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EFRUXIFERMIN REDUCED FIBROSIS AND SEPTA AREA BY QUANTITATIVE DIGITAL PATHOLOGY IN PARTICIPANTS WITH COMPENSATED CIRRHOSIS DUE TO MASH: RESULTS FROM THE 96-WEEK, PLACEBO-CONTROLLED, PHASE 2B SYMMETRY TRIAL

Poster #5024

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INTRODUCTION

- Efruxifermin is a bivalent FGF21 analog in development for treatment of MASH.
- Efruxifermin improved liver fibrosis by conventional pathology (NASH CRN) in the 96-week SYMMETRY trial in participants with MASH and compensated cirrhosis (F4c).[1]
- AI-based digital pathology tailored for precise histopathological assessment of MASH cirrhosis can aid in assessment of nuanced drug effects.[2]
- Using AI-based digital pathology, changes in cirrhosis features such as fibrosis burden and septa area have been correlated with clinical outcomes such as varices, HVPG, and clinically significant portal hypertension (CSPH).[3]

AIM

Using AI-based digital pathology, evaluate the impact of efruxifermin on overall fibrosis burden and septa area, features of cirrhosis that are associated with clinical outcomes.

METHODS

- SYMMETRY was a phase 2b, randomized, placebo-controlled, double-blind trial that included 181 participants with MASH and biopsy-confirmed compensated cirrhosis.
- Unstained liver biopsies were available at Baseline and Week 96 for 130 participants (placebo n=44, efruxifermin 28 mg n=40, efruxifermin 50 mg n=46).
- Biopsies were imaged using second harmonic generation/two-photon excitation fluorescence microscopy and analyzed by:
  a) qFibrosis for continuous and categorical fibrosis changes and
  b) qSepta for changes in septa area.
- CSPH risk was evaluated using Baveno VII criteria based on LSM-VCTE (kPa) and platelet count (10^9/L).[4] CSPH: LSM≥25, Probable CSPH: LSM 20-25 and platelets <150 or LSM 15-20 and platelets <110; Rule out CSPH: LSM <15 and platelets ≥150.

RESULTS

Figure 1. Representative Images Showing Overall Reduction in Fibrosis, including Decrease in Septa Area, with Efruxifermin at Week 96

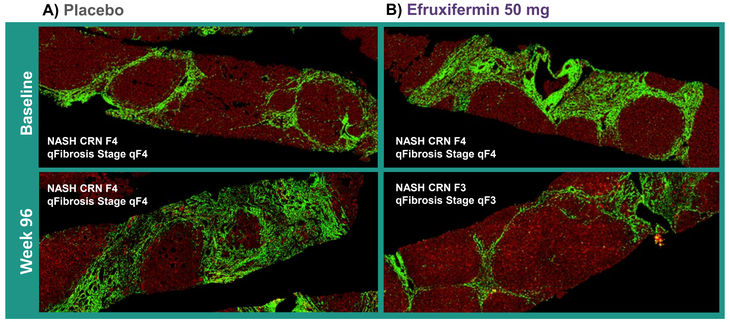

***Figure 1**. (A) SHG/TPEF image of a placebo case participant showing qFibrosis remained at F4 at Baseline and Week 96 with a qualitative increase in septa area. (B) SHG/TPEF image of an efruxifermin 50 mg case participant with qFibrosis. improvement from F4 at Baseline to F3 at Week 96 with a qualitative decrease in septa area reflecting reduction of collagen.*

Figure 2A. qFibrosis Corroborated NASH CRN Results for Fibrosis Improvement with Efruxifermin

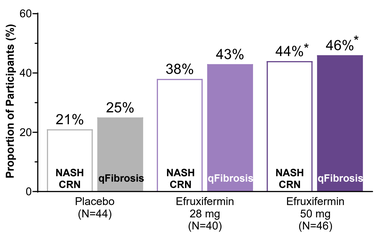

Figure 2B. Septa Area was Reduced in Participants Treated with Efruxifermin

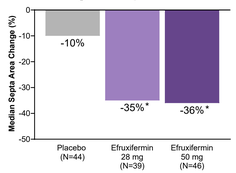

Figure 2C. Septa Area was Reduced in a Greater Proportion of Efruxifermin Participants Than Placebo

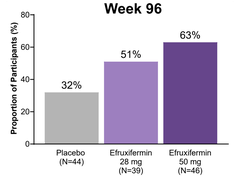

***Figure 2**. (A) Fibrosis improvement ≥1-stage at Week 96 evaluated by NASH CRN criteria and digital pathology (qFibrosis). *p<0.05 vs placebo within analysis method (NASH CRN or digital pathology) (B). Septa area change (median) at Week 96.*p<0.05 vs placebo. (C) Proportion of participants with ≥30% reduction in septa area at Week 96. Not analyzed for statistical significance.*

Figure 3. Higher Risk of CSPH is Associated with Greater Septa Area and Septa Area was Reduced in the Subgroup of Efruxifermin Participants with Higher Baseline CSPH Risk

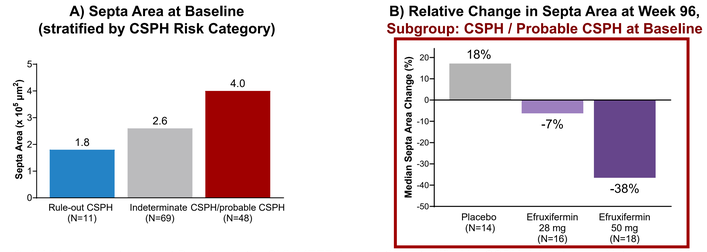

***Figure 3**. (A) Median septa area at Baseline in the SYMMETRY population, stratified by CSPH risk category. Not analyzed for statistical significance. (B) Median septa area change at Week 96 in the subgroup with CSPH/probable CSPH at Baseline. Not significant for efruxifermin vs placebo.*

Figure 4. Septa Area was Reduced with Efruxifermin Regardless of NASH CRN Responder Status

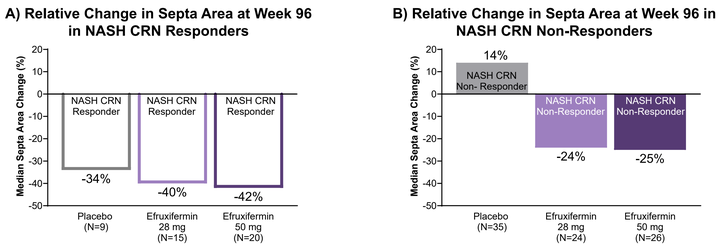

***Figure 4. (A)** Median septa area change at Week 96 evaluated in NASH CRN responders (≥1 stage fibrosis improvement). Not analyzed for statistical significance. **(B)** Median septa area change at Week 96 evaluated in NASH CRN non-responders. Not analyzed for statistical significance.*

Figure 5. Septa Area Reduced by Efruxifermin Regardless of Change in CSPH Risk Category

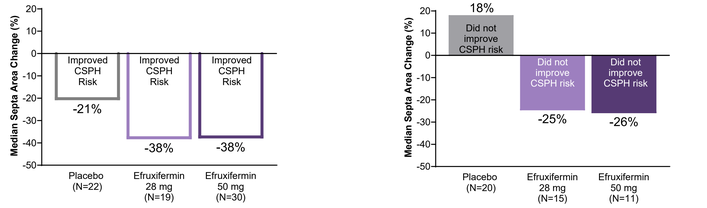

***Figure 5. (A)** Median septa area change at Week 96 in participants that improved CSPH Risk category (of participants that were not rule-out at Baseline). Not analyzed for statistical significance.**(B)** Median septa area change at Week 96 in participants that did not improve CSPH Risk category (of participants that were not rule-out at Baseline). Not analyzed for statistical significance.Two participants were excluded due to missing data.*

CONCLUSIONS

- In participants with F4c MASH, AI-based digital pathology confirmed fibrosis improvement with efruxifermin at Week 96, previously observed with NASH CRN pathology.[1]
- Digital analysis of septa area also revealed subtle changes in fibrosis with efruxifermin.
- Treatment with efruxifermin reduced septa area consistently across all participants, including participants with CSPH/probable CSPH at Baseline, NASH CRN fibrosis non-responders, and participants that did not improve CSPH risk category.
- Efruxifermin is being evaluated in phase 3 clinical trials for treatment of MASH.

REFERENCES

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DISCLOSURES

- M.E.R. provides scientific consulting for Akero Therapeutics, BMS, Boehringer Ingelheim, Cytodyn, GSK, Intercept Pharmaceuticals, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, 89Bio, Lilly and Sonic Incytes.
- Y.C., G.G., E.C., and D.T. are employees of HistoIndex.
- C.B. is a consultant for Akero Therapeutics, Boehringer Ingelheim, ICON, and Pathology Institute, TX and is a part time associate at the University of California.
- D.C., L.L., E.J.T., M.B., S.K. B., R.S.; T.R. K.Y are employees and shareholders of Akero Therapeutics.
- M.N. provides consulting for Akero, Altimmune, Alligos, AstraZeneca, BI, Boston Pharma, Curve bioscience, Cytodyn, GSK, Histoindex, Kryia , Lilly, Madrigal, Merck, Novo Nordisk, OPKO, Rivus, Sagimet, Terns, Takeda. M.N. is principal investigator for a drug study of at 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, Zydus. M.N. is a shareholder of OPKO, Kryia, and Akero. MN is on the speaking bureau of Madrigal and Novo Nordisk.

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