NGM282 Maintains a Durable Off-Treatment Response on Hepatic Steatosis, Inflammation and Fibrogenesis in Patients with Biopsy-Confirmed Nonalcoholic Steatohepatitis: Results of a Multi-Center Phase 2 Dose-Finding Study

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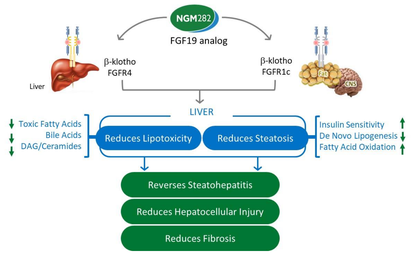
BACKGROUND AND AIMS

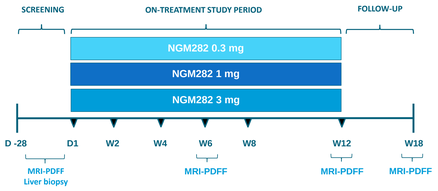
- NGM282 is an engineered, non-tumorigenic analogue of human FGF19 [1-2]
- NGM282 has demonstrated rapid and significant reductions in steatosis, liver transaminases and fibrosis markers, and improvements in liver histology, in 12 weeks in patients with biopsy-confirmed NASH [3-4]
- In this phase 2, dose-finding study, we aim to evaluate the durability of treatment response after cessation of NGM282 therapy

Pharmacologic Activity of NGM282 in NASH



METHODS

- Eighty-five biopsy-proven NASH patients (NAS≥4, F1-F3) received NGM282 0.3 mg (n=21), 1 mg (n=44) or 3 mg (n=19) for 12 weeks, with a follow-up visit at week 18 (W18, 6 weeks off-treatment)
- Key inclusion criteria included biopsy-proven NASH with NAS ≥4 (at least 1 point each in steatosis, inflammation and ballooning), stage 1-3 fibrosis, absolute liver fat content ≥8% by MRI-PDFF
- The primary endpoint was ≥5% reduction in absolute liver fat content (LFC) by MRI-PDFF at week 12 (W12)
- LFC, ALT, Pro-C3 were evaluated at baseline, week 6 (W6), W12 and W18 (6 weeks off treatment)
- Serum levels of 7-alpha-hydroxy-4-cholesten-3-one (C4) and total bile acids were measured during and off treatment to determine target engagement of FGFR4-KLB and suppression of CYP7A1

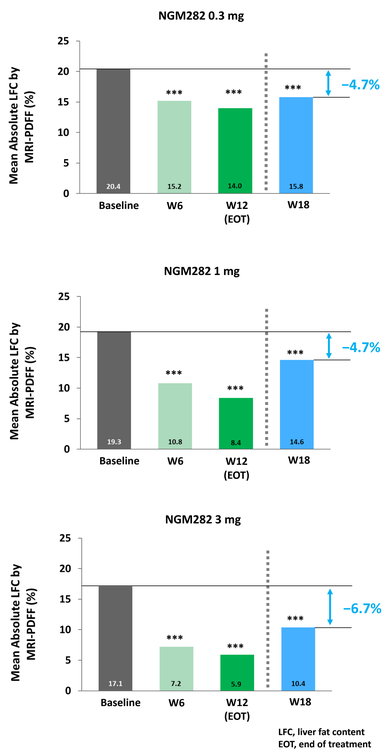


RESULTS

Liver Fat Content

- At week 12, 56%, 89% and 100% of patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups, respectively, achieved ≥5% reduction in absolute liver fat content
- The reduction in liver fat content persisted at week 18 (6 weeks off treatment), with 55%, 37% and 74% of patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups, respectively, still maintaining ≥5% reduction in absolute liver fat content
- At week 18 (6 weeks off treatment), 45%, 39% and 68% of patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups, respectively, achieved a clinically meaningful reduction of relative LFC (≥30%, which has been demonstrated to correlate with histologic changes)

Absolute Change in Liver Fat Content

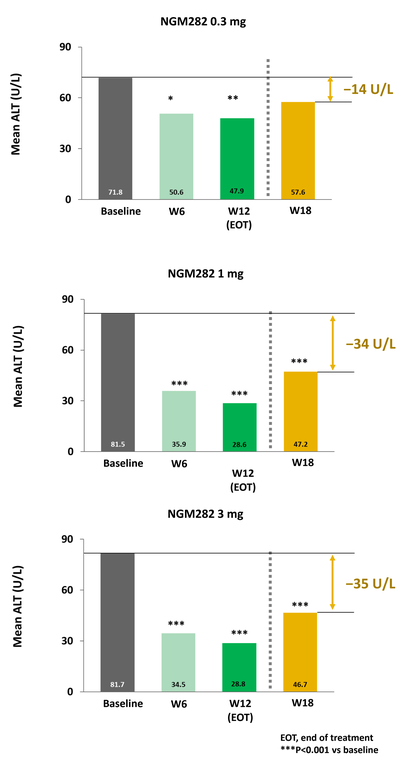


LFC, liver fat content
EOT, end of treatment
***P<0.001 vs baseline

ALT

- Alanine aminotransferase (ALT) is a well-recognized marker of liver injury and inflammation
- Reductions in ALT have been shown to be associated with histological improvement in NAS and fibrosis scores [5]
- At week 12, patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups achieved reductions in ALT of 33%, 61% and 60%, respectively
- The benefit of ALT-lowering sustained at week 18 (6 weeks off treatment), with patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups still maintaining reductions in ALT of 18%, 38% and 39%, respectively
- At week 18 (6 weeks off treatment), 43%, 66% and 68% of patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups, respectively, achieved ≥30% reduction in ALT

Absolute Change in ALT

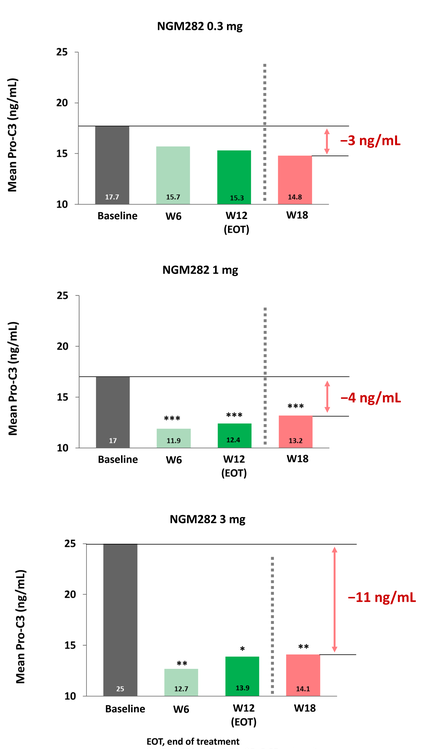


EOT, end of treatment
***P<0.001 vs baseline

Pro-C3

- Pro-C3 measures a neo-epitope of type III collagen during collagen formation and reflects fibrogenic activity [6]
- PRO-C3 increases with fibrosis stage and is independently associated with advanced fibrosis in patients with NAFLD [7]
- At week 12, patients in the NGM282 0.3 mg, 1 mg and 3 mg dose groups achieved reductions in Pro-C3 of 7%, 21% and 33%, respectively
- The effect of NGM282 on Pro-C3-lowering persisted at week 18 (6 weeks off treatment), with patients in the NGM282 0.3 mg, 1 mg and 3 mg groups still maintaining reductions in Pro-C3 of 11%, 17% and 36%, respectively

Absolute Change in Pro-C3



EOT, end of treatment
***P<0.001, **P<0.01, *P<0.05 vs baseline

C4 and Bile Acids

- Serum levels of 7alpha-hydroxy-4-cholesten-3-one (C4), a marker of target engagement, were suppressed by 51%, 75% and 93% with NGM282 0.3 mg, 1 mg and 3 mg doses, respectively, at week 12
- At week 18, C4 levels returned to near or above baseline, consistent with the absence of persistent CYP7A1 suppression
- Similar findings were observed for serum concentrations of total bile acids

Safety

- Favorable safety and tolerability profile consistent with the previously reported double-blind, placebo-controlled study in patients with NASH [3]
- No new safety signals identified
- Mild GI symptoms (loose/frequent stools and nausea) remain the most common treatment emergent adverse events; majority were mild and resolved during treatment phase

CONCLUSION

- **Administration of NGM282 results in dose-dependent, clinically meaningful improvements in hepatic steatosis, inflammation and fibrogenesis in 12 weeks in patients with NASH**
- **NGM282 maintains persistent benefits from the maximum improvements at week 12 in liver fat content, ALT and Pro-C3, six weeks after cessation of therapy**
- **This long-lasting treatment effect appears to be independent of continued CYP7A1 suppression**
- **The enduring off-treatment biologic activity of NGM282 supports evaluating less frequent dosing regimen as a chronic therapy in patients with NASH**

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References:

1. *Zhou et al., Cancer Res 2014; 74:3306-3316*
2. *Luo et al., Sci Transl Med 2014; 6:247ra100*
3. *Harrison et al., Lancet 2018; 391:1174*
4. *Harrison et al., EASL 2018*
5. *Hoofnagle et al., Aliment Pharmacol Ther 2013; 38:134*
6. *Nielsen et al., Am J Transl Res 2013;5:303-315*
7. *Daniels et al., Hepatology 2018; doi: 10.1002*

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Author disclosures on file at ADA