A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, MULTIPLE CENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF NGM282 ADMINISTERED FOR 12 WEEKS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC)

PROTOCOL NUMBER 15-0106

for

NGM Biopharmaceuticals, Inc.

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STUDY IDENTIFICATION

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ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACG	American College of Gastroenterology
ADA	anti-drug antibody
AE	adverse event
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration–time curve
$C_{2h\ post\text{-}dose}$	concentration at 2 hours post-dose
C4	7-alpha-hydroxy-4-cholesten-3-one
CA19-9	carbohydrate antigen 19-9
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
C_{max}	maximum drug concentration
CRO	contract research organization
C_{trough}	trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DVM	data validation manual
EASL	European Association for the Study of the Liver
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
ERCP	endoscopic retrograde cholangiopancreatography

FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IA	Interim Analysis
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
IgG4	immunoglobulin G4
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
ISR	injection-site reaction
[redacted]	[redacted]
LDL	low-density lipoprotein
LISSA	local injection-site symptom assessment
LS	least square
LLT	Lowest Level Term (MedDRA)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MRCP	magnetic resonance cholangiopancreatography
NAb	neutralizing antibody
NASH	nonalcoholic steatohepatitis
NGM	NGM Biopharmaceuticals, Inc.
NGM282	a recombinant protein of 190 amino acids; engineered variant of humanized FGF19 under development for the treatment of type 2 diabetes
NOAEL	no-observed-adverse-effect level

NRS	Numeric Rating Scale
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PBC	primary biliary cirrhosis
PD	pharmacodynamics; pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetics; pharmacokinetic
PPS	Per Protocol Set
PSC	primary sclerosing cholangitis
PT	preferred term
SAE	serious adverse event
SAERF	Serious Adverse Event Report Form
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
SUSAR	suspected, unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UA	urinalysis
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
U.S.	United States
WHO-DD	World Health Organization Drug Dictionary Enhanced

1 SYNOPSIS

Title of Study:	A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for 12 Weeks in Patients with Primary Sclerosing Cholangitis (PSC)
Protocol Number:	15-0106
Phase:	2
Investigational Product:	NGM282
Objectives:	Primary Objective: • Evaluate the treatment effect of NGM282 as measured by the mean change in alkaline phosphatase (ALP) from Baseline to Week 12 in patients with PSC. Secondary Objectives: • Assess the safety and tolerability of NGM282 in patients with PSC with 12 weeks of treatment. • Evaluate the percentage change from Baseline at Week 12 in ALP. • Evaluate the absolute and percentage changes from Baseline at Week 12 of the following: o Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total, direct), and gamma-glutamyl transpeptidase (GGT) o Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides o 7-alpha-hydroxy-4-cholesten-3-one (C4) and serum bile acids o Bile-mediated absorption as measured by fat-soluble vitamins and fecal fat content • Evaluate changes in pruritus and fatigue • Compare NM282 versus placebo with respect to the incidence and severity of: o Inflammatory bowel disease (IBD)-associated intestinal symptoms during the study period. o Acute cholangitis during the study period. • Evaluate the exposure of 1 mg and 3 mg of NGM282 in patients with PSC. • Compare the dose-related changes in safety, tolerability, and pharmacodynamic (PD) parameters. Exploratory Objectives: • [redacted]

Methodology/ Study Design:	This is a multiple-center evaluation of NGM282 in a randomized, double-blind, placebo-controlled, parallel-group study when administered for 12 weeks as a daily subcutaneous (SC) injection in patients with PSC. Approximately 60 patients will be randomized across approximately 40–45 sites worldwide. Patients to be studied will have confirmed PSC as defined by an elevated ALP and either cholangiography or liver histology consistent with PSC. The presence of IBD is allowed as well as treatment with a stable regimen of biologic, immunosuppressant, or systemic corticosteroid therapy. Ursodeoxycholic acid (UDCA) therapy is allowed at stable doses for at least 12 weeks and < 27 mg/kg/day. Patients with decompensated cirrhosis, cholangiocarcinoma (diagnosed or suspected), acute cholangitis, or recently placed bile-duct stents will be excluded from this study. All patients with concomitant IBD will be required to have had a colonoscopy within 12 months of Screening with no evidence of dysplasia. All patients will undergo a magnetic resonance cholangiopancreatography (MRCP) at Screening. Patients will sign the Informed Consent Form (ICF) at or prior to the Screening Visit, and will undergo screening assessments to verify eligibility for the study (up to 6 weeks). On Day 1, subjects will be randomized into one of the three treatment arms (NGM282 1 mg, NGM282 3 mg, or placebo) in a 1:1:1 ratio. Subjects will be stratified at randomization, according to concurrent UDCA or no-UDCA status to ensure an even distribution across the three groups. Study-drug self-administration instructions and training will be provided to the subjects and a weekly study-drug kit will be dispensed. Treatment assignment will be blinded to the sites, subjects, Sponsor, and Medical Monitor throughout the study period. The first dose (Day 1) and doses at Weeks 1, 2, 4, 8, and 12 will be self-administered in the clinic, with all other doses through Week 12 self-administered at home. Self-administration should occur at approximately the same time in the morning for every dose in both the clinic and at home. Subjects will return to the clinic on Weeks 1, 2, 4, and 8 for on-treatment assessments and to receive weekly study-drug kits. Week 12 will be the End of Treatment (EOT) clinic visit. Subjects will return to the clinic at Week 16 (or 4 weeks after last dose) for an End of Study (EOS) follow-up visit.
Number of Subjects:	Approximately 60 subjects will be randomized.
Number of Study Sites:	Approximately 40–45 sites worldwide.
Test Product(s), Dose, and Mode of Administration:	The NGM282 final product will be supplied in pre-filled syringes intended to deliver 0.3 mL of 1 mg NGM282, 3 mg of NGM282, or placebo for SC injection. Subjects will be instructed to self-administer SC injections of study drug at approximately the same time in the morning.
Duration of Treatment:	Patients will sign the ICF at or prior to the Screening Visit, and will undergo screening assessments to verify eligibility for the study (up to 6 weeks). All subjects will be treated with NGM282 or placebo for 12 weeks, and will be monitored after completing their final dose of NGM282 or placebo (4 weeks). The total duration of individual participation will be approximately 22 weeks.

Criteria for Evaluation: Safety	Safety and tolerability will be assessed by monitoring adverse events (AEs) and concomitant medications; conducting local injection-site symptom assessments (LISSAs), physical examinations (PEs), and 12-lead electrocardiograms (ECGs); measuring vital signs; and collecting clinical laboratory assessments.
Criteria for Evaluation: Pharmacokinetics	Pharmacokinetics (PK) will be analyzed to determine the steady-state trough and 2-hour post-dose NGM282 levels in PSC patients and to compare to the levels in normal volunteers and in patients with other medical conditions (primary biliary cirrhosis, nonalcoholic steatohepatitis [NASH], and type 2 diabetes [T2D]), and to explore PK/PD correlations in terms of drug efficacy, toxicity, and other parameters of the disease activity.

Criteria for Evaluation: Efficacy & Pharmacodynamics	The primary efficacy endpoint for this study will be the mean change in ALP in patients with confirmed PSC after 12 weeks of treatment.
	The following secondary endpoints will be investigated:
	Efficacy and PD
	• Percent change from Baseline at Week 12 in ALP
	• Changes and percent changes from Baseline at Week 12 in
	  o ALT, AST, bilirubin (total, direct), and GGT
	  o C4 and serum bile acids
	• Bile-mediated absorption as measured by fat-soluble vitamins and fecal fat content
	• Changes in pruritus and fatigue, as measured by the weekly mean of the daily Numeric Rating Scale scores
	• Incidence and severity of IBD-associated intestinal symptoms
	• Incidence and severity of acute cholangitis
	Changes in cholestatic symptoms, safety, and tolerability
	• Safety and tolerability of NGM282 in subjects with PSC with 12 weeks of treatment though the prevalence of AEs, LISSA results, changes in clinical safety laboratory assessments, changes in vital signs, changes in ECGs, changes in physical examination, and the prevalence of concomitant medications
	• The absolute and percentage changes from Baseline at Week 12 of total cholesterol, HDL cholesterol, and LDL cholesterol
	Pharmacokinetics
	• The exposure of 1 mg and 3 mg of NGM282 in subjects with PSC after 12 weeks of treatment
	Exploratory pharmacodynamics
	• [redacted]

Statistical Methods:	The primary efficacy analysis will consist of comparing each NGM282 treatment group against the placebo group, within a mixed-effect model repeated measures analysis of the primary efficacy endpoint. The primary efficacy analysis will be repeated for each continuous secondary efficacy endpoint. The categorical secondary efficacy endpoints will be analyzed using confidence intervals of treatment differences. The safety and tolerability endpoints will be summarized. At the planned interim analysis, the evidence regarding the safety and efficacy of NGM282 in the PSC indication will be assessed, in order to evaluate the appropriateness of continuing the study.

2 INTRODUCTION

2.1 BACKGROUND

2.1.1 Primary Sclerosing Cholangitis (PSC)

PSC is a chronic cholestatic liver disease that is characterized by diffuse inflammation and fibrosis of the bile ducts (Chapman et al. 2010). The intra and/or extrahepatic bile ducts can be affected; ongoing destruction often leads to cholestasis, advanced fibrosis, liver cirrhosis, and eventually liver failure with its consequent complications such as portal hypertension and increased risk of malignancy, in particular cholangiocarcinoma (Ali et al. 2015). PSC is frequently associated with inflammatory bowel disease (IBD), more frequently ulcerative colitis (UC) than Crohn's disease, with the prevalence ranging from 21% to 80%, depending on screening programs and nationality (Tsaitas et al. 2014).

The disease is slowly progressive and its course may be variable from one patient to another (Angulo and Lindor 1999). Males are affected twice as often as females and are usually diagnosed with the disease in their fifth decade of life (Molodecky et al. 2011). Patients are often diagnosed incidentally, and nearly 50% are asymptomatic at the time of diagnosis (Hirschfield et al. 2013). Despite being asymptomatic, patients with PSC have a shorter average time of survival compared with matched controls from the general population.

Various review articles that consider the epidemiology of PSC on a global basis note a high degree of variability in prevalence and incidence figures (0.02–1.6 per 10,000 and 0–0.13 per 10,000, respectively) with the greatest incidence and prevalence in Scandinavia, the UK, and the U.S. (Boonstra et al. 2012). Several studies have suggested an increasing trend in PSC incidence and prevalence rates. However, these apparent increases are more likely due to increasing awareness of the disease, greater understanding of the coincidence with IBDs, and improved diagnostics revealing more patients at the asymptomatic stage of disease.

The etiology of PSC remains unclear although it is likely caused by multiple factors. These include autoimmunity, portal bacteremia, absorption of toxins, ischemic injury, viral infections, toxic bile acids, and a genetic predisposition (Hirschfield and Karlsen 2014). The pathogenesis of PSC involves the exposure of genetically predisposed individuals to an environmental antigen that subsequently elicits an aberrant immune response, leading to development of the disease.

The diagnosis of PSC is challenging as most patients are asymptomatic or display nonspecific symptoms (Andraus et al. 2011). The diagnosis of PSC is typically achieved after a complication such as cholangitis or hepatic dysfunction occurs. Patients may experience periods of remission. The severity and symptoms can vary between individuals who suffer from PSC as it is made up of more than one disease subtype, which include small-duct PSC, classic PSC, and immunoglobulin G4 (IgG4) PSC. A diagnosis of PSC is

made in patients with unexplained elevated serum alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) and when magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) show characteristic bile-duct changes with multifocal strictures and segmental dilatations, and causes of secondary sclerosing cholangitis and other cholestatic disorders are excluded (Lindor et al. 2015). A marked increase in serum autoantibody levels occurs in patients with PSC as well, with anti-neutrophil cytoplasmic antibodies (ANCAs) in 87%, anticardiolipin antibodies in 66%, and antinuclear antibodies in 53%. Patients who present with clinical, biochemical, and histological features compatible with PSC but have normal cholangiograms are classified as having small-duct PSC. Where a patient presents with IBD with increased liver test values, they should be immediately suspected of having concurrent PSC. However, these abnormal values do not reflect the severity of the underlying disease and at present there is no specific diagnostic serologic test for PSC.

Changes observed from liver biopsies in PSC patients in general are nonspecific although periductal concentric ("onion skinning") fibrosis is a typical finding and so may support the diagnosis of PSC (Chapman et al. 2010; Lindor et al. 2015). If a patient is suspected of having small-duct PSC or there are concerns that the patient also has autoimmune hepatitis then liver biopsy can be used to help diagnose PSC. PSC has been described to progress through four stages:

- Stage 1: Lymphocyte infiltration and epithelial cell degeneration of the bile duct in the portal triads
- Stage 2: Inflammatory infiltrates and early fibrogenesis in the periportal parenchyma with piecemeal necrosis and enlarged bile ducts with minimal ductopenia
- Stage 3: Portal-to-portal bridging fibrosis with severe degeneration of the ducts and ductopenia
- Stage 4: End-stage liver disease with frank cirrhosis

The most frequent clinical symptoms in PSC are fatigue and pruritus, with other less common symptoms being abdominal discomfort, jaundice, and weight loss (Benito de Valle et al. 2012). Other symptoms may include vitamin deficiencies and bone disease and, in advanced liver disease, portal hypertension, coagulopathy, and liver failure (Hirschfield et al. 2013). Secondary complications of PSC include bacterial cholangitis, gall stones, and malignancy—in particular cholangio- and hepatocellular carcinoma (Lindor et al. 2015).

2.1.2 Treatment of PSC

Currently, the primary therapy for PSC is endoscopic or radiologic dilatation or stenting of bile-duct strictures targeted at reducing or halting progression of the disease (Kaya et al. 2001; Lindor et al. 2015). Although there is no established or approved pharmacologic therapy for PSC, ursodeoxycholic acid (UDCA) has been studied in multiple prospective

clinical studies and is considered the only pharmacologic treatment option with a significant biochemical response. However, the data supporting a beneficial effect on clinical endpoints and long-term outcomes remain conflicting. Several prospective, randomized controlled trials have evaluated different doses of UDCA ranging from 10–15 mg/kg/day to 17–23 mg/kg/day and most recently up to 28–30 mg/kg/day (Triantos et al. 2011). Currently, neither the American Association for the Study of Liver Diseases (AASLD) nor the European Association for the Study of the Liver's (EASL) Clinical Guidelines makes a recommendation for general use of UDCA in PSC (Beuers et al. 2009; Chapman et al. 2010). However, recent American College of Gastroenterology (ACG) guidelines have put a limitation on doses only above 27 mg/kg/day with a suggestion that intermediate doses may offer an improved biochemical response associated with improved outcomes (Lindor et al. 2015). ALP is the traditional marker of cholestasis and biochemical response to UDCA in PSC and recent studies have demonstrated it as predictive of disease progression and outcomes of treated and untreated patients. Patients with PSC and very high serum ALP activity usually fail to respond to UDCA therapy, whereas patients with PSC with low serum ALP activity treated with UDCA have an excellent long-term prognosis (Stanich et al. 2011). Guidance from clinical experts has suggested a trial of 6 months of UDCA and to continue treatment if the ALP is reduced by 40% from baseline or < 1.5 x upper limit of normal (ULN) and no significant tolerability or safety issues are observed (Tabibian and Lindor 2014).

A number of immunosuppressive (prednisolone, budesonide, azathioprine, cyclosporine, methotrexate, mycophenolate, tacrolimus), anti-inflammatory (pentoxifylline, etanercept, other anti-TNF monoclonal antibodies) and anti-fibrotic (colchicine, penicillamine, pirfenidone) agents approved for other indications have been evaluated as primary or adjunctive treatments for PSC (Hirschfield et al. 2013). None of these agents have demonstrated a significant clinical benefit in the treatment of PSC. Small pilot studies are currently studying the role of antibiotics in PSC, with liver enzyme reductions seen after treatment with metronidazole or oral vancomycin, but this approach is still considered experimental.

Orthotopic liver transplantation remains the only clinically proven treatment, shown to prolong survival with 5-year survival rates of up to 80% (Williamson and Chapman 2015). However, PSC recurs in the donor liver in approximately 20%–25% of patients at 5 years. Additionally, patients with PSC have a 10%–15% lifetime risk of developing cholangiocarcinoma (Rizvi et al. 2015). Liver transplantation has been a disappointment in the treatment of cholangiocarcinoma, with significantly lower patient survival due to recurrent disease (Neumann and Schmeding 2015). Thus, most transplant centers are not transplanting these patients outside of study protocols.

Therefore, a significant unmet medical need still exists for novel agents for the treatment of PSC and its subsequent complications.

2.1.3 Therapeutic Rationale for NGM282 in PSC

Fibroblast growth factor 19 (FGF19) is a naturally occurring protein selectively expressed and secreted in the gastrointestinal tract. FGF19 functions as an ileal hormone that directly regulates the classic pathway of hydrophobic ("toxic") bile acid synthesis by altering the activity of the CYP7A1 enzyme through binding to the FGFR4–β-klotho co-receptor complex in the liver (Goetz et al. 2007; Kurosu et al. 2007). Hepatic bile acid synthesis is largely controlled by a complex enterohepatic feedback regulatory mechanism that is directly mediated by FGF19. Changes in the FGF19 activity have been shown to significantly alter both the size and composition of the bile acid pool (Russell 2003). Both nonclinical and clinical studies support the role of FGF19 in the regulation of classical bile acid synthetic pathways (Lundasen et al. 2006; Schaap et al. 2009; Kir et al. 2011; Lenicek et al. 2011; Pattni et al. 2012). Recent clinical data have demonstrated a relationship between FGF19 levels and PSC. FGF19 mRNA expression and gall bladder levels of FGF19 are reduced in PSC versus non-PSC patients (Zweers et al. 2012). These reduced FGF19 levels in bile may contribute to chronic inflammation and fibrosis in both the intra- and extrahepatic bile ducts of PSC patients through the dysregulation of FGF19-mediated bile acid synthesis.

NGM282 is a recombinant protein of 190 amino acids with a molecular weight of 21.3 kDa and an amino acid sequence 95.4% identical to that of human FGF19. Extensive in vivo structure–activity relationship analyses have been conducted to define and manipulate the distinct functional domains in FGF19 protein that are responsible for its metabolic and proliferative features. More than 160 variants of human FGF19 were engineered, of which NGM282 was selected as the clinical candidate based on robust efficacy with no evidence of the proliferative activity previously observed in *db/db* mice.

NGM282 effectively mimics the actions of FGF19 on bile acid synthesis through the binding of FGFR4c–β-klotho co-receptor (Study 12-MP-NGM282-1006). In vitro studies have demonstrated that NGM282 binds to human hepatocytes with affinity similar to that of FGF19 (Studies 11-MP-NGM282-1002 and 13-MP-NGM282-1005). Additionally, NGM282 specifically inhibits only CY7A1 activity without inhibiting other bile acid synthetic enzymes (Study 12-MP-NGM282-1006). In vivo studies have shown that systemic administration NGM282 can potently and rapidly suppress the expression of the *Cyp7a1* gene in *db/db* mice (Study 11-PD-NGM282-1001). Serum levels of 7-alpha-hydroxy-4-cholesten-3-one (C4), a key biomarker of CYP7A1 biologic activity, were also reduced in the 28-day monkey toxicology study (Study 11-TX-NGM282-1002) and the 26-week toxicology study in monkeys (Study 13-TX-NGM282-1004). Significant reductions in serum C4 levels were also observed after administration of NGM282 in normal volunteers (Study 12-0101) as well as in patients with primary biliary cirrhosis (PBC) (Study 13-0103). NGM282 has also demonstrated improvements in liver biochemistries and histology in the bile duct ligation and α-napthylisothiocyanate mouse models of severe cholestatic injury (Studies 14-PD-NGM282-1006 and 14-PD-NGM282-1007). Similar improvements were seen in MDR2-deficient mice that develop liver histopathology and

injury similar to PSC in humans (Study 14-PD-NGM282-1009). In humans, treatment with NGM282 also caused significant reductions in ALP and serum transaminases in PBC patients who were incomplete responders to UDCA, consistent with a decrease in hepatobiliary injury.

Based on the identified pharmacologic activities in animals and humans as well as the favorable safety and tolerability profiles in normal volunteers and PBC patients, NGM282 represents a potentially important therapeutic option for the treatment of other bile acid disorders such as PSC through pharmacologic FGF19 signaling to reduce the synthesis of toxic bile acids.

2.2 NONCLINICAL STUDIES

NGM has completed a series of in vitro and in vivo nonclinical studies supportive of the clinical development of NGM282 in patients with PSC. Please refer to the Investigator's Brochure (IB) for additional information on these studies.

2.2.1 Nonclinical Safety Assessment

The nonclinical safety of NGM282 has been assessed in general toxicity studies in CD-1 mice and cynomolgus monkeys for up to 26 weeks of treatment and in embryo–fetal toxicity studies in CD-1 mice and New Zealand White rabbits. NGM282 was pharmacologically active in the mouse and monkey for up to 26 weeks of treatment.

In the monkey, NGM282 was clinically well tolerated as clinical signs were limited to increased hair loss at doses ≥ 0.1 mg/kg and slight reductions in body-weight gain at 1 mg/kg at 26 weeks of treatment. In the mouse, NGM282 produced transient clinical signs (e.g., hypoactivity or partial eye closure) at doses ≥ 1 mg/kg that were not dose limiting and resolved with continued treatment for up to 26 weeks. In the mouse, microscopic findings limited to the liver (minimal to moderate hepatocellular hypertrophy) were associated with slight increases in albumin, total protein, and liver weight. These changes were not considered adverse and were reversible.

In the mouse and rabbit, NGM282 did not produce any adverse effects on embryo–fetal development at the highest doses tested (10 mg/kg). In the rabbit, the no-observed-adverse-effect level (NOAEL) was 1 mg/kg due to maternal toxicity associated with body-weight gain reduction and associated reduction in fetal uterine weight at 10 mg/kg.

Based on the cumulative nonclinical safety profile of NGM282 for up to 26 weeks of treatment, the NOAELs in the mouse and monkey were determined to be 1 and 3 mg/kg, respectively. A sufficient safety margin exists for NGM282 at the proposed maximal clinical dose of 6 mg (0.0864 mg/kg) where estimated exposure is estimated to be 2- or 14-fold below that at the NOAELs in the mouse or monkey, respectively (see Table 2.2.1-1).

Table 2.2.1-1. Estimated Safety Exposure Margin of NGM282

Nonclinical Species	NOAEL (mg/kg) [a]	Plasma AUC (hr • ng/mL) [b]	Exposure Margin Relative to Maximum Human Therapeutic Dose [c]
Monkey	1	6610	~14X
Mouse	3	1062	~2X

AUC = area under the concentration–time curve; hr = hour; NOAEL = no-observed-adverse-effect level.

[a] Determined from the 6-month chronic toxicity studies.

[b] Systemic exposure at Day 1 after a single dose was used as the most conservative estimate of exposure given the presence of anti-drug antibody formation with repeat dosing in animals leading to drug accumulation (plasma AUC 7-fold above Day 1 levels).

[c] Based on a maximal therapeutic dose of 6 mg (0.0864 mg/kg based on a 70-kg patient) where plasma AUC is projected to be 482 hr • ng/mL (Study 12-0101).

2.3 CLINICAL STUDIES

NGM has conducted a Phase 1 clinical trial in normal volunteers as well as Phase 2a and 2b trials in PBC patients. These studies are supportive of the clinical development of NGM282 in patients with PSC. Please refer to the IB for additional detailed information on these studies.

2.4 RATIONALE FOR DOSE SELECTION OF NGM282 FOR PSC

The doses selected for the Phase 2 trial in PSC are supported by both the nonclinical and clinical data generated to date. The dose range for the first-in-human Phase 1 clinical trial (0.1–30 mg) was based on a broad approach to dose calculation considering the pharmacology of FGF19, beyond sole reliance on the NOAEL obtained in the GLP 28-day toxicology program. The dose range also took into consideration safe starting-dose principles for first-in-human administration as outlined in both FDA and CHMP guidance. Dose-proportional changes in pharmacokinetic (PK) parameters were observed with both single and multiple dosing in the Phase 1 trial, consistent with predictions from animal models. All doses were safe and well tolerated, thus establishing the initial clinical safety of this dose range.

The proposed doses of 1 and 3 mg for evaluation in patients with PSC are based on a cumulative broad approach to dose calculation considering the pharmacology of FGF19 in PSC, clinical data from normal volunteers and subjects with PBC, and exposure safety margins obtained in the GLP 26-week toxicology program relative to the clinical doses proposed. The proposed doses of 1 and 3 mg are within the current safety margins in both monkeys and mice (Table 2.2.1-1). The drug exposure is comparable between normal volunteers and all populations studied to date (type 2 diabetes [T2D], PBC) and, therefore, expected to be comparable in the PSC population.

The selection of the 1- and 3-mg doses was based on the efficacy, safety, and tolerability observed in the PBC Phase 2a trial in which NGM282 doses of 0.3 and 3 mg were evaluated.

A total of 45 patients were enrolled and randomized into the three study arms of 0.3 mg (n = 14), 3.0 mg (n = 16), or placebo (n = 15). A progressive and statistically significant decrease in mean absolute ALP from Baseline to Day 28 was noted in both active treatment groups ($p < 0.025$). A dose-related response was observed in absolute change in ALP from Baseline to the respective visits, with greater decreases in ALP shown with the higher (3.0 mg) dose of NGM282 (absolute change from Baseline to Day 28: –48.9 IU/L in the 0.3-mg group, –69.0 IU/L in the 3.0-mg group, and 3.9 IU/L in the placebo group). Statistically significant overall treatment effects were demonstrated for both 0.3-mg and 3.0-mg doses for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) whereas only for the 3.0-mg dose for GGT and serum C4 levels. The majority of the treatment-emergent adverse events (TEAEs) reported in this study were either mild or moderate in intensity. The frequency of related TEAEs was slightly higher in the 3.0-mg treatment group compared to the other two treatment groups. Diarrhea was the most frequently reported and treatment-related TEAE; 3 of 14 subjects (21.4%) in the 0.3-mg group reported three events, 4 of 16 subjects (25.0%) in the 3.0-mg group reported six events, and 1 of 15 subjects (6.7%) in the placebo group reported two events. Overall, the study drug was well tolerated by the subjects. The majority of subjects in all treatment groups reported "no reaction" to the injection site. Of those reported, all but one were mild and predominantly reported as erythema at the injection site. No evidence of drug-induced pruritus was observed, as assessed through both the Visual Analogue Scale and the 5D Pruritus Scale. In summary, NGM282 demonstrated significant reductions in key markers of hepatobiliary injury and has a favorable safety and tolerability profile in PBC patients treated for 28 days.

The PBC study subjects represent a population similar to the PSC population based on the underlying role of bile acids in the associated inflammation and hepatobiliary injury. Based on the above data, the selected doses should allow a balance of optimizing the biologic activity versus safety and tolerability in the studied population.

3 STUDY OBJECTIVES

Primary Objective:

- Evaluate the treatment effect of NGM282 as measured by the mean change in ALP from Baseline to Week 12 in patients with PSC.

Secondary Objectives:

- Assess the safety and tolerability of NGM282 in patients with PSC with 12 weeks of treatment.
- Evaluate the percentage change from Baseline at Week 12 in ALP.
- Evaluate the absolute and percentage changes from Baseline at Week 12 of the following:
    - ALT, AST, bilirubin (total, direct), and GGT
    - Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides
    - C4 and serum bile acids
    - Bile-mediated absorption as measured by fat-soluble vitamins and fecal fat content
- Evaluate changes in pruritus and fatigue.
- Compare the incidence and severity of IBD-associated intestinal symptoms.
- Compare the incidence and severity of acute cholangitis during the study period.
- Evaluate the exposure of 1 mg and 3 mg of NGM282 in patients with PSC.
- Compare the dose-related changes in safety, tolerability, and pharmacodynamic (PD) parameters.

Exploratory PD Objectives:

- [redacted]

4 STUDY DESIGN

This is a multiple-center, randomized, double-blind, placebo-controlled, parallel-group study of NGM282 when administered for 12 weeks as a daily subcutaneous (SC) injection in patients with PSC. Approximately 60 subjects will be randomized across approximately 40–45 sites worldwide.

Patients will sign the Informed Consent Form at or prior to the Screening Visit and will undergo screening assessments to verify eligibility for the study (up to 6 weeks). Patients to be studied will have confirmed PSC as defined by an elevated ALP and either liver histology or cholangiography consistent with PSC. The presence of IBD is allowed as well as treatment with a stable regimen of biologic, immunosuppressant, or systemic corticosteroid therapy. UDCA therapy is allowed at stable doses for at least 12 weeks and < 27 mg/kg/day. Patients with decompensated cirrhosis, cholangiocarcinoma (diagnosed or suspected), acute cholangitis, or recently placed bile-duct stents will be excluded from this study. All subjects with concomitant IBD will be required to have had a colonoscopy within 12 months of Screening with no evidence of dysplasia. All subjects will undergo MRCP at Screening.

On Day 1, subjects will be randomized into one of the three treatment arms (NGM282 1 mg, NGM282 3 mg, or placebo) in a 1:1:1 ratio. The randomization will be stratified according to concurrent UDCA or no-UDCA status to ensure an even distribution across the three groups. Study-drug SC self-administration instructions and training will be provided to the subjects and a weekly study-drug kit will be dispensed. Treatment assignment will be blinded to the sites, subjects, Sponsor, and Medical Monitor throughout the study period.

The first dose (Day 1) and doses at Weeks 1, 2, 4, 8, and 12 will be self-administered in the clinic, with all other doses through Week 12 self-administered at home. Self-administration should occur at approximately the same time in the morning for every dose in both the clinic and at home.

Subjects will return to the clinic on Weeks 1, 2, 4, and 8 for on-treatment assessments and to receive weekly study-drug kits. Week 12 will be the End of Treatment (EOT) clinic visit. Subjects will return to the clinic at Week 16 (or 4 weeks after last dose) for an End of Study (EOS) follow-up visit.

4.1 STUDY STOPPING CRITERIA

The entire study may be discontinued at the discretion of the Sponsor based on the occurrence of the following:

- Adverse events (AEs) with respect to their nature, frequency, severity, and/or duration
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development

The entire study will be discontinued by the sponsor if there are three or more related Grade 3 TEAEs of the same Common Terminology Criteria for Adverse Events (CTCAE) category.

5 SUBJECT SELECTION

5.1 INCLUSION CRITERIA

Patients who meet the following criteria may be included in the study:

1. Males and females between 18 and 75 years of age inclusive who are able to comprehend instructions and follow the study procedures, and are willing to sign an Informed Consent Form (ICF).
2. Confirmed diagnosis of PSC based any **two** of the following three criteria:
    a. Historical evidence of an elevated ALP > ULN from any laboratory
    b. Liver biopsy consistent with PSC
        i. Patients with small-duct PSC on liver biopsy must also have a concurrent diagnosis of IBD
    c. Abnormal cholangiography consistent with PSC as measured by MRCP, ERCP, or percutaneous transhepatic cholangiography
3. Subjects must have certain additional laboratory parameters in specified ranges at Screening, as follows:
    a. ALP > 1.5 × ULN
    b. Total bilirubin ≤ 2.5 mg/dL
    c. ALT and AST < 5 × ULN
    d. Serum creatinine < 2 mg/dL or creatinine clearance > 60 mL/min by Cockroft-Gault calculation
    e. Platelets ≥ 100 K/uL
    f. International Normalized Ratio (INR) ≤ 1.3 (in the absence of warfarin or other anticoagulant therapy)
    g. Carbohydrate antigen 19-9 (CA19-9) ≤ 130 U/mL
        i. Patients with a CA 19-9 > 130 U/mL may be enrolled if they have two results a mínimum of 4 weeks but not greater than 1 year apart and not more than 50 U/mL difference between the two results
4. Patients taking UDCA will be allowed to enroll if meeting the following criteria:
    a. Total daily dose of < 27 mg/kg/day
    b. Minimum of 12 weeks of treatment
    c. No significant dosage changes during 8 weeks prior to Screening
    d. Minimum of 12-week washout period prior to Screening if UDCA is stopped

5. Patients with concomitant IBD are allowed to enroll upon meeting the following criteria:
    a. A colonoscopy within 12 months of Screening with no evidence of dysplasia
    b. No episode of an IBD flare or IBD flare–related bloody diarrhea within 6 months of Screening and through Day 1
    c. Stable regimen of biologic treatments, immunosuppressive, or systemic corticosteroids (< 10 mg/day) for > 12 weeks prior to Screening and through Day 1
        i. Vedolizumab is an excluded biologic treatment
6. Female patients are eligible for the study if they meet the following criteria:
    a. Are not pregnant or nursing
    b. Of non-childbearing potential defined as women who have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, or are documented postmenopausal (follicle-stimulating hormone > 40 mIU/mL)

    OR

    Of childbearing potential defined as including women < 55 years of age with 2 years of amenorrhea and **both** the following criteria:
        i. Both a negative serum pregnancy test at Screening and urine pregnancy test prior to Randomization
        ii. Correct and consistent use of one of the following methods of birth control in addition to a male partner using a condom from Screening to 30 days after the last dose of study drug:
            1. hormone-containing contraceptive
            2. intrauterine device with a failure rate < 1% per year
            3. cervical cap or diaphragm with spermicidal agent
            4. tubal sterilization
            5. vasectomy in male partner
7. Male subjects must agree to consistently and correctly use a condom in combination with one of the above methods of birth control from date of consent to 30 days after the last dose of study drug.
8. Subjects must be able to comply with the SC self-administration instructions for study drug and be able to complete the study schedule of procedures.

5.2 EXCLUSION CRITERIA

Any of the following will exclude potential subjects from the study:

1. Clinically significant acute or chronic liver disease of an etiology other than PSC.

a. Patients with stable treated overlapping PSC and autoimmune hepatitis (AIH) will be allowed to enroll into the study.

i. Stable treated overlapping PSC/AIH is defined as on a consistent regimen of immunosuppressive therapy for a minimum of 12 weeks and no evidence of a hepatic flare during that time period.

2. Secondary or IgG4-related sclerosing cholangitis

3. Presence of a dominant stricture of **clinical** concern on MRCP at Screening.

a. Patients with dominant stricture can be enrolled if the investigator feels there is no evidence on magnetic resonance imaging or cholangiography indicative of cholangiocarcinoma or that the stricture will not result in significant fluctuations in ALP during Screening or Study period.

b. Patients with a dominant stricture must have a total bilirubin of ≤ 2.5 mg/dL for at least 6 months prior to Screening.

4. Placement of a bile-duct stent or percutaneous bile-duct drain within 3 months of Screening

a. Patients who have undergone a balloon dilation procedure of a stricture will be allowed to enroll into the study after a minimum of 4 weeks post-procedure.

5. History, evidence, or high suspicion of cholangiocarcinoma or other hepatobiliary malignancy based on imaging, screening laboratory values, and/or clinical symptoms

6. Acute cholangitis within 12 weeks of Screening and through Day 1

a. Chronic preventive antibiotics for cholangitis will be allowed in the study.

b. Intermittent courses of antibiotics for the presumptive treatment of cholangitis are allowed if outside the 12-week window prior to Screening.

7. Evidence of decompensated cirrhosis (Child-Pugh B or C) based on histology, relevant medical complications, or laboratory parameters.

a. Patients with compensated cirrhosis will be allowed to enroll into the study.

b. Patients with pre-sinusoidal esophageal varices with no history or evidence of bleeding may be enrolled as long as there is no other evidence of hepatic decompensation.

8. Prior liver transplantation

9. Any contraindication or inability to obtain a screening MRCP or colonoscopy (only in patients with concomitant IBD, if historical colonoscopy within the 12-month window is not available)

10. Screening electrocardiogram (ECG) with clinically significant abnormalities as determined by the Investigator
11. Positive for HBsAg, HCV-RNA, or anti-HIV
12. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to Screening); subjects under evaluation for malignancy are not eligible.
13. Clinically-relevant drug or alcohol abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication.
14. Use of any prohibited concomitant medications as described in Section 5.7 within 4 weeks of Day 1 visit
15. Patients with severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies
16. Participation in a study of another investigational agent within 4 weeks or five half-lives of the investigational drug (whichever is longer) prior to Screening
17. History of clinically significant unstable or untreated illness or any other major medical disorder that may interfere with subject treatment, assessment, or compliance with the protocol
18. Any acute or chronic condition or other disease that, in the opinion of the Investigator, would limit the patient's ability to complete and/or participate in this clinical study
19. Presence of any other conditions (e.g., geographic or social), actual or projected, that the investigator feels would restrict or limit the patient's participation for the duration of the study
20. Employment by NGM, participating contract research organization (CRO), or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or are immediate family of an NGM employee, participating CRO, or study-site employee (hence, conflict of interest issues). Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

The Investigator has discretion to repeat assessments/procedures if he/she believes there is a good chance the results were spurious and do not accurately represent the subject's true values. Repeat assessments/procedures must be conducted within the 6-week Screening Period, prior to randomization, and a subject may only be rescreened for these labs a single time.

5.3 DISCONTINUATION OF STUDY TREATMENT IN AN INDIVIDUAL SUBJECT

Study treatment will be discontinued if any of the following CTCAE categories or abnormal elevations in liver function tests occurs on-treatment:

- Any Grade 3 TEAE related to study drug
- Any Grade 4 or higher TEAE
- Elevation of ALT **and** total bilirubin > 2 times above subject-specific baseline value calculated using the median of the Screening and Day 1 value
    - ALT, AST, and total bilirubin must be re-tested within 72 hours.
    - Subjects with persistent elevations should be discontinued from treatment, independent of whether or not they are symptomatic.
- Elevation of ALT > 2 times above subject-specific baseline
    - ALT, AST, and total bilirubin must be re-tested within 72 hours.
    - Subjects with persistent elevations who are asymptomatic may continue treatment under protocol-defined *close observation* criteria.
    - Subjects with persistent elevations who are symptomatic must discontinue treatment.
    - Subjects continuing treatment under *close observation* should implement study procedures and assessments as part of the study conduct:
        1. Repeat liver enzyme and serum bilirubin tests two or three times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
        2. Repeat additional tests to evaluate liver synthetic function (e.g., INR, direct bilirubin) as appropriate.
        3. Obtain a detailed history of symptoms and prior or concurrent diseases.
        4. Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, environmental toxin exposure, and special diets.
        5. Rule out acute viral hepatitis and other acute or chronic hepatobiliary diseases.

Dose reductions or increases are not allowed as part the study conduct.

5.4 DISCONTINUATION OF SUBJECTS FROM STUDY PARTICIPATION

Patients will be informed that they are free to withdraw from the study at any time and for any reason. The Principal Investigator (PI) may remove a subject from the study if, in the PI's opinion, it is not in the best interest of the subject to continue the study. Subjects may be discontinued due to subject's personal withdrawal of consent, due to subject's

non-compliance of the study-drug prescription, due to a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects subject safety, due to a site/subject's protocol deviation, due to subject being considered lost-to-follow-up, due to any code-breaking requested by investigator/safety, due to NGM opting to terminate study, due to a subject experiencing an AE(s), due to a subject experiencing a pregnancy, or due to an administration of non-permitted concomitant medication that might affect subject safety or study assessments/objectives. Notification of discontinuation will be made immediately to the Sponsor's Medical Monitor. In case of premature discontinuation of study participation, efforts will be made to perform all final Week 12 (EOT) and Week 16 (EOS) visits/assessments. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects will be followed until resolution of any AEs or until any unresolved AEs are judged by the PI to have stabilized.

5.5 SCHEDULE OF STUDY PROCEDURES

The Schedule of Study Procedures is shown in Table 5.5-1. The visits should occur as close to the intended dates as possible. However, there is an acceptable ± 3-day window for individual scheduled visits. Subjects attending any visits out of windows from Day 1 to Week 12/Early Withdrawal (EOT) Visit should be brought back into compliance with the overall study-visit schedule as soon as possible thereafter. Subjects will then return to the clinic at Week 16 (or 4 weeks after last dose) for an EOS follow-up visit.

Table 5.5-1 Schedule of Study Procedures

Study Procedure	Days –42 to –1 (Screening) [a]	Day 1	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 (EOT)/ Early Withdrawal	Wk 16 (EOS)/ Follow-up
Informed consent	X							
Demographics	X							
Medical history	X							
Inclusion/exclusion criteria	X	X						
Height	X							
Body weight	X	X			X	X	X	X
Physical exam	X	X		X	X	X	X	X
12-lead electrocardiogram	X	X					X	X
Vital signs	X	X	X	X	X	X	X	X
Colonoscopy [b]	X							
MRCP [c]	X							
Prior and concomitant medications	X	X	X	X	X	X	X	X
Randomization		X						
Study drug self-administration training		X	X	X	X			
Dispense study drug		X	X	X	X	X		
Study-drug compliance			X	X	X	X	X	
Adverse event evaluations		X	X	X	X	X	X	X
LISSA evaluations [d]		X	X	X	X	X	X	X
PK blood samples [e]		X	X	X	X	X	X	X
NRS Itch/Fatigue [f]		X	X		X		X	
5-D Pruritus		X	X	X	X	X	X	X
Mayo Partial IBD Score [g]	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
Urinalysis	X	X			X		X	X
Lipid panel		X					X	
CA19-9 [h]	X							
p-ANCA	X							
ELF panel		X					X	

Table 5.5-1 Schedule of Study Procedures (cont'd)

Study Procedure	Days –42 to –1 (Screening)	Day 1	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 (EOT)/ Early Withdrawal	Wk 16 (EOS)/ Follow-up
Hepatitis and HIV screen	X							
Urine drug screen	X							
Pregnancy test [i]	X	X					X	X
C4 and serum bile acids		X					X	
Vitamin D		X					X	X
INR	X	X					X	X
[redacted]		[redacted]					[redacted]	
Anti-drug antibodies		X	X	X	X	X	X	X
Neutralizing antibodies		X	X	X	X	X	X	X
Exploratory biomarkers		X	X	X	X	X	X	X

C4 = 7-alpha-hydroxy-4-cholesten-3-one; CA19-9 = carbohydrate antigen 19-9; ELF = enhanced liver fibrosis; EOS = End of Study; EOT = End of Treatment; ERCP = endoscopic retrograde cholangiopancreatography; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; INR = International Normalized Ratio; LISSA = local injection-site symptom assessment; MRCP = magnetic resonance cholangiopancreatography; NRS = Numeric Rating Scale; p-ANCA = perinuclear anti-neutrophil cytoplasmic antibodies; PK = pharmacokinetic; Wk = week.

[a] There must be a minimum of 14 days between Screening and Day 1 visits for adequate separation of the repeated Chemistry (liver function tests) and INR assessments.

[b] Colonoscopy will be performed only in patients with concomitant IBD and who do not have a colonoscopy available within 12 months of Screening.

[c] MRCP will be performed in all subjects at Screening.

[d] LISSA evaluations will be performed pre-dose for all on-treatment visits.

[e] PK blood samples will be collected before subjects dose themselves in the clinic (pre-dose). At Day 1 and Week 12, an additional PK blood sample will be collected 2 hours post-dose.

[f] NRS Itch/Fatigue will be completed as a daily diary during Day 1 and Study Weeks 1, 4, and 12. Diary will be dispensed at the study visit prior to the collection week.

[g] Mayo Partial IBD Score will be collected in all patients, independent of whether they have IBD or not.

[h] A second CA19-9 sample may be collected during the Screening period a minimum of 4 weeks from the original Screening sample in order to meet Inclusion Criteria 3g.

[i] A serum pregnancy test will be performed on all female subjects at Screening, Week 12, and Week 16. A urine pregnancy test will be performed on all female subjects at Day 1 (pre-dose).

5.6 STUDY VISIT PROCEDURES

5.6.1 Day –42 to Day –1 (Screening) Procedures

Patients will report to this visit fasted for 10 hours with only water allowed. The following screening procedures will be performed for all potential subjects at a visit (or visits) conducted within 42 days prior to dosing:

- Obtain informed consent.
- Collect demographic data.
- Review medical history.
- Assess inclusion/exclusion criteria.
- Measure height.
- Measure body weight.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- In patients with concomitant IBD, obtain colonoscopy report from eligible historical colonoscopy or undergo a colonoscopy procedure to obtain a new report if outside the 12-month window prior to MRCP.
- Obtain historical MRCP or ERCP for PSC diagnosis and dominant stricture assessment.
- Obtain new MRCP for baseline assessment.
- Record prior and concomitant medications.
- Perform Mayo Partial IBD Score.
- Obtain ~10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - INR
    - Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)
    - CA19-9
    - Serum pregnancy test (all female subjects)
    - HIV antibody and hepatitis screen
- Obtain urine samples for the following:
    - Urinalysis (UA)
    - Selected drugs of abuse

5.6.2 Day 1 Procedures

Subjects will report to this visit fasted for 10 hours with only water allowed. The following procedures will be performed at the Day 1 Visit:

Pre-dose:

- Reassess inclusion/exclusion criteria.
- Measure body weight.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Assess for concomitant medications.
- Assess for AEs from Screening period.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - Hematology
  - Lipids
  - C4 and serum bile acids
  - Vitamin D
  - INR
  - Enhanced liver fibrosis (ELF) panel
  - PK (pre-dose)
  - Anti-drug antibodies (ADAs)
  - Neutralizing antibodies (NAbs)
  - Exploratory biomarkers
- [redacted]
- Obtain urine samples for the following:
  - Pregnancy test
  - UA
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.
- Perform and then dispense Numeric Rating Scale (NRS) daily diary for Week 1 assessments.

In-clinic dosing:

- Confirm inclusion/exclusion criteria.
- Perform randomization.

- Dispense initial study-drug kit/diary (for recording of date/time of study-drug dosing).
- Provide study-drug SC self-administration instructions/training.
- Oversee subject study-drug SC self-administration.
- Perform local injection-site symptom assessment (LISSA) evaluation.

Before clinic discharge:

- Obtain 2-hour post-dose PK sample.
- Assess for AEs.
- Schedule subject for Week 1 visit.
- Instruct subjects to not self-administer their study drug until they are on-site.

5.6.3 Week 1 Procedures

Subjects will report to this visit fasted for 10 hours with only water allowed and undosed. The following procedures will be performed at the Week 1 visit:

Pre-dose:

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Assess for concomitant medications.
- Assess for AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - PK (pre-dose)
    - ADAs
    - NAbs
    - Exploratory biomarkers
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.
- Collect Week 1 NRS daily dairy.

Dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject study-drug SC self-administration (from new kit).

Discharge (20 minutes after dosing):

- Assess for AEs.
- Schedule subject for Week 2 visit.
- Instruct subjects to not self-administer their study drug until they are on-site.

5.6.4 Week 2 Procedures

Subjects will report to this visit fasted for 10 hours with only water allowed and undosed. The following procedures will be performed at the Week 2 visit:

Pre-dose:

- Conduct physical examination.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Assess for concomitant medications.
- Assess for AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - PK (pre-dose)
    - ADAs
    - NAbs
    - Exploratory biomarkers
- Perform LISSA evaluation.
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.
- Dispense NRS daily diary for Week 4 assessments.

Dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject study-drug SC self-administration (from new kit).

Discharge (20 minutes after dosing):

- Assess for AEs.
- Schedule subject for Week 4 visit.
- Instruct subjects to not self-administer their study drug until they are on-site.

5.6.5 Week 4 Procedures

Subjects will report to this visit fasted for 10 hours with only water allowed and undosed. The following procedures will be performed at the Week 4 visit:

Pre-dose:

- Conduct physical examination.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Assess for concomitant medications.
- Assess for AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - PK (pre-dose)
    - ADAs
    - NAbs
    - Exploratory biomarkers
- Obtain urine samples for UA.
- Perform LISSA evaluation.
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.
- Collect Week 4 NRS daily diary.

Dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject study-drug self-administration (from new kit).

Discharge (20 minutes after dosing):

- Assess for AEs.
- Schedule subject for Week 8 visit.
- Instruct subjects to not self-administer their study drug until they are on-site.

5.6.6 Week 8 Procedures

Subjects will report to this visit fasted for 10 hours with only water allowed and undosed. The following procedures will be performed at the Week 8 visit:

Pre-dose:

- Conduct physical exam.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Assess for concomitant medications.
- Assess for AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - PK (pre-dose)
    - ADAs
    - NAbs
    - Exploratory biomarkers
- Perform LISSA evaluation.
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.
- Dispense Week 12 NRS daily diary.

Dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject study-drug SC self-administration (from new kit).

Discharge (20 minutes after dosing):

- Assess for AEs.
- Schedule subject for Week 12 (End of Treatment) visit.
- Instruct subjects to not self-administer their study drug until they are on-site.

5.6.7 Week 12 (End of Treatment)/Early Withdrawal Procedures

Subjects will report to this visit fasted for 10 hours with only water allowed and undosed. The following procedures will be performed at the Week 12/Early Withdrawal Visit:

Pre-dose:

- Measure body weight.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Assess for concomitant medications.
- Assess for AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - Hematology
  - Lipid panel
  - C4 and serum bile acids
  - Vitamin D
  - INR
  - ELF panel
  - Serum pregnancy test (all female subjects)
  - PK (pre-dose)
  - ADAs
  - NAbs
  - Exploratory biomarkers
- [redacted]
- Obtain urine sample for UA.
- Perform LISSA evaluation.
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.
- Collect Week 12 NRS daily diary.

Dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Oversee subject study-drug SC self-administration (from old kit) (not applicable for Early Withdrawal subjects).

Discharge:
(NOTE: Before-clinic-discharge assessments [PK sampling and AE recording evaluation] are not applicable for Early Withdrawal subjects. However, Early Withdrawal subjects should be scheduled for a 4-week Follow-up Visit.)

- Obtain 2-hour post-dose PK blood sample.
- Assess for AEs.
- Schedule subject for Week 16 (End of Study) Visit.

5.6.8 Week 16 (End of Study) Procedures

This visit will be performed 4 weeks after last dose of study medication. Subjects will report to this visit fasted for 10 hours with only water allowed. The following procedures will be performed at the Week 16 visit:

- Measure body weight.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - PK
    - Vitamin D
    - INR
    - Serum pregnancy test (all female subjects)
    - ADAs
    - NAbs
    - Exploratory biomarkers
- Obtain urine sample for UA.
- Perform LISSA evaluation.
- Perform 5-D Pruritus Scale.
- Perform Mayo Partial IBD Score.

5.7 CONCOMITANT MEDICATIONS

Any medication taken within 4 weeks prior to Screening and during the study period, as well as the reason for use, will be recorded in the source documents and the eCRFs.

Subjects should refrain from the use of any new prescription medications or products or change in the dose or frequency of existing therapies within 4 weeks prior to Day 1 until EOS. The Medical Monitor should be informed of any changes or addition of medications during this time period.

The following medications are prohibited from 4 weeks prior to Day 1 and through the end of treatment:

- Investigational agents, other than NGM282, or devices for any indication
- Known hepatotoxic agents
    - Concomitant medication can be screened at http://livertox.nih.gov
- Agents which can increase or decrease ALP
    - Patients on stable doses of a medication that may impact ALP for a minimum of 12 weeks can be considered for enrollment.
    - Medications which decrease ALP (such as UDCA, fibrates, bile acid resins) should also be screened for and not be started at any time point during the screening or study period.
- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria (see Section 5.2)
- Off-label use of therapies for PSC such as oral vancomycin, other antibiotics, or vedolizumab within 12 weeks of Screening through the EOS visit
- Any herbal medications other than standard vitamin supplements

In addition:

- Subjects taking medications for IBD must have been on a stable regimen of these medications for at least 12 weeks prior to Day 1 and should maintain if possible a stable dose during the study period.
- Subjects taking UDCA are eligible but must have been on stable doses of < 27 mg/kg/day for at least 12 weeks prior to their Screening. No significant dosage changes should be made during 8 weeks prior to Screening and a minimum 8-week washout period should occur prior to Screening if UDCA is stopped. Subjects not taking UDCA should not start it during the study period.

5.8 DIET AND ACTIVITY CONTROL

Subjects should maintain their normal level of physical activity, diet, and lifestyle throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

5.9 CLINICAL EVALUATIONS

5.9.1 Colonoscopy

Due to the high risk of colonic dysplasia in UC patients with PSC, a 2010 guideline from the AASLD recommends that patients with PSC and IBD undergo surveillance colonoscopy every 1–2 years from the time of diagnosis of PSC (Chapman et al. 2010). Patients with PSC without IBD should undergo surveillance colonoscopy every 5 years. If surveillance biopsies and flow cytometry show no evidence of dysplasia or aneuploidy, follow-up colonoscopy can be performed in 2–3 years. A possible exception would be those patients with > 20 years' duration of colitis; in such patients it is reasonable to perform annual surveillance colonoscopy because of the high risk of dysplasia. If surveillance biopsies show no evidence of dysplasia, but flow cytometry is not available, a repeat colonoscopy is recommended annually. If surveillance biopsies reveal indefinite dysplasia, repeat surveillance colonoscopy is recommended every 6–12 months. If low-grade dysplasia is detected, a variety of options may be considered, including total colectomy. It would also be reasonable to repeat a surveillance colonoscopy within 3–6 months to confirm a diagnosis of low-grade dysplasia. If there are multiple sites of low-grade dysplasia or multiple inflammatory polyps that preclude adequate surveillance, colectomy should be recommended. However, if low-grade dysplasia is present in only one biopsy specimen, repeat surveillance colonoscopy in 6–12 months may also be considered. If high-grade dysplasia is detected, colectomy should be strongly recommended.

Because of the increased risk of dysplasia and colon cancer in PSC, all subjects with concomitant IBD in Study 15-0106 should have a colonoscopy with no evidence of dysplasia within 12 months of Screening (Table 5.5-1).

5.9.2 Magnetic Resonance Cholangiopancreatography

MRCP is a noninvasive technique for evaluating the intrahepatic and extrahepatic bile ducts and the pancreatic duct. Unlike conventional ERCP, MRCP does not require contrast material to be administered into the ductal system; thus, the morbidity associated with endoscopic procedures and contrast materials is avoided. However, MRCP does not permit interventions to be performed such as stone extraction, stent insertion, or biopsy. The optimal protocol to perform MRCP has not been defined; variation continues across centers. As a general rule, the protocol depends upon the specific magnetic resonance magnet being used, including its field strength (e.g., 1.5 versus 3T) and the manufacturer, as well as institutional experience and preferences. However, all acquisition protocols obtain heavily T2-weighted images as thick slabs and the images are reformatted in planes to optimize depiction of the extrahepatic ducts. Volume-rendered images may be used to depict the intra- and extrahepatic bile ducts.

In Study 15-0106, MRCP can be performed as one of the criteria for the diagnosis of PSC and will be performed in all subjects during Screening as a baseline assessment (Table 5.5-1).

5.9.3 Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis of NGM282 levels will be collected before dosing on Day 1 and Weeks 1, 2, 4, 8, 12, and 16 (no dose administered) as outlined in the Schedule of Study Procedures (Table 5.5-1). On Day 1 and Week 12, an additional PK blood sample will be collected 2 hours post-dose.

Processing, storage, and shipping instructions for these PK blood samples will be presented in a separate Lab Manual.

5.9.4 Clinical Laboratory Assessments

Clinical laboratory evaluations including chemistry (fasted at least 10 hours), hematology, and UA will be collected as outlined in the Schedule of Study Procedures (Table 5.5-1).

Laboratory assessments of lipid panel (total cholesterol, LDL, HDL, and triglyceride) will be performed as outlined in the Schedule of Study Procedures (Table 5.5-1).

Laboratory assessments for C4 and serum bile acids will be performed as outlined in the Schedule of Study Procedures (Table 5.5-1).

Laboratory assessments for changes in bile-mediated absorption as measured by vitamin D and INR will be performed as outlined in the Schedule of Study Procedures (Table 5.5-1).

CA19-9 and p-ANCA will be collected at Screening as outlined in the Schedule of Study Procedures (Table 5.5-1).

ELF panel will be performed as outlined in the Schedule of Study Procedures (Table 5.5-1).

Hepatitis screen and HIV antibody screen will be performed at Screening.

A urine screen for drugs of abuse will be performed at Screening.

A stool sample will be collected at Day 1 and Week 12. If necessary, in order to obtain a sample, kits will be provided to patients for at-home collection and aliquoting, for return to clinic at Day 1 and Week 12 visits. Stool samples will be analyzed for calprotectin, microbiome (bacterial composition), and fecal fat content.

A serum qualitative pregnancy test (all female subjects) will be performed at Screening and Weeks 12 and 16. A urine pregnancy test (all female subjects) will be performed at Day 1.

Samples for analysis of ADAs, NAbs, and exploratory biomarkers will be collected as outlined in the Schedule of Study Procedures (Table 5.5-1). All NAb samples will be collected as scheduled and analyzed only if necessary based on ADA results.

Processing, storage, and shipping instructions for the above will be presented in a separate Lab Manual.

5.9.5 12-Lead Electrocardiograms

12-lead ECGs will be performed after the subject has been supine for at least 5 minutes, and as outlined in the Schedule of Study Procedures (Table 5.5-1).

5.9.6 Vital Signs

Vital signs (including temperature, respiratory rate, and seated blood pressure and pulse) will be obtained at Screening and at all study visits as outlined in the Schedule of Study Procedures (Table 5.5-1).

Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.

5.9.7 Physical Examinations

A routine physical examination will be performed at Screening, Day 1, and Weeks 2, 4, 8, 12, and 16 as outlined in the Schedule of Study Procedures (Table 5.5-1). The physical examination may be performed by a physician, trained physician's assistant, or a nurse practitioner, as acceptable according to local regulation.

5.9.8 Weight

Subjects will be weighed at Screening, Day 1, and Weeks 4, 8, 12, and 16 as outlined in the Schedule of Study Procedures (Table 5.5-1).

5.9.9 Local Injection-Site Symptom Assessments

Injection-site evaluation will be made and documented (including photographs, as needed) by the PI or clinic staff using a LISSA (Appendix A).

The LISSA is to be administered pre-dose at Day 1 and Weeks 1, 2, 4, 8, 12, and 16 (End of Study) as outlined in the Schedule of Study Procedures (Table 5.5-1).

The instructions below are to be followed for the pre-dose LISSA:

- The injection-site area(s) should be examined for any injection-site reaction (ISR) at every visit.
- If a single ISR is observed, the LISSA should be used to rate that ISR.
- If multiple ISRs are observed, the LISSA should be used to rate the most severe ISR.
- The study visit note should document the total number of ISRs seen on examination.

The LISSA is intended to be a "snapshot" of the ISRs at the time of clinic assessment. The LISSA is not intended to capture ISR data (frequency, severity, duration, etc.) in between

clinic visits. As with any other potential AE, Investigator judgment should be used as to whether any ISR is recorded as an AE.

In addition to this, Mild to Severe Reactions (LISSA Grade 1–3) are reported as AEs at the discretion of the investigator unless standard serious adverse event (SAE) criteria are met and then must be reported as an SAE. Life-threatening (LISSA Grade 4) meet SAE criteria and must be reported as such.

LISSAs may be performed if necessary and as clinically indicated by the PI to capture ISRs outside of the routine scheduled assessment time points.

The 2007 FDA Toxicity Grading Scale (Appendix A) will be used to assess any ISRs (U.S. Department of Health and Human Services 2007). The documented record will include all of the symptoms, severity, and any local reaction (including pain, tenderness, redness, and swelling) and size of injection-site skin reactions identified and observed by the subject or clinic personnel. LISSA scores will be documented on the subject's eCRF.

5.9.10 Numeric Rating Scale for Pruritus and Fatigue

An 11-point numeric rating scale for both pruritus and fatigue will be completed by subjects as a daily diary during Day 1 and Weeks 1, 4, and 12 as outlined in the Schedule of Study Procedures (Table 5.5-1). Diary will be dispensed at the study visit prior to the collection week. Subject will use the scale (Appendix B) to rate severity ranging from 0 "none" to 10 "worst possible."

5.9.11 5-D Pruritus Scale

The 5-D Pruritus Scale (Appendix C) is a modified version of the Total Neuropathy Scale (Elman et al. 2010). It is a brief multidimensional questionnaire used to measure the chronic itch. The instrument claims to serve as a monitoring instrument for the long-term course of pruritus. This instrument has not been validated in numerous cohorts of subjects with either primary or secondary pruritus; none had PBC. The 5-D Pruritus Scale has five questions that assess degree, duration, direction, disability, and distribution of pruritic symptoms.

The 5-D Pruritus Scale is to be administered pre-dose at Day 1 and Weeks 1, 2, 4, 8, 12, and 16 (End of Study) as outlined in the Schedule of Study Procedures (Table 5.5-1).

5.9.12 Mayo Partial IBD Score

The Mayo Partial IBD Score (Appendix D) is a non-invasive 9-point partial Mayo score used as an outcome measure for clinical trials assessing therapy for ulcerative colitis (Lewis et al. 2008). The partial score evaluates changes in stool frequency, rectal bleeding, and physician assessment of disease severity, with defined changes in the score correlating with clinical responses to treatment. The Mayo Partial IBD Score will be assessed by study-site personnel at all study visits in all subjects, including Screening and EOS.

The Mayo Partial IBD Score is to be administered pre-dose at Day 1 and Weeks 1, 2, 4, 8, 12, and 16 (End of Study) as outlined in the Schedule of Study Procedures (Table 5.5-1).

6 STUDY DRUG

6.1 CLINICAL SUPPLIES

6.2 STUDY DRUG ACCOUNTABILITY

The PI is responsible for ensuring that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time. Each shipment of drug supply for the study will contain a shipping manifest to assist the PI in maintaining current and accurate inventory records.

Upon receipt of the investigational drug, the designated site personnel will visually inspect the shipment, verify the number and condition of study drug received, and confirm receipt of study drug. Study-drug reconciliation will be performed based on the study-drug kits and the remaining returned syringes and compared to recorded results in the study-drug diary.

At the completion of the study, all unused study-drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinic, per the Sponsor's (or designee's) written instructions.

6.3 STUDY DRUG STORAGE

At the clinical site, study drug is to be stored refrigerated at 2°C–8°C (36°F–46°F) in a secure, controlled-access location protected from light.

At the subject's home, study drug is to be stored refrigerated at 2°C–8°C (36°F–46°F) in a location protected from light (e.g., their refrigerator). Subjects will be instructed to take care in keeping study drug out of the reach of children and other family members who may have access to the storage location.

6.4 DOSE PREPARATION AND ADMINISTRATION

Subjects will be instructed to self-administer/dose at approximately the same time each morning over the 12-week treatment period. Study-drug syringes for SC injection should be

brought to room temperature prior to use. Study drug will be administered as a SC injection in the abdomen. On Day 1, subjects will be trained on self-administering a SC injection. On Weeks 1, 2, 4, 8, and 12, self-administration will occur in the clinic under observation by clinic staff. Re-training will be provided as required. Written preparation and study drug self-administration instructions will be provided to each subject. Subjects will be required to complete a daily study-drug administration diary.

6.5 REMOVAL OF STUDY BLIND

This will be a double-blind, placebo-controlled study. Breaking of the blind will be available to the PI through an [redacted]. The subject's treatment assignment will be available to the PI in the event of a medical emergency or an AE that necessitated identification of the study drug for the welfare of that subject. Except in the case of a medical emergency, the PI and clinic staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). The date and time when the PI removed the study blind for an individual subject will be documented by the [redacted] and an automated notification will be sent to the Sponsor. The contracted CRO's pharmacovigilance team may also be required to break the blind for regulatory reporting purposes.

7 ADVERSE EVENTS

7.1 DEFINITION AND GRADING OF SEVERITY OF ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject of clinical investigational participation administered a pharmaceutical product, whether or not considered drug related. A TEAE is an AE that is reported after administration of a dose of study drug.

AEs include the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant diseases or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods or under placebo are also to be designated as AEs.

All AEs, regardless of how identified (e.g., volunteered, elicited, noted on physical examination), will be recorded throughout the study (i.e., from time of consent until final Follow-up visit).

Subjects will be followed for resolution of AEs, by querying the subjects for an ongoing AE until resolved or until any unresolved AEs are judged by the PI to have stabilized or if lost to follow-up. Resolution of all AEs will be promptly documented by the clinic on the subject's eCRF.

Any pregnancy diagnosed during the study must be reported immediately to the PI and Sponsor, including pregnancy in female partners of male subjects. The pregnancy will be followed to term and/or outcome and this outcome must be reported to the Sponsor. Pregnancy, in and of itself, is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or method.

Medication overdose may have occurred when an additional dose of a medication is known or suspected to have been taken (accidentally or intentionally) or when the dose administered exceeds the dose mandated by the protocol. An overdose can involve any study medication and should be reported whether or not there is an associated AE. An overdose is only considered an SAE if any of the defined criteria are met. Associated AEs should be recorded and assessed in the standard manner defined by the protocol. In cases of a discrepancy in drug accountability, an overdose will only be established when it is clear the subject has taken an extra dose or the investigator has reason to suspect additional doses were taken.

The PI will rate the severity of AEs using the CTCAE v4.03. Each CTCAE v4.03 term is a Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT). The CTCAE displays Grades 1–5 with unique clinical descriptions of severity for each AE. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and, therefore, is not an option.

7.2 CRITERIA FOR DETERMINING RELATIONSHIP TO DRUG

The PI will make a blinded determination of the relationship of the AE to the study drug (including placebo) using a four-category system (not related, possible, probable, definite) according to the following guidelines:

- **NOT RELATED** = an AE that does not follow a reasonable temporal sequence from administration of the drug and that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment;
- **POSSIBLE** = an AE that follows a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that cannot be excluded as being possibly caused by the drug (e.g., existence of similar

reports attributed to the drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable;

- **PROBABLE** = an AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.
- **DEFINITE** = an AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), follows a known or hypothesized cause–effect relationship, and (if appropriate) satisfies the following:
    - Positive results obtained in drug sensitivity tests
    - Toxic level of the drug present in blood or other body fluids

7.3 REPORTING

An SAE is any untoward medical occurrence at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., places the subject, in the view of the PI, at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unexpected adverse drug event is any adverse drug event the specificity or severity of which is not consistent with the current IB or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

An AE is associated with the use of the drug if a reasonable possibility exists that the event may have been caused by the drug.

SAEs that are unexpected and related are reportable to Regulatory Authorities. Reportable SAEs will be reported by the PI to the Sponsor and the responsible Institutional Review Board (IRB) or Ethics Committee (EC).

The Sponsor's assigned Safety Representative will be electronically notified via the Medidata system. The reporting in the system must be completed by study personnel within 24 hours of when an SAE is first recognized or reported. Written reports should only be used if the site has issues accessing Medidata. The Safety Representative will subsequently notify the Sponsor and the Sponsor's assigned Medical Monitor of all reported SAEs.

7.3.1 Serious Adverse Events Notification Requirements

Any SAE must be reported by the Investigator, immediately or within 24 hours of awareness of the event, through data entry in the Adverse Event eCRF via the Medidata Rave® electronic data capture system. If the Investigator does not become aware of the SAE immediately (e.g., study subject seeks initial treatment elsewhere), he/she is to report the event within 24 hours after learning of it and document the time he/she first learned of the SAE.

Immediate notification to NGM (via the contracted CRO's pharmacovigilance safety hotline telephone number) must occur if the SAE is fatal or life-threatening, irrespective of the extent of available AE information.

In the rare case the Medidata Rave system is not available, the paper Serious Adverse Event Report Form (SAERF) should be used and faxed to the contracted CRO's pharmacovigilance safety hotline fax number, according to the instructions provided in the study-specific regulatory binder. Once the Medidata Rave system is available the event details should be entered as soon as possible.

For all SAEs, the Investigator is obligated to pursue and provide detailed information to NGM in accordance with the timeframes for reporting specified above. In addition, the Investigator may be required to obtain additional follow-up information in an expedited fashion.

At the time of first notification, the Investigator or designee should provide the following information, if available.

- Protocol number
- Reporter (study site and investigator)
- Patient's study number
- Patient's date of birth
- Patient's gender
- Date of first dose of investigational product
- Date of last dose of investigational product, if applicable
- Action taken with investigational product
- Adverse Event term

- Time and date of occurrence of the event (start and stop dates if known)
- Severity
- Outcome
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria (on) that were met
- Concomitant medication at onset of the event, if known
- Relevant past history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to investigational product. ("Is there a reasonable possibility that the investigational product caused the SAE? Yes or No?")

If requested by the contracted CRO's pharmacovigilance unit, any missing or additional relevant information concerning the SAE should be entered into the Medidata Rave system or faxed to the safety hotline fax number. The Investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his/her health authorities, IRB, principal and coordinating Investigators, study Investigators, and institutions.

NGM or its designee is responsible for submitting expedited safety reports to the appropriate regulatory agency for all confirmed suspected, unexpected serious adverse reactions (SUSARs). These reports will comply with the applicable regulatory requirements and with the International Conference on Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). In the case of a fatal or life-threatening SUSAR, NGM or its designee will notify the appropriate regulatory agency as soon as possible but in no case later than 7 calendar days after NGM's initial receipt of the information. For a non–life-threatening SUSAR, the report will be submitted no later than 15 days after NGM is made aware of the event.

An SAE may qualify for expedited reporting to regulatory authorities if it is determined to be a SUSAR.

8 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Details of statistical parameters and methods to be applied will be provided in a detailed Statistical Analysis Plan (SAP) prior to database lock (unblinding).

8.1 SAMPLE SIZE

A sample size of 20 subjects randomized per treatment group was chosen in light of logistical needs and so as to accumulate sufficient safety data on NGM282. The associated power to detect a treatment difference in the primary efficacy analysis, for either NGM282 comparison versus placebo, is at least 90%, based on the following assumptions:

A. ALP Population Mean Change from Baseline:

	NGM282 (either 1 mg or 3 mg)	Placebo
Subjects taking UDCA at Baseline	–75	0
Subjects not taking UDCA at Baseline	–475	0

UDCA = ursodeoxycholic acid.

B. Equal numbers of completing subjects for each of the four cells above
C. Population (not sample) standard deviation (SD) between subjects within each of the four cells above: 200
D. Analysis of variance with treatment, UDCA (yes/no), treatment with UDCA (all as classification variables), and baseline value (as a continuous covariate) in the model
E. 20% dropout rate, from randomization to Week 12, yielding 16 completing subjects per treatment group
F. Dunnett's 1-step adjustment for multiplicity, requiring a type 1 error rate of 0.027 (2-sided) for each comparison versus placebo

Assumptions underlying the means and SDs are based on studies evaluating UDCA as a first-line therapy and in studies where secondary or combination therapies with UDCA have been utilized. The power in the primary efficacy analysis may be slightly higher, since it incorporates Dunnett's step-down adjustment and utilizes repeated measures to reduce the power losses due to dropouts. On the other hand, power may decrease slightly, to the degree that unequal numbers of subjects are randomized taking and not taking UDCA. In addition, the probability that the observed least square (LS) mean treatment difference exceeds 30% of the placebo LS mean change has not been examined.

To randomize 60 subjects, approximately 90 will be screened.

If, in contrast, the population SD is 300, the power is roughly 81% for each NGM282 comparison versus placebo.

8.2 RANDOMIZATION

At Day 1, all eligible subjects will be randomized [redacted] to one of the three treatment arms (NGM282 1 mg, NGM282 3 mg, or placebo) in a 1:1:1 ratio. The randomization will be stratified by UDCA status (yes/no), to ensure an even distribution across the three treatment groups. That status will be based on concomitant medication history. Additional randomization specifications will be detailed in the randomization plan.

8.3 TEST OF HYPOTHESIS AND SIGNIFICANCE LEVELS

The null hypothesis being tested for this study will be that there is no difference between the active (1 mg or 3 mg NGM282, as applicable) and the Placebo treatment groups at Week 12 in the population mean change from Baseline in ALP. However, trial success will depend on both rejection of that null hypothesis at the 5% two-sided significance level, and observing the difference between either of the NGM282 groups and the placebo group, in the LS mean changes from Baseline of at least 30% of the placebo LS mean change from Baseline.

8.4 ANALYSIS SETS

The analysis sets are detailed below. Details of any others will be described in the SAP.

8.4.1 Randomized Set

All randomized subjects will be included in the Randomized Set. In analyses using this set, subjects will be grouped according to randomized treatment if this differs from actual treatment received.

8.4.2 Safety Set

All randomized subjects who receive at least one dose (full or partial) of study drug and have at least one post-dose safety evaluation will be included in the Safety Set. In analyses using this set, subjects will be grouped according to actual treatment received if this differs from the randomized treatment.

8.4.3 Full Analysis Set

All randomized subjects who receive at least one dose (full or partial) of study drug and have at least one valid, non-missing post-dose efficacy/PD parameter value will be included in the Full Analysis Set (FAS). This will be the set for the primary analyses of efficacy and PD endpoints. In FAS analyses, subjects will be grouped according to randomized treatment if this differs from actual treatment received.

8.4.4 Per Protocol Set

The Per Protocol Set (PPS) will constitute a subset of the FAS. It will include subjects who have at least one valid, non-missing post-dose ALP measurement. In addition, FAS subjects who deviate from the conduct of the study or have an AE deemed by the Medical Monitor to be impactful on the primary endpoint will be excluded from the PPS. In associated analyses, subjects will be grouped according to actual treatment received, if it differs from the randomized treatment.

8.4.5 Pharmacokinetic Set

All randomized participants who receive at least one dose (full or partial) of blinded drug, had a pre-dose (Baseline) blood draw, and provided at least one qualified (above the limit of quantification) post-dose sample will be included in the PK Set. Subjects with protocol violations will be assessed by the medical monitor for inclusion in this set. In associated analyses, subjects will be grouped according to the actual treatment received, if it differs from that to which the subject was randomized.

8.5 SUBJECT DISPOSITION

Individual data listings for subject disposition will be presented for each subject, including enrollment date, treatment start date, treatment discontinuation date, discontinuation reason, and analysis set flags. The number and percentage of subjects entering and discontinuing the study will be presented by treatment group. The reasons for discontinuation will also be summarized. Subject disposition will be summarized using the FAS.

8.6 TREATMENT EXPOSURE

Measures of extent of treatment exposure include the total number of doses per subject and compliance. Treatment compliance is defined as the number of doses administered per protocol/number of doses prescribed per protocol. These measures will be summarized using the Safety Set.

8.7 PROTOCOL DEVIATIONS

Protocol deviations will be summarized using the FAS.

8.8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics, medical history, and other Baseline characteristics will be summarized using the Randomized Set, FAS, and Safety Set.

8.9 EFFICACY AND PHARMACODYNAMICS

8.9.1 Efficacy and Pharmacodynamic Endpoints

The primary efficacy endpoint is the mean change in ALP from Baseline at Week 12.

The secondary efficacy and PD endpoints are the following:

- Percent change from Baseline at Week 12 in ALP
- Absolute and percent changes from Baseline at Week 12 in the following:
  - ALT, AST, bilirubin (total, direct), and GGT
  - C4 and serum bile acids
  - Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides
- Bile-mediated absorption as measured by fat-soluble vitamins and fecal fat content
- Changes in pruritus and fatigue, as measured by the weekly mean of the daily pruritus and fatigue NRS assessments
- Incidence and severity of IBD-associated intestinal symptoms
- Incidence and severity of acute cholangitis

Exploratory PD Endpoints:

- [redacted]

8.9.2 Analysis of Primary Efficacy Endpoint

As the primary efficacy analysis, the population mean change in ALP from Baseline to Week 12 will be compared between treatment groups using a mixed-effect model repeated measures (MMRM) analysis of covariance (ANCOVA) of the primary efficacy endpoint, using the FAS. The model will contain treatment group, visit, treatment group by visit interaction, UDCA (yes/no), treatment group by UDCA interaction, and diabetic status as classification variables and the Baseline value as a continuous covariate. An unstructured covariance matrix will be assumed; however, if the modeling using that matrix does not converge, then other matrices will be explored. For each treatment and treatment comparison versus placebo, the least squares mean, associated standard error (SE), 95% confidence interval, and corresponding p-value will be presented. The overall type 1 error rate for the two primary comparisons versus placebo will be controlled using the step-down Dunnett multiple-testing procedure (Dmitrienko and D'Agostino 2013).

As secondary analyses within the same MMRM, the linear combinations

$$\mu_1 - \mu_3$$

and

$$(\mu_1+\mu_3)/2 - \mu_p$$

will be estimated, where μ_1, μ_3, and μ_p are the population LS means for the primary efficacy endpoint of the 1 mg NGM282, 3 mg NGM282, and placebo groups, respectively.

Further explanatory variables may be included in additional modeling using the FAS, similar to the primary efficacy analysis, depending on the relevance to the endpoint; such modeling will be specified in the SAP.

If strong evidence of marked deviations from normality is noted in the distribution of the residuals of the primary MMRM ANCOVA, then FAS analyses using data transformations of the primary efficacy endpoint, and/or non-parametric approaches, will be explored.

As sensitivity analyses,

a. The primary analysis for the primary endpoint will be repeated for the PPS.
b. The treatments will be compared with respect to the population mean of the primary endpoint using the FAS and an ANCOVA model having treatment group, UDCA (yes/no), and treatment by UDCA interaction as classification variables, and the baseline value as the continuous covariate. The overall type 1 error rate for the two pairwise comparisons versus placebo will be controlled using the step-down Dunnett multiple-testing procedure. Missing data will be imputed using the last post-baseline observation carried forward methodology. Subjects with no post-baseline observations will be excluded.

8.9.3 Analysis of Secondary Endpoints

The analysis of secondary endpoints will be based on the FAS.

The primary efficacy analysis will be repeated for each continuous secondary efficacy endpoint. Further explanatory variables may be included in the modeling depending on the relevance to the endpoint analyzed and will be specified in the SAP.

In addition, for each NGM282 treatment group, the LS mean rate (slope, per week) of change in ALP during Weeks 1–4 will be compared to that during Weeks 5–12; the changes in slopes will be estimated. This estimation will be performed using a MMRM similar to that of the primary efficacy analysis. It will also be repeated using percent change in ALP.

Categorical secondary efficacy endpoints (reflecting incidence and severity of IBD-associated symptoms and acute cholangitis) will be analyzed using confidence intervals of differences of population treatment proportions.

8.9.4 Analysis of Exploratory PD Endpoints

The analysis of exploratory PD endpoints will be based on the FAS.

The primary efficacy analysis will be repeated for each continuous exploratory PD endpoint. Further explanatory variables may be included in the modeling depending on the relevance to the endpoint analyzed and will be specified in the SAP.

8.10 SAFETY AND TOLERABILITY

Safety and tolerability will be assessed by clinical review and summaries of the following parameters:

1. AEs
2. Clinical laboratory test results
3. Physical examination results
4. LISSAs
5. ECG results
6. ISRs
7. Changes and percent changes in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides
8. Vital signs

All safety and tolerability analyses will be conducted using the Safety Set.

8.10.1 Adverse Events

AEs, including SAEs, will be coded using the MedDRA. The number and percentage of subjects experiencing an AE will be summarized for each system organ class (SOC) and preferred term (PT) by treatment group. In addition, AEs will be tabulated according to severity, causality, and relation to the study drug.

All AE summaries will be restricted to TEAEs only, defined as AEs that commence on or after the time of start of first study-drug administration and before 30 days after the last dose of blinded drug. AEs without an onset date or time will be defined as treatment emergent, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to the start of first administration of study drug or if the AE stop date indicates that the event started or stopped prior to the start of first administration of study drug.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA preferred term) more than once will be counted only once for that event. Separate summaries will be provided for AEs by severity, causality, and relationship to study drug.

All AEs will be listed. SAEs will be summarized and listed.

8.10.2 Clinical Laboratory Evaluations

The values and percentage changes from Baseline at Week 12 of total cholesterol, HDL cholesterol, and LDL cholesterol will be summarized.

Observed values and absolute changes from Baseline for routine chemistry, hematology, and urinalysis values will be summarized at each per-protocol time point for each treatment group and overall. Shift tables may also be presented for select chemistry and hematology parameters, as identified in the SAP.

In data listings, laboratory values will be compared to normal ranges; out-of-range and clinically significant laboratory values will be identified.

8.10.3 Physical Examinations

Physical examination results will be listed for each subject.

8.10.4 Vital Signs

Observed values as well as changes from Baseline will be summarized for all vital-sign parameters, by time point and treatment group.

8.10.5 Pregnancy Test

Urine and serum pregnancy test data will be listed for each female subject.

8.10.6 Electrocardiogram

Observed values as well as changes from Baseline will be summarized for all ECG parameters, by time point and treatment group.

8.10.7 Injection-Site Reactions

Frequency tabulations of ISRs will be presented at each time point by treatment group.

8.10.8 Prior and Concomitant Medications

Non-study medications will be classified as prior and concomitant, and coded using the current version of the World Health Organization Drug Dictionary Enhanced (WHO-DD). Prior medications are defined as those taken at least once during the 28 days before Screening. Concomitant medications are defined as those taken at least once from 28 days prior to Screening through the EOS visit. Medications stopped in the 28 days prior to the Screening time point will not be considered concomitant.

Prior medications and concomitant medications will be listed separately. In addition, concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC)

class and PT using frequency counts and percentages. For the summaries of concomitant medications, subjects who take the same medication (in terms of PT) more than once will be counted only once for that medication.

8.10.9 Interim Analysis

An unblinded interim analysis (IA) will be conducted when approximately 24 subjects (a minumum of 8 subjects per arm) have completed the Week 12 visit. At the IA, the evidence regarding the safety and efficacy of NGM282 in the PSC indication will be assessed, in order to evaluate the appropriateness of continuing the study.

A separate SAP for the IA will be generated, describing the conduct of the IA in detail.

8.11 PHARMACOKINETICS

The following PK parameters will be calculated using the PK Set and the validated PK software, Phoenix WinNonlin, Version 5.3 (or higher; Certara Corporation; Princeton, NJ, U.S.):

- Day 1; Weeks 1, 2, 4, 8, and 12: trough concentration (C_{trough})
- Day 1 and Week 12: C_{trough}; concentration at 2 hours post-dose ($C_{2h\ post\text{-}dose}$)

PK data will be used to evaluate the accumulation of NGM282 in the plasma of PSC patients following multiple-dose administration at 1 and 3 mg per day. This will be done by comparing the steady-state trough NGM282 levels in PSC subjects to results obtained on Day 1 in the same subject and, more generally, in the dosing cohort. In addition, determination of NGM282 concentrations 2 hours post-dose on Day 1 and Week 12 will enhance information obtained on accumulation and provide an indication of expected maximum drug concentration (C_{max}) in patients. This information will be directly compared to Phase 1 results obtained in healthy volunteers (Study 12-0101) and with other medical conditions (PBC, nonalcoholic steatohepatitis [NASH], and T2D). In addition, PK data will be used to explore PK/PD correlations in terms of drug efficacy and toxicity, where data allow. Actual sample times will be used in the data analysis.

The exposure of 1 mg and 3 mg of NGM282 will also be evaluated.

9 DATA MANAGEMENT AND ELECTRONIC SYSTEMS

9.1 DATA MANAGEMENT

A data validation manual (DVM) will specify all relevant aspects of data processing and handling for the study, including how data will be managed and cleaned. Relevant sections of the DVM includes the following: standard operating procedures to be followed; eCRF data entry and flow, tracking and filing; coding and coding review plan; reconciliation of

SAEs; external and vendor data integration, import, and reconciliation; and general listing review.

9.2 ELECTRONIC SYSTEMS

Electronic systems used to collect and process data in this study will include the following:

- Contracted CRO's [redacted] randomization and dispensing study-drug supply
- Medidata Rave for general data capture
- PreClarus – real-time study data and analysis
- Statistical Analysis Software (SAS) – data reconciliation/packaging and statistical analysis and review

10 ADMINISTRATIVE ASPECTS

10.1 PROTOCOL ADHERENCE

The PI must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any changes to the protocol prior to seeking approval from the EC.
No alterations in the protocol will occur without agreement between the Sponsor and the PI.
No alterations in the protocol affecting subject safety will occur without the express written approvals of the Sponsor, PI, and EC.

10.2 DISCLOSURE

All information provided regarding the study as well as all information collected/documented during the course of the study will be regarded as confidential. The PI agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the PI or their representative(s) shall require prior notification and review within a reasonable time frame by the Sponsor and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

10.3 MONITORING

The Sponsor's or designee's monitor (i.e., "the monitor") will be responsible for monitoring this clinical trial. The monitor will review the study conduct, proper eCRF and source documentation completion and retention, and accurate study-drug accountability. To this end, the monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The PI will grant access to all documents (related to the study and the individual subjects) at any time these are requested by the sponsor or designee. In turn, the monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The PI and PI's staff will be expected to cooperate

with the monitor, to be available during a portion of the monitoring visit to answer questions, to resolve discrepancies, and to provide any missing information.

10.4 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/EC for approval. IRB/EC approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The PI is responsible for keeping the IRB/EC advised of the progress of the study and of any changes made to the protocol as deemed appropriate but, in any case, at least once a year. The PI is also responsible for notifying the IRB/EC of any reportable AEs that occur during the study.

10.5 INFORMED CONSENT

This study will be conducted in compliance with ICH E6 Good Clinical Practice: Consolidated Guidelines pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, patients must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. The informed consent document must be signed and dated by the patient and PI, or designee, prior to study participation. A copy of the informed consent document must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by Sponsor or its representative at any time.

10.6 RECORDS

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers and initials.

The completed eCRFs will be transferred to the Sponsor or designee. Copies of each eCRF will be retained by the PI. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

Sponsor will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest (longest) standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor standards/procedures; otherwise, the

retention period will default to the retention period of 15 years following completion of the clinical trial.

10.7 DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) will be established in order to protect subject welfare, preserve study integrity, and provide recommendations as needed regarding study conduct. The DMC will be comprised of two external liver disease clinical experts as well as a statistician and a medical team member from the sponsor. The DMC will meet at predefined time points and on an as-needed basis based on enrollment, treatment milestones, and safety. Formal minutes and recommendations will provided by the DMC to the sponsor regarding additional data requests and the continuation of the conduct of the study as outlined in the current protocol. The DMC will operate under the guidance of an agreed-upon charter.

10.8 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Research Agreement.

INVESTIGATOR PROTOCOL REVIEW AND SIGNATURE FORM

Protocol Number: 15-0106

Protocol Title: A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for 12 Weeks in Patients with Primary Sclerosing Cholangitis (PSC)

I have read the above-mentioned Protocol Amendment 2 dated 27 May 2016.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator (Please PRINT)

_____ _____

Principal Investigator (Signature) **Date**

_____

Name of Institution (Please PRINT)

SPONSOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Number: 15-0106

Protocol Title: A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for 12 Weeks in Patients with Primary Sclerosing Cholangitis (PSC)

I have read the above-mentioned Protocol Amendment 2 dated 27 May 2016.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

[redacted]

27 May 2016
Date

Senior Director, Clinical Development and Medical Affairs
NGM Biopharmaceuticals, Inc.

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APPENDIX A–FOOD AND DRUG ADMINISTRATION TOXICITY GRADING SCALE IN LOCAL INJECTION-SITE SYMPTOM ASSESSMENTS

Local Reaction to Injection Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness [a]	2.5–5 cm	5.1–10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling [b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Notes: The FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials can be found at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775 htm.

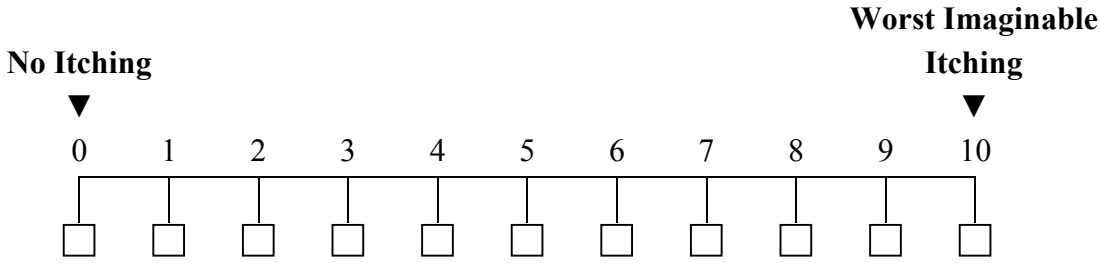
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurements should be recorded as a continuous variable.

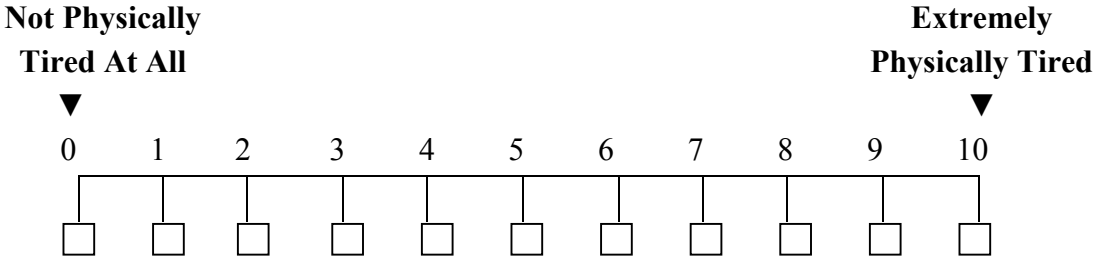
[b] Induration or swelling should be evaluated and graded using the functional scale as well as the actual measurement.

APPENDIX B—NUMERIC RATING SCALE FOR ITCH AND FATIGUE

ITCH SEVERITY

Instructions:
Please clearly mark an 'x' in the box (☒) that best describes your **itching** in the **past 24 hours**.





APPENDIX C—5-D PRURITIS SCALE

5-D Pruritus Scale

1. Duration : During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Degree : Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. Direction : Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. Disability: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Distribution: Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX D—MAYO PARTIAL IBD SCORE (INFLAMMATORY BOWEL DISEASE SCALE)

Components of the Partial Mayo Score

Stool Frequency
0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding [a]
0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone
Physician rating of disease activity
0 = Normal
1 = Mild
2 = Moderate
3 = Severe

[a] A score of 3 for bleeding required patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.