Efruxifermin in metabolic dysfunction-associated steatohepatitis: phase 2b results and implications for ongoing phase 3 trials

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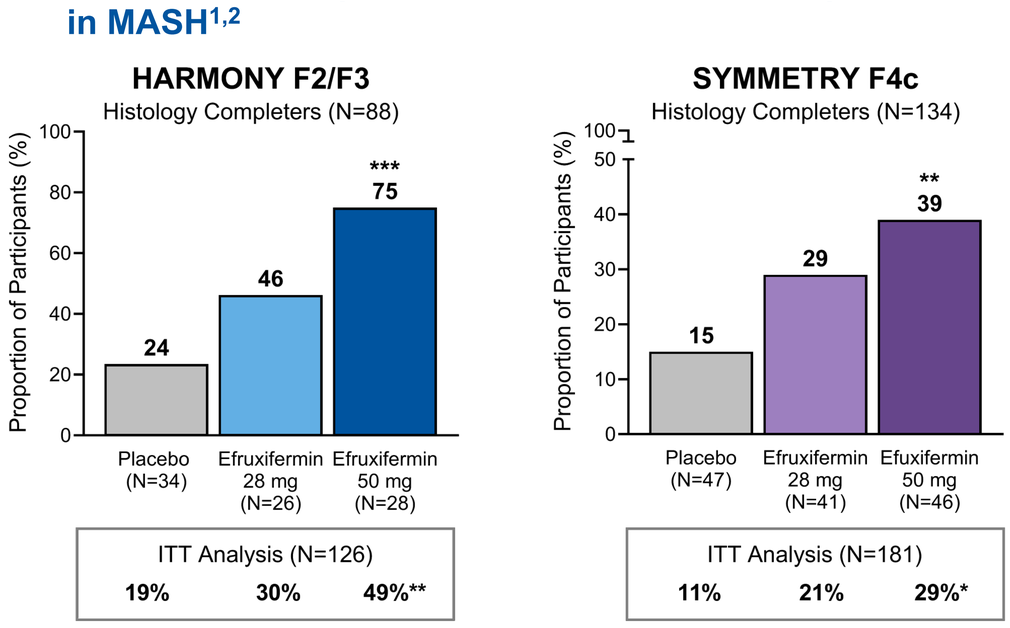
Background: Phase 2b Clinical Trials

- Efruxifermin is a bivalent FGF-21 analog in development for treatment of MASH.

Efficacy

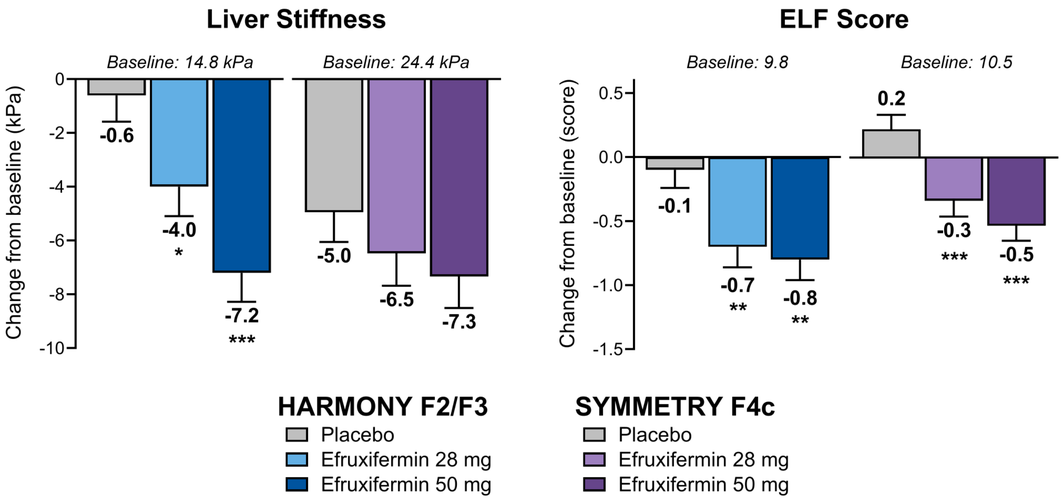
- Efruxifermin improved histology-defined fibrosis at Week 96 in participants with MASH and F2/F3 fibrosis or compensated cirrhosis (F4c) (Figure 1).[1,2]
- Efruxifermin also improved noninvasive fibrosis measures (Figure 2), markers of liver injury, lipid profile, and insulin sensitivity.[1,2]

Figure 1. Efruxifermin improved fibrosis at Week 96 in phase 2b trials in MASH[1,2]



**p<0.05, **p<0.01, ***p<0.01 vs placebo (Cochran-Mantel-Haenszel test). The Histology Completers analysis included all participants with baseline and Week 96 liver biopsies. The ITT analyses included all randomized and dosed participants, with Week 96 missing biopsy imputed as nonresponse. Fibrosis response was defined as participants with ≥1-stage fibrosis improvement and no worsening of MASH. Abbreviations: ITT, intent to treat.*

Figure 2. Efruxifermin improved noninvasive measures of fibrosis at Week 96 in phase 2b trials in MASH[1,2]

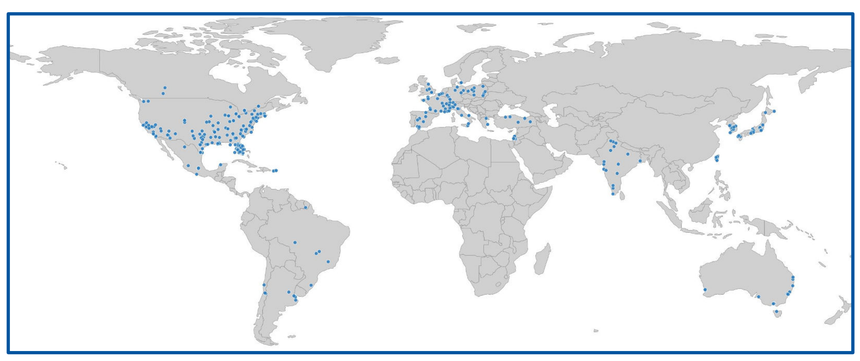


p<0.05,p<0.01, ***p<0.001 vs placebo (MMRM analysis). Data are change from baseline at Week 96 with observed values for the ITT population in HARMONY (N=126) and SYMMETRY (N=181). Baseline values are population mean for all randomized participants (HARMONY) or all randomized and dosed participants (SYMMETRY). Liver stiffness was assessed by vibration-controlled transient elastography (FibroScan). Abbreviations: ELF, Enhanced Liver Fibrosis test; ITT, intent to treat; MMRM, mixed-model repeated-measures.*

Safety and Tolerability

- Efruxifermin was generally well tolerated.[1,2]
- The most common adverse events (AEs) with efruxifermin were gastrointestinal (GI), particularly diarrhea and nausea. The majority of GI AEs were mild or moderate and transient.
  - Treatment discontinuations due to GI AEs ranged from 5 to 13% of participants in the efruxifermin groups. Most occurred within 3 to 4 months of treatment initiation.
  - Mitigation strategies included managing timing of concomitant medications (eg, metformin, GLP-1RAs), use of antiemetics or antidiarrheal medications, and brief interruptions of study drug.
- Other common AEs with efruxifermin included injection site reactions (erythema) and increased appetite (there were no clinically meaningful changes in average body weight).

Figure 3. SYNCHRONY phase 3 clinical trial sites to date



Countries with SYNCHRONY trial sites to date: Argentina, Australia, Belgium, Brazil, Canada, Chile, Denmark, France, Germany, Greece, India, Israel, Italy, Japan, Mexico, Poland, Puerto Rico, South Korea, Spain, Switzerland, Taiwan, Türkiye, United Kingdom, United States.

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References
[1] Noureddin et al. Lancet. 2025;406(10504):719–730.; [2] Noureddin et al. N Engl J Med. 2025;392(24):2413–2424.

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Phase 3 SYNCHRONY Program

- **The SYNCHRONY phase 3 program comprises 3 randomized, placebo-controlled, double-blind clinical trials designed to evaluate the safety and efficacy of efruxifermin across the spectrum of MASH at over 300 global sites (Figures 3, 4).**

Figure 4. SYNCHRONY clinical trial design

synchrony HISTOLOGY

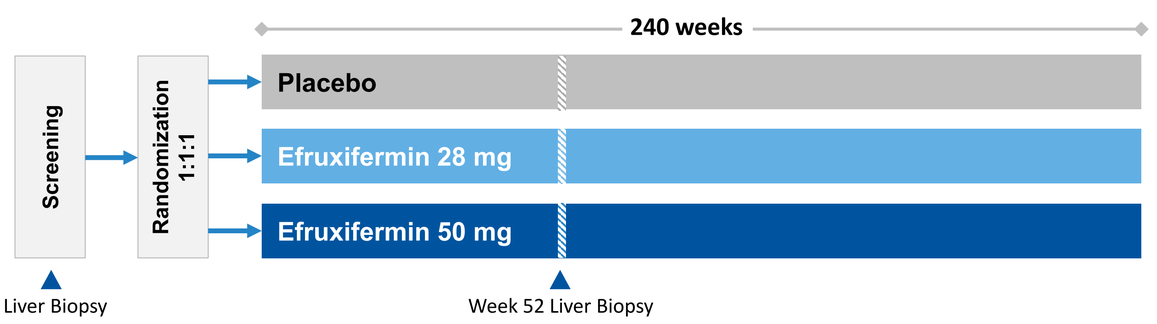
Study: AK-US-001-0105
Registration: NCT06215716

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

Primary Clinical Outcome Event
- Time to first clinical event (including disease progression, liver decompensation, liver transplantation, and all-cause mortality)

Population F2/F3 MASH, *Biopsy-defined moderate to advanced fibrosis (N≈1650)*

Eligibility
Cohort 1 Biopsy-defined NASH/MASH with fibrosis stage 2 or 3 and a non-alcoholic fatty liver disease (NAFLD) activity score (NAS) of ≥ 4 with at least a score of 1 in each of the following NAS components: steatosis, ballooning degeneration, lobular inflammation.
Cohort 2 Biopsy-defined fibrosis stage 3



synchrony OUTCOMES

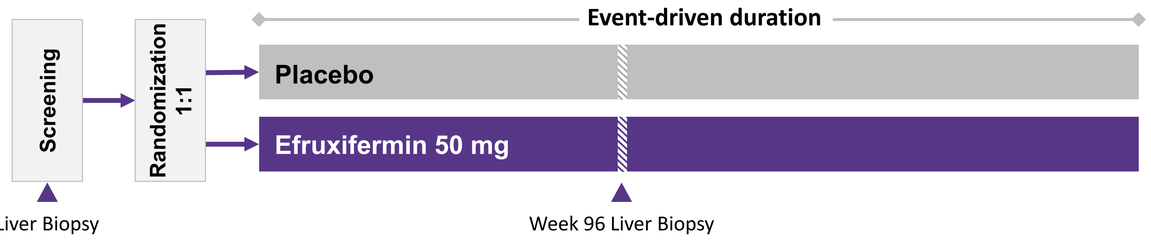
Study: AK-US-001-0106
Registration: NCT06528314

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

Primary Clinical Outcome Event
- Time to first clinical event (including disease progression, liver decompensation, liver transplantation, and all-cause mortality)

Population F4c MASH, *Compensated cirrhosis (N≈2150)*

Eligibility
Cohort 1 Biopsy-defined compensated cirrhosis (stage 4 fibrosis) due to MASH and NAS score ≥3 (≥1 in each category) or evidence of steatosis and ≥2 features of metabolic syndrome.
Cohort 2 Biopsy-defined ***or noninvasively diagnosed*** compensated cirrhosis due to NASH/MASH



synchrony REAL-WORLD

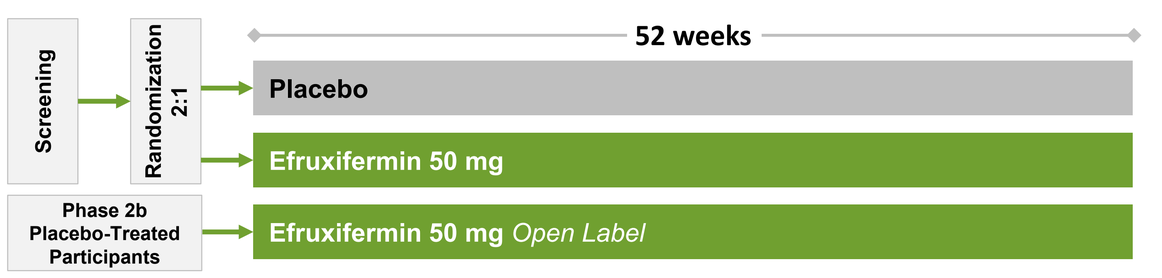
Study: AK-US-001-0107
Registration: NCT06161571

Primary Endpoint
- Safety and tolerability

Key Secondary Endpoints
- Change in noninvasive fibrosis tests: enhanced liver fibrosis (ELF) test and liver stiffness by transient elastography (FibroScan)

Population F1-F4c MASLD/MASH, *Mild fibrosis to compensated cirrhosis (N≈700)*

Eligibility MASLD/MASH with biopsy-defined fibrosis (F1-F4c) OR noninvasive diagnosis of fibrosis and confirmation of elevated liver fat content.



Summary and Conclusions

- **The phase 3 SYNCHRONY program will evaluate the safety and efficacy of efruxifermin across the spectrum of MASH, including cirrhosis.**
  - In the clinic, MASH cirrhosis is often noninvasively diagnosed and monitored. SYNCHRONY Outcomes (Study 106) Cohort 2 allows for enrollment of patients noninvasively diagnosed with compensated cirrhosis due to MASH.
- **The most common AEs with efruxifermin were mild to moderate gastrointestinal AEs. Proactive management of common AEs, especially in the first few months of treatment, is expected to increase retention and improve evaluation of clinical benefit.**
- **The SYNCHRONY Histology and Outcomes trials are designed to confirm the clinical benefit of efruxifermin in MASH.**

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