

Aldafermin (NGM282) reduces the cross-linked pro-peptides of type III collagen Pro-C3X, a novel biomarker, in non-alcoholic steatohepatitis and primary sclerosing cholangitis patients



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INTRODUCTION

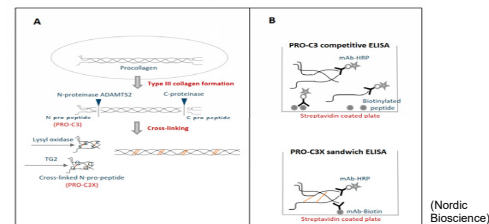
- Cross-linking of collagen is a key contributor to tissue stiffness. Not only the amount and pattern of fibrillar collagens, but also the plasticity to change, are important during fibrosis progression and reversal¹
- The novel biomarker Pro-C3X specifically detects the cross-linked pro-peptides of type III collagen. Recent studies have shown that circulating concentrations of Pro-C3X are elevated in HCC patients, and are superior to Pro-C3 in predicting progression-free survival and overall survival independent of AFP²
- Aldafermin (NGM282), a non-tumorigenic FGF19 analogue³, is a potent regulator of bile acid synthesis with anti-fibrotic effects in clinical trials⁴⁻⁵
- We determined plasma levels of Pro-C3X in phase 2 trials of aldafermin in NASH and PSC

AIM

- We aimed to investigate the effect of aldafermin on the novel biomarker, Pro-C3X, in patients with NASH or PSC enrolled in aldafermin phase 2 trials

METHOD

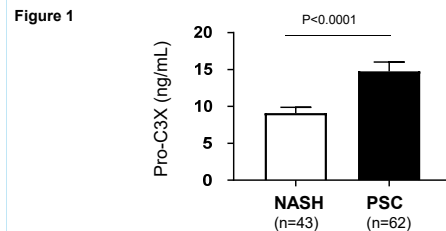
- 43 NASH subjects, with NAS \geq 4 (at least 1 point in each component), stage 1-3 fibrosis and absolute liver fat content by MRI-PDFF \geq 8%, received aldafermin 1mg or 3mg daily for 12 weeks (W12)⁵
- 62 PSC subjects, with an elevated ALP $>$ 1.5xULN at baseline (BL), received aldafermin 1mg, 3mg or placebo daily for 12 weeks⁶
- The Pro-C3X sandwich ELISA only detects cross-linked type III collagen pro-peptides (Nordic Bioscience)
- Pro-C3 competitive ELISA quantifies the sum of single-stranded and cross-linked pro-peptides (Nordic Bioscience)



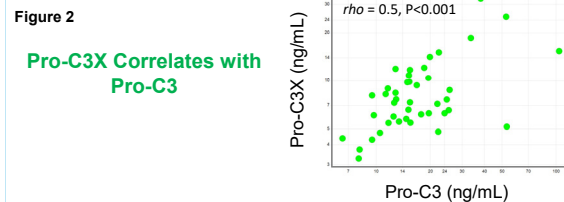
RESULTS

- At baseline, circulating Pro-C3X concentrations were significantly lower in subjects with NASH than PSC (9.1 ng/mL vs 14.7 ng/mL), while Pro-C3 levels were similar in NASH and PSC

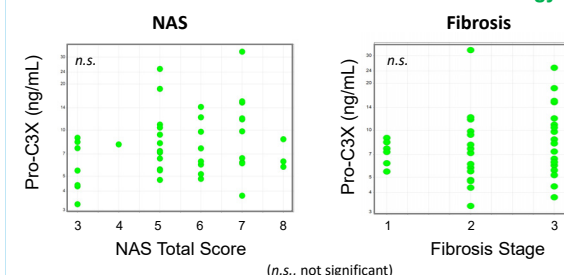
Lower Levels of Cross-Linked Type III Collagen in NASH than in PSC



- At baseline, serum levels of Pro-C3X correlated with concentrations of Pro-C3 in patients with NASH
- However, Pro-C3X did not correlate with liver histology in NASH
- Given that Pro-C3X only recognizes cross-linked collagen, this novel biomarker may provide additional granularity in collagen characteristics beyond histology

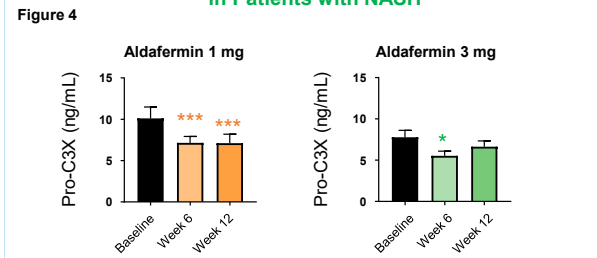


Lack of Correlation between Pro-C3X and Histology



- Pro-C3X declined rapidly and significantly with aldafermin therapy in NASH (-2.7 and -2.8 at W6 and W12 in the 1mg group, p<0.001 vs BL for both comparisons) and PSC (-0.8 and -0.7 at W2 and W12 with aldafermin 1mg; -2.8 and -3.1 at W2 and W12 with aldafermin 3mg; p<0.01 vs BL for all comparisons).
- In contrast, no significant change in Pro-C3X was observed with placebo (0 and +0.5 at W2 and W12 in PSC).

Aldafermin Reduces Cross-Linked Type III Collagen in Patients with NASH



Aldafermin Reduces Cross-Linked Type III Collagen in Patients with PSC

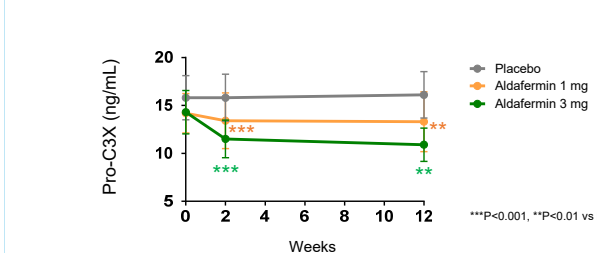


Table 1

	PRO-C3X (ng/mL)				
	BL	W12	Change from BL to W12	P (vs BL)	P (vs Placebo)
NASH Population					
Aldafermin 1 mg	9.9	7.2	-2.8	<0.001	NA
Aldafermin 3 mg	7.9	6.7	-1.2	0.07	NA
PSC Population					
Placebo	15.8	16.1	0.5	0.62	
Aldafermin 1 mg	14.2	13.3	-0.7	0.004	0.008
Aldafermin 3 mg	14.3	10.9	-3.1	0.001	0.006

CONCLUSIONS

- The novel biomarker Pro-C3X detects cross-linked pro-peptides of type III collagen, and has the potential to differentiate the different collagen characteristics beyond histology
- NASH patients had much lower type III collagen cross-linking than PSC patients, indicating that the collagens in NASH may be more plastic and malleable than originally thought
- Aldafermin significantly reduces Pro-C3X, a novel noninvasive marker of cross-linked type III collagen, in both NASH and PSC populations
- These results further support the rapid fibrosis reversal with aldafermin therapy in a dynamic extracellular matrix environment across metabolic and cholestatic liver disease

ACKNOWLEDGEMENTS

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