

NGM282 for Treatment of Patients With Primary Biliary Cholangitis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Patients with primary biliary cholangitis (PBC) who had an inadequate response to ursodiol have few treatment options. Alkaline phosphatase (ALP) and bilirubin levels correlate with the risk of liver transplant or death in PBC patients. Fibroblast growth factor (FGF) 19 is a hormone that acts directly in the liver to regulate bile acid synthesis. We evaluated NGM282, an engineered analogue of FGF19, for the treatment of PBC. In this 28-day, double-blind, placebo-controlled phase 2 trial, 45 PBC patients who had an inadequate response to ursodiol were randomly assigned 1:1:1 to receive subcutaneous daily doses of either NGM282 at 0.3 mg (n = 14), 3 mg (n = 16), or placebo (n = 15). The primary endpoint was a change in ALP from baseline after 28 days of treatment. At day 28, ALP was significantly reduced with NGM282 treatment at both 0.3 mg (least-squares mean -51.0 IU/L [standard error (SE) 15.4]) and 3 mg (-66.0 IU/L [SE 16.0]) versus placebo (3.3 IU/L [SE 14.8]), with least-squares mean differences of -54.3 IU/L (95% confidence interval -104.2 to -4.5 ; $P = 0.0149$) and -69.3 IU/L (95% confidence interval -120.5 to -18.3 ; $P = 0.0030$), respectively. Fifty percent (7 of 14) of patients receiving NGM282 0.3 mg and 46% (6 of 13) of those receiving NGM282 3mg achieved 15% or greater reduction in ALP levels from baseline, compared with 7% (1 of 15) of patients receiving placebo. NGM282 also significantly reduced serum concentrations of transaminases and immunoglobulins. Most adverse events were grade 1 (mild) to grade 2 (moderate) in severity, with gastrointestinal disorders more frequent in the NGM282 treatment groups. No worsening of pruritus was observed with NGM282 treatment. **Conclusion:** NGM282 administered for 28 days resulted in significant improvements in ALP and transaminase levels compared with placebo, with an acceptable safety profile in patients with PBC. (*Hepatology Communications* 2018;2:1037-1050)

Primary biliary cholangitis, previously called primary biliary cirrhosis (PBC), is a chronic cholestatic liver disease that is the most common cholangiopathy in adults.⁽¹⁾ Global PBC prevalence rates range from 20 to 40 cases per 100,000 persons. PBC primarily affects women with a female

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ANCOVA, analysis of covariance; AST, aspartate transaminase; C4, 7 α -hydroxy-4-cholesten-3-one; CA, cholic acid; CDCA, chenodeoxycholic acid; CYP7A1, cytochrome P450 family 7 subfamily A member 1; DCA, deoxycholic acid; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GGT, gamma glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; IgG, immunoglobulin G; IgM, immunoglobulin M; LCA, lithocholic acid; LDL-C, low-density lipoprotein cholesterol; LS, least squares; OCA, obeticholic acid; PBC, primary biliary cholangitis; SE, standard error; TC, total cholesterol; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TG, triglyceride; TLCA, tauroolithocholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of the normal; and VAS, visual analog scale.

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preponderance of 9 to 12:1, and affects patients primarily in their fifth to seventh decades of life. The pathogenesis of PBC involves the inflammation and destruction of interlobular bile ducts resulting in cholestasis, cholangitis, ductopenia, and eventually, cirrhosis and end-stage liver diseases.

Diagnosis of PBC is based on sustained elevation of alkaline phosphatase (ALP), a serum marker of cholestasis, and the presence of either serum antimitochondrial antibodies or histological cholangiopathy.^(2,3) Higher levels of ALP correlate with disease progression, and are associated with higher risk of liver transplantation or death.⁽⁴⁾ Elevated bilirubin levels, which occur later in advanced diseases, are a strong predictor of patient outcomes. The most frequent symptoms in PBC are fatigue and pruritus, occurring in up to 85% and 70% of patients, respectively. Median survival in untreated individuals has been reported to be 7.5 to 16 years, and only 1.4 to 4.1 years in patients with advanced disease. Reduction in ALP levels has been validated as a surrogate marker of slower disease progression as well as improved transplant-free overall survival.⁽⁴⁾

Two medications have been licensed for the treatment of PBC: ursodiol (ursodeoxycholic acid), a hydrophilic bile acid, and obeticholic acid (OCA), a modified bile acid farnesoid X receptor (FXR) agonist.⁽⁵⁾ Treatment with ursodiol has been shown to reduce ALP levels and delay the time to liver transplantation,⁽⁶⁾ but only 40% to 60% of patients respond adequately to ursodiol.⁽⁷⁾ Treatment with OCA, alone or in combination with ursodiol, resulted in a reduction

in ALP levels, but was associated with worsening pruritus and increased serious adverse events.⁽⁸⁾ However, a significant number of patients do not respond to either treatment and/or continue to have clinical symptoms. New therapies, such as agonists of peroxisome proliferator-activated receptors, reduce ALP levels but are associated with elevated transaminase concentrations or creatinine levels.⁽⁹⁾ Thus, there remains a significant need for additional therapeutic options for patients with PBC.

FGF19 is an endocrine hormone that is induced in the gut by activation of FXR.⁽¹⁰⁾ FGF19 acts directly on the liver to suppress expression of CYP7A1, the gene-encoding cholesterol 7 α -hydroxylase, the enzyme that catalyzes the first and rate-limiting step in the classic pathway of bile acid synthesis.⁽¹¹⁾ Administration of FGF19 has been shown to protect mice against liver injury in models of intrahepatic and extrahepatic cholestasis.^(12,13) However, the therapeutic potential of FGF19 is limited by concerns about tumorigenicity, as ectopic overexpression of FGF19 in mice results in the development of hepatocellular carcinoma.⁽¹⁴⁾

NGM282 is a nontumorigenic analogue of FGF19 being evaluated for the treatment of PBC. NGM282 (also referred to as M70) differs from FGF19 in the amino terminus, a key region of the protein involved in receptor interactions and signaling modulation.⁽¹⁵⁾ In NGM282, a 5-amino acid deletion (P24-S28) coupled with substitution of three amino acids at critical positions (A30S, G31S, H33L) within the amino terminus bias FGFR4 signaling so that NGM282 retains the ability to potently repress CYP7A1 expression

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Conflicts of interest: Dr. Ling, Dr. Rossi, and Dr. DePaoli are employees and stockholders of NGM Biopharmaceuticals Inc.

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through the FGFR4- β Klotho receptor complex.⁽¹⁵⁾ In contrast, NGM282 does not activate STAT3, a signaling pathway essential for FGF19-mediated hepatocarcinogenesis.⁽¹⁶⁾ In animal models of cholestasis and cholangiopathy, NGM282 inhibited bile acid synthesis, reduced excess hepatic bile acid accumulation, and protected mice from liver injury induced by intrahepatic or extrahepatic cholestasis without carcinogenesis.^(13,17) In healthy human subjects, NGM282 reduced serum concentration of 7 α -hydroxy-4-cholesten-3-one (C4), a surrogate marker for enzymatic activity of CYP7A1, and was found to be safe and well tolerated.⁽¹³⁾ In a double-blind, placebo-controlled trial in patients with nonalcoholic steatohepatitis, NGM282 produced rapid and significant reductions in liver fat content and serum levels of transaminases.⁽¹⁸⁾ Taken together, these observations indicate that NGM282 represents a potential therapeutic option for the treatment of chronic liver diseases.

We conducted a phase 2, multicenter, international, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of NGM282 in reducing ALP and other serum markers of cholestasis, as well as its safety and tolerability, in patients with PBC.

Materials and Methods

STUDY DESIGN AND PARTICIPANTS

This trial was a multicenter evaluation of NGM282 in a randomized, double-blind, placebo-controlled study. NGM282 was administered for 28 consecutive days as a daily subcutaneous administration in patients with PBC who had inadequate response to ursodiol. Between March 27, 2014, and December 13, 2014, we enrolled patients 18–75 years of age who had received a PBC diagnosis^(2,3) across 22 sites in Australia and the United States. The study protocol was approved by institutional review boards and national ethics and regulatory agencies and was conducted in accordance with the International Conference on Harmonization E6 Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent. This trial was registered with ClinicalTrials.gov (NCT02026401).

Entry criteria were an ALP level of at least 1.67 times the upper limit of the normal (ULN) range, total bilirubin less than or equal to 2 times ULN, and alanine transaminase (ALT) and aspartate transaminase

(AST) less than or equal to 10 times ULN. Patients were also required to have an inadequate response to ursodiol, according to the following criteria: taking ursodiol for at least 12 months at doses of 12 mg/kg or more, at a stable dose for 3 or more months prior to screening, and having no ursodiol-related side effects at screening. Patients continued on ursodiol treatment during the study period at their current, prestudy dose. Key exclusion criteria included clinically significant liver disease of a non-PBC etiology, such as autoimmune hepatitis (including patients with overlapping PBC and autoimmune hepatitis), hepatitis B or C virus, alcoholic liver disease and nonalcoholic steatohepatitis, and evidence of clinically significant hepatic decompensation, based on relevant medical complications and laboratory parameters associated with portal hypertension (Supporting Tables S1 and S2).

RANDOMIZATION AND MASKING

Patients were randomized 1:1:1 using an interactive voice/web response system to once-daily subcutaneous NGM282 doses of 0.3 mg, NGM282 3 mg, or placebo for 28 days. NGM282 and placebo were provided as identical prefilled syringes in identical containers labeled 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 retained at the trials unit and was accessible only by the database programmer and the statistician. Patients were stratified according to their pruritus status, as defined by the severity assessment in the 5-D itch questionnaire,⁽¹⁹⁾ to ensure equitable distribution across the treatment arms. Investigators, patients, sponsor, clinical site staff, and medical monitor remained blinded throughout the study period.

PROCEDURES

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 (day 1) and doses at days 7, 14, 21, and 28 were self-administered in the clinic with all other doses self-administered at home. Patients were evaluated at randomization (day 1) and returned for study visits on days 7, 14, and 21 for on-treatment assessments, at the end of treatment on day 28, and on day 42 for an end-of-study follow-up visit. Blood samples were obtained at these visits for routine biochemical tests and assessment of fasting concentrations of glucose. Body weight, body

mass index, and waist circumferences were measured at screening, day 1, and day 28/end of treatment. Fasting lipid panel, C4, and bile acid levels were determined on day 1 and day 28.

The 5-D itch questionnaire, which measures the degree, duration, direction (improvement or worsening), disability (effect on daily activities), and distribution of itching on a numeric rating scale,⁽¹⁹⁾ as well as the visual analog scale (VAS), which measures the severity of itch on a visual rating scale,⁽²⁰⁾ were both administered at each study visit. The PBC-40 questionnaire was administered for the assessment of quality of life at the initial assessment and at treatment completion.⁽²¹⁾

Adverse events were evaluated at each study visit. Adverse events were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, the MedDRA preferred term, severity, and causal relationship (as assessed by the individual investigators).

OUTCOMES

The primary endpoint of the study was the absolute change in ALP from baseline to day 28 in patients with PBC who have inadequate response to ursodiol. Secondary efficacy endpoints included levels of ALT, AST, γ -glutamyl transpeptidase (GGT), total and direct bilirubin, C4, and bile acids. Other secondary endpoints included results of categorical analysis of ALP levels; symptom of pruritus, as assessed by the 5-D itch questionnaire⁽¹⁹⁾ and VAS pruritus scale⁽²⁰⁾; symptom of fatigue, as measured by the fatigue domain of the PBC-40 score; and changes in quality of life, as measured by the PBC-40 questionnaire.⁽²¹⁾ Changes in serum lipids (total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], and calculated low-density lipoprotein cholesterol [LDL-C]) were assessed as exploratory safety endpoints. Additional exploratory assessments, such as autoimmune aspects of the disease as measured by serum immunoglobulin M (IgM) and immunoglobulin G (IgG) levels and bile-mediated absorption as measured by changes in vitamin D concentrations, were conducted. *Post hoc* analyses to assess the correlation between disease severity (baseline ALP \geq 275 IU/L) and response to study drug, and the correlation between pruritus and chemistry or the individual bile acid species, were also performed. Detailed methods are provided in the Supplementary Information.

STATISTICAL ANALYSIS

On the basis of a two-sided test of equality of binomial proportions at an alpha level of 5%, we calculated that a sample of 12 patients per group would provide the trial with 90% power to detect a significant difference between the study drug group and the placebo group, in agreement with previous studies.^(22,23) Allowing for a 15% drop-out rate per treatment group, it was estimated that 15 subjects were needed to be allocated to each treatment group, requiring a total sample size of 45 for the study.

The efficacy population was used to assess efficacy and pharmacodynamics endpoints and included all randomized subjects who received at least one dose (full or partial) of drug, and had at least one valid, non-missing postdose value for efficacy or pharmacodynamic parameter. Three patients in the 3 mg NGM282 group were excluded from the efficacy analysis: 1 patient withdrew consent, 1 patient missed at least 5 doses, and 1 patient discontinued dosing on day 23 and delayed the final lab draw for 3 days.

Results of laboratory tests, the PBC-40 questionnaire, the 5-D itch scale, and VAS were compared between the NGM282 groups and the placebo group with the use of an analysis of covariance (ANCOVA) model with treatment group as fixed factor, and baseline value as a covariate, using a two-sided test at a 5% level of significance. Categorical secondary endpoints (e.g., percentage of patients achieving at least a 15% reduction from baseline) were analyzed using chi square test or Fisher's exact test. Statistical analyses were done with SAS version 9.4 (SAS Institute, Cary, NC).

Safety and tolerability analyses were conducted using the safety population (including all randomized patients who received at least one dose, full or partial, of study drug and had at least one postdose safety evaluation). All safety endpoints were analyzed descriptively.

ROLE OF THE FUNDING SOURCE

The trial protocol was designed jointly by consultant academic investigators in PBC and representatives of the funder. Data were collected by investigators, and managed, validated, and analyzed by Novotech. The corresponding author and the funder had access to all data in the study and had full responsibility for the decision to submit for publication. All authors participated in the manuscript preparation and provided final approval to submit.

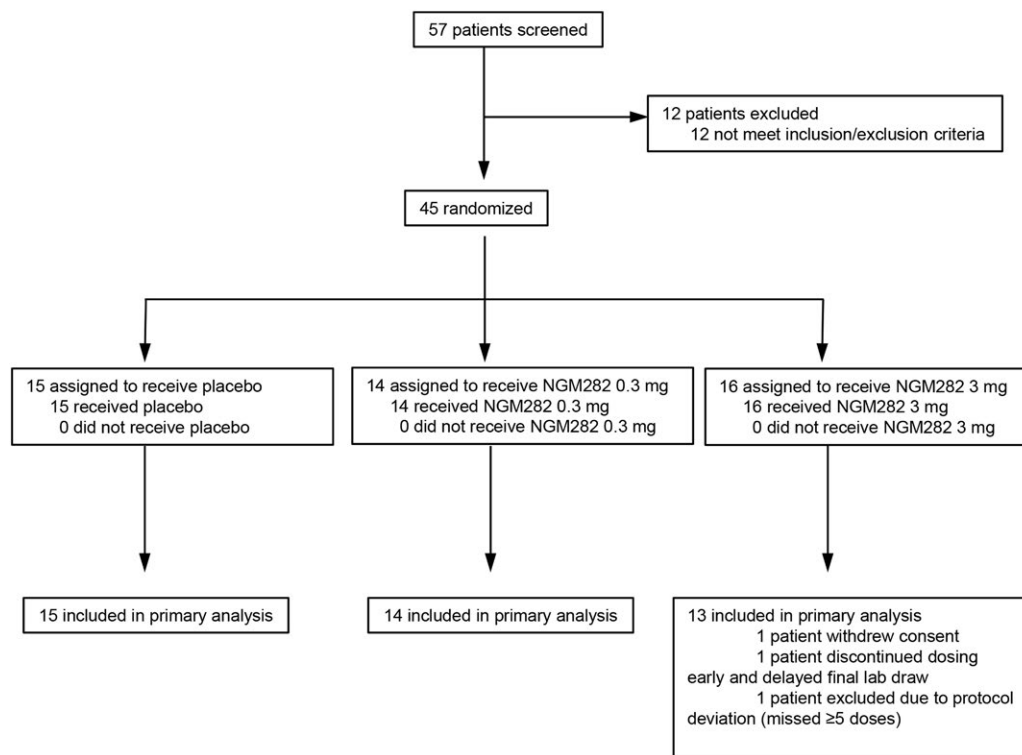


FIG. 1. Trial profile (CONSORT diagram).

Results

PATIENT CHARACTERISTICS

Between March 27, 2014, and December 13, 2014, a total of 57 patients were screened, of whom 45 patients were randomly assigned to receive NGM282 0.3 mg ($n = 14$), NGM282 3 mg ($n = 16$), or placebo ($n = 15$) (Fig. 1). Forty-two patients were included in the efficacy analysis, as 3 patients in the NGM282 3 mg group were excluded from the efficacy analysis (1 patient withdrew consent, 1 patient missed 5 or more doses, and 1 patient discontinued dosing on day 23 and delayed final lab draw for 3 days). A total of 45 patients were included in the safety analysis.

Baseline demographics and disease characteristics of the three groups were similar (Table 1). Similar to other clinical trials of patients with PBC, 91% of the participants were female and 100% were white; the mean age of the patients was 56 years. All patients took ursodiol at baseline and throughout the trial; the mean daily dosage of ursodiol was 15.6 (SD 3.8) mg/kg. Sixty-two percent of the patients reported pruritus at baseline. The mean baseline ALP level was slightly higher in

the NGM282 3 mg group (332.7 [122.2] IU/L) compared with that of the NGM282 0.3 mg (277.8 [117.4] IU/L) and the placebo group (294.4 [135.9] IU/L).

ALKALINE PHOSPHATASE

At day 28, ALP levels were significantly reduced with NGM282 treatment at both 0.3 mg (least squares [LS] mean -51.0 IU/L [standard error (SE) 15.4]) and 3 mg (-66.0 IU/L [SE 16.0]) versus placebo (3.3 IU/L [SE 14.8]), with LS mean differences of -54.3 IU/L (95% confidence interval [CI] -104.2 to -4.5 ; $P = 0.0149$) and -69.3 IU/L (95% CI -120.5 to -18.3 ; $P = 0.0030$), respectively (Table 2). Response to NGM282 was rapid, with a significant decrease in ALP concentrations in both NGM282 groups on day 7, and was sustained throughout the duration of treatment (Fig. 2A and Supporting Fig. S1). Percentage change in ALP levels indicates a significant decrease in both the 0.3 mg (-15.9%) and 3 mg (-19.0%) groups, compared with the placebo group (-1.2%) (Supporting Fig. S1). Fifty percent (7 of 14) of patients receiving NGM282 0.3 mg and 46% (6 of 13) of those receiving NGM282 3 mg achieved at least a 15% reduction in

TABLE 1. BASELINE DEMOGRAPHICS AND CHARACTERISTICS

	Placebo (n = 15)	NGM282, 0.3 mg (n = 14)	NGM282, 3 mg (n = 16)	Total (n = 45)
Age (years)*				
Mean (SD)	55.7 (12.7)	56.6 (8.5)	56.5 (9.8)	56.2 (10.3)
Range	31-75	46-75	38-74	31-75
Gender, n (%)				
Female	13 (86.7%)	13 (92.9%)	15 (93.8%)	41 (91.1%)
Male	2 (13.3%)	1 (7.1%)	1 (6.3%)	4 (8.9%)
Race, n (%)				
White	15 (100.0%)	14 (100.0%)	16 (100.0%)	45 (100.0%)
Ethnicity, n (%)				
Hispanic or Latino	2 (13.3%)	2 (14.3%)	0	4 (8.9%)
UDCA daily dose (mg/kg) Mean (SD)	15.9 (3.8)	15.4 (2.6)	15.4 (5.0)	15.6 (3.8)
ALP Mean (SD), IU/L	294.4 (135.9)	277.8 (117.4)	332.7 (122.2)	300.7 (124.8)
Total bilirubin, mg/dL	0.74 (0.29)	0.82 (0.65)	0.92 (0.50)	0.82 (0.49)
Pruritus, n (%)	10 (66.7%)	9 (64.3%)	7 (53.8%)	26 (61.9%)
Mild, n (%)	4 (40.0%)	6 (66.7%)	2 (28.6%)	12 (46.2%)
Moderate, n (%)	5 (50.0%)	2 (22.2%)	2 (28.6%)	9 (34.6%)
Severe, n (%)	0	1 (11.1%)	3 (42.9%)	4 (15.4%)
Unbearable, n (%)	1 (10.0%)	0	0	1 (3.8%)

Abbreviations: ALP, alkaline phosphatase; SD, standard deviation; UDCA, ursodeoxycholic acid (ursodiol).

TABLE 2. CHANGE IN ALKALINE PHOSPHATASE FROM BASELINE TO DAY 28

	Placebo (n = 15)	NGM282, 0.3 mg (n = 14)	NGM282, 3 mg (n = 13)
Change in ALP, IU/L			
LS mean (SE)	3.3 (14.8)	-51.0 (15.4)	-66.0 (16.0)
LS mean difference (95%CI)		-54.3 (-104.2 to -4.5)	-69.3 (-120.5 to -18.2)
P value		0.0149	0.0030
Percent change in ALP			
LS mean (SE)	-1.2% (3.7%)	-15.9% (3.9%)	-19.0% (4.0%)
LS mean difference (95%CI)		-14.7% (-25.6% to -3.9%)	-17.9% (-29.0% to -6.7%)
P value		0.0092	0.0025
ALP \geq 15% reduction n (%)	1 (6.7%)	7 (50.0%)	6 (46.2%)

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; LS, least squares; SE, standard error.

ALP from baseline, compared with 7% (1 of 15) of patients receiving placebo.

Levels of GGT, a second marker of cholestasis in addition to ALP, were also decreased in both NGM282 groups (Fig. 2B and Table 3). Subgroup analyses revealed that greater reductions in ALP concentration (percent and absolute) were achieved in patients with more severe cholestasis at baseline, as evidenced by responses in patients with baseline levels of ALP

greater than or equal to 275 IU/L or GGT greater than or equal to 150 IU/L (Supporting Table S3).

SERUM TRANSAMINASES

Significant decreases in ALT levels from baseline to day 28 were observed in both NGM282 groups (LS mean difference -17.1 IU/L for 0.3 mg group, $P = 0.002$; -17.5 IU/L for 3 mg group, $P = 0.003$)

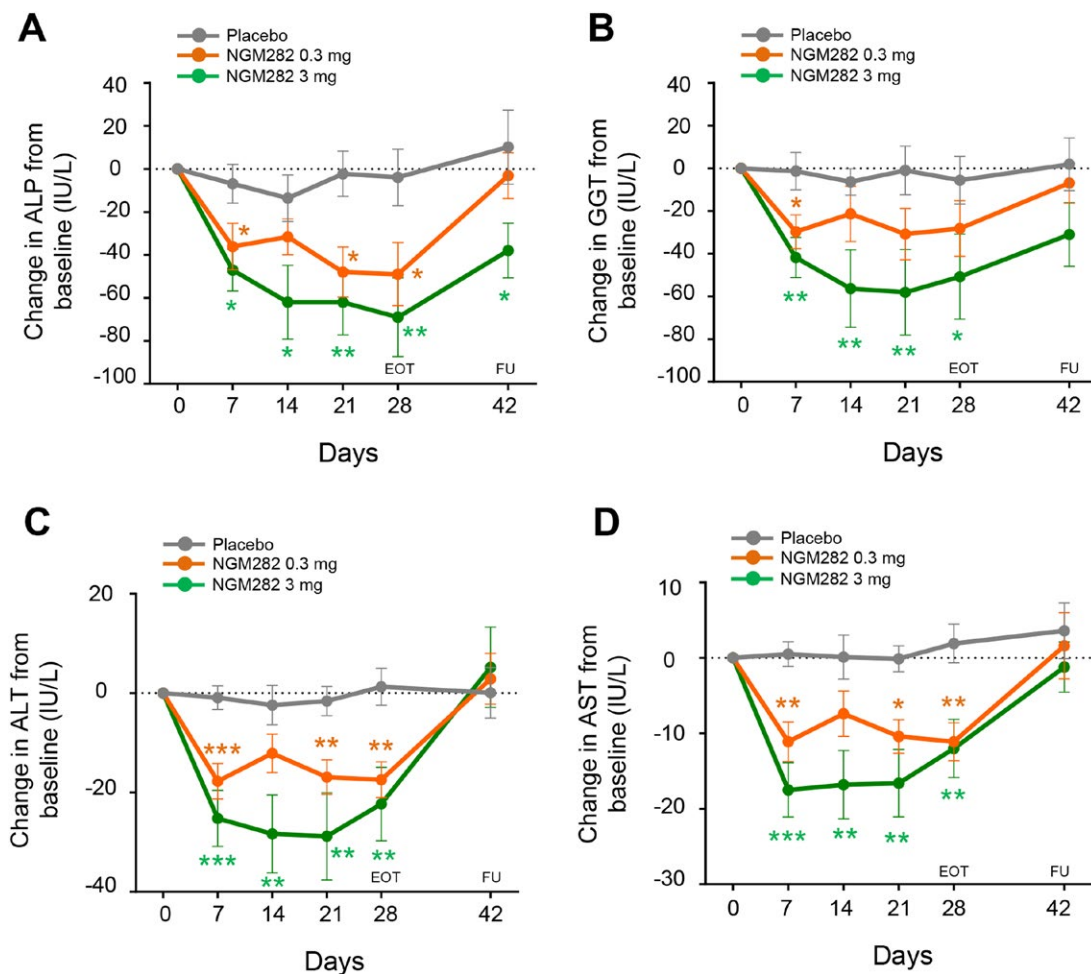


FIG. 2. Change in liver enzymes from baseline over time. (A) Change in ALP over time. (B) Change in GGT over time. (C) Change in ALT over time. (D) Change in AST over time. Data are mean (SE). Abbreviations: EOT, end of treatment; FU, follow up. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$ versus placebo.

(Fig. 2C and Table 3). There were similar decreases in AST levels from baseline to day 28 in both NGM282 groups (LS mean difference -12.7 IU/L for 0.3 mg group, $P = 0.003$; -12.2 IU/L for 3 mg group, $P = 0.007$) (Fig. 2D).

BILE ACIDS

NGM282 treatment for 28 days was associated with dose-dependent decreases in C4 levels in both NGM282 groups, findings that are consistent with suppression of *de novo* bile acid synthesis through the classical pathway. The absolute change in C4 levels from baseline was greater in the 3 mg group (LS mean -14.9 ng/mL, $P < 0.0001$) than in the 0.3 mg group (-3.4 ng/

mL) or the placebo group (2.8 ng/mL) (Fig. 3A). There was a dose-dependent decrease in serum concentrations of total bile acids, but this did not reach statistical significance (Fig. 3B). Among glycine-conjugated and taurine-conjugated primary bile acids (glycocholic acid [GCA], trichloroacetic acid [TCA], glycochenodeoxycholic acid [GCDCA], and taurochenodeoxycholic acid [TCDC]) and secondary bile acids (glycodeoxycholic acid [GDCA], taurodeoxycholic acid [TLCA], glycolithocholic acid [GLCA], and tauroolithocholic acid [TLCA]), only GCA was significantly reduced in the NGM282 3 mg group when compared with the placebo group (Fig. 3C,D). Despite inhibition of the classical pathway of *de novo* bile acid synthesis, no significant changes in serum vitamin D levels, an indicator

TABLE 3. CHANGES IN KEY ENDPOINTS FROM BASELINE TO DAY 28

	Change from baseline to day 28, mean (SD)			LS mean difference (95% CI) (NGM282 vs. placebo)			
	Placebo (n=15)	NGM282, 0.3 mg (n=14)	NGM282, 3 mg (n=13)	NGM282, 0.3 mg	<i>P</i> value	NGM282, 3 mg	<i>P</i> value
Serum liver tests							
ALT (IU/L)	1.3 (14.5)	-17.4 (13.5)	-22.3 (26.6)	-17.1 (-27.4;-6.7)	0.002	-17.5 (-28.5;-6.4)	0.003
AST (IU/L)	1.9 (9.9)	-11.1 (9.4)	-12.0 (13.9)	-12.7 (-20.8;-4.7)	0.003	-12.2 (-20.8;-3.6)	0.007
GGT (IU/L)	-5.6 (47.3)	-28.2 (48.7)	-50.8 (71.9)	-24.2 (-66.2;17.9)	0.25	-46.6 (-89.4;-3.7)	0.03
Total bilirubin (mg/dL)	0.0 (0.1)	-0.2 (0.4)	0.0 (0.2)	-0.2 (-0.3;0.0)	0.07	0.0 (-0.2;0.2)	0.98
Direct bilirubin(mg/dL)	0.0 (0.1)	-0.1 (0.4)	0.0 (0.2)	-0.1 (-0.2;0.1)	0.23	0.1 (-0.1;0.2)	0.31
Albumin (g/L)	0.0 (0.3)	0.0 (0.2)	0.1 (0.2)				
Lipids							
Cholesterol (mg/ dL)	5.5 (22.0)	5.6 (16.4)	-12.5 (24.3)	-1.5 (-17.1;14.1)	0.85	-19.7 (-35.6;-3.7)	0.02
HDL-C (mg/dL)	3.0 (6.4)	-3.4 (7.0)	-0.7 (20.0)	-6.6 (-16.0;2.9)	0.17	-4.3 (-14.2;5.5)	0.38
LDL-C (mg/dL)	2.5 (18.4)	8.1 (15.9)	-10.2 (22.1)	3.9 (-10.0;17.8)	0.58	-13.1 (-27.1;1.0)	0.07
Triglycerides (mg/dL)	-1.7 (24.1)	6.0 (21.5)	-9.5 (28.8)	10.0 (-7.2;27.2)	0.24	-6.3 (-23.8;11.2)	0.47
Bile acid-related							
C4 (ng/mL)	1.2 (20.8)	-1.1 (8.3)	-15.5 (27.1)	-6.3 (-13.8;1.3)	0.10	-17.7 (-25.4;-10.0)	<0.0001
Total bile acids (μ M)	4.3 (15.4)	-0.6 (36.6)	-22.6 (45.1)	2.1 (-21.2;25.5)	0.86	-14.9 (-39.4;9.5)	0.22
Immune-related							
IgM (mg/dL)	-3.9 (47.0)	-31.3 (45.9)	-45.5 (31.6)	-32.5 (-67.1;2.0)	0.06	-46.2 (-80.8;-11.5)	0.01
IgG (mg/dL)	4.0 (132.7)	-74.1 (132.9)	-51.9 (118.2)	-107.1 (-200.1;-14.1)	0.02	-77.1 (-170.6;16.4)	0.10
Other							
INR	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (-0.1;0.1)	0.94	0.0 (0.0;0.1)	0.18
Weight (kg)	0.0 (1.5)	-0.2 (1.7)	0.0 (1.4)				
Pruritus							
5-D itch	-0.2 (3.8)	-1.4 (4.3)	-2.1 (4.7)	-1.4 (-3.9;1.1)	0.27	-1.8 (-4.4;0.9)	0.18
VAS	-6.2 (15.6)	-3.8 (12.9)	-12.6 (24.9)	-0.2 (-8.4;8.0)	0.97	-4.5 (-13.2;4.3)	0.31
PBC-40							
Fatigue	-3.1 (6.2)	-4.6 (10.3)	-1.9 (4.3)	-1.1 (-6.4;4.1)	0.67	0.7 (-4.7;6.0)	0.80
Symptom	-1.2 (3.5)	-0.9 (3.7)	-0.2 (3.4)	-0.2 (-2.6;2.2)	0.86	-0.1 (-2.6;2.4)	0.92
Cognition	-0.1 (2.6)	-1.4 (2.0)	-0.8 (2.4)	-1.2 (-2.9;0.5)	0.17	-1.1 (-2.8;0.6)	0.21
Social	-2.2 (3.7)	-1.4 (3.4)	0.3 (2.9)	0.6 (-1.6;2.8)	0.59	1.8 (-0.5;4.2)	0.12
Emotional	-0.5 (1.9)	-0.4 (1.6)	-0.9 (1.8)	0.2 (-0.9;1.3)	0.75	-0.5 (-1.6;0.6)	0.37

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7 α -hydroxy-4-cholesten-3-one; CI, confidence interval; GGT, gamma glutamyl transferase; HDL-C, high density lipoprotein cholesterol; INR, international normalized ratio; LDL-C, low density lipoprotein cholesterol; LS, least squares; SD, standard deviation; VAS, visual analog scale.

of fat-soluble vitamin absorption, were observed in NGM282-treated patients (Supporting Table S4).

IMMUNOGLOBULINS

Serum concentrations of IgM and IgG were elevated at baseline in all groups and were reduced to a greater extent in the NGM282 treatment groups than in the

placebo group (Fig. 4). As compared with the placebo treatment, the IgM levels decreased from baseline in the NGM282 0.3 mg (LS mean difference -32.5 mg/dL, *P* = 0.06) and 3 mg groups (-46.2 mg/dL, *P* = 0.01). Levels of IgG also decreased in patients treated with 0.3 mg (LS mean difference -107.1 mg/dL, *P* = 0.02) and 3 mg (-77.1 mg/dL, *P* = 0.10) of NGM282.

LIPID PROFILES

Patients at baseline had elevated levels of TC, LDL-C and HDL-C, and normal to low levels of TGs. A dose-dependent decrease in TC of -1.5 mg/dL and -19.7 mg/dL ($P = 0.02$) was observed in NGM282 0.3 mg and 3 mg groups versus placebo (Table 3). LDL-C levels in the NGM282 3 mg group showed a trend toward improvement (-13.1 mg/dL), albeit not significant ($P = 0.07$). No significant changes in HDL-C or TGs were detected in NGM282-treated patients (Supporting Fig. S2).

OTHER CLINICAL PARAMETERS

There were no significant differences between the NGM282 groups and the placebo group with respect to levels of bilirubin or albumin, body weight, or international normalized ratio (Table 3). Other clinical laboratory parameters showed no remarkable changes during the course of the study. Measures of the vital signs were similar among the three groups and there were no abnormal clinically significant electrocardiogram results for any of the patients.

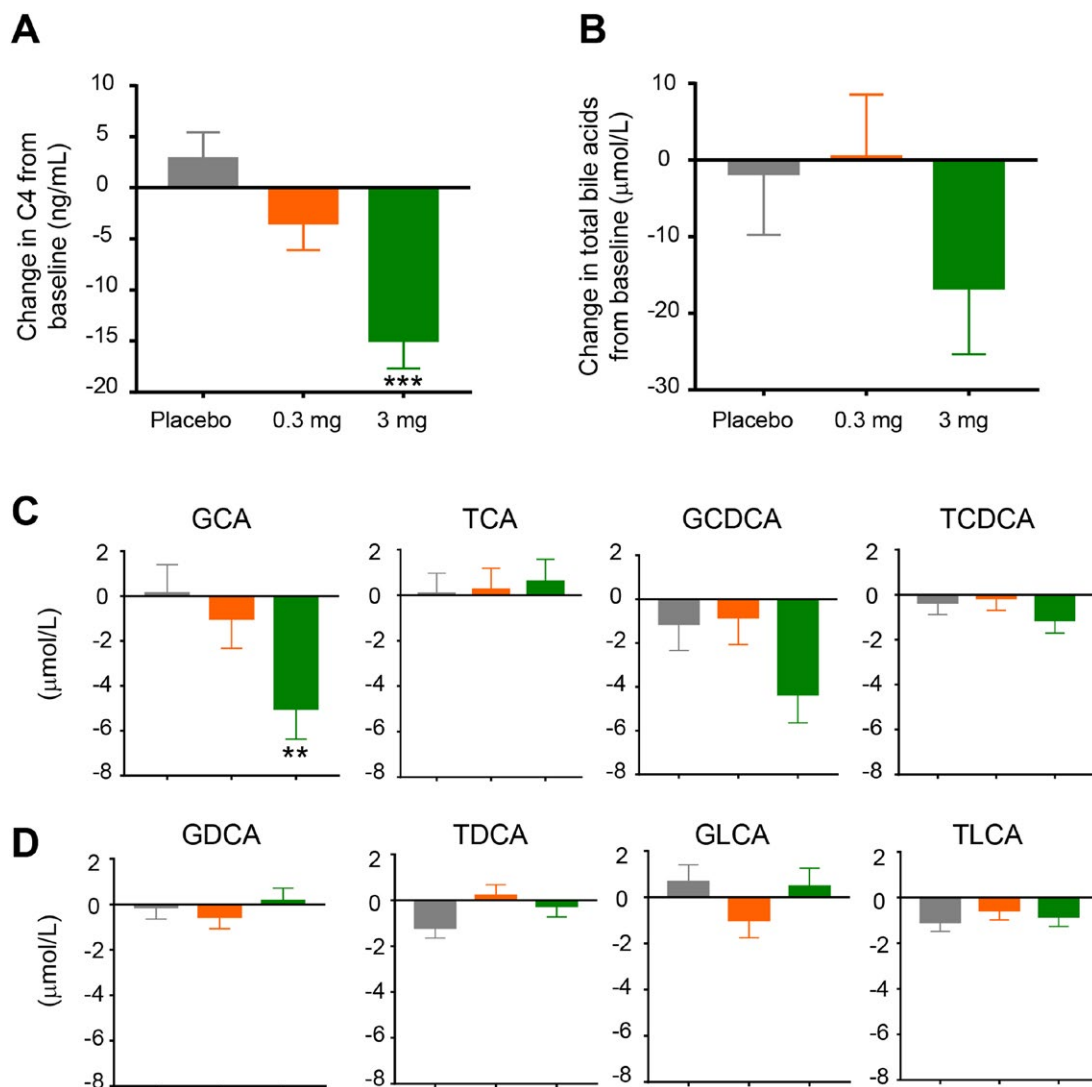


FIG. 3. Change in bile acid-related parameters from baseline to day 28. (A) Change in C4 from baseline to day 28. (B) Change in total bile acids from baseline to day 28. (C) Change in conjugated primary bile acids from baseline to day 28. (D) Change in conjugated secondary bile acids from baseline to day 28. Data are mean (SE). *** $P < 0.001$, ** $P < 0.01$, versus the placebo group by ANCOVA.

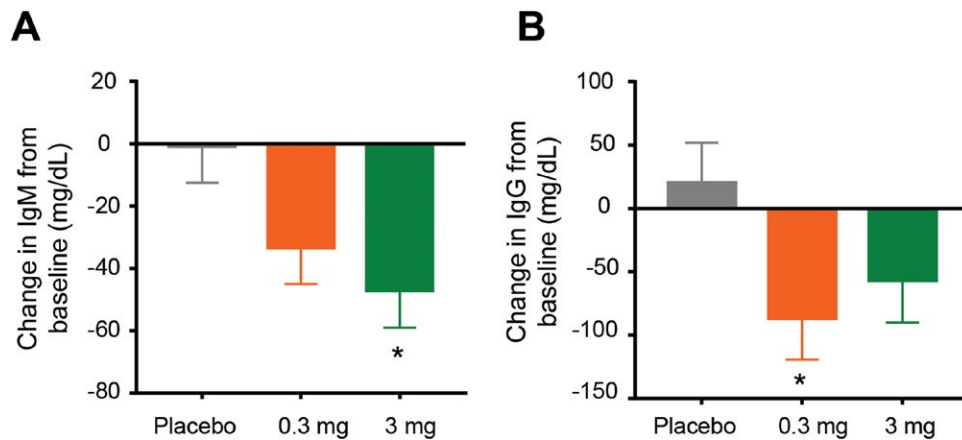


FIG. 4. Change in immune-related parameters from baseline to day 28. (A) Change in IgM from baseline to day 28. (B) Change in IgG from baseline to day 28. Data are mean (SE). * $P < 0.05$ versus the placebo group by ANCOVA.

TOLERABILITY

Overall, NGM282 was well-tolerated in PBC patients. Almost all adverse events were grade 1 (mild) to grade 2 (moderate) in severity, transient, and similar in the NGM282 and placebo groups for all organ classes and symptoms, with the exception of gastrointestinal disorders (Table 4). A higher incidence of diarrhea/loose stools was observed in the NGM282 0.3 mg and 3 mg groups than in the placebo group. Only 1 patient withdrew from the study after randomization: After receiving 16 days of NGM282 3 mg treatment, the patient presented with flu-like symptoms on the day following the last dose of treatment, withdrew consent, and terminated participation in the study. One patient in the placebo group completed all treatments but did not complete the study due to severe diarrhea and was lost to follow-up. No difference in the assessment of injection site reaction was noted among any of the three treatment groups predose versus postdose. A single serious adverse event occurred during the trial when 1 patient in the NGM282 3 mg group had dizziness resulting in hospitalization. This condition was resolved without sequelae and deemed unrelated to treatment by the investigator. There were no deaths or potentially life-threatening adverse events reported during the study.

PRURITUS, FATIGUE, AND QUALITY OF LIFE

Pruritus was monitored at baseline and throughout the study in all patients using the 5-D itch

questionnaire and the VAS. Overall, there was good agreement between the VAS and 5-D itch methods in measuring categorical change from baseline in pruritus severity ($k = 0.56$, $P < 0.0001$). Changes from baseline in the 5-D itch and VAS scores for pruritus showed no significant differences when comparing NGM282 groups with the placebo group (Table 3 and Supporting Table S5). Two patients in the placebo group versus 1 patient in the NGM282 0.3 mg group and none in the 3 mg group developed worsening of pruritus during the study by the 5-D itch method. One patient in the placebo group versus none in either the NGM282 0.3 mg or 3 mg group developed worsening of pruritus during the study by VAS method. No patient had their dose reduced or elected to discontinue treatment due to pruritus. These results demonstrate that treatment with NGM282 does not induce or worsen pruritus symptoms in PBC patients.

Post hoc analysis revealed that the severity of pruritus at baseline did not correlate with total serum bile acids, although it did correlate with ALP, ALT, and bilirubin levels (Supporting Fig. S3). We further investigated the correlation between serum levels of individual bile acids and the severity of cholestatic pruritus. Baseline severity of pruritus correlated positively with levels of conjugated primary bile acids (e.g., GCA, TCA, GCDCA, and TCDCA) by both the 5-D itch and VAS methods (Supporting Fig. S4). Change from baseline in pruritus severity was found to positively correlate with GCA levels by VAS, whereas it was more broadly correlated with levels of GCA and GCDCA by the 5-D itch method (Supporting Fig. S5).

TABLE 4. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

	Placebo (n = 15)	NGM282, 0.3 mg (n = 14)	NGM282, 3 mg (n = 16)
Treatment emergent adverse events			
At least one TEAE, n (%)	12 (80.0%)	9 (64.3%)	13 (81.3%)
Treatment emergent adverse events by severity			
Grade 1, n (%)	7 (46.7%)	8 (57.1%)	6 (37.5%)
Grade 2, n (%)	5 (33.3%)	1 (7.1%)	6 (37.5%)
Grade 3, n (%)	0 (0%)	0 (0%)	1 (6.3%)
Grade 4, n (%)	0 (0%)	0 (0%)	0 (0%)
Most common ($\geq 10\%$) adverse events, n (%)			
Diarrhea	1 (6.7%)	3 (21.4%)	4 (25%)
Loose stools / fecal urgency	1 (6.7%)	0	2 (12.5%)
Nausea	1 (6.7%)	2 (14.3%)	2 (12.5%)
Increased appetite	0	0	4 (25.0%)
Abdominal pain / discomfort	4 (26.7%)	0	2 (12.5%)
Dyspepsia	2 (13.3%)	1 (7.1%)	0
Feces discolored / pale	0	0	2 (12.5%)
Vitamin D deficiency	0	0	2 (12.5%)
Headache	1 (6.7%)	2 (14.3%)	4 (25.0%)
Dizziness	1 (6.7%)	1 (7.1%)	2 (12.5%)
Mouth ulceration	0	2 (14.3%)	1 (6.3%)
Dry eye	0	2 (14.3%)	0
Fatigue	1 (6.7%)	0	2 (12.5%)
Upper respiratory tract infection	3 (20.0%)	2 (14.3%)	1 (6.3%)
Injection site bruising / erythema	3 (20.0%)	1 (7.1%)	2 (12.5%)
Serious adverse event			
At least one serious adverse event	0 (0%)	0 (0%)	1 (6.3%)
Treatment-related adverse events			
At least one treatment-related AE, n (%)	7 (46.7)	3 (21.4%)	11 (68.8)

NGM282 did not result in any significant worsening in symptoms as measured by the PBC-40 questionnaire on day 28 (Table 3 and Supporting Table S6). Overall, there were no significant changes in quality of life, as assessed by the PBC-40 questionnaire, among patients who were treated with NGM282.

Discussion

In this double-blind, randomized, placebo-controlled phase 2 trial, treatment with NGM282, an engineered analogue of FGF19, reduced ALP levels, as well as markers of cholestasis, hepatocellular injury, immunity and inflammation, in patients with PBC who had inadequate response to ursodiol. ALP levels decreased in a significant, progressive, dose-dependent manner from baseline to day 28 in both the 0.3 mg and 3 mg NGM282 treatment groups. Almost half of the patients in the NGM282 groups, as compared with 7% of those in the placebo group, achieved at least a 15%

reduction in ALP from baseline. Significant decreases in the levels of ALT, AST, and GGT were also observed in patients treated with NGM282. NGM282 was generally safe and well tolerated. Most treatment-related adverse events were gastrointestinal and mild in severity. The mechanism by which an FGF19 analogue could cause loose or frequent stools is unknown and requires further investigation.

Recent data have revealed the importance of ALP as a surrogate of clinical outcomes in patients with PBC.⁽⁴⁾ Elevated levels of ALP are prognostic of worse clinical outcomes in PBC, with lower levels of ALP associated with longer transplant-free survival and improved overall survival. As a prognostic marker rather than a validated surrogate endpoint, ALP is considered “reasonably likely” to predict clinical outcome by the Food and Drug Administration for accelerated approval under subpart H/E.⁽²⁴⁾ Despite the fact that meta-analyses of randomized clinical trials of a number of drug classes have not shown consistent

improvement in ALP and lower risk of liver complications or death in PBC patients,⁽²⁵⁻²⁸⁾ ALP-lowering is regarded as an important treatment strategy and the primary efficacy outcome for clinical trials in PBC. Although patients in the NGM282 group experienced reductions in ALP levels, NGM282 treatment did not result in a significant change in the proportions of patients achieving ALP normalization or less than 1.67× ULN. Treatment with NGM282 was also associated with decreases in the levels of IgM and IgG, indicative of potential immune disease-modifying activity. Results from this study demonstrate that an FGF19 analogue can safely modulate disease activity in patients with PBC.

FGF19 expression is induced in response to FXR activation in the ileum.⁽¹⁰⁾ FXR is increasingly recognized as a master regulator of bile acid metabolism in human physiology and health, and synthetic activators of FXR have been recently approved or are currently in clinical development for treatment of chronic liver diseases.⁽²⁹⁾ A significant component of FXR-mediated biological activity is attributed to the induction of endogenous FGF19. Given that mice expressing a FGF19 transgene develop hepatocellular carcinomas,⁽¹⁴⁾ the potential risk of tumorigenicity in patients treated with FXR agonists may need to be monitored. In contrast, NGM282 is a nontumorigenic analogue of FGF19 that retains its metabolic activity.^(13,15) Furthermore, FXR activation alters transcriptome beyond the induction of endogenous FGF19, affecting numerous target genes including bile acid transporters in the liver.⁽³⁰⁾ The long-term consequence of these transcriptional changes is uncertain.

Patients with PBC typically present with hyperlipidemia, showing elevated levels of TC, HDL-C and LDL-C,⁽³¹⁾ which is not associated with increased atherosclerotic diseases in this population.⁽³²⁾ Treatment with 3 mg NGM282 significantly reduced levels of TC, primarily due to reductions in LDL-C. No changes in levels of either HDL-C or TGs were observed in NGM282-treated patients. In contrast, OCA, a recently approved therapy for PBC, was associated with reduced levels of HDL-C, with unclear implications on long-term cardiovascular outcome.⁽⁸⁾

Pruritus is the most common symptom in patients with PBC, and can be further exacerbated by OCA, a recently approved therapy.^(8,22,23) Although the pathogenesis of pruritus is poorly understood, proposed pruritogens include bile acids, lysophosphatidic acid/autotaxin, and modulators of the TGR5 receptor,

opioidergic, or serotonergic pathways.^(33,34) In the current study, treatment with NGM282 did not worsen pruritus. The severity of pruritus at baseline had a significant positive correlation with liver chemistry parameters, although there was no correlation among any of the liver chemistry parameters and the change in pruritus from baseline. Both baseline severity of pruritus and changes in pruritus correlated with serum levels of conjugated primary bile acids, but not secondary bile acids or total serum bile acid levels. Interestingly, changes in GCA levels correlated with changes in pruritus, and consequently, GCA concentration may serve as a marker of pruritus response to treatment. Our data suggest that direct suppression of hepatic bile acid synthesis may have differential effects on pruritus by altering the amount and composition of bile acids present in blood and tissues, although further evaluation in trials of longer duration are warranted.

This study has a number of strengths. First, this is the first randomized, placebo-controlled trial to report the effect of an FGF19 analogue in patients with PBC. Second, this multicenter, international study population included patients with inadequate response to ursodiol, who are more difficult to treat and at greatest risk for adverse outcomes. Third, pruritus and other symptoms of PBC were monitored throughout the trial and detailed records of these data were collected for analysis.

This study also has some limitations. In particular, the results reported here were collected during a study that involved a short duration of treatment (28 days) with NGM282, and consequently, the corresponding analysis was limited to surrogate biomarkers and symptoms. The sample size was similar to previous proof-of-concept studies, albeit smaller than some later-stage phase 2 studies. Liver biopsies are not routinely conducted to assess disease progression in patients with PBC; therefore, assessment of fibrosis was not performed in this trial. Finally, the study population consisted entirely of Caucasian patients.

In conclusion, 28 days of treatment with NGM282, administered subcutaneously in patients with PBC who had inadequate response to ursodiol, resulted in improvement in the serum levels of ALP, ALT, AST, GGT, IgG, IgM, and other biochemical markers of disease. There was no worsening of pruritus, either in incidence or severity, in response to NGM282 treatment. Future studies should focus on assessing the durability of biochemical response and whether these treatment-related changes can translate into improved

clinical outcomes, such as decreases in hepatic decompensation or death, or the need for liver transplantation.

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Supporting Information

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