Efruxifermin in Compensated Cirrhosis due to NASH/MASH: Results from a Randomized, Double-blind, Placebo-controlled, Phase 2b Trial (SYMMETRY)

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Disclosures

Stephen A. Harrison

I disclose the following financial relationship(s) with a commercial interest:

- Scientific advisor or consultant for Akero, Aligos, Altimmune, Arrowhead, Boxer Capital, Chronwell, Echosens, Foresite Labs, Galectin, Galecto, Gilead, GSK, Hepagene, Hepion, Hepta Bio, HistoIndex, Humana, Intercept, Ionis, Inventiva, Madrigal, Medpace, Merck, NeuroBo Pharmaceuticals, Northsea, Novo Nordisk, Perspectum, Pfizer, Sonic Incytes, Sagimet, Terns, Viking.
- Stock options: Akero, Chronwell, Galectin, Hepion, Hepta Bio, HistoIndex, Northsea
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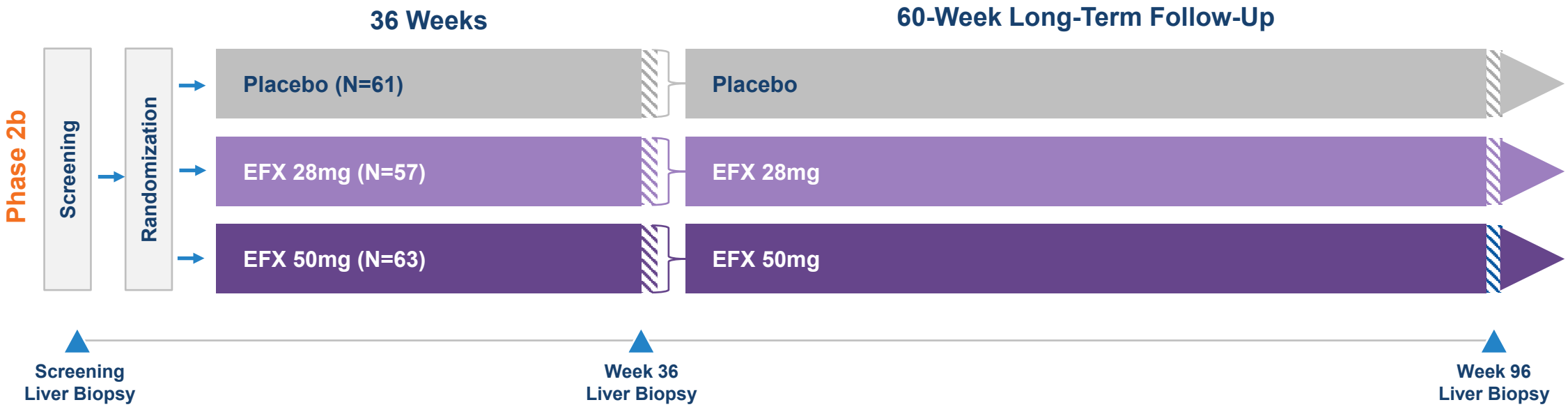
SYMMETRY Trial Design: Compensated Cirrhosis Due to NASH (F4)

Key Inclusion Criteria[1]
- F4 NASH (compensated)
- T2D or 2 of 4 components of metabolic syndrome

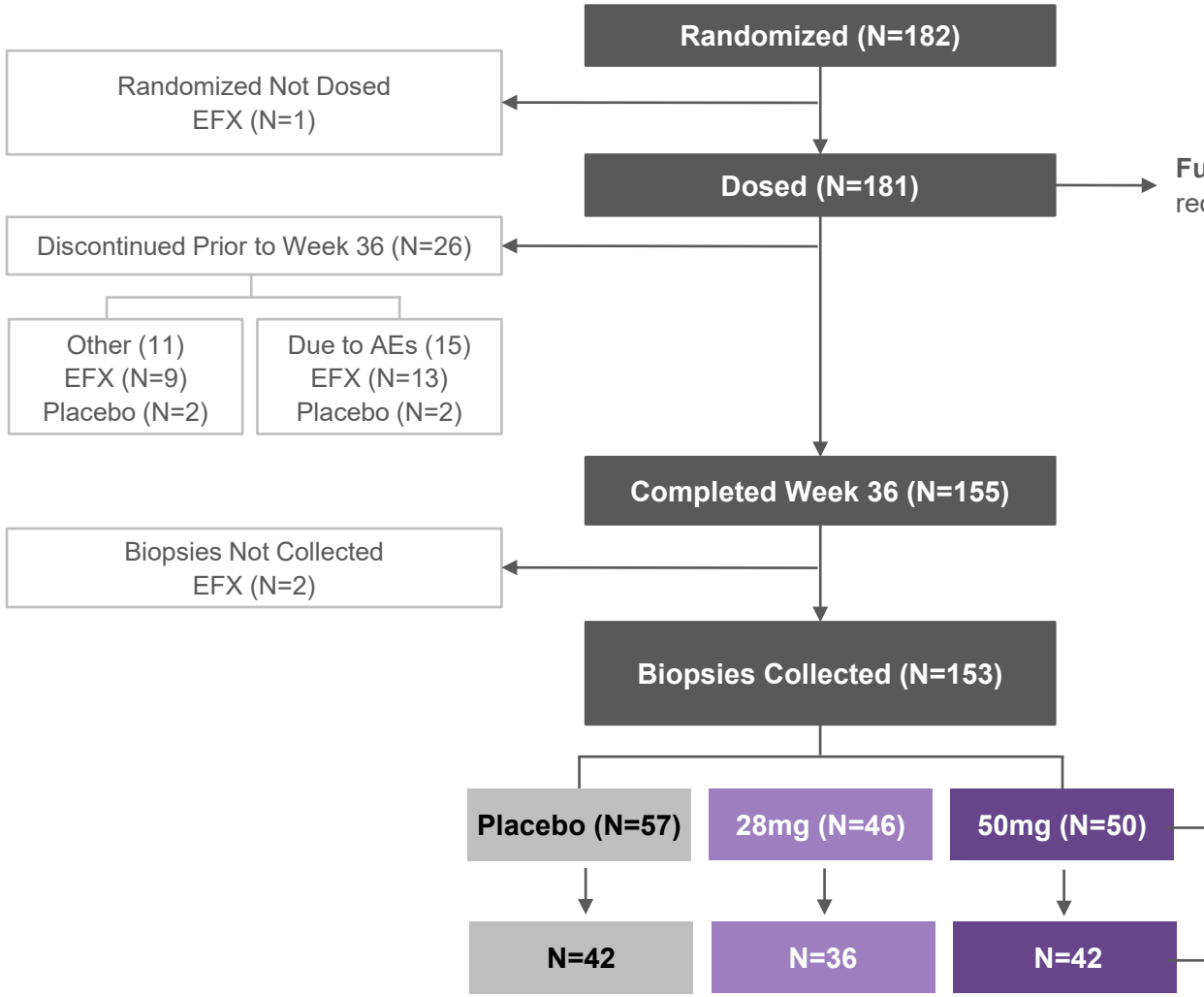
Phase 2b Primary Endpoint
- ≥1 Stage Fibrosis Improvement with no Worsening of NASH at Week 36

Key Secondary Efficacy Endpoints
- NASH 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 NASH or cryptogenic cirrhosis presumed secondary to NASH. Subjects with cryptogenic cirrhosis were limited to approximately 20% of the total study population.

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

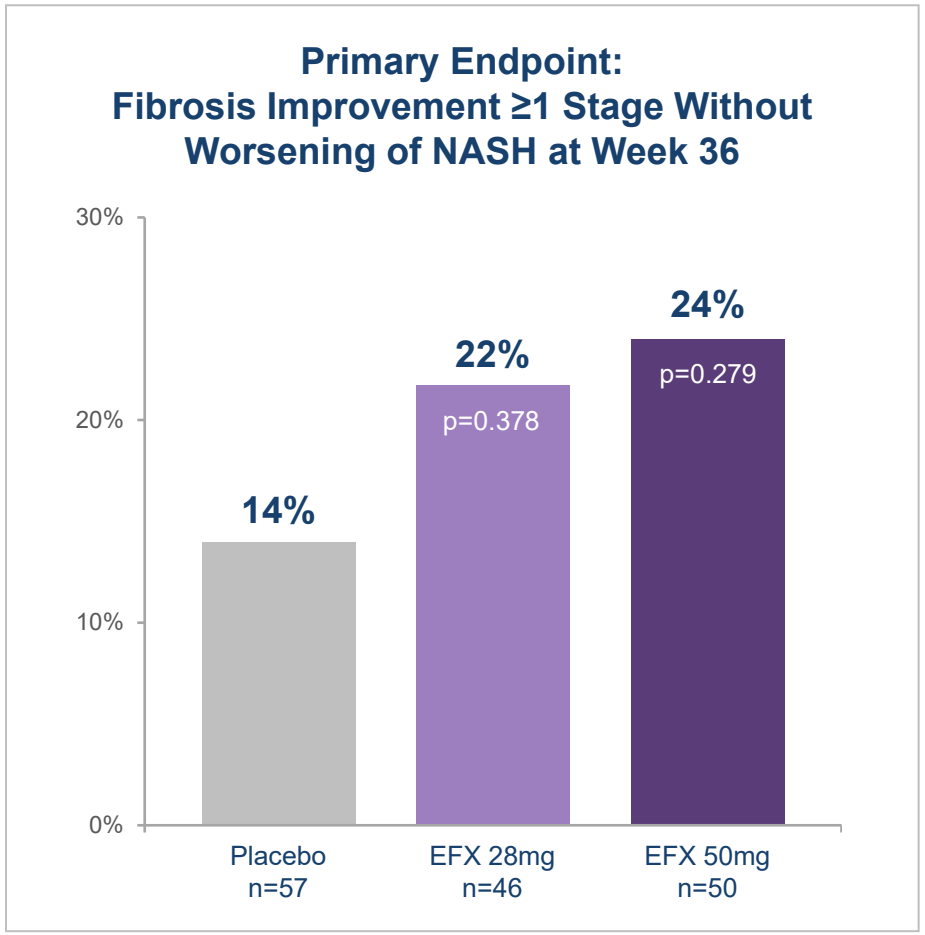
Secondary Histological Endpoints
Liver Biopsy Analysis Set (Definitive NASH[1] Only)
Excludes all subjects with cryptogenic cirrhosis

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

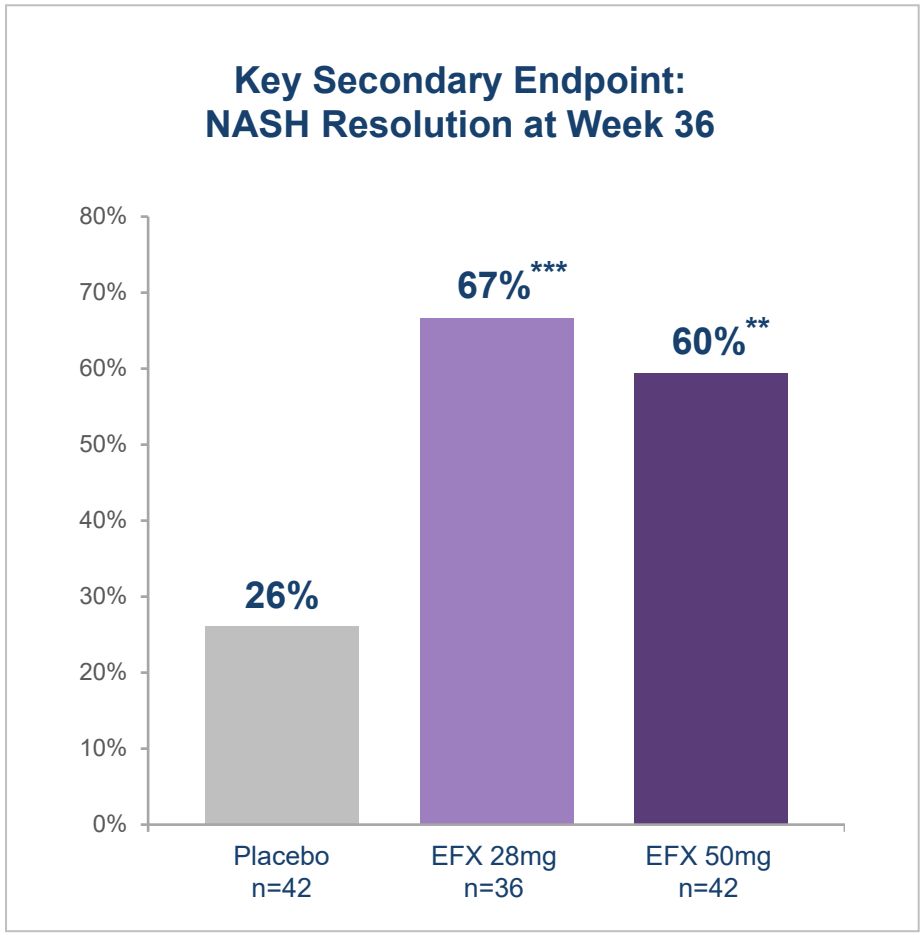
Baseline Demographics

Parameter (Mean)	Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
Age (Years)	**61**	**62**	**59**
Sex (% Female)	**62**	**68**	**70**
Definitive NASH (%) / 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
Platelets (10^9/L)	182	184	182
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

Fibrosis Improvement and NASH Resolution



P values are from Cochran–Mantel–Haenszel test (CMH)

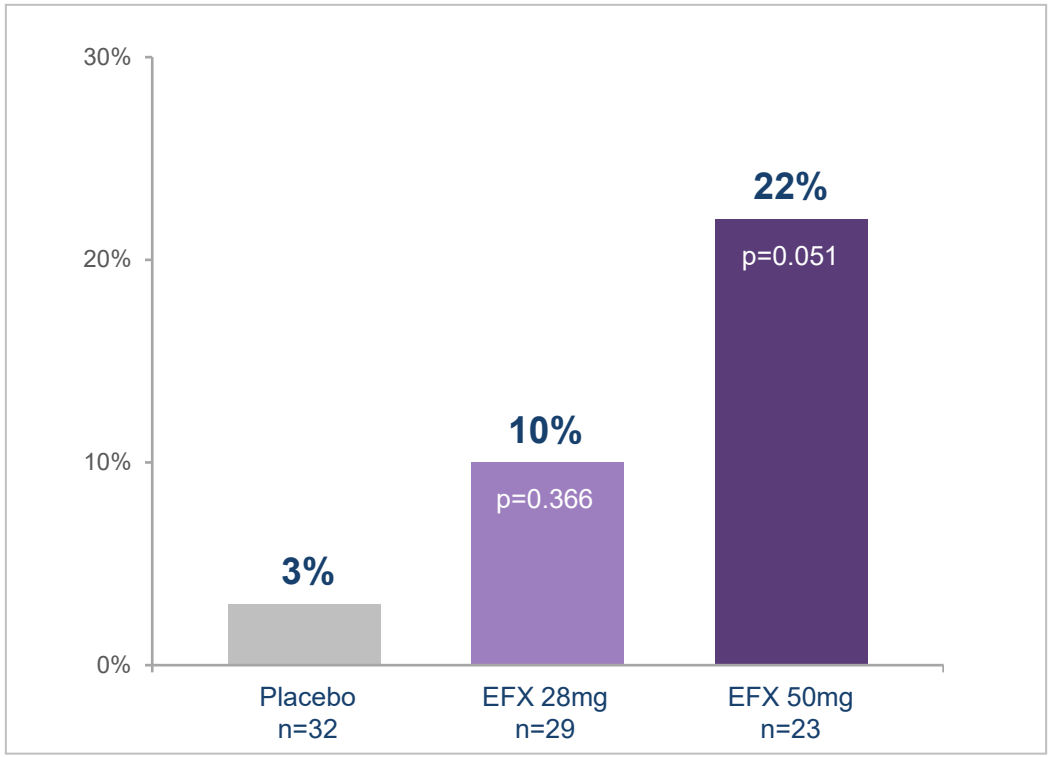


** p<0.01, *** p<0.001, versus placebo (CMH)

Source Data: Fibrosis Improvement (Liver Biopsy Analysis Set); NASH Resolution (Liver Biopsy Analysis Set [definitive NASH only]); Topline preliminary data

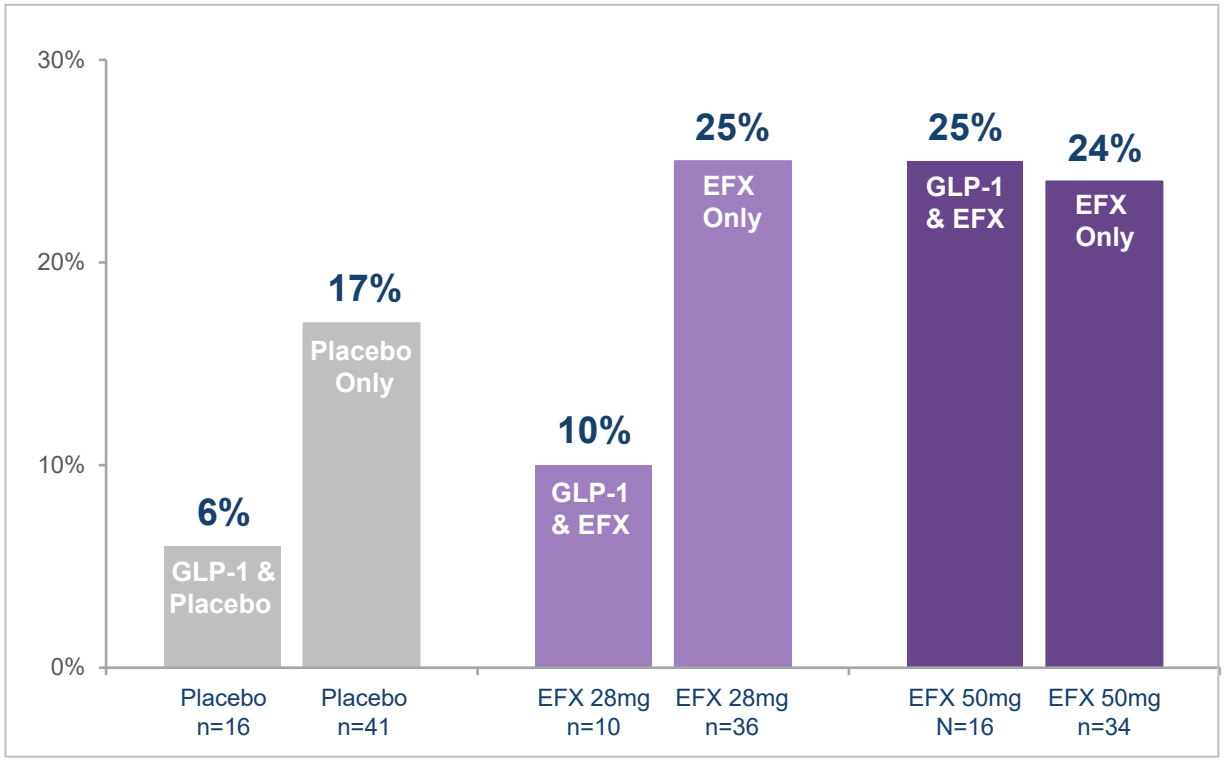
Fibrosis Improvement Subgroup Analyses
(≥1 Stage Improvement in Fibrosis and No Worsening of NASH)

Cirrhosis Diagnosed for ≥ 6 Months at Baseline or Baseline Cryptogenic Cirrhosis



P values are from CMH test

Baseline GLP-1 Use vs. No Baseline GLP-1 Use



Source Data: Liver Biopsy Analysis Set; Topline preliminary data

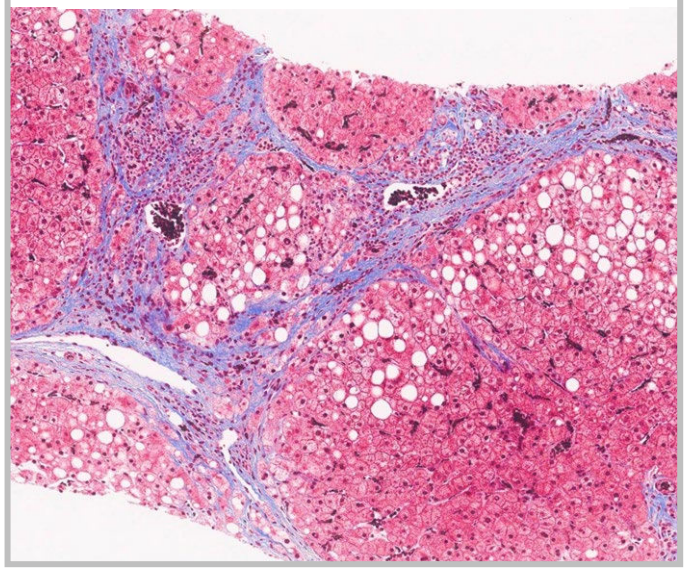
Improvement in Fibrosis by ≥2 Stages Without Worsening of NASH

Two subjects (4%) in each EFX group achieved ≥2 stage improvement in fibrosis without worsening of NASH compared to none on placebo

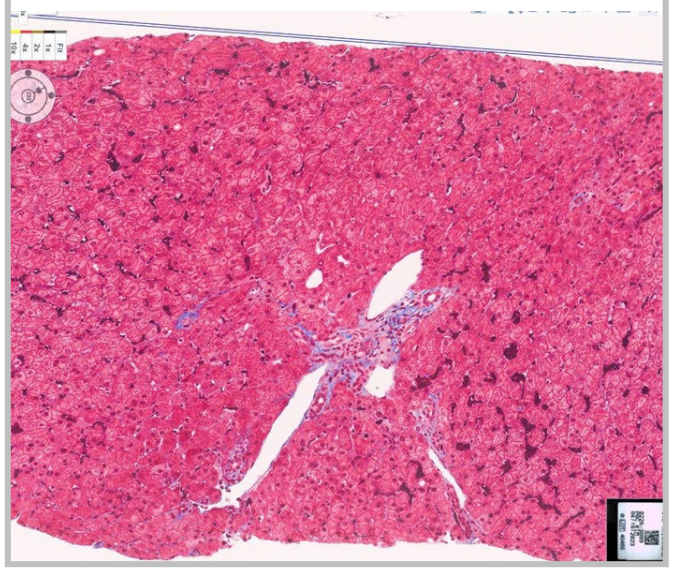
Case Study (EFX 50mg)

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

Baseline Biopsy



Week 36 Biopsy



Fibrosis Stage

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

NAFLD 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**

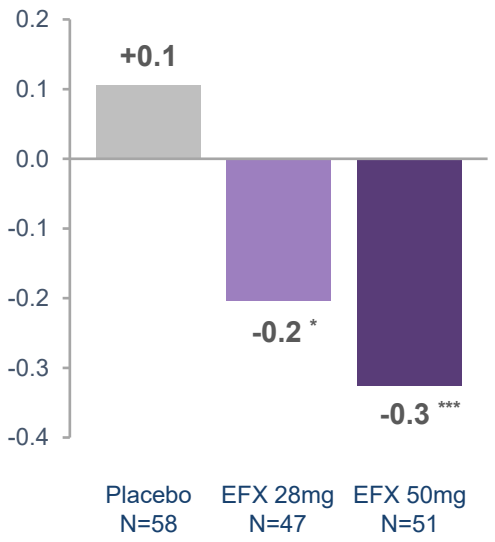
Non-Invasive Fibrosis Markers

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**

Evidence of Anti-Fibrotic Activity: Improvements in Non-Invasive Fibrosis Markers

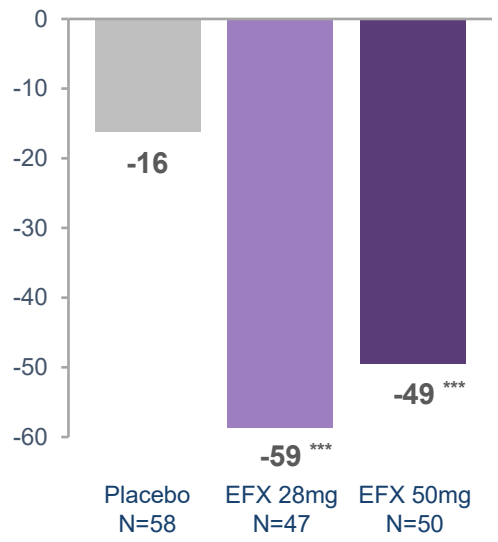
LS Mean Change From Baseline to Week 36

ELF Score[1]



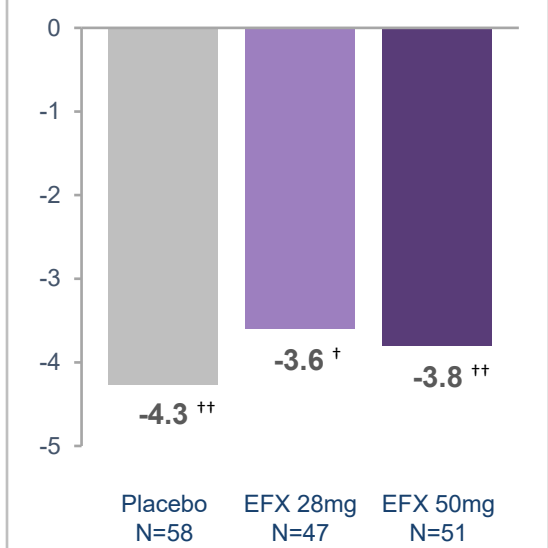
* p<0.05, ** p<0.01, versus placebo
(Mixed Model Repeated Measures [MMRM])

Pro-C3 (µg/L): Generation 2 ELISA



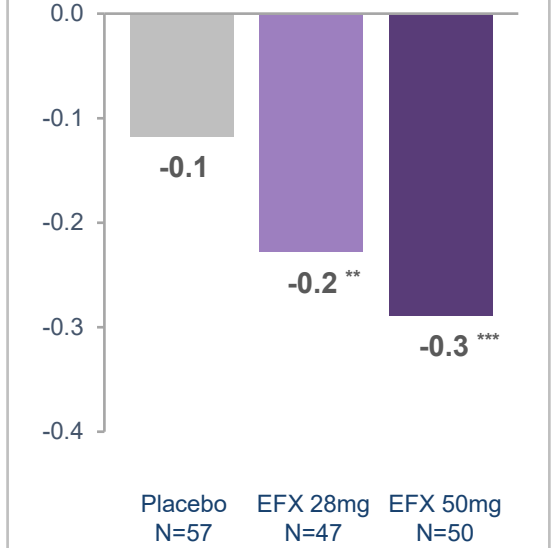
*** p<0.001, versus placebo (MMRM)

Liver Stiffness (kPa)[1]



† p<0.05, †† p<0.01, versus baseline (MMRM)
[1] Measured by FibroScan

FAST Score

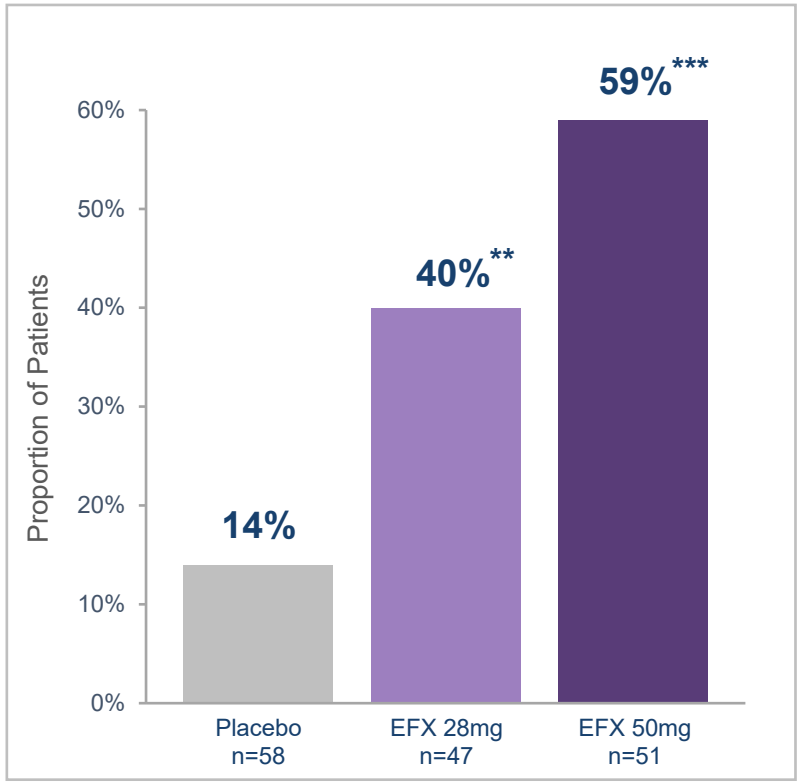


** p<0.01, *** p<0.001, versus placebo (MMRM)

Source Data: 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

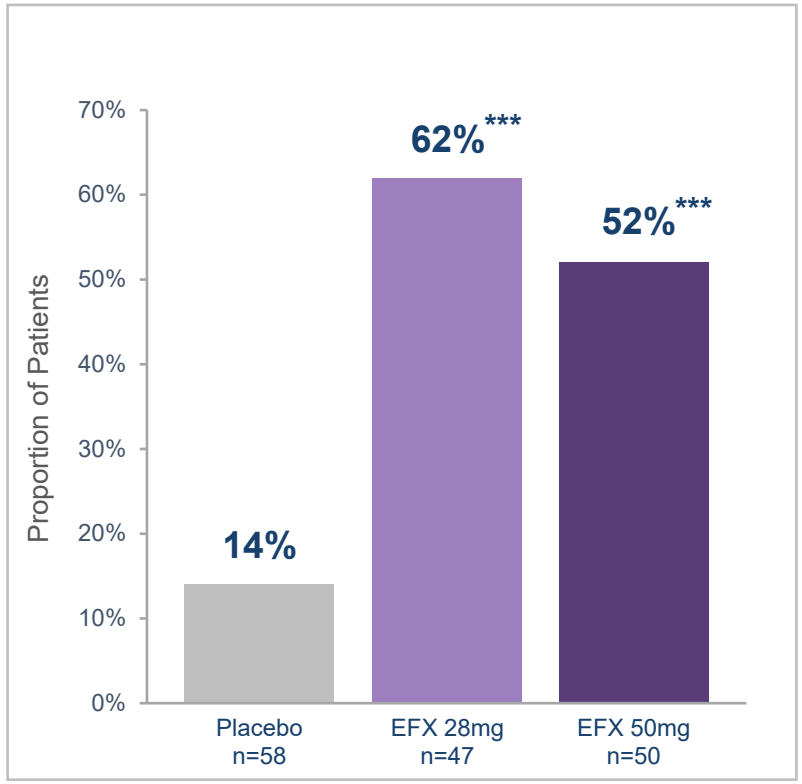
ELF Reductions of ≥0.5 Points



** 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 correlate with a 1-stage improvement in fibrosis

Pro-C3 (GEN2) Reductions of ≥35%

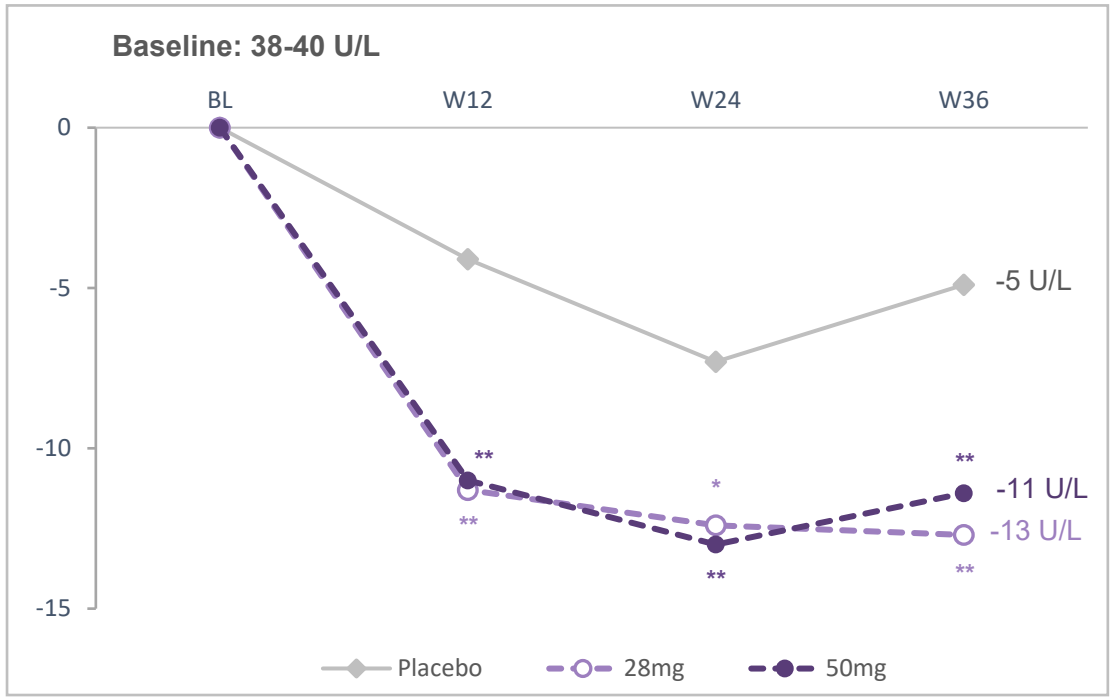


*** p<0.001, versus placebo (CMH)

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

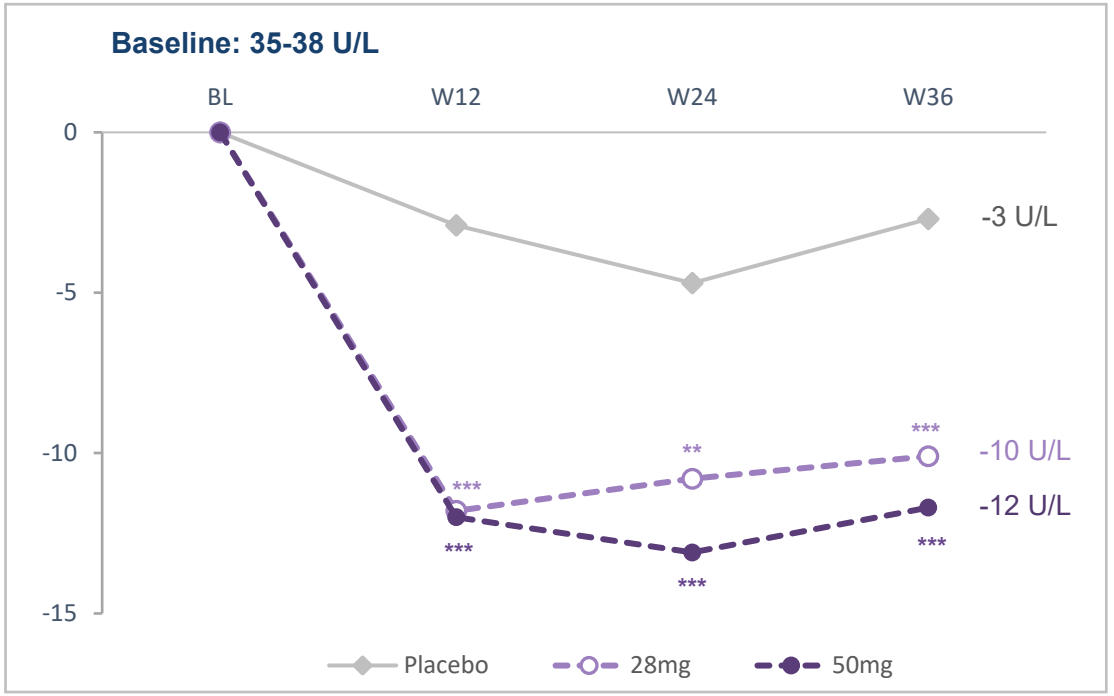
SYMMETRY: Early and Sustained Statistically Significant Improvements in Markers of Liver Injury

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)

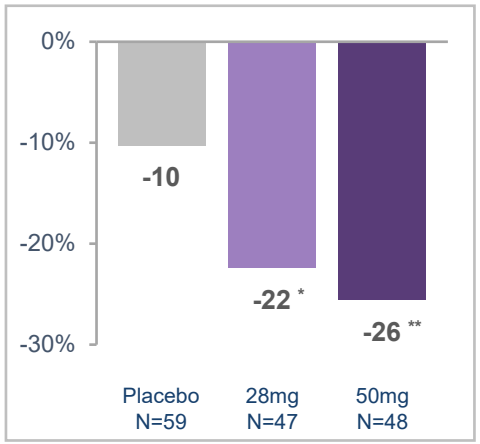


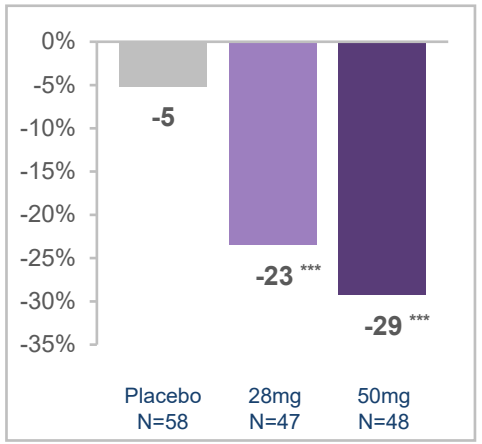
** p<0.01, *** p<0.001, versus placebo (MMRM)

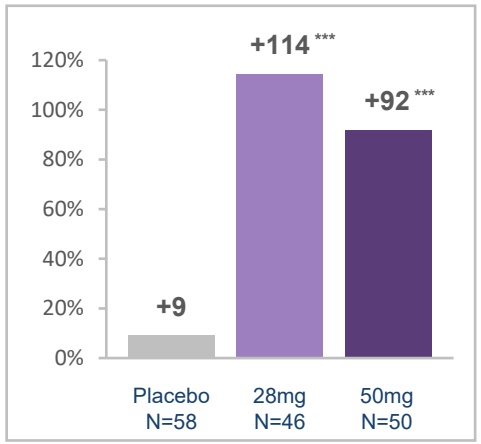
Statistically significant improvements from baseline observed for platelet counts for both EFX groups

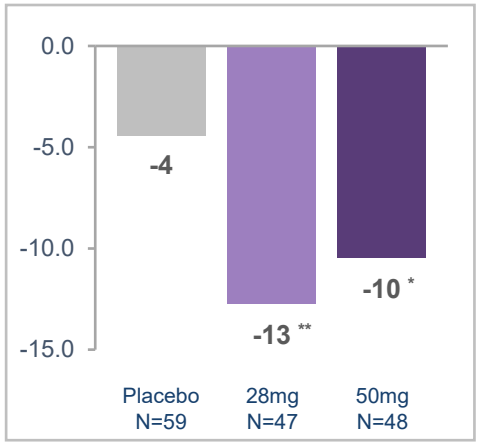
Source Data: Full Analysis Set; Topline preliminary data

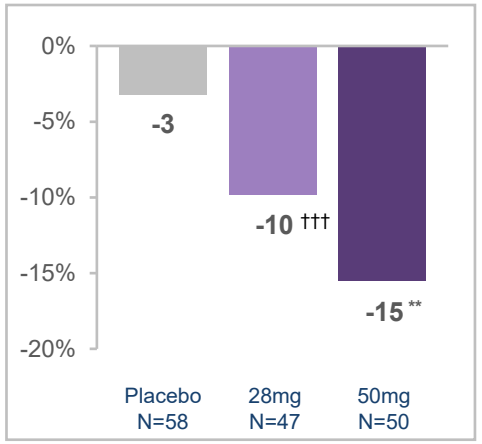
EFX Improved Whole-Body Metabolic Health in Patients with Cirrhosis, Consistent with Prior Studies

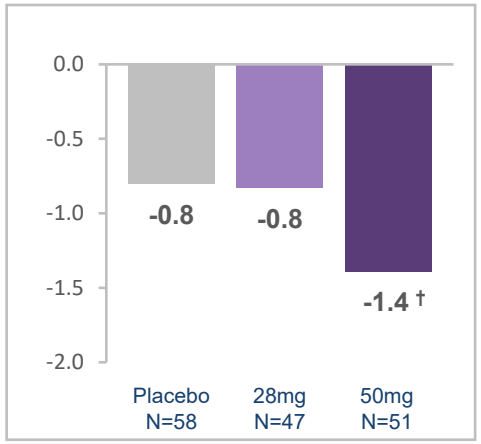












[1] Relative percent change from baseline; * p<0.05, ** p<0.01, *** p<0.001, versus placebo (MMRM); † p<0.05, ††† p<0.001, versus baseline (MMRM)

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

Laboratory Findings

- Markers of liver function and hemostasis remained stable, including INR, bilirubin, MELD, and CP score
- No cases of confirmed drug-induced liver injury

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 corticosteroids, may have confounded observed changes
- Incidence of fractures balanced across treatment groups

Key Takeaways

- In this challenging well-compensated cirrhotic population, a clinically meaningful but not yet significant clinical benefit was seen in as early as 36 weeks.
- The totality of the data to include markers of liver injury and fibrosis suggest overall improvement of liver health at this early timepoint.
- Additional benefits are seen in lipid and glucose metabolism, consistent with prior studies in non-cirrhotic patients.
- There is a favorable safety/tolerability profile, consistent with prior studies in non-cirrhotic patients, including transient mild and moderate gastrointestinal events.
- Patients will remain on treatment and liver biopsy assessment will be repeated at 96 weeks.

Acknowledgements

Thank you to the patients and their families, as well as the investigators and their teams, who have participated in the ongoing SYMMETRY study.

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