Restoring Balance. Renewing Life.

Corporate Presentation

December 2024

Safe Harbor and Legal Disclaimers

This presentation may contain “forward-looking statements” of Akero Therapeutics, Inc. (“we,” “us,” “our,” “Akero” or the “Company”) within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to current express or implied beliefs, expectations and assumptions regarding: the future of our business; future plans and strategies, including our expectations around the therapeutic potential and clinical benefits of Efruxifermin (“EFX”), including in combination with GLP-1 receptor agonist therapies; our development plans for EFX, including our belief in the unique potential of EFX as a foundational MASH therapy; our preclinical and clinical results, including our safety/tolerability, laboratory measures and histology data from our Phase 2b HARMONY study, Phase 2b SYMMETRY study, and the Cohort D expansion of our Phase 2b SYMMETRY study; the expected timing to report the week 96 results of the SYMMETRY study; the potential benefits resulting from the PRIME, Breakthrough Therapy and Fast Track designations of EFX; the SYNCHRONY Phase 3 program, including the SYNCHRONY *Histology,* SYNCHRONY *Real-World, and* SYNCHRONY *Outcomes* studies, their respective trial designs and expected timing to report results for the respective primary endpoints; the availability of a new drug product formulation to support Phase 3 clinical trials; risks related to the competitive landscape; the timing and potential benefits of our regulatory interactions; and our use of capital, expenses and other future financial results, including the expected cash runway. Words such as, but not limited to, “look forward to,” “believe,” “expect,” “anticipate,” “estimate,” “intend,” “plan,” “would,” “should” and “could,” and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in our most recent annual report on Form 10-K filed with the Securities and Exchange Commission (the “SEC”), as well as discussions of potential risks, uncertainties, and other important factors in our other subsequent filings with the SEC. All information in this presentation is as of the date hereof, and we undertake no duty to update this information unless required by law.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company’s own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

EFX: Potential Best-in-Class MASH Drug with Near-Term Milestones

1 Potential to Treat Pre-Cirrhotic MASH (F2-F3)

- HARMONY: 96-wk Ph2b study
- Week 96 data provided strongest reported efficacy data to date across MASH field:
  - ≥1 stage fibrosis improvement
  - 2 stage fibrosis improvement
  - MASH resolution
  - Fibrosis improvement and MASH resolution

Unprecedented Fibrosis Improvement After 96 Weeks of Treatment

2 Potential to Treat MASH Due to Cirrhosis (F4, compensated)

- SYMMETRY: 96-wk Ph2b study
- Week 36 data provided encouraging evidence of activity in difficult-to-treat population
- Statistically significant MASH resolution
- Opportunity to build on fibrosis improvement observed at Week 36

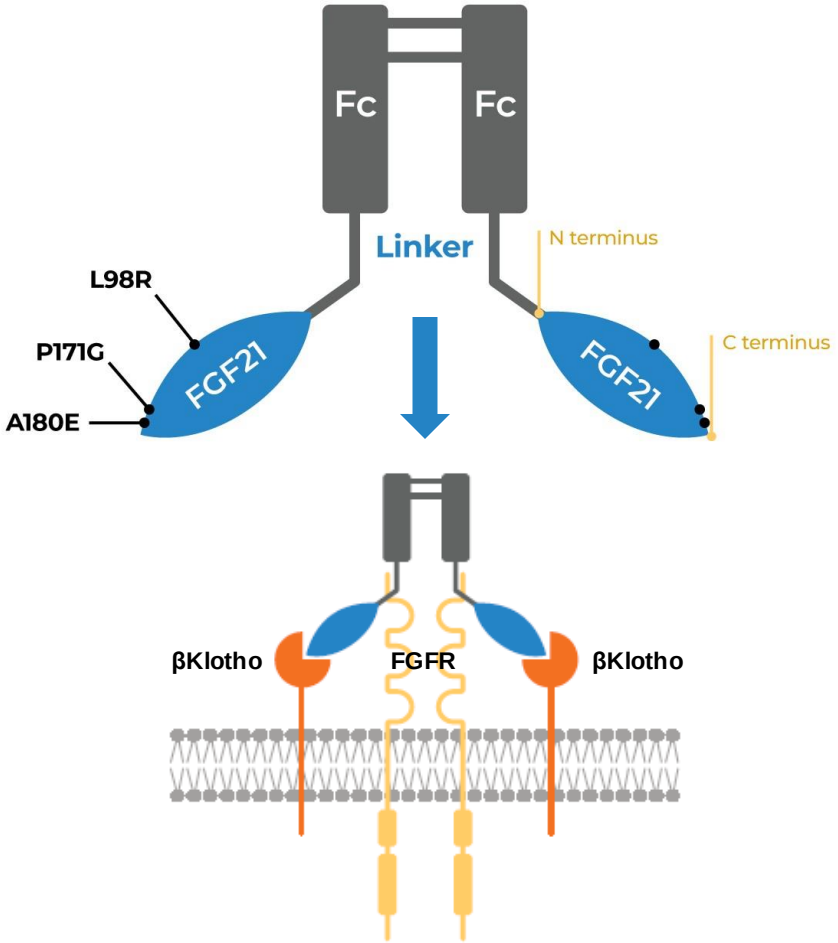
SYMMETRY Week 96 Readout with Histology Expected February 2025

3 Global Phase 3 SYNCHRONY Program Underway (F1-F4, compensated)

- Phase 3 SYNCHRONY program comprised of three clinical trials
  - *Histology* (F2-F3), readout with histology expected 1H'27
  - *Real-World* (F1-F3), non-invasive tests only, readout expected 2026
  - *Outcomes* (F4, compensated)

All three SYNCHRONY studies are actively enrolling patients

EFX Bivalent Structure Potentially Optimal for MASH Efficacy, With Convenient Once-weekly Dosing



Bivalent FGF21 Analog Brings:

- **High β-Klotho affinity**
- **High systemic exposure**
- **Maintained agonism of FGFRs throughout weekly dosing interval**
- **Sustained pharmacodynamic effect through week 24 (F2-F3) and week 36 (F4, compensated)**

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

EFX Direct And Indirect Anti-fibrotic Effects

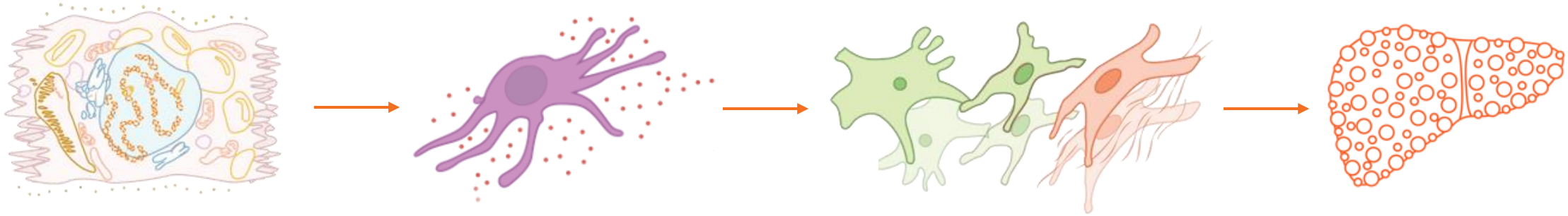
Pathogenesis of Fibrosis

Hepatocyte Stress & Death

Kupffer Cell Activation

Myofibroblast Differentiation

Fibrogenesis



EFX Anti-Fibrotic Activity

Bao, L *et al.* (2018) *Br J Pharmacol* 175:3379-3393; Fisher, FM *et al.* (2014) *Gastroenterology* 147:1073-1083.e6; Jimenez, V *et al.* (2018) *EMBO Mol Med* 10:e8791; Lee, JH *et al.* (2016) *Am J Transl Res* 8:4750-4763; Sanyal, A *et al.* (2018) *Lancet* 392:2705-2717; Le, CT *et al.* (2018) *PLOS one* 13:e0192146; Xu, P *et al.* (2016) *Toxicol Appl Pharmacol* 290:43-53; Yu, Y *et al.* (2016) *Int Immunopharmacol* 38:144-152

**Cited literature available on company website*

Key Regulatory Designations Based on EFX Therapeutic Profile

Breakthrough Therapy (US FDA - 2022)

- Enables expedited development
- Signifies potential for substantial improvement over available therapy on clinically significant endpoints
- Based on Phase 2b HARMONY data

Fast Track (US FDA - 2021)

- Enables more frequent regulatory interactions to resolve development issues with potential eligibility for priority review
- Signifies potential to fill an unmet medical need
- Based on Phase 2a BALANCED data

PRIME (EMA - 2020)

- Enables enhanced regulatory support
- Signifies potential to offer a major therapeutic advantage over existing treatments or benefit patients without treatment options
- Based on Phase 2a BALANCED data

Efruxifermin was the first investigational MASH drug to receive all three designations

FDA, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (2014);
European Medicines Agency, Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME) (Draft 2015)

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

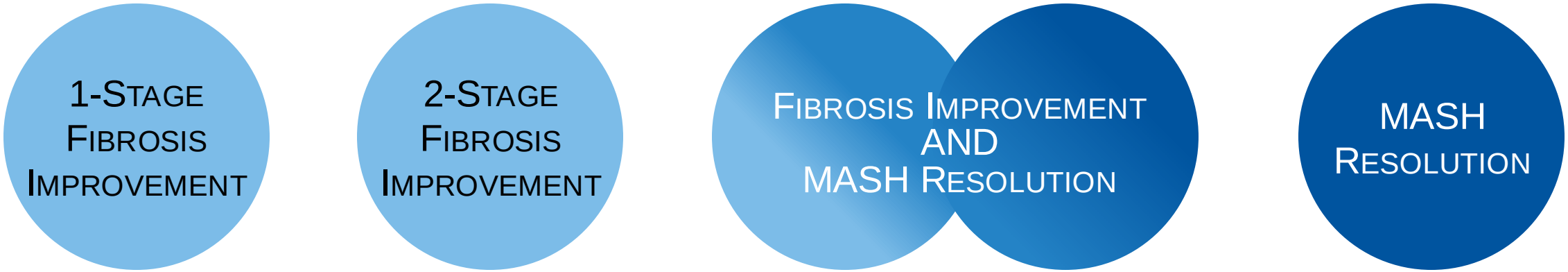
[1] HARMONY Phase 2b 24-Week Results published in Lancet Gastro Hepatol 2023; 8(12):1080–1093

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

EFRUXIFERMIN (EFX): A Bivalent Fc-FGF21 Fusion Protein

HARMONY

Statistically Significant Effects after 96 Weeks



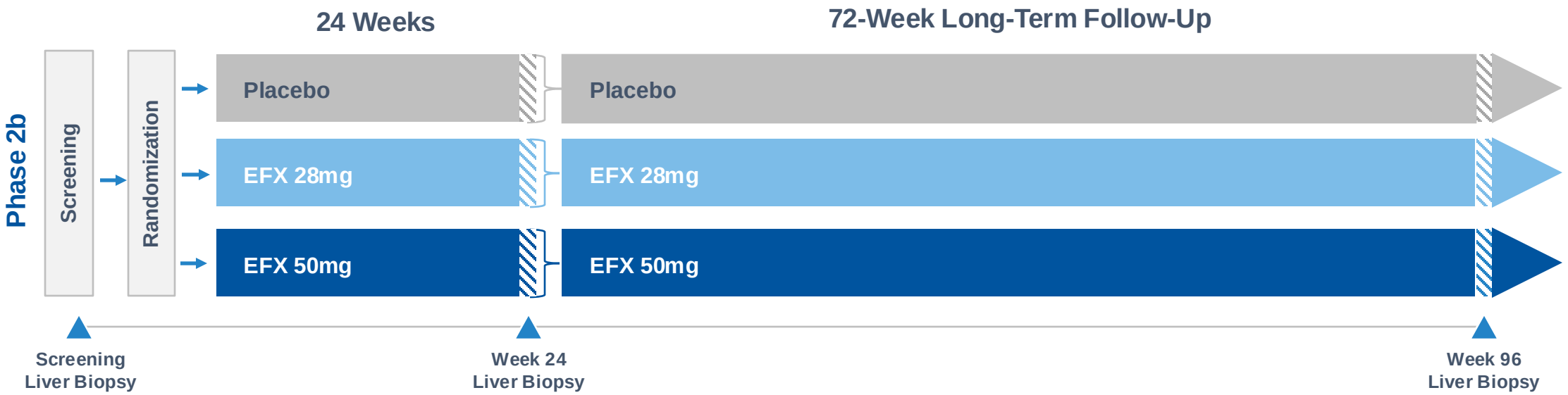
HARMONY Trial Design: Pre-Cirrhotic (F2-F3) MASH with Liver Histology at 24 and 96 weeks

Week 24 Primary Endpoint

- ≥ 1 stage fibrosis improvement & no worsening of MASH

Week 96 Primary Analyses

- ≥ 1 or 2 stages fibrosis improvement & no worsening of MASH
- MASH Resolution & No Worsening of Fibrosis
- Fibrosis Improvement & MASH Resolution
- *Fully powered for week 24 primary endpoint; **not** fully powered for week 96 endpoints*



Analysis Sets

Analysis Set	N	Description
Full Analysis Set	128	All randomized subjects
Safety Set / Modified Full Analysis Set (ITT) Placebo (N=43) 28mg (N=40) 50mg (N=43)	126	All randomized and dosed subjects[1]
Week 24 Liver Biopsy Analysis Set Placebo (N=41) 28mg (N=38) 50mg (N=34)	113	All subjects with baseline and Week 24 biopsy results
Week 96 Liver Biopsy Analysis Set Placebo (N=34) 28mg (N=26) 50mg (N=28)	88	All subjects with completed second on-study biopsy

[1] The Modified Full Analysis Set includes subjects that were randomized and received at least one dose of study drug per the Statistical Analysis Plan.

Baseline Demographics

Parameter (Units)	Placebo (N=43)	EFX 28mg (N=42)	EFX 50mg (N=43)
Age (Years)	55	57	52
Sex (% Female)	63	69	53
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) (GEN 2 ELISA)	125	113	145
Liver Stiffness by VCTE[3] (FibroScan) (kPa)	15	14	16
Hepatic Fat Fraction by MRI-PDFF[4] (%)	17.1	18.5	17.5
MASLD Activity Score (MAS)	5.4	5.1	5.6
Alanine Aminotransferase (ALT) (U/L)	62	50	63
Aspartate Aminotransferase (AST) (U/L)	57	42	52

[1] All patients either fibrosis stage 2 (F2) or stage 3 (F3); [2] Procollagen 3 N-Terminal Propeptide; [3] Vibration-controlled transient elastography; [4] Magnetic Resonance Imaging Proton Density Fat Fraction

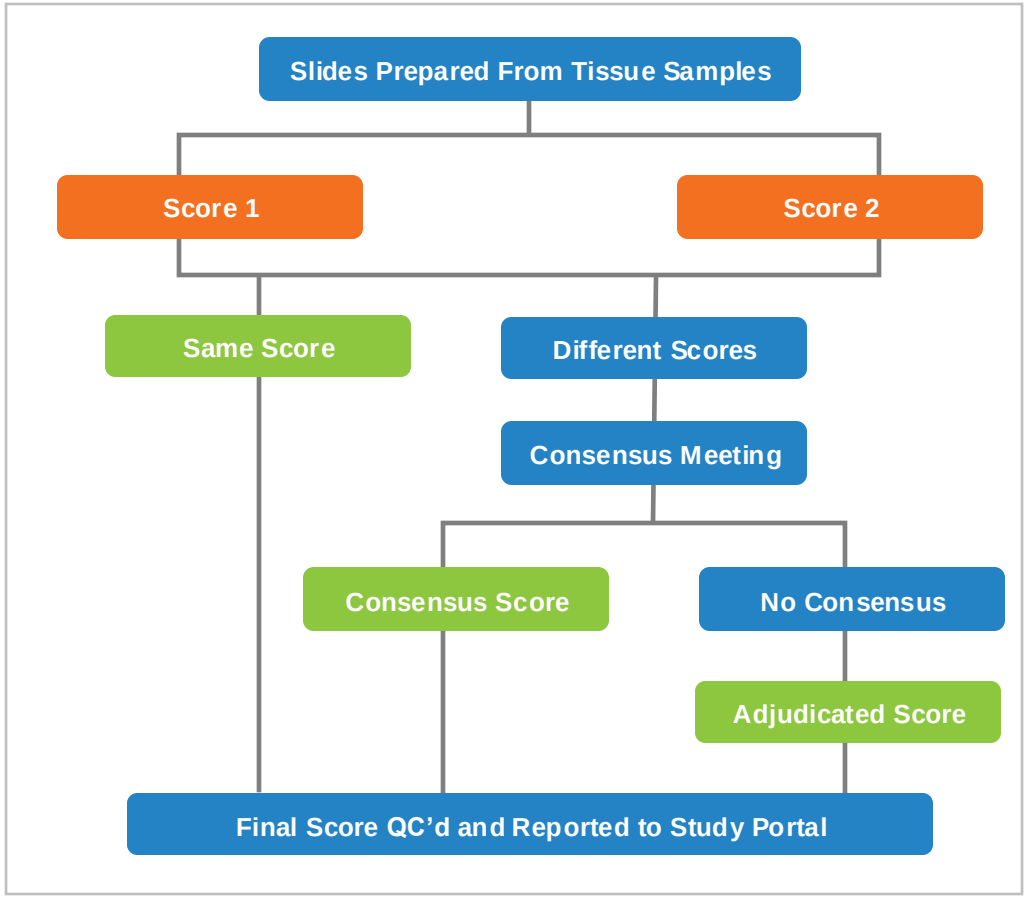
Source Data: Full Analysis Set (FAS)

Consensus Reading of Biopsies: Rigorous Approach to Histopathology Based on FDA Input to Minimize Variability

Key Features of EFX Biopsy Analysis Plan

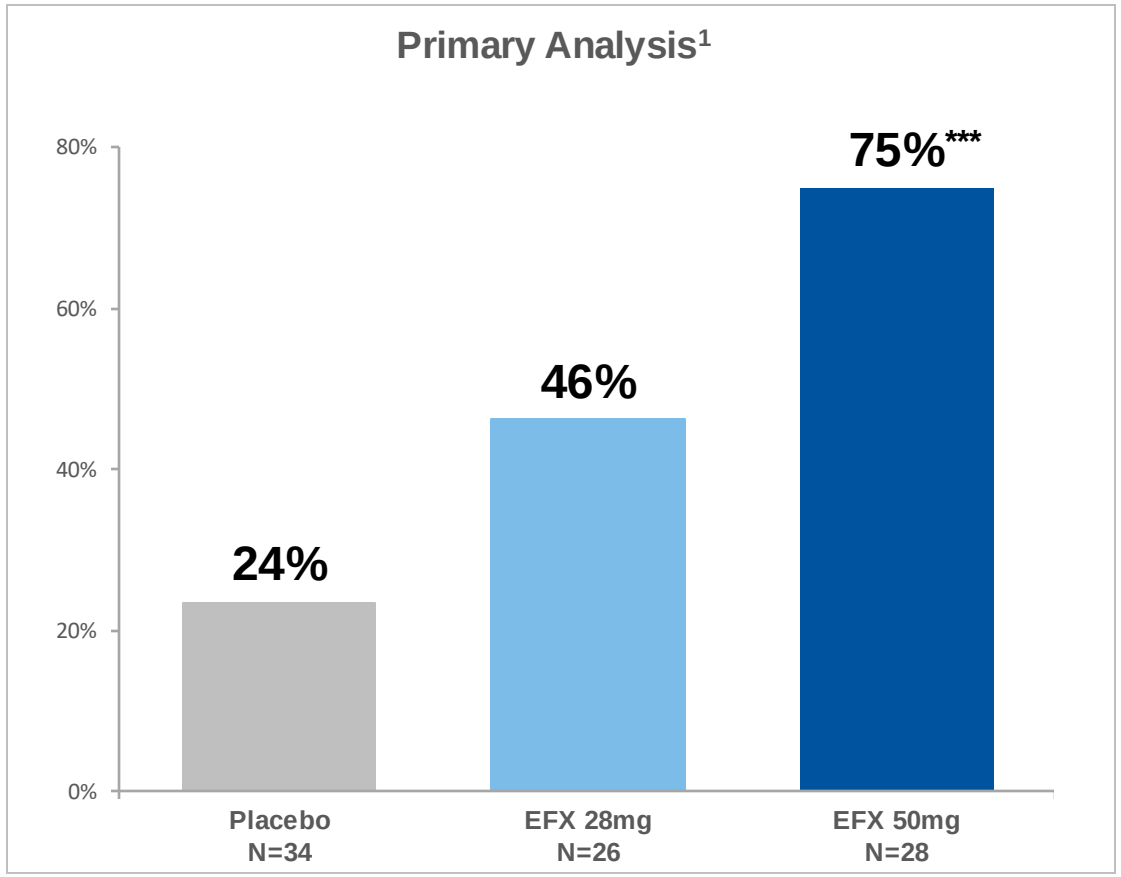
- Biopsies independently scored by two pathologists, with a third pathologist available to adjudicate in absence of consensus
- Pathologists underwent protocol-specific training to align on MASH-CRN scoring interpretation
- Pathologists blinded to subject, treatment, and sequence
- No paired biopsy reads (i.e., pre- and on-treatment biopsies not read side-by-side)

Consensus Biopsy Analysis Flow Chart



≥1 Stage Fibrosis Improvement & No Worsening of MASH:
Statistically Significant Response Observed for 50mg EFX at Week 96

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



[1] All subjects with baseline and Week 96 biopsies

*** p<0.001, versus placebo (Cochran-Mantel-Haenszel Test [CMH])

ITT Analysis[2]

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

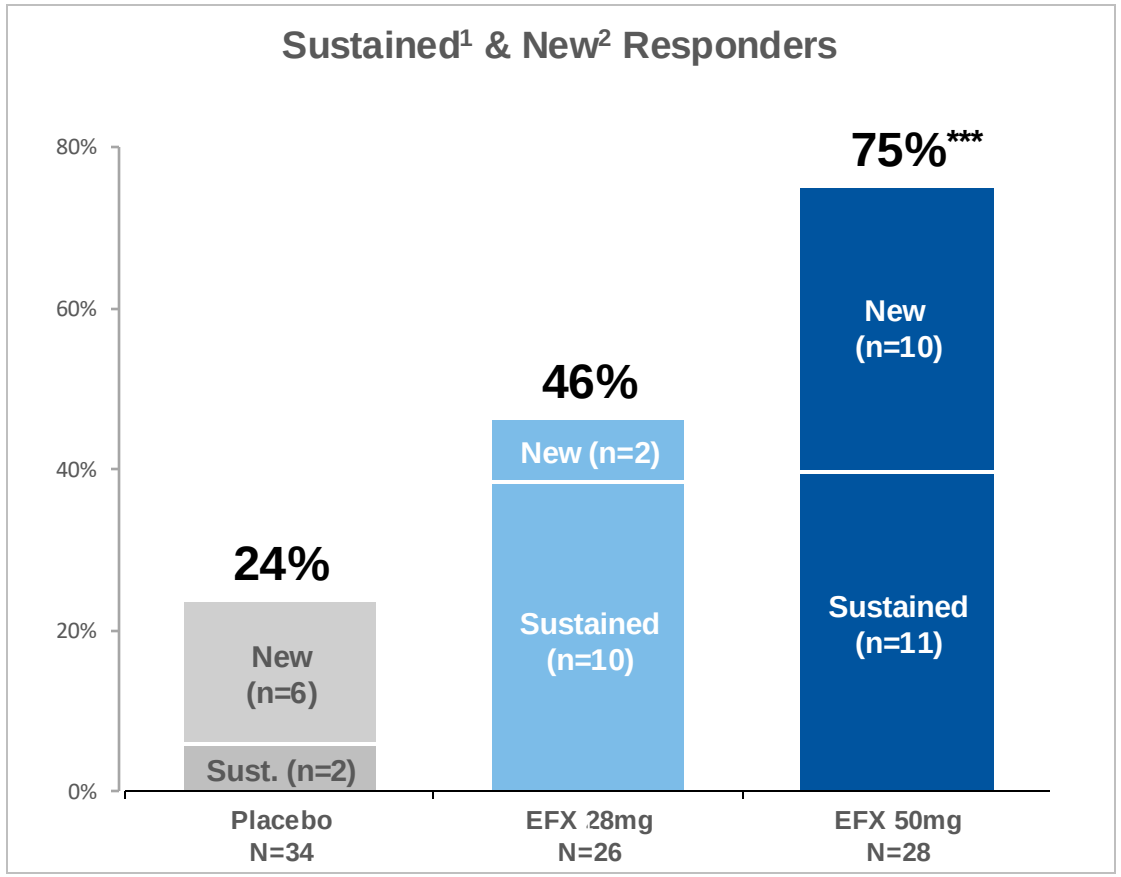
[2] All missing biopsies are imputed as a non-responder

** p<0.01, versus placebo (CMH)

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

≥1 Stage Fibrosis Improvement & No Worsening of MASH:
Sustained, Broad and Durable Response

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



[1] Responder at Weeks 24 & 96; [2] Responder at Week 96

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

Proportion of Week 24 Responders with Sustained Response at Week 96[3,5]

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

Proportion of Week 24 Non-Responders with New Response at Week 96[4,5]

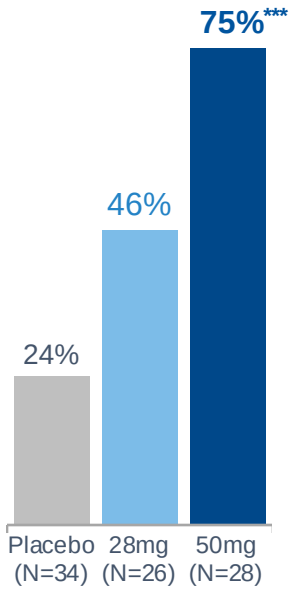
Placebo (N=29)	EFX 28mg (N=14)	EFX 50mg (N=16)
6 (21%)	2 (14%)	10 (63%)

[3] Among Week 24 responders with Week 96 biopsies
[3] Among Week 24 non-responders with Week 96 biopsies
[5] Not analyzed for statistical significance

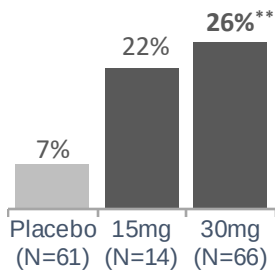
Source Data: LBAS-96

EFX Fibrosis Improvement in Context: Pre-Cirrhotic MASH:
≥1 Stage Improvement in Fibrosis & No Worsening of MASH

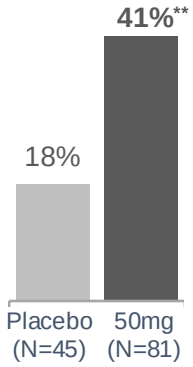
Efruxifermin
Phase 2b (F2-F3)
96 Wks / 66% F3
Consensus Reading
Completers[7]



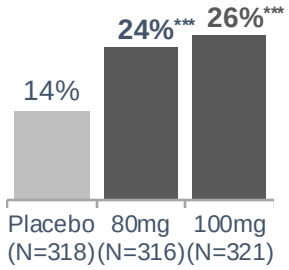
Pegozafermin[1]
Phase 2b (F2-F3)
24 Wks / 65% F3
Algorithmic Scoring
Completers[7]



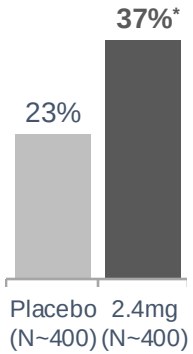
Denifanstat[2]
Phase 2b (F2-F3)
52 Wks / 58% F3
Single Pathologist
Completers[7]



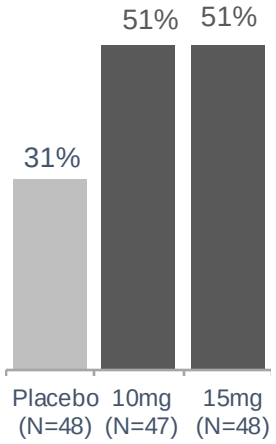
Rezdiffra[3]
Phase 3 (F1-F3)
52 Wks / 62% F3
Statistically Combined
ITT[8]



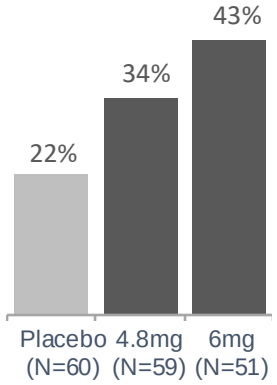
Semaglutide[4]
Phase 3 (F2-F3)
72 Wks / ?% F3
Consensus Reading
ITT[10]



Tirzepatide[5]
Ph2b (F2-F3)
52 Wks / 57% F3
Consensus Reading
ITT[11]



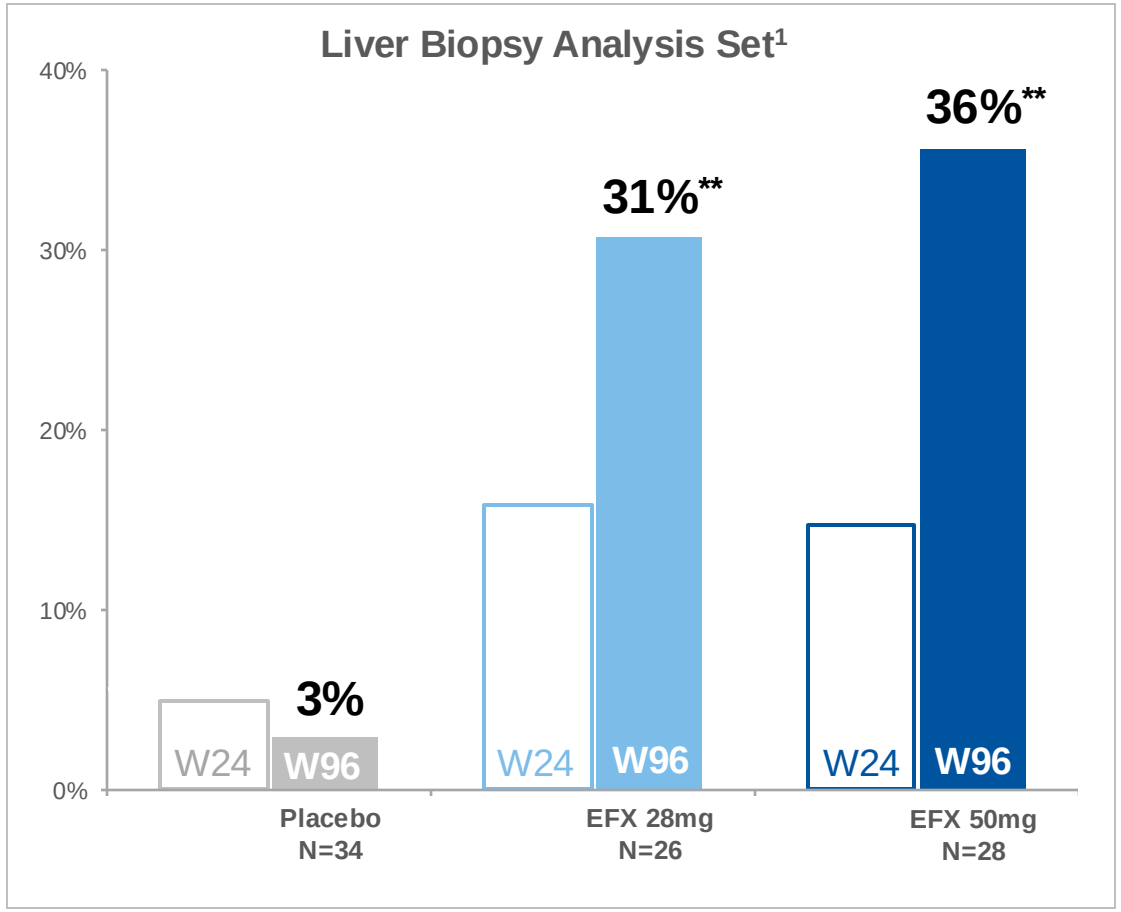
Survodutide[6]
Ph 2b (F2-F3[5])
48 Wks / 46% F3
Single Pathologist
ITT[8,9]



[1] 89Bio (2023) Mar 22 Corp Pres; [2] Sagimet (2024) Aug Corp Pres; [3] Madrigal (2022) Dec 19 Press Rel; [4] Novo Nordisk (2024) Nov 1 Press Rel; [5] Loomba et al. (2024) New Engl J Med 391, 299-310; [6] Sanyal et al. (2024) New Engl J Med 391, 311-9; [7] Baseline and end-of-study biopsies available; [8] Missing biopsies (or [9] failure to reach target dose) imputed as non-responders; [10] Based on treatment policy estimand: treatment effect regardless of treatment adherence; [11] Missing biopsies imputed assuming they follow the pattern of the placebo group. All trademarks are the property of their respective owners. * p<0.05, ** p<0.01, *** p<0.001, versus placebo (CMH). *Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.*

Rate of 2-Stage Fibrosis Improvement Doubled from Week 24 to 96

Fibrosis Improvement 2 Stages & No Worsening of MASH, Weeks 24 and 96



[1] All subjects with baseline and Week 24 or Week 96 biopsies

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

Week 96 ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
2%	20%**	23%**

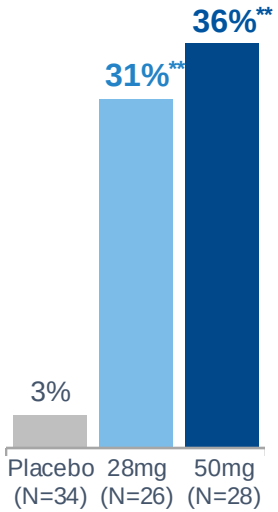
[2] Subjects with missing biopsies are imputed as non-responders

** p<0.01, versus placebo (CMH)

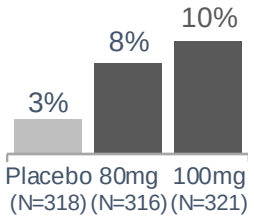
Source Data: LBAS-96; ITT

EFX Fibrosis Improvement in Context: Pre-Cirrhotic MASH:
≥2 Stage Improvement in Fibrosis & No Worsening of MASH

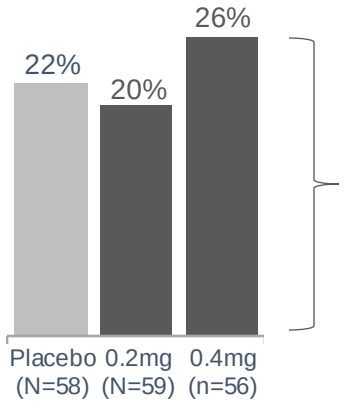
Efruxifermin
Phase 2b (F2-F3)
96 Wks / 66% F3
Consensus Readers
Completers[1]



Resmetirom
Phase 3 (F1-F3)
52 Wks / 62% F3
Two Readers
ITT[2]



Semaglutide
Phase 2b (F2-F3)
72 Wks / 69% F3
Consensus Readers
ITT[2]



Fibrosis Improvement Only (Worsening of MASH Not Reported)

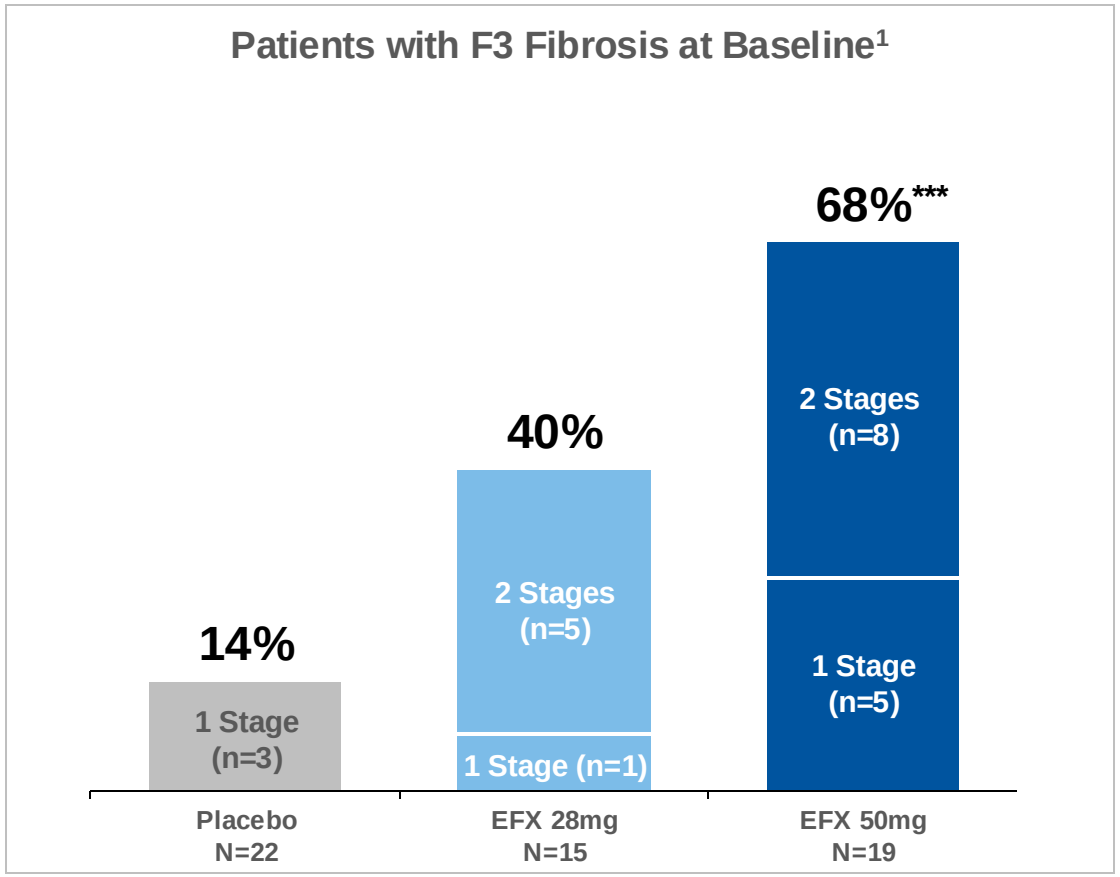
Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

** p<0.01, versus placebo (CMH)

[1] Baseline and end-of-study biopsies available; [2] Missing biopsies imputed as non-responders
Resmetirom – Madrigal (2022) December 19 Press Release; Semaglutide - Newsome et al. (2021) New Engl J Med 384, 1113-24

≥1 Stage Fibrosis Improvement & No Worsening of MASH:
Statistically Significant Response **Among F3 Patients** Observed for 50mg EFX

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

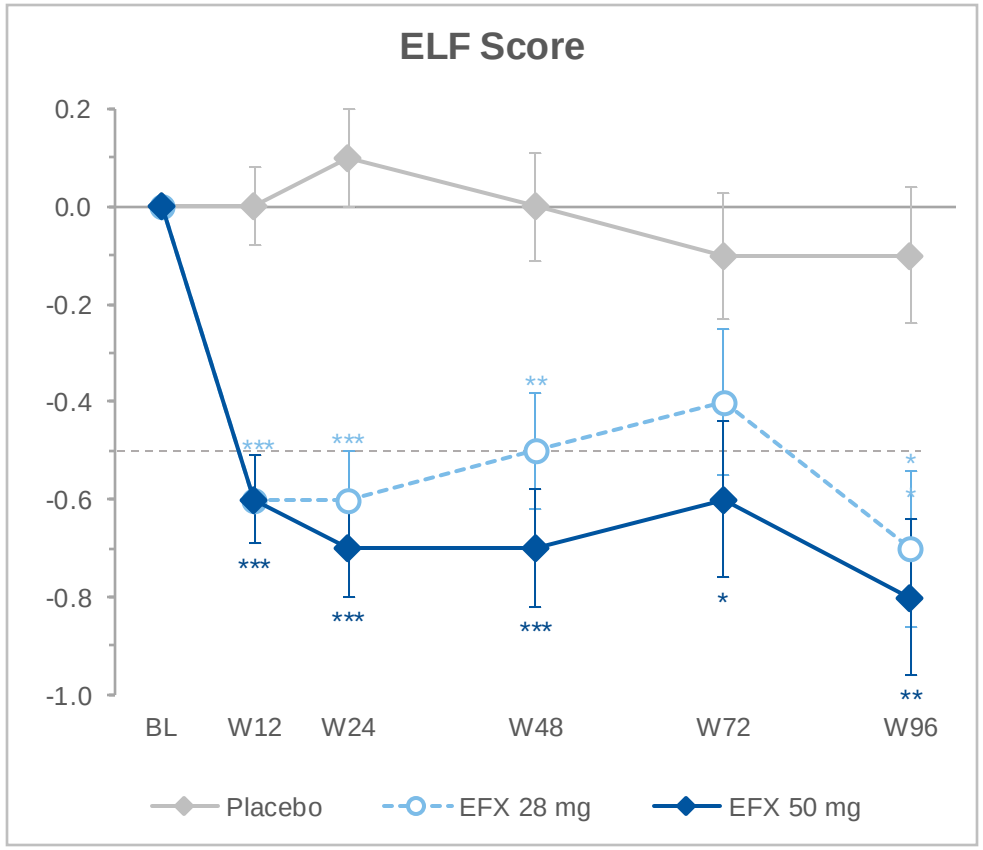


*** p<0.001, versus placebo (CMH)

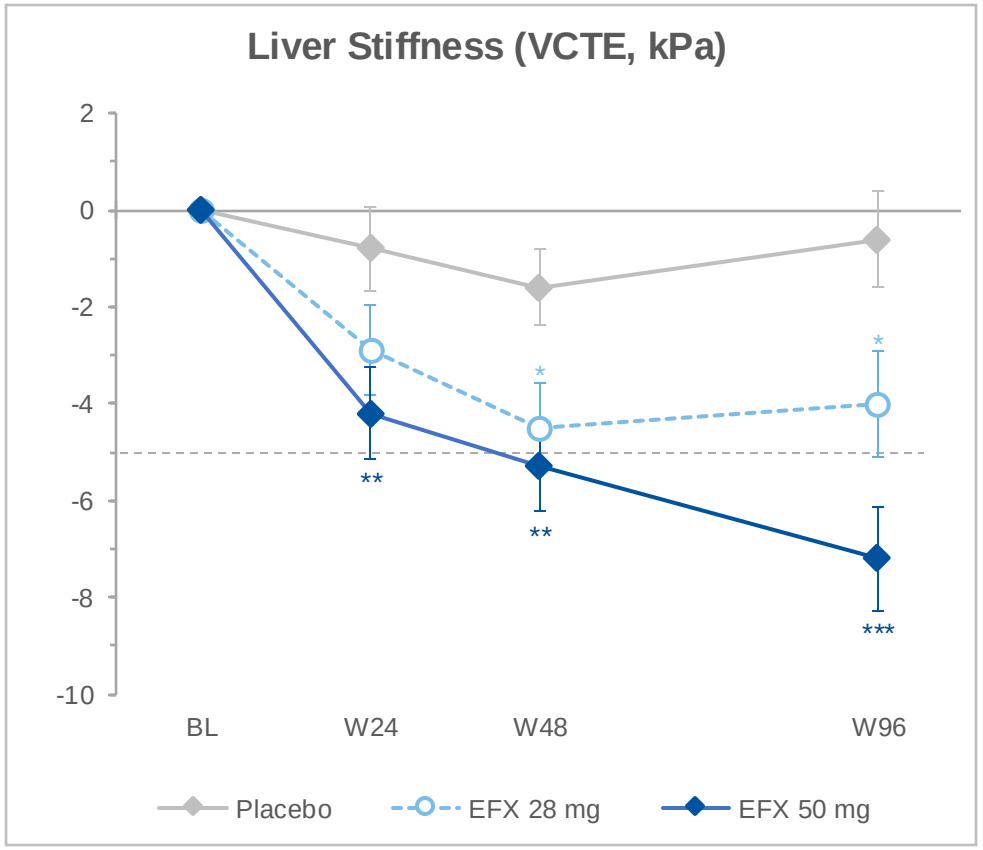
Source Data: LBAS-96 (F3 Subgroup, N=56)

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



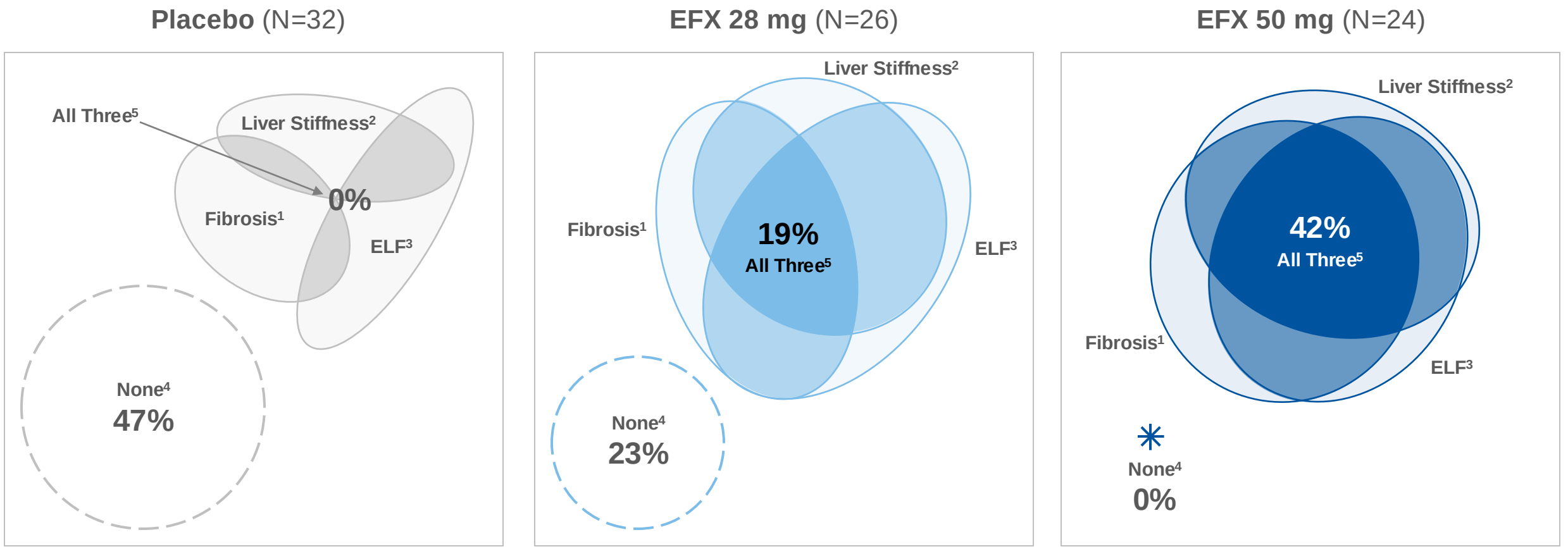
*p<0.05, **p<0.01, ***p<0.001 versus placebo (MMRM)



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

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

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



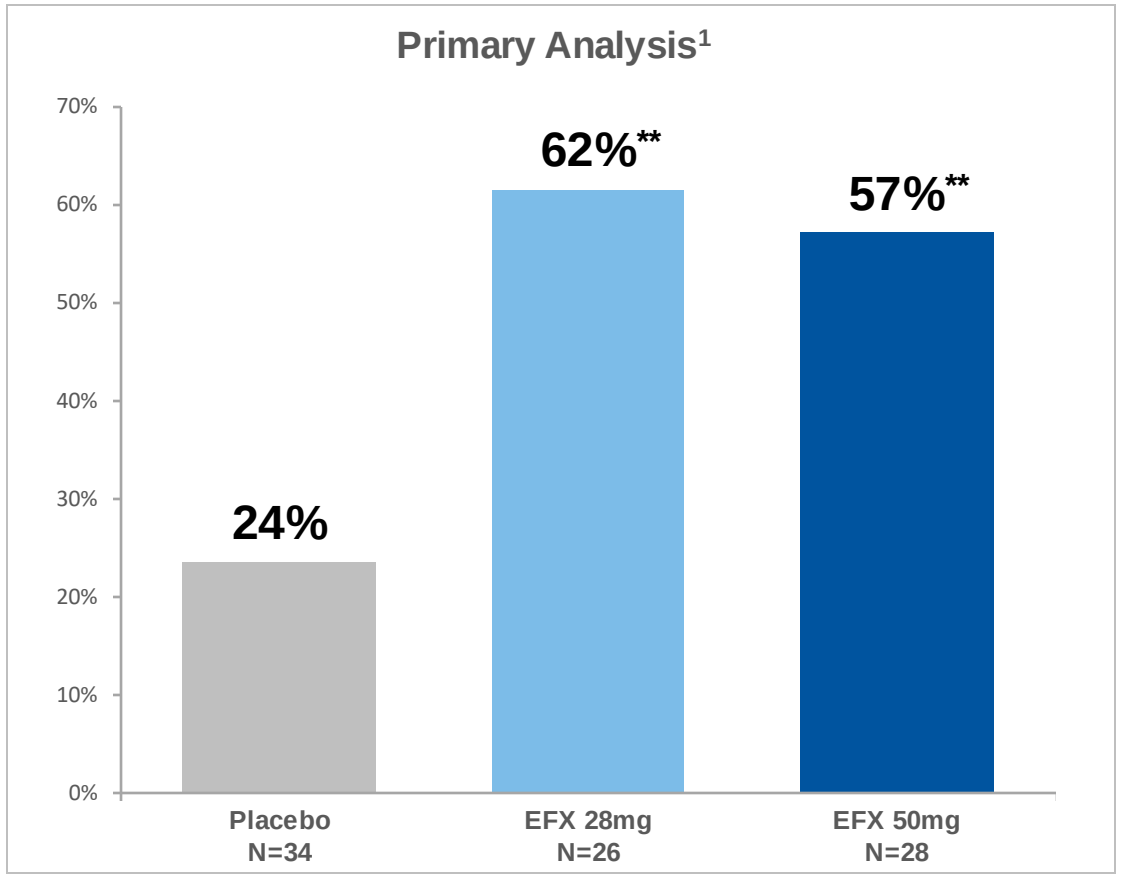
[1] Proportion with **histological fibrosis response** (improvement ≥1 stage without MASH worsening); [2] Proportion with **liver stiffness response** (≥30% reduction by FibroScan [VCTE]); [3] Proportion with **ELF response** (≥0.5 reduction in ELF Score); [4] None: Proportion without any of fibrosis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

MASH Resolution & No Worsening of Fibrosis:
Statistically Significant Response Observed for Both EFX Groups

MASH Resolution & No Worsening of Fibrosis at Week 96



[1] All subjects with baseline and Week 96 biopsies

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

ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
19%	40%*	37%*

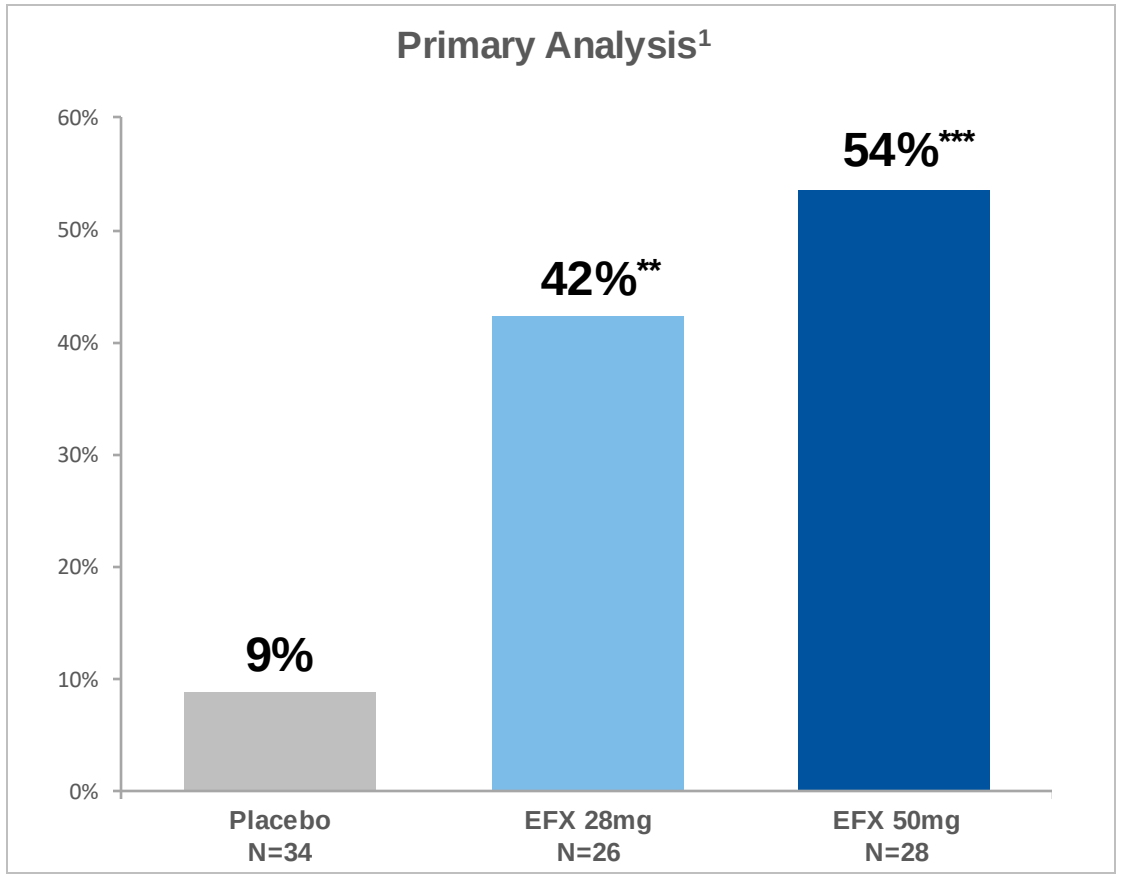
[2] Subjects with missing biopsies are imputed as non-responders

* p<0.05, versus placebo (CMH test)

Source Data: LBAS-96; ITT

≥1 Stage Fibrosis Improvement AND MASH Resolution:
Statistically Significant Response Observed for Both EFX Groups

Fibrosis Improvement ≥1 Stage AND MASH Resolution at Week 96



[1] All subjects with baseline and Week 96 biopsies

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

ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
7%	28%**	35%**

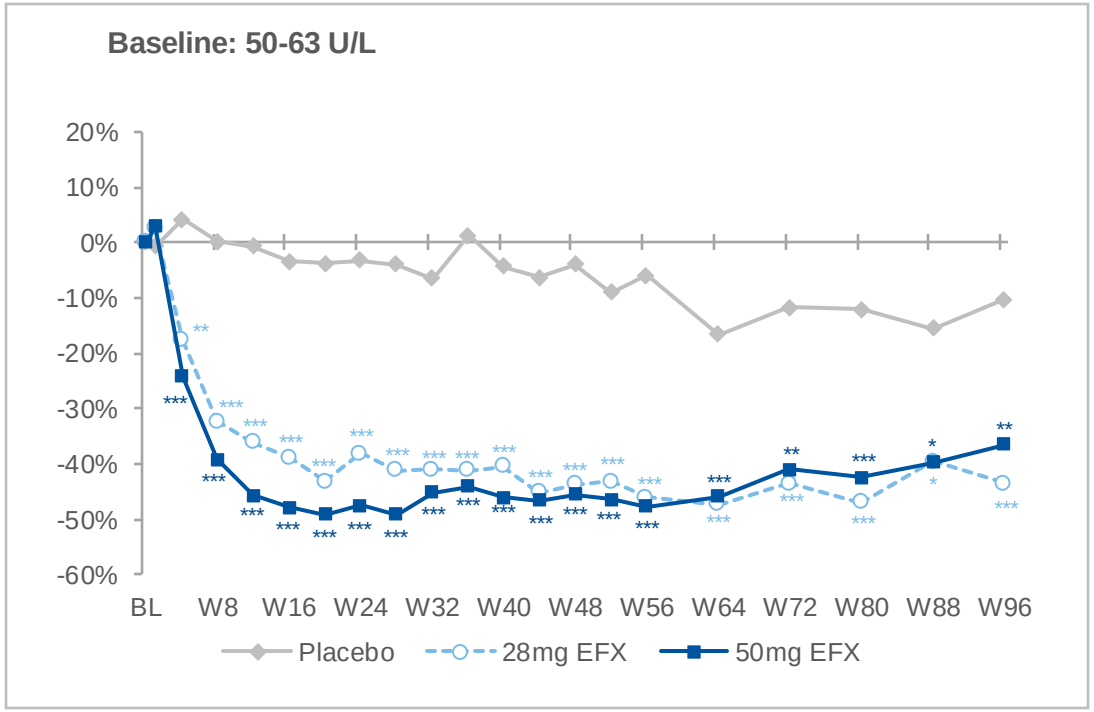
[2] Subjects with missing biopsies are imputed as non-responders

** p<0.01, versus placebo (CMH)

Source Data: LBAS-96; ITT

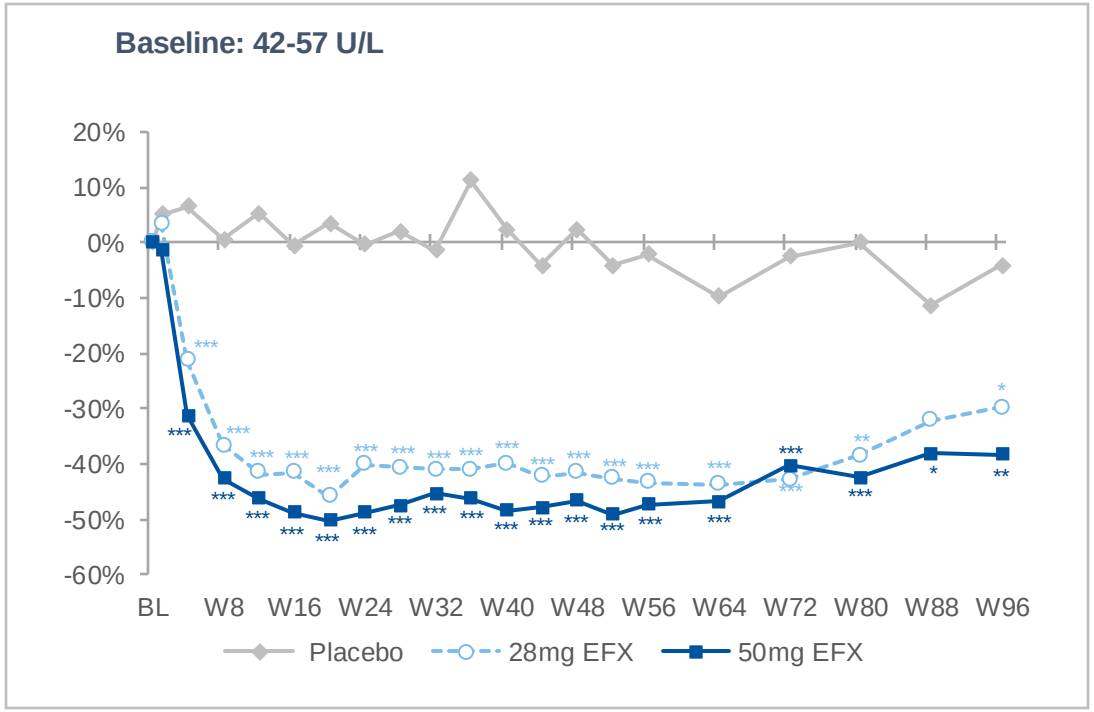
Statistically Significant Improvements in Markers of Liver Injury Sustained Through Week 96

ALT
LS Mean Percent Change from Baseline



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

AST
LS Mean Percent Change from Baseline



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

Source Data: FAS

Treatment-Emergent Adverse Events (TEAE)
From Baseline through Week 96

TEAE Overview	Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
TEAE Leading to Death	0 (0%)	0 (0%)	0 (0%)
Serious Adverse Event (SAE)	4 (9%)	4 (10%)	7 (16%)
Drug-Related SAE	0 (0%)	1 (2%)[a]	1 (2%)[b]
Drug-Related TEAE Leading to Discontinuation	0 (0%)	4 (10%)[c,d]	3 (7%)[e,f]
Most Frequent (≥15%) Drug–Related TEAEs	**Placebo**	**EFX 28mg**	**EFX 50mg**
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%)

[a] Post week 24: pancreatitis (not confirmed on imaging and discharged within 24 hours)
[b] Previously reported: esophagitis
[c] Previously reported: (1) increased appetite & weight gain; (2) diarrhea;
[d] Post week 24: (1) pancreatitis (SAE reported above); (2) diarrhea
[e] Previously reported: (1) esophagitis & vomiting; (2) nausea
[f] Post week 24: (1) diarrhea

Source Data: Safety Set

Safety Overview

Blood Pressure

- No statistical difference versus placebo in systolic & diastolic BP at week 96

Markers of Liver Function and Hemostasis

- Remained stable, including platelets, bilirubin, INR[1], MELD[2] and CP[3] score

Progression to Cirrhosis

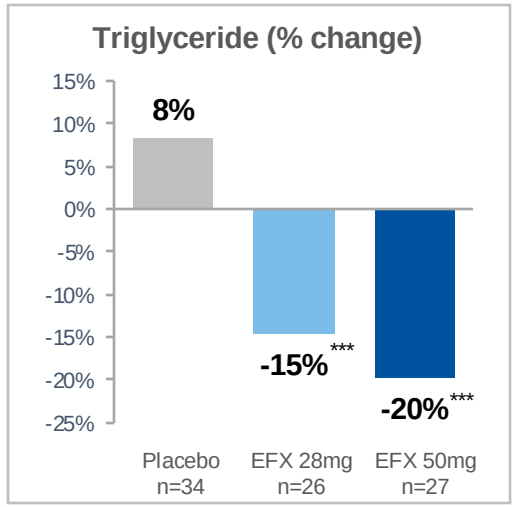
- Balanced across dose groups

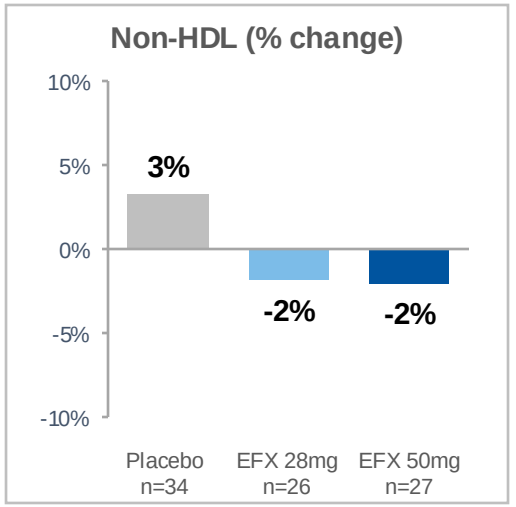
Bone Mineral Density

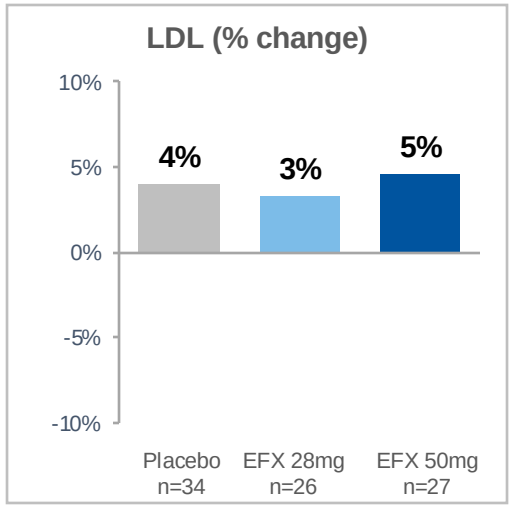
- At week 48, no significant changes versus placebo for lumbar spine and femoral neck regions
- At week 96, significant reductions versus placebo for lumbar spine (3-4%, both EFX groups) and femoral neck regions (< 3%, 50mg EFX only)
- One vertebral fracture (L1) observed in placebo group; no vertebral fractures observed in EFX groups

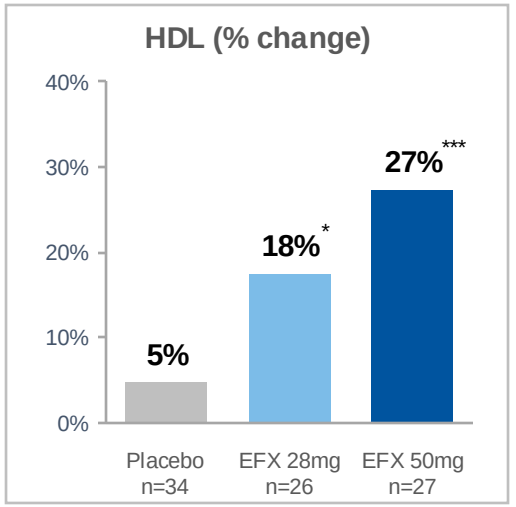
[1] Prothrombin International Normalized Ratio; [2] Model for End-Stage Liver Disease; [3] Child-Pugh

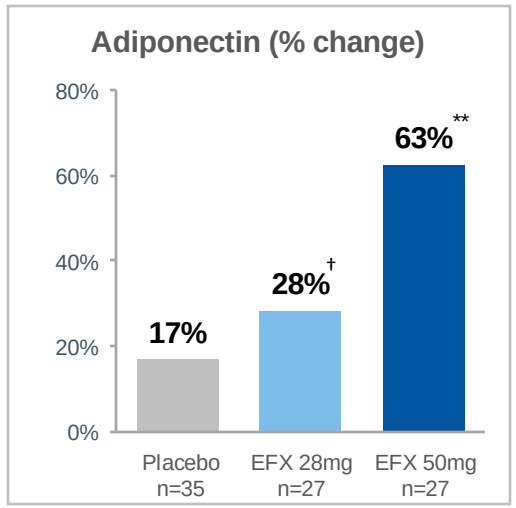
Improvement in Lipoproteins, Markers of Insulin Sensitivity and Body Weight After 96 Weeks, LS Mean Change From Baseline

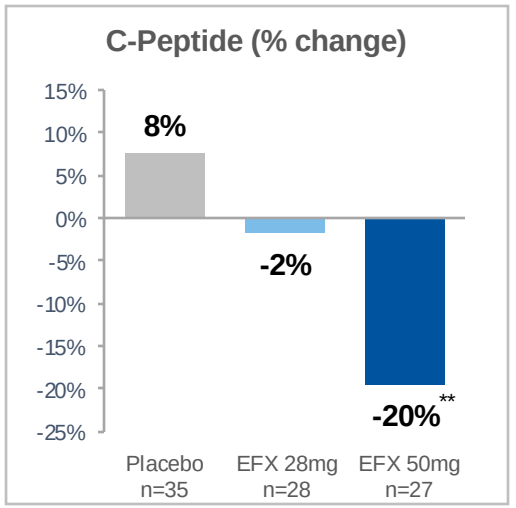


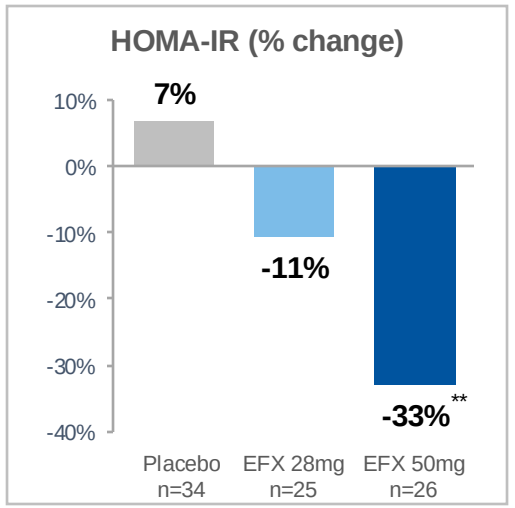


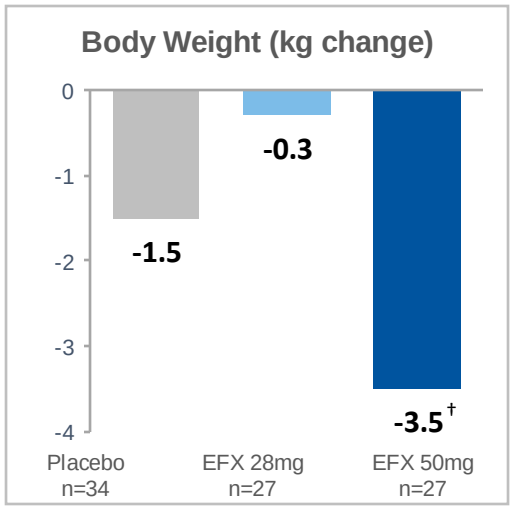












* p<0.05, ** p<0.01, *** p<0.001, versus placebo (MMRM); † p<0.05, versus baseline (MMRM)

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

HARMONY Take-Aways: 50mg EFX After 96 Weeks

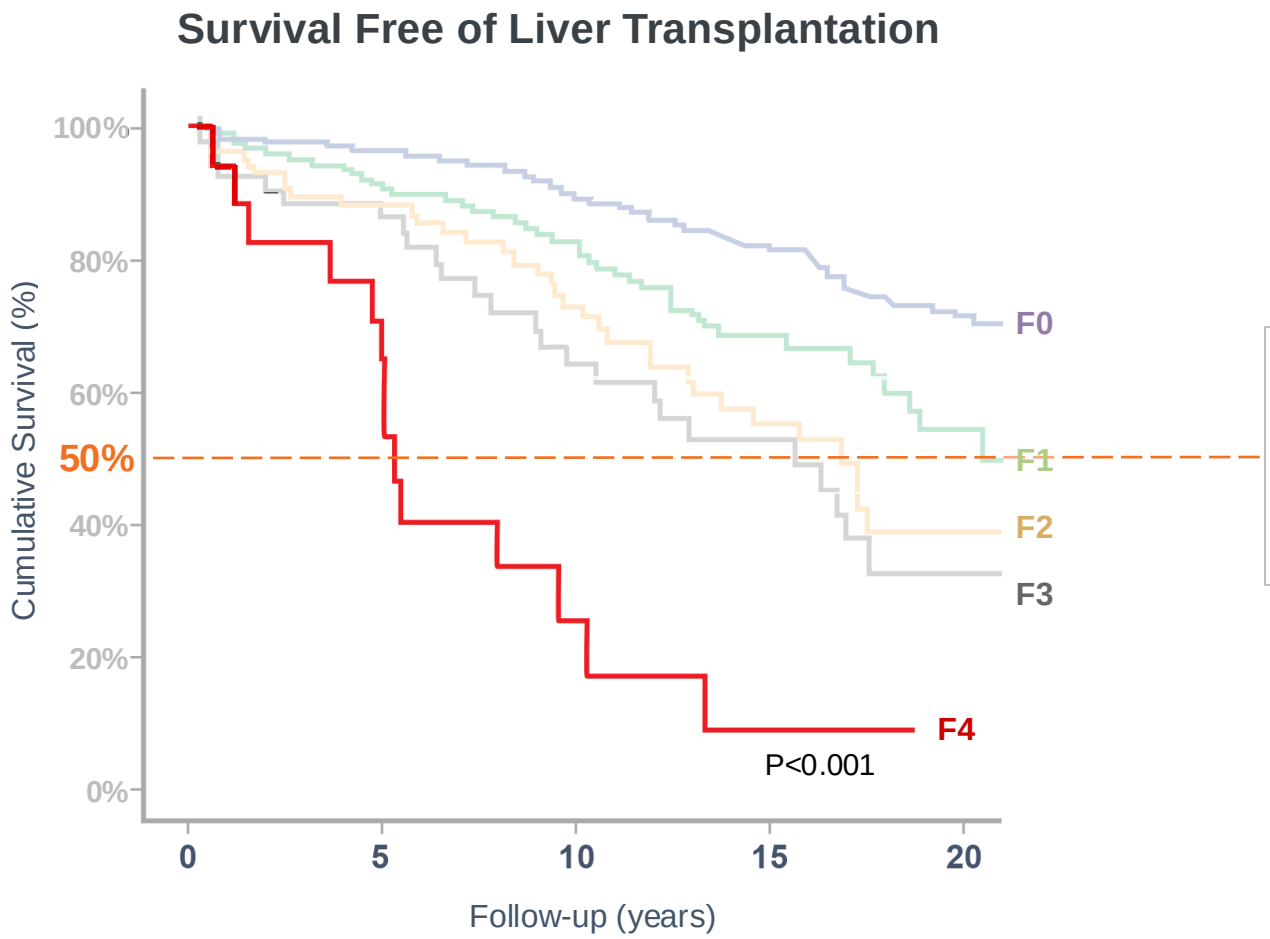
Unprecedented	Deep	Broad	Durable	Advanced
≥1 Stage Improvement In Fibrosis[1]	2-Stage Improvement In Fibrosis[2]	Conversion Of Non-Responders[3]	Week 24 to Week 96 Fibrosis Response[4]	Fibrosis Improvement Among F3 Patients[5]
75%* vs. 24%** (50mg EFX vs. Placebo)	**36%*** vs. 3%** (50mg EFX vs. Placebo)	**63% vs. 20%[6]** (50mg EFX vs. Placebo)	**92% vs. 40%[6]** (50mg EFX vs. Placebo)	**68%*** vs. 14%** (50mg EFX vs. Placebo)

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

[1] ≥1 stage improvement in fibrosis without worsening of MASH; [2] 2 stages improvement in fibrosis without worsening of MASH; [3] proportion of Week 24 non-responders who converted to week 96 responders; [4] proportion of Week 24 responders who were also week 96 responders; [5] ≥1 stage improvement in fibrosis without worsening of MASH among patients with week 96 biopsies and F3 fibrosis at baseline; [6] Not evaluated for statistical significance

Source Data: LBAS-96

High Risk of Mortality Associated with Cirrhosis Due to MASH



~50%

5-year mortality
without liver transplant
for **F4 patients**

Angulo, P et al. (2015) Gastroenterology 149:389-397

SYMMETRY Trial Design: Compensated Cirrhosis Due to MASH (F4) with Liver Histology at 36 and 96 weeks

Key Inclusion Criteria[1]

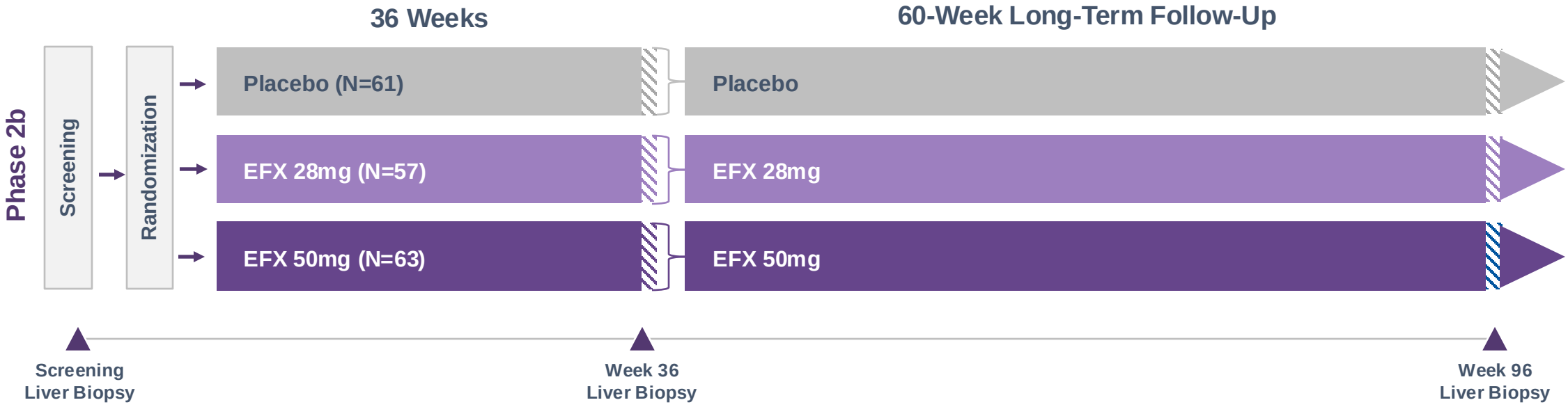
- F4 MASH (compensated)
- T2D or 2 of 4 components of metabolic syndrome

Phase 2b Primary Endpoint

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

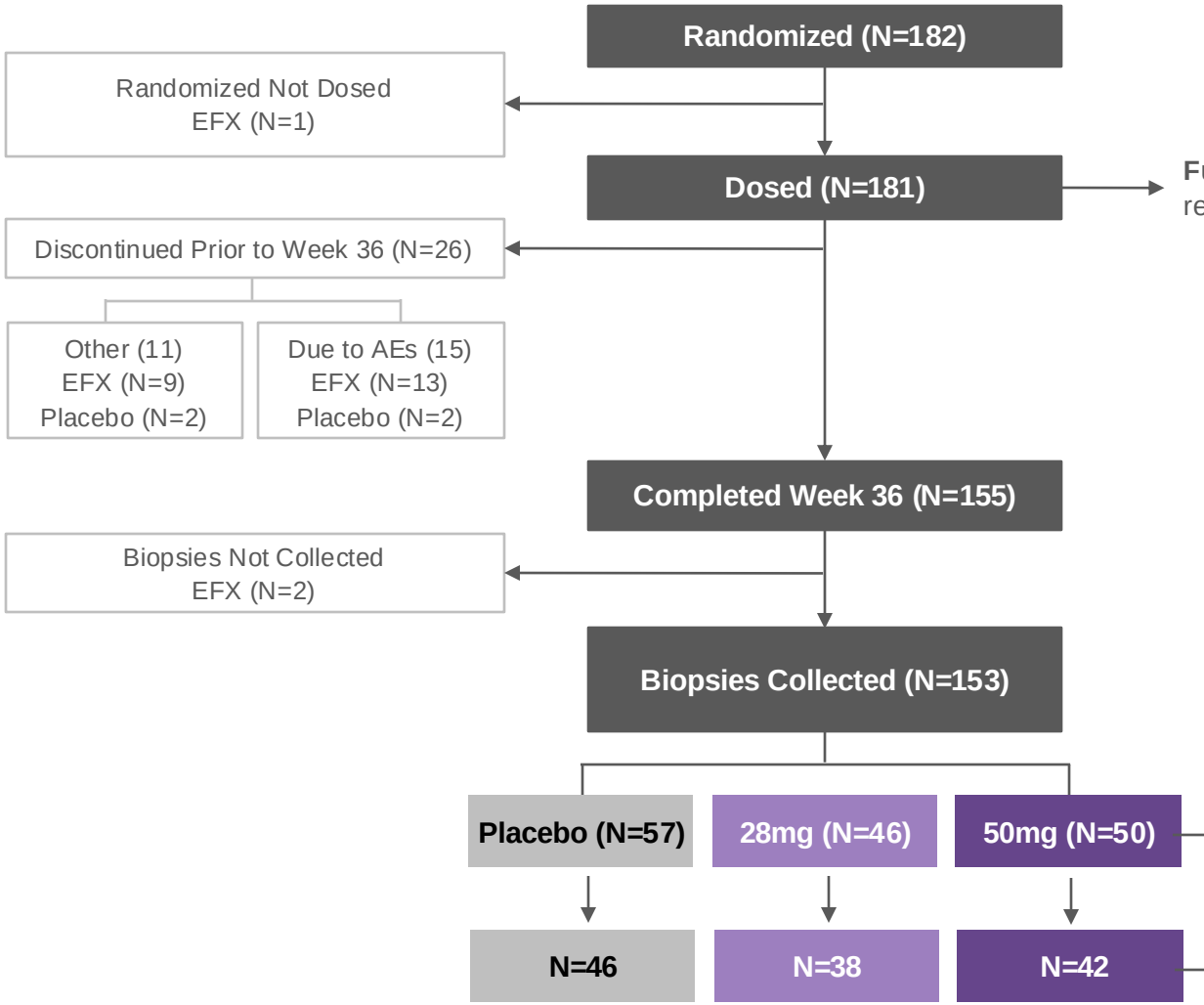
Key Secondary Efficacy Endpoints

- MASH Resolution
- Fibrosis Markers
- Lipoproteins
- Glycemic Control
- Weight Change
- Liver Injury Markers



[1] All patients had biopsy-proven compensated cirrhosis (fibrosis stage 4) due to definitive MASH or cryptogenic cirrhosis presumed secondary to MASH. Subjects with cryptogenic cirrhosis were limited to approximately 20% of the total study population.

SYMMETRY Week 36 Patient Disposition & Key Analysis Sets



Full Analysis Set / Safety Set – All subjects who were randomized and received at least one dose of study drug

Primary Endpoint
Liver Biopsy Analysis Set
All subjects who have Baseline & Week 36 liver biopsy results

Secondary Histological Endpoints
Liver Biopsy Analysis Set (Definitive MASH[1] Only)
Excludes all subjects with cryptogenic cirrhosis

[1] MAS ≥ 3 with a score of ≥ 1 for each of steatosis, inflammation and ballooning

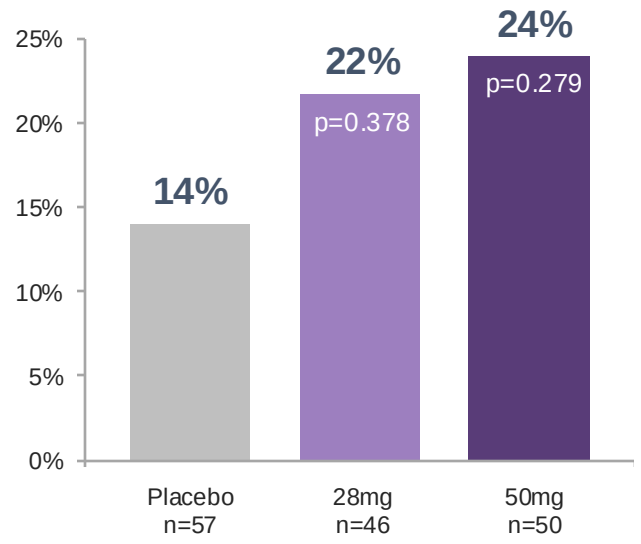
SYMMETRY Baseline Demographics

Parameter (Mean)	Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
Age (Years)	61	62	59
Sex (% Female)	62	68	70
Definitive MASH (%) / Cryptogenic Cirrhosis (%)	74 / 26	79 / 21	83 / 17
Enhanced Liver Fibrosis (ELF) Score	10.4	10.6	10.5
Pro-C3 (µg/L) (Generation 2 ELISA)	132	142	147
Liver Stiffness by VCTE (FibroScan) (kPa)	24.7	24.1	24.5
FAST Score	0.60	0.60	0.62
Alanine Aminotransferase (ALT) (U/L)	40.3	40.1	38.4
Aspartate Aminotransferase (AST) (U/L)	35.5	37.1	37.5
Type 2 Diabetes (%)	82	81	78
HbA1c (%)	6.8	6.8	6.6
Baseline Use of GLP-1 (%) / Sulfonylurea / (%) Insulin (%)	28 / 20 / 16	21 / 21 / 11	32 / 30 / 21
Triglycerides (mg/dL)	143	148	159
Statin Use (%)	52	46	43
Weight (kg)	102	99	95

Summary of Week 36 SYMMETRY Liver Histology

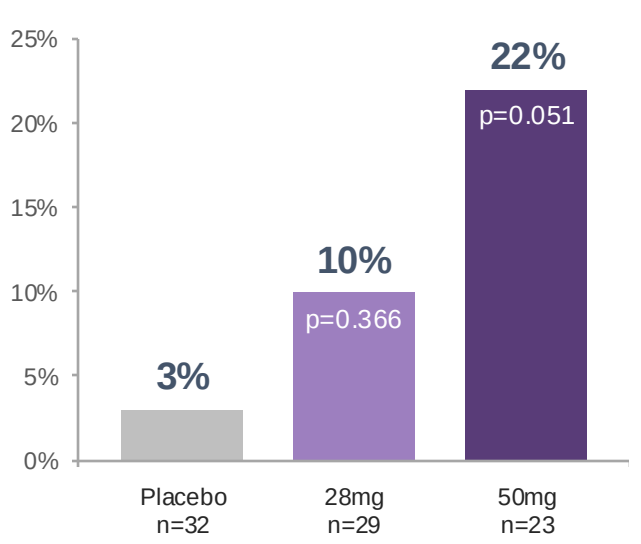
Fibrosis Improvement ≥1 Stage Without Worsening of MASH at Week 36

All Patients with Baseline and Week 36 Biopsies (Primary Endpoint) (N=153)



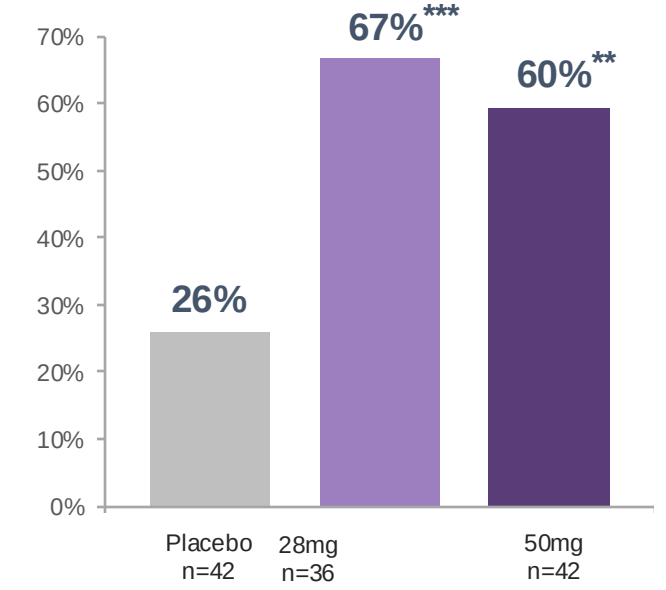
Statistically significant fibrosis improvement without worsening of MASH in patients with cirrhosis has not been reported for any investigational drug to date.

Subgroup: Cirrhosis Diagnosed ≥ 6 Months or Cryptogenic Cirrhosis (N=84)



Longer duration of cirrhosis at baseline may increase proportion of liver with features of F4 cirrhosis versus F3, thus reducing probability of reversal to F3 for placebo patients.

MASH Resolution at Week 36



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

The Phase 2b SYMMETRY study is the first known report of statistically significant response rates for MASH resolution.

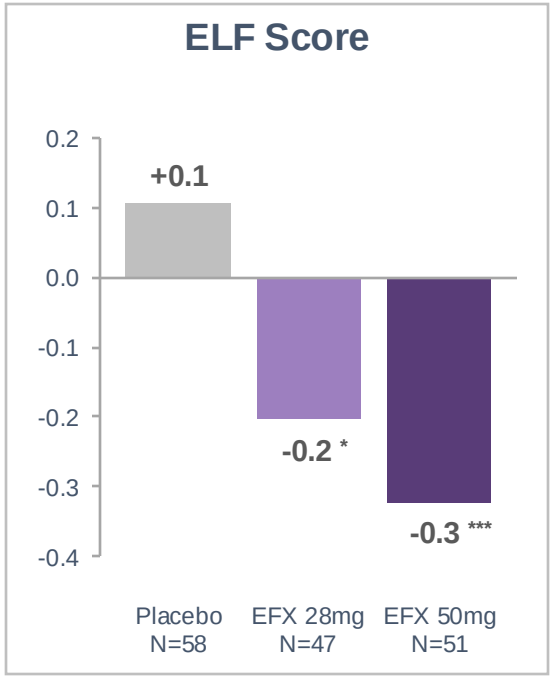
4 patients experienced 3- or 2-stage fibrosis improvement without worsening of MASH at Week 36

Source Data: Week 36 Interim Liver Biopsy Analysis Set; Topline preliminary data

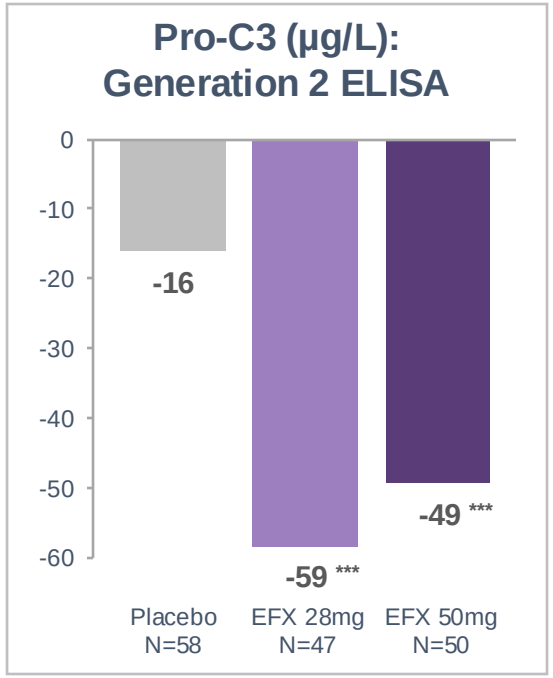
SYMMETRY Evidence of Anti-Fibrotic Activity:
Analysis of Noninvasive Fibrosis Markers

akero

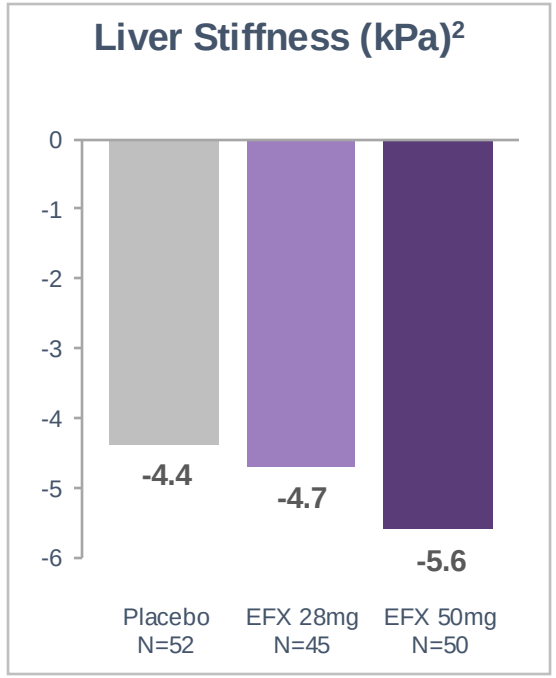
Change[1] From Baseline to Week 36

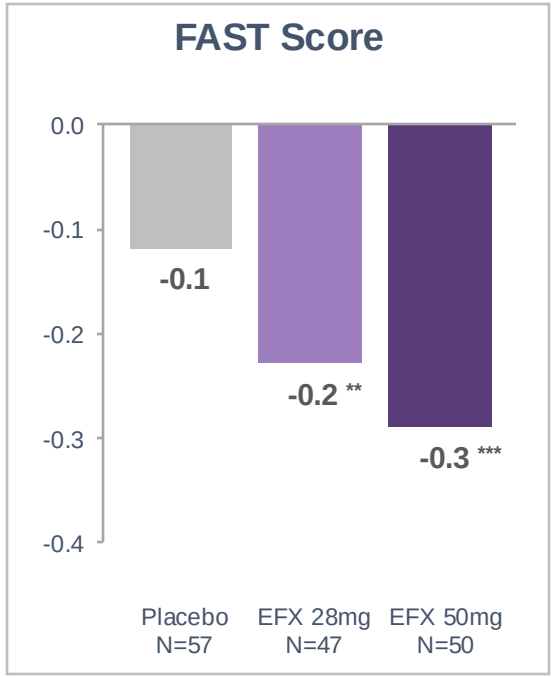


* p<0.05, ** p<0.01, versus placebo (Mixed Model Repeated Measures [MMRM])



*** p<0.001, versus placebo (MMRM[1])





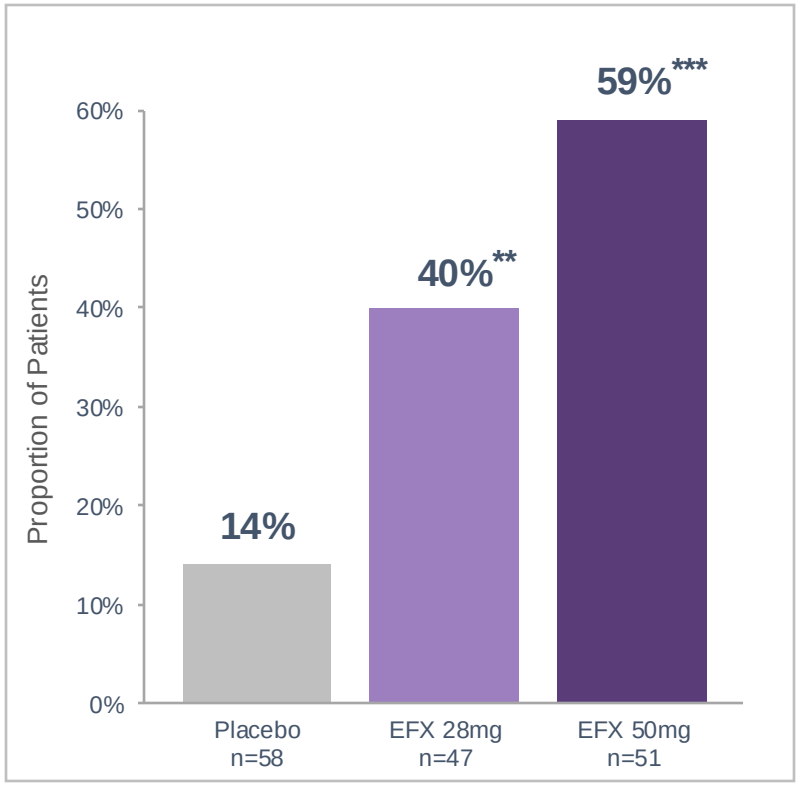
** p<0.01, *** p<0.001, versus placebo (MMRM[1])

[1] LS Mean (ELF Score, Pro-C3 and FAST Score); Arithmetic Mean (Liver Stiffness); [2] Measured by FibroScan

Source Data: Week 36 Interim Full Analysis Set (non-missing values only, no imputation); Topline preliminary data

Substantially More EFX-Treated Patients Achieved Clinically Meaningful Reductions of ELF and Pro-C3

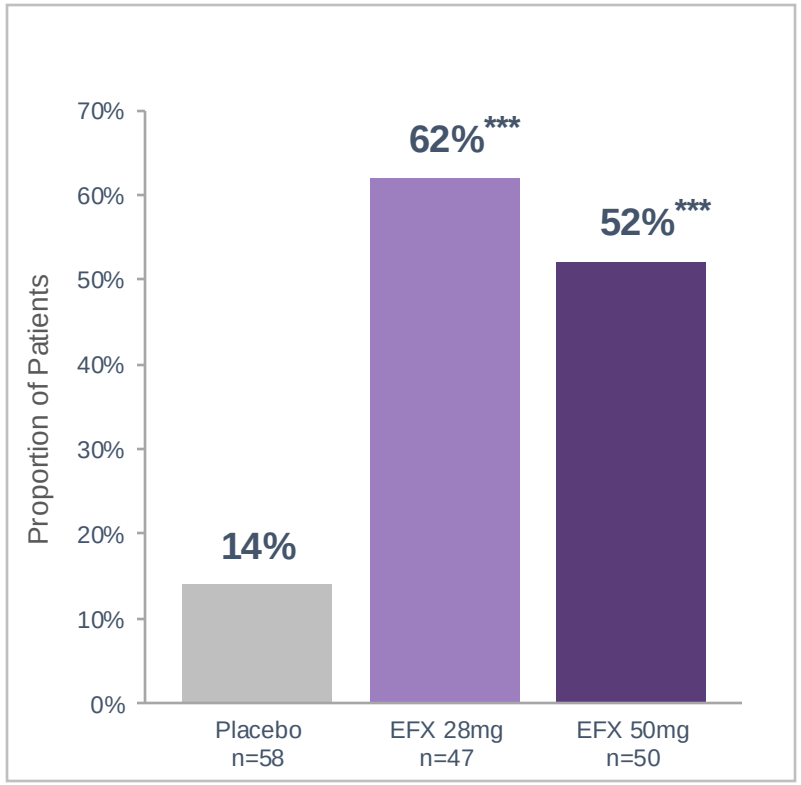
ELF Reductions of ≥0.5 Points



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

Reductions of 0.5 in ELF Score and ≥20% in Pro-C3 (GEN1) have each been reported to be associated with reduced disease progression

Pro-C3 (GEN2) Reductions of ≥35%



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

Harrison, SA et al. (2020) J Hepatology 73:26-39; Luo, Y et al. (2018) Scientific Reports 8:12414

Case Study: 3-Stage Fibrosis Improvement & MASH Resolution

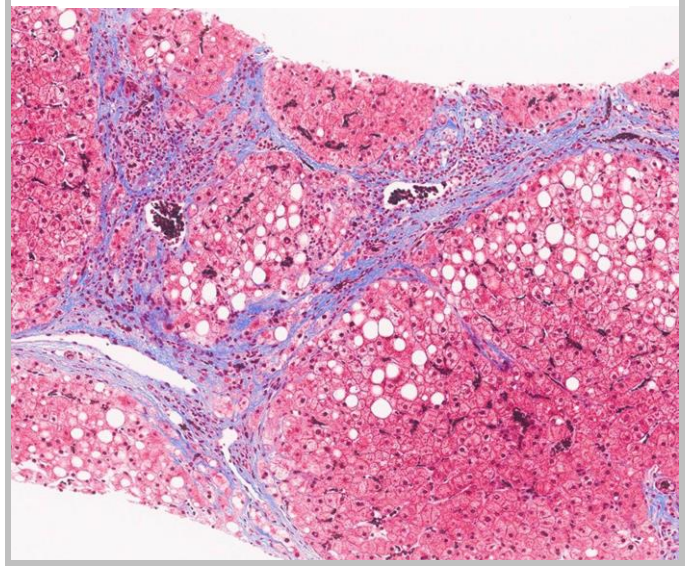
Histological Observations Consistent with Noninvasive Tests

Patient Background & Weight Loss During Study

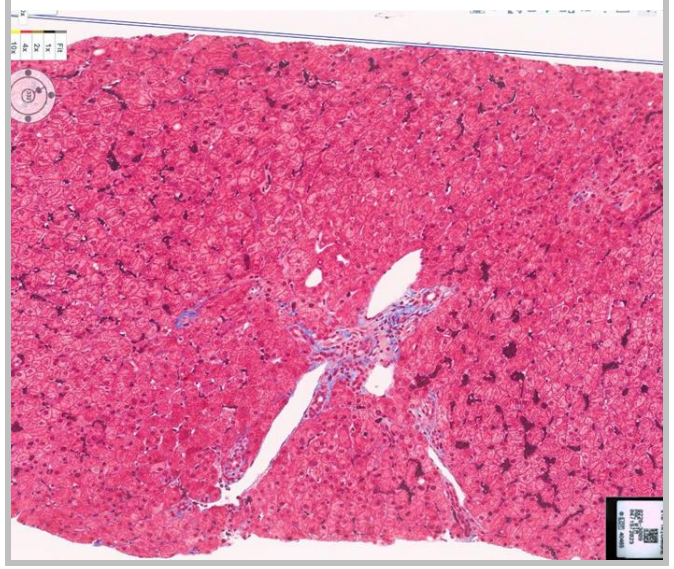
69-year-old female; T2D; cirrhosis diagnosed 17.4 months prior to first dose; no GLP-1 use at baseline; weight loss of 2 Kg (-3%) at Week 36

Comparison of Biopsy Features

Baseline Biopsy



Week 36 Biopsy



Comparison of Histology and Fibrosis Markers

Fibrosis Stage

Measure	Baseline	Week 36	Change
Fibrosis Stage	4	1	**-3**

MASLD Activity Score

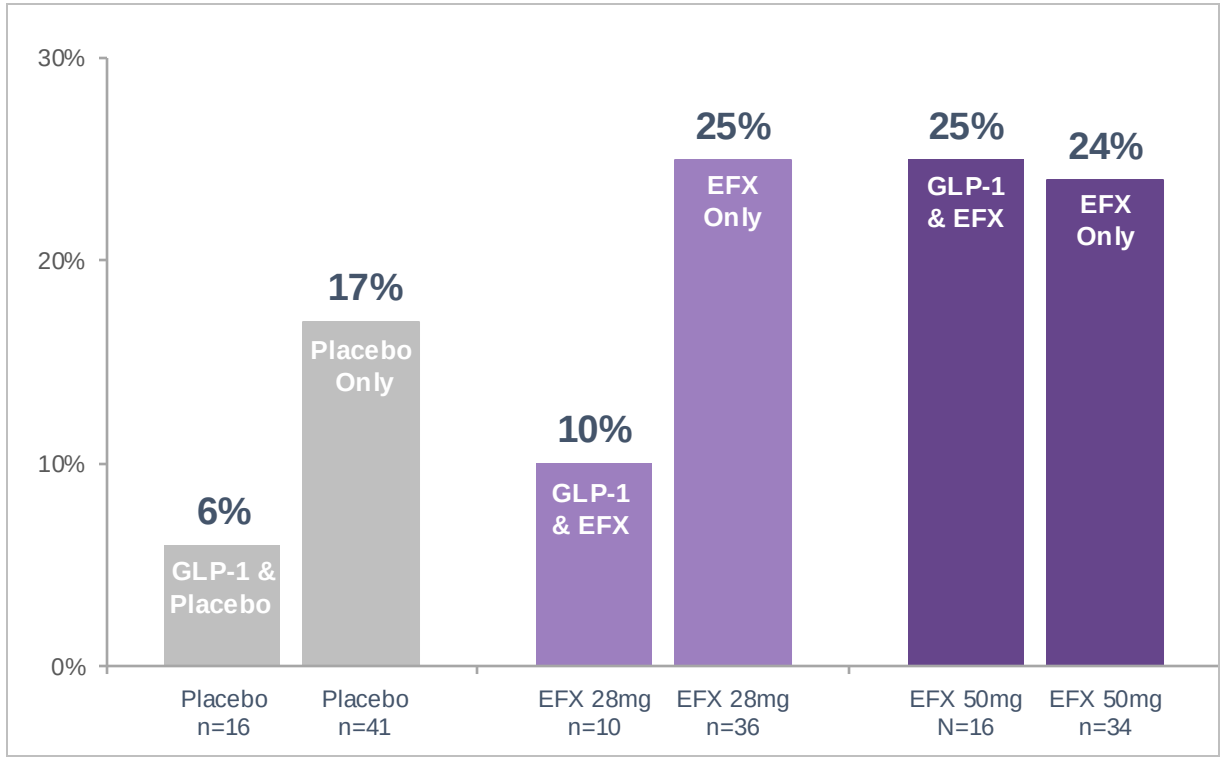
Measure	Baseline	Week 36	Change
Total Score	**5**	**0**	**-5**
Steatosis	1	0	**-1**
Ballooning	2	0	**-2**
Lobular Inflammation	2	0	**-2**

Non-Invasive Fibrosis Markers

Measure	Baseline	Week 36	Change
ALT (U/L)	29	14	**-52%**
AST (U/L)	32	20	**-38%**
Pro-C3 (µg/L)	73	54	**-26%**
ELF Score	10.57	9.44	**-1.13**
FAST Score	0.45	0.15	**-0.30**

Concomitant Use of GLP-1 with EFX Does Not Appear to Contribute to Fibrosis Improvement Response Rates

Fibrosis Improvement ≥1 Stage Without Worsening of MASH at Week 36:
Baseline GLP-1 Use vs. No Baseline GLP-1 Use



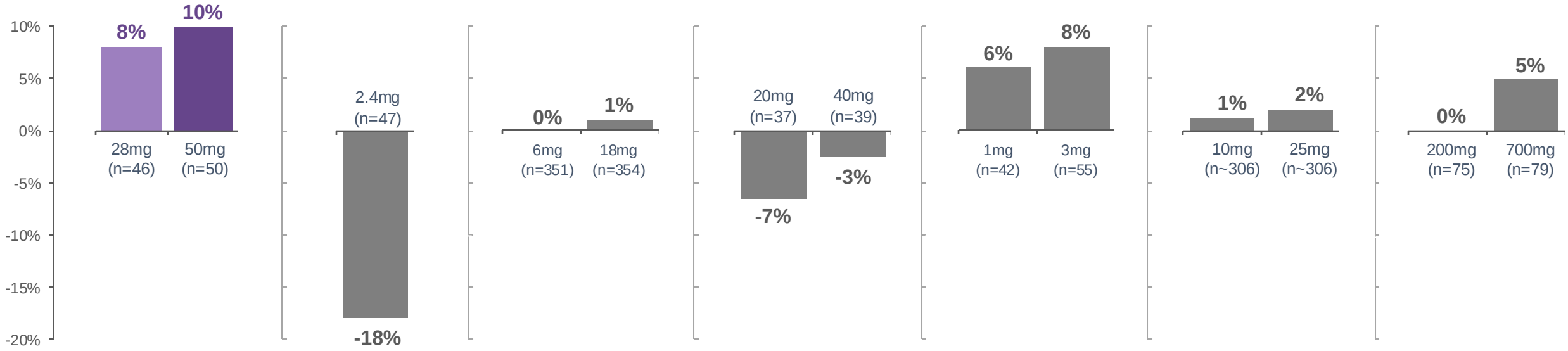
- If GLP-1 agonist therapy was responsible for histological treatment response, we would expect to observe higher response rates for the subgroups receiving GLP-1 therapy at baseline
- Smaller proportions of patients treated with GLP-1 & placebo or GLP-1 & EFX 28mg experienced fibrosis improvement without worsening of MASH than those treated with placebo or EFX 28mg alone
- Patients treated with GLP-1 & EFX 50mg experienced fibrosis improvement without worsening of MASH at about the same rate as patients treated with EFX 50mg alone

Source Data: Week 36 Liver Biopsy Analysis Set; Topline preliminary data

Landscape for Cirrhosis Due to MASH:
Placebo-Corrected Fibrosis Improvement With No Worsening of MASH

Fc-FGF21	GLP-1	ASK-1	Peg-FGF21	FGF19	FXR	LOXL-2
Efruxifermin	**Semaglutide**	**Selonsertib**	**Pegbelfermin**	**Aldafermin**	**Obeticholic acid**	**Simtuzumab**
36 Wks / Ph2b	48 Wks / Ph2b	48 Wks / Ph3	48 Wks / Ph2b	48 Wks / Ph2b	78 Wks / Ph3	96 Wks / Ph2b
Active	Active	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Placebo Rate → 14%	29%	13%	31%	15%	10%	8%

By Treatment Duration



Includes results from publicly reported placebo-controlled studies in patients with compensated cirrhosis due to MASH reporting either ≥ 1-stage fibrosis improvement and no worsening of MASH (EFX, semaglutide, selonsertib, pegbelfermin, obeticholic acid) or only ≥ 1-stage fibrosis improvement (aldafermin, simtuzumab); numerical values represent percent responders

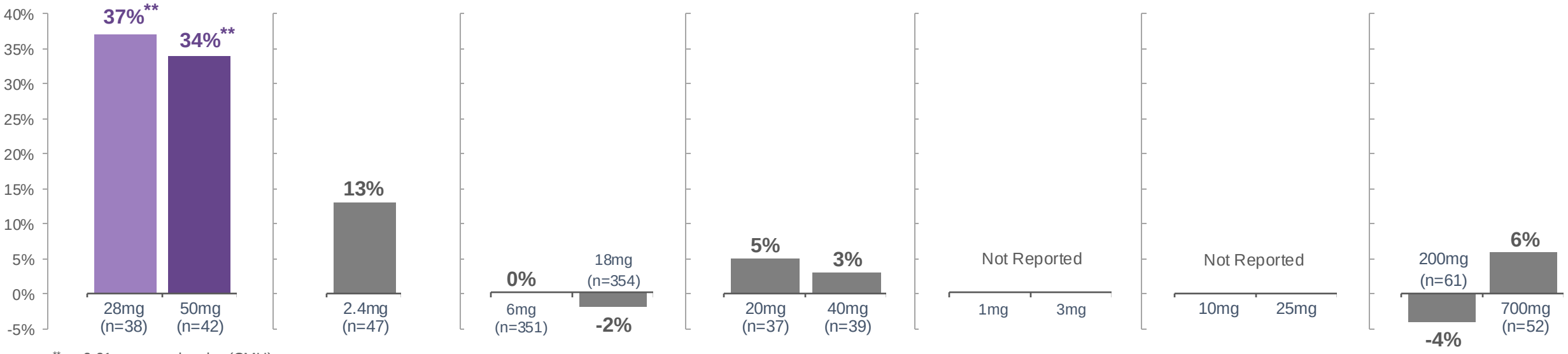
Semaglutide – Loomba, R et al. (2023) Lancet Gastro Hep 8:511-22; Selonsertib – Harrison, SH et al. (2020) J Hepatol 73(1):26-39; Pegbelfermin – Abdelmalek, MF et al. (2023) Clinical Gastro Hep 23:S1542-3565; Aldafermin – NGM Bio (2023) September Corporate Overview; Obeticholic acid - Intercept (2022) September 30 Press Release; Simtuzumab – Harrison, SA et al. (2018) Gastroenterology 155:1140–1153

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted.

Landscape for Cirrhosis Due to MASH:
Placebo-Corrected MASH Resolution

	Fc-FGF21	GLP-1	ASK-1	Peg-FGF21	FGF19	FXR	LOXL-2
	Efruxifermin	Semaglutide	Selonsertib	Pegbelfermin	Aldafermin	Obeticholic acid	Simtuzumab
	36 Wks / Ph2b	48 Wks / Ph2b	48 Wks / Ph3	48 Wks / Ph2b	48 Wks / Ph2b	78 Wks / Ph3	96 Wks / Ph2b
	Active	Active	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Placebo Rate	26%	21%	4%	0%	NA	NA	6%

By Treatment Duration



** p<0.01, versus placebo (CMH)

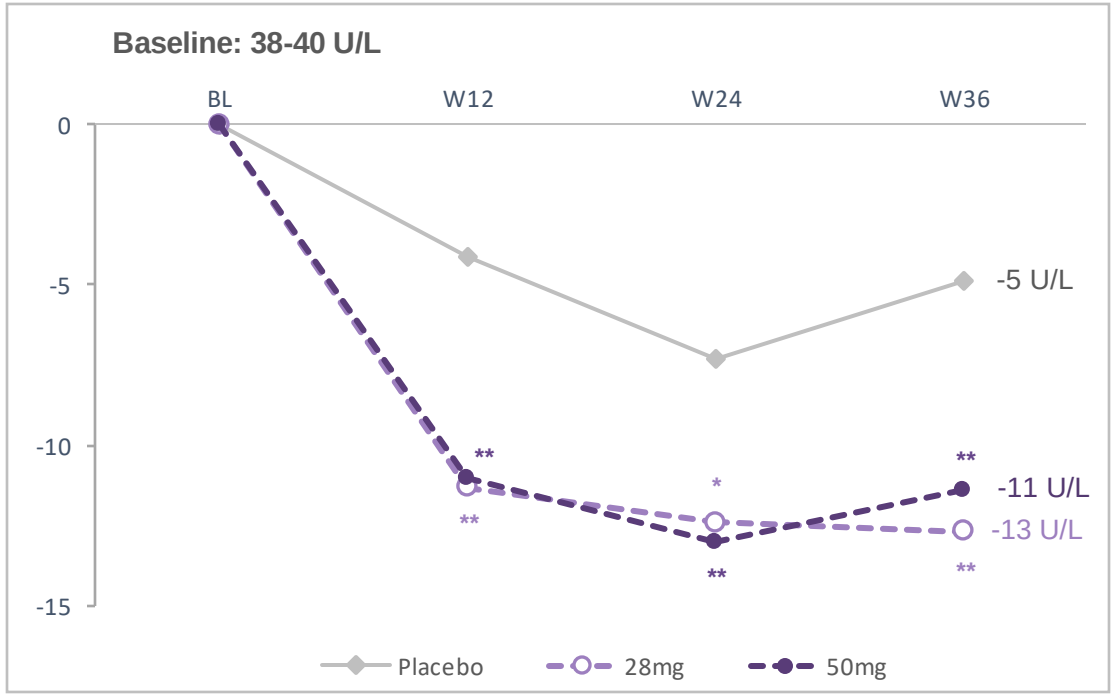
Includes results from publicly reported placebo-controlled studies in patients with compensated cirrhosis due to MASH reporting either ≥ 1-stage fibrosis improvement and no worsening of MASH (EFX, semaglutide, selonsertib, pegbelfermin, obeticholic acid) or only ≥ 1-stage fibrosis improvement (aldafermin, simtuzumab); numerical values represent percent responders

Semaglutide – Loomba, R et al. (2023) Lancet Gastro Hep 8:511-22; Selonsertib – Harrison, SH et al. (2020) J Hepatol 73(1):26-39; Pegbelfermin – Abdelmalek, MF et al. (2023) Clinical Gastro Hep 23:S1542-3565; Aldafermin – NGM Bio (2023) September Corporate Overview; Obeticholic acid - Intercept (2022) September 30 Press Release; Simtuzumab – Harrison, SA et al. (2018) Gastroenterology 155:1140–1153

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted.

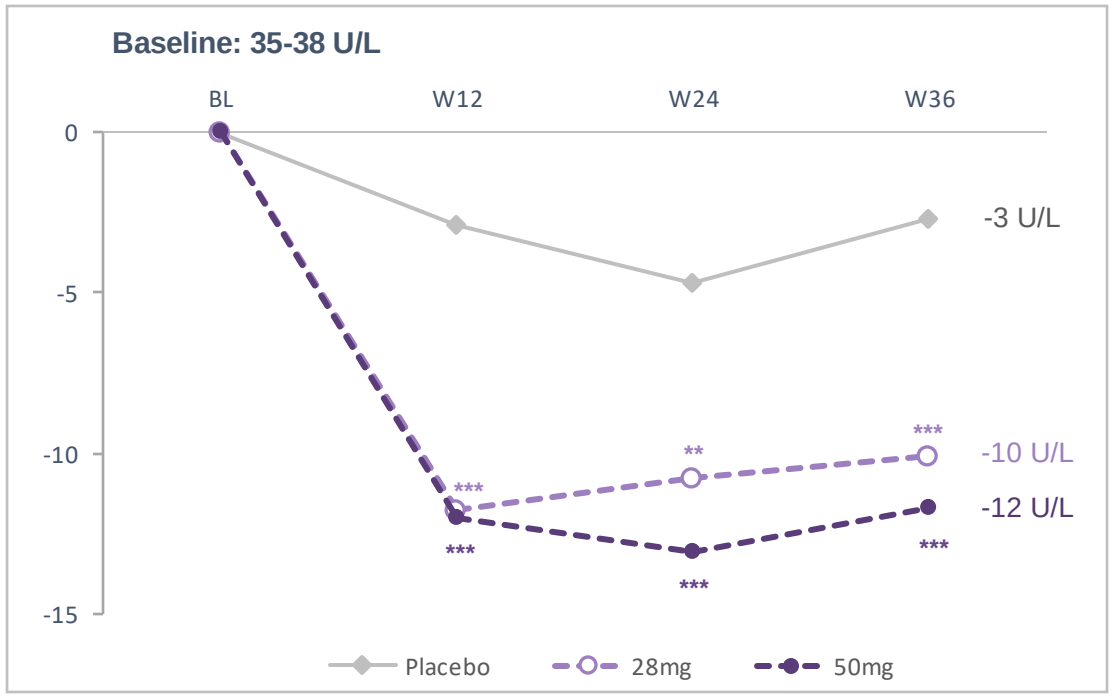
SYMMETRY: Early and Sustained Statistically Significant Improvements in Markers of Liver Injury

ALT
LS Mean Change from Baseline (U/L)



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

AST
LS Mean Change from Baseline (U/L)



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

Statistically significant improvements from baseline observed for platelet counts for both EFX groups

Source Data: Full Analysis Set; Topline preliminary data

Treatment-Emergent Adverse Events

TEAE Overview	Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
TEAE Leading to Death	1 (2%) [a]	0 (0%)	0 (0%)
Treatment-Emergent Serious Adverse Event (SAE) [b]	6 (10%)	9 (16%)	6 (10%)
TEAEs Leading to Discontinuation	2 (3%)	5 (9%)	8 (13%)
Most Frequent (≥15%) Drug-Related TEAEs	**Placebo (N=61)**	**EFX 28mg (N=57)**	**EFX 50mg (N=63)**
Diarrhea, n (%)	9 (15%)	10 (18%)	19 (30%)
Nausea, n (%)	7 (11%)	11 (19%)	18 (29%)
Increased appetite, n (%)	3 (5%)	7 (12%)	17 (27%)
Injection site erythema, n (%)	5 (8%)	8 (14%)	13 (21%)

[a] Pneumonia

[b] None of the SAEs were deemed by the investigator to be drug-related

Source Data: Safety Set; Topline preliminary data

Safety Overview

ECGs and Vital Signs

- No clinically significant changes in ECGs, heart rate or diastolic BP
- Increases of 4-7 mmHg noted in systolic BP at Week 36

Markers of Liver Function and Hemostasis

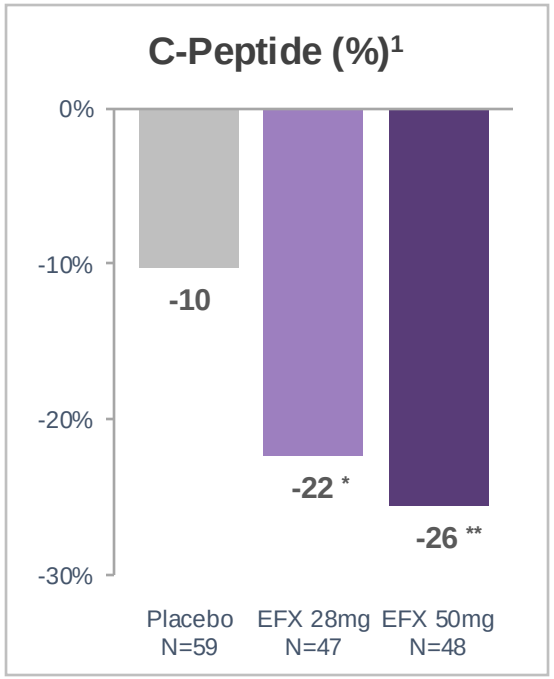
- Remained stable, including INR, bilirubin, MELD, and CP score

Bone Mineral Density

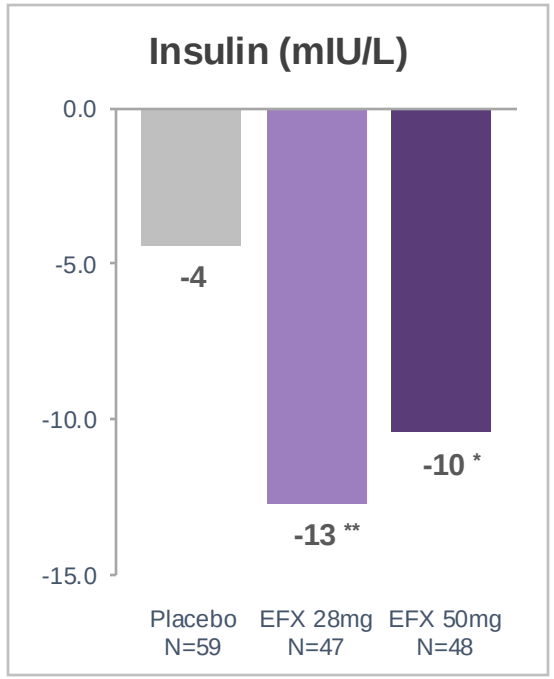
- Cirrhosis has been associated with poor bone health
- Relative reductions in the lumbar spine region (≤1%) and the femoral neck region (2-3%) were observed for the EFX dose groups at Week 36
- Concomitant medications, including oral corticosteroids, may have confounded observed changes

SYMMETRY: Statistically Significant Improvements Observed in Insulin Sensitivity

LS Mean Change From Baseline to Week 36



[1] Relative percent change from baseline
* p<0.05, ** p<0.01, versus placebo (MMRM)



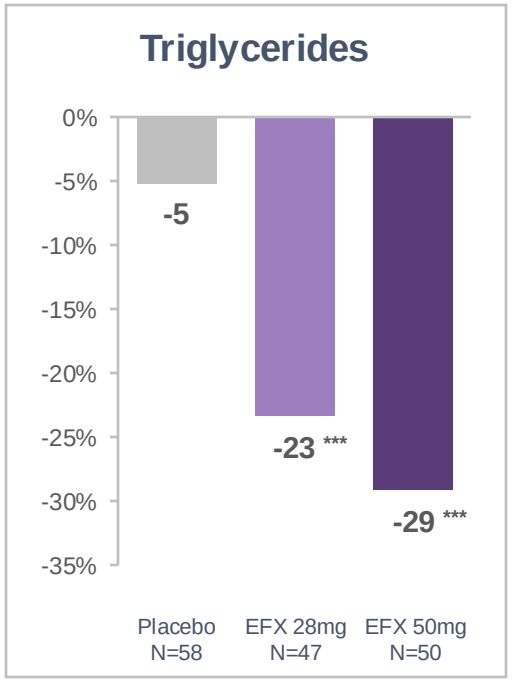
* p<0.05, ** p<0.01, versus placebo (MMRM)

[2] Absolute change from baseline, %
†† p<0.01, versus baseline (MMRM)

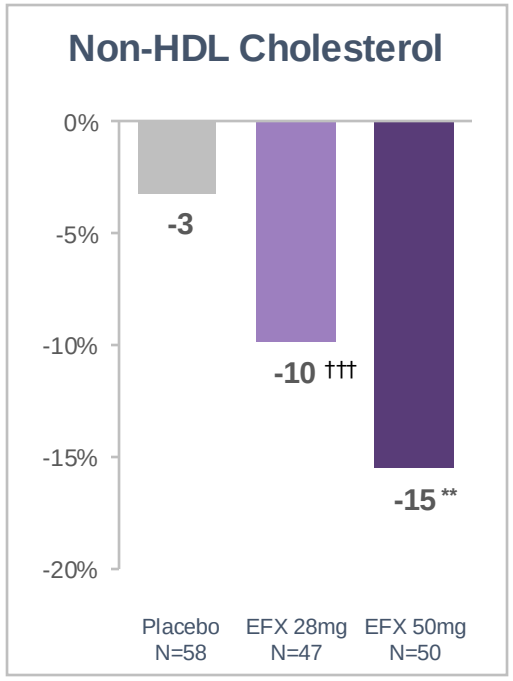
Source Data: Full Analysis Set; Topline preliminary data

SYMMETRY: Statistically Significant Improvements Observed in Lipoprotein Profile

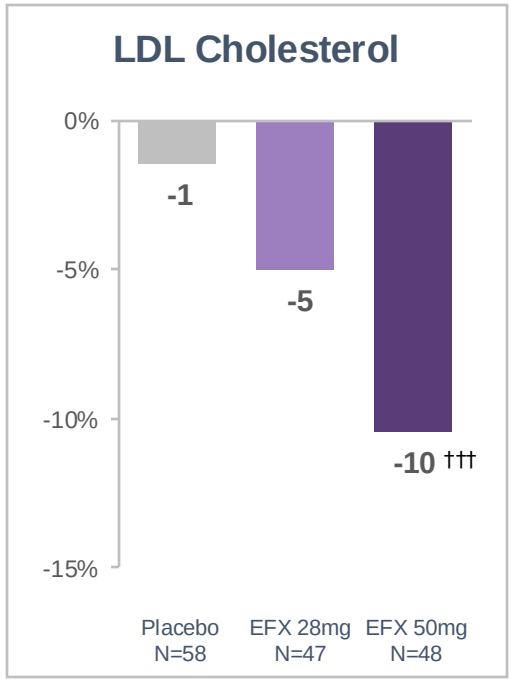
LS Mean Percent Change From Baseline to Week 36



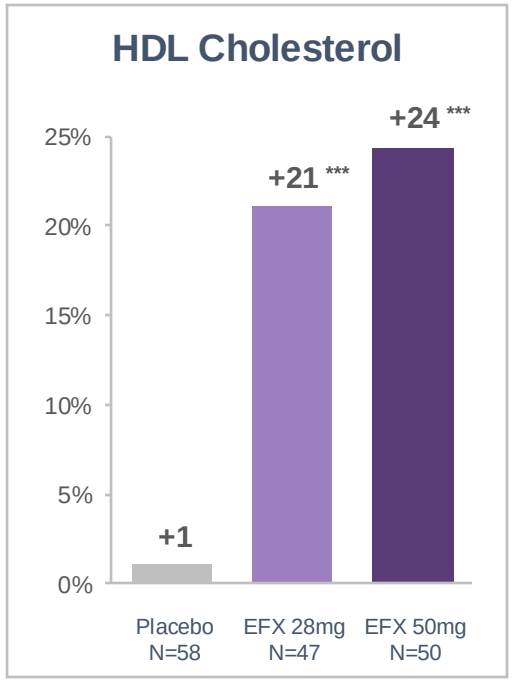
*** p<0.001, versus placebo (MMRM)



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



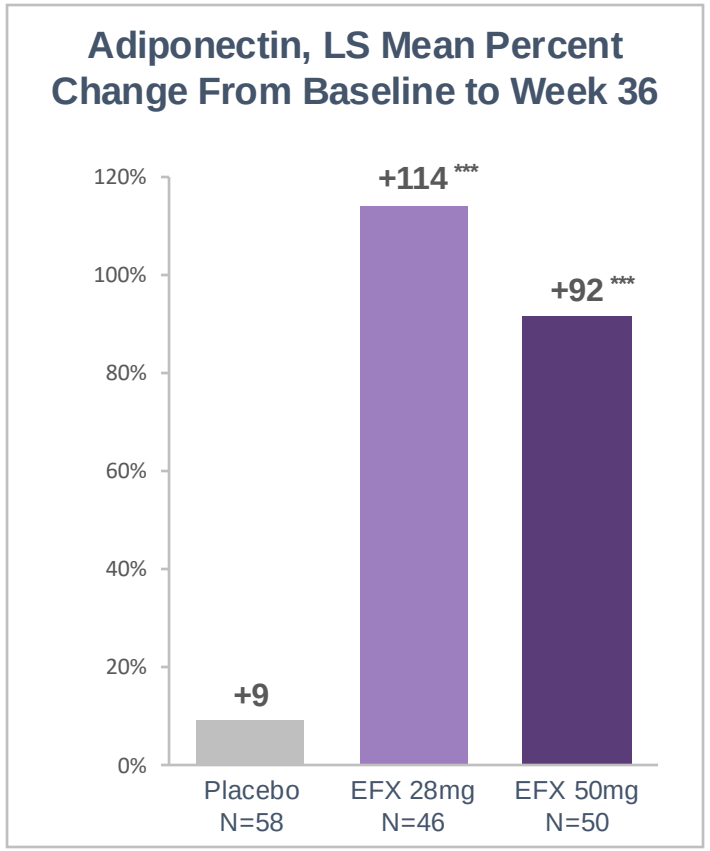
††† p<0.001, versus baseline (MMRM)



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

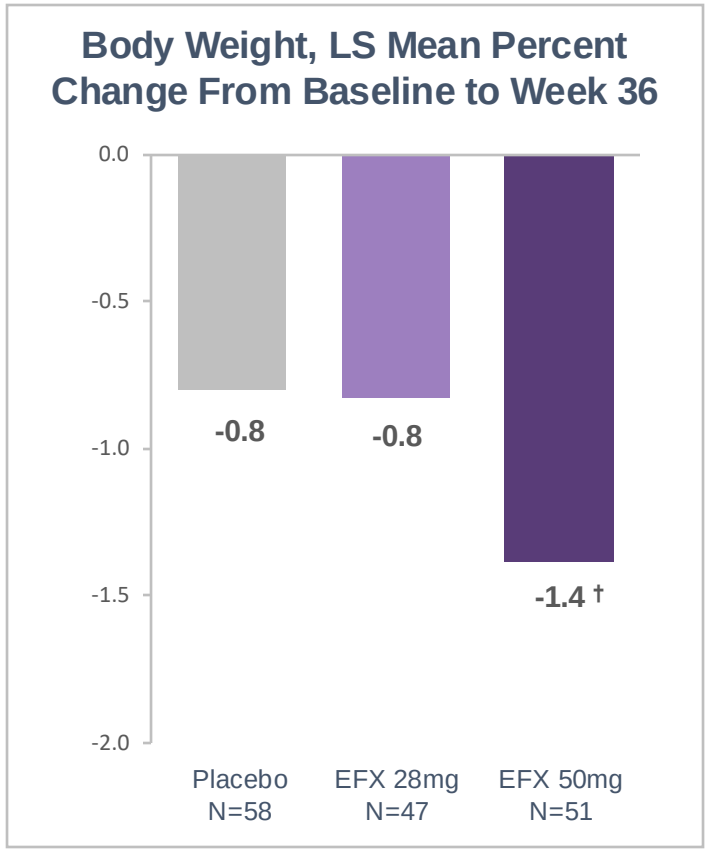
Source Data: Full Analysis Set; Topline preliminary data

SYMMETRY: Significant Increases Observed in Adiponectin,
PD Marker for EFX's Action on Adipose Tissue



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

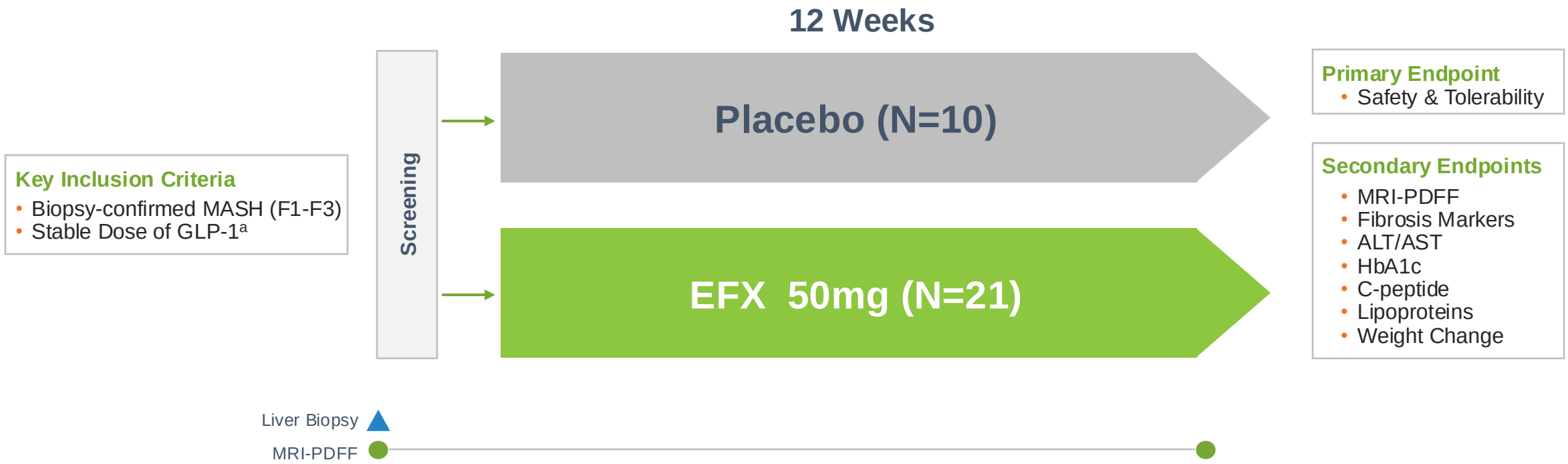
SYMMETRY: Trend Toward Weight Loss for 50mg EFX Dose Group



† p<0.05 versus baseline (MMRM)

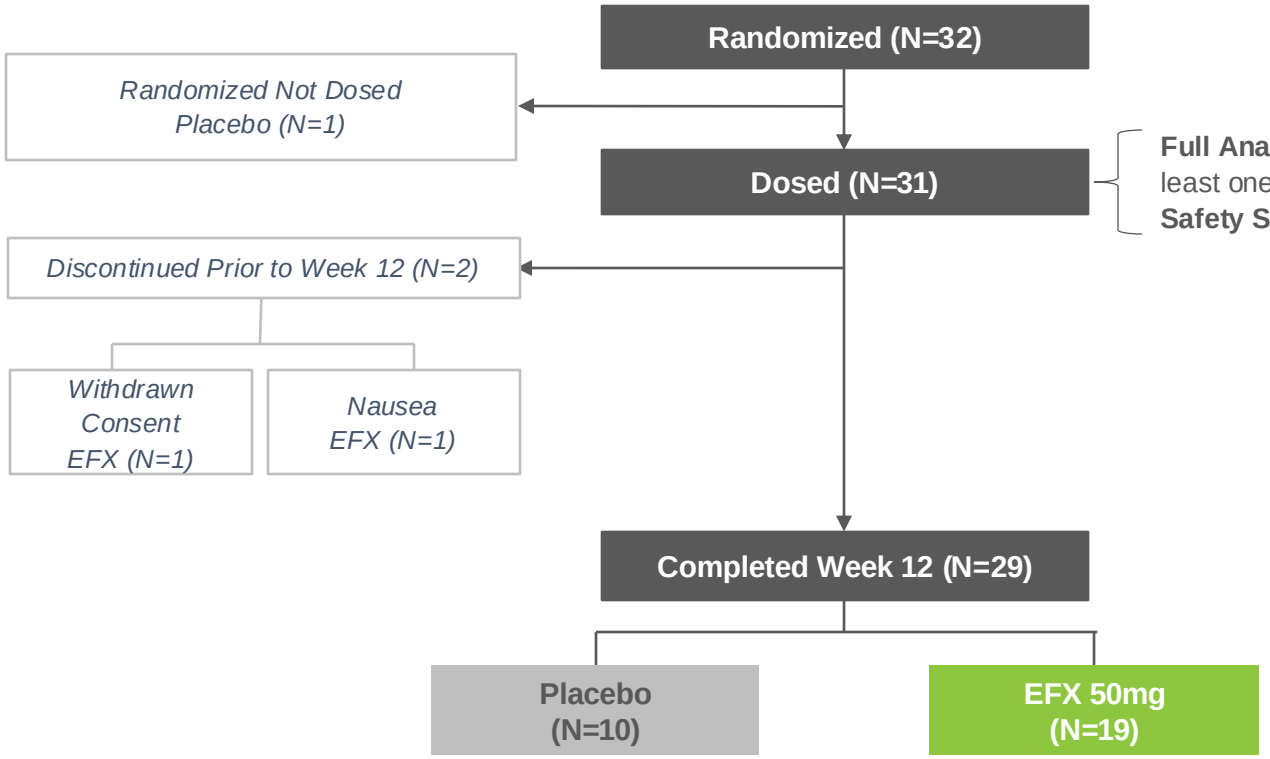
Source Data: Full Analysis Set; Topline preliminary data

Cohort D Trial Design:
EFX in Combination with GLP-1 Receptor Agonist Therapy (GLP-1) at Diabetic Doses



[a] Approximately two-thirds of randomized patients were on a stable dose of GLP-1 for more than one year; all patients were on a stable dose for at least three months.

Cohort D: Week 12 Patient Disposition & Key Analysis Sets



Full Analysis Set – All patients who were randomized and received at least one dose of study drug

Safety Set - All subjects who received at least one dose of study drug

Cohort D: Baseline Demographics

Parameter (Mean)	Placebo (N=10)	EFX 50mg (N=21)
Age (Years)	55	59
Sex (% Female)	90	43
Weight (kg)	96	101
Fibrosis Stage (% F1 / F2 / F3)	40 / 10 / 50	38 / 33 / 29
Hepatic Fat Fraction by MRI-PDFF[1] (%)	15	11
Pro-C3[2] (µg/L)	34	33
Enhanced Liver Fibrosis (ELF) Score	9.6	9.2
Liver Stiffness by VCTE[3] (FibroScan) (kPa)	12	10
Alanine Aminotransferase (ALT) (U/L)	31	35
Aspartate Aminotransferase (AST) (U/L)	24	26
HbA1c (%)	6.5	7.0
Triglycerides (mg/dL)	171	163
LDL-Cholesterol (mg/dL)	98	73
Statin Use (%)	50	81

[1] Magnetic Resonance Imaging Proton Density Fat Fraction; [2] Procollagen 3 N-Terminal Propeptide; [3] Vibration-controlled transient elastography

Cohort D: Concomitant Diabetic Medications at Baseline

GLP-1s	Placebo (N=10)	EFX 50mg (N=21)
Semaglutide	60%	43%
Dulaglutide	30%	52%
Liraglutide	10%	5%
Tirzepatide[1]	0%	0%
Other Diabetic Medications	**Placebo**	**EFX 50mg**
Metformin	70%	76%
Insulin	30%	48%
SGLT-2	20%	33%
Sulfonylureas	20%	24%
DPP-IV	0%	10%

[1] With one exception, all patients remained on their baseline GLP-1 therapy through Week 12; one patient entered treatment on a stable dose of semaglutide but switched to tirzepatide after the Week 10 visit due to unavailability of semaglutide.

Source Data: Safety Analysis Set

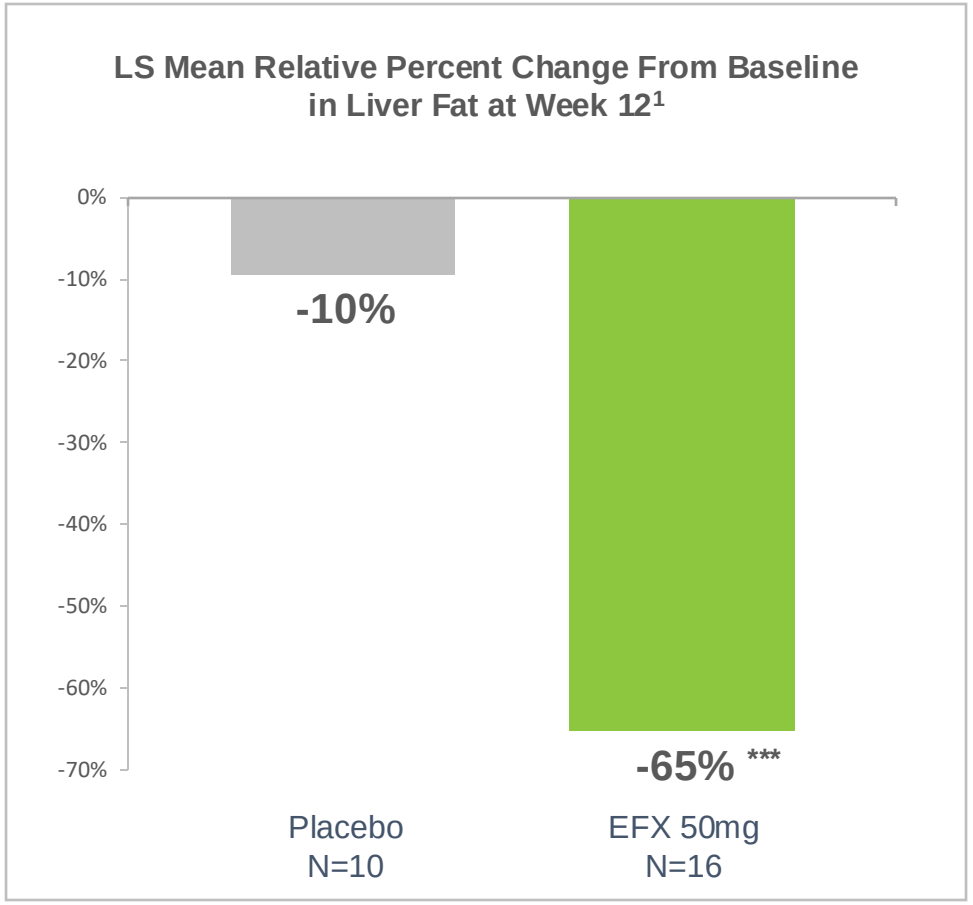
Cohort D Primary Endpoint: Comparable Safety and Tolerability Across Both Treatment Groups

Treatment-Emergent Adverse Event (TEAE) Overview	Placebo (N=10)	EFX 50mg (N=21)
TEAE Leading to Death	0 (0%)	0 (0%)
Drug-Related Serious Adverse Event (SAE)	0 (0%)	0 (0%)[a]
Drug-Related TEAE Leading to Discontinuation	0 (0%)	1 (5%)[b]
Most Frequent (≥15%) Drug-Related TEAEs	**Placebo**	**EFX 50mg**
Diarrhea	3 (30%)	4 (19%)
Nausea	1 (10%)	7 (33%)
Increased Appetite	0 (0%)	5 (24%)
Decreased Appetite	2 (20%)	3 (14%)

[a] Two SAEs in the EFX group were not drug related: post-procedural hemorrhage and uterine cancer.
[b] Nausea

Source Data: Safety Analysis Set

Cohort D: Significantly Greater Relative Reductions in Liver Fat by MRI-PDFF for EFX Combined with GLP-1 than GLP-1 Alone

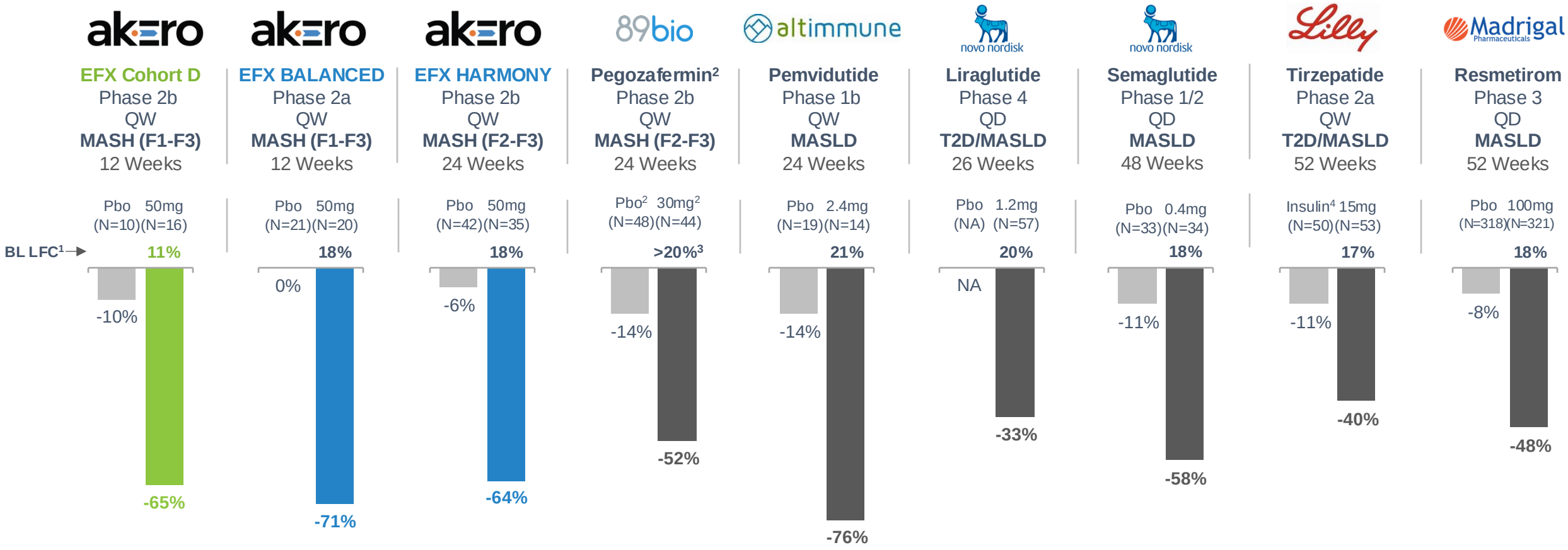


*** p<0.001, versus placebo (Analysis of Covariance [ANCOVA])

[1] Including the baseline MRI-PDFF measurements for three subjects with baseline MRI-PDFF measurements after the first dose lowers the LS Mean result for the EFX group from -65.3% to -63.2% (N=19) and the placebo group from -9.6% to -9.0% (N=10)

Source Data: MRI-PDFF Analysis Set (all subjects with pre-dose baseline and on-study measurement assessed by MRI-PDFF [N=16]); Topline preliminary data

EFX Liver Fat Reduction in Context: MASLD & Pre-Cirrhotic MASH



[1] Baseline Liver Fat Content

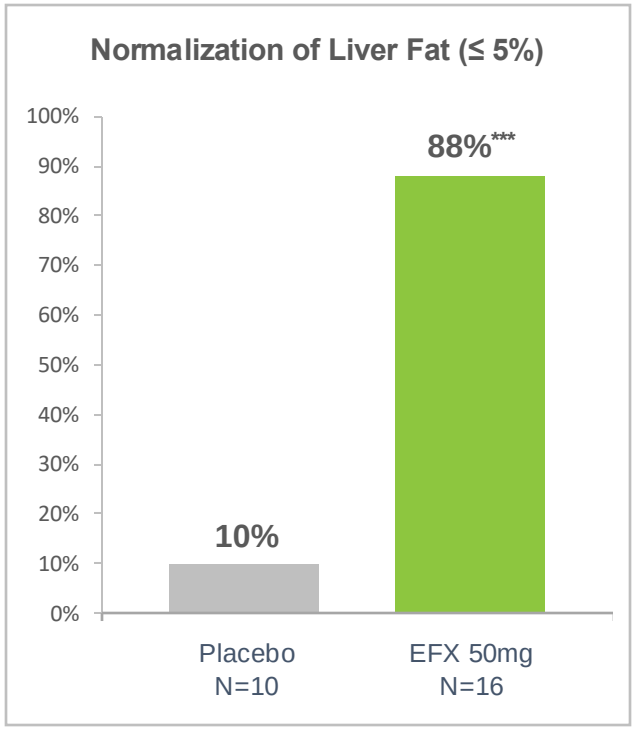
Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

[2] Reported reductions only for subset of patients with liver fat content ≥10% at baseline
[3] Estimated for subset of patients with LFC ≥10% at baseline
[4] Insulin Degludec

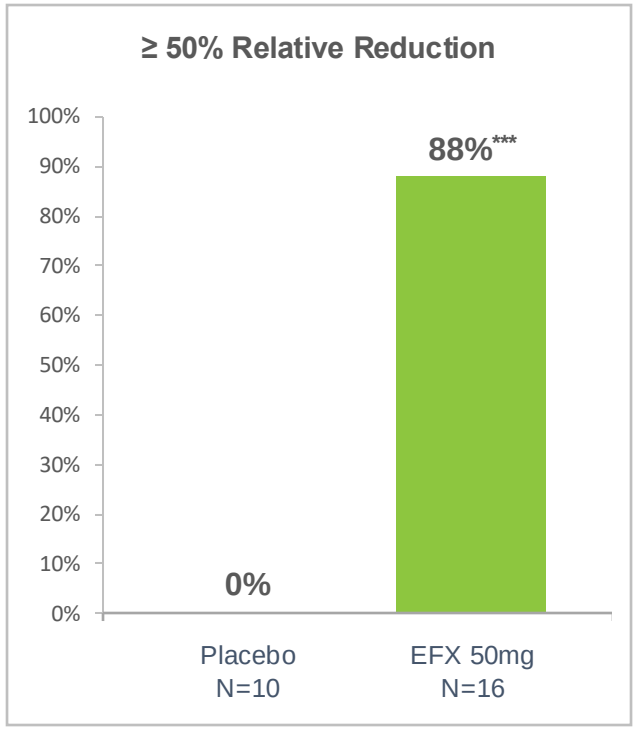
Pegozafermin - 89Bio (2023) May 6 Corporate Presentation; Pemvidutide - Altimmune (2023) March Evercore NASH Renaissance Presentation; Liraglutide - Petit et al (2017) J Clin Endocrinol Metab 102(2):407-15; Tirzepatide - Gastaldelli et al (2022) Lancet Diabetes Endocrinol 10(6):P393-406; Resmetirom - Madrigal (2023) May Corporate Presentation; Semaglutide - Flint et al. (2021) Aliment Pharmacol Ther 54(9):1150-61. All trademarks are the property of their respective owners.

More Patients Treated with EFX Combined with GLP-1 Met Higher Thresholds of Liver Fat Reduction and Normalization than GLP-1 Alone

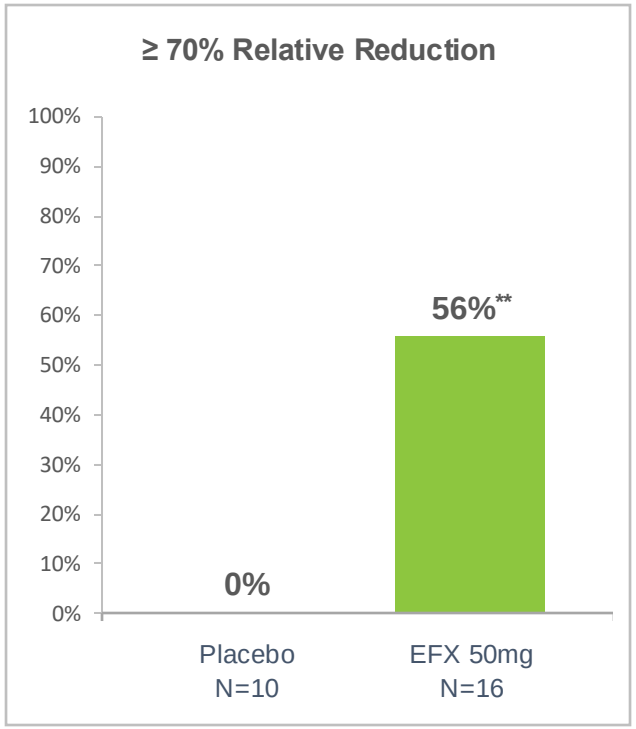
Proportion of Patients Achieving Liver Fat Reduction Thresholds at Week 12[1]



*** p<0.001, versus placebo (CMH[2])



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



** p<0.01, versus placebo (CMH)

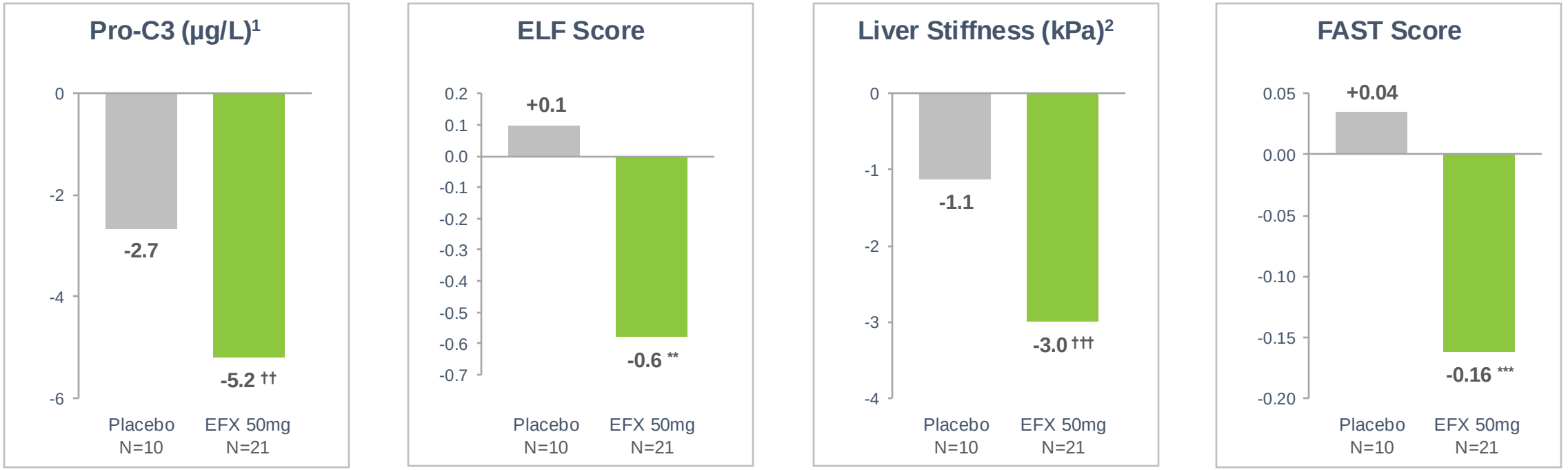
In the HARMONY Study, patients whose liver fat was normalized had 3-fold higher odds of achieving MASH Resolution and Fibrosis Improvement

[1] When three EFX-treated patients with baseline measurements after the first dose are included in liver fat analyses, normalization of liver fat increased from 87.5% (14 of 16) to 89.5% (17 of 19) and the proportion of patients achieving ≥50% and ≥70% relative reduction in liver fat decreased, respectively, to 84.2% (16 of 19) and 52.6% (10 of 19); [2] Cochran–Mantel–Haenszel test

Source Data: MRI-PDFF Analysis Set; Topline preliminary data

Greater Reductions in Markers of Fibrosis for EFX Combined with GLP-1 than GLP-1 Alone

LS Mean Change From Baseline to Week 12



†† p<0.01, versus baseline (MMRM[1])

** p<0.01, versus placebo (MMRM)

††† p<0.001, versus baseline (MMRM)

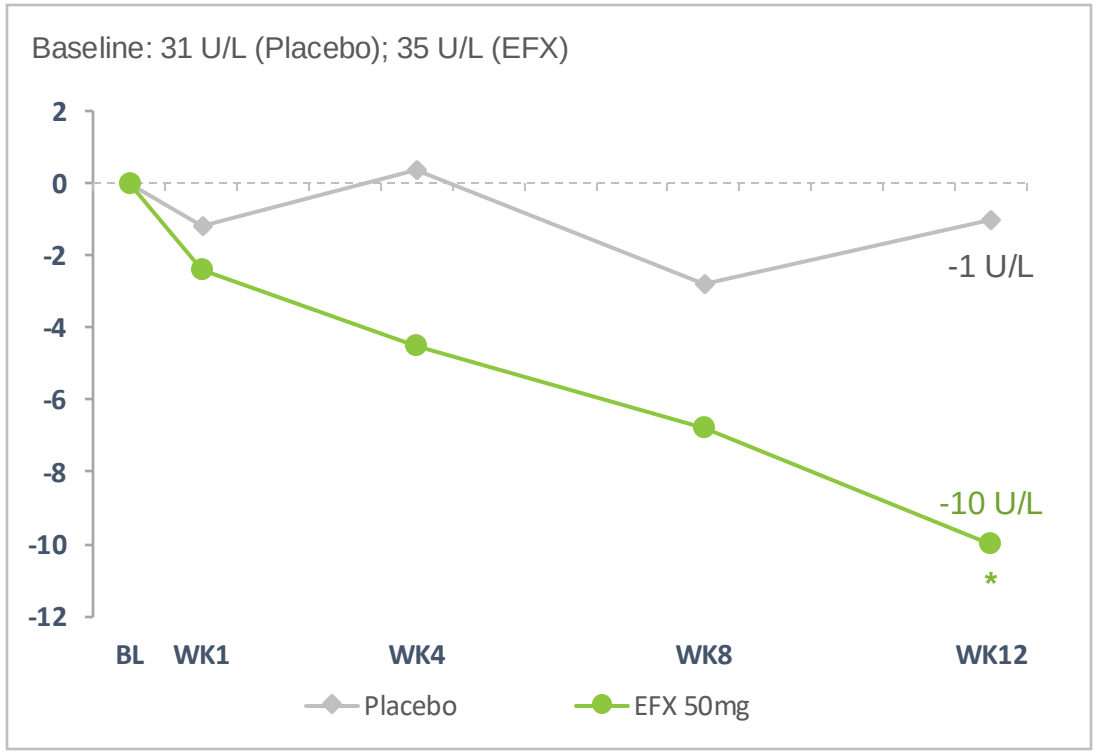
*** p<0.001, versus placebo (MMRM)

[1] Mixed Model Repeated Measures; [2] Measured by FibroScan

Source Data: Full Analysis Set; Topline preliminary data

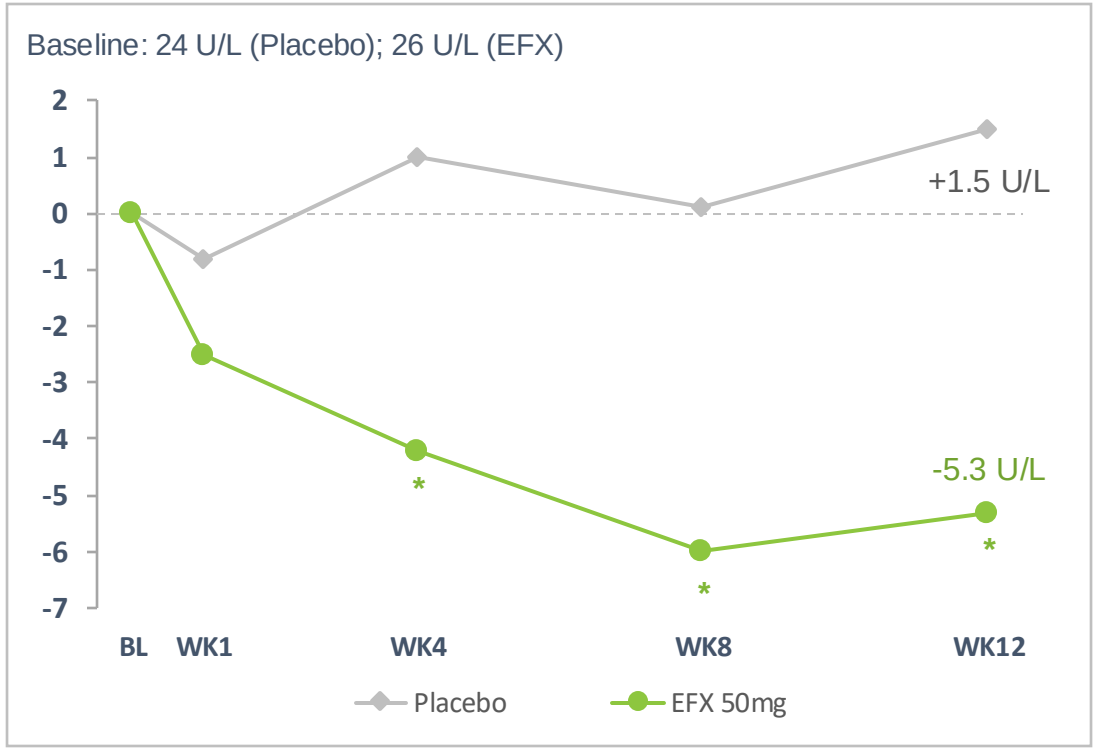
Greater Reductions in Markers of Liver Injury for EFX Combined with GLP-1 than GLP-1 Alone

ALT
LS Mean Change from Baseline (U/L)



* p<0.01, versus placebo (MMRM)

AST
LS Mean Change from Baseline (U/L)

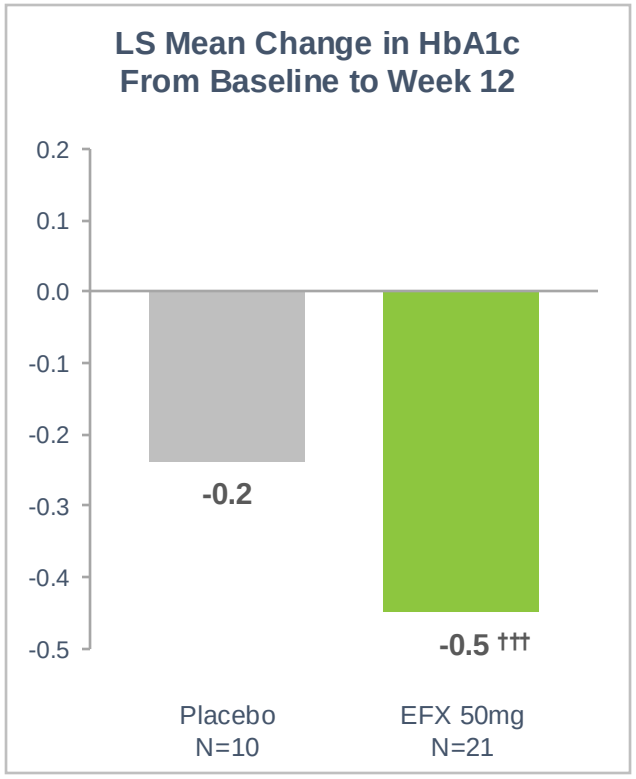


* p<0.01, versus placebo (MMRM)

Source Data: Full Analysis Set; Topline preliminary data

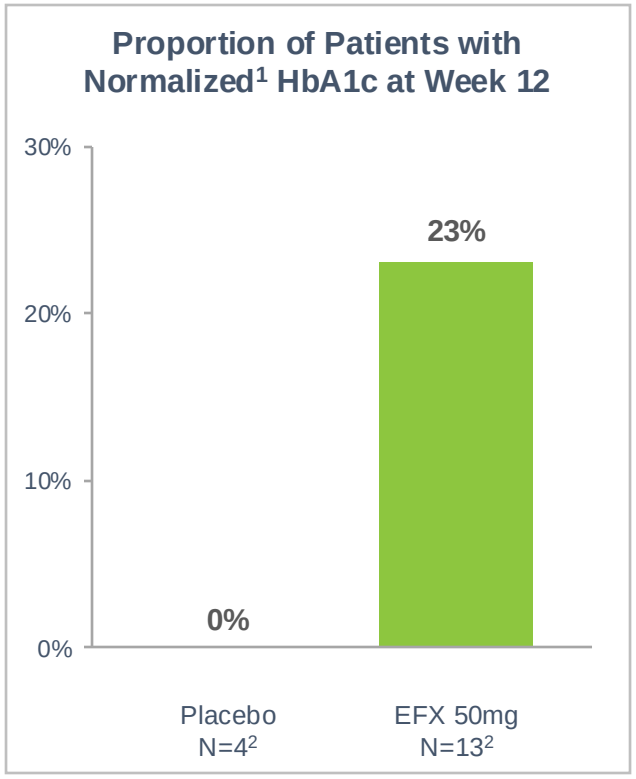
Clinically Meaningful Improvements in HbA1c after Only 12 Weeks

HbA1c



††† p<0.001, versus baseline (MMRM)

HbA1c Normalization[1]

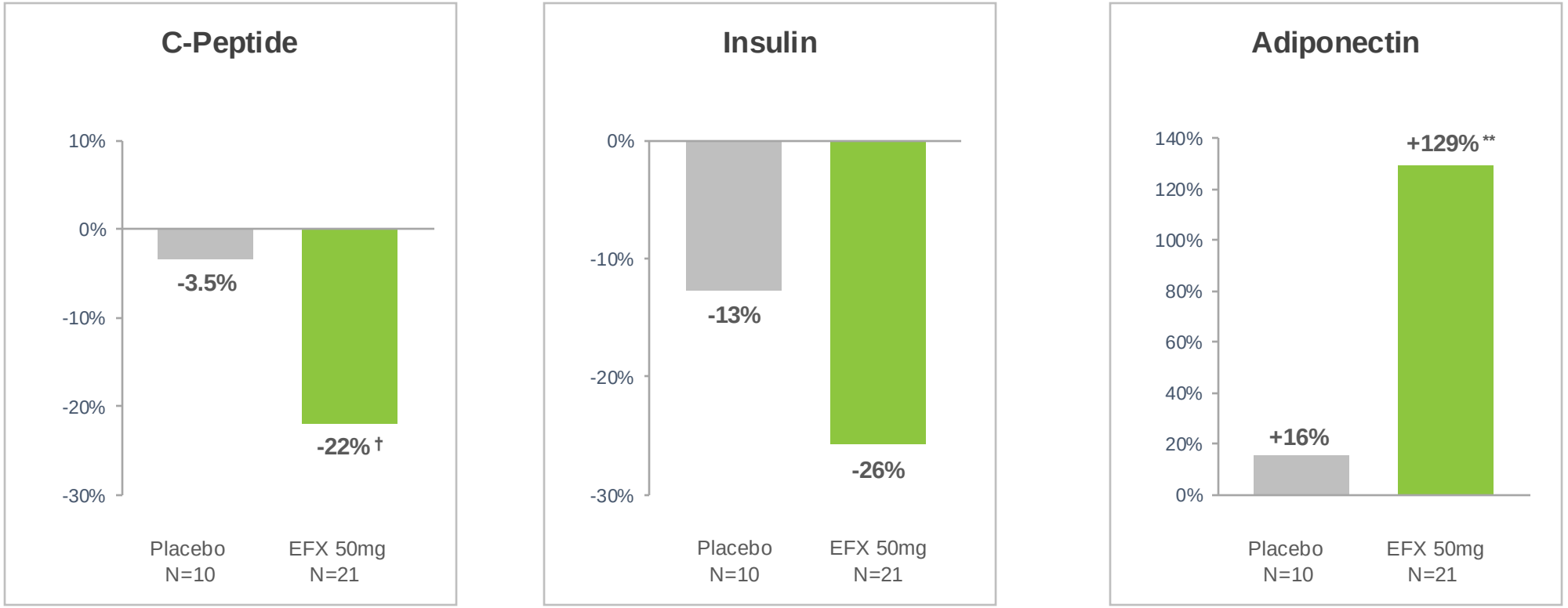


[1] Normalization of HbA1c defined as an HbA1c of ≥6.5 at baseline and <6.5 at week 12
[2] Number of patients with HbA1c ≥6.5 at baseline

Source Data: Full Analysis Set; Topline preliminary data

EFX Complements GLP-1 by Increasing Sensitivity to Insulin

LS Mean Change From Baseline to Week 12



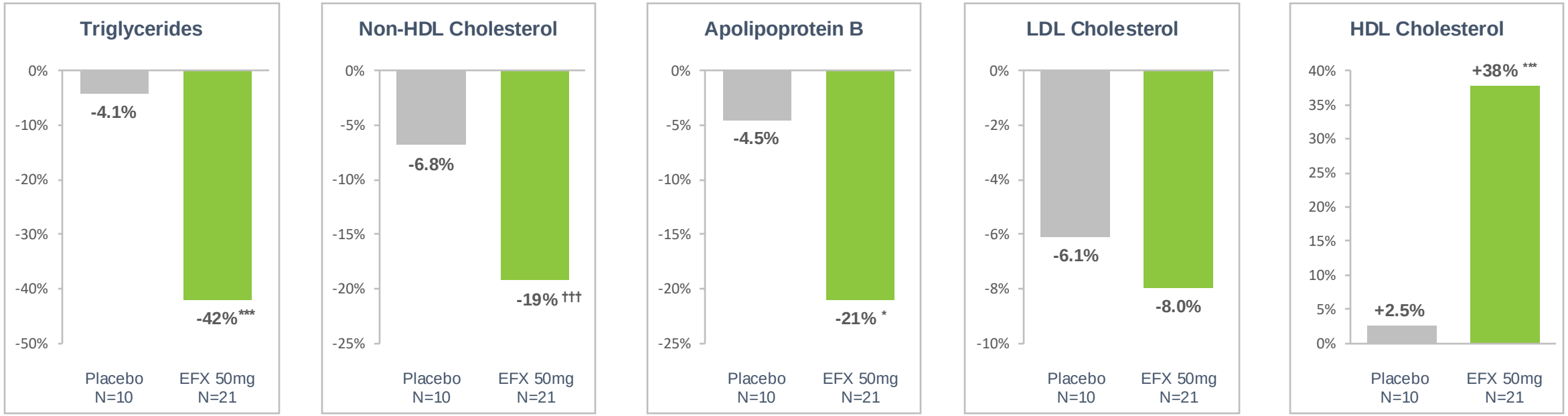
† p<0.001, versus baseline (MMRM)

** p<0.01, versus placebo (MMRM)

Source Data: Full Analysis Set; Topline preliminary data

Much Greater Improvements in Lipids for Patients Treated with EFX in Combination with GLP-1 than GLP-1 Alone

LS Mean Percent Change From Baseline to Week 12



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

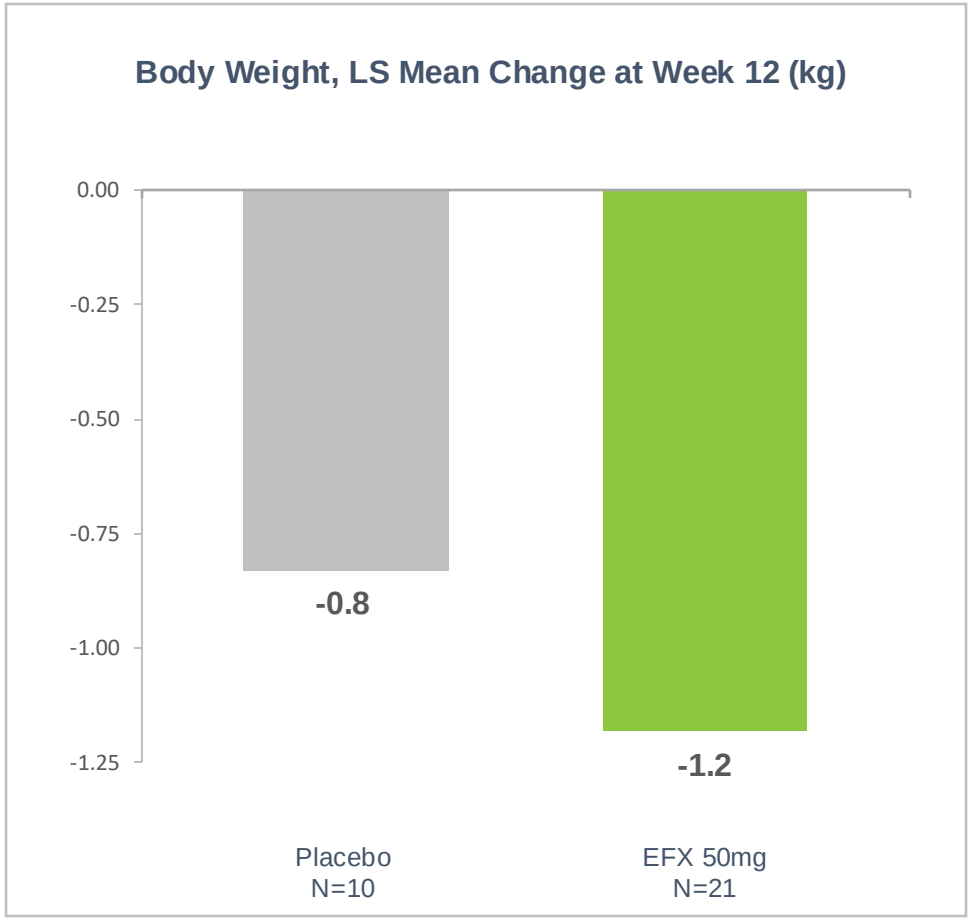
††† p<0.01, versus baseline (MMRM)

* p<0.05, versus placebo (MMRM)

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

Source Data: Full Analysis Set; Topline preliminary data

Weight Loss Maintained for EFX Combined with GLP-1



Source Data: Full Analysis Set; Topline preliminary data

Cohort D Adds to a Growing Body of Evidence for EFX's Potential as a Cornerstone MASH Treatment

Key Take-Aways

- EFX and GLP-1 have complementary mechanisms of action.
- Addition of EFX to GLP-1 in patients with MASH and type 2 diabetes was well tolerated, without additive GI side effects.
- EFX with GLP-1 showed multiple benefits over GLP-1 alone: reduced markers of liver steatosis, injury and fibrosis with improved glycemic control, dyslipidemia and weight loss maintained.
- The Cohort D EFX profile was comparable to that seen in the previous BALANCED and HARMONY studies with EFX.

Complementing GLP-1

Potential for EFX on Top of GLP-1 to be More Effective than GLP-1 Alone

Phase 3 SYNCHRONY Trial Designs:
Histology (F2-F3), Outcomes (F4, Compensated), and *Real-World* (F1-F4, Compensated)

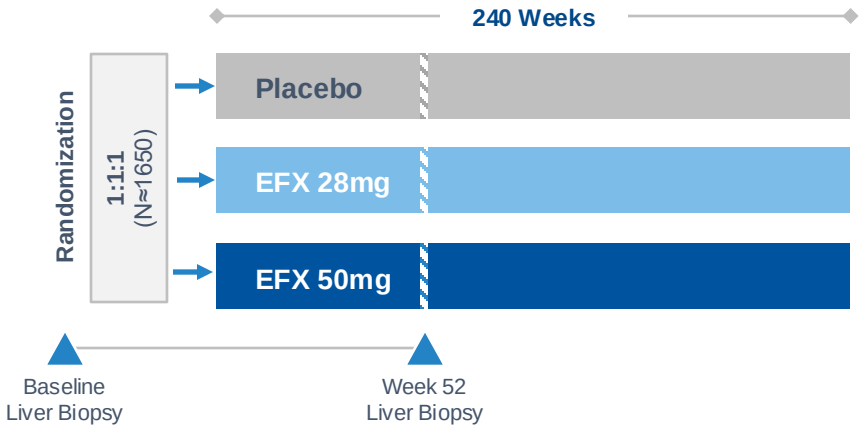
Phase 3 SYNCHRONY program (N ~3500) is comprised of two efficacy studies with both histology and long-term clinical outcomes endpoints and a third one-year study evaluating safety and tolerability

synchrony HISTOLOGY

Primary Histology Endpoint
≥ 1-stage fibrosis improvement **and** MASH resolution at Week 52

Patient Population
Biopsy-confirmed F2-F3 MASH

Primary Outcomes Endpoint
Evaluated at 240 Weeks

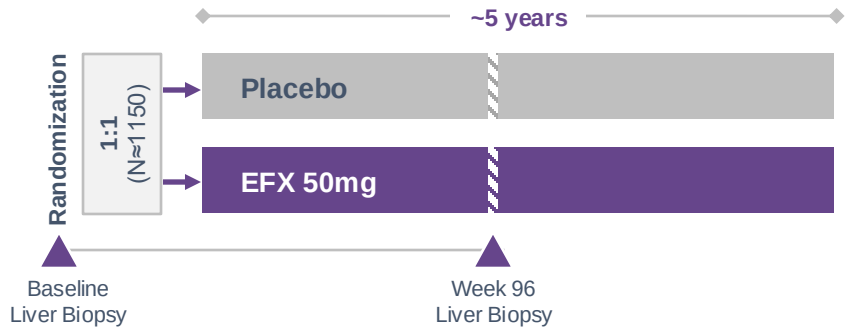


synchrony OUTCOMES

Primary Histology Endpoint
≥ 1-stage fibrosis improvement and no worsening of MASH at Week 96

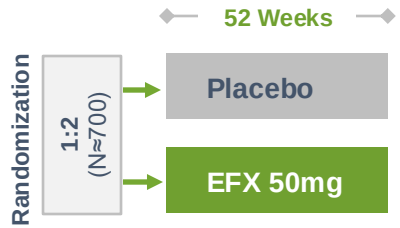
Patient Population
Compensated Cirrhosis (F4)
Due to MASH

Primary Outcomes Endpoint
Time to first occurrence of protocol-specified clinical events



synchrony REAL-WORLD

Patient Population
Non-invasively Diagnosed MASH/MASLD



Primary Endpoint
Safety & Tolerability

Key SYNCHRONY Secondary Efficacy Endpoints

- Fibrosis Markers
- Lipoproteins
- Glycemic Control
- Weight Change
- Liver Injury Markers

Commercial Supply Chain of API and Drug Product/Device: Supply Authorized Globally for Initiated Phase 3 Studies

Drug Substance (API)

Boehringer Ingelheim

- Commercial scale
- High Titer E. Coli Expression
- Process validation complete

Drug Product/Device Combination

VETTER

- Commercially precedented
- 1 mL lyo/liquid Dual Chamber Syringe
- Self-administered, stable at 2-25ºC

Recent Progress & Near-Term Milestones

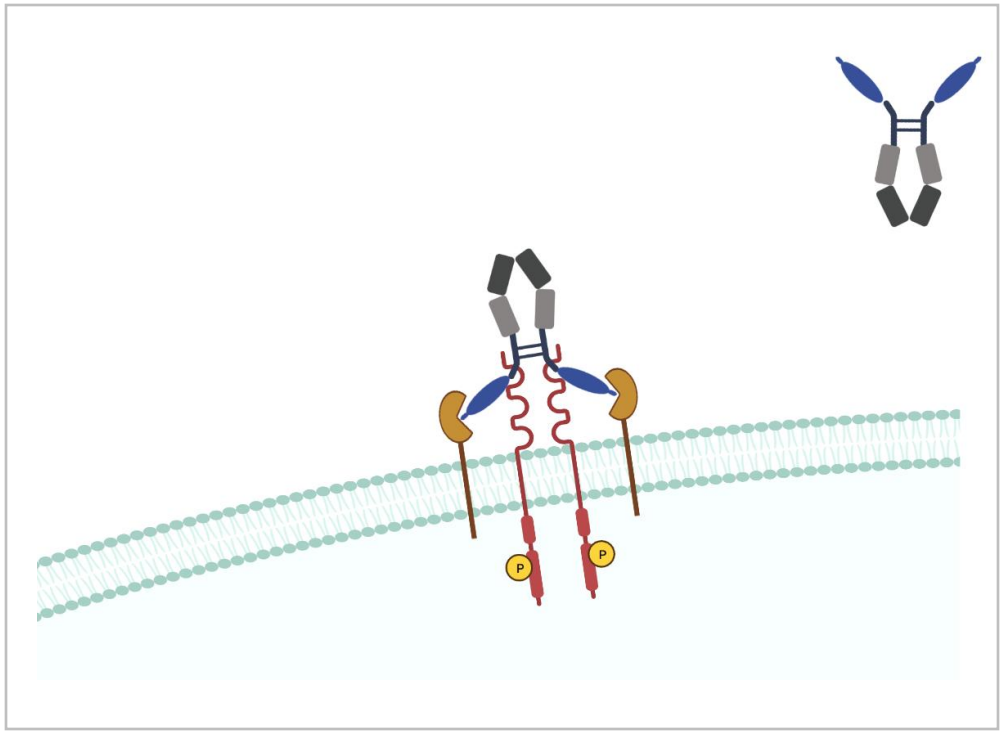
Cash sufficient to fund our Phase 3 SYNCHRONY *Histology* and *Real-World* studies through their respective primary endpoints and our current operating plan into the second half of 2027, with ~$787M cash on hand[1] as of September 30, 2024

[1] Cash, cash equivalents, and short-term marketable securities

Backup Slides

EFX's Four Attachment Points to Cellular Surface May Contribute to Stronger Receptor Binding and Enhanced Efficacy

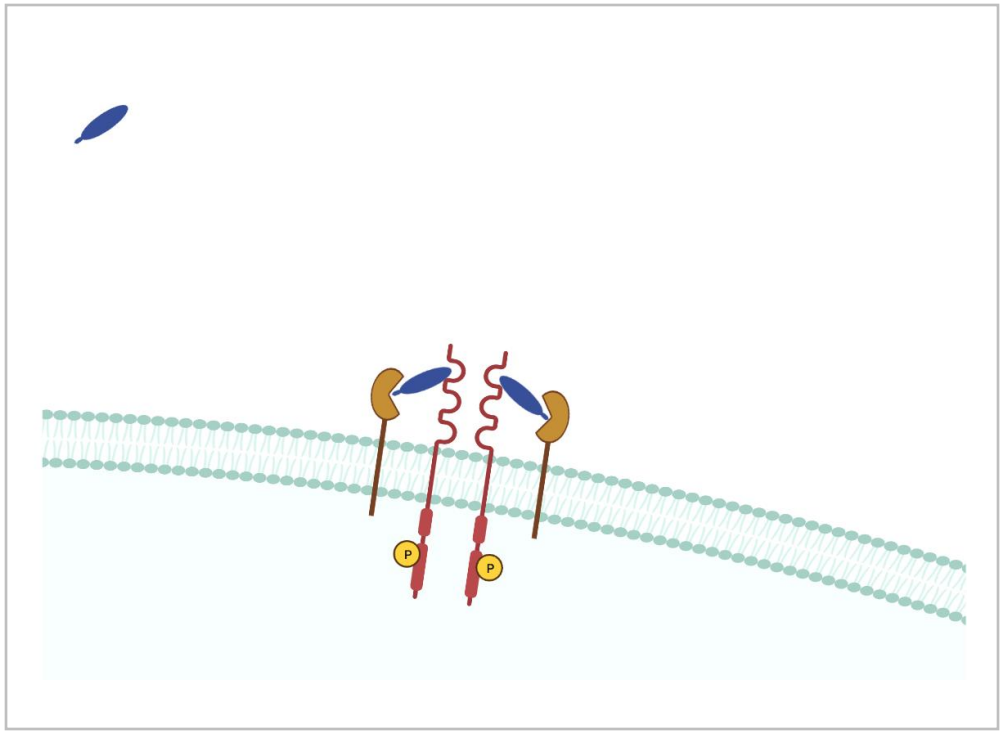
EFX



Dimer structure may enable cooperative binding and enhance avidity effects

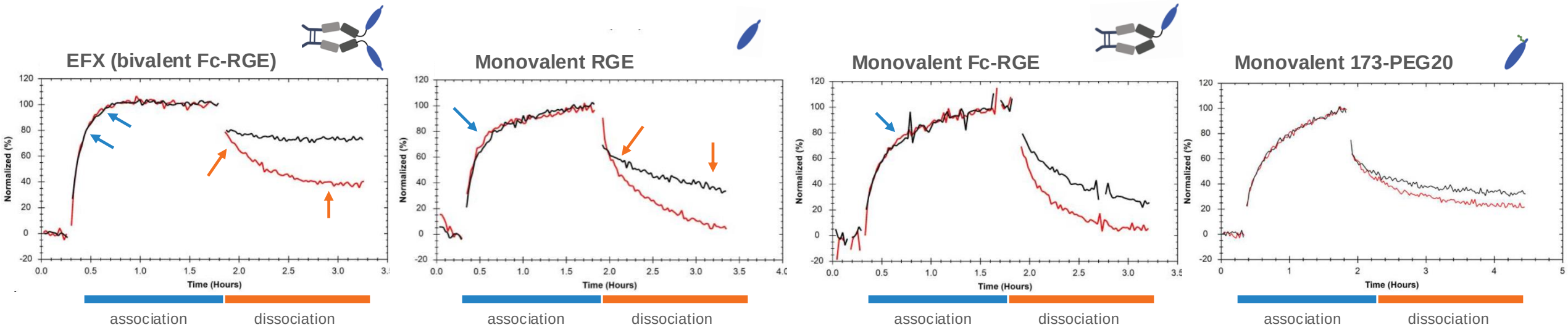
vs

Single-chain FGF21



Two independent binding events preclude cooperative binding or avidity effects

Supportive Evidence for EFX's Cooperative Binding to Cell Surface



— No chase (labeled ligand removed)
— Chase with 10x unlabeled excess

Single-chain FGF21 has slower association, faster and more complete dissociation

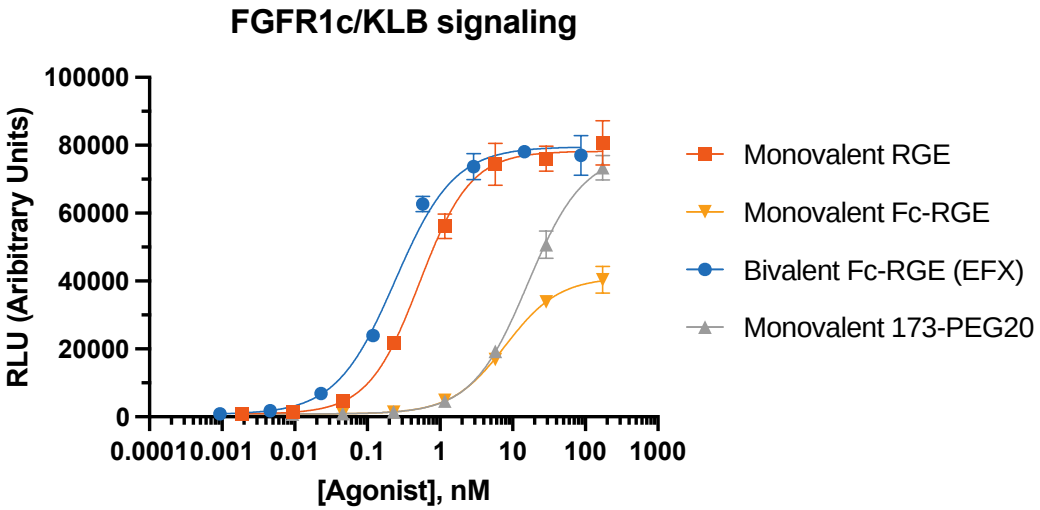
Addition of Fc or 20 kDa PEG to single-chain FGF21 analog further slows association

FGF21 Analog	k_a (1/[M*s])	k_d (1/s)	K_D (M)
EFX	1.8×10^{5}	3.3×10^{-6}	1.8×10^{-11}
Monovalent RGE	4.7×10^{4}	1.4×10^{-4}	3.0×10^{-9}
Monovalent Fc-RGE	2.1×10^{4}	1.1×10^{-4}	5.4×10^{-9}
Monovalent 173-PEG20	1.7×10^{4}	8.3×10^{-5}	4.8×10^{-9}

>100-fold tighter binding (K_D) of EFX vs. all monovalent analogs, i.e., RGE, Fc-RGE, or 173-PEG20:
- faster rate of association [k_a] AND
- much slower rate of dissociation [k_d]

FITC-labeled FGF21 analog binding analysis to the surface of FGFR1c/KLB-expressing HEK293

Single FGF21 chain analogs fused to “half-life extenders” are **15- to 30-Fold** Less Potent than EFX with two FGF21 chains’ or “unmodified FGF21”



	Bivalent Fc-RGE (EFX)	Monovalent RGE	Monovalent Fc-RGE	Monovalent 173-PEG20
Half-life extension	Fc-fusion	minimal	Fc-fusion	20 kDa PEG at residue 173
FGF21-receptor hindrance	N-terminus linked to IgG1 Fc	none	N-terminus linked to IgG1 Fc	20 kDa PEG at residue 173
mol. FGF21 / mol. analog	2	1	1	1
K_D (affinity) on live cells	**.018 nM**	3 nM	5.4 nM	4.8 nM
EC_{50} (potency), cell-based bioassay	0.24 nM	0.52 nM	7.93 nM	16.2 nM

- Monovalent Fc-RGE is **less potent** (higher EC_{50}) and a **partial agonist** (smaller fold induction) than Monovalent RGE
  - *Likely steric hindrance effect due to Fc*
- Adding a second FGF21(RGE) to monovalent Fc-RGE, forming bivalent Fc-RGE (EFX) restores **full agonism** and is **much more potent** (lower EC_{50})
  - *More than overcomes steric hindrance of Fc*
- Addition of 20 kDa PEG at residue 173 appears to maintain **full agonism** but is associated with **lower potency** (higher EC_{50})

NASDAQ: AKRO

AKERO THERAPEUTICS
601 Gateway Boulevard
Suite 350
South San Francisco, CA 94080