Primary sclerosing cholangitis (PSC) is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical interventions.

NGM282 is an engineered, non-tumorigenic analogue of human FGFR1.\(^1\)

NGM282 produced significant improvements in ALT, AST, and Enhanced Liver Fibrosis score (ELF), without reducing alkaline phosphatase (ALP). In a 23-week phase 2 trial in patients with PSC,\(^2\)

In this secondary analysis, we aim to assess the impact of NGM282 on bile acids that may be implicated in fibrosis, and to evaluate the correlation of individual bile acids with 7α-hydroxy-4-cholesten-3-one (C4), a marker of the native bile acid synthesis and Pro-C3 (a marker of fibrogenesis).

**BACKGROUND AND AIMS**

- Levels of ALT correlate with serum concentrations of ALT, AST and TIMP-1
- Levels of ALP do not correlate with ELF score or in 3 components (the N-terminal pro-peptide of type III collagen [PIIINP], the tissue inhibitors of metalloproteinase 1 [TIMP-1] and hyaluronic acid [HA])
- Given that PRO-C3 is an independent predictor of transplant-free survival \(^6\), and that PSC patients with high baseline serum levels of Pro-C3 (the N-terminal pro-peptide of type III collagen [PIIINP]) and hyaluronic acid (HA) \(^4\)
- Levels of ALP correlate with serum concentrations of ALT, AST and TIMP-1

**RESULTS**

**Correlation Between ALP and Laboratory Parameters**

- Serum levels of 7α-hydroxy-4-cholesten-3-one (C4), a marker of de novo bile acid synthesis, were significantly suppressed in the NGM282 1 mg and 3 mg groups, but not in placebo, at week 12
- Serum levels of bile acids were significantly reduced at week 12 compared to baseline in the NGM282 groups

**PSC Patients with Increased Fibrogenesis Had Higher Serum Bile Acids at Baseline**

- We measured serum concentrations of Pro-C3, a neo-epitope of type III collagen during collagen formation reflecting true fibrogenic activity \(^3\)
- In the current study, baseline Pro-C3 levels of ≥20 ng/mL, compared with <20 ng/mL, were associated with significantly higher levels of serum bile acids, in patients with PSC.
- Given that Pro-C3 is an independent predictor of transplant-free survival in PSC, and that PSC patients with high baseline serum levels of Pro-C3 had shorter survival compared to patients with low baseline serum levels \(^7\), these results suggest that bile acids may play a causative role in increased fibrogenesis and worsened outcomes in these patients.

**CONCLUSION**

- Serum concentrations of individual bile acids, and conjugated primary bile acids in particular, significantly correlated with Pro-C3
- The lack of correlation of serum bile acids with C4 likely reflects the adaptive suppression of the de novo bile acid synthesis in cholestasis in this patient population

- Both ALP and Pro-C3 levels were significantly decreased with NGM282 1 mg and 3 mg, respectively, versus +11% (P=0.08) with placebo
- At Week 12, relative changes in Pro-C3 from baseline were −21% (P=0.006) and −27% (P=0.002) with NGM282 1 mg and 3 mg, respectively, versus +15% (P=0.08) with placebo

**References:**

1. Hirschfield et al., Lancet 2013; 382:1587-1599
2. Zhou et al., Cancer Res 2014; 74:3306-3316
4. Hirschfield et al., J Hepatol 2019; 70:483-493
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Author disclosures on file at EASL 2019.