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Effect of NGM282, a FGF19 analogue, in Primary Sclerosing Cholangitis: a Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial

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Conflict of Interest Statement

GMH reports being on advisory committees or review panels for Intercept, GSK; consulting for Cymabay, Novartis; grant/research support from Falk, BioTie, and Takeda

OC reports board membership for Intercept, Mayoly Spindler; grant/research support from Aptalis; is on speakers’ bureaus for Falk

DT reports being on advisory committees for Intercept; is on speaker bureaus for Falk and Intercept

SAH reports grant/research support from Allergan, Conatus, Galectin, Galmed, Genfit, Gilead, Immuron, Intercept, Madrigal, Cymabay, and TaiwanJ; is on speakers’ bureaus for Alexion and Abbvie; is a consulting advisor for Allergan, Chronic Liver Disease Foundation, Cymabay, Cirius, Echosens, Genfit, Gilead, Intercept, Madrigal, Novartis, Novo Nordisk, Perspectum, Pippin, CiVi, Hightide, Innovate, PPD, IQVIA, Medpace, and Pfizer

MJM reports being on advisory committees or review panels for GSK; grant/research support from Gilead, Cymabay, Intercept, Mallinckrodt, Novartis, Target, GSK, and Genfit

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DJL, MAK reports being employee and stockholder of Nordic Bioscience

LL, KHK, SJR, RMS, AMD report being employees and stockholders of NGM Bio
UB reports consulting for Novartis, Intercept; grant/research support from Norwegian, American, and South African PSC patient foundations and German DCCV; received lecture fees from Abbvie, Falk Foundation, Gilead, Intercept, Novartis, Roche, Shire, and Zambon

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Author Contributions

GMH, OC, DT, MJM, SJR, UB participated in study design

GMH, OC, JPD, DT, SAH, CL, AJM, JFT, DJL, MAK, UB were responsible for data collection

GMH, DT, MJJ, LL, SJR, UB participated in data analysis

GMH, DT, SAH, MJM, MAK, LL, SJR, RMS, AMD, UB participated in data interpretation

All authors participated in manuscript review and writing

GMH, MII, LL, SJR were responsible for preparation of the tables and figures

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ABSTRACT

BACKGROUND AND AIMS

Primary Sclerosing Cholangitis (PSC) is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical intervention. NGM282, an engineered, non-tumorigenic FGF19 analogue, potently regulates CYP7A1-mediated bile acid homeostasis. We assessed the activity and safety of NGM282 in patients with PSC.

METHODS

In this double-blind, placebo-controlled phase 2 trial, patients who had PSC confirmed by cholangiography or biopsy and an elevated alkaline phosphatase (ALP) >1.5xULN were randomly assigned 1:1:1 to receive NGM282 1 mg, 3 mg or placebo once daily for 12 weeks. The primary outcome was the change in ALP from baseline to week 12. Secondary and exploratory outcomes included changes in serum biomarkers of bile acid metabolism and fibrosis. Efficacy analysis was by intention-to-treat.

RESULTS

62 patients were randomized to receive NGM282 1 mg (n=21), NGM282 3 mg (n=21) or placebo (n=20). At 12 weeks, there were no significant differences in the mean change from baseline in ALP between the NGM282 and placebo groups, and therefore, the primary endpoint was not met. However, NGM282 significantly reduced levels of 7alpha-hydroxy-4-cholesten-3-one (a marker of hepatic CYP7A1 activity, LS mean differences −6.2 ng/mL [95% CI −10.7 to −1.7; P=0.008] and −9.4 ng/mL [−14.0 to −4.9; P<0.001] in the NGM282 1 mg and 3 mg groups, respectively, compared with
placebo) and bile acids. Importantly, fibrosis biomarkers that predict transplant-free survival, including Enhanced Liver Fibrosis score and Pro-C3, were significantly improved following NGM282 treatment. Most adverse events were mild to moderate in severity, with gastrointestinal symptoms more frequent in the NGM282 treatment groups.

**CONCLUSIONS**

In patients with PSC, NGM282 potently inhibited bile acid synthesis and decreased fibrosis markers, without significantly affecting ALP levels.

(Abstract Word Count: 274)

**LAY SUMMARY**

We present for the first time, the clinical and laboratory effects of a first-in-class, engineered analogue of the endocrine hormone FGF19 in patients with PSC. By incorporating non-invasive markers of fibrosis, beyond standard liver injury markers, we show that NGM282 impacted on fibrosis turnover and hepatic inflammation without changing alkaline phosphatase. Our findings demonstrate the complexities of using highly potent rational agents in PSC, and furthermore challenge the dogma about what the appropriate endpoints should be for trials in PSC.
INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by strictures of the biliary tree and presently devoid of medical treatment[1]. Of the histopathological hallmarks of PSC, periductal inflammation and “onion skin”-like fibrosis, referring to concentric layers of collagen fibers circumferential to the cholangiocyte lining of the bile ducts, characterize a progressive fibrosing cholangiopathy[2]. Patients frequently present with concurrent inflammatory bowel disease (IBD), and are at increased risk of developing hepatobiliary and colon cancers. More than 50% of patients need liver transplantation within 10-15 years of symptom development[1]. Biochemically, PSC is characterized by elevated serum liver tests, and alkaline phosphatase (ALP) levels associate with future risk of adverse events.

There remains no single specific cause of PSC, and etio-pathogenesis is believed to encompass genetic, chemical, environmental (including microbiome factors) and immunologic pathways to selective biliary epithelial damage[1]. A prevalent “toxic bile” hypothesis posits that early pathogenesis of disease results from injury on the integrity of biliary epithelium, leading to retention of bile acids and intrahepatic inflammation and fibrosis. Treatments that ameliorate bile acid toxicity, or that increase the efflux of bile acids, may slow the progression of PSC[3]. UDCA, a hydrophilic bile acid, has been widely prescribed in PSC but without definitive evidence of its clinical benefit, seemingly having choleretic properties but not anti-fibrotic efficacy.
Fibroblast growth factor 19 (FGF19), an endocrine gastrointestinal hormone, controls bile acid metabolism via actions on CYP7A1, the first and rate-limiting enzyme in the classic pathway of bile acid synthesis[4, 5]. Circulating FGF19 concentration is increased in patients with PSC, further suggesting that FGF19 may represent an adaptive mechanism in PSC-related progressive liver diseases[6, 7]. However, the therapeutic potential of FGF19 has been hindered by its hepatocarcinogenicity[8].

NGM282 (also known as M70), a non-tumorigenic analogue of FGF19, was designed to retain CYP7A1 suppression to reduce bile acid-associated biliary injury[9]. In NGM282, a five-amino acid deletion (P24-S28) coupled with the substitution of three amino acids at critical positions (A30S, G31S, H33L) within the amino terminus, enable biased FGFR4 signaling so that NGM282 does not activate signal transducer and activator of transcription 3, a signaling pathway essential for FGF19-mediated hepatocarcinogenesis[10]. In animal models of PSC, treatment with NGM282 resulted in a rapid and robust reduction in ALP, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, as well as a clear improvement in histological features associated with PSC, including hepatic inflammation and “onion skin”-like periductal fibrosis[11]. NGM282 was safe and well tolerated in healthy volunteers and in patients with non-alcoholic steatohepatitis (NASH)[12, 13].

We therefore conducted a phase 2, multicenter, international, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of NGM282 versus placebo in adult patients with PSC.
PATIENTS AND METHODS

OVERSIGHT

The trial protocol was approved by the ethics committees and institutional review boards at each participating site prior to study initiation. The study was conducted according to the provisions of the Declaration of Helsinki and in compliance with International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent before participation in the trial. An independent data and safety monitoring board reviewed safety data. This study was designed by expert clinicians who had experience in treating PSC in conjunction with representatives of the sponsor. Data were collected by investigators, and managed, validated and analyzed by Pharmaceutical Product Development (Morrisville, NC). The authors had access to the data after unblinding, participated in data analysis and interpretation, and vouch for the fidelity of the study to the protocol and the accuracy of the data. All authors participated in the manuscript development and provided final approval to submit.

PATIENTS

This multicenter, international trial included male and female patients, 18 to 75 years of age, who met the diagnostic criteria for PSC according to the EASL and AASLD guidelines[14, 15]. Patients were eligible if they met the following inclusion criteria: 18 to 75 years of age at the time of screening; confirmed diagnosis of PSC (based on any 2 of the 3 criteria: abnormal cholangiography consistent with PSC as measured by magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography; liver biopsy consistent with
PSC; historical evidence of elevated ALP; ALP >1.5xULN; ALT and AST <5xULN; bilirubin ≤2.5 mg/dL.

Patients taking UDCA were allowed to enroll if on stable dose (<27 mg/kg/day) within 2 months of screening. Patients were also allowed to enroll if they had dominant strictures with no evidence of clinical concern, IBD with no episode of flare, autoimmune hepatitis on stable immunosuppressive regimen with no hepatic flare, compensated cirrhosis or pre-sinusoidal esophageal varices with no history of bleeding and no other evidence of hepatic decompensation. Exclusion criteria included clinically significant acute or chronic liver disease of an etiology other than PSC; evidence of secondary or immunoglobulin G4-related sclerosing cholangitis per EASL guidelines [14]; placement of a bile duct stent or percutaneous bile duct drain within 3 months of screening; decompensated cirrhosis; and liver transplantation. A complete list of inclusion and exclusion criteria is provided in Supplementary Table 1.

**RANDOMIZATION AND MASKING**

Patients were randomly assigned by means of an Interactive Web Response System in a 1:1:1 ratio to once daily subcutaneous NGM282 (NGM Biopharmaceuticals, South San Francisco) 1 mg, NGM282 3 mg or placebo. Randomization was stratified according to UDCA use (yes or no) to ensure an even distribution across the treatment arms. The determination of UDCA status was based on medical history and concomitant medication at randomization. NGM282 and placebo were provided as identical pre-filled syringes in identical containers labelled with unique code numbers, in keeping with Good Manufacturing Practice for medicinal products guidelines. A master control list of the pack identification numbers and treatment was accessible by the statistician who prepared the randomization schedule. The list was also provided to the contract research organization of the
emergency un-blinding service. Investigators, staff, patients, sponsor, and medical monitor remained blinded throughout the study period.

**OUTCOMES**

The primary outcome measure was the change in ALP from baseline to end of treatment (EOT) at week 12. Secondary and exploratory outcomes included changes in 7alpha-hydroxy-4-cholesten-3-one (C4, a serum marker of hepatic CYP7A1 activity indicative of target engagement), bile acids, ALT, AST, and markers of fibrosis, such as total enhanced liver fibrosis (ELF) score (including the N-terminal pro-peptide of type III collagen [PIIINP], the tissue inhibitor of metalloproteinase 1 [TIMP-1] and hyaluronic acid; measured on ADVIA Centaur® CP Immunoassay System from Siemens) and Pro-C3 (which measures a neo-epitope of type III collagen during collagen formation and reflects fibrogenic activity[16]; Nordic Bioscience). AEs were assessed using the Common Terminology Criteria for Adverse Events v4.03. A complete list of outcome measures is provided in Supplementary Table 2.

**PROCEDURES**

The trial was conducted at 27 sites in Europe and US and was designed to have a screening period of 4 weeks, a treatment period of 12 weeks and a follow-up period of 4 weeks. During the screening period, patients underwent MRCP for baseline assessment. Patients with concomitant IBD also underwent a colonoscopy procedure if historical reports were obtained 12 months or more prior to randomization. On day 1, study drug self-administration instructions and training were provided to patients, and a weekly study drug kit was dispensed. The first dose of study drug and doses at weeks 1, 2, 4, 8 and 12
were self-administered in the clinic; all other doses were administered at home. Patients were instructed to inject the study drug at the same time every morning.

Laboratory and Pro-C3 were assessed at day 1, week 1, 2, 4, 8, 12 and 16 (follow-up). Levels of C4, bile acids, lipids and ELF scores were measured on day 1 and week 12 (EOT). Adverse events (AEs) and concomitant medications were evaluated at each study visit. The schedule for the study visits and data collection is summarized in the Supplementary Table 3.

**STATISTICAL ANALYSIS**

Analyses were conducted on the basis of the intention-to-treat principle and involved all patients who were randomized to receive NGM282 or placebo. All tests of effects were conducted at a two-sided alpha level of 0.05. A minimal sample size of 60 patients was selected for the pre-study power calculation. Allowing for a 20% dropout rate, sample size calculations were based on a minimum of 16 completing patients per group.

The mean change from baseline at week 12 in ALP (primary outcome) was compared vs placebo using the Wilcoxon Rank Sum test. Continuous outcomes measured repeatedly over weeks were analyzed with the use of a mixed-effect model repeated measures (MMRM) analysis of covariance (ANCOVA), with treatment group, visit, treatment group by visit interaction, UDCA use, treatment group by UDCA use interaction as classification variables and baseline value as covariate. For outcomes assessed only at baseline and at week 12, changes were examined using an ANCOVA model with treatment group, visit, treatment group by visit interaction, UDCA use, treatment group by UDCA use interaction as
classification variables and baseline value as covariate. The overall type 1 error was controlled using the step-down Dunnett multiple testing procedure. **Missing data were imputed using the last post-baseline observation carried forward methodology.** SAS version 9·4 (SAS Institute, Cary, NC) was used to conduct the analyses. Safety and tolerability analyses were conducted in all randomized patients who received at least one dose, full or partial, of study drug and had at least one post-dose safety evaluation. All safety endpoints were analyzed descriptively. The trial was registered with ClinicalTrials.gov (NCT02704364).

**RESULTS**

**Population**

Between February 25, 2016 and February 1, 2017, 95 patients underwent screening, and 62 eligible patients were randomized to receive NGM282 1 mg (n=21), NGM282 3 mg (n=21) or placebo (n=20) (Fig. 1). Baseline demographics and disease characteristics of the three dosing groups were similar (Table 1 and Supplementary Table 4). A total of 58 patients (95% of the patients in the NGM282 1 mg group, 90% of those in the NGM282 3 mg group and 95% of those in the placebo group) completed the 12-week treatment; 4 patients (1 in the NGM282 1 mg group, 2 in the NGM282 3 mg group and 1 in the placebo group) withdrew from the trial before end of treatment.

**Primary Outcome**

At 12 weeks, there was no significant difference in ALP with NGM282 1 mg (least squares [LS] mean difference, −14.0 U/L; 95% CI, −68.0 to 28.0; P=0.43) and NGM282 3 mg (13.0 U/L, −41.0 to 71.0; P=0.65) compared with placebo (Fig. 2A and Table 2). MMRM analyses showed significant decreases in
ALP by the NGM282 1 mg group at week 1, 2 and 4 compared to baseline; however, the effects were not maintained at week 12 (Supplementary Fig. 1). Pre-specified subgroup analyses showed a similar pattern of response in ALP irrespective of concomitant UDCA use. Similar changes in GGT were also observed (Supplementary Fig. 2).

**Secondary Outcomes**

Significant reductions in C4 were observed in patients who received NGM282 (Fig. 2B and Table 2). At 12 weeks, the LS mean differences in C4 were $-6.2$ ng/mL (95% CI $-10.7$ to $-1.7$; $P=0.008$) in the NGM282 1 mg group and $-9.4$ ng/mL (95% CI $-14.0$ to $-4.9$; $P<0.001$) in the NGM282 3 mg group compared with placebo (Table 2). Furthermore, treatment with NGM282 resulted in decreases in circulating bile acids, and secondary bile acids in particular (DCA, GDCA, TDCA, GLCA, TLCA), compared with placebo-treated patients (Fig. 2C and Table 3). Despite significant inhibition of the classic pathway of *de novo* bile acid synthesis as evidenced by C4 reduction, no significant changes in serum vitamin D levels, an indicator of fat-soluble vitamin absorption, were observed in NGM282-treated subjects (Supplementary Table 5).

Significant decreases in ALT and AST from baseline were in the NGM282 3 mg group during treatment (Figs. 2D-E). The LS mean changes in ALT levels from baseline to week 12 were $8.5$ U/L ($P=0.41$) and $-45.1$ U/L ($P<0.001$) for NGM282 1 mg and 3 mg, respectively, versus $-12.1$ U/L ($P=0.25$) for placebo. The LS mean changes in AST levels from baseline to week 12 were $-0.2$ U/L ($P=0.97$) and $-30.9$ U/L ($P<0.001$) for NGM282 1 mg and 3 mg, respectively, versus $-13.3$ U/L ($P=0.07$) for placebo. Pre-specified subgroup analyses showed similar reductions in transaminases by NGM282 treatment in
patients on concomitant UDCA to those not on UDCA (Supplementary Figs. 3-4). Post hoc analyses revealed that the trend of improvement in liver enzymes was also observed in patients with suppressed C4 levels at baseline, a population previously linked to worse outcomes in PSC[7], and in patients with large duct disease or dominant strictures (Supplementary Figs. 5-7).

No significant placebo-adjusted changes from baseline to week 12 were observed for the NGM282 groups in levels of triglycerides, total cholesterol, HDL cholesterol or LDL cholesterol (Table 2 and Supplementary Fig. 8). Changes from baseline to week 12 in additional parameters are summarized in Table 2 and Supplementary Table 6.

**Serum Fibrosis Biomarkers**

Levels of ELF and Pro-C3, non-invasive fibrosis biomarkers that predict transplant-free survival in patients with PSC[17-19], were measured at baseline and after 12 weeks of NGM282 treatment. Serum ELF test showed a reduction in fibrosis in patients receiving NGM282 compared with placebo (Fig. 3A and Table 2). The LS mean changes in ELF from baseline to week 12 were −0.29 (P=0.028) and −0.37 (P=0.009) for NGM282 1 mg and 3 mg, respectively, versus 0.07 (P=0.56) for placebo. Improvements in the individual components of ELF (PIIINP, TIMP-1 and hyaluronic acid) were also observed in patients treated with NGM282 (Supplementary Fig. 9). Post hoc subgroup analysis revealed that patients with a higher risk of disease progression (ELF >9.8 at baseline[17, 18]) had a greater reduction in ELF than did patients with a lower disease risk, with LS mean changes of −0.52 (P<0.001) and −0.58 (P=0.007) for NGM282 1 mg and 3 mg, respectively, versus −0.01 (P=0.97) for placebo (Fig. 3A).
Pro-C3 measures a neo-epitope of type III collagen during collagen formation and directly reflects fibrogenic activity[16]. Reductions in Pro-C3 levels were greater for both NGM282 1 mg and 3 mg groups compared with the placebo group at all time points during treatment (Fig. 3B-C). At week 12, significant reductions in Pro-C3 were observed in the NGM282 1 mg group (LS mean difference, −9.5; 95% CI −17.1 to −2.0; P=0.01) and 3 mg group (−13.3; −21.0 to −5.6; P=0.001) compared with the placebo (Table 2). Improvements in Pro-C3 were most pronounced in patients with advanced fibrogenesis (Pro-C3 >20 ng/mL) at baseline (Supplementary Fig. 10).

Safety

17/21 patients (81%) in the NGM282 1 mg group, 20/21 patients (95%) in the NGM282 3 mg group and 18/20 patients (90%) in the placebo group had adverse events, most of which were grade 1 and grade 2, during the study period (Table 4). The most commonly reported adverse events due to any cause were injection site reaction and diarrhea. Injection site reaction occurred more frequently in the NGM282 3 mg group, but appeared to be tolerated over time, as measured by the local injection site symptom assessment tool (Supplementary Fig. 11). Diarrhea was reported in a higher percentage of patients in the NGM282 groups than placebo, none higher than grade 2 in severity. Assessment of gastrointestinal symptoms by Mayo Partial IBD score revealed that NGM282 treatment increased stool frequency, but not rectal bleeding (Supplementary Fig. 12). A total of 3 serious adverse events were reported during the trial. One patient from the NGM282 1 mg group had an elevation in bilirubin due to PSC progression and one patient from the NGM282 3 mg group had an intervertebral discitis; neither was considered related to treatment by site investigators. One patient with concomitant ulcerative colitis in the NGM282 3 mg group had a bowel obstruction during the follow-up period after
EOT, which resolved in three days. This event was considered by the investigator to be possibly related to the study drug. No adverse events at or above grade 4 were noted. No deaths occurred during the course of the study.

None of the patients tested positive for antidrug antibodies (ADA) at baseline. ADA occurred after baseline during the study period in 5 of 62 patients, all from the NGM282 3 mg group. Neutralizing antibodies to FGF19 were not detected in any of these patients. There was no evidence of clinical safety events associated with a positive antidrug antibody test.

DISCUSSION

PSC is a chronic inflammatory, fibrosing and cholestatic liver disease, associated with poor outcomes for patients, in which the need for novel therapies is acute[20]. In our randomized, placebo-controlled, phase 2 trial of NGM282, drug administration did not meet the pre-specified primary endpoint of reductions in the serum marker of cholestasis, ALP, after 12 weeks of treatment. However, NGM282, a first-in-class FGF19 analogue, demonstrated potent target engagement, as evidenced by significant reductions in C4 and bile acids. The resulting reduction in levels of transaminases and fibrosis biomarkers (ELF and Pro-C3) nevertheless highlights the compartmentalized potential efficacy of this new treatment. In keeping with reported efficacy of NGM282 at a similar stage of drug development for non-alcoholic steatohepatitis[13], our trial data for the first time in PSC demonstrated a significant potential anti-fibrotic activity of a therapeutic agent using a novel biomarker (Pro-C3) in participants.
NGM282 was generally well tolerated at both doses, with most treatment-related AEs being mild in severity.

The slow rate of disease progression, together with heterogeneous pathogenic mechanisms, the lack of defined surrogates of treatment efficacy and the impracticality of frequent liver biopsies (as opposed to blood sampling), have limited the development of therapeutics for PSC. At present, there are no established surrogate endpoints for regulatory approval in PSC. Several surrogate endpoints, including ALP, were recommended by an international PSC study group[21, 22]. The observation that ALP reduction after UDCA treatment can predict outcomes (liver transplantation and death) in primary biliary cholangitis (PBC) has inspired studies to assess the association between ALP reduction and clinical outcome after UDCA treatment in PSC. However, unlike in PBC, ALP has a more unpredictable fluctuating nature in PSC, which may limit the value of single measurements at any point in time for patient follow-up or clinical trials[2]. Cholangitis, biliary calculi or dominant strictures can cause transient elevations in ALP, generating difficulty in assessing disease stage and prognosis. Multiple trials of UDCA (13-23 mg/kg) suggested improvements in ALP but not hard endpoints such as death or liver transplantation[23-25]. A landmark, long-term, randomised, double-blind, placebo-controlled study of high-dose UDCA (28-30 mg/kg) in 150 PSC patients was terminated after 6 years due to worsened outcome (difference in the total number of all endpoints reached: development of cirrhosis, esophageal varices and cholangiocarcinoma, listing for liver transplant, and death) despite a significant reduction in ALP[26-29]. The relevance of ALP for treatment response in PSC is unclear at present.
Diagnosis of PSC depends on identification of fibrotic strictures of the intrahepatic or extrahepatic biliary systems, by cholangiography or biopsy[20]. The pathognomonic lesion in PSC is an “onion skin” scar, referring to concentric layer of fibrosis circumferential to the cholangiocyte lining of the bile ducts. Despite the association between liver fibrosis stage and transplant-free survival[30], liver biopsy was not routinely performed due to its invasive nature and inherent sampling variability in PSC. In contrast to previous trials, we evaluated the fibrosis biomarkers in addition to the widely-used primary endpoint ALP. ELF score, a composite panel of three components of fibrogenesis and matrix remodeling, has been demonstrated to be a strong predictor of transplant-free survival in patients with PSC[17, 18]. In particular, a change in ELF score of $-0.19$ from baseline to week 12 has been shown to predict survival free of PSC-related clinical events, such as ascites, encephalopathy, variceal hemorrhage, cholangiocarcinomas, jaundice, liver transplant or death[31]. The administered doses of NGM282 reduced ELF ($-0.29$ and $-0.37$ from baseline to week 12 for 1 mg and 3 mg, respectively), with the most pronounced improvement in patients who had an advanced stage of disease ($-0.52$ and $-0.58$ from baseline to week 12 for 1 mg and 3 mg, respectively, in patients with baseline ELF >9.8). Serum levels of Pro-C3 reflect fibrogenesis directly by detecting a neo-epitope of collagen III[16]. Pro-C3 has recently been demonstrated to be an independent predictor of transplant-free survival in PSC, with an odds ratio of 13.8[19]. NGM282 treatment produced rapid, robust and sustained effect in lowering Pro-C3. The anti-fibrotic activity of NGM282 in this trial supports the notion that NGM282 may eliminate toxic effects due to bile acid accumulation in the liver at a stage before the deposition of fibrillary proteins, and is consistent with results from animal models[11] and clinical studies in non-alcoholic steatohepatitis[13]. Overall, the significant reduction in the levels of fibrotic and inflammation markers that are correlated with disease activity supports a long-held hypothesis that
dysregulated bile acids are a key driver of intrahepatic inflammation and fibrosis, rather than only the bystander of an autoimmune response. This, in turn, supports the view that a therapy targeting bile acid metabolism could deliver clinical benefit without having an early biochemical response in ALP.

Both doses of NGM282 that were administered in this trial were associated with a high level of target engagement, sufficient to reduce C4 by 61-87%. It is possible that the magnitude of reduction in C4 was simply insufficient to create a measurable effect in change from baseline in ALP, especially when baseline C4 levels are already suppressed by elevated FGF19 in PSC patients[3, 7], contrasting observations in animal models[11]. We did note a reduction in ALP within 1 week of treatment initiation with NGM282 1 mg, which was sustained through week 4, but diminished in magnitude at week 12. These findings suggest that the effects of NGM282 on ALP might be transient and reversed by adaptive mechanisms to re-establish a new equilibrium. In contrast, the decrease in transaminases is sustained and enduring in patients on NGM282 3 mg, thus the protective effect of NGM282 may be more parenchymal-focused rather than biliary.

NGM282 was generally well tolerated in the study population. Injection site reactions occurred more frequently in the NGM282 3 mg group, but appeared to be tolerated over time. Gastrointestinal symptoms were transient and mild to moderate in severity, as observed with NGM282 treatment in patients with NASH[13]. Although elevation of LDL cholesterol due to inhibition of its conversion to bile acid was noted in previous trial of NGM282 in patients with NASH[13], we observed no significant change in LDL cholesterol in PSC patients. Patients with PSC frequently develop disabling pruritus and fatigue. NGM282 did not worsen pruritus or fatigue.
As a master regulator of bile acid metabolism in human physiology and health, the Farnesoid X receptor (FXR)-FGF19 axis is increasingly recognized as an area of great potential for the treatment of chronic liver disease. A significant component of FXR-mediated biological activity is attributed to the induction of endogenous FGF19, a bona fide FXR target gene in the gut[4]. Synthetic activators of FXR have been recently approved or are currently in clinical development in PBC, PSC and NASH[32-34]. We have recently shown that administration of NGM282 for 28 days resulted in significant improvements in ALP and transaminase levels compared with placebo in patients with PBC who had inadequate response to ursodiol. In contrast with results presented in this report, ALP was significantly reduced with NGM282 treatment (LS mean differences of −54 IU/L (P=0.0149) and −69 U/L (P=0.0030) for 0.3 mg and 3 mg, respectively, versus placebo)[35]. Whereas ALP is considered “reasonably likely” to predict clinical outcome by the Food and Drug Administration for accelerated approval under Subpart H/E for PBC [36], ALP-lowering alone is not regarded as the primary efficacy outcome for clinical trials in PSC. Nevertheless, significant decreases in the levels of transaminases (ALT and AST) were observed in patients treated with NGM282 across PSC, PBC, and NASH populations[13, 35], indicating robust activity of NGM282 against liver injury.

Our trial had several strengths. These include the enrollment of a broader patient population that is more reflective of real world experience. For example, patients with dominant strictures have significantly worse survival than do those without dominant strictures[37]; 16% of the patients in this study have dominant strictures compared with 0% of the patients in recent PSC trials (OCA, norUDCA, simtuzumab)[33, 38, 39]. Patients with small duct disease, features of autoimmune hepatitis, and compensated cirrhosis were included in our trial but were excluded from the other studies.
Importantly, we included fibrosis biomarkers that predict clinical outcome in PSC (ELF) and are novel in monitoring fibrogenesis (Pro-C3).

Limitations of this study included a relatively short treatment period and small overall number of subjects. The non-invasive fibrosis biomarkers (Pro-C3 and ELF) used in this study are only of prognostic value\cite{17, 19, 40}, and have not yet been shown to change with disease course. Further studies are therefore needed to examine whether longitudinal change in these markers correlates with disease course, and their potential as surrogate endpoints. Whilst accepting that small duct PSC is an area of controversy, we elected to include such patients to ensure that the study, performed in expert centres with experienced Hepatologists, recruited patients for evaluation reflecting the spectrum of clinical PSC looked after in the community. Additional limitations include a lack of MRCP at the end of the treatment, although all patients had an MRCP exam during screening. As cholangiographic changes define the diagnosis of PSC, evaluation of therapeutics should also focus on the imaging of bile duct changes, given the recent study showing that MRCP score correlates with clinical outcome (variceal bleeding, decompensation, transplant, death) in patients with PSC\cite{41}. Additionally, participants did not undergo liver biopsy at the end of the trial, therefore, it is uncertain whether NGM282-mediated anti-fibrotic effects can be seen at the histological level.

The current trial confirms the clinical relevance of the FGF19 pathway in PSC patients and the concept that it could be harnessed therapeutically to change the course of the disease. Longer trials with a larger number of patients are however needed to better understand the effects of NGM282 therapy in PSC. Given that liver biopsies are not routinely conducted to assess disease progression in patients.
with PSC, future trials should examine longitudinal change in transient elastography and MRCP, and correlate with serum markers of fibrosis turnover and hepatic inflammation. These studies will have important implications as they may demonstrate the complexities of testing therapeutic agents in PSC, and challenge the dogma about what the appropriate endpoints should be for trials in PSC.

**CONCLUSIONS**

In conclusion, in patients with PSC, NGM282 demonstrated significant and robust activities on bile acid metabolism and anti-fibrotic effects, without reducing ALP. Further trials with NGM282 in patients with PSC should focus on longer term administration and an array of biochemical and imaging end-points that reflect closer the underlying pro-fibrotic nature of PSC.

**ACKNOWLEDGEMENTS**

We would like to express our appreciation to all of the patients who participated in this study, and the investigators, study coordinators, and staff of all of the participating clinical centers for their support and assistance.
REFERENCES

Author names in bold designate shared co-first authorship


FDA. Gastrointestinal Drug Advisory Committee (GIDAC) Meeting on Obeticholic Acid for the Treatment of Primary Biliary Cholangitis. April 7, 2016.


# TABLES

## Table 1. Baseline Patient Demographics and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=20)</th>
<th>NGM282 1 mg (n=21)</th>
<th>NGM282 3 mg (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, years</strong></td>
<td>43.4±12.4</td>
<td>46.0±15.9</td>
<td>40.2±13.0</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>12 (60)</td>
<td>14 (67)</td>
<td>12 (57)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>8 (40)</td>
<td>7 (33)</td>
<td>9 (43)</td>
</tr>
<tr>
<td><strong>Duration of PSC, years</strong></td>
<td>8.1±7.2</td>
<td>7.3±6.1</td>
<td>7.8±7.6</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>4 (20)</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>White</td>
<td>16 (80)</td>
<td>18 (86)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (5)</td>
<td>1 (5)</td>
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<td><strong>Ethnic origin, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hispanic/Latino</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
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<tr>
<td><strong>UDCA status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant UDCA</td>
<td>13 (65)</td>
<td>13 (62)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>No concomitant UDCA</td>
<td>7 (35)</td>
<td>8 (38)</td>
<td>8 (38)</td>
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<tr>
<td><strong>Cholangiography by MRCP or ERCP, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Large duct PSC</td>
<td>13 (65)</td>
<td>10 (48)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Dominant stricture</td>
<td>5 (25)</td>
<td>2 (10)</td>
<td>3 (14)</td>
</tr>
<tr>
<td><strong>Bile acid-related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4 (ng/mL)</td>
<td>10.5±11.2</td>
<td>12.9±12.8</td>
<td>16.9±18.2</td>
</tr>
<tr>
<td>C4 ≤2 ng/mL</td>
<td>5 (25)</td>
<td>4 (19)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Endogenous bile acids (µmol/L)</td>
<td>30.2±33.0</td>
<td>39.1±42.4</td>
<td>20.1±32.0</td>
</tr>
<tr>
<td>Endogenous FGF19 (pg/mL)</td>
<td>433.3±339.1</td>
<td>339.7±279.5</td>
<td>305.8±241.1</td>
</tr>
<tr>
<td><strong>Serum liver tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>355.5±137.9</td>
<td>383.2±181.4</td>
<td>353.7±194.0</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>90.5±51.8</td>
<td>116.7±70.2</td>
<td>96.1±67.3</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>71.1±36.9</td>
<td>92.6±59.7</td>
<td>70.3±46.4</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td>12.1±6.0</td>
<td>17.9±8.4</td>
<td>10.7±4.3</td>
</tr>
<tr>
<td><strong>Fibrosis biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pro-C3 (ng/mL)</td>
<td>26.1±16.4</td>
<td>26.7±17.9</td>
<td>24.2±16.7</td>
</tr>
<tr>
<td>Pro-C3 ≥20 ng/mL</td>
<td>12 (60)</td>
<td>10 (48)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>ELF score</td>
<td>10.0±1.4</td>
<td>10.2±1.2</td>
<td>9.5±1.1</td>
</tr>
<tr>
<td>Hyaluronic acid (µg/L)</td>
<td>160.8±261.6</td>
<td>203.8±488.7</td>
<td>60.1±60.2</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>PIIINP (µg/L)</strong></td>
<td>14.2±8.3</td>
<td>13.9±6.3</td>
<td>12.6±4.2</td>
</tr>
<tr>
<td><strong>TIMP-1 (µg/L)</strong></td>
<td>338.6±113.6</td>
<td>310.4±74.6</td>
<td>338.4±94.1</td>
</tr>
<tr>
<td><strong>ELF &gt;9.8</strong></td>
<td>9 (45)</td>
<td>12 (57)</td>
<td>5 (24)</td>
</tr>
</tbody>
</table>

Shown are mean±SD or n(%). BMI, body mass index; C4, 7alpha-hydroxy-4-cholesten-3-one; ELF, Enhanced Liver Fibrosis; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; PIIINP, N-terminal propeptide of type III collagen; Pro-C3, neoepitope-specific N-terminal propeptide of type III collagen; SD, standard deviation; TIMP-1, tissue inhibitor of metalloproteinase 1; UDCA, ursodeoxycholic acid.
### Table 2. Key Outcomes at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Mean Change From Baseline to Week 12 (SD)</th>
<th>LS Mean Difference (95% CI) (NGM282 vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=20)</td>
<td>NGM282 1mg (n=21)</td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ALP (U/L)</td>
<td>-0.6 (79.5)</td>
<td>25.6 (100.3)</td>
</tr>
<tr>
<td>Concomitant UDCA</td>
<td>-10.2 (73.5)</td>
<td>27.1 (122.8)</td>
</tr>
<tr>
<td>No concomitant UDCA</td>
<td>17.1 (93.0)</td>
<td>23.1 (54.0)</td>
</tr>
<tr>
<td><strong>7alpha-hydroxy-4-cholesten-3-one (C4)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4 (ng/mL)</td>
<td>0.5 (11.7)</td>
<td>-7.9 (13.3)</td>
</tr>
<tr>
<td><strong>Liver function test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>-4.5 (31.6)</td>
<td>-2.8 (62.8)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-5.3 (25.6)</td>
<td>-11.2 (62.2)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>18.7 (111.6)</td>
<td>123.8 (263.9)</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td>0.7 (3.2)</td>
<td>10.0 (45.8)</td>
</tr>
<tr>
<td><strong>Fibrosis biomarkers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pro-C3 (ng/mL)</td>
<td>3.5 (8.8)</td>
<td>-6.3 (14.3)</td>
</tr>
<tr>
<td>ELF score</td>
<td>0.1 (0.5)</td>
<td>-0.3 (0.5)</td>
</tr>
<tr>
<td>Hyaluronic acid (µg/L)</td>
<td>-12.3 (71.9)</td>
<td>-37.6 (129.4)</td>
</tr>
<tr>
<td>PIIINP (µg/L)</td>
<td>1.4 (5.3)</td>
<td>-3.6 (3.7)</td>
</tr>
<tr>
<td>TIMP-1 (µg/L)</td>
<td>2.6 (59.5)</td>
<td>-31.1 (43.2)</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.1 (0.3)</td>
<td>0 (0.6)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>0.2 (0.7)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>-0.1 (0.2)</td>
<td>0 (0.5)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>0.1 (0.5)</td>
<td>0.1 (0.8)</td>
</tr>
</tbody>
</table>

Change from baseline at week 12 in ALP (primary outcome) was compared vs placebo using the Wilcoxon Rank Sum test. Change from baseline at week 12 in other measures was compared vs placebo using an ANCOVA model with treatment group, visit, treatment group by visit interaction, UDCA use, treatment group by UDCA use interaction as classification variables and baseline value as covariate.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares mean; PIIINP, N-terminal pro-peptide of type III collagen; Pro-C3, neoepitope-specific N-terminal pro-peptide of type III collagen; SD, standard deviation; SE, standard error; TIMP-1, tissue inhibitor of metalloproteinase 1.
Table 3. Change in Bile Acids from Baseline to Week 12

<table>
<thead>
<tr>
<th>Conjugated Primary Bile Acids</th>
<th>Placebo (n=20)</th>
<th>NGM282 1mg (n=21)</th>
<th>NGM282 3mg (n=21)</th>
<th>LS Mean Difference (95% CI) (NGM282 vs Placebo)</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCA (µmol/L)</td>
<td>−1.1 (6.8)</td>
<td>−10.6 (25.4)</td>
<td>−2.9 (10.1)</td>
<td>−1.3 (−4.8, 2.1)</td>
<td>0.44</td>
<td>−2.8 (−6.2, 0.6)</td>
</tr>
<tr>
<td>TCA (µmol/L)</td>
<td>0.8 (5.4)</td>
<td>−4.5 (15.3)</td>
<td>−1.2 (5.0)</td>
<td>−0.6 (−4.4, 3.1)</td>
<td>0.73</td>
<td>−3.0 (−6.6, 0.7)</td>
</tr>
<tr>
<td>GCDCA (µmol/L)</td>
<td>−3.9 (14.6)</td>
<td>−7.6 (14.7)</td>
<td>−2.7 (11.3)</td>
<td>−3.0 (−7.6, 1.6)</td>
<td>0.20</td>
<td>−2.6 (−7.3, 2.0)</td>
</tr>
<tr>
<td>TCDA (µmol/L)</td>
<td>−1.1 (10.7)</td>
<td>−1.1 (5.1)</td>
<td>−0.8 (3.7)</td>
<td>−0.9 (−3.9, 2.1)</td>
<td>0.55</td>
<td>−2.4 (−5.5, 0.7)</td>
</tr>
</tbody>
</table>

**Conjugated Secondary Bile Acids**

| GLCA (µmol/L)                | 0 (0.3)        | −0.1 (0.2)        | −0.1 (0.3)        | −0.1 (−0.2, 0.0)                              | 0.036 | −0.1 (−0.2, 0.0) | 0.027 |
| TLCA (µmol/L)                | 0.03 (0.09)    | −0.02 (0.04)      | −0.04 (0.09)      | −0.05 (−0.10, -0.01)                          | 0.024 | −0.06 (−0.11, −0.02) | 0.007 |

**Unconjugated Primary Bile Acids**

| CA (µmol/L)                  | 0.2 (0.6)      | −0.1 (0.5)        | 0 (0.2)           | −0.2 (−0.4, 0.1)                              | 0.27 | −0.1 (−0.4, 0.2) | 0.51 |
| CDCA (µmol/L)                | 0.1 (0.8)      | −0.1 (0.3)        | 0.1 (0.2)         | −0.2 (−0.5, 0.1)                              | 0.17 | 0 (−0.3, 0.2) | 0.78 |

**Unconjugated Secondary Bile Acids**

| DCA (µmol/L)                 | 0 (0.2)        | −0.1 (0.1)        | −0.2 (0.4)        | −0.1 (−0.2, −0.1)                             | <0.001 | −0.2 (−0.2, −0.1) | <0.001 |
| LCA (µmol/L)                 | 0 (0.03)       | −0.02 (0.05)      | −0.05 (0.15)      | −0.01 (−0.03, 0.01)                           | 0.31 | −0.02 (−0.04, 0.01) | 0.16 |

**UDCA and derivatives**

| GUDCA (µmol/L)               | −10.0 (39.2)   | −9.7 (26.8)       | 1.0 (20.1)        | −2.2 (−18.1, 13.7)                            | 0.78 | 3.2 (−12.9, 19.3) | 0.69 |
| TUDCA (µmol/L)               | −2.0 (7.5)     | −0.7 (2.8)        | 0 (1.5)           | −0.2 (−2.1, 1.7)                              | 0.86 | −0.6 (−2.5, 1.4) | 0.57 |
| UDCA (µmol/L)                | −3.0 (10.1)    | −0.5 (4.1)        | 1.2 (7.1)         | 1.1 (−2.6, 4.9)                               | 0.55 | 2.5 (−1.2, 6.3) | 0.18 |

**Total endogenous bile acids**

| TEBA (µmol/L)                | −4.1 (27.4)    | −19.7 (37.0)      | −9.6 (31.8)       | −8.6 (−20.8, 3.6)                             | 0.16 | −12.7 (−25.0, −0.5) | 0.042 |

Change from baseline at week 12 in bile acids was compared vs placebo using an ANCOVA model with treatment group, visit, treatment group by visit interaction, UDCA use, treatment group by UDCA use interaction as classification variables and baseline value as covariate.

CA, cholic acid; CDCA, chenocholecholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenocholecholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenocholecholic acid; TDCA, taurodeoxycholic acid; TEBA, total endogenous bile acids; TLCA, tauro lithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.
Table 4. Summary of Adverse Events

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n=20)</th>
<th>NGM282 1 mg (n=21)</th>
<th>NGM282 3 mg (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18 (90)</td>
<td>17 (81)</td>
<td>20 (95)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>8 (40)</td>
<td>9 (43)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>9 (45)</td>
<td>7 (33)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At least one drug-related adverse event, n (%)</td>
<td>13 (65)</td>
<td>13 (62)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>At least one serious adverse event</td>
<td>0</td>
<td>1# (5)</td>
<td>2^ (10)</td>
</tr>
<tr>
<td>At least one adverse event leading to study drug discontinuation</td>
<td>0</td>
<td>1# (5)</td>
<td>1* (5)</td>
</tr>
</tbody>
</table>

Most Common (>10%) Adverse Events, n (%)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n=20)</th>
<th>NGM282 1 mg (n=21)</th>
<th>NGM282 3 mg (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (5)</td>
<td>8 (38)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (10)</td>
<td>3 (14)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (20)</td>
<td>2 (10)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Nasopharygitis</td>
<td>4 (20)</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>0 (0)</td>
<td>4 (19)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>3 (14)</td>
</tr>
</tbody>
</table>

Investigators rated the severity of each adverse event (mild [grade 1], moderate [grade 2], or severe [grade 3]). The events were classified according to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. No grade 4 or grade 5 (death) events were reported during the trial period (including follow up period after end of treatment). No cases of pancreatitis were reported.

#SAE PSC progression (not related)

^SAEs were bowel obstruction (possibly related) and intervertebral discitis (not related)

*Diarrhea
FIGURE LEGENDS

**Figure 1. Trial Profile.** AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment.

**Figure 2. Key Outcome Measures.** (A) Serum levels of ALP at baseline and week 12. (B) Serum levels of C4 at baseline and week 12. (C) Serum levels of total endogenous bile acids at baseline and week 12. (D) Change in ALT from baseline over time. (E) Change in AST from baseline over time.

All data are mean ± s.e.m. Statistical tests were ANCOVA (panels A-C) or mixed-effect model repeated measures (panels D-E) analyses. ***P<0.001, **P<0.01, *P<0.05. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7alpha-hydroxy-4-cholesten-3-one; EOT, end of treatment at week 12.

**Figure 3. Changes in Biomarkers of Liver Fibrosis.** (A) Change in ELF from baseline to week 12. Left panel: all patients; middle panel: patients with baseline ELF ≤9.8; right panel: patient with baseline ELF >9.8. (B) Serum concentrations of Pro-C3 over time. (C) Percent change in Pro-C3 from baseline over time. All data are mean ± s.e.m. Statistical tests were ANCOVA (panel A) or mixed-effect model repeated measures (panels B-C) analyses. ***P<0.001, **P<0.01, *P<0.05. ELF, Enhanced Liver Fibrosis score; EOT, end of treatment at week 12; FU, follow-up at week 16; Pro-C3, neoepitope-specific N-terminal propeptide of type III collagen.
Highlights for manuscript JHEPAT-D-18-01614R1 by Hirschfield et al.

NGM282 for Primary Sclerosing Cholangitis: a Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial

- NGM282 is a first-in-class, engineered analogue of the endocrine hormone FGF19
- Administration of NGM282 did not significantly affect alkaline phosphatase levels in patients with primary sclerosing cholangitis
- However, NGM282 significantly inhibited bile acid synthesis and improved serum markers of fibrogenesis and liver injury
- These findings challenge the dogma about what the appropriate endpoints should be for trials in PSC
95 patients screened

62 randomized

20 assigned to receive placebo
20 received placebo

21 assigned to receive NGM282 1 mg
21 received NGM282 1 mg

21 assigned to receive NGM282 3 mg
21 received NGM282 3 mg

1 discontinued treatment 1 patient choice

1 discontinued treatment 1 due to AE

2 discontinued treatment 1 due to AE 1 patient choice

33 excluded:
10 did not meet ALP criteria
4 did not meet ALT, AST or bilirubin criteria
1 withdrew consent
18 did not meet criteria (other)

20 included in intention-to-treat analysis
21 included in intention-to-treat analysis
21 included in intention-to-treat analysis

Hirschfield et al., Figure 1
Hirschfield et al., Figure 2

A. ALP (U/L)

B. C4 (ng/mL)

C. Serum Endogenous Bile Acids (μmol/L)

D. Change in ALT From Baseline (U/L)

E. Change in AST From Baseline (U/L)
Hirschfield et al., Figure 3

A

Baseline ELF ≤9.8

Baseline ELF >9.8

Change in ELF
From Baseline to Week 12

P=0.023

P=0.23

P=0.049

P=0.90

P=0.029

Change in ELF
From Baseline to Week 12

P=0.23

P=0.016

0.08 0.12

-0.24

Baseline ELF ≤9.8

Baseline ELF >9.8

BC

40

30

0

Change in Pro-C3
From Baseline (ng/mL)

Weeks

Placebo (n=20)

1 mg (n=21)

3 mg (n=21)

***

***

***

***

20

16

14

12

10

8

6

4

2

0

EOT

FU

Weeks

0

2

4

6

8

10

12

14

16

25

%Change in Pro-C3
From Baseline

***

***

***

**

Weeks

0

2

4

6

8

10

12

14

16

-50

-25
Patients with Primary Sclerosing Cholangitis

NGM282
(FGF19 analogue)

↓ de novo bile acid synthesis
↓ ALT, AST
↓ Fibrogenesis
No change in ALP

Liver image from Hirschfield et al., Lancet. 2013;382:1587