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

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## INTRODUCTION

- Higher serum bile acid levels are associated with an increased risk of cirrhosis and liver-related morbidity and mortality [1-3]
- Serum bile acids correlate with portal hypertension, and can predict decompensation, liver failure and transplant-free survival in chronic liver disease [2]
- 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 [4]
- 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

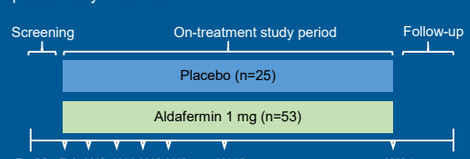
**Aldafermin**


## AIM

To evaluate change in serum bile acid profile in a 24-week study of aldafermin in patients with NASH

## METHOD

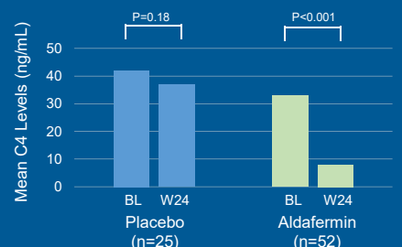
- 78 subjects were randomized 1:2 to receive placebo (n=25) or aldafermin 1 mg (n=53) SC QD for 24 weeks at 9 US study sites [4]
- Key inclusion criteria included biopsy-proven NASH with NAS≥4, F2 or F3 fibrosis and absolute liver fat content ≥8%
- Fasting serum samples were collected at baseline (BL) and week 24 (W24)
- Concentrations of individual bile acids and 7alpha-hydroxy-4-cholesten-3-one (an intermediate of bile acid synthesis and a surrogate of hepatic CYP7A1 activity) were measured by mass spectrometry methods



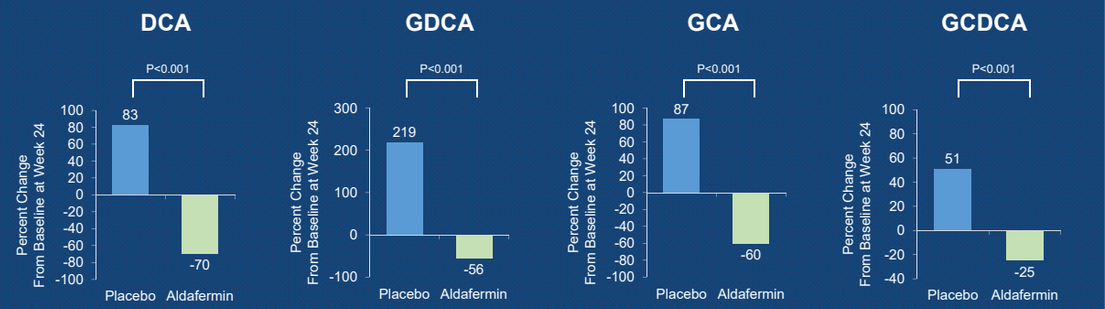

## RESULTS

- *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 robustly greater reduction from baseline in C4 was observed in the aldafermin group compared to placebo (−65% and +1% in aldafermin and placebo groups, respectively, P<0.001 vs placebo)*

**7alpha-hydroxy-4-cholesten-3-one**

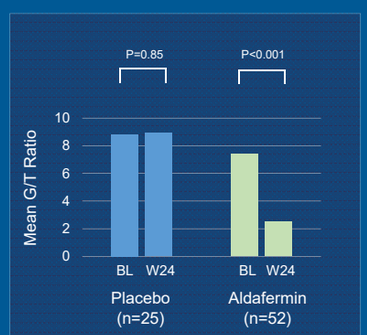



**Individual Bile Acids**



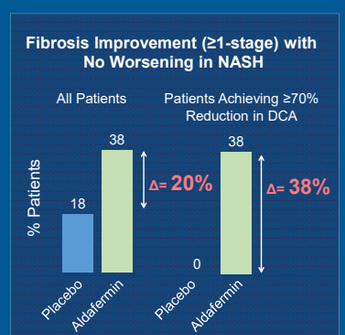

*Aldafermin treatment reduced concentrations of deoxycholic acid (DCA), glycodeoxycholic acid (GDCA), glycocholic acid (GCA) and glychochenodeoxycholic acid (GCDCA), with changes of −0.6 umol/L, −0.7 umol/L, −0.6 umol/L and −0.9 umol/L at week 24 (p<0.001 vs placebo for all comparisons), corresponding to relative changes of −70%, −56%, −60% and −25%, respectively, in subjects receiving aldafermin. No reductions in tauro-conjugated bile acids were seen with aldafermin treatment. Furthermore, aldafermin lowered total CA, total CDCA, total DCA, total LCA, total primary bile acids and total secondary bile acids.*

**G/T Ratio**




*The ratio of glycine to taurine conjugates (G/T ratio), a measure of differential conjugation of bile acids and bile acid toxicity, were decreased with aldafermin treatment.*

**Histology**




*Aldafermin demonstrated greater anti-fibrotic efficacy (placebo-subtracted response rate) in patients who achieved ≥70% reduction in DCA.*

## CONCLUSIONS

- 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 [5]

## REFERENCES

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