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NGM282, a novel variant of FGF19, significantly reduces hepatic steatosis and key biomarkers of NASH: results of a Phase 2, multicenter, randomized, double-blinded, placebo controlled trial in biopsy-confirmed NASH patients

Stephen A. Harrison* [1], Manal F. Abdelmalek[2], James F. Trotter[3], Angelo H. Paredes[4], Hays L. Arnold[5], Marcelo Kugelmas[6], Mustafa R. Bashir[2], Lei Ling[7], Stephen J. Rossi[7], Alex M. DePaoli[7], Mary E. Rinella[8], Rohit S. Loomba[9]
[1]Pinnacle Clinical Research, Live Oak, [2]Duke University, Durham, [3]Texas Digestive Disease Consultants, Dallas, [4]Brooke Army Medical Center, San Antonio, [5]Gastroenterology Consultants of San Antonio, Live Oak, [6]South Denver Gastroenterology, Englewood, [7]NGM Bio, South San Francisco, [8]Northwestern University, Chicago, [9]University of California, San Diego, San Diego, United States

Background and Aims: NASH is a rapidly growing cause of chronic liver disease with a significant medical need for highly effective treatments. NGM282 is a non-tumorigenic engineered variant of human fibroblast growth factor 19 (FGF19) with similar bile acid and metabolic activity. The aim of this study was to assess the safety/tolerability and biologic activity of NGM282 in patients with biopsy-confirmed NASH.

Methods: Eighty-two subjects were randomized to NGM282 3mg or 6mg or placebo as a daily SC injection for 12 wks and stratified by diabetes status. Histologic inclusion criteria included biopsy-proven NASH with a NAS ≥4 (1 point in each component), stage 1-3 fibrosis and ≥8% liver fat content (LFC) by MRI-PDFF. The primary endpoint was ≥5% reduction in absolute LFC by MRI-PDFF.

Results: Significant reductions in absolute and relative LFC were seen with both doses (Table 1), with LFC normalization (<5% on MRI-PDFF) in 26% and 42% of subjects at 3mg and 6mg, respectively. ALT levels declined rapidly, with significant decreases at Wk1, and ALT normalization in 35% and 37% of subjects with 3 mg and 6 mg at Wk 12, respectively. C4 levels, a key marker of bileacid synthesis and NGM282 target engagement, were decreased by >90%, with undetectable levels noted in 65% of subjects at Wk12. Triglyceride decreases were consistent with FGF19/R1c activity, while significant LDL increases reflect potent FGF19/R4- mediated CYP7A1 inhibition. There were highly significant correlations between decreases in LFC and reductions in ALT, AST and C4. PIIINP and TIMP-1 were significantly reduced, supporting a potential antifibrotic effect. The most common adverse events were increased stool frequency, loose stools, nausea and injection site erythema, the majority of which were mild and dose-dependent.

Table 1

	Placebo (n = 27)	**NGM282 3 mg (n = 27)**	**NGM282 6 mg (n = 26)**
MRI-PDFF (Absolute)	-0.9%	-9.7%*	-11.9%*
Pts w/ MRI-PDFF >20% at Baseline	-0.3%	-12.9%*	-18.9%*
MRI-PDFF (Relative)	-1%	-47%*	-61%*
#(%) of pts w/ >30% relative change	2 (7.4%)	23 (85%)*	24 (92%)*
Response Rate	7%	74%*	85%*
ALT (Absolute, U/L)	-2	-35*	-33*
Pts w/ ALT >60 U/L at Baseline (U/L)	-10	-63*	-55*
ALT (Relative)	-1%	-43%*	-45%*
*p <0.001			

Conclusions: Treatment of NASH patients with NGM282 for 12 wks showed rapid and highly significant reductions in LFC, serum aminotransferases and other biomarkers suggestive of improvements in NASH. Targeting the FGF19 pathway with pharmacologic doses of NGM282 appears to affect multiple relevant biologic pathways and supports further development in NASH.

Disclosure of Interest: S. Harrison: Grant: NGM Bio, Consultant: NGM Bio, M. Abdelmalek: Grant: NGM Bio, Consultant: NGM Bio, J. Trotter: Grant: NGM Bio, A. Paredes: Grant: NGM Bio, H. Arnold: Grant: NGM Bio, M. Kugelmas: Grant: NGM Bio, M. Bashir: Grant: NGM Bio, L. Ling: Stockholder: NGM Bio, Employee: NGM Bio, S.Rossi: Stockholder: NGM Bio, Employee: NGM Bio, A. DePaoli: Stockholder: NGM Bio, Employee: NGM Bio, M. Rinella: Grant: NGM Bio, Consultant: NGM Bio, R. Loomba: Grant: NGM Bio, Consultant: NGM Bio