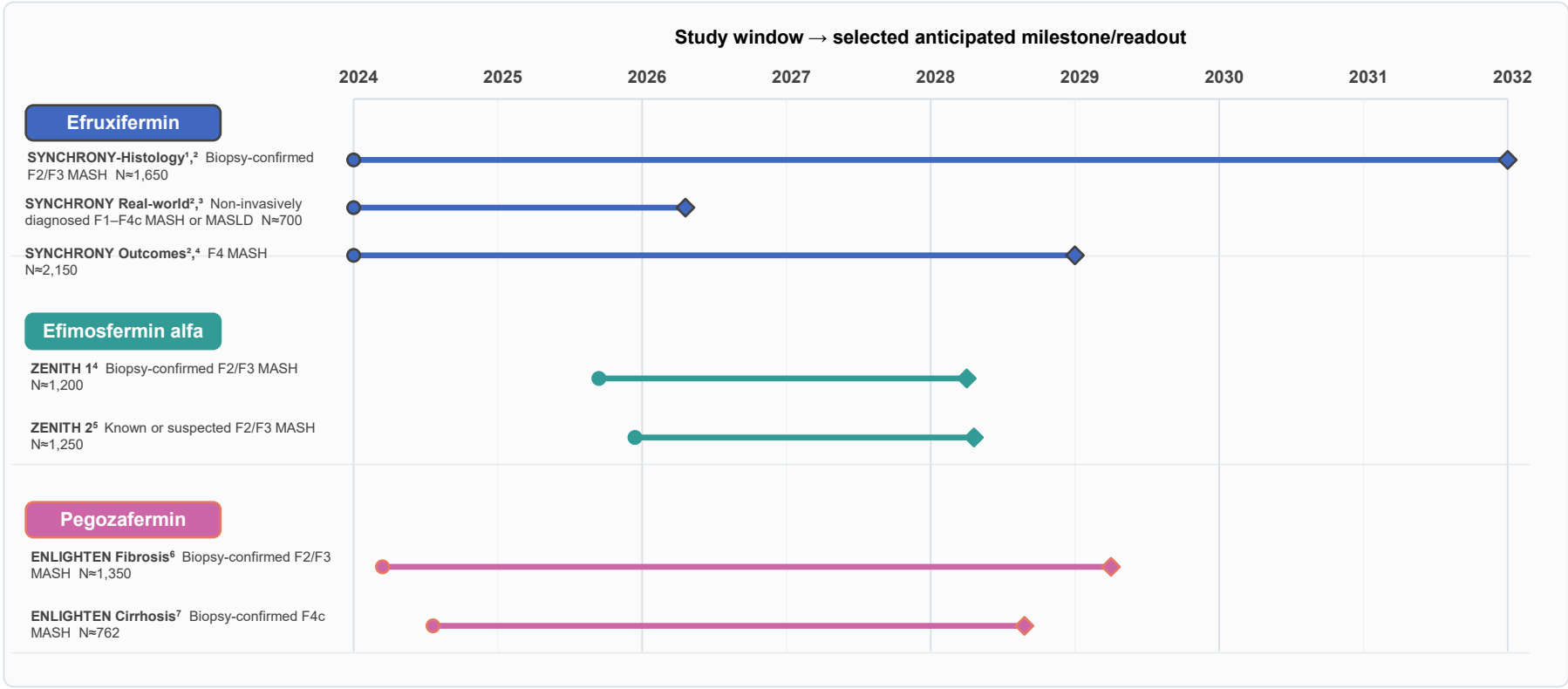
Please select your answer now.

CME OUTFITTERS

Ongoing Phase III Trials of FGF21 Analogues in Liver Disease



These therapies are under clinical investigation and not FDA approved for the treatment of MASH. Dates shown represent selected anticipated study milestones/readouts.
F4c = fibrosis stage 4 compensated cirrhosis; MASLD = metabolic dysfunction-associated steatotic liver disease.
ClinicalTrials.gov. Identifiers: 1. NCT06215716. 2. NCT06161571. 3. NCT06528314. 4. NCT07221227. 5. NCT07221188. 6. NCT06318169. 7. NCT06419374.

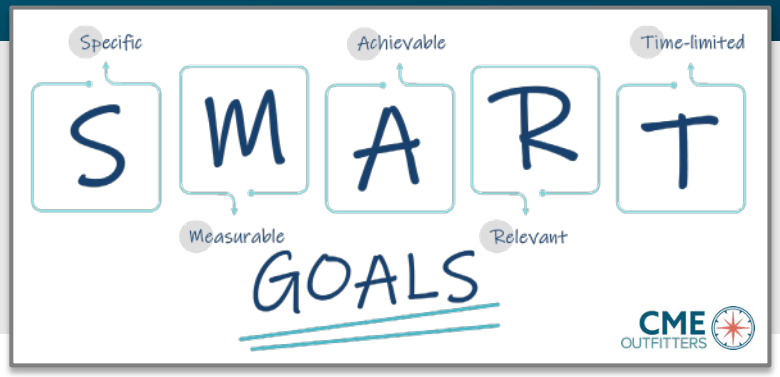
CME OUTFITTERS

Future Perspectives on FGF21 Agents

- Tolerability / side effects
- Position among the current landscape of therapies
- Unmet needs
- What patients benefit most
- What to watch for as phase III data mature

- What do we know about the tolerability of these agents? What side effects are seen most?
- In the broader landscape of therapies for MASH, how do you see these agents fitting in with those already established in care pathways?
- From your experience with these agents in trials, what patients do you see benefiting most (or what unmet needs do you see these agents addressing)?
- What should we be watching for as phase III data continue to mature?

CME OUTFITTERS



Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- Over the next 12 months, review the FGF21 analogue development pipeline at least quarterly, noting agents in active F2–F3 MASH development, their phase, and their metabolic and antifibrotic rationale.
- Within 60 days, critically appraise at least two Phase IIb/III FGF21 analogue trials in F2–F3 MASH, comparing fibrosis improvement, MASH resolution, assessment timing, and durability of response.
- Within 90 days, compare at least two FGF21 studies in compensated cirrhosis with studies enrolling F2–F3 patients, including treatment duration, assessment timing, and endpoint selection, and explain how these differences affect interpretation of antifibrotic effects.

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.