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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Abstract 981 (EASL 2021)

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 CYPTA1, 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

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 OD for 24 weeks at 8 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 hepatic CYPTA1 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.

G/T Ratio

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>W24</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>219</td>
<td>219</td>
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<tr>
<td>Aldafermin (n=53)</td>
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<td>219</td>
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</tbody>
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Fibrosis Improvement (21-stage) with No worsening in NASH

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<tr>
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<th>% Patients</th>
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<tbody>
<tr>
<td>All Patients</td>
<td>38</td>
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<tr>
<td>Patients Achieving &gt;70% Reduction in DCA</td>
<td>&gt;38</td>
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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.

REFERENCES
5. Sanyal et al., Patient suppression of hydrophobic bile acids by aldaferrin in CBD/Primary sclerosing cholangitis, AASLD 2021.

Author Affiliations

EASL Conference, April 23-28, 2021
Amsterdam, Netherlands