

NGM282 (Aldafermin), an FGF19 Analogue, Reduces Net Deposition of Collagen III in Non-alcoholic Steatohepatitis and Primary Sclerosing Cholangitis

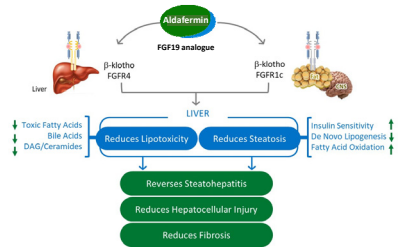


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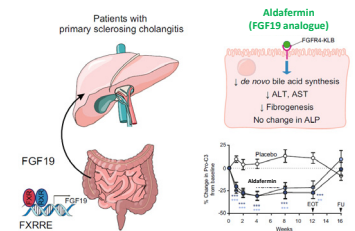
BACKGROUND

NGM282 (aldafermin), a non-tumorigenic FGF19 analogue¹⁻³, is a potent regulator of bile acid synthesis with anti-fibrotic effect in clinical trials in non-alcoholic steatohepatitis (NASH)^{4,6} and primary sclerosing cholangitis (PSC)⁷

Pharmacologic Activity of Aldafermin in NASH

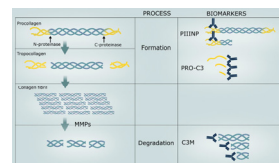


Pharmacologic Activity of Aldafermin in PSC



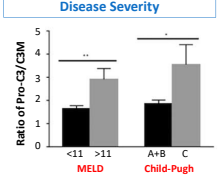
Remodeling of collagen type III plays an important role in the progression and regression of liver fibrosis/cirrhosis in chronic liver diseases such as NASH and PSC⁸

The ratio, Pro-C3/C3M, of the collagen type III formation marker Pro-C3 (a neo-epitope of type III collagen during formation)⁹ and the degradation marker C3M (which measures the matrix metalloproteinase-degraded type III collagen)¹⁰ is a novel indicator of extracellular matrix turnover that reflects net deposition of collagen type III

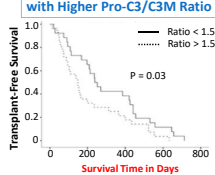


The Pro-C3/C3M ratio increases with worsened clinical outcomes (e.g., decompensation, liver failure, mortality)¹¹

Pro-C3/C3M Ratio Increases with Disease Severity



Worsened Survival in Patients with Higher Pro-C3/C3M Ratio



We determined the Pro-C3/C3M ratio in phase 2 trials of NGM282 in NASH and PSC to evaluate net collagen deposition across metabolic and cholestatic liver disease

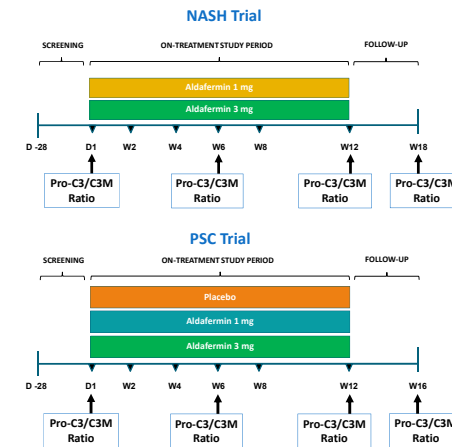
METHODS

43 NASH subjects, with NAS ≥ 4 (at least 1 point in each component), stage 1-3 fibrosis and absolute liver fat content by MRI-PDFF $\geq 8\%$, received aldafermin 1 mg or 3 mg daily for 12 weeks (W12)

62 PSC subjects with an elevated ALP $> 1.5 \times \text{ULN}$ at baseline (BL), received aldafermin 1 mg, 3 mg or placebo daily for 12 weeks

Serum Pro-C3 and C3M were measured by ELISA (Nordic Bioscience)

We used Wilcoxon signed rank test (vs baseline) and an analysis of covariance (ANCOVA) model (vs placebo) with treatment group and baseline value as covariates at the 5% level of significance

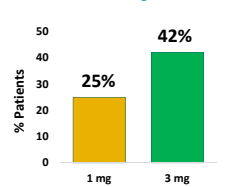


RESULTS

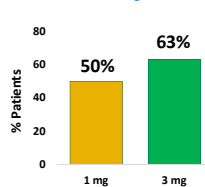
At Week 12, NASH patients treated with aldafermin 1 mg or 3 mg achieved significant improvement in:

- Histological parameters: fibrosis and NAS by NASH CRN criteria
- Biochemical parameters: ALT, AST, ELF, Pro-C3
- imaging parameters: MRI-PDFF

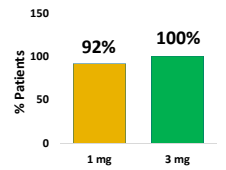
Fibrosis Improvement by ≥ 1 Stage with No Worsening of NASH



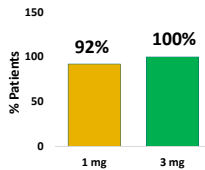
NAS Improvement by ≥ 2 Points with No Worsening of NASH



$\geq 30\%$ Relative Reduction in MRI-PDFF



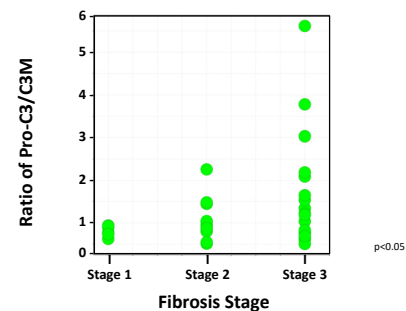
$\geq 5\%$ Absolute Reduction in MRI-PDFF



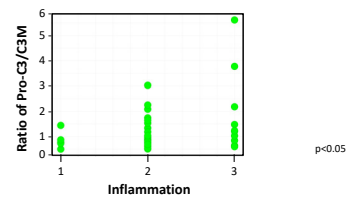
Correlation Between Pro-C3/C3M Ratio and Histology at Baseline

- Among F1-F3 NASH patients, ratios of Pro-C3 and C3M correlated with fibrosis stage at baseline
- At baseline, ratios of Pro-C3 and C3M also correlated with the inflammation score
- There is a trend of correlation between Pro-C3/C3M ratio with ballooning score
- No correlation was observed between Pro-C3/C3M ratio and total NAS or the steatosis score

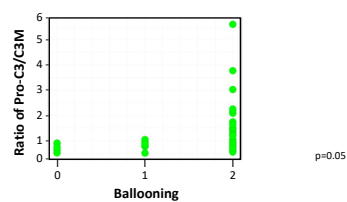
Pro-C3/C3M Ratio Correlates with Fibrosis Stage



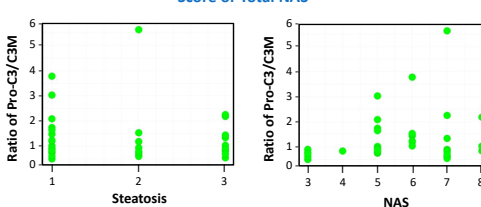
Pro-C3/C3M Ratio Correlates with Inflammation Score



Trend of Correlation Between Pro-C3/C3M Ratio and Ballooning



Lack of Correlation Between Pro-C3/C3M Ratio and Steatosis Score or Total NAS

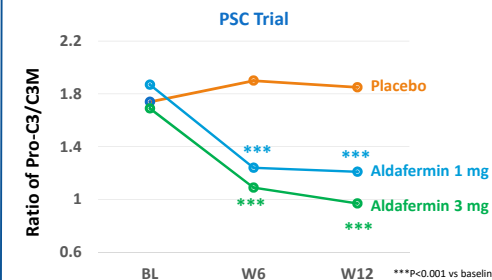
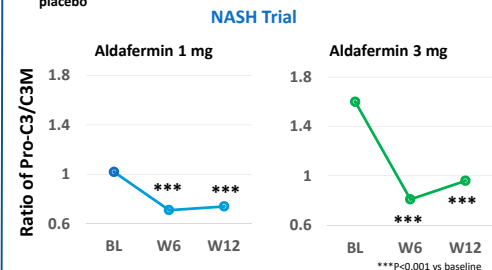


Effects of Aldafermin on Pro-C3/C3M Ratio in NASH and PSC

At baseline, levels of Pro-C3/C3M were comparable among subjects with NASH or PSC

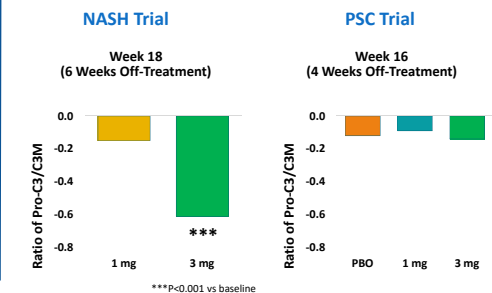
On-Treatment Effect

- Pro-C3/C3M values declined significantly with aldafermin therapy at Week 6 and Week 12 (EOT) in patients with NASH
- Similarly, ratio of Pro-C3/C3M declined rapidly and significantly with aldafermin therapy at Week 2 and Week 12 (EOT) in patients with PSC
- In contrast, no significant change in Pro-C3/C3M was observed with placebo



Off-Treatment Effect

- Aldafermin-associated reduction in net deposition of collagen III was maintained at 6 weeks off-treatment in NASH subjects (-0.6 in the 3 mg group, at W18)
- However, reduction in net deposition of collagen III was not maintained at 4 weeks off-treatment in PSC subjects



Summary

	Ratio of Pro-C3/C3M			
	BL	W12	Change from BL at W12	P (vs BL) (vs PBO)
NASH Population				
Aldafermin 1 mg	1.02	0.74	-0.28	<0.0001 NA
Aldafermin 3 mg	1.60	0.96	-0.58	0.0009 NA
PSC Population				
Placebo	1.74	1.85	0.22	0.23
Aldafermin 1 mg	1.86	1.20	-0.62	0.0001 0.0005
Aldafermin 3 mg	1.69	0.97	-0.66	<0.0001 0.0003

BL, baseline; W12, Week 12; PBO, placebo

CONCLUSION

- The ratio of Pro-C3 (reflecting collagen III formation) and C3M (reflecting collagen III degradation) is a novel serum marker of net collagen deposition that correlates with liver histology and clinical outcome
- NGM282 (aldafermin) produced rapid and robust reductions in the Pro-C3/C3M ratio in patients, irrespective of NASH or PSC disease etiology
- These results suggest an important role of aldafermin on halting net collagen deposition, supporting the anti-fibrotic activity of aldafermin in a spectrum of chronic liver disease

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Author disclosures on file at AASLD

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