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Lipid Management in a 24-Week, Randomized, Double-Blind, Placebo-Controlled Study of Aldafermin (NGM282)

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NGMBio

INTRODUCTION

- Aldafermin (previously known as NGM282), an engineered FGF19 analog, significantly inhibits bile acid synthesis and regulates metabolic homeostasis [1-5]
- In a 24-week, randomized, double-blind, placebo-controlled study in NASH patients with paired liver biopsies, aldafermin treatment resulted in liver fat reduction, fibrosis improvement and NASH resolution [6]
- However, aldafermin increased serum cholesterol levels by inhibiting CYP7A1, which encodes the rate-limiting enzyme in the conversion of cholesterol to bile acids
- Recent society guidelines (AHA/ACC and ESC/EAS) recommend initiating statins if cardiovascular risk scores ≥7.5% or diabetes for patients 40-75 with LDL-C ≥70 mg/dL [7-9]
- Here we report the protocol-specified lipid management approach and results on lipids and lipoprotein particles from the study

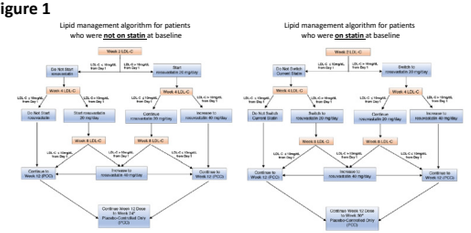
AIM

To assess the effectiveness of a protocol-specified lipid management algorithm on controlling aldafermin-associated cholesterol change

MATERIAL & METHODS

- 78 patients were randomized 1:2 to receive placebo (n=25) or aldafermin 1mg (n=53) SC QD at 9 US study sites [6]
- Key inclusion criteria included biopsy-proven NASH with NAS≥4, stage 2-3 fibrosis and absolute liver fat content ≥8% as measured by magnetic resonance imaging-proton density fat fraction
- Patients were to start with 20 mg rosuvastatin if statin naïve or switch to 20 mg rosuvastatin if already on statin therapy, to treat LDL-C elevations of >10 mg/dL from baseline at week 2. Patients were allowed to up-titrate to 40 mg rosuvastatin at weeks 4, 8 and 12 if LDL-C elevation remained >10 mg/dL from baseline. No dose modification on rosuvastatin occurred after week 12 (Figure 1)
- Fasting lipid panel as well as concentrations and size of lipoprotein particles were measured
- Atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated at baseline and week 24

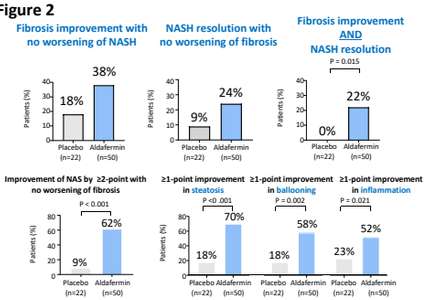
Figure 1



RESULTS

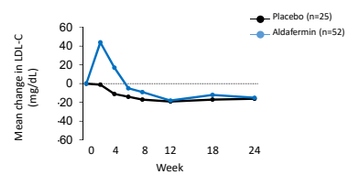
- A 24-week treatment with aldafermin improves liver histology in patients with NASH and fibrosis

Figure 2



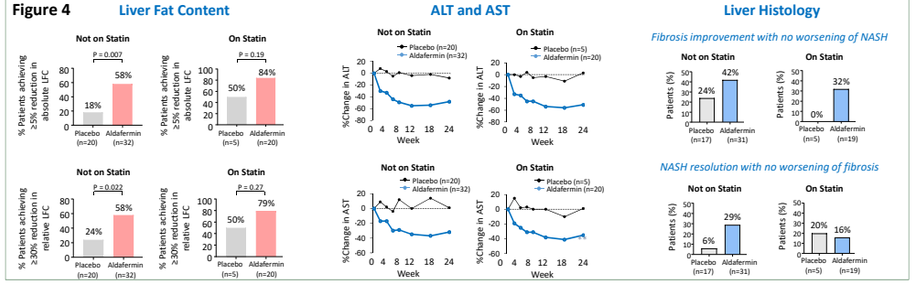
- Serum levels of low density lipoprotein cholesterol (LDL-C) were increased at week 2 in patients receiving aldafermin, consistent with on-target inhibition of the conversion of cholesterol to bile acids
- Aldafermin-associated elevations in LDL-C were effectively managed with rosuvastatin using a protocol-specified algorithm, reaching levels below baseline at week 24

Figure 3 Change in LDL-C From Baseline



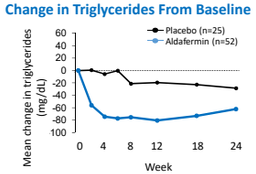
- Aldafermin produced similar efficacy on liver fat content, liver enzymes (ALT and AST) and liver histology in patients who were on statin and those who were not on statin at baseline

Figure 4 Liver Fat Content / ALT and AST / Liver Histology



- Serum triglyceride concentrations declined over time in patients treated with aldafermin but not placebo
- No decrease in HDL-C was seen in aldafermin group compared to placebo

Figure 5 Change in Triglycerides From Baseline



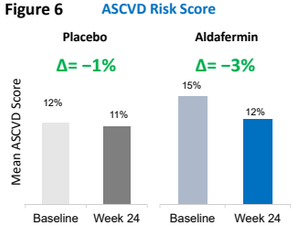
- Lipids and lipoprotein particles did not differ between groups at the end of treatment

Table 1 Lipids and Lipoprotein Particles

Change from Baseline at Week 24	Placebo (n=25)	Aldafermin 1 mg (n=52)	Difference Aldafermin vs Placebo (95% CI)	P
Lipids				
Δ Total cholesterol (mg/dL)	−21.3 (26.5)	−26.8 (31.8)	−3.3 (−16.7 to 10.1)	0.63
Δ HDL-C (mg/dL)	−0.7 (9.8)	1.9 (10.3)	2.0 (−2.8 to 6.8)	0.42
Δ LDL-C (mg/dL)	−16.0 (27.8)	−19.0 (30.2)	−2.3 (−16.3 to 11.6)	0.74
Δ Triglycerides (mg/dL)	−28.5 (56.0)	−62.2 (136.8)	−13.1 (−36.1, 10.0)	0.26
VLDL particles				
Δ VLDL-P (nmol/L), total	1.7 (15.3)	−12.7 (23.0)	−8.8 (−17.5 to −0.1)	0.047
Δ VLDL-P (nmol/L), large	−1.4 (2.8)	−3.0 (4.1)	−1.1 (−2.5 to 0.3)	0.12
Δ VLDL-P (nmol/L), small	4.4 (13.4)	−2.9 (18.8)	−5.6 (−12.6 to 1.4)	0.11
Δ VLDL-P size (nm)	−4.1 (6.4)	−3.7 (8.7)	−0.3 (−3.8 to 3.3)	0.88
LDL particles				
Δ LDL-P (nmol/L), total	−108.9 (264.4)	−153.3 (141.1)	10.3 (−114.1 to 152.7)	0.77
Δ LDL-P (nmol/L), large	−47.4 (154.5)	−56.9 (183.9)	−16.5 (−100.8 to 67.8)	0.70
Δ LDL-P (nmol/L), small	−68.7 (276.2)	−43.7 (263.3)	80.2 (−17.9 to 178.3)	0.11
Δ LDL-P size (nm)	−0.2 (0.3)	−0.2 (0.5)	0 (−0.2 to 0.2)	0.76
HDL particles				
Δ HDL-P (mmol/L), total	0.6 (5.1)	2.6 (5.1)	1.7 (−0.9 to 4.2)	0.20
Δ HDL-P (mmol/L), large	0.2 (1.6)	0.1 (2.4)	0 (−1.1 to 1.1)	0.99
Δ HDL-P (mmol/L), small	0.9 (5.3)	−0.1 (7.5)	−1.4 (−4.7 to 1.9)	0.40
Δ HDL-P size (nm)	0 (0.3)	0 (0.4)	0 (−0.2 to 0.1)	0.59

- Mean changes from baseline in ASCVD risk score were −3.4% and −1.2% for aldafermin and placebo groups, respectively, at W24 (P=0.032 vs placebo)

Figure 6 ASCVD Risk Score



CONCLUSION

- Rosuvastatin can safely manage the cholesterol increase seen in NASH patients treated with aldafermin
- At week 24, patients in the aldafermin group had an overall favorable lipid and lipoprotein profile, and an improved 10-year ASCVD risk compared with placebo
- Given the recent revisions in society guidelines [7-9], lipid management strategy based on the 10-year ASCVD risk, rather than a particular LDL-C target value, should be implemented in future trials

REFERENCES

1. DePaoli et al., FGF19 Analog as a Surgical Factor Mimetic That Contributes to Metabolic Effects Beyond Glucose Homeostasis. Diabetes. 2019;68:1315-1328.

2. Zhou et al., Separating tumorigenicity from bile acid regulatory activity for endocrine hormone FGF19. Cancer Res 2014;74:3306-16.

3. Harrison et al., NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2018;391:1174-1185.

4. Harrison et al., NGM282 improves liver fibrosis and histology in 12 weeks in patients with nonalcoholic steatohepatitis. Hepatology 2020;71:1198-1212.

5. Rinella et al., Rosuvastatin improves the FGF19 analogue NGM282-associated lipid changes in patients with non-alcoholic steatohepatitis. J Hepatol 2019;70:735-744.

6. Harrison et al., Efficacy and Safety of Aldafermin, an Engineered FGF19 Analog, in a Randomized, Double-Blind, Placebo-Controlled Trial of Patients With Nonalcoholic Steatohepatitis. Gastroenterology 2020;doi: 10.1053/j.gastro.2020.08.004. Online ahead of print.

7. Grundy et al., 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol.

8. Arnett et al., 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.

9. Mach et al., 2019 ESC/EAS Guidelines for the management of dyslipidaemias.

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