Efruxifermin Significantly Improved Liver Fibrosis at Week 96 in the HARMONY Study Across Subgroups, and Improvements Were Associated With Changes in Biomarkers

Mazen Noureddin[1], Juan P Frias[2], Guy Neff[3], Gary A Abrams[4], K Jean Lucas[5], William Sanchez[6], Sudhanshu Gogia[7], Muhammed Y Sheikh[8], Cynthia Behling[9], Pierre Bedossa[10], Lan Shao[11], Doreen Chan[12], Erica Fong[12], Brittany de Temple[12], Matt Minerva[12], Kim Barrett[12], Reshma Shringarpure[12], Erik J Tillman[12], Timothy Rolph[12], Andrew Cheng[12], Kitty Yale[12] , Stephen A. Harrison[13]

1 Houston Research Institute; Houston Methodist Hospital, Houston, TX, USA; 2 Velocity Clinical Research, Los Angeles, CA, USA; 3 Covenant Metabolic Specialists, Sarasota, FL, USA; 4 Department of Medicine, Prisma Health Upstate, Greenville, SC, USA; 5 Lucas Research, Morehead, NC, USA; 6 Floridian Clinical Research, Miami Lakes, FL, USA; 7 Texas Digestive Disease Institute, Webster, TX, USA; 8 Fresno Clinical Research Center, Fresno, CA, USA; 9 Department of Pathology, Sharp Memorial Hospital, San Diego, CA, USA; 10 Liverpat, Paris, France; 10 Institute of Cellular Medicine, University of Newcastle, Newcastle upon Tyne, UK; Statistics, 11 Fortrea Inc, 12 Akero Therapeutics, South San Francisco, CA, USA; 13 Pinnacle Clinical Research; San Antonio and Austin, TX

November 17, 2024, 2 PM

AASLD The Liver Meeting®

Dr. Mazen Noureddin - 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

Comprehensive Phase 3 SYNCHRONY Program Builds on Data from Two Biopsy-based Phase 2b MASH Studies

Comprehensive Phase 3 SYNCHRONY program (N ~3500) builds on two biopsy-based Phase 2b studies (N ~300) in corresponding patient populations

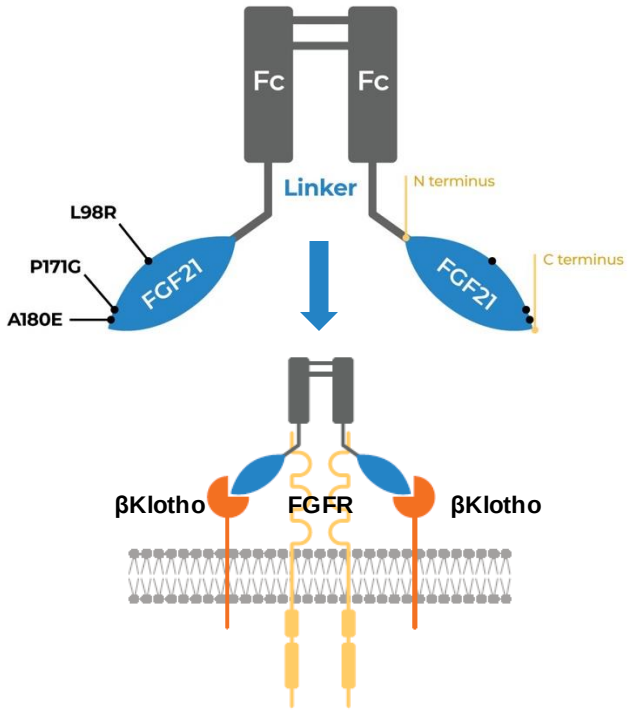
	HARMONY[1]	synchrony HISTOLOGY	symmetry[2] FOR CIRRHOTIC NASH	synchrony OUTCOMES
Fibrosis Stage	**F2-F3**	**F2-F3**	**F4, Compensated**	**F4, Compensated**
Phase	2b	3	2b	3
N	128	1650	182	1150
Weeks	96	240	96	~260

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

[1] HARMONY Phase 2b 24-Week Results published in Lancet Gastro Hepatol 2023; 8(12):1080–1093

[2] SYMMETRY Phase 2b 36-Week Results presented at AASLD 2023, LB-5005 *Hepatology* 2024; 79:E33-E85

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



Key attributes

- Increases half-life from < **2 hours** to ~**3 days**
- Bivalent structure enables **avidity effect** of Fc-FGF21
- **High affinity** for β-Klotho
- **Balanced potency** at FGFR1c, 2c, 3c
- **Inactive** at FGFR4

Stanislaus, S *et al.* (2017) *Endocrinology* 158(5): 1314-27; Lee, S *et al.* (2018) *Nature* 553: 501-505; Kharitonenkov, A *et al.* (2007) Endocrinology 148(2)774-781

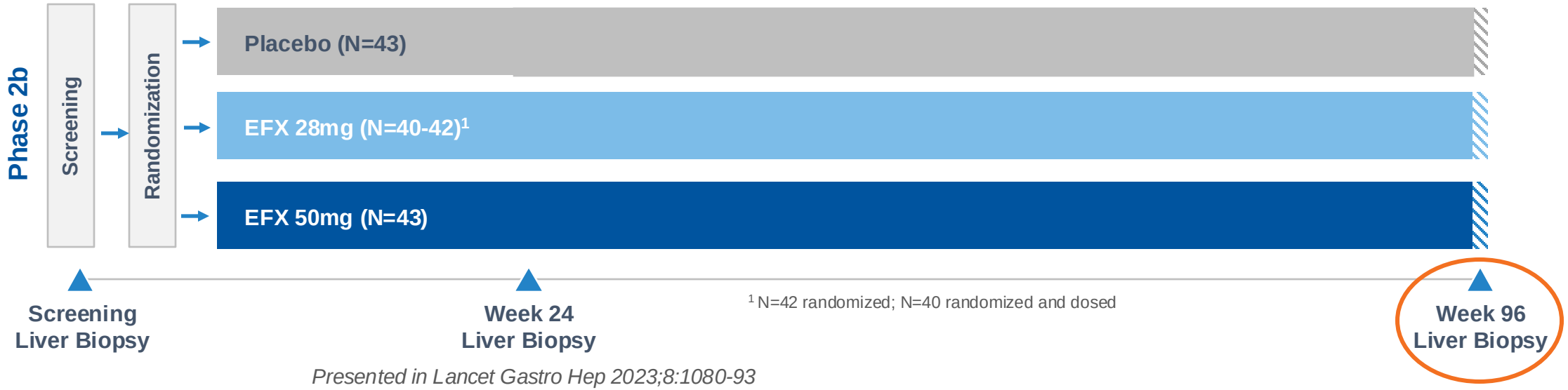
HARMONY Phase 2b Trial Design: Pre-Cirrhotic (F2-F3) MASH with Liver Histopathology at 24 and 96 Weeks

Week 24 Primary Endpoint

≥1-stage fibrosis improvement & no worsening of MASH

Week 96 Endpoints

- ≥1- or 2-stage fibrosis improvement & no worsening of MASH
- MASH Resolution & No Worsening of Fibrosis
- Fibrosis Improvement & MASH Resolution



[1] N=42 randomized; N=40 randomized and dosed

Presented in Lancet Gastro Hep 2023;8:1080-93

Baseline Demographics

Parameter (Units), mean unless noted	Placebo N=43	EFX 28mg N=42	EFX 50mg N=43
Age (Years)	55	57	52
Sex (% Female)	63	69	53
Body Weight (kg)	108	104	103
Type 2 Diabetes (%)	65	76	70
Fibrosis Stage (F3), (%)[1]	70	64	63
Enhanced Liver Fibrosis (ELF) Score	9.8	9.7	9.8
Pro-C3[2] (µg/L)	125	113	145
Liver Stiffness by VCTE[3] (FibroScan) (kPa)	15	14	16
Hepatic Fat Fraction by MRI-PDFF (%)	17.1	18.5	17.5
Alanine Aminotransferase (ALT) (U/L)	62	50	63

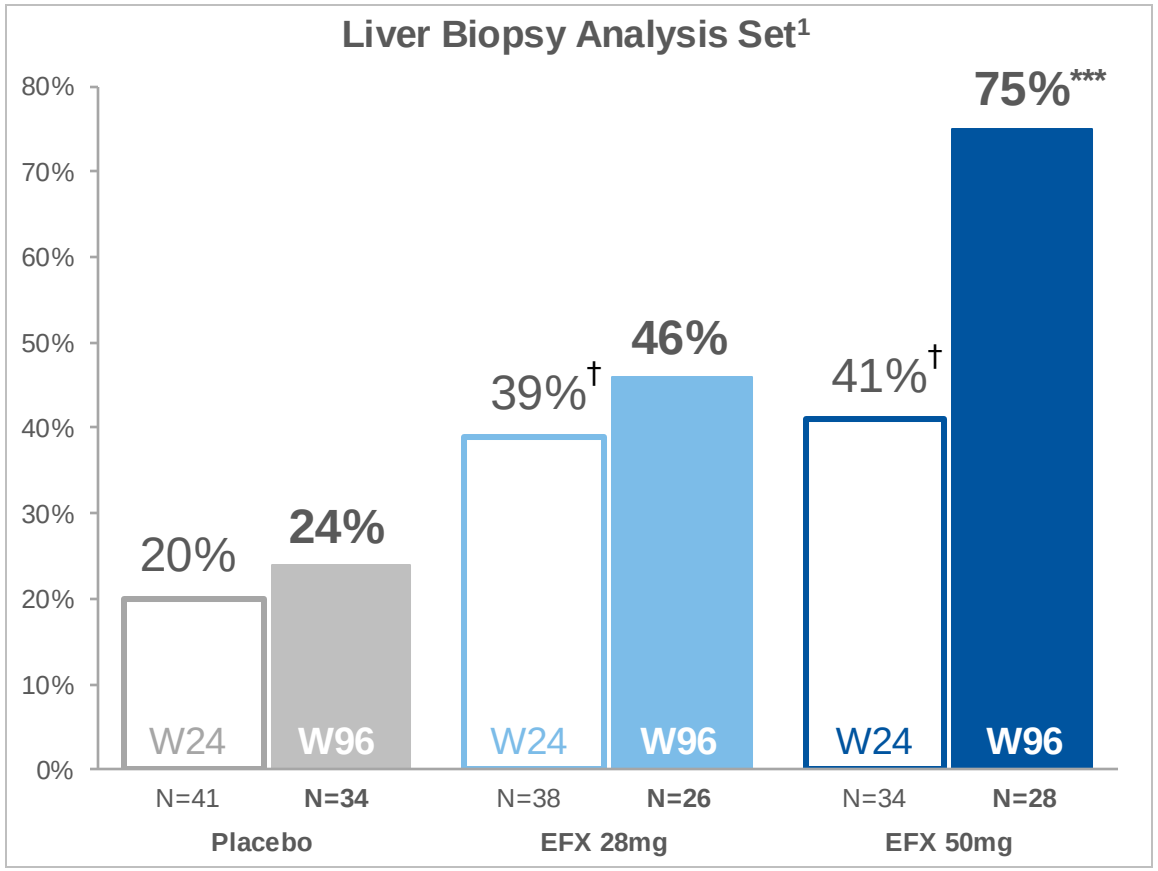
Specified Analysis Sets (N)	Placebo	EFX 28mg	EFX 50mg
Safety Set / Modified Full Analysis Set (mFAS)[4]	43	40	43
Week 24 Liver Biopsy Analysis Set (LBAS-24)[5]	41	38	34
Week 96 Liver Biopsy Analysis Set (LBAS-96)[6]	34	26	28

[1] All participants either fibrosis stage 2 (F2) or stage 3 (F3); [2] Type III collagen N-Terminal Propeptide (GEN 2 ELISA); [3] Vibration-controlled transient elastography; [4] All randomized participants who received at least one dose of study drug; [5] All Full Analysis Set participants who have baseline and Week 24 liver biopsy results ; [6] All Full Analysis Set participants who have baseline and Week 96 liver biopsy results.

Source Data: Week 96 Modified Full Analysis Set (ITT)

Substantial Improvement in Fibrosis Between Weeks 24 and 96 for Participants Treated with 50mg EFX

Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Weeks 24 and 96



[1] All participants with baseline and specified timepoint
†p<0.05, versus placebo at W24; *** p<0.001, versus placebo at W96 (Cochran-Mantel-Haenszel Test [CMH])

Week 96 ITT Analysis[2]

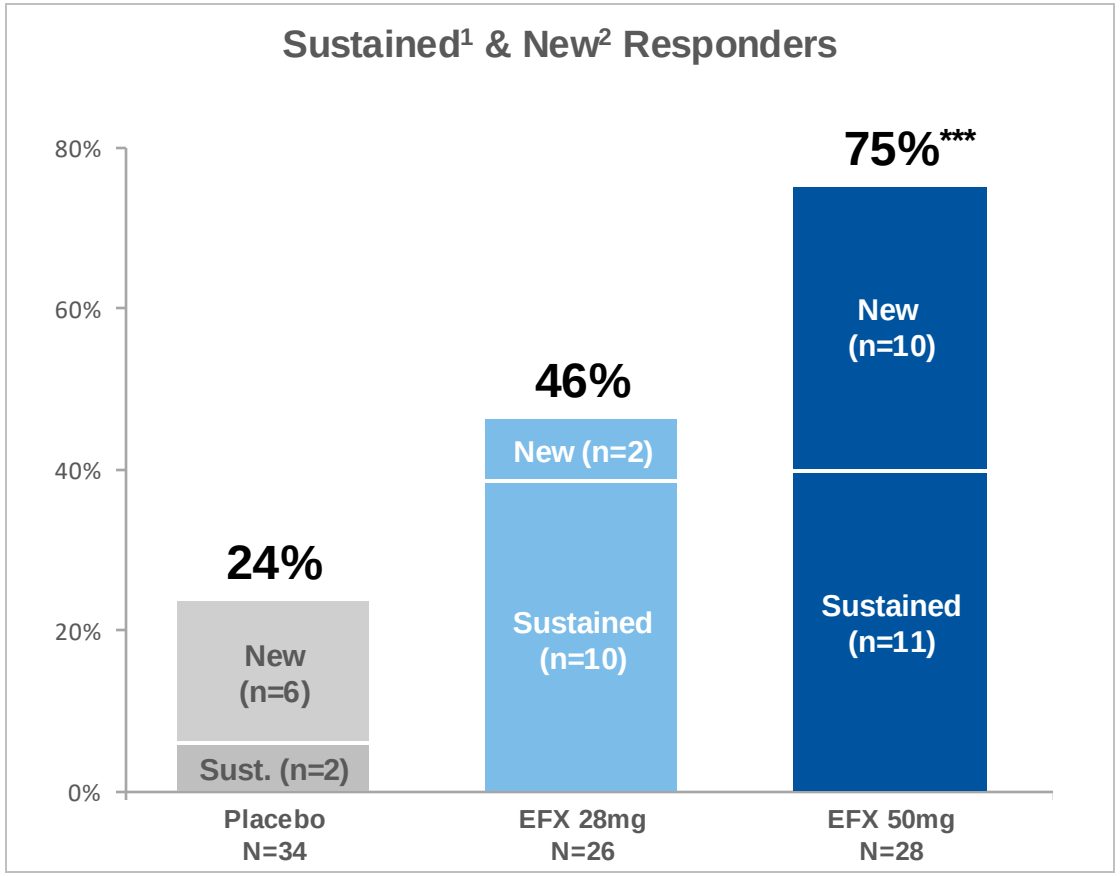
Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
19%	30%	49%**

[2] Source data: Modified Full Analysis Set (ITT); All missing biopsies are imputed as a non-responder
**p<0.01 versus placebo (CMH)

Biopsy Reading Method: Biopsies were independently scored by two NASH-CRN trained pathologists, blinded to participant, treatment, and sequence. A third pathologist was available to adjudicate in absence of consensus.

Fibrosis Improvement Sustained and Expanded from Weeks 24 to 96

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



[1] Responder at Weeks 24 & 96; [2] Responder at Week 96, but not Week 24
*** p<0.001 versus placebo (CMH)

Proportion of Week 24 Responders with Sustained Response through Week 96[3,4]

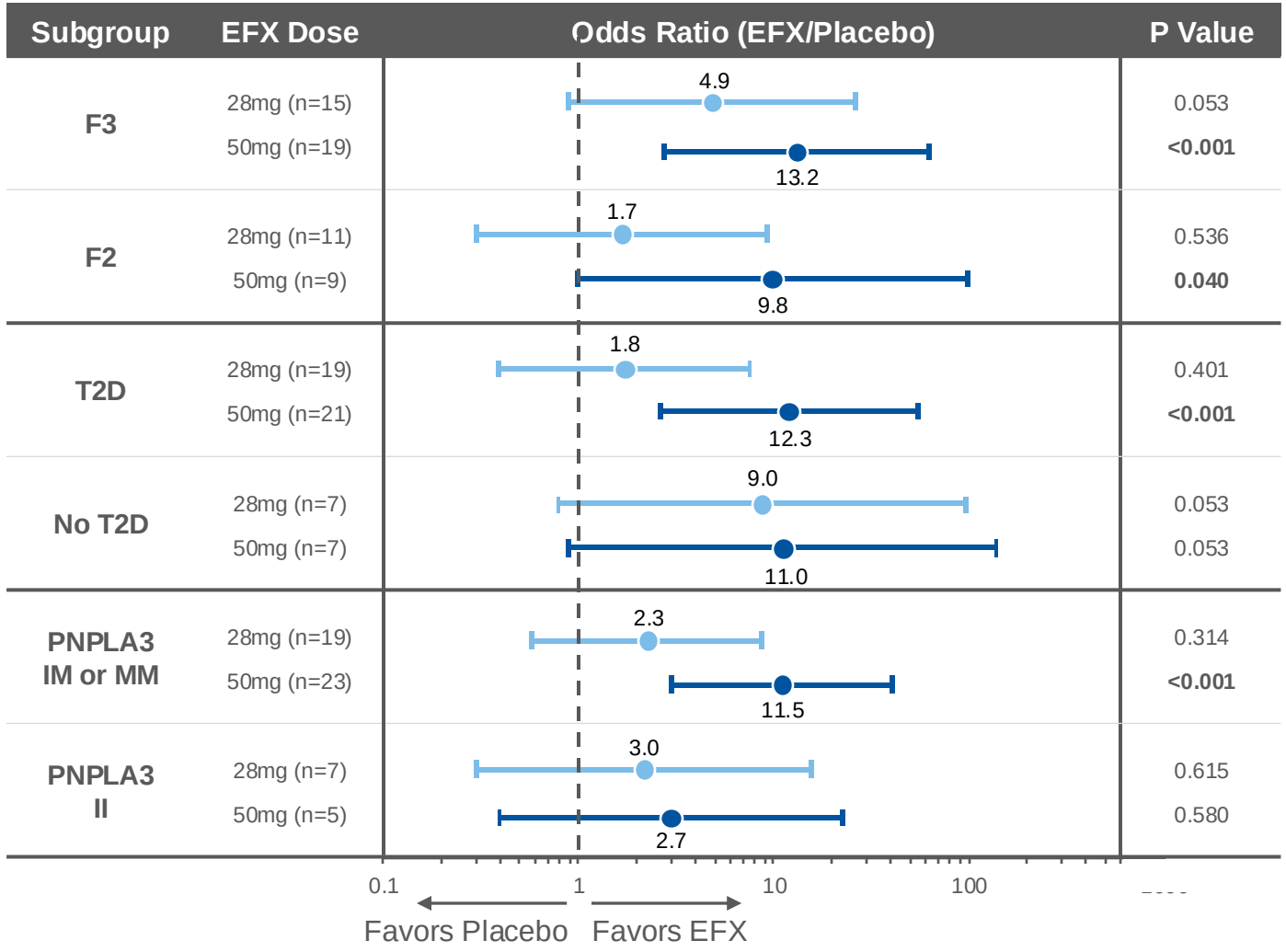
Placebo (N=5)	EFX 28mg (N=12)	EFX 50mg (N=12)
2 (40%)	10 (83%)	11 (92%)

[3] Among Week 24 responders with Week 96 biopsies
[4] Not analyzed for statistical significance

Source Data: LBAS-96; Modified Full Analysis Set (ITT)

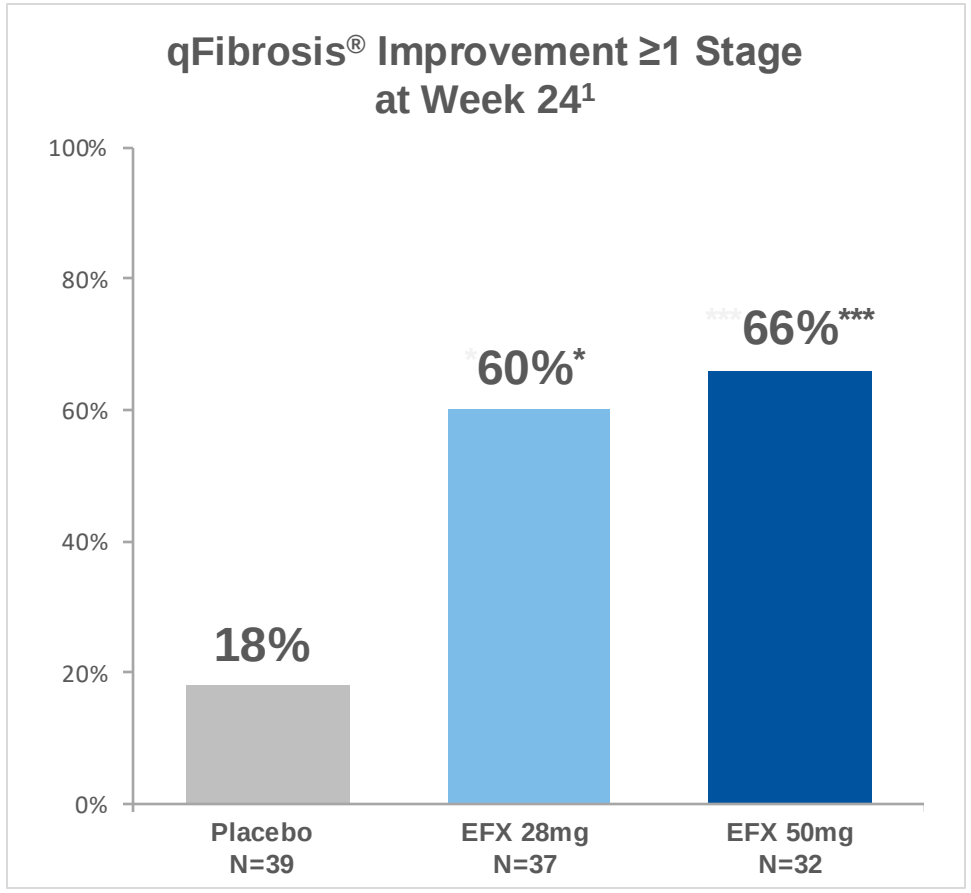
Consistent Anti-Fibrotic Response Across High-Risk Subgroups

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

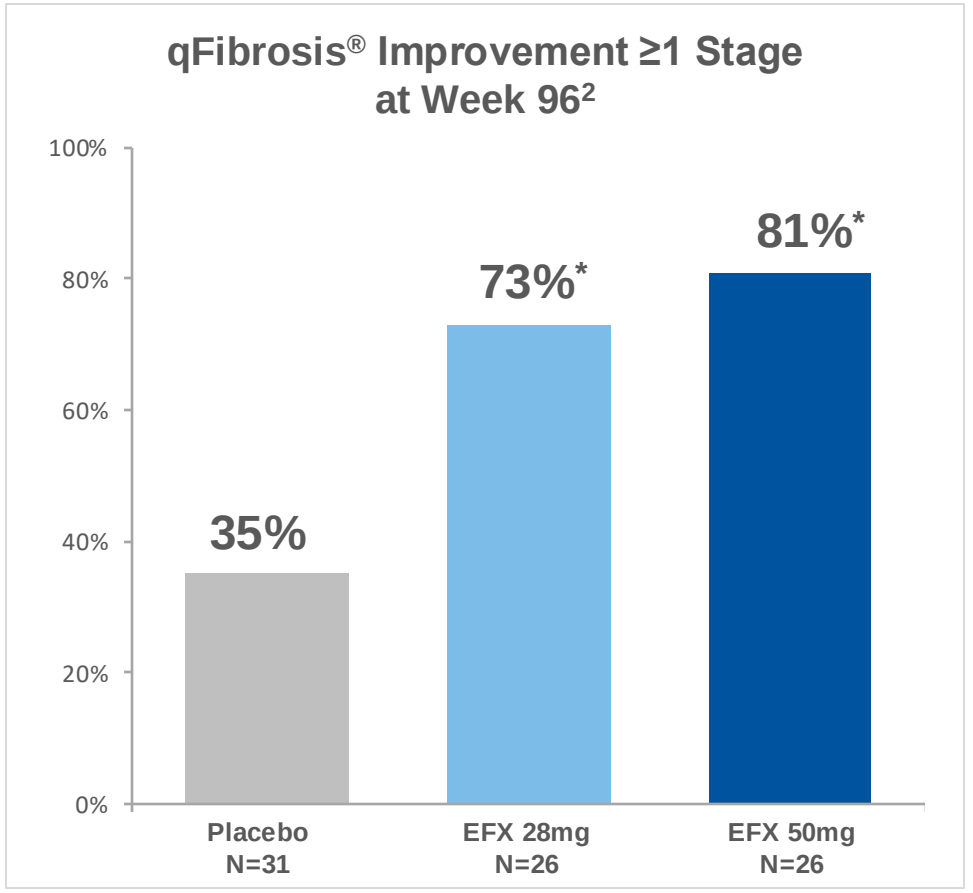


Source Data: Subgroups of LBAS-96 with available data; two-sided p value, Fisher's exact test (PNPLA3); CMH (all others)

AI-Based Digital Pathology (Steatosis-corrected qFibrosis®) Scoring Corroborates Conventional Histopathology



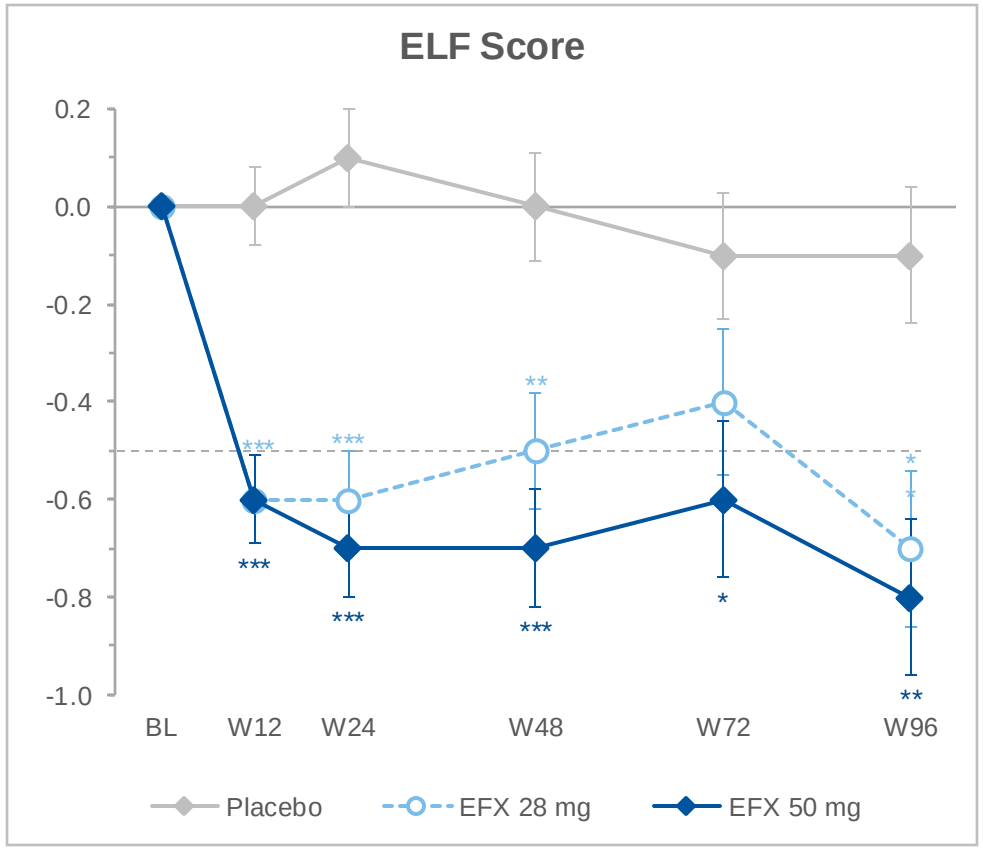
[1]Participants with available baseline and W24 biopsies
* p<0.05, *** p<0.001 versus placebo (CMH)



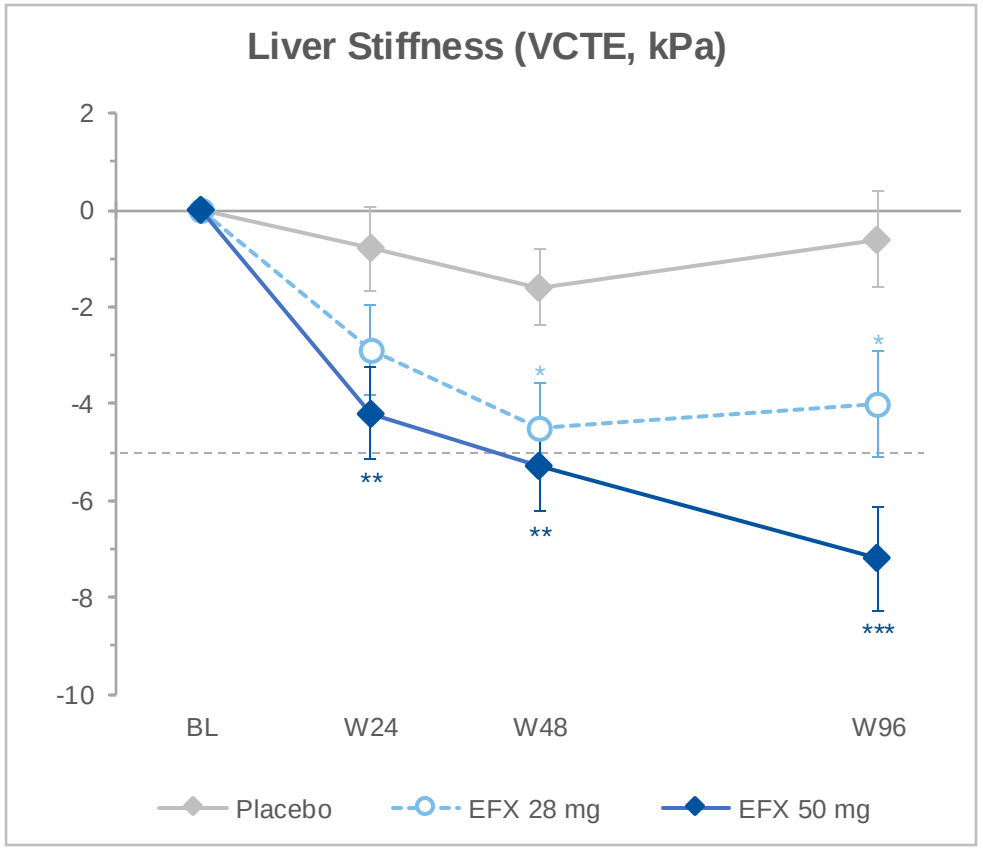
[2]Participants with available baseline and W96 biopsies
* p<0.05 versus placebo (CMH)

Pattern of Reductions in Imaging and Circulating Biomarkers of Fibrosis Corroborate Histological Improvement in Fibrosis

LS Mean (SE) Absolute Change From Baseline to Week 96



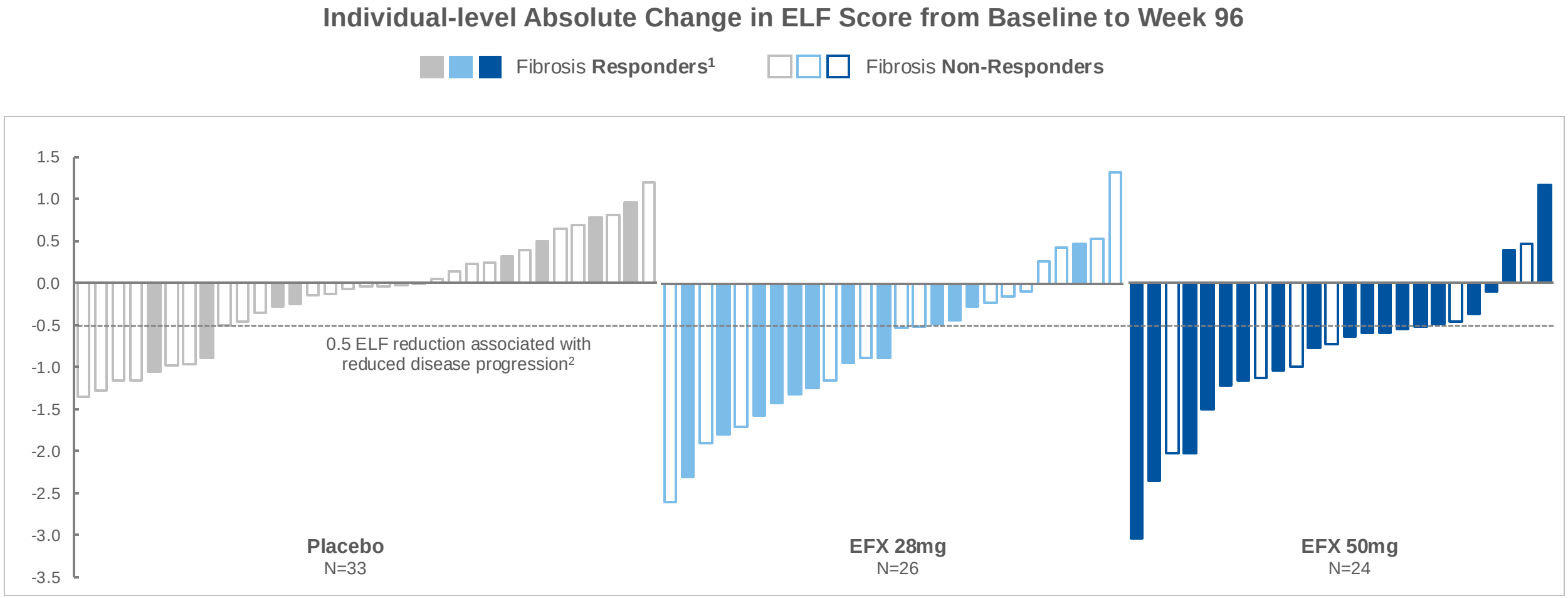
*p<0.05, **p<0.01, ***p<0.001 versus placebo (MMRM)



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

Source Data: FAS (non-missing values only, no imputation)

Larger Reductions in ELF Score Associated with Histological Fibrosis Improvement among EFX-treated Participants



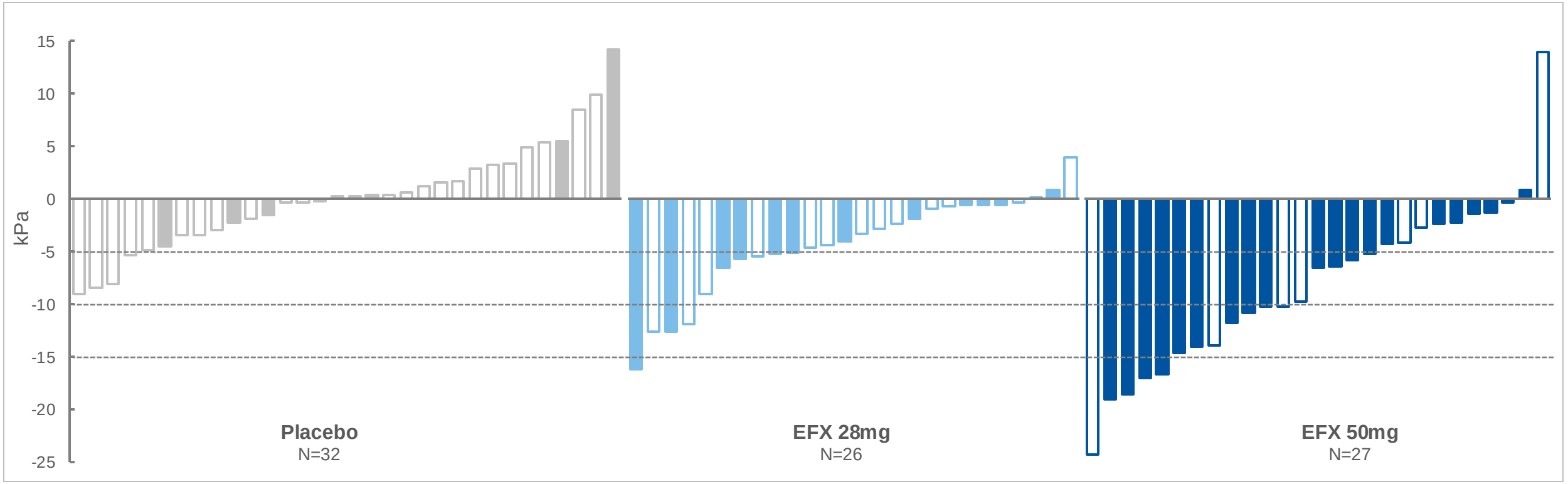
[1] ≥1-stage improvement in fibrosis and no worsening of MASH at week 96

[2] Harrison SA, et al. *J Hepatol*. 2020;73(1):26-39

Source Data: LBAS-96

Larger Reductions in Liver Stiffness Associated with Fibrosis Improvement among EFX-treated Participants

Individual-level Absolute Change in FibroScan VCTE from Baseline to Week 96

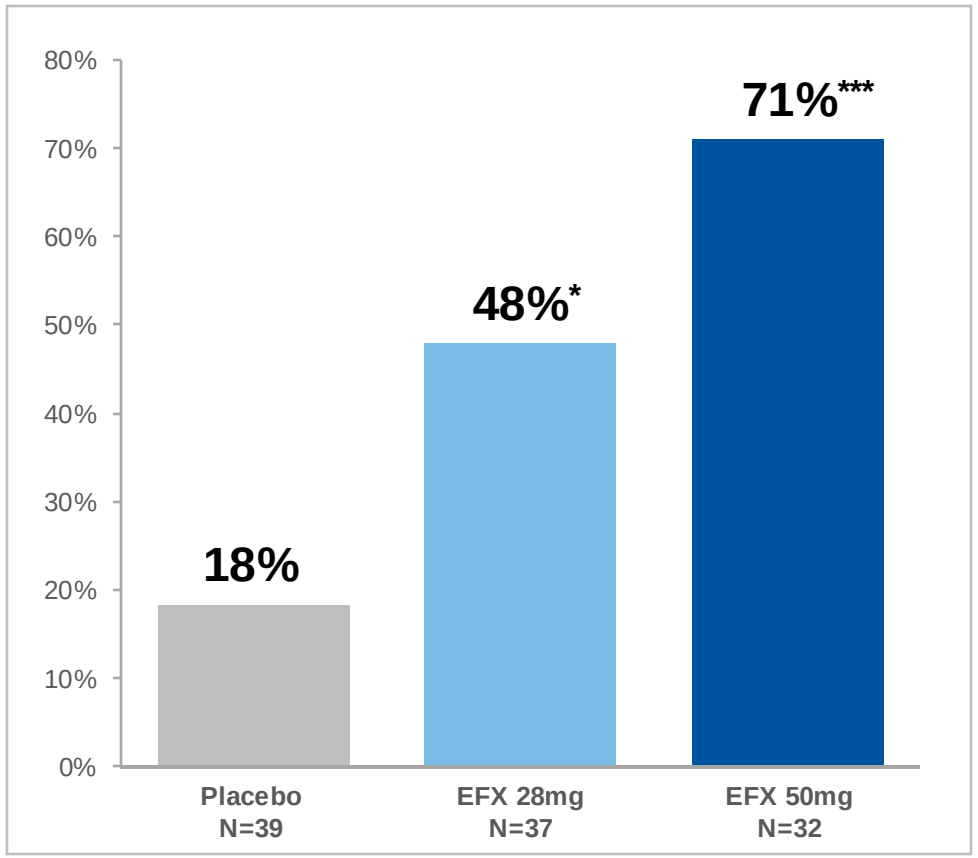


[1] ≥1-stage improvement in fibrosis and no worsening of MASH at week 96

Source Data: LBAS-96

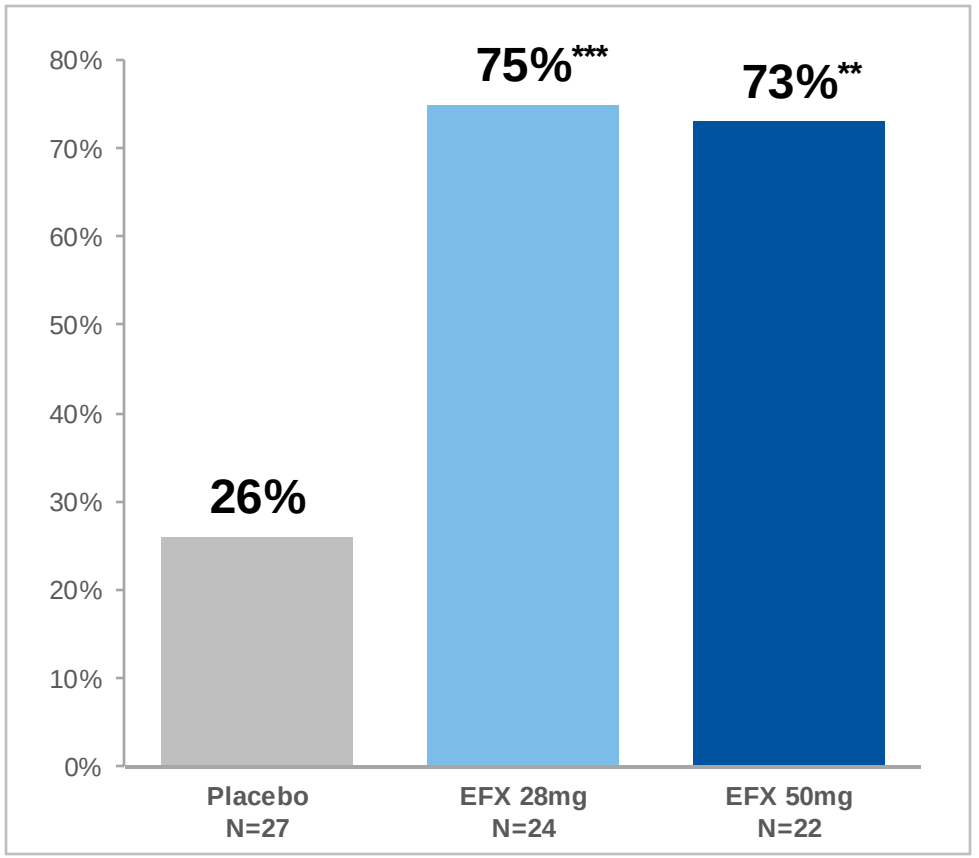
EFX was Associated with Significant and Clinically Meaningful Reductions in Liver Stiffness

Participants with ≥30% relative reduction in Liver Stiffness (VCTE) at Week 96



*p<0.05, ***p<0.001 versus placebo (CMH)

Proportion with liver stiffness <10 kPa at Week 96, of those with baseline liver stiffness ≥10 kPa

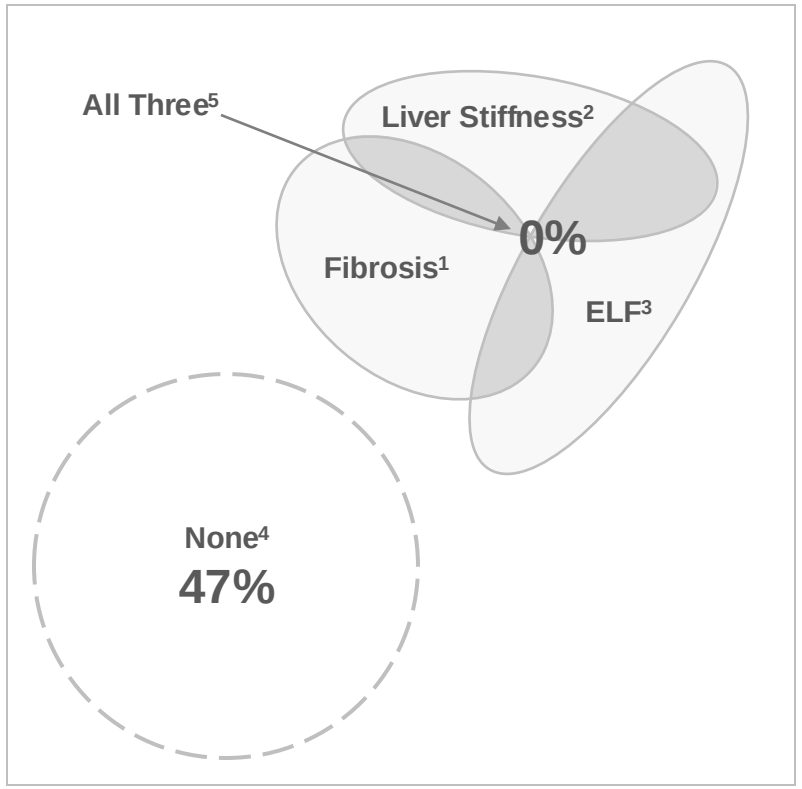


**p<0.01, ***p<0.001 versus placebo (CMH)

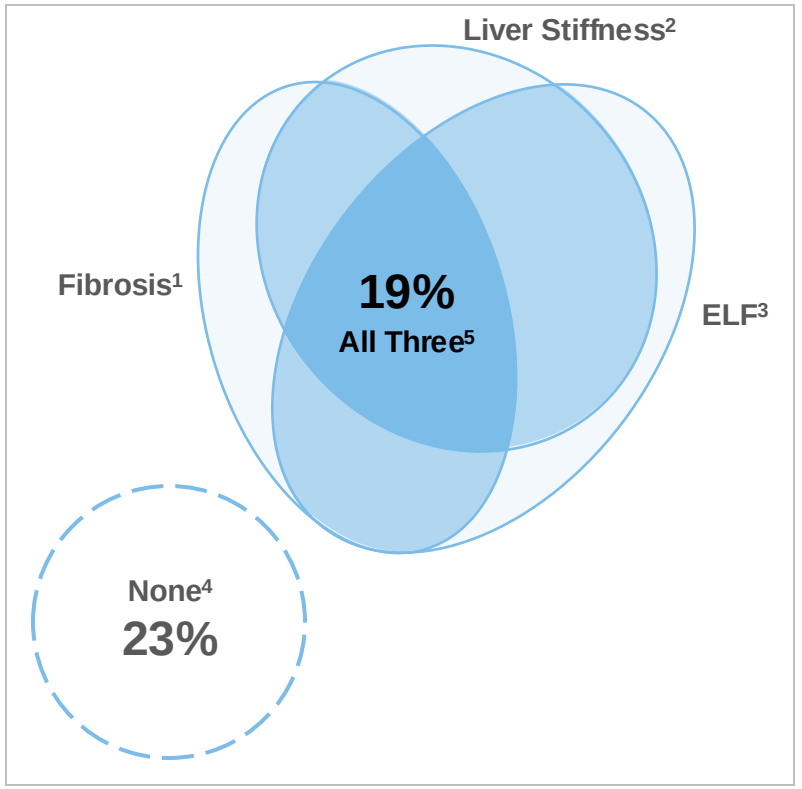
Source Data: FAS (non-missing values only, no imputation)

Overlap of Imaging and Circulating Biomarkers of Fibrosis at 96 Weeks Corroborate Conventional Histopathology only in EFX-treated Individuals

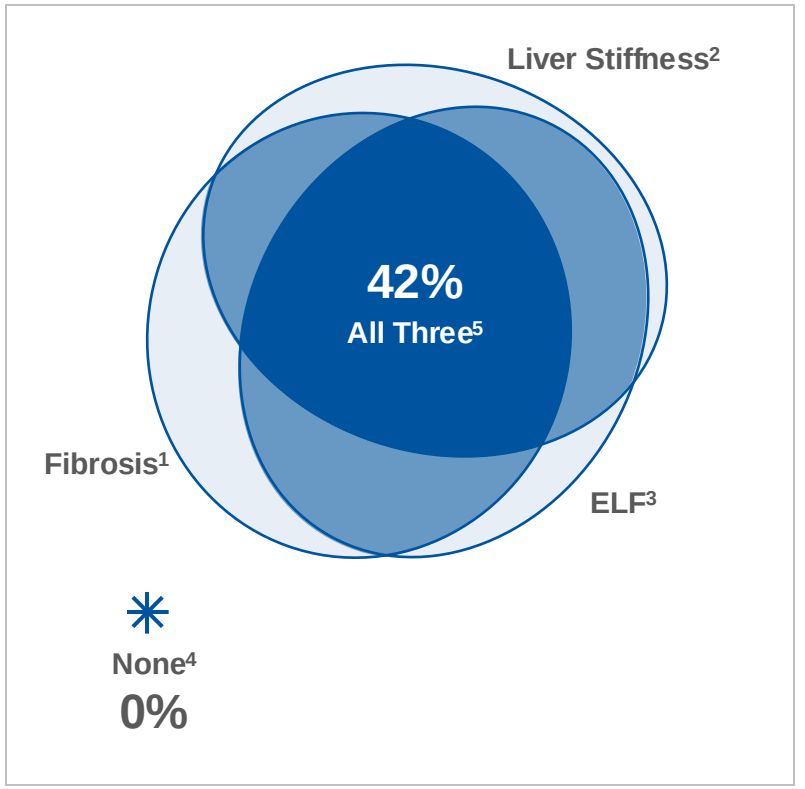
Placebo (N=32)



EFX 28 mg (N=26)



EFX 50 mg (N=24)



[1] Proportion with **histological fibrosis response** (improvement ≥1 stage without MASH worsening); [2] Proportion with **liver stiffness response** (≥30% reduction by FibroScan [VCTE]); [3] Proportion with **ELF response** (≥0.5 reduction in ELF Score); [4] None: Proportion without any of fibrosis improvement, liver stiffness response, or ELF response; [5] All Three: proportion with fibrosis improvement, liver stiffness response, and ELF response

Areas, including overlaps, are proportional to response percentage

Source Data: Subset of the LBAS-W96 with available data

Safety and Tolerability through 96 Weeks of Dosing

TEAE Overview	Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
TEAE Leading to Death	0 (0%)	0 (0%)	0 (0%)
Treatment-Emergent SAEs	4 (9%)	4 (10%)	7 (16%)
TEAE Leading to D/C	0 (0%)	4 (10%)	5 (12%)

SAE, serious adverse event; D/C, discontinuation of IP

Most Frequent (≥15%) Drug–Related TEAEs	Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
Diarrhea	7 (16%)	16 (40%)	16 (37%)
Nausea	5 (12%)	12 (30%)	14 (33%)
Increased Appetite	3 (7%)	7 (18%)	10 (23%)
Injection Site Erythema	6 (14%)	8 (20%)	7 (16%)
Injection Site Bruising	2 (5%)	6 (15%)	3 (7%)

- Incidence and pattern of SAEs was consistent with prevalent comorbidities of the population
- GI AEs were mild-to-moderate, transient, and generally occurred early in treatment period
- No significant change in BP at Week 96
- No significant change in BMD at Week 48
- Modest but statistically significant reductions in BMD after 96 weeks, clinical relevance to be determined
- No reported events of DILI
- Markers of liver function and hemostasis remained stable

Source Data: Safety Set

Conclusion: Unprecedented Antifibrotic Activity Observed for EFX after 96 Weeks

- 30% treatment effect for EFX 50mg compared to placebo (mITT, missing biopsy = non-response) for fibrosis improvement with no MASH worsening
  - Early fibrosis response at Week 24 sustained and expanded through Week 96
- Consistent anti-fibrotic response across high-risk subgroups (F3, T2D, *PNPLA3* risk allele carriers)
- Conventional histopathology corroborated by AI-based digital pathology, imaging, and circulating biomarkers of fibrosis
- Almost half of EFX 50mg-treated participants were responders by all three measures of fibrosis (conventional histopathology, ELF score, or liver stiffness)
- Acceptable safety and tolerability profile, with mostly mild-to-moderate, transient GI events

Acknowledgements

Thank you to the patients and their families, **Dr. Stephen Harrison**, the investigators, and their teams, who have participated in the completed HARMONY study**.**

Investigators: ***Stephen Harrison, MD*** • *Gary Abrams, MD* • *Naim Alkhouri, MD* • *Rafael Amaro, MD* • *Christian Andrade, MD* • *Robert Barish, MD* • *Shekhar Challa, MD* • *Andrew deLemos, MD* • *Michael Fine, MD* • *Juan Frias, MD* • *Michael Fuchs, MD* • *Sudhanshu Gogia, MD* • *Paul Hellstern, MD* • *Robert Herring, MD* • *Robert Jenders, MD* • *Arun Khazanchi, MD* • *Anita Kohli, MD* • *Donald Lazas, MD* • *Mark Leibowitz, MD* • *Kathryn Lucas, MD* • *Fernando Membreno, MD* • *Apurva Modi, MD* • *Ann Moore, NP* • *Robert Morin Jr., MD* • *Abdullah Mubarak, MD* • *Guy Neff, MD* • *Mazen Noureddin, MD* • *Grisell Ortiz-Lasanta, MD* • *Rashmee Patil, MD* • *Robert Rahimi, MD* • *Gary Reiss, MD* • *Peter Ruane, MD* • *William Sanchez, MD* • *Aasim Sheikh, MD* • *Muhammad Sheikh, MD* • *Elliot Shin, MD* • *Mohammad Siddiqui, MD* • *Scott Wofford, MD* • *Cynthia Wright, MD* • *Ju Dong Yang, MD*