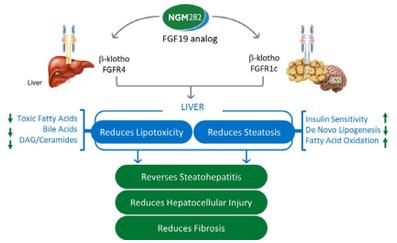
Changes in Serum Bile Acids Correlate with 7alpha-Hydroxy-4-Cholesten-3-One and Fibrogenesis Biomarker Pro-C3 with NGM282 Therapy in Patients with Nonalcoholic Steatohepatitis

Arun Sanyal [1], Lei Ling [2], Mark J. Jaros [3], Bryan Baxter [2], Kris V. Kowdley [4], Alex M. DePaoli [2] and Stephen A. Harrison [5]

BACKGROUND AND AIMS

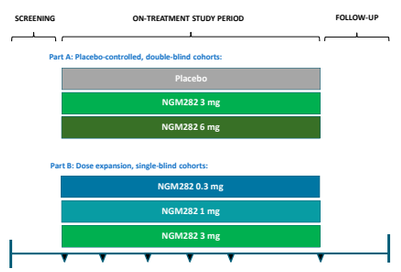
- Emerging evidence supports a role for bile acids in the pathogenesis of liver fibrosis and inflammation in NASH [1]
- NGM282, a non-tumorigenic FGF19 analogue [2-3], significantly reduced 7alpha-hydroxy-4-cholesten-3-one (C4, a marker of bile acid synthesis), ameliorated steatosis and improved hepatic inflammation and fibrosis in patients with NASH [4-6]
- To identify potential biomarkers of NGM282 therapy, we sought to evaluate the correlation of individual bile acid species with C4 and Pro-C3 (a marker of fibrogenesis) using pooled data from NGM282 phase 2 trials in patients with NASH [4-6]

Pharmacologic Activity of NGM282 in NASH



METHODS

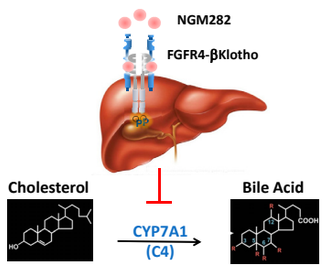
- We conducted a two-part study in biopsy-proven NASH patients to evaluate the effect of NGM282 administered for 12 weeks
  - Part A: a randomized, double-blind, placebo-controlled study [4]
  - Part B: a dose expansion, single blind study [5-6]
- Serum concentrations of individual bile acid species and C4 were determined by mass spectrometry (Mayo Clinic)
- Serum Pro-C3 was measured by an ELISA method (Nordic Bioscience)
- 163 subjects who received NGM282 0.3 mg, 1 mg, 3 mg, 6 mg or placebo were included in correlation analysis using Spearman's method



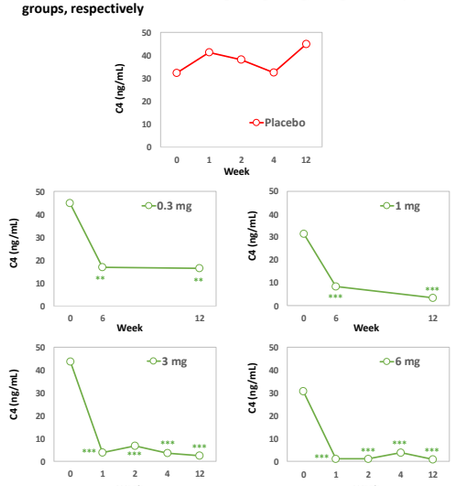
RESULTS

NGM282 Suppresses the Classical Bile Acid Synthetic Pathway

- As an FGF19 analogue, NGM282 suppresses the classical bile acid synthetic pathway through FGFR4-βKlotho receptor complex located on hepatocytes [7]
- We measured serum levels of C4, a surrogate marker of hepatic activity of CYP7A1, which catalyzes the first and rate-limiting step in the classical bile acid synthesis



- At Week 12 (end of treatment), serum levels of C4 were significantly reduced in NGM282-treated patients (−51%, −77%, −93%, −79% and +43% from baseline in the 0.3 mg, 1 mg, 3 mg, 6 mg and the placebo groups, respectively



*(***P<0.001, **P<0.01, *P<0.05 vs baseline)*

NGM282 Lowers Serum Bile Acids

- Administration of NGM282 produced dose-dependent reductions in bile acid species, and the more toxic, hydrophobic, glyco-conjugated bile acids in particular, in patients with NASH
- Bile acid species previously associated with the presence and severity of NASH [8], such as DCA, GCA and GCDCA, were reduced by NGM282
- Ratios of primary to secondary BA were increased with NGM282 therapy
- Given that bile acids can cause hepatic stellate cell activation, mitochondrial dysfunction and endoplasmic reticulum stress when accumulated within hepatocytes, agents that reduce bile acid levels may provide a therapeutic option for patients with NASH

Change in Serum Bile Acids From Baseline to Week 12

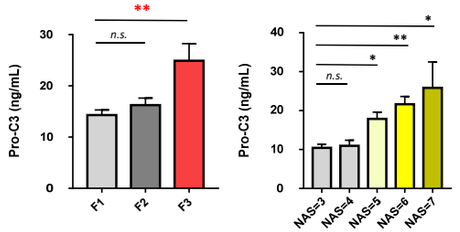
	Change from Baseline to Week 12, mean				
		NGM282			
	Placebo	0.3 mg	1 mg	3 mg	6 mg
Conjugated Primary Bile Acids					
GCA (μmol/L)	0.02	−0.12*	−0.28***	−0.31***	−0.16***
TCA (μmol/L)	0.02	0.03	0	−0.05	−0.01
GCDCA (μmol/L)	−0.16	−0.36	−0.70***	−1.17***	−0.46**
TCDCA (μmol/L)	−0.01	0.12	0.09	0.04	0.12*
Conjugated Secondary Bile Acids					
GDCA (μmol/L)	−0.54	−0.25*	−0.97***	−0.64***	−0.55***
TDCA (μmol/L)	−0.08	−0.01	−0.24***	−0.18**	−0.10*
GLCA (μmol/L)	−0.01	−0.01**	−0.02**	−0.02***	−0.02***
TLCA (μmol/L)	0	0	0	0	0
Unconjugated Primary Bile Acids					
CA (μmol/L)	0.05	−0.16	−0.14	−0.23**	−0.07
CDCA (μmol/L)	0.01	−0.42**	−0.27**	−0.65***	−0.22*
Unconjugated Secondary Bile Acids					
DCA (μmol/L)	−0.05	−0.31***	−0.64***	−0.70***	−0.63***
LCA (μmol/L)	0	0	−0.01**	−0.02***	−0.02***

*(***P<0.001, **P<0.01, *P<0.05 vs baseline)*

CA, cholic acid; CDCA, chenocholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenocholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenocholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid

Higher Baseline Pro-C3 in NASH Patients with Advanced Fibrosis

- Pro-C3 measures a neo-epitope of type III collagen during collagen formation and reflects fibrogenic activity [9]
- Pro-C3 has been shown to be significantly elevated in patients with advanced fibrosis and can predict fibrosis progression in chronic hepatitis [10]
- In the current study, baseline Pro-C3 levels increased with fibrosis stage and total NAS in patients with NASH



*(**P<0.01, *P<0.05; n.s., not significant)*

Changes in Serum Bile Acids Correlate with Changes in Pro-C3

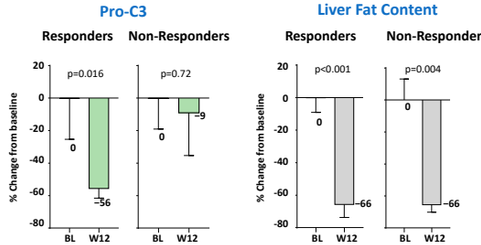
- NGM282 reduced serum Pro-C3 levels at all time points assessed on-treatment
- At Week 12, changes in Pro-C3 from baseline were −2.1 ng/mL (p=0.20), −4.5 ng/mL (p<0.001), −8.0 ng/mL (p=0.001), −3.6 ng/mL (p=0.04) and −1.2 ng/mL (p=0.58) with NGM282 0.3 mg, 1 mg, 3 mg, 6 mg and placebo, respectively
- Reductions from baseline in C4 and Pro-C3 were strongly associated with reductions in glyco-conjugated bile acids, but less well with tauro-conjugated BA

	Δ C4%		Δ Pro-C3%	
	r	p	r	p
Conjugated Primary Bile Acids				
Δ GCA%	0.50	<0.001	0.33	0.002
Δ TCA%	0.10	0.23	0.26	0.014
Δ GCDCA%	0.36	<0.001	0.33	0.002
Δ TCDCA%	−0.12	0.13	0.21	0.05
Conjugated Secondary Bile Acids				
Δ GDCA%	0.39	<0.001	0.31	0.003
Δ TDCA%	0.14	0.09	0.24	0.024
Unconjugated Primary Bile Acids				
Δ CA%	0.38	<0.001	0.23	0.031
Δ CDCA%	0.43	<0.001	0.22	0.037
Unconjugated Secondary Bile Acids				
Δ DCA%	0.50	<0.001	0.36	<0.001

(r, correlation coefficient by Spearman's method)

Greater Reductions in Pro-C3 in Histological Responders

- In a histology cohort of patients receiving NGM282 3 mg for 12 weeks with paired biopsies, 63% of the patients improved NAS by two or more points without fibrosis worsening, and 42% of the patients improved liver fibrosis by one stage or more without worsening of steatohepatitis [6]
- Greater reductions in Pro-C3, but not in liver fat content, were observed in histological responders (improve NAS ≥2 or fibrosis ≥1) than in non-responders



CONCLUSION

- NGM282 potently suppresses de novo bile acid synthesis in patients with NASH
- NASH patients with advanced fibrosis or more severe NASH have higher serum Pro-C3 at baseline
- Changes in circulating levels of bile acids highly correlated with changes in Pro-C3 in NASH patients treated with NGM282, indicating that bile acid may be a molecular trigger of hepatic fibrogenesis
- NGM282 demonstrated significant and robust activity on lowering serum bile acids and Pro-C3, signifying potential disease-modifying activity in reversing fibrosis

Author Affiliations:

[1]Virginia Commonwealth University, Richmond, United States; [2]NGM Biopharmaceuticals, South San Francisco, United States; [3]Summit Analytical, Denver, United States; [4]Swedish Medical Center, Seattle, United States; [5]Pinnacle Clinical Research, San Antonio, United States

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This study was funded by NGM Biopharmaceuticals
Author disclosures on file at EASL 2019