Atherosclerotic Cardiovascular Risk Assessment in a 24-Week, Randomized, Double-Blind, Placebo-Controlled Study of Aldafermin

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INTRODUCTION

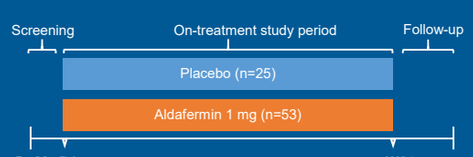
- Non-alcoholic steatohepatitis (NASH) is associated with an increased risk of cardiovascular disease [1]
- Recent society guidelines recommend initiating statins in patients with elevated cardiovascular risk [2-4]
- Aldafermin is an engineered FGF19 analogue that inhibits bile acid synthesis and regulates metabolic homeostasis [5]. In a 24-week, randomized, double-blind, placebo-controlled study in NASH patients with serial liver biopsies, aldafermin treatment resulted in liver fat reduction, fibrosis improvement and NASH resolution [5]
- However, aldafermin increased serum cholesterol levels by inhibiting CYP7A1, which encodes the rate-limiting enzyme in the conversion of cholesterol to bile acids
- Here we report results on cardiovascular risk assessment and key lipoproteins implicated in atherosclerosis from this study

AIM

To assess changes in the 10-year atherosclerotic cardiovascular disease risk score (ASCVD) and atherogenic lipoproteins in a 24-week study of aldafermin in patients with NASH

METHOD

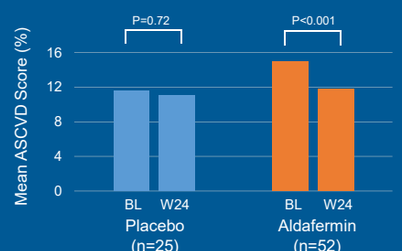
- 78 subjects were randomized 1:2 to receive placebo (n=25) or aldafermin 1 mg (n=53) SC QD for 24 weeks
- Key inclusion criteria included biopsy-proven NASH with NAS≥4, stage 2-3 fibrosis and absolute liver fat content ≥8%
- As pre-specified in the protocol, subjects were to start with rosuvastatin if statin naïve or switch to rosuvastatin if already on statin therapy, to treat LDL-C elevations of >10 mg/dL from baseline [5]
- 10-year atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated per ACC/AHA guidance [2-3] at baseline (BL) and week 24 (W24)
- Triglyceride and cholesterol content in the triglyceride-rich lipoproteins (TRL), concentrations of apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1), and the lipoprotein insulin resistance index (LP-IR) were measured at baseline and week 24 on Vantera nuclear magnetic resonance (NMR) clinical analyzer



RESULTS

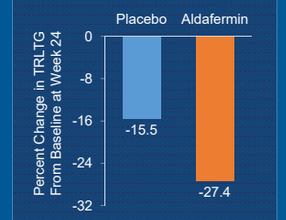
- *At baseline, mean 10-year ASCVD risk scores were 15.0% and 11.6% in the aldafermin and placebo groups, respectively*
- *At week 24, a greater reduction from baseline in the ASCVD risk score was observed in the aldafermin group compared to placebo (−3.4% and −1.2% in absolute ASCVD score in aldafermin and placebo groups, respectively, P=0.032 vs placebo)*

10-Year ASCVD Risk Score



TRL Triglyceride Content

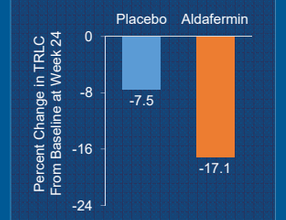
	Placebo (n=25)	Aldafermin (n=52)
Baseline TRLTG (mg/dL)	118.8 (115.5)	127.4 (67.6)



Triglyceride content in TRL declined in the aldafermin group but not the placebo group (−27.4%, P=0.006 vs placebo).

TRL Cholesterol Content

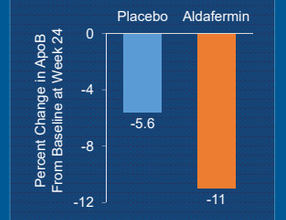
	Placebo (n=25)	Aldafermin (n=52)
Baseline TRLC (mg/dL)	33.7 (22.6)	34.5 (14.0)



Cholesterol content in TRL declined in the aldafermin group but not the placebo group (−17.1%, P=0.006 vs placebo).

ApoB

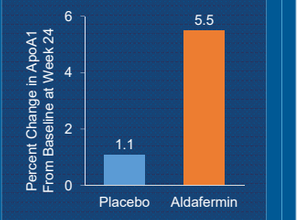
	Placebo (n=25)	Aldafermin (n=52)
Baseline ApoB (mg/dL)	86.0 (23.8)	88.1 (20.4)



The aldafermin group, but not the placebo group, had significant reductions in the pro-atherogenic lipoprotein ApoB (−11.0%, P=0.002 vs baseline)

ApoA1

	Placebo (n=25)	Aldafermin (n=52)
Baseline ApoA1 (mg/dL)	139.3 (25.0)	136.7 (23.0)

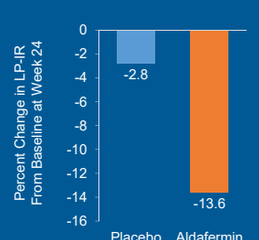


The aldafermin group, but not the placebo group, had significant increases in the anti-atherogenic lipoprotein ApoA1 (+5.5%, P=0.037 vs baseline)

Lipoprotein Insulin Resistance Index (LP-IR)

- *LP-IR combines lipoprotein parameters into a simple score that enables routine assessment of a patient's insulin resistance status* [6]
- *At week 24, patients in the aldafermin group, but not the placebo group, had significant reductions from baseline in LP-IR (P<0.001 and P=0.33 for aldafermin and placebo groups, respectively)*

	Placebo (n=25)	Aldafermin (n=52)
Baseline LP-IR	62.1 (21.6)	67.7 (18.9)



- *No significant change in other lipids and lipoprotein particles was seen in the aldafermin group compared to placebo at week 24*
- *No patients experienced cardiovascular events during the study*

CONCLUSIONS

- Aldafermin-associated cholesterol increase can be safely managed with a statin
- At the end of treatment, a greater reduction in the 10-year ASCVD risk score was achieved in the aldafermin group compared with placebo
- Patients in the aldafermin group had lower triglyceride and cholesterol content in TRL, lower levels of pro-atherogenic lipoprotein ApoB, and higher levels of the anti-atherogenic lipoprotein ApoA1 at week 24
- Patients in the aldafermin group, but not the placebo group, had reductions from baseline in lipoprotein insulin resistance index at week 24
- In this study in patients with NASH and fibrosis, an overall favorable cardiovascular risk profile was achieved in the aldafermin arm

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