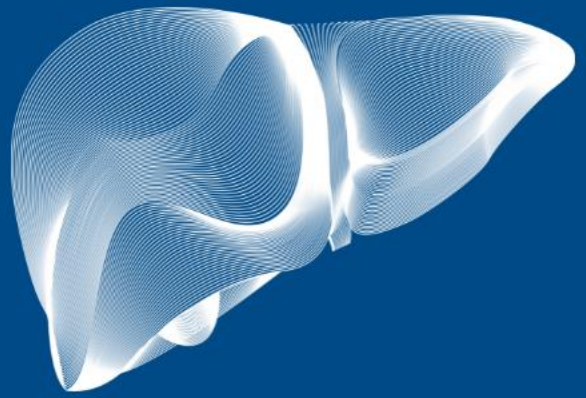

EASL CONGRESS
7-10 May 2025
Amsterdam, the Netherlands

Efruxifermin improves fibrosis in participants with compensated cirrhosis due to MASH: results of a 96-week, randomized, double-blind, placebo-controlled, phase 2b trial (SYMMETRY)

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Disclosures

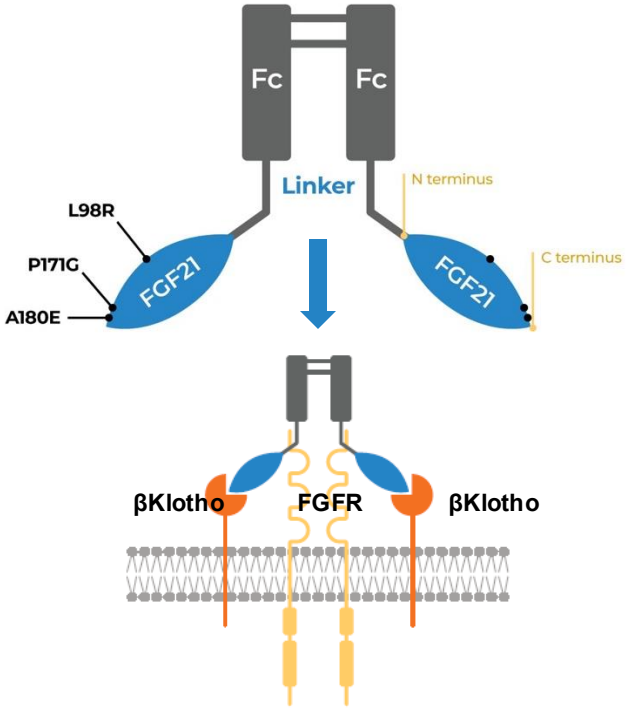
Advisory Board/Consulting: Akero, Altimmune, Alligos, AstraZeneca, BI, Boston Pharma, Cytodyn, GSK, Lilly, Madrigal, Merck, Novo Nordisk, Sagimet, Terns and Takeda.

Principal Investigator for a Drug Study: Allergan, Altimmune, Akero, BI, BMS, Boston Pharma, Conatus, Corcept, Gilead, Galectin, Genfit, GSK, Kowa, Enanta, Madrigal, Lilly, Merck, Novartis, Novo Nordisk, Rivus, Shire, Takeda, Terns, Viking and Zydus.

Stockholder: Rivus Pharma, Cytodyn, Akero and ChronWell.

Speaking bureau: Madrigal.

Efruxifermin (EFX) is an Engineered, Bivalent Fc-FGF21 Analog



- Akero proprietary Fc-FGF21, Point mutations
- Increases half-life from < **2 hours** to **~3 days**
- **High affinity** for β-Klotho
- Better translation to **human** pharmacology
- **Balanced potency** at FGFR1c, 2c, 3c
- **Inactive** at FGFR4

Stanislaus (2017) *Endocrinology;* Lee (2018) *Nature*; Kharitonenkov (2007) *Endocrinology.*

Comprehensive Phase 3 SYNCHRONY Program in ~3500 participants with MASH

Builds on two biopsy-based Phase 2b studies (N ~300) in corresponding patient populations treated for 96 weeks

	HARMONY[1,2]	synchrony HISTOLOGY	symmetry FOR CIRRHOTIC NASH[3]	synchrony OUTCOMES
Fibrosis Stage	**F2-F3**	**F2-F3**	**F4, Compensated**	**F4, Compensated**
Phase	2b	3	2b	3
N	128	1650	182	1150
Weeks	96	240	96	~260

synchrony REAL-WORLD	*Phase 3 study evaluating safety & tolerability in ~700 clinically-diagnosed participants (F1 to F4, compensated) for 52 weeks* *Recruitment Complete*

[1] Harrison (2023) *Lancet Gastroenterol Hepatol;* [2] Harrison (2024) *Clin Gastroenterol Hepatol*; [3] Noureddin (2025) *N Engl J Med*.

Phase 2b SYMMETRY Trial Design: Compensated Cirrhosis (F4) Due to MASH with Liver Histology at 36 and 96 Weeks

Key Inclusion Criteria[1]

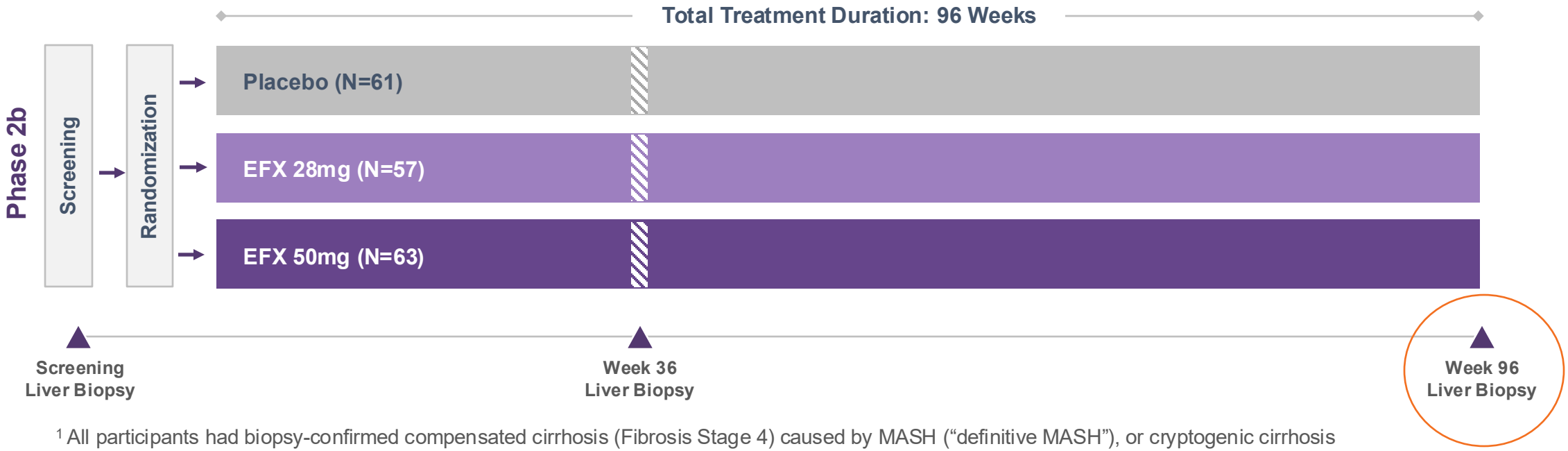
- F4 MASH, Child-Pugh A
- T2D or 2 of 4 components of metabolic syndrome[3]
- Alternative causes of liver disease excluded
- NAS ≥3[2]
- LSM ≥15kPa or ELF >9.8 if no historical liver biopsy
- Platelet count ≥100 x 10^9/L

Phase 2b Primary Endpoint

- ≥1 Stage Fibrosis Improvement with no Worsening of MASH at **Week 36**

Secondary Endpoints

- ≥1 Stage Fibrosis Improvement with no Worsening of MASH at **Week 96**
- MASH Resolution
- Fibrosis Markers
- Liver Injury Markers



[1] All participants had biopsy-confirmed compensated cirrhosis (Fibrosis Stage 4) caused by MASH ("definitive MASH"), or cryptogenic cirrhosis attributed to MASH. Participants with cryptogenic cirrhosis attributed to MASH were limited to approximately 20% of the total study population.
[2] Except those with cryptogenic cirrhosis attributed to MASH.
[3] Obesity, dyslipidemia, elevated blood pressure, and elevated fasting glucose.

SYMMETRY Analysis Sets

	N	Description
Full Analysis Set (FAS) / Safety Set Placebo (N=61) EFX 28mg (N=57) EFX 50mg (N=63)	181	All randomized participants who received at least one dose of study drug
Week 36 Liver Biopsy Analysis Set (LBAS) Placebo (N=57) EFX 28mg (N=46) EFX 28mg (N=51)	154	All participants with baseline and Week 36 biopsy results
Week 96 LBAS Placebo (N=47) EFX 28mg (N=41) EFX 28mg (N=46)	134	All participants with baseline and Week 96 biopsy results

ITT Analyses are based on FAS, where missing biopsy = non-response

Completers Analyses are based on LBAS (Week 36 or Week 96)

All reported results are topline preliminary data.

Baseline Demographics

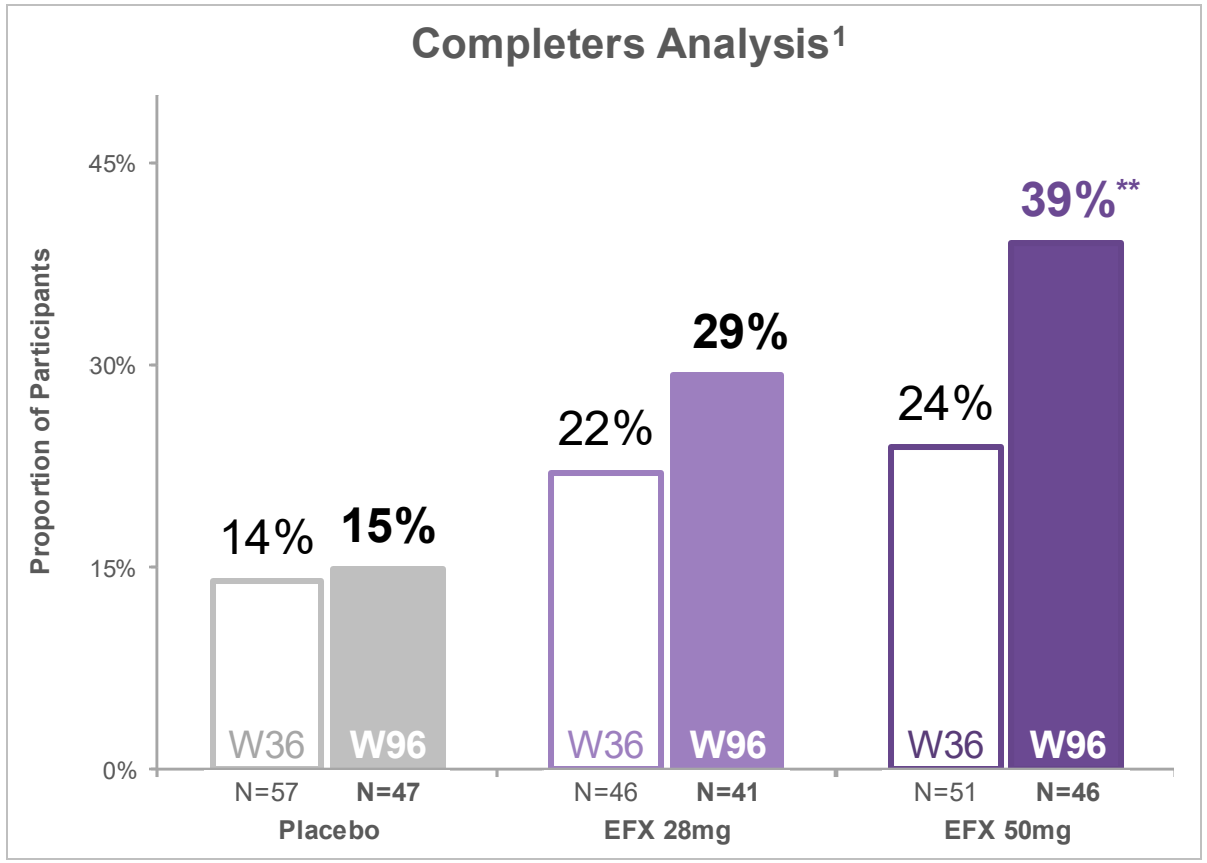
Parameter (Mean)	Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
Age (Years)	61	62	59
Sex (% Female)	62	68	70
BMI (kg/m^2)	36.7	36.1	34.5
Cryptogenic cirrhosis[1] (%)	**26**	**21**	**17**
Enhanced Liver Fibrosis (ELF) Score	10.4	10.6	10.5
Liver Stiffness by VCTE (FibroScan) (kPa)	**24.7**	**24.1**	**24.5**
Alanine Aminotransferase (ALT) (U/L)	40.3	40.1	38.4
Aspartate Aminotransferase (AST) (U/L)	35.5	37.1	37.5
Total Bilirubin (mg/dL)	0.7	0.7	0.7
Platelet count (x10^9/L)	181	183	185
Prothrombin Time International Normalized Ratio (INR)	1.1	1.1	1.1
Albumin (g/dL)	4.3	4.2	4.3
Type 2 Diabetes (%)	82	81	78
HbA1c (%)	6.8	6.8	6.6
Triglycerides (mg/dL)	143	148	159
GLP-1 Receptor Agonist Use (%)	**26**	**19**	**33**
Statin Use (%)	**53**	**46**	**43**

[1]Biopsy-confirmed cryptogenic cirrhosis attributed to MASH

Source Data: FAS; Noureddin (2025) *N Engl J Med*

Significant Improvement in Fibrosis ≥1 Stage with No Worsening of MASH Observed with EFX 50mg at Week 96

Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Weeks 36 and 96[1]



[1] All participants with baseline and Week 36 or 96 biopsies

** p<0.01, versus placebo (CMH test[1])

ITT Analysis (Week 96)[2]

Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
11%	21%	29%*

[2] Missing biopsy = non-responder

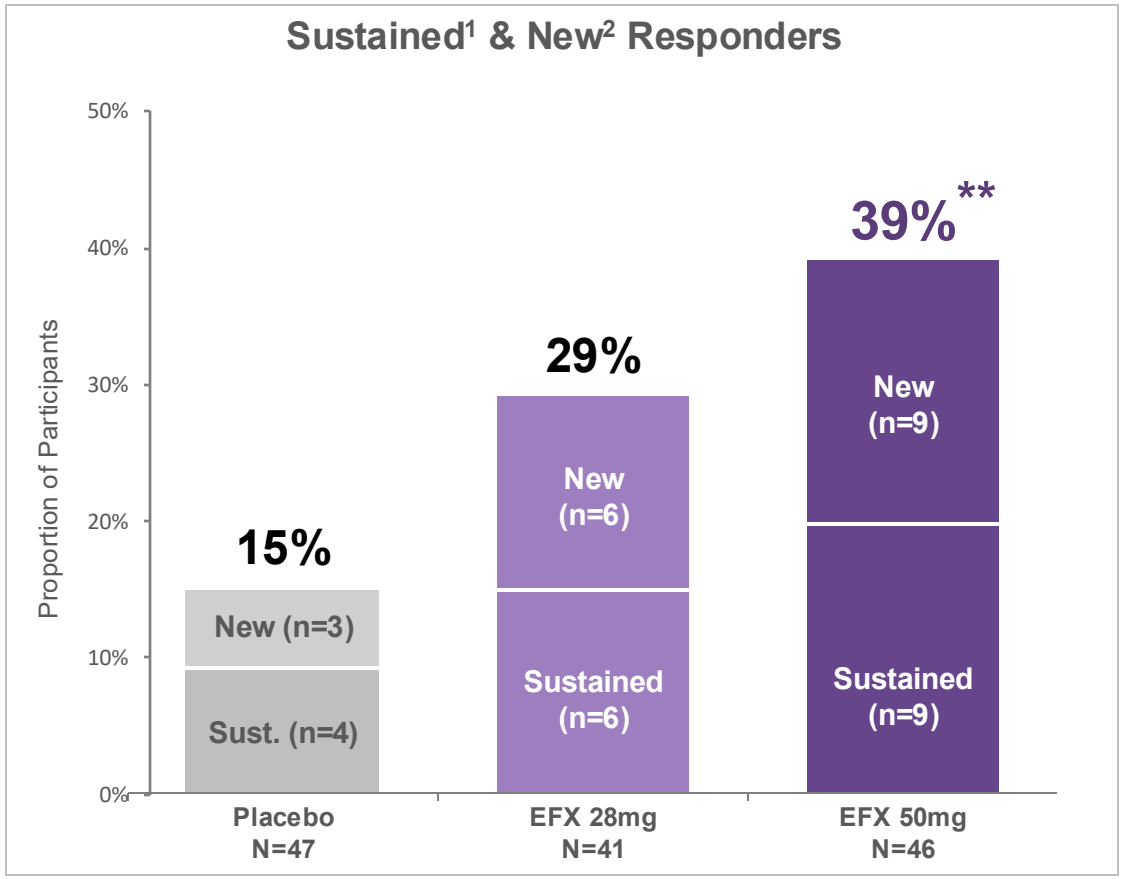
* p<0.05, versus placebo (CMH test)

[1] Cochran-Mantel-Haenszel test

Source Data: LBAS; ITT; Noureddin (2025) *N Engl J Med*

Sustained and Expanded Fibrosis Improvement Observed with Longer Treatment

Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Week 96



[1] Responder at Weeks 36 & 96; [2] Responder at Week 96

** p<0.01, versus placebo (CMH test)

Sustained Response

Proportion of Week 36 Responders with Sustained Response at Week 96[3]

Placebo (N=8)	EFX 28mg (N=9)	EFX 50mg (N=12)
4 (50%)	6 (67%)	9 (75%)

Expanded Response

Proportion of Week 36 Non-Responders with New Response at Week 96[3]

Placebo (N=39)	EFX 28mg (N=32)	EFX 50mg (N=34)
3 (8%)	6 (19%)	9 (26%)

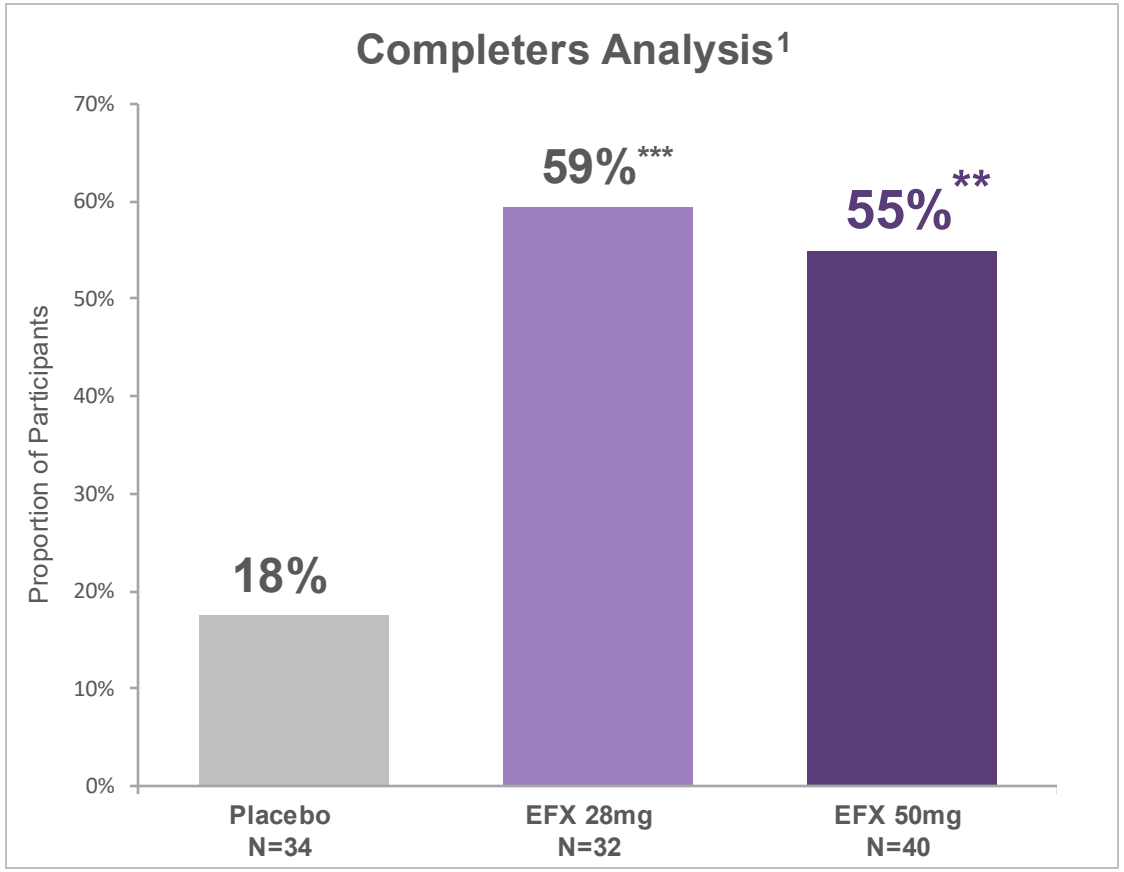
[3] Not analyzed for statistical significance

Source Data: LBAS; Noureddin (2025) *N Engl J Med*

MASH Resolution Observed at Week 96

MASH Resolution

Completers Analysis[1]



[1] All participants with baseline and Week 96 biopsies who had biopsy-confirmed compensated cirrhosis caused by MASH ("definitive MASH") at baseline

** p<0.01, *** p<0.001, versus placebo (CMH test)

ITT Analysis[2]

Placebo (N=45)	EFX 28mg (N=45)	EFX 50mg (N=52)
13%	42%**	42%**

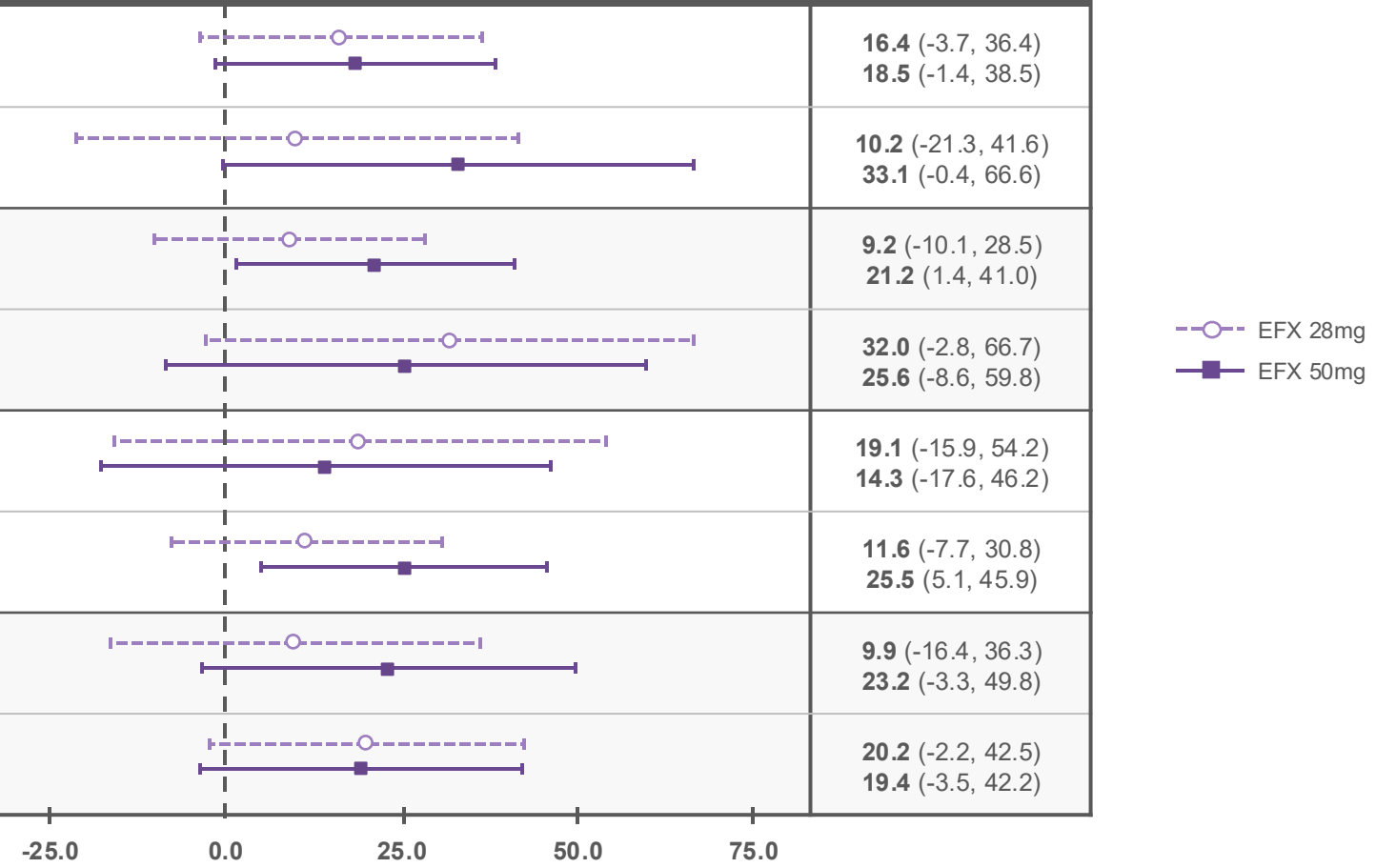
[2] Missing biopsy = non-responder

** p<0.01, versus placebo (CMH test)

Source Data: LBAS subgroup; FAS; Noureddin (2025) *N Engl J Med*

Consistent Response across Multiple Baseline Subgroups for Primary Histological Endpoint at Week 96

Baseline Subgroup	EFX Dose	Estimated Proportion Difference (95% CI) for EFX vs Placebo
Cirrhosis caused by MASH[1]	28mg (N=32) 50mg (N=40)	**16.4** (-3.7, 36.4) **18.5** (-1.4, 38.5)
Cryptogenic Cirrhosis[2]	28mg (N=9) 50mg (N=6)	**10.2** (-21.3, 41.6) **33.1** (-0.4, 66.6)
T2D	28mg (N=33) 50mg (N=36)	**9.2** (-10.1, 28.5) **21.2** (1.4, 41.0)
No T2D	28mg (N=8) 50mg (N=10)	**32.0** (-2.8, 66.7) **25.6** (-8.6, 59.8)
GLP-1RA Use	28mg (N=9) 50mg (N=17)	**19.1** (-15.9, 54.2) **14.3** (-17.6, 46.2)
No GLP-1RA Use	28mg (N=32) 50mg (N=29)	**11.6** (-7.7, 30.8) **25.5** (5.1, 45.9)
Statin Use	28mg (N=17) 50mg (N=19)	**9.9** (-16.4, 36.3) **23.2** (-3.3, 49.8)
No Statin Use	28mg (N=24) 50mg (N=27)	**20.2** (-2.2, 42.5) **19.4** (-3.5, 42.2)

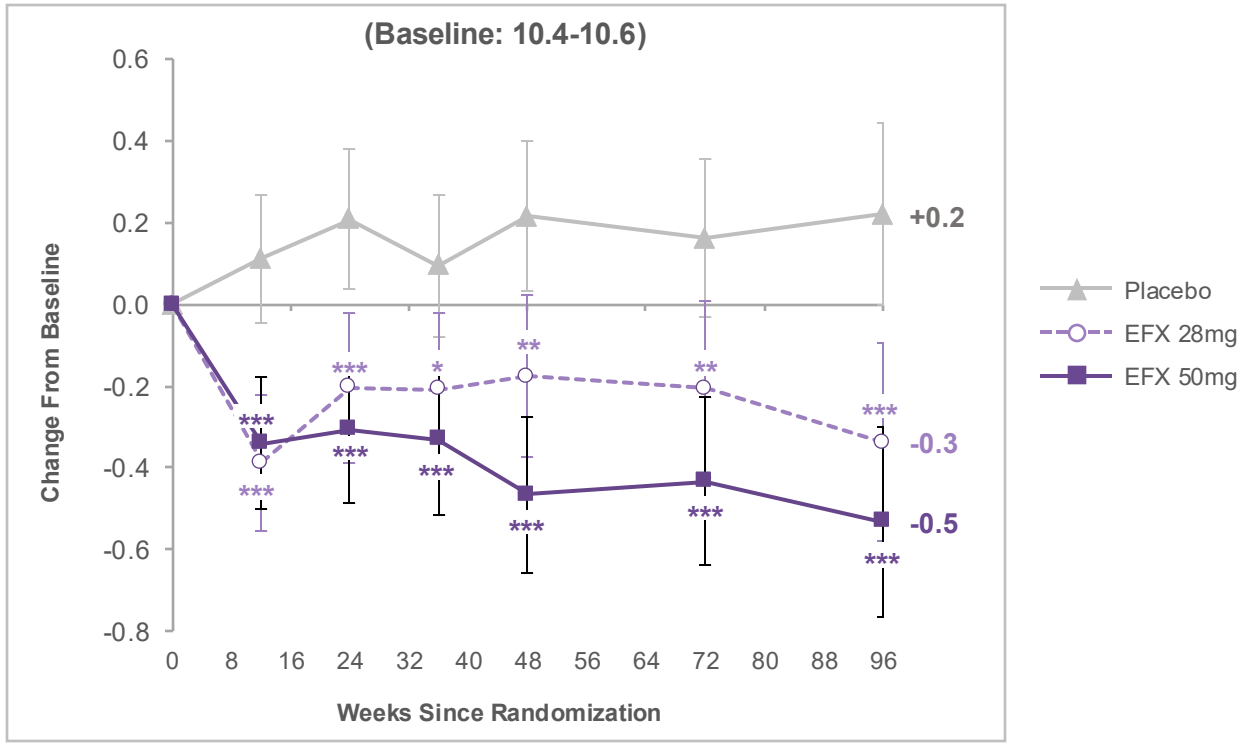


[1] Biopsy-confirmed compensated cirrhosis caused by MASH ("definitive MASH") [2] Biopsy-confirmed cryptogenic cirrhosis attributed to MASH

Source Data: Subgroups of LBAS; Noureddin (2025) *N Engl J Med*

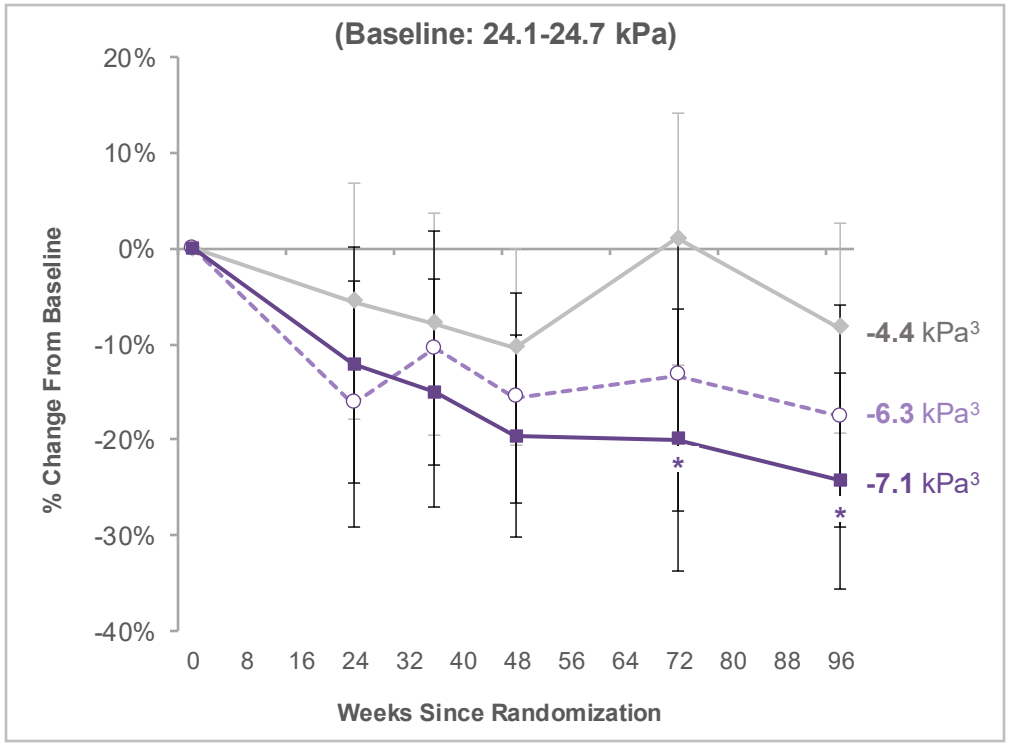
Temporal Pattern for Non-Invasive Tests (NITs) of Fibrosis **Corroborates** Histological Improvement in Cirrhosis

ELF Score[1]



* p<0.05,** p<0.01, *** p<0.001, versus placebo (MMRM)

Liver Stiffness Measurement (kPa)[1,2]



* p<0.05, versus placebo (MMRM)

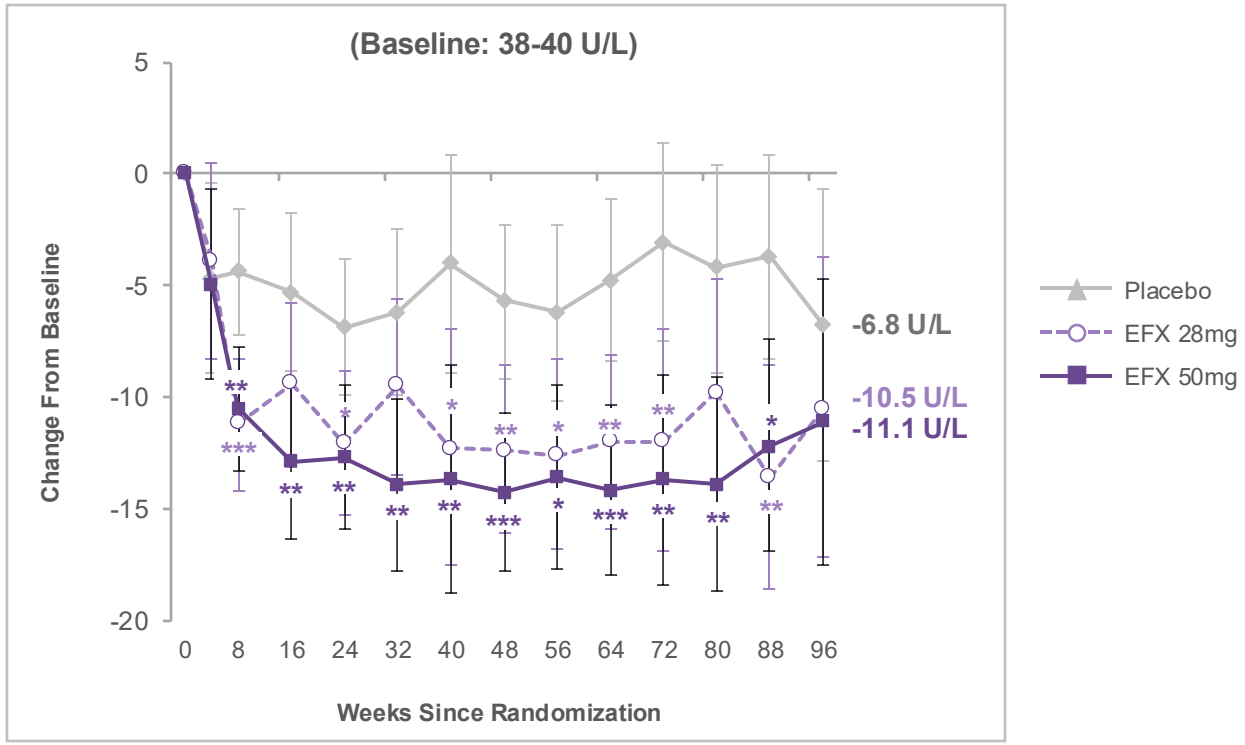
[2]Valid measurements only; [3]LSMean absolute change from baseline

[1]LS mean and 95% CI for the change from baseline

Source Data: FAS (non-missing values only, no imputation); Noureddin (2025) *N Engl J Med*

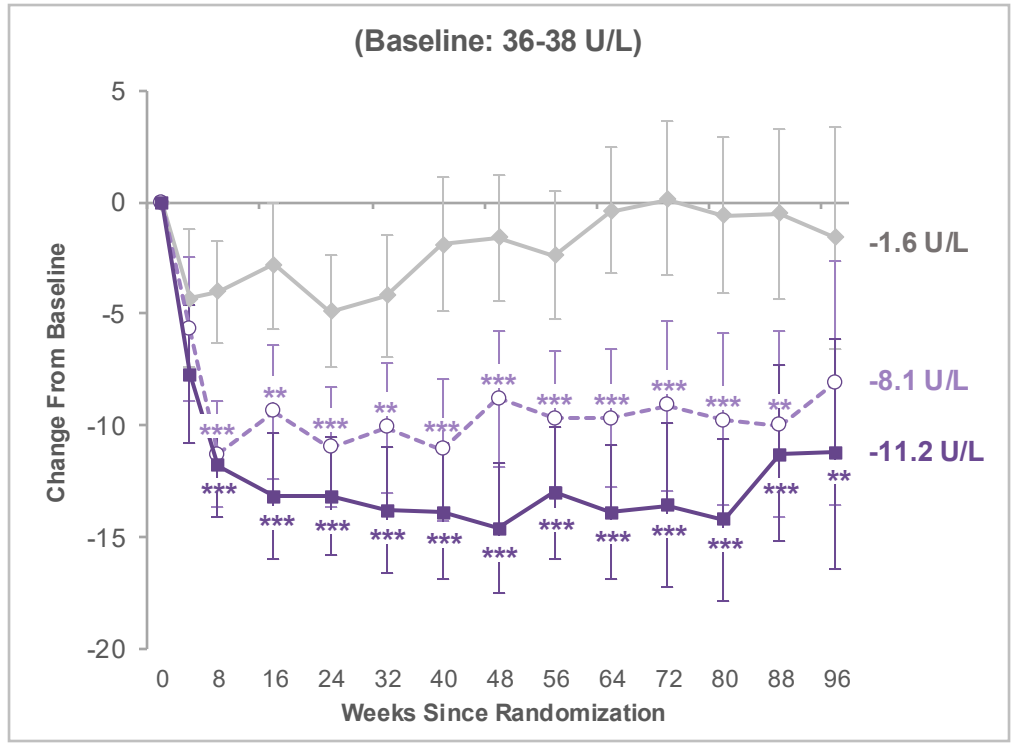
Rapid and Sustained Reductions in **Markers of Liver Injury** through Week 96

ALT (U/L)[1]



* p<0.05,** p<0.01, *** p<0.001, versus placebo (MMRM)

AST (U/L)[1]

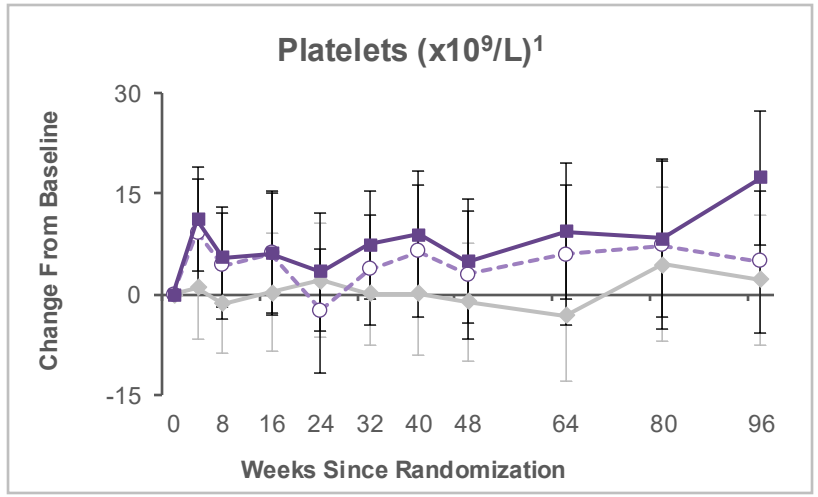


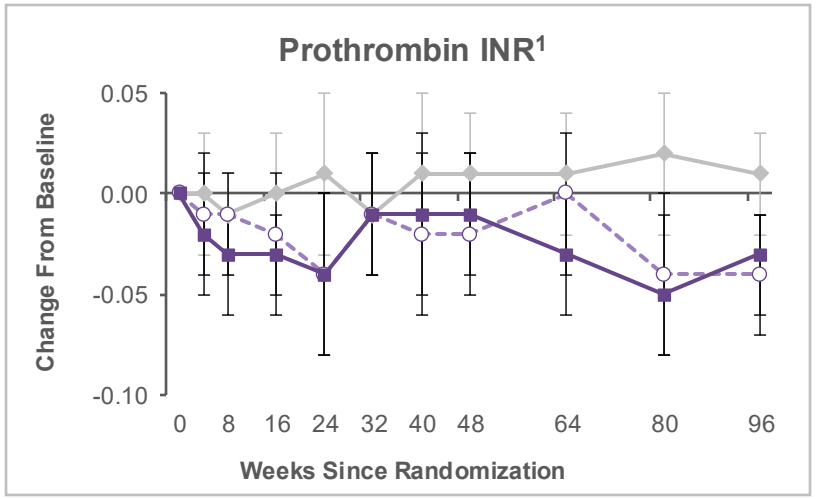
** p<0.01, *** p<0.001, versus placebo (MMRM)

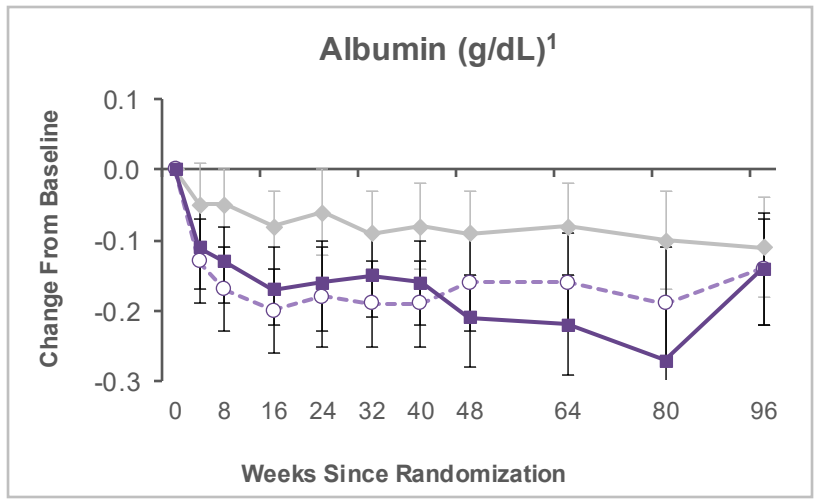
[1]LS mean and 95% CI for the change from baseline

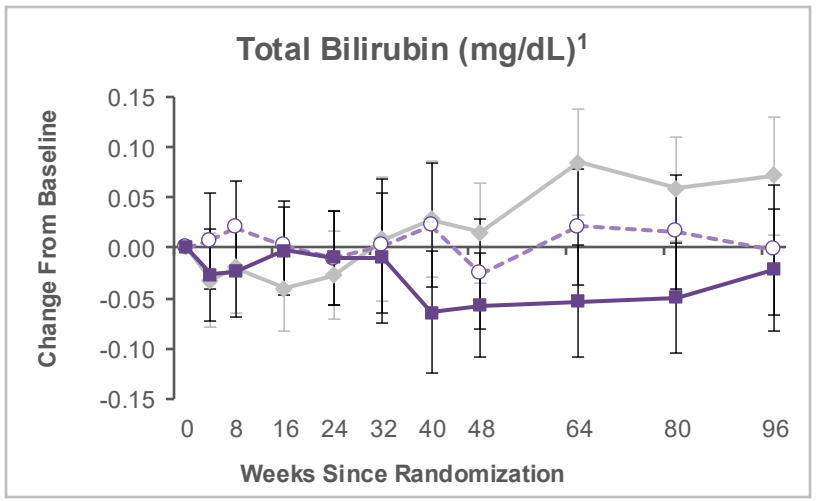
Source Data: FAS (non-missing values only, no imputation); Noureddin (2025) *N Engl J Med*

Markers of Liver Function Maintained or Slightly Improved through Week 96









[1]LS mean and 95% CI for the change from baseline

Source Data: FAS (non-missing values only, no imputation); Noureddin (2025) *N Engl J Med*

Adverse Events:
Cumulative from Baseline through Week 96

Number of Participants, n (%)	Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
Serious Adverse Events (SAEs)[a]	11 (18%)	15 (26%)	15 (24%)
AEs Leading to Death	1 (2%)[b]	0	0
AEs Leading to Discontinuation of Treatment	2 (3%)	6 (11%)	11 (17%)
Prior to Week 36	2 (3%)	5 (9%)	9 (14%)
After Week 36 and prior to Week 96	0	[b] 1 (2%)	2 (3%)

Most Frequent (≥15%) Drug-Related AEs	Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
Diarrhea	10 (16%)	11 (19%)	19 (30%)
Nausea	8 (13%)	11 (19%)	18 (29%)
Increased Appetite	3 (5%)	7 (12%)	18 (29%)
Injection Site Erythema	5 (8%)	10 (18%)	14 (22%)

[a] None of the SAEs considered related to study drug; [b] Pneumonia (prior to week 36)

Source Data: Safety Set; Noureddin (2025) *N Engl J Med*

Changes in **Bone Mineral Density**

- Poor bone health is a common complication of cirrhosis.[1,2]
  - Across all treatment groups, 43% of participants had osteopenia[3] at baseline, but only 4% were treated with bisphosphonates.
- Placebo-adjusted, significant relative reductions in bone mineral density (~5%) for spine and hip were observed for both EFX groups at Week 96, or about 2-3% per year.
- Number of participants experiencing fractures was equal across all treatment groups.

[1] Thomson (2024) *Aliment Pharmacol Ther.* [2] Danford (2020) *J Clin Densitom.* [3] T-score <-1.0 by DXA

Conclusions

- Unprecedented improvement in fibrosis observed in participants with compensated cirrhosis due to MASH after 96 weeks of treatment with EFX 50mg.
- Improvement in histologic fibrosis corroborated by non-invasive tests of liver fibrosis.
- Overall picture of liver injury and function suggest liver health is maintained or slightly improved by EFX compared to placebo.
- Acceptable safety & tolerability profile, with AEs predominantly gastrointestinal and transient.
- Based on a greater response across multiple parameters, EFX 50mg dose selected for confirmatory Phase 3 study in participants with compensated cirrhosis
  - Currently enrolling [NCT06528314]; includes assessment of liver-related outcomes and all-cause mortality.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efruxifermin in Compensated Liver Cirrhosis Caused by MASH

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