Aldafermin Reduces Hydrophobic Bile Acids in a 24-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study in Patients with Nonalcoholic Steatohepatitis

- Higher serum bile acid levels are associated with an increased risk of cirrhosis and liver-related morbidity and mortality.\(^1\)
- Serum bile acids correlate with portal hypertension, and can predict decompensation, liver failure and transplant-free survival in chronic liver disease.\(^1\)
- Aldafermin, an engineered FGF19 analog, potently inhibits bile acid synthesis via the suppression of CYP7A1, which encodes the first and rate-limiting enzyme in the classic bile acid synthetic pathway.\(^2\)
- Here we report results from a secondary analysis of aldafermin on circulating bile acid profile in a 24-week, randomized, double-blind, placebo-controlled trial in patients with NASH.

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1Horvatits et al., Liver Int 2017;37:224–231 2Harrison et al., Gastroenterology 2021;160:219-231
Robust Reduction of 7alpha-Hydroxy-4-Cholesten-3-One, A Surrogate of Bile Acid Synthesis, by Aldafermin

- Serum level of 7alpha-hydroxy-4-cholesten-3-one (C4), a surrogate of hepatic CYP7A1 activity, is a pharmacodynamics marker of aldafermin activity.

- At week 24, a greater reduction from baseline in C4 was observed in the aldafermin group compared to placebo (P<0.001).

![Chart showing mean C4 levels](chart.png)
Aldafermin Treatment Produced Marked Reductions in Hydrophobic Bile Acids, and DCA in Particular

DCA, deoxycholic acid; GDCA, glycodeoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid
Greater Anti-Fibrotic Effects with Aldafermin in Patients Who Achieved ≥70% Reduction in DCA

Fibrosis Improvement (≥1-stage) with No Worsening in NASH

All Patients

\[ \Delta = 20\% \]

Patients Achieving ≥70% Reduction in DCA

\[ \Delta = 38\% \]

Sanyal et al., Abstract 981 (EASL 2021)

1 Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening of NASH (no worsening of steatosis, lobular inflammation or hepatocyte ballooning grade) from baseline to W24
Conclusion

• Administration of aldafermin produced significant reductions in bile acids, and the more toxic, hydrophobic bile acids in particular

• Among individual bile acids, aldafermin generated the most robust reduction in the secondary bile acid DCA

• The preferential reduction of the more hydrophobic, glycine-conjugated bile acids, rather than the more hydrophilic, taurine-conjugated, bile acids by aldafermin resulted in a lower G/T ratio and reduced bile acid toxicity

• Aldafermin had greater anti-fibrotic effects in patients who achieved ≥70% reduction in DCA

• Results from this 24-week study in an independent cohort confirm and validate previous findings from 12-week studies

Acknowledgment

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1 Sanyal et al., JHEP Reports 2021;3:100255