TITLE PAGE

Protocol Title: A Phase 1/2 Dose-Finding Study Followed by Expansion Cohorts of NGM120, a GFRAL Antagonist Monoclonal Antibody Blocking GDF15 Signaling, in Subjects With Advanced Solid Tumors and Pancreatic Cancer Using Combination Therapy

Protocol Number: 18-0402

Amendment Number: 6

Product: NGM120

Short Title: Phase 1/2 Dose-Finding and Dose-Expansion Study of NGM120 in Subjects With Advanced Solid Tumors and Pancreatic Cancer Using Combination Therapy

Study Phase: 1/2

Sponsor Name: NGM Biopharmaceuticals, Inc.

Legal Registered Address: 333 Oyster Point Boulevard, South San Francisco, CA 94080, United States of America

Regulatory Agency Identifying Number(s): IND 140647

Date of Protocol: Version 7.0, 07 Apr 2022

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

{See appended electronic signature page}

[redacted] **Date**

Medical Monitor name and contact information can be found in Appendix 3.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

PROTOCOL CHANGE HISTORY

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/2 Dose-Finding Study Followed by Expansion Cohorts of NGM120, a GFRAL Antagonist Monoclonal Antibody Blocking GDF15 Signaling, in Subjects With Advanced Solid Tumors and Pancreatic Cancer Using Combination Therapy

Short Title: Phase 1/2 Dose-Finding and Dose-Expansion Study of NGM120 in Subjects With Advanced Solid Tumors and Pancreatic Cancer Using Combination Therapy

Objectives and Endpoints

Part 1 (Phase 1a):

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of NGM120 in subjects with select solid tumors	• Maximum tolerated dose (MTD) or maximum feasible dose (MFD) as evidenced by dose limiting toxicities (DLTs), adverse events (AEs), serious AEs (SAEs), discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters, electrocardiograms (ECGs), vital signs, and local injection-site symptom assessment
Secondary	
• To characterize the pharmacokinetics (PK) of NGM120 in subjects with select solid tumors	• Serum concentrations of NGM120 at specified timepoints PK parameters (including, but not limited to, maximum observed serum concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve (AUC), clearance, apparent volume of distribution, and apparent terminal half-life ($t_{1/2}$)
• To characterize the immunogenicity against NGM120 in subjects with select solid tumors	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor and anticachexia efficacy of NGM120 in subjects with select solid tumors	• Percent change from baseline in tumor measurements • Body weight, body composition, and lean body mass changes • Patient Reported Outcomes (PROs): Functional Assessment of Anorexia/Cachexia Treatment (FAACT) and Appetite Loss Numerical Scale
• Characterize changes in body weight and skeletal muscle index during therapy with NGM120	• Change in body weight • Percent change in skeletal muscle mass and adiposity at level of L3 on serial computed tomography scans

Objectives	Endpoints
Exploratory	
• [redacted]	[redacted]

Part 2 (Phase 1b/2):

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of NGM120 when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Maximum tolerated dose (MTD), maximum feasible dose (MFD), or optimal efficacious dose (OED) as evidenced by DLTs, AEs, SAEs, discontinuation of investigational product due to toxicity, PK/PD correlation, and changes from baseline in laboratory parameters, ECGs, vital signs, and local injection-site symptom assessment

Objectives	Endpoints
Secondary	
• To characterize the PK of NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• C_{max}, t_{max}, AUC, clearance, apparent volume of distribution, and apparent $t_{1/2}$
• To characterize the immunogenicity against NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor and anticachexia efficacy of NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Overall response rate, disease control, duration of response, progression-free survival, and overall survival • Body weight, body composition, and lean body mass changes • PROs: FAACT and Appetite Loss Numerical Scale
• Characterize changes in body weight and skeletal muscle index during therapy with NGM120	• Change in body weight • Percent change in skeletal muscle mass and adiposity at level of L3 on serial computed tomography scans
Exploratory	
• [redacted]	• [redacted]

Objectives	Endpoints
• [redacted]	[redacted]

Part 3 (Phase 1b):

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of NGM120 when administered in metastatic castration resistant prostate cancer (mCRPC) patients who have progressed under 1 or more lines of androgen deprivation therapies (ADT)	• AEs, SAEs, discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters, ECGs, vital signs, and local injection-site symptom assessment
Secondary	
• To characterize the PK of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• C_{max}, t_{max}, AUC, clearance, apparent volume of distribution, and apparent $t_{1/2}$
• To characterize the immunogenicity against NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor efficacy of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• **Prostate Specific Antigen (PSA) response** defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. • **Time to PSA progression (TTPP)** defined as the time interval between the date of randomization and the date of first documented PSA progression. PSA progression is defined as: 1) If decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart; 2) If no decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint • **Progression-free survival** defined as the time interval between the date of randomization and the date of the first documentation of any of the following events: - Radiological tumor progression by RECIST 1.1 or Prostate Cancer Working Group 2 (PCWG2) - Symptomatic progression - Pain progression

Objectives	Endpoints
	- Death due to any cause • **Objective tumor response** in patients with measurable disease (RECIST 1.1) • **Duration of tumor response** • **Symptomatic skeletal events (SSE) rate**, occurrence of SSE (by clinical evaluation) is defined as: - The occurrence of a new symptomatic pathological fracture, or - The use of external beam radiation to relieve bone pain, or - The occurrence of spinal cord compression, or - Tumor-related orthopedic surgical intervention • **Time to occurrence of SSE** defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE. • **24-month OS** defined as the time interval from the date of randomization to the date of death due to any cause within a 24-month time frame
• Health status/utility	• EuroQol 5 dimension 5 level (EQ-5D-5L) • Change in body weight
Exploratory	
• [redacted]	[redacted]

Overall Design:

This is a multicenter, Phase 1/2, study consisting of 3 parts, with Part 1 as the Phase 1a portion of the study, Part 2 as the Phase 1b/2 portion, and Part 3 as the Phase 1b portion. The aim of the study is to evaluate the safety and tolerability, as well as to obtain preliminary evidence of antitumor activity and anti-CACS activity, of NGM120 monotherapy in subjects with select advanced solid tumors (Part 1), NGM120 in combination with gemcitabine and Abraxane for the management of metastatic pancreatic cancer (Part 2), and NGM120 in metastatic castration-resistant prostate cancer (mCRPC) patients who have progressed under 1 or more lines of ADT (Part 3).

Part 2 will start at the same time as Part 1 and run concurrently. Part 3 was implemented with protocol version 6.0.

Part 1 and Part 2 Dose-Finding and Dose Expansion

Part 1 and Part 2 of the study will be split into a dose-finding portion followed by a dose-expansion portion. The study has dose-finding and dose-expansion criteria that will need to be met before either expanding a cohort or initiating an expansion cohort.

The dose-finding portion will consist of 2 cohorts in a 3+3 dose-finding design with 2 dose levels. Depending on the dose level/cohort a subject is enrolled to, the subject will receive a dose of either 100 mg or 30 mg of NGM120. Following completion of the final dose-finding meeting, another dose level of NGM120 may be investigated as selected by the Safety Review Committee. Therefore, depending on drug safety/tolerability profiles, a maximum tolerated dose (MTD) or a maximum feasible dose (MFD) will be identified (Part 1 and Part 2). If the drug safety/tolerability is not limiting, an optimal efficacious dose (OED) (Part 2) will be identified based on PK/PD correlation in the consideration of maximal PD activity and adequate drug exposure. Additional cohorts may be added, as new research and clinical data become available.

After all subjects in a dose-finding cohort complete their first cycle of treatment, the Safety Review Committee will be convened to evaluate the available safety, PK, and PD data. The Safety Review Committee will determine whether to proceed with another dose level or whether the MTD/MFD (Part 1 and Part 2) has been reached. Following selection of the NGM120 MTD/MFD (Part 1) or MTD/MFD/OED (Part 2), enrollment to the dose-expansion cohort may begin as determined by the Safety Review Committee.

Part 1 and Part 2 of the study have dose-finding (see Section 4.5) and dose-expansion criteria (see Section 4.6) that will need to be met before either expanding a cohort or initiating the expansion cohort.

Blinding

Part 1 will be open-label for both the dose-finding cohorts and the PD dose-expansion cohorts. NGM120 will administered on a once every 3 weeks (Q3W) cycle in subjects with solid tumors who have exhausted all standard therapies for their underlying cancer.

Part 2 will be open-label for the dose-finding cohorts. The dose-expansion cohort will be single-blind (Sponsor unblinded) with subjects randomly allocated to treatment with either NGM120, or a matching placebo, administered on a once every 4 weeks (Q4W) cycle. All subjects in Part 2 will also receive gemcitabine (1000 mg/m^2) and Abraxane (125 mg/m^2) weekly for the first 3 weeks of the 4-week cycle.

Part 3 will be open label. Subjects will receive NGM120 100 mg Q3W. All subjects will continue their current hormonal therapy for mCRPC in combination with NGM120.

Dose-Finding Criteria

As of June 2020 (protocol version 3.0), based on emerging PK and PD data, the NGM120 200 mg dose was removed, and the NGM120 30 mg dose was added. The study design was modified from a dose-escalation design to a dose-finding design.

As of December 2021 (protocol version 5.0), emerging safety, PD (cachexia and tumor), and PK data suggest that the RP2D has not been determined and therefore the Part 2 Phase 1b dose finding cohort (NGM120 30 mg) was increased to add 6 subjects and the Part 2 Phase 2 dose expansion cohort was modified from a 1:1 to a 0:1 (placebo:NGM120 100 mg) randomized design.

Part 1 and Part 2 will follow a modified 3+3 dose-finding design with 2 dose levels (100 mg and 30 mg). Subsequently, dose-expansion cohorts will be enrolled.

Three subjects will initially be enrolled in each cohort. If there are no DLTs observed in Cycle 1 of any of the initial 3 subjects, enrollment to the next cohort could proceed. If 1 of the 3 subjects (33%) experiences a DLT, the cohort will be expanded to 6 subjects (3 additional subjects enrolled). Dose limiting toxicities will also be monitored in the expansion cohort(s) and the dose may be reconsidered if the DLT rate exceeds 33% of study treatment-administered subjects as determined by the Safety Review Committee.

All subjects in a cohort will be followed for a minimum of 1 cycle of treatment (3-week cycle in Part 1 and 4-week cycle in Part 2), followed by the Safety Review Committee review before the next cohort begins NGM120 administration.

The DLT evaluation will be done as follows:

- DLTs will be assessed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria Version 5.0.
- DLTs will be any Grade 3 or higher AEs that are at least possibly related to NGM120, except the following:

  - Grade 3 fatigue lasting <5 days.
  - Grade 3 nausea, vomiting, or diarrhea lasting <72 hours in subjects who have not received standard antiemetic or antidiarrheal therapy.
  - Asymptomatic Grade 3 to 4 laboratory abnormalities that persist for <72 hours, or asymptomatic Grade 3 or 4 laboratory abnormalities that do not meet SAE criteria.
  - Grade 4 neutropenia lasting <5 days.
  - Grade 3 thrombocytopenia in the absence of hemorrhage.

As of December 2021 (protocol version 5.0), the Part 2 Phase 1b dose-finding cohort (30 mg cohort) was updated to add 6 subjects.

Dose-Level Expansion

Upon completion of the dose-finding cohorts and determination of the MTD/MFD (Part 1) or MTD/MFD/OED (Part 2), the Safety Review Committee will review all available data from the cohorts before permitting the dose-level expansion. Note: For Part 1, the Safety Review Committee will review available data from the first dose-finding cohort (100 mg) and the first 3-6 subjects in the PD expansion cohort (30 mg) only. All available data will be reviewed according to a separately prepared Cohort Management Plan.

Determination of the MTD/MFD/OED

The selection of 100 mg or 30 mg NGM120 as the expansion dose will be based on the safety profiles, PK, PD, and additional considerations of the doses in the dose-finding cohorts. Following completion of the final dose-finding meeting, another dose level of NGM120 may be selected, by the Safety Review Committee, for further investigation.

If the 100 mg dose is not safe and well-tolerated, and the 30 mg dose selected by the Safety Review Committee is deemed safe (defined as DLTs ≤33% within the 21-day window for Part 1 and 28-day window for Part 2) and well tolerated, the 30 mg dose will be the MTD and expanded thereafter.

If both the 100 mg and 30 mg doses are deemed safe (defined as DLTs ≤33% within the 21-day window for Part 1 and 28-day window for Part 2) and well tolerated, the OED will be selected based on PK/PD correlation in the consideration of maximal PD activity and adequate drug

exposure will be chosen for the expansion. If the 30 mg dose is chosen as the expansion dose, a loading dose of 100 mg could be used to accelerate the time to steady-state drug concentrations.

All available data will be reviewed according to a separately prepared Cohort Management Plan.

Number of Investigators and Study Centers:

Approximately 25 Investigators and study centers are expected to participate in this study in the United States.

Number of Subjects:

Part 1:

Approximately 15 to 21 subjects will be included in Part 1. Three to 6 subjects will be entered in a 3+3 dose-finding design with 2 dose levels (100 mg and 30 mg) followed by 12 subjects entered into a dose-expansion cohort. Subjects in the dose-finding cohorts who discontinue prior to completing their DLT evaluation period will be replaced. Subjects who are withdrawn because of a DLT will not be replaced.

Part 2:

Approximately 59 subjects will be included in Part 2. Three to 6 subjects were planned to be entered in a 3+3 dose--finding design with 2 dose levels (100 mg and 30 mg); a total of 4 subjects were enrolled at each dose level (30 mg and 100 mg). Six additional subjects are planned to be added to Part 2 Phase 1b dose-finding cohort (30 mg) after protocol version 5.0.

The dose-expansion cohort (Part 2 Phase 2) enrolled approximately 30 subjects prior to protocol version 5.0. After protocol version 5.0, the randomization changed from a 1:1 ratio to a 0:1 ratio (placebo:NGM120 100 mg). At final enrollment, it is anticipated that approximately 15 subjects will have been randomized to placebo and approximately 30 subjects will have been randomized to NGM120 100 mg [redacted]

Subjects in the dose-finding cohorts who discontinue prior to completing their DLT evaluation period will be replaced. Subjects who are withdrawn because of a DLT will not be replaced.

Part 3:

Approximately 10 subjects will be included in Part 3, which is expandable to 25.

Treatment Groups and Duration:

After a screening period of 4 weeks, eligible subjects will be entered sequentially into a treatment cohort. During the treatment period, subjects will be administered NGM120 for a

minimum of 6 cycles (18 weeks in Parts 1 and 3) or 4 cycles (16 weeks in Part 2). Afterwards, following Medical Monitor and Principal Investigator approval based on assessment of the subject's Week 18 (Parts 1 and 3) or Week 15 (Part 2) data, the subjects who are tolerating NGM120 and have not experienced disease progression, may continue the allocated study treatment up to 24 months or until disease progression, intolerable toxicity, the need for other anticancer therapy, pregnancy, or a physician or subject decision to withdraw from the study, whichever comes first. A follow-up visit will be held 4 weeks after the subject receives his/her last study treatment administration. All visits will be outpatient, day visits. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST (Parts 1 and 2) or PCWG2 (Part 3) at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first.

In Part 1, subjects will receive NGM120 Q3W as monotherapy while in Part 2 subjects will receive NGM120 or a matching placebo (dose-expansion cohort only), Q4W together with gemcitabine (1000 mg/m^2 weekly for first 3 weeks of the 4-week cycle) and Abraxane (125 mg/m^2 weekly for first 3 weeks of the 4-week cycle).

Depending on the dose-finding cohort enrolled to, a subject would receive NGM120 at a dose of either 100 mg or 30 mg. The Safety Review Committee will review the data from the first treatment cycle of each cohort to determine if the dose-finding and dose expansion is to proceed.

In Part 1, the PD dose-expansion cohorts will receive 2 different NGM120 doses (30 mg and 100 mg) as determined by the Safety Review Committee. In Part 2, the dose-expansion cohorts will receive NGM120 30 mg or 100 mg based on the MTD/MFD/OED recommendation from the Safety Review Committee. A loading dose of 100 mg could be considered for the 30 mg dose if the drug safety/tolerability is not limiting for the 100 mg dose. The subjects will be randomly allocated to treatment with NGM120 or matching placebo, together with gemcitabine and Abraxane.

Following completion of the final dose-finding meeting, another dose level of NGM120 may be investigated as selected by the Safety Review Committee.

All subjects in Part 1 and Part 3 who continue NGM120 treatment beyond (18 weeks) will continue their assigned NGM120 dose until they leave the study. However, subjects in the Part 2 dose-finding cohorts who continue NGM120 treatment, will be changed to the selected NGM120 for the dose-expansion cohort, once determined by the Safety Review Committee.

Statistical Methods:

Descriptive statistics including the number of non-missing observations (n), arithmetic mean, standard deviation, median, minimum, and maximum will be presented for continuous variables.

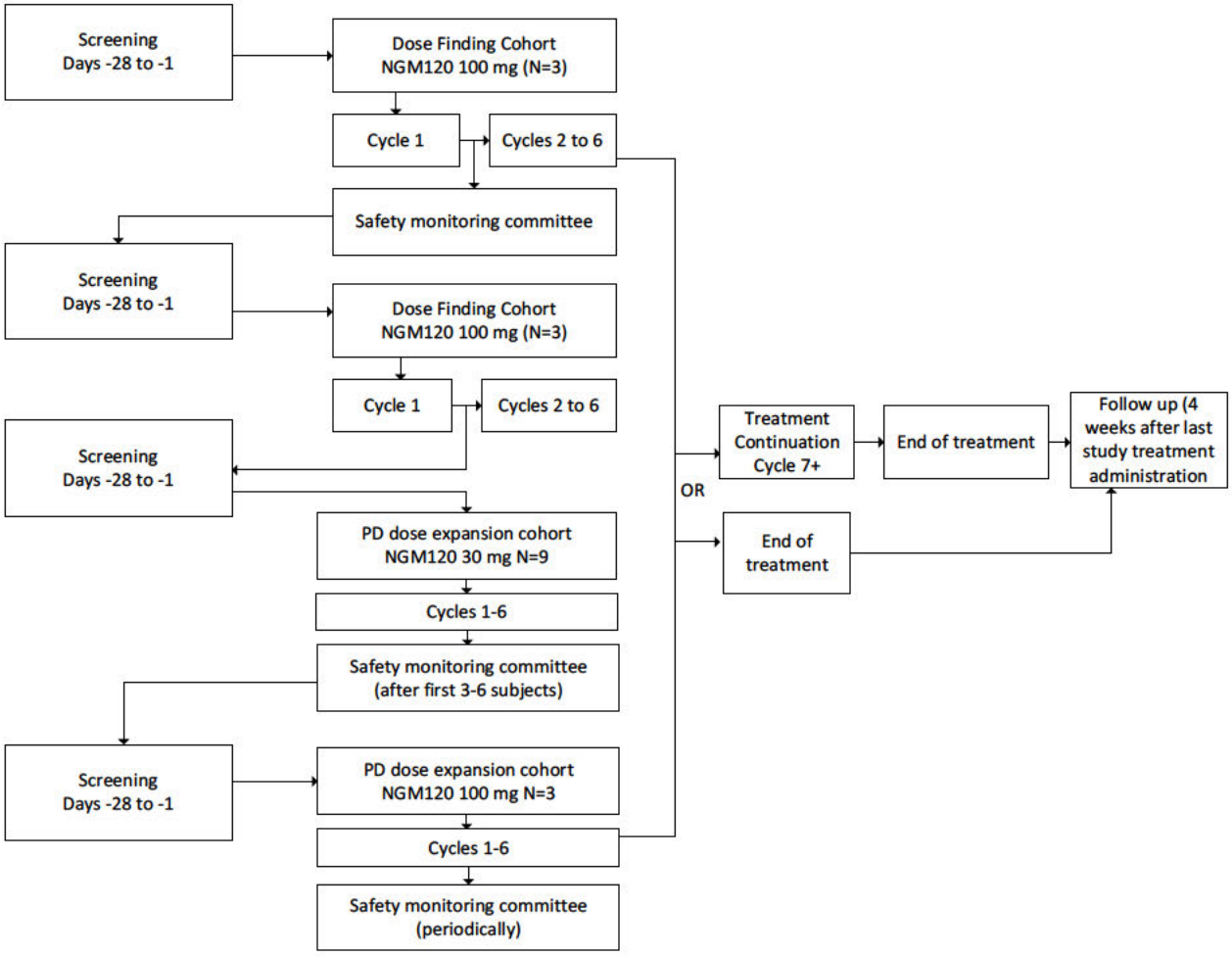
Frequency and percentage distribution will be presented for categorical variables. Kaplan-Meier estimates will be presented for time-to-event variables. Adverse events will be coded using Medical Dictionary for Regulatory Activities and will be summarized by primary System Organ Class and Preferred Terms.

Data Monitoring Committee:

A Safety Review Committee will be convened to evaluate available data and decide on the dose-finding and expansion cohorts as well as to determine the MTD/MFD/OED.

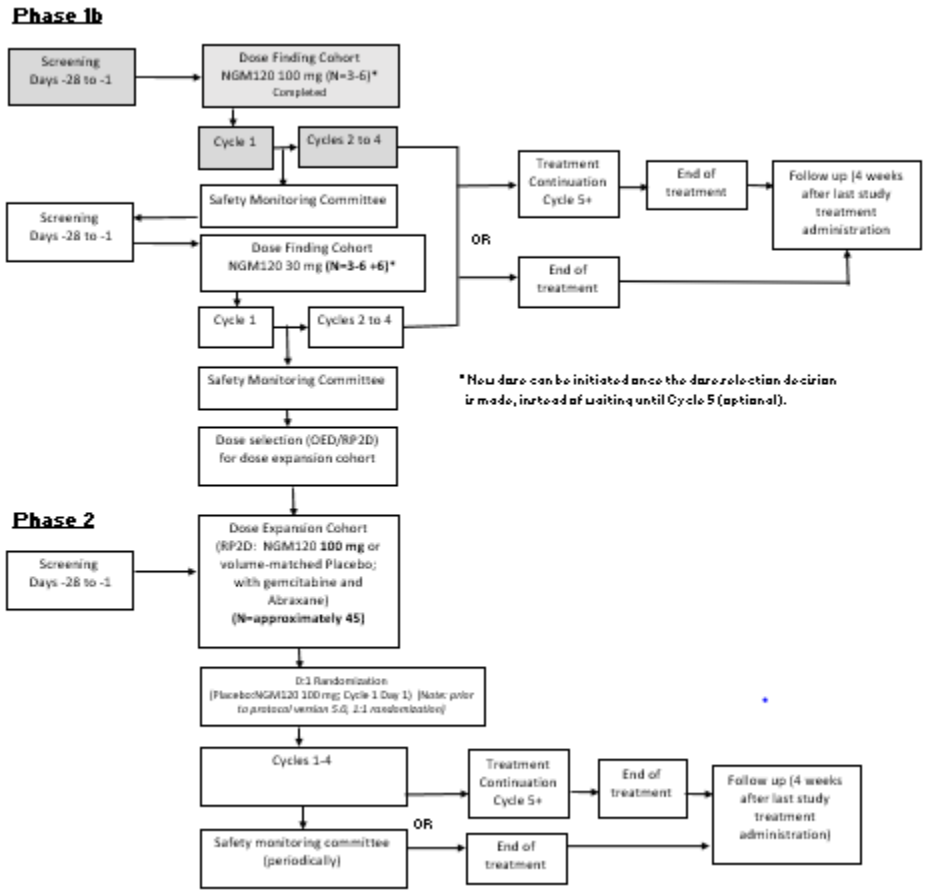
1.2 Schema

Figure 1-1 Study Schema of Part 1 (Phase 1a)



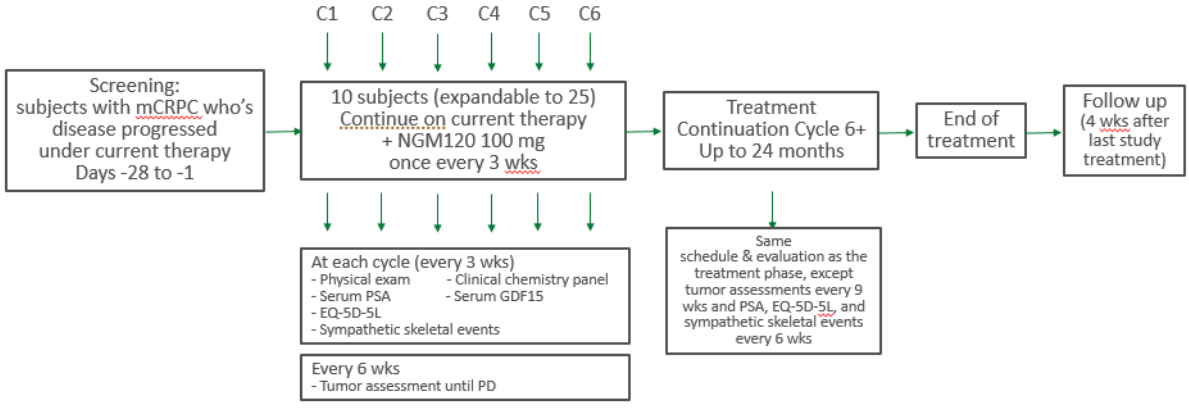
Note: For the 100 mg dose-expansion cohort, the Safety Review Committee will meet quarterly, or as needed (ad hoc).

Figure 1-2 Study Schema of Part 2 (Phase 1b/2)



Note: For the dose-expansion cohort, the Safety Review Committee will meet quarterly, or as needed (ad hoc).

Figure 1-3 Study Schema of Part 3 (Phase 1b)



1.3 Schedule of Study Procedures

Table 1-1 Schedule of Study Procedures – Part 1

Activity/Assessment	Cycle:	1		2		3		4	5	6		Wk 20 (EOS/EW) [a]
	Day:	1	15	1	15	1	15	1	1	1	15	
	Screening (Days -28 to -1)	Wk 1	Wk 3	Wk 4	Wk 6	Wk 7	Wk 9	Wk 10	Wk 13	Wk 16	Wk 18 (EOT) [a]	
	Study Day	1	15	22	36	43	57	64	85	106	120	
Visit Windows (Days)			± 1	± 1	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Informed consent	X											
Demographics	X											
Medical/surgical history	X											
Inclusion/exclusion criteria	X	X										
Urine drug screen	X											
Tuberculosis screen [b]	X											
Archival tumor sample (within 5 years) [c]	X											
[redacted]		[redacted]										
Height [d]	X											
Weight [d]	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference [d]	X	X	X	X	X	X	X	X	X	X	X	X
Body mass index	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [e]	X	X	X		X		X	X	X		X	X
12-Lead ECG [f]	X	X	X		X		X		X		X	X
Vital signs [g]	X	X	X	X	X	X	X	X	X	X	X	X

Activity/Assessment	Cycle:	1		2		3		4	5	6		Wk 20 (EOS/EW) [a]
	Day:	1	15	1	15	1	15	1	1	1	15	
	Screening (Days -28 to -1)	Wk 1	Wk 3	Wk 4	Wk 6	Wk 7	Wk 9	Wk 10	Wk 13	Wk 16	Wk 18 (EOT) [a]	
	Study Day	1	15	22	36	43	57	64	85	106	120	
Visit Windows (Days)			± 1	± 1	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Pregnancy test [h]	X	X										X
NGM120 administration [i]		X		X		X		X	X	X		
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X
LISSA evaluations [j]	X	X		X		X		X	X	X		
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X		X		X	X	X	X	X
[redacted]	■	■	■	■		■		■		■	■	■	■
[redacted]	■	■	■	■	■	■	■	■		■	■	■	■
[redacted]	■	■	■	■	■	■	■	■		■	■	■	■
[redacted]	■	■	■	■		■		■		■	■	■	■
[redacted]	■	■	■	■		■		■		■	■	■	■
[redacted]	■	■	■		■		■		■	■	■	■	■
[redacted]	■	■	■	■		■		■		■	■	■	■
[redacted]	■	■	■		■		■		■	■	■	■	■
[redacted]	■	■	■		■		■						■
[redacted]		■			■		■						
[redacted]	■	■	■		■		■		■		■		■

Activity/Assessment	Cycle:	1		2		3		4	5	6		Wk 20 (EOS/EW) [a]
	Day:	1	15	1	15	1	15	1	1	1	15	
	Screening (Days -28 to -1)	Wk 1	Wk 3	Wk 4	Wk 6	Wk 7	Wk 9	Wk 10	Wk 13	Wk 16	Wk 18 (EOT) [a]	
	Study Day	1	15	22	36	43	57	64	85	106	120	
Visit Windows (Days)			± 1	± 1	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3
[redacted]		[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Pharmacokinetics [k]		X	X	X	X	X	X	X	X	X	X	X
Antidrug antibodies		X				X			X		X	X
Neutralizing antibodies		X				X			X		X	X
ECOG performance status	X			X			X		X		X	X
Lean body mass (CT/MRI) [l]	X						X				X	X [m]
RECIST assessment (CT/MRI) [n]	X						X				X	X [m]
[redacted]		[redacted]		[redacted]			[redacted]		[redacted]			[redacted]
[redacted]		[redacted]		[redacted]			[redacted]		[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]						[redacted]				[redacted]	[redacted]

Abbreviations: [redacted]; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOS, end of study; EOT, end of treatment; EW, early withdrawal; GDF15, growth differentiation factor 15; LISSA, local injection-site symptom assessment; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; Wk, Week.

Note: All visits will be performed as outpatient day visits. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.

Note: All assessments to be completed before study treatment administration.

Note: Based on assessment of a subject's Week 18 data, and following Medical Monitor and Principal Investigator approval, subjects who are tolerating NGM120 and have not experienced disease progression, may continue the allocated study treatment according to the schedule of study procedures detailed in Table 1-2.

[a] The EOT and EOS/EW (4 weeks following last dose administration) visits/assessments to be performed if a subject chooses not to proceed with additional treatment or discontinues from the study before completing 6 cycles of treatment. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first. The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

[b] Tuberculosis testing may be performed locally when a 37°C incubator is not available on site. Local testing results must be entered in the eCRF.

[c] If an archival sample is unavailable, a fresh biopsy can be obtained during Screening. If archival tissue or biopsy sample is unavailable, the subject is ineligible.

[d] The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

[e] Complete physical examination including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[f] A single 12-lead ECG will be obtained at Screening and triplicate ECGs will be obtained at all subsequent assessments. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Measurements of ECG and heart rate will be recorded in a supine position after the subject has been resting for at least 5 minutes.

[g] Temperature, pulse rate, blood pressure, and respiratory rate are to be assessed. Vital signs will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

[h] A serum pregnancy test will be performed (for women of childbearing potential) at Screening. Subsequently, the pregnancy test is to be performed per institutional standards.

[i] Single subcutaneous administration of NGM120 in the abdomen.

[j] LISSA evaluation to be performed predose and postdose (approximately 30 minutes postdose).

[k] A single predose pharmacokinetic sample is to be collected at all indicated visits. On visits when NGM120 is administered, the sample is to be collected prior to dosing (i.e., predose).

[l] A CT scan of the abdomen is the preferred imaging method. Lean body mass will be calculated at the level of L3. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. All subsequent scans should use the same methodology.
The CT scan results will also be used to determine the subject's skeletal muscle index.

[m] The CT/MRI only to be performed for subjects who withdraw from the study early due to reasons other than radiographically documented disease progression and to be performed only if EW visit is ≥4 weeks from last CT/MRI.

[n] CT scans of the neck, chest, abdomen, and pelvis are the preferred imaging method for tumor assessment. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. The target and nontarget lesions will be selected based on the initial scan, and all subsequent scans should use the same methodology.

Table 1-2 Schedule of Study Procedures – Part 1 (Treatment Continuation – Starting from Week 19 [Cycle 7 Day 1])

Activity/Assessment	**Q3W**	**Q6W**	**EOT/EOS/EW [a]**
Visit Windows (Days)	**± 3**	**± 3**	**± 3**
Weight [b]	X		X
Waist circumference [b]	X		
Body mass index	X		X
Physical examination [c]	X		X
12-Lead ECG [d]	X		X
Vital signs [e]	X		X
NGM120 administration [f]	X		
Prior and concomitant medications	X		X
Adverse event	X		X
LISSA evaluations [g]	X		
Clinical chemistry	X		
Hematology	X		X
Urinalysis	X		X
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		

Activity/Assessment	Q3W	Q6W	EOT/EOS/EW [a]
Visit Windows (Days)	**± 3**	**± 3**	**± 3**
Pharmacokinetics [h]	X		X
Antidrug antibodies	X		
Neutralizing antibodies	X		
ECOG performance status		X	
Lean body mass (CT/MRI) [i]		X	
RECIST assessment (CT/MRI) [j]		X	
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

Abbreviations: CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, end of study; EOT, end of treatment; EW, early withdrawal; GDF15, growth differentiation factor 15; LISSA, local injection-site symptom assessment; MRI, magnetic resonance imaging; Q3W, once every 3 weeks; Q6W, once every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Note: All visits will be performed as outpatient day visits. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.

Note: All assessments to be completed before study treatment administration.

[a] The EOT and EOS/EW (4 weeks following last dose administration) visits/assessments to be performed if a subject chooses not to proceed with additional treatment (4 weeks after the last study treatment administration) or discontinues from the study for any reason. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, , subject withdraws consent, death, or study termination by the Sponsor, whichever comes first. The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

[b] The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

[c] Complete physical examination including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[d] A single 12-lead ECG will be obtained at Screening and triplicate ECGs will be obtained at all subsequent assessments. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Measurements of ECG and heart rate will be recorded in a supine position after the subject has been resting for at least 5 minutes.

[e] Temperature, pulse rate, blood pressure, and respiratory rate are to be assessed. Vital signs will consist of 1 pulse rate and 3 blood pressure measurements

(3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

[f] Single subcutaneous administration of NGM120 in the abdomen.

[g] LISSA evaluation to be performed predose and postdose (approximately 30 minutes postdose).

[h] A single predose pharmacokinetic sample is to be collected at all indicated visits. On visits when NGM120 is administered, the sample is to be collected prior to dosing (i.e., predose).

[i] A CT scan of the abdomen is the preferred imaging method. Lean body mass will be calculated at the level of L3. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. All subsequent scans should use the same methodology.

The CT scan results will also be used to determine the subject's skeletal muscle index.

[j] CT scans of the neck, chest, abdomen, and pelvis are the preferred imaging method for tumor assessment. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. The target and nontarget lesions will be selected based on the initial scan, and all subsequent scans should use the same methodology.

Table 1-3 Schedule of Procedures – Part 2

Activity/Assessment	Cycle:	1			2			3			4			Wk 19 (EOS/ EW) [a]	OS [b]
	Day:	1	8	15	1	8	15	1	8	15	1	8	15		
	Screening (Days -28 to -1)	Wk 1	Wk 2	Wk 3	Wk 5	Wk 6	Wk 7	Wk 9	Wk 10	Wk 11	Wk 13	Wk 14	Wk 15 (EOT) [a]		
	Study Day:	1	8	15	29	36	43	57	64	71	85	92	99		
Visit Windows (Days)				± 1	± 1	± 2	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Informed consent	X														
Demographics	X														
Medical/surgical history	X														
Inclusion/exclusion criteria	X	X													
Urine drug screen	X														
Tuberculosis screen [b]	X														
Lean body mass (CT/MRI) [d]	X							X						X [e]	
RECIST assessment (CT/MRI) [f]	X							X						X [e]	
Archival tumor sample (within 5 years) [g]	X														
[redacted]		[redacted]													
Height [h]	X														
Weight [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist circumference [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body mass index	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination [i]	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG [j]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs [k]	X	X	X	X	X	X	X	X	X	X	X	X	X		

Activity/Assessment	**Cycle:**	**1**			**2**			**3**			**4**			**Wk 19 (EOS/ EW) [a]**	**OS [b]**
	Day:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		
	Screening (Days -28 to -1)	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 13**	**Wk 14**	**Wk 15 (EOT) [a]**		
	Study Day:	**1**	**8**	**15**	**29**	**36**	**43**	**57**	**64**	**71**	**85**	**92**	**99**		
Visit Windows (Days)				**± 1**	**± 1**	**± 2**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Pregnancy test [l]	X	X										X		X	
Randomization [m]		X													
NGM120/placebo administration [n]		X			X			X			X				
Abraxane administration (125 mg/m^2) [n]		X	X	X	X	X	X	X	X	X	X	X	X		
Gemcitabine administration (1000 mg/m^2) [n]		X	X	X	X	X	X	X	X	X	X	X	X		
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LISSA evaluations [o]	X	X			X			X			X			X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X			X			X			X		X	X	
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	

Activity/Assessment	Cycle:	1			2			3			4			Wk 19 (EOS/ EW) [a]	OS [b]
	Day:	1	8	15	1	8	15	1	8	15	1	8	15		
	Screening (Days -28 to -1)	Wk 1	Wk 2	Wk 3	Wk 5	Wk 6	Wk 7	Wk 9	Wk 10	Wk 11	Wk 13	Wk 14	Wk 15 (EOT) [a]		
	Study Day:	1	8	15	29	36	43	57	64	71	85	92	99		
Visit Windows (Days)				± 1	± 1	± 2	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Cancer antigen 19-9	X	X			X			X			X			X	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]			[redacted]		[redacted]	
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Pharmacokinetics [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Antidrug antibodies		X			X			X			X		X	X	
Neutralizing antibodies		X			X			X			X		X	X	
ECOG performance status	X				X			X			X		X	X	
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]							[redacted]						[redacted]	
[redacted] contact [c, q]															X [p]

Abbreviations: CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOS, end of study; EOT, end of treatment; EW, early withdrawal; GDF15, growth differentiation factor 15; LISSA, local injection-site symptom assessment; MRI, magnetic resonance imaging; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; Wk, Week.

Note: All visits will be performed as outpatient day visits. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.

Note: All assessments to be completed before study treatment administration.

Note: Based on assessment of a subject's Week 15 data, and following Medical Monitor and Principal Investigator approval, subjects who are tolerating NGM120 and have not experienced disease progression, may continue the allocated study treatment according to the schedule of study procedures detailed in

Table 1-4.

[a] The EOT and EOS/EW (4 weeks following last dose administration) visits/assessments to be performed if a subject chooses not to proceed with additional treatment or discontinues from the study before completing 4 cycles of treatment. If the subject chooses to halt study participation or withdraws from the study, it should be clarified with the subject as to whether he/she agrees to be followed up for survival and this should be documented. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first. The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

[b] Tuberculosis testing may be performed locally when a 37°C incubator is not available on site. Local testing results must be entered in the eCRF.

[c] Overall survival to be collected every 3 months for at least 24 months after the last study treatment administration. See Section 8.4 for more details.

[d] A CT scan of the abdomen is the preferred imaging method. Lean body mass will be calculated at the level of L3. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. All subsequent scans should use the same methodology.

The CT scan results will also be used to determine the subject's skeletal muscle index.

[e] The CT/MRI only to be performed for subjects who withdraw from the study early due to reasons other than radiographically documented disease progression and to be performed only if EW visit is ≥4 weeks from last CT/MRI.

[f] CT scans of the neck, chest, abdomen, and pelvis are the preferred imaging method for tumor assessment. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. The target and nontarget lesions will be selected based on the initial scan, and all subsequent scans should use the same methodology.

[g] If an archival sample is unavailable, a fresh biopsy can be obtained during Screening. If archival tissue or biopsy sample is unavailable, the subject is ineligible.

[h] The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

[i] Complete physical examination including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[j] A single 12-lead ECG will be obtained at Screening and triplicate ECGs will be obtained at all subsequent assessments. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Measurements of ECG and heart rate will be recorded in a supine position after the subject has been resting for at least 5 minutes.

[k] Temperature, pulse rate, blood pressure, and respiratory rate are to be assessed. Vital signs will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

[l] A serum pregnancy test will be performed (for women of childbearing potential) at Screening. Subsequently, the pregnancy test is to be performed per institutional standards.

[m] Only applicable to Part 2 expansion cohort. Randomization to NGM120 or matching placebo to occur before study treatment administration.

[n] Study treatment administration will occur in the following sequential order:

1. NGM120 or placebo (single subcutaneous administration in the abdomen).

2. Abraxane (30 to 40 minutes intravenous infusion).
3. Gemcitabine (30 to 40 minutes intravenous infusion).

[o] LISSA evaluation to be performed predose and postdose (approximately 30 minutes postdose).

[p] A single predose pharmacokinetic sample is to be collected at all indicated time points. On visits when NGM120 is administered, the sample is to be collected prior to dosing (i.e., predose).

[q] At the minimum, the following should be confirmed: disease status, subject survival, subsequent non-study treatment, adverse event, concomitant medications.

Table 1-4 Schedule of Study Procedures – Part 2 (Treatment Continuation – Starting From Week 17)

Activity/Assessment	**Odd Cycles (Starting at Cycle 5 [Week 17]) ***			**Even Cycles (Starting at Cycle 6 [Week 21]) ***			**EOT/ EOS/ EW [a]**	**OS [b]**
Day	**1**	**8**	**15**	**1**	**8**	**15**		
Visit Windows (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Weight [c]	X			X			X	
Waist circumference [c]	X			X			X	
Body mass index	X			X			X	
Physical examination [d]	X			X			X	
12-Lead ECG [e]	X			X			X	
Vital signs [f]	X			X			X	
NGM120/placebo administration [g]	X			X				
Abraxane administration (125 mg/m^2) [g]	X	X	X	X	X	X		
Gemcitabine administration (1000 mg/m^2) [g]	X	X	X	X	X	X		
Prior and concomitant medications	X			X			X	X
Adverse event	X			X			X	X
LISSA evaluations [h]	X			X				
Clinical chemistry	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Urinalysis	X			X			X	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	

Activity/Assessment	Odd Cycles (Starting at Cycle 5 [Week 17]) *			Even Cycles (Starting at Cycle 6 [Week 21]) *			EOT/ EOS/ EW [a]	OS [b]
Day	1	8	15	1	8	15		
Visit Windows (Days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	
Pharmacokinetics [i]	X	X	X	X	X	X	X	
Antidrug antibodies	X			X			X	
Neutralizing antibodies	X			X			X	
ECOG performance status				X			X	
Lean body mass (CT/MRI) [j]	X#							
RECIST assessment (CT/MRI) [k]	X#							
[redacted]				[redacted]			[redacted]	
[redacted]				[redacted]			[redacted]	
[redacted]				[redacted]			[redacted]	
[redacted]				[redacted]			[redacted]	
Telephonic contact [b, l]								X [m]

* Odd cycles include Cycles 5, 7, 9, 11, 13, etc.; Even cycles include Cycles 6, 8, 10, 12, 14, etc.

CT/MRI for RECIST and lean body mass assessments are every 8 weeks, which happens on D1 of the Odd cycles (Cycles 5, 7, 9, 11, 13, etc.).

Abbreviations: CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, end of study; EOT, end of treatment; EW, early withdrawal; GDF15, growth differentiation factor 15; LISSA, local injection-site symptom assessment; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; Q4W, once every 4 weeks; Q8W, once every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Note: All visits will be performed as outpatient day visits. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.

Note: All assessments to be completed before study treatment administration.

Note: Continuation of treatment according to the above schedule allowed for up to 24 months.

[a] The EOT/EOS/EW (4 weeks following last dose administration) visits/assessments to be performed if a subject chooses not to proceed with additional treatment (4 weeks after the last study treatment administration) or discontinues from the study for any reason. If the subject is withdrawn from the study, it should be clarified with the subject as to whether he/she agrees to be followed up for survival and this should be documented. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first. The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

[b] Overall survival to be collected every 3 months for at least 24 months after the last study treatment administration. See Section 8.4 for more details.

[c] The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

[d] Complete physical examination including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[e] A single 12-lead ECG will be obtained at Screening and triplicate ECGs will be obtained at all subsequent assessments. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Measurements of ECG and heart rate will be recorded in a supine position after the subject has been resting for at least 5 minutes.

[f] Temperature, pulse rate, blood pressure, and respiratory rate are to be assessed. Vital signs will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

[g] Study treatment administration will occur in the following sequential order:

1. NGM120 or placebo (single subcutaneous administration in the abdomen).
2. Abraxane (30 to 40 minutes intravenous infusion) for the first 3 weeks of the 4-week cycle.
3. Gemcitabine (30 to 40 minutes intravenous infusion) for the first 3 weeks of the 4-week cycle.

[h] LISSA evaluation to be performed predose and postdose (approximately 30 minutes postdose).

[i] A single predose pharmacokinetic sample is to be collected at all indicated time points. On visits when NGM120 is administered, the sample is to be collected prior to dosing (i.e., predose).

[j] A CT scan of the abdomen is the preferred imaging method. Lean body mass will be calculated at the level of L3. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. All subsequent scans should use the same methodology.
The CT scan results will also be used to determine the subject's skeletal muscle index.

[k] CT scans of the neck, chest, abdomen, and pelvis are the preferred imaging method for tumor assessment. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. The target and nontarget lesions will be selected based on the initial scan, and all subsequent scans should use the same methodology.

[l] At the minimum, the following should be confirmed: disease status, subject survival, subsequent non-study treatment, adverse event, concomitant medications.

Table 1-5 Schedule of Study Procedures – Part 3

Activity/Assessment	Cycle:	1				2		3				4	5	6	Post Treatment				
	Day:	1	4	8	15	1	15	1	4	8	15	1	1	1	(EOS/EW) [a]	OS [m]	Days after Last Dose		
	Screening (Days -28 to -1)	Wk1		Wk2	Wk3	Wk4	Wk6	Wk7		Wk8	Wk9	Wk10	Wk13	Wk16					
	Study Day	1	4	8	15	22	36	43	46	50	57	64	85	106			43	57	85
Visit Windows (Days)			± 1	± 1	± 1	± 1	± 2	± 3	± 1	± 1	± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7
Informed consent	X																		
Demographics	X																		
Medical/surgical history	X																		
Inclusion/exclusion criteria	X	X																	
Urine drug screen	X																		
Tuberculosis screen [b]	X																		
Archival tumor sample (within 5 years) [c]	X																		
[redacted]		[redacted]																	
Height [d]	X																		
Weight [d]	X	X			X	X	X	X			X	X	X	X	X				
Body mass index	X	X			X	X	X	X			X	X	X	X	X				
Physical examination [e]	X	X			X		X				X	X	X		X				
12-Lead ECG [f]	X																		
Vital signs [g]	X	X			X	X	X	X			X	X	X	X	X				

Activity/Assessment	Cycle:	1				2		3				4	5	6	Post Treatment				
	Day:	1	4	8	15	1	15	1	4	8	15	1	1	1	(EOS/EW) [a]	OS [m]	Days after Last Dose		
	Screening (Days -28 to -1)	Wk1		Wk2	Wk3	Wk4	Wk6	Wk7		Wk8	Wk9	Wk10	Wk13	Wk16					
	Study Day	1	4	8	15	22	36	43	46	50	57	64	85	106			43	57	85
Visit Windows (Days)			± 1	± 1	± 1	± 1	± 2	± 3	± 1	± 1	± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7
NGM120 administration [h]		X				X		X				X	X	X					
Prior and concomitant medications	X	X			X	X	X	X			X	X	X	X	X	X			
Adverse event	X	X			X	X	X	X			X	X	X	X	X	X			
LISSA evaluations [i]	X	X				X		X				X	X	X					
Clinical chemistry	X	X				X		X				X	X	X	X				
Hematology	X	X				X		X				X	X	X	X				
Urinalysis	X	X						X					X		X				
Coagulation	X																		
GDF15	X	X			X		X				X		X		X				
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		
Pharmacokinetics (PK)		X[j]	X	X	X	X[j]	X	X[j]	X	X	X	X[j]	X[j]	X[j]			X	X	X
Antidrug antibodies (ADA)		X				X		X				X	X	X			X	X	X
Neutralizing antibodies (nAb)		X				X		X				X	X	X			X	X	X
ECOG performance status	X					X					X		X		X				

Activity/Assessment	Cycle:	1				2		3				4	5	6	Post Treatment				
	Day:	1	4	8	15	1	15	1	4	8	15	1	1	1	(EOS/EW) [a]	OS [m]	Days after Last Dose		
	Screening (Days -28 to -1)	Wk1		Wk2	Wk3	Wk4	Wk6	Wk7		Wk8	Wk9	Wk10	Wk13	Wk16					
	Study Day	1	4	8	15	22	36	43	46	50	57	64	85	106			43	57	85
Visit Windows (Days)			± 1	± 1	± 1	± 1	± 2	± 3	± 1	± 1	± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7
Tumor assessment (CT/MRI and bone scan) [k]	X							X					X		X [l]				
Symptomatic skeletal events	X	X				X		X				X	X	X	X				
PSA	X	X				X		X				X	X	X	X				
Serum testosterone	X																		
[redacted]	[redacted]	[redacted]				[redacted]		[redacted]				[redacted]	[redacted]	[redacted]	[redacted]				
Telephone contact																X			

Abbreviations: cfDNA, [redacted]; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOS, end of study; EOT, end of treatment; EW, early withdrawal; GDF15, growth differentiation factor 15; LISSA, local injection-site symptom assessment; MRI, magnetic resonance imaging; PCWG2=Prostate Cancer Working Group 2; Wk, Week.

Note: All visits will be performed as outpatient day visits. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.

Note: All assessments to be completed before study treatment administration.

[a] The EOT and EOS/EW (4 weeks following last dose administration) visits/assessments to be performed if a subject chooses not to proceed with additional treatment or discontinues from the study before completing 6 cycles of treatment. Subjects who discontinue study treatment for reasons other than PD will be assessed per PCWG2 at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first. The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

[b] Tuberculosis testing may be performed locally when a 37°C incubator is not available on site. Local testing results must be entered in the eCRF.

[c] If an archival sample is unavailable, a fresh biopsy can be obtained during Screening. If archival tissue or biopsy sample is unavailable, the subject is ineligible.

[d] The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

[e] Complete physical examination including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[f] A single 12-lead ECG will be obtained at Screening (no more than 8 days before randomization). Triplicate ECGs will be obtained only if clinically indicated or a cardiac event occurs during the treatment period. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Measurements of ECG and heart rate will be recorded in a supine position after the subject has been resting for at least 5 minutes.

[g] Temperature, pulse rate, blood pressure, and respiratory rate are to be assessed. Vital signs will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

[h] Single subcutaneous administration of NGM120 in the abdomen.

[i] LISSA evaluation to be performed predose and postdose (approximately 30 minutes postdose).

[j] A single predose pharmacokinetic sample is to be collected prior to NGM120 dosing.

[k] Tumor assessment within 4 weeks prior to randomization (6 weeks for bone scan): whole body (abdominal/pelvic/chest) CT or MRI, bone scan, and all other assessments as clinically indicated (e.g., brain CT or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON-TARGET lesions (measurable and non-measurable). CT/MRI will be preferred to x-ray for the purposes of efficacy assessment. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (i.e., CT or MRI, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition. If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.

[l] The CT/MRI and bone scan only to be performed for subjects who withdraw from the study early due to reasons other than radiographically documented disease progression and to be performed only if EW visit is ≥4 weeks from last CT/MRI.

[m] Overall survival to be collected every 3 months for at least 24 months after the last study treatment administration. See Section 8.4 for more details.

Table 1-6 Schedule of Study Procedures – Part 3 (Treatment Continuation – Starting From Week 19 [Cycle 7 Day 1])

Activity/Assessment	Odd Cycles (Starting Cycle 7) Day 1	Even Cycles (Starting Cycle 8) Day 1	Post Treatment				
			EOT/EOS/EW [a]	OS [i]	Days after Last Dose		
					43	57	85
Visit Windows (Days)	**± 3**	**± 3**	**± 3**		**± 7**	**± 7**	**± 7**
Weight [b]	X	X	X				
Body mass index	X	X	X				
Physical examination [c]	X	X	X				
Vital signs [d]	X	X	X				
NGM120 administration [e]	X	X					
Prior and concomitant medications	X	X	X	X			
Adverse event	X	X	X	X			
LISSA evaluations [f]	X	X					
Clinical chemistry	X	X	X				
Hematology	X	X	X				
Urinalysis	X		X				
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]			X		
Pharmacokinetics (PK)	X [g]	X [g]			X	X	X
Antidrug antibodies (ADA)	X	X			X	X	X
Neutralizing antibodies (nAb)	X	X			X	X	X
ECOG performance status	X		X				
Tumor assessment (CT/MRI and bone scan) [h]	X (Cycle 7 Day 1 then every 9 weeks)		X				
Symptomatic skeletal events	X		X				

Activity/Assessment	Odd Cycles (Starting Cycle 7) Day 1	Even Cycles (Starting Cycle 8) Day 1	Post Treatment				
			EOT/EOS/EW [a]	OS [i]	Days after Last Dose		
					43	57	85
Visit Windows (Days)	**± 3**	**± 3**	**± 3**		**± 7**	**± 7**	**± 7**
PSA	X		X				
[redacted]	[redacted]		[redacted]				
Telephone contact				X			

Abbreviations: CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, end of study; EOT, end of treatment; EW, early withdrawal; GDF15, growth differentiation factor 15; LISSA, local injection-site symptom assessment; MRI, magnetic resonance imaging; Q3W, once every 3 weeks; Q6W, once every 6 weeks; PCWG2=Prostate Cancer Working Group 2.

Note: All visits will be performed as outpatient day visits. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.

Note: All assessments to be completed before study treatment administration.

[a] The EOT and EOS/EW (4 weeks following last dose administration) visits/assessments to be performed if a subject chooses not to proceed with additional treatment (4 weeks after the last study treatment administration) or discontinues from the study for any reason. Subjects who discontinue study treatment for reasons other than PD will be assessed per PCWG2 at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, , subject withdraws consent, death, or study termination by the Sponsor, whichever comes first. The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

[b] The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

[c] Complete physical examination including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[d] Temperature, pulse rate, blood pressure, and respiratory rate are to be assessed. Vital signs will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

[e] Single subcutaneous administration of NGM120 in the abdomen.

[f] LISSA evaluation to be performed predose and postdose (approximately 30 minutes postdose).

[g] A single predose pharmacokinetic sample is to be collected prior to NGM120 dosing.

[h] Tumor assessments performed every 9 weeks: whole body (abdominal/pelvic/chest) CT or MRI, bone scan, and all other assessments as clinically indicated (e.g., brain CT or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON-TARGET lesions (measurable and non-measurable). CT/MRI will be preferred to x-ray for the purposes of efficacy assessment. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (i.e., CT or MRI, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). When available, spiral CT acquisition should be done. Slice thickness

should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition. If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.

[i] Overall survival to be collected every 3 months for at least 24 months after the last study treatment administration. See Section 8.4 for more details.

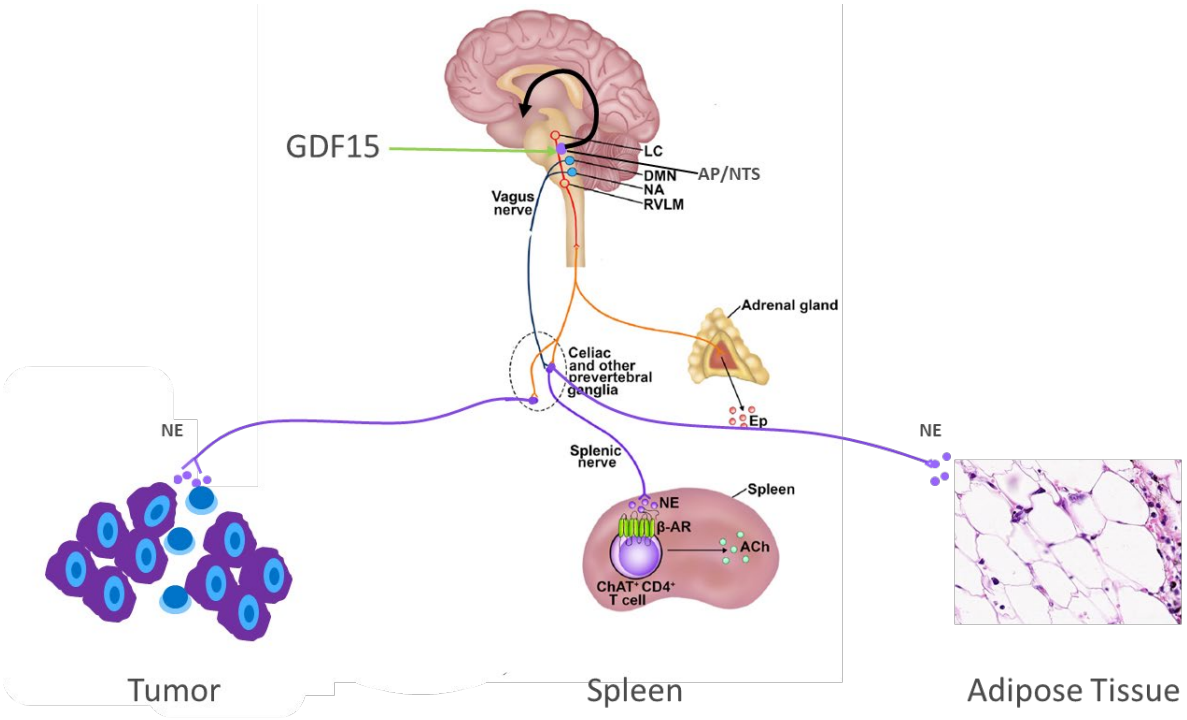
2.0 INTRODUCTION

2.1 Biology of GDF15/GFRAL in Cancer

Growth differentiation factor 15 (GDF15) is a protein of 25 kDa expression and secretion of which is increased in response to stress or injury. Increased GDF15 concentrations in serum have been associated with numerous pathophysiological conditions, including chronic inflammation, dyserythropoietic diseases, cancer, and heart failure.[1] GDF15 is elevated in a number of tumor types including non-small cell lung cancer, melanoma, pancreatic, prostate, colorectal, gastric, and esophageal ovarian cancer. Increased serum GDF15 levels are associated with worse prognosis in prostate[2], colorectal[3], esophageal[4] and ovarian cancers.[5] In cancer, elevated GDF15 levels can be derived from cancer cell-intrinsic expression or by macrophages responding to tissue damage, such as that induced by chemotherapy treatment. Multiple classes of chemotherapies have been reported to increase serum GDF15 levels by 2- to 20-fold above normal in cancer patients.[6] Studies in preclinical models revealed the central role of GDF15 in appetite suppression and weight loss, suggesting that elevated GDF15 levels in cancer patients may contribute to cancer associated weight loss or cachexia.[7,8]

In an effort to identify the endogenous GDF15 receptor(s), NGM Biopharmaceuticals, Inc (hereafter referred to as the Sponsor) discovered glial cell line-derived neurotrophic factor receptor alpha-like (GFRAL) as the sole receptor for GDF15.[8] Based on extensive research in GFRAL knockout mice, the in vivo effects of GDF15 are strictly dependent on GFRAL, including reduction in food consumption, increased lipolysis, and body weight loss.[8,9,10,11] The restricted tissue distribution of GFRAL messenger ribonucleic acid and protein to the area postrema (AP)/nucleus of the solitary tract (NTS) in rodents, nonhuman primates and humans have provided new mechanistic insights to GDF15 activity.[8,9,10,11] Whereas most regions of the brain do not have access to circulating soluble factors, the AP/NTS is uniquely situated outside of the blood-brain barrier, enabling communication with peripherally derived GDF15. The expression of GFRAL in the AP and NTS, which are well described neural networks that regulate food intake and energy expenditure[12,13], is consistent with the observed effects of GDF15 pharmacology in vivo in rodents and nonhuman primates. In addition to communicating with neighboring regions in the brain to influence appetite suppression, chronic and persistent GFRAL signaling leads to distal effects in peripheral tissues through the activation of the sympathetic nervous system (SNS) (Figure 2-1). Exogenous GDF15 administration in healthy mice leads to increased norepinephrine (NE) levels in white adipose tissue and spleen (Figure 2-1). Chemical sympathectomy studies with 6-hydroxydopamine prevented GDF15-induced lipolysis (Figure 2-1), highlighting the requirement of the SNS to mediate the switch to lipid metabolism. GDF15 may signal for tumor growth alongside “immune effects” (spleen) and metabolic effects (adipose).

Figure 2-1 GDF15/GFRAL Engages Sympathetic Nervous System for its Peripheral Effects



Abbreviations: AP, area postrema; GDF15, growth differentiation factor 15; GFRAL, glial cell line-derived neurotrophic factor receptor alpha-like; NE, norepinephrine; NTS, nucleus of the solitary tract; SNS, Sympathetic nervous system.

GDF15 activates GFRAL, which is expressed in the neurons located at AP/NTS and triggers the central "emergency circuit" (black arrow) as well as efferent limb of SNS (orange line). The SNS signals are further relayed through prevertebral ganglions before the neural transmitter, NE, is released at peripheral tissues, such as adipose tissue, spleen, and tumor, to mediate metabolic and immune effects. This figure is modified based on the review by Chavan (2017, Immunity).[14]

The downstream effects of the SNS have been well-documented in mediating stress responses and metabolic changes, as well as in promoting tumor metastasis and immunosuppression via adrenergic receptors in cancer.[15,16,17] Broad inhibition of SNS function with beta adrenergic blocking drugs has shown encouraging results in cancer. Propranolol treatment improved disease-free survival in surgically resected melanoma (Hazard ratio = 0.18, p = 0.3) [18], and combined with chemotherapy in angiosarcoma patients, resulting in 100% response rate.[19] Furthermore, a large body of epidemiologic data showed improved overall survival (Hazard ratio = 0.79, p = 0.004) and disease-free survival (Hazard ratio = 0.60, p = 0.009) in a meta-analysis spanning 12 cancer studies.[20,21] Together, these results support the notion that targeting the SNS pathway may have beneficial outcomes in cancer patients. However, due to the reliance on the SNS in multiple physiologic pathways, more specific means to impair cancer associated SNS activation may be required to achieve optimal antitumor activity. Cancer-associated factors that are responsible for initiating SNS activation have remained elusive. Elevated GDF15 levels,

either from cancer cells that have co-opted GDF15 expression or from normal cells responding to chemotherapy may serve as an important link between cancer-associated stress response and SNS activation (Figure 2-1).

In addition to these well-characterized roles of GDF15/GFRAL in food intake and metabolism, an emerging body of literature suggests that GDF15 harbors immunosuppressive activity. In autoimmune models of arthritis, transgenic or exogenous GDF15 reduces disease severity.[22] Conversely, GDF15 knockout mice exhibit increased inflammatory response to lipopolysaccharides, culminating in exacerbated renal and cardiac injury.[23] Since GFRAL is not expressed by immune cells, the immunosuppressive effects of the GDF15/GFRAL pathway are hypothesized to employ the SNS, similar to the manner in which GDF15 alters whole body metabolism (Figure 2-1). The inhibitory effect of NE-adrenergic signaling on cancer immunosurveillance has been firmly established through both genetic and pharmacologic studies.[24,25,15] In naïve healthy mice, recombinant GDF15 administration is sufficient to increase splenic NE levels and reduce activated/memory cluster of differentiation 4 T cell and macrophage populations, suggesting a link between GDF15 and the SNS, to immunosuppression.

2.2 Rationale for Development of NGM120 in Treatment of Cancer

The hallmarks of cancer are defined by cancer cell intrinsic mechanisms to promote proliferation and survival, and a tumor microenvironment that can regulate cancer immunosurveillance and energy metabolism. Cancer cells communicate with tumor distal sites including lymphoid tissues to promote immunosuppression, or with adipose tissues to alter the utilization of lipids as the primary fuel source. Orchestration of these tumor extrinsic activities can be achieved through soluble factors or through the utilization of the peripheral nervous system to favor cancer growth.[14,15] Common to both immune regulation and alterations in whole-body energy metabolism, the SNS innervates these tumor distal tissues, and is chronically activated under stress conditions. Perineural invasion is commonly observed in multiple cancer types [26], and autonomic nerve fibers promotes prostate cancer development and dissemination.[27] The release of NE, the signature SNS neurotransmitter, signals through beta adrenergic receptors to suppress immune cell activation in secondary lymphoid tissues as well as in the tumor microenvironment.[15,25] Additionally, NE induces a metabolic switch that mobilizes lipids from adipose tissues and generates ketone bodies in the liver. Increased lipolysis by chronic and persistent SNS activity is hypothesized to contribute to a wasting syndrome in advanced cancer patients referred to as cancer-associated cachexia. Therefore, interruption of cancer-induced SNS activity represents an attractive strategy to treat cancer by activating antitumor immunity and preventing cancer-associated cachexia. In support of this, broad inhibition of SNS function with beta adrenergic blocking drugs has shown encouraging results in cancer.[18,19] However, due to the reliance on the SNS in multiple physiologically important pathways, more specific means to impair cancer associated SNS activation may be required to achieve optimal antitumor activity.

The Sponsor has found that the murine parental antibody of NGM120 [redacted] reduces colonization by Lewis Lung Carcinoma cells in lungs of immunocompetent mice. Furthermore, 3[redacted] also inhibited syngeneic Panc-02 orthotopic tumor growth, which confirmed the published data that reducing tumor intrinsic GDF15 expression impaired tumor growth in an immune replete setting.[28] NGM120/[redacted] was also tested in the combination with chemotherapy or anti-PD-1 antibody. In the subcutaneous (SC) xenograft BxPC3 pancreatic cancer model, these tumors regressed upon the treatment with gemcitabine and Abraxane, and the regrowth phase was significantly delayed when NGM120 was combined with this doublet chemotherapy. In addition, NGM120 enhanced antitumor activity of anti-PD-1 antibodies in the mouse syngeneic MBT2 bladder cancer model.

In addition, the Sponsor has evaluated the role of NGM120 in blocking metabolic readouts of GDF15/GFRAL pathway. NGM120 inhibits anorexia and cachexia in multiple tumor-bearing mouse models with elevated serum levels of GDF15. In these models, GDF15 is being expressed and secreted by the cancer cells in the tumor. In addition, as treatment with many chemotherapeutic agents increases GDF15 in damaged host tissue, the Sponsor found that NGM120 also prevents chemotherapy induced anorexia and cachexia in both tumor-bearing and non-tumor-bearing mice. Importantly, NGM120 prevents tumor- and chemotherapy-induced skeletal muscle atrophy and loss of muscle function, as measured by fore-limb grip strength in mice.

Taken together, inhibiting the GDF15/GFRAL pathway by NGM120 represents a novel and promising strategy to promote anti-cancer immunity as well as treat cancer anorexia cachexia syndrome (CACS), which are urgently needed to improve treatment outcome and patients' quality of life, respectively.

2.3 Pharmacokinetics of NGM120

The PK properties and exposure of NGM120 have been evaluated in mice, rats, monkeys, and human. Serum maximum observed serum concentration (C_{max}) and area under the concentration-time curve (AUC) increased proportionally with dose within the dose ranges tested (1 to 3 mg/kg in mice, 0.3 to 50 mg/kg in rats, and 0.1 to 30 mg/kg in monkeys, 10 to 10 mg in human).

Overall, the nonclinical and clinical PK/toxicokinetic behavior observed for NGM120 is consistent with that expected for a humanized immunoglobulin 1 monoclonal antibody that demonstrated minimal target-mediated disposition at the dose range tested. The estimated terminal half-life ($t_{1/2}$) of NGM120 ranged from approximately 12 to 14 days in mice, 12 to 15 days in rats, 14 to 18 days in cynomolgus monkeys, and ~35 days in humans.
The bioavailability of NGM120 was determined to be approximately 95%, 68%, and 81% in mice, rats, and monkeys, respectively, following SC injection.

From the 12-week Good Laboratory Practice toxicity studies, the observed no-observed-adverse-effect level (NOAEL) of NGM120 following multiple once every 2 weeks (Q2W) SC administrations is 50 and 30 mg/kg in rats and cynomolgus monkeys, respectively. The corresponding human equivalent doses of the NOAEL in rats and cynomolgus monkeys are 8 and 10 mg/kg Q2W (or 16 and 20 mg/kg once every 4 weeks [Q4W]), respectively (Table 2-1).

In addition, by comparing the observed PK exposure (C_{max} and AUC) at NOAEL in rats and cynomolgus monkeys with the PK in humans, the Sponsor calculated the safety margins to be 17- to 28-fold for a proposed 100 mg starting dose in patients with solid tumors. In addition, a top dose of 400 mg evaluated in healthy volunteers (Study 17-0401) provides adequate exposure coverage for the 100 mg starting dose in patients with solid tumors.

2.4 Toxicology of NGM120

The nonclinical safety of NGM120 has been evaluated in rats and cynomolgus monkeys for up to 12 weeks of repeat dosing with a 12-week treatment-free period. The rat and cynomolgus monkey were appropriate nonclinical species because NGM120 binds to the rat and cynomolgus monkey GFRAL with comparable affinity to that in humans and is pharmacologically active in both species.

NGM120 was well tolerated in rats and cynomolgus monkeys up to the highest doses tested (50 and 30 mg/kg, respectively) with no clinical signs of toxicity. NGM120 had no effects on body weight, food consumption, ophthalmology, and clinical pathology parameters. NGM120 did not have an effect on the safety pharmacology assessments, including neurobehavioral parameters in rats and cardiovascular parameters, blood gas parameters, and neuromuscular examinations in cynomolgus monkeys.

Following 12 weeks of treatment and a 12-week treatment-free period, animals treated with NGM120 had no differences in gross pathology and organ weights as compared to control animals. No treatment-related microscopic changes were observed in rats and cynomolgus monkeys, including the brain and AP and NTS regions with GFRAL expression.

Treatment with NGM120 did not have any effects on safety pharmacology parameters, as no NGM120 treatment-related changes were observed in neurobehavioral parameters in rats and respiratory (blood gas) and cardiovascular parameters in cynomolgus monkeys. The Sponsor also considered the consequence of blocking GDF15 signaling with NGM120 in the context of chemotherapeutic-induced cardiovascular disease, given that treatment with anthracycline chemotherapeutic agents can increase the incidence of cardiovascular disease in patients, and that serum GDF15 is elevated in patients treated with chemotherapeutic agents as well as in patients with cardiovascular disease.[29,30,31,6,32] Using a rat model of doxorubicin-induced cardiomyopathy. The Sponsor demonstrated that treatment with NGM120 did not alter the development of doxorubicin-induced cardiomyopathy.

Exposure margins (serum AUC) of approximately ~12- and ~7-fold exist between the NOAEL in toxicity studies in rats and monkeys, respectively, relative to the 200 mg (2.86 mg/kg based on a 70 kg subject) maximum dose in the proposed clinical trial (Table 2-1).

Table 2-1 Predicted Exposure Margins for NGM120 in Phase 1/2 Clinical Study

	NGM120 Exposure		Estimated Exposure Margins					
			SAD		Phase 1/2			
	at NOAEL		400 mg		100 mg, 4 × Q3W		200 mg, 4 × Q3W	
	C_{max} µg/mL	$AUC_{0\text{-}28d}$ day*µg/mL	C_{max} µg/mL	$AUC_{0\text{-}28d}$ day*µg/mL	C_{max} µg/mL	$AUC_{0\text{-}28d}$ day*µg/mL	C_{max} µg/mL	$AUC_{0\text{-}28d}$ day*µg/mL
Rat	1240	25,600	~16	~13	~28	~24	~14	~12
Monkey	871	15,000	~12	~7.5	~20	~14	~10	~7

Abbreviations: $AUC_{0\text{–}28d}$, area under the concentration–time curve from time zero to 28 days; C_{max}, maximum observed concentration; NOAEL, no-observed-adverse-effect level; Q3W, once every 3 weeks; SAD, single ascending dose.

The NOAEL was determined from the 12-week Good Laboratory Practice toxicity studies in the rat and cynomolgus monkey where systemic exposure at Day 57 dosing cycle was used to project safety margin. NOAEL in monkey was considered to be 30 mg/kg (Q2W; SC). The NOAEL in rat was considered to be 50 mg/kg (Q2W; SC). Predicted human values following 4 cycles of SC dosing of NGM120 at 100 and 200 mg (once every 3 weeks [Q3W]) were modeled using data from a single SC dose of 100 mg SC in Study 17-0401. Subject weight of 70 kg was assumed; 100 mg: predicted human C_{max} and AUC from time zero to 28 days ($AUC_{0\text{-}28d}$) values are 44.4 µg/mL and 1070 day*µg/mL, respectively; 200 mg: predicted human C_{max} and $AUC_{0\text{–}28d}$ values are 88.8 µg/mL and 2140 day*µg/mL, respectively.

2.5 Phase 1 Clinical Study in Normal Volunteers – Study 17-0401 and Safety Update from 100 mg Cohort in Part 1 of the Current Study 18-0402

Study 17-0401 is a completed single-center, randomized, placebo-controlled, single- and multiple ascending dose (SAD/MAD) study to evaluate the safety, tolerability, and PK of SC administered NGM120 in healthy volunteers conducted in Australia. The SAD doses of 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg and the MAD doses of 10 mg, 30 mg, 100 mg, and 200 mg were evaluated in this Phase 1 study. A total of 92 subjects were randomized, 48 to the SAD portion and 44 to the MAD portion. In the SAD portion, 8 subjects each were randomized to active treatment in Cohorts 1 to 4, 7 subjects were randomized to active treatment in Cohort 5, and 9 subjects were randomized to placebo. In the MAD portion, 9 subjects each were randomized to active treatment in Cohorts 6 to 8, 8 subjects were randomized to active treatment in Cohort 9, and 9 subjects were randomized to placebo.

In the SAD portion of the study, the median T_{max} ranged from 4 to 15 days following a single SC dose of NGM120. Mean C_{max} and $AUC_{0\text{-}56d}$ values increased in an approximately

dose-proportional manner among the 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg dose levels. Across the dose groups, the mean CL/F had a range of 87.9 to 118 mL/day and the $t_{1/2}$ (geometric mean) ranged from 28.3 to 40.0 days. Due to the limited sampling time points in the terminal phase of the PK profiles, the estimates for $t_{1/2}$ and CL/F parameters should be interpreted with caution.

In the MAD portion of the study, the median T_{max} was approximately 7 days after single and multiple dosing (i.e., Days 1 and 57, respectively). Exposure (based on C_{max} and $AUC_{0\text{-}28d}$) after Q4W dosing of 10 mg, 30 mg, 100 mg, or 200 mg NGM120 was approximately 2-fold higher than that after a single dose. Mean accumulation after the fourth dose ranged from 1.6 to 2.0 for C_{max} values, and 1.7 to 2.2 for $AUC_{0\text{-}28d}$ values.

NGM was safety and well-tolerated in both the SAD and MAD portions of the study. In the SAD portion, a total of 36 subjects (75.0%) experienced 76 TEAEs, of which 37 TEAEs were drug-related and experienced by 24 subjects (50.0%). There were no severe TEAEs, serious TEAEs, or TEAEs leading to discontinuation. In the MAD portion, a total of 30 subjects (68.2%) experienced 63 TEAEs, of which 19 TEAEs were drug-related and experienced by 13 subjects (29.5%). Most TEAEs were mild or moderate in severity. There were 3 severe TEAEs in 3 subjects (6.8%) which were also considered as serious TEAEs, and all 3 were considered unrelated to study treatment. These were bipolar disorder (1 Cohort 8 subject), panic attack (1 placebo subject), and renal colic (1 Cohort 8 subjects). The serious and severe TEAE in the 1 placebo subject also led to drug discontinuation and subject withdrawal from the study. No clear dose-related trends were observed. In both the SAD and MAD portions of the study, the most frequently reported TEAE was upper respiratory tract infection (20.8% of SAD subjects, 11.4% of MAD subjects), followed by headache (20.8% of SAD subjects and 11.4% of MAD subjects). Common AEs (reported in >6% of subjects per cohort) deemed related to study drug in the SAD portion included headache, constipation, and injection site reactions, reported by 10.4%, 8.3%, and 6.3% of subjects, respectively. In the MAD portion of the study, a common TEAE deemed related to the study drug was upper respiratory tract infection, reported among 6.8% of the subjects. Finally, no notable observations were made with regard to vital signs, ECG, or physical examination results.

In the current study (Study 18-0402), the Cohort 1 100 mg cohort from Part 1 was completely enrolled and all subjects completed the initial 21-day DLT follow up. Overall, the safety data showed no dose-limiting toxicity identified at the current dose level, and no new safety signals. The PK data are consistent with the expected drug exposure. As of December 2021 (protocol version 5.0), emerging safety, PD (cachexia and tumor), and PK data suggest that the RP2D has not been determined (NGM120 is safe and well tolerated at both 30 and 100 mg, antitumor response observed at both 30 and 100 mg, PK are proportional to dose) and therefore, the Part 2 Phase 1b dose finding cohort (NGM120 30 mg) was increased to add 6 subjects. In addition, potential antitumor activity of NGM120 in combination with gemcitabine/Abraxane may be

observed in patients with metastatic pancreatic cancer; to allow for effective antitumor signal seeking, the Part 2 Phase 2 dose expansion cohort was modified from a 1:1 to a 0:1 (placebo:NGM120 100 mg) randomized design with protocol version 5.0.

2.6 Gemcitabine

Gemcitabine (GEMZAR®) is a nucleoside metabolic inhibitor indicated for use in relapsed ovarian cancer, metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer. Gemcitabine is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas.

See the product label for more details.[33]

2.7 Abraxane

Abraxane® (paclitaxel protein-bound particles for injectable suspension) is a microtubule inhibitor indicated for the treatment of metastatic breast cancer, non-small cell lung cancer, and metastatic adenocarcinoma of the pancreas in combination with gemcitabine.

See the product label for more details.[34]

2.8 Benefit/Risk Assessment

The risk/benefit profile for NGM120 in humans defined mainly from the Phase 1 SAD/MAD study in healthy volunteers (see Section 2.5). NGM120 was well-tolerated, and risks may include injection site reactions, but with no clinically significant or dose-related AEs. Furthermore, based on nonclinical studies, NGM120 exhibited both antitumor and anti-CACS activities in animal models. Patients (hereafter referred to as subjects) taking part in Part 2 would receive gemcitabine and Abraxane which are approved treatments for pancreatic cancer.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of NGM120 may be found in the Investigator's Brochure.

The most common (≥20%) adverse reactions for gemcitabine as a single agent are nausea/vomiting, anemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema. See the product label for more details.[33]

The most common (≥20%) adverse reactions of Abraxane in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. See the product label for more details.[34]

Additional details regarding precautions and warnings for gemcitabine and Abraxane are presented in Section 6.4.2.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information related to NGM120 becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

3.0 OBJECTIVES AND ENDPOINTS

The objectives and matching endpoints for the study are indicated for Part 1 in Table 3-1, Part 2 in Table 3-2, and Part 3 in Table 3-3.

Table 3-1 Study Objectives and Endpoints for Part 1

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of NGM120 in subjects with select solid tumors	• Maximum tolerated dose (MTD)/maximum feasible dose (MFD) as evidenced by dose limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters, electrocardiograms (ECGs), vital signs, and local injection-site symptom assessment.
Secondary	
• To characterize the pharmacokinetics of NGM120 in subjects with select solid tumors	• Serum concentrations of NGM120 at specified timepoints • Pharmacokinetic parameters (including, but not limited to, maximum observed serum concentration [C_{max}], time to maximum observed concentration [T_{max}], area under the concentration-time curve [AUC], clearance, apparent volume of distribution, and apparent terminal half-life [$t_{1/2}$])
• To characterize the immunogenicity against NGM120 in subjects with select solid tumors	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor and anticachexia efficacy of NGM120 in subjects with select solid tumors	• Percent change from baseline in tumor measurements • Body weight, body composition, and lean body mass changes • Patient Reported Outcomes: Functional Assessment of Anorexia/Cachexia Treatment (FAACT) and Appetite Loss Numerical Scale
• Characterize changes in body weight and skeletal muscle index during therapy with NGM120.	• Change in body weight • Percent change in skeletal muscle mass and adiposity at level of L3 on serial computed tomography scans

Objectives	Endpoints
[redacted]	

Abbreviation: GDF15, growth differentiation factor 15.

Table 3-2 Study Objectives and Endpoints for Part 2

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of NGM120 when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Maximum tolerated dose (MTD)/maximum feasible dose (MFD)/optimal efficacious dose (OED) as evidenced by dose limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), discontinuation of investigational product due to toxicity, PK/PD correlation, and changes from baseline in laboratory parameters, electrocardiograms (ECGs) , vital signs, and local injection-site symptom assessment

Objectives	Endpoints
Secondary	
• To characterize the pharmacokinetics of NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Maximum observed serum concentration [C_{max}], time to maximum observed concentration [T_{max}], area under the concentration-time curve [AUC], clearance, apparent volume of distribution, and apparent terminal half-life [$t_{1/2}$]
• To characterize the immunogenicity against NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor and anticachexia efficacy of NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Overall response rate, disease control, duration of response, progression-free survival, and overall survival • Body weight, body composition, and lean body mass changes • Patient Reported Outcomes: Functional Assessment of Anorexia/Cachexia Treatment (FAACT) and Appetite Loss Numerical Scale
• Characterize changes in body weight and skeletal muscle index during therapy with NGM120	• Change in body weight • Percent change in skeletal muscle mass and adiposity at level of L3 on serial computed tomography scans
Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
	• Correlation of GDF15 and other genetic polymorphism to response (applicable only to subjects who consent to providing an optional pharmacogenetic sample; analyses will be reported separately) • Pharmacokinetic and pharmacodynamic relationship
• Characterize changes in functional status during therapy with NGM120	• Change in hand grip strength • Change in daily movement as measured by a wearable biometric sensor
• Collection of optional pharmacogenetic sample for future analysis	• Buccal swab collected

Abbreviation: GDF15, growth differentiation factor 15.

Table 3-3 Study Objectives and Endpoints for Part 3

Part 3 (Phase 1b):

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of NGM120 when administered in metastatic castration resistant prostate cancer (mCRPC) patients who have progressed under 1 or more lines of androgen deprivation therapy (ADT)	• AEs, SAEs, discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters, ECGs, vital signs, and local injection-site symptom assessment
Secondary	
• To characterize the PK of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• C_{max}, t_{max}, AUC, clearance, apparent volume of distribution, and apparent $t_{1/2}$
• To characterize the immunogenicity against NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies

Objectives	Endpoints
• To obtain preliminary evidence of antitumor efficacy of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• **PSA response** defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. • **Time to PSA progression (TTPP)** defined as the time interval between the date of randomization and the date of first documented PSA progression. PSA progression is defined as: 1) If decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart; 2) If no decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint. • **Progression-free survival** defined as the time interval between the date of randomization and the date of the first documentation of any of the following events: - Radiological tumor progression by Prostate Cancer Working Group 2 (PCWG2) - Symptomatic progression - Pain progression - Death due to any cause • **Objective tumor response** in patients with measurable disease (PCWG2) • **Duration of tumor response** • **Symptomatic skeletal events (SSE) rate**, occurrence of SSE (by clinical evaluation) is defined as: - The occurrence of a new symptomatic pathological fracture, or - The use of external beam radiation to relieve bone pain, or - The occurrence of spinal cord compression, or - Tumor-related orthopedic surgical intervention. • **Time to occurrence of SSE** defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE. • **24-month OS** (defined as the time interval from the date of randomization to the date of death due to any cause within a 24-month time frame)

Objectives	Endpoints
• Health status/utility	• EQ-5D-5L • Change in body weight
Exploratory	
• [redacted] •	

4.0 STUDY DESIGN

4.1 Overall Design

This is a multicenter, Phase 1/2, study consisting of 3 parts, with Part 1 as the Phase 1a portion of the study, Part 2 as the Phase 1b/2 portion, and Part 3 as the Phase 1b portion. The aim of the study is to evaluate the safety and tolerability, as well as to obtain preliminary evidence of antitumor activity and anti-CACS activity, of NGM120 monotherapy in subjects with select advanced solid tumors (Part 1), of NGM120 in combination with gemcitabine and Abraxane for the management of metastatic pancreatic cancer (Part 2), and of NGM120 in metastatic castration-resistant prostate cancer (mCRPC) patients who have progressed under 1 or more lines of ADT (Part 3).

Part 2 will start at the same time as Part 1 and run concurrently. Part 3 was implemented with protocol version 6.0.

Part 1 and Part 2 Dose-Finding and Dose Expansion

Part 1 and Part 2 of the study will be split into a dose-finding portion followed by a dose-expansion portion. The study has dose-finding and dose-expansion criteria that will need to be met before either expanding a cohort or initiating an expansion cohort and are presented in Section 4.5 and Section 4.6, respectively.

The dose-finding portion will consist of 2 cohorts in a 3+3 dose-finding design with 2 dose levels. Depending on the dose level/cohort a subject is enrolled to, the subject will receive a dose of either 100 mg or 30 mg of NGM120. Following completion of the final dose-finding meeting, another dose level of NGM120 may be investigated as selected by the Safety Review Committee. Therefore, depending on the drug safety/tolerability profile, a maximum tolerated dose (MTD) or maximum feasible dose (MFD) (Part 1 and Part 2) will be identified. If the drug safety/tolerability is not limiting, an optimal efficacious dose (OED) (Part 2) will be identified based on PK/PD correlation in the consideration of maximal PD activity and adequate drug exposure. Additional cohorts may be added, as new research and clinical data become available.

After all subjects in a dose-finding cohort complete their first cycle of treatment, the Safety Review Committee will be convened to evaluate the available safety, PK, and PD data. The Safety Review Committee will determine whether to proceed with another dose level or whether the MTD/MFD (Part 1) or MTD/MFD/OED (Part 2) has been reached (see Section 4.7). Following selection of the NGM120 MTD/MFD (Part 1) or MTD/MFD/OED (Part 2), enrollment to the dose-expansion cohorts may begin as determined by the Safety Review Committee.

Part 1 and Part 2 of the study have dose-finding (see Section 4.5) and dose-expansion criteria (see Section 4.6) that will need to be met before either expanding a cohort or initiating the expansion cohort.

Blinding

Part 1 will be open-label for both the dose-finding cohorts and the dose-expansion cohorts. NGM120 will administered on a Q3W cycle in subjects with solid tumors who have exhausted all standard therapies for their underlying cancer.

Part 2 will be open-label for the dose-finding cohorts. The dose-expansion cohort will be single--blind (Sponsor unblinded) with subjects randomly allocated to treatment with either NGM120 or a matching placebo, administered on a Q4W cycle. All subjects in Part 2 will also receive gemcitabine (1000 mg/m^2) and Abraxane (125 mg/m^2) weekly for the first 3 weeks of the 4-week cycle.

Part 3 will be open-label. Subjects will receive NGM120 100 mg Q3W. All subjects will continue their current hormonal therapy for mCRPC in combination with NGM120.

Study Design

After a screening period of 4 weeks, eligible subjects will be entered sequentially into a treatment cohort. During the treatment period, subjects will be administered NGM120 for a minimum of 6 cycles (18 weeks in Parts 1 and 3) or 4 cycles (16 weeks in Part 2). Afterwards, following Medical Monitor and Principal Investigator approval based on assessment of the subject's Week 18 (Parts 1 and 3), Week 15 (Part 2) data, the subjects who are tolerating NGM120 and have not experienced disease progression, may continue the allocated study treatment for 24 months or until disease progression, intolerable toxicity, the need for other anticancer therapy, pregnancy, or a physician or subject decision to withdraw from the study. A follow-up visit will be held 4 weeks after the subject receives his/her last study treatment administration. All visits will be outpatient, day visits. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST (Parts 1 and 2) or PCWG2 (Part 3) at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first.

All subjects in Part 1 and Part 3 who continue NGM120 treatment beyond 6 cycles (18 weeks) will continue their assigned NGM120 dose until they leave the study. However, subjects in the Part 2 dose-finding cohorts who continue NGM120 treatment will be changed to the selected NGM120 for the dose-expansion cohort, once determined by the Safety Review Committee.

An interim clinical study report will be prepared once all subjects have completed the treatment period (6 cycles [18 weeks in Part 1 and Part 3] or 4 cycles [16 weeks in Part 2]). The full clinical study report will be prepared once all subjects in Part 2 have completed the required survival follow-up.

4.2 Scientific Rationale for Study Design

This will be a multicenter, Phase 1/2 study consisting of 2 parts, with Part 1 as the Phase 1a portion of the study and Part 2 as the Phase 1b/2 portion. The aim of the study is to evaluate the safety and tolerability, and to obtain preliminary evidence of antitumor activity and anti-CACS activity of NGM120 monotherapy in subjects with select advanced solid tumors (Part 1) and of NGM120 in combination with gemcitabine and Abraxane for the management of metastatic pancreatic cancer (Part 2), and of NGM120 in metastatic castration-resistant prostate cancer (mCRPC) patients who have progressed under 1 or more lines of ADT (Part 3).

Details of the study design are presented in Section 4.1.

Populations

A subject selection strategy based on serum GDF15 level is employed to enrich for subjects in the expansion portion of Part 1 and Part 2 and in the study treatment period of Part 3 so that there is an increased likelihood to observe the PD effects of NGM12[redacted]Based on nonclinical data, pancreatic cancer appears to be one of the best indications for evaluating the possible action of NGM120 and was selected for evaluation in Part 2. Based on clinical data in the current study (Phase 1a), mCRPC appears to be an indication that is associated with significant elevation of serum GDF15 and has shown response to NGM120 and was selected for evaluation in Part 3.

Combination Treatment

In Part 2, it is planned to study the combination of NGM120 with gemcitabine and Abraxane in subjects with metastatic pancreatic cancer. NGM120 does not affect the efficacy of gemcitabine+Abraxane when used in combination. Furthermore, pancreatic xenograft tumors regressed upon the treatment with gemcitabine and Abraxane, and the regrowth phase was significantly delayed when NGM120 was combined with this doublet chemotherapy. The combination of these chemotherapeutic agents is a common first-line therapy in pancreatic cancer.

In Part 3, it is planned to study the subject's current hormonal therapy in combination with NGM120. Per Section 5.1, Part 3 specific inclusion criteria, the subject's current hormonal therapy could consist of ADT as per standard of care OR 2 or more lines of ADT (see Section 5.1, for allowed ADT).

Starting Dose

See Section 4.3 for the selected starting dose.

Blinding and Randomization

The dose-finding cohorts (Part 1 and Part 2) and the Part 1 dose-expansion cohorts will be open-label as all subjects will receive NGM120. However, in the dose-expansion cohort of Part 2, subjects will be randomly allocated to treatment with either NGM120 or a matching placebo. The randomization will be stratified by GDF15 levels [redacted] at baseline. A placebo-controlled design was selected to allow for objective assessment of the safety of NGM120. Randomization and single-blind (Sponsor unblinded) blinding will be used to minimize bias arising from the assignment of subjects to treatment groups and the expectations of subjects, Investigators, and individuals collecting data. After protocol version 5.0, randomization will be changed from 1:1 to 0:1 placebo:NGM120 100 mg. Subjects enrolled prior to protocol version 5.0 will remain under single blind blinding (Sponsor unblinded).

Part 3 of the study will be open-label as all subjects will receive NGM120.

Pharmacokinetic Samples

PK sampling (blood) and measurement of the NGM120 concentrations will enable the assessment of the PK profile of the study treatment at the selected escalating dose levels. The duration of PK sampling has been chosen to sufficiently characterize the PK of NGM120.

Patient Reported Outcomes

A number of Patient Reported Outcomes (PROs) were selected to be completed by the subjects enrolled in Parts 1, 2, and 3; see Section 8.5.4 for details on the PROs to be completed.

The PROs measure quality of life, symptoms, subject functioning, and subject perceptions of care; PROs are essential for gaining a full understanding of cancer care and the impact of cancer on people's lives. Repeatedly captured PROs could play an important role in quality monitoring and improvement, benchmarking, advocacy, policy making, and research.

[redacted]

4.3 Justification for Dose

4.3.1 Justification for Starting Dose

The previous healthy volunteer study tested varying doses at 10, 30, 100, 200, and 400 mg. A starting dose of 100 mg NGM120 was selected by the Sponsor based on safety profile and expected active dose. Based on emerging PK and PD data, the NGM120 200 mg dose was removed, and the NGM120 30 mg dose was added (see page 7, Protocol Changes History).

4.3.2 Justification for Optimal Efficacious Dose/Recommended Phase 2 Dose

Two doses of NGM120 (30 mg and 100 mg) have been tested in the current study (Study 18-0402). Based on the available PK data, NGM120 concentrations appear approximately 30%-60% lower in oncology patients compared with healthy volunteers (Figure 4-1), possibly due to increased protein catabolism in cancer patients.[40] There appears to be a dose-proportional increase in NGM120 exposure from 30 mg to 100 mg, although the PK data for the 30 mg dose is still limited. NGM120 accumulation was observed for the 100 mg dose, with accumulation ratios ranging 1.33-1.64 for Part 1 (based on Cycles 1-2 trough concentrations), and 1.92-2.32 for Part 2 (based on Cycles 1-4 trough concentrations). These data are consistent with the expected long half-life (~35 days) for NGM120 observed in the healthy volunteer study.

Figure 4-1 NGM120 Exposures in Study 18-0402 and Predicted NGM120 Exposures from Healthy Volunteers

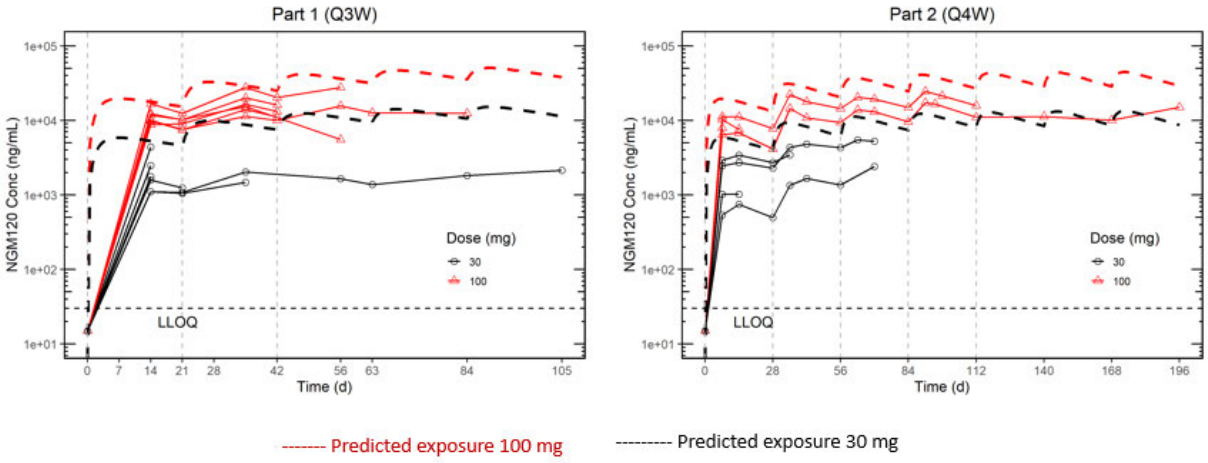


Figure 4-1: Individual concentration-time profiles observed in cancer patients (solid lines) dosed at 30 mg (black) and 100 mg (red), overlaid with the predicted typical PK profile in healthy volunteers at the respective doses (dashed lines) in Part 1 (Q3W) and Part 2 (Q4W) of the study. The study is ongoing, and the plots are based on partial data to date.

GDF15 induces lipolysis, thereby increasing the production of ketone bodies. Blocking GFRAL has been shown to decrease their production in nonclinical models. In addition, blocking GFRAL increases appetite and decreases lipolysis, thereby increasing body weight. Therefore, ketone bodies such as β-hydroxybutyrate and body weight are useful PD readouts to evaluate whether there is dose-dependent PD readout. In the Part 1 monotherapy, there was a 57% increase in β-hydroxybutyrate for the 30 mg cohort, but a 27% decrease for the 100 mg cohort on Cycle 2 Day 1 (Figure 4-2), reaching statistical significance ($p = 0.033$). Furthermore, body weight was increased 1.35% for the 100 mg cohort but decreased 1.23% for the 30 mg cohort on Cycle 2 Day 1 ($p<0.01$; Figure 4-2). The same PD readouts were also performed for the Part 2 subjects, who showed more variable responses, likely due to the complication of adding gemcitabine and abraxane doublet chemotherapy. Based on these PK and PD analyses, the data support that there is a dose-dependent increase in the PD effect from 30 mg to 100 mg, suggesting that 100 mg affords more complete blockade of the GDF15/GFRAL pathway. A simulation and modeling analysis has also been performed to estimate the ratio between NGM120 to target (i.e., GFRAL) at steady-state PK exposure in order to support the dose selection, which shows that GFRAL is well saturated at 100 mg dose at Q4W.

Figure 4-2 Pharmacodynamic Changes (β-hydroxybutyrate and Body Weight) in Study 18-0402

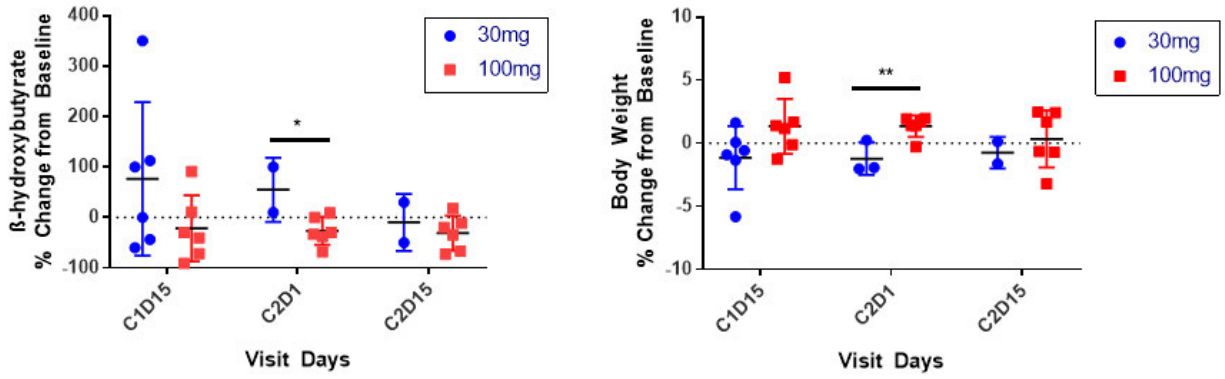


Figure 4-2: PD Biomarker Analysis. Changes in β-hydroxybutyrate and body weight were tracked for the first 3 time points after the first dose. Percent changes were calculated from Cycle 1 Day 1 unless unavailable at which point Screening value was used as baseline.
* p = 0.03
**p <0.01

As of March 2021 (protocol version 4.0), the Safety Review Committee concluded that there were no DLT(s) for either dose level in Part 1 or Part 2. There was no obvious correlation between NGM120 dose and AE/SAE prevalence in Part 1 NGM120 monotherapy. The common AEs for both dose levels were fatigue (43%), insomnia (29%), constipation (21%), diarrhea (21%), nausea (21%), anemia (21%), headache (21%), sepsis (21%), UTI (14%), and edema (14%). All SAEs were due to pre-existing diseases. In the Part 2 Phase 1b combination dose-finding cohorts, 5 pancreatic cancer patients experienced multiple SAEs, including sepsis, febrile neutropenia, pancreatitis, diarrhea, vomiting, retroperitoneal hemorrhage, acute kidney injury, cardiac arrest, and encephalopathy, none of which were deemed related to the treatment of NGM120 after medical safety review. The related SAEs were attributed to gemcitabine and Abraxane. Therefore, based on PK, PD, and safety data, NGM120 100 mg is the OED, and therefore, the RP2D for the Phase 2 randomized study (in combination with gemcitabine and Abraxane) in subjects with pancreatic cancer.

As of December 2021 (protocol version 5.0), emerging safety, PD (cachexia and tumor), and PK data suggest that the RP2D has not been determined and did not support NGM120 mg as the OED. Therefore, the Part 2 Phase 1b dose finding cohort (NGM120 30 mg) was increased to add 6 subjects and the Part 2 Phase 2 dose expansion cohort was modified from a 1:1 to a 0:1 (placebo:NGM120 100 mg) randomized design with protocol version 5.0.

4.4 End of Study/Study Completion Definition

The study stopping criteria is defined in Section 4.8.

The end of study/study completion definition is defined as 1 year after the last subject receives the last dose of NGM120 or study termination by the Sponsor, whichever comes first. Survival data may be collected beyond the end of study. All subjects will be contacted for survival every 3 months for at least 24 months after the last study treatment administration.

Radiologic tumor assessments will continue to be collected every 8 weeks (Parts 1 and 2)/9 weeks (Part 3) until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first.

4.5 Dose-Finding Criteria

As of June 2020 (protocol version 3.0), based on emerging PK data, the NGM120 200 mg dose was removed, and the NGM120 30 mg dose was added. The study was modified from a dose-escalation design to a dose-finding design.

As of December 2021 (protocol version 5.0), emerging safety, PD (cachexia and tumor), and PK data suggest that the RP2D has not been determined and therefore the Part 2 Phase 1b dose finding cohort (NGM120 30 mg) was increased to add 6 subjects and the Part 2 Phase 2 dose expansion cohort was modified from a 1:1 to a 0:1 (placebo:NGM120 100 mg) randomized design with protocol version 5.0.

The study schema of Part 1 (Phase 1a), Part 2 (Phase 1b/2), and Part 3 (Phase 1b) are presented in Figure 1-1, Figure 1-2, and Figure 1-3, respectively.

Part 1 and Part 2 will follow a modified 3+3 dose-finding design with 2 dose levels (100 mg and 30 mg). Subsequently, dose-expansion cohorts will be enrolled, see Section 4.6 for more details.

Three subjects will initially be enrolled in each cohort. If there are no dose-limiting toxicities (DLTs) observed in Cycle 1 of any of the initial 3 subjects, enrollment to the next cohort could proceed. If 1 of the 3 subjects (33%) experiences a DLT, the cohort will be expanded to 6 subjects (3 additional subjects enrolled). Dose-limiting toxicities will also be monitored in the expansion cohort(s) and the dose may be reconsidered if the DLT rate exceeds 33% of study treatment-administered subjects as determined by the Safety Review Committee.

All subjects in a cohort will be followed for a minimum of 1 cycle of treatment (3-week cycle in Part 1 and 4-week cycle in Part 2), followed by the Safety Review Committee review before the next cohort begins NGM120 administration.

The DLT evaluation will be done as follows:

- DLTs will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) criteria Version 5.0.
- DLTs will be any Grade 3 or higher AEs that are at least possibly related to NGM120, except the following:
  - Grade 3 fatigue lasting <5 days.
  - Grade 3 nausea, vomiting, or diarrhea lasting <72 hours in subjects who have not received standard antiemetic or antidiarrheal therapy.
  - Asymptomatic Grade 3 to 4 laboratory abnormalities that persist for <72 hours, or asymptomatic Grade 3 or 4 laboratory abnormalities that do not meet SAE criteria (see Appendix 5 of the protocol for the serious criteria).
  - Grade 4 neutropenia lasting <5 days.
  - Grade 3 thrombocytopenia in the absence of hemorrhage.

4.6 Dose-Level Expansion

Upon completion of the dose-finding cohorts and determination of the MTD/MFD (Part 1) or MTD/MFD/OED (Part 2), the Safety Review Committee will review all available data from the cohorts before permitting the dose-level expansion. Note: For Part 1, the Safety Review Committee will review all available data from the first dose-finding cohort (100 mg) and the first 3-6 subjects in the PD expansion cohort (30 mg) only. All available data will be reviewed according to a separately prepared Cohort Management Plan.

See Section 4.7 for details on the MTD/MFD (Part 1) or MTD/MFD/OED (Part 2) selection and dose selection for administration in the dose-expansion cohorts.

All subjects in Part 1 who continue NGM120 treatment beyond 6 cycles (18 weeks) will continue their assigned NGM120 dose until they leave the study. However, subjects in the Part 2 dose-finding cohorts who continue NGM120 treatment will be changed to the selected NGM120 for the dose-expansion cohort, once determined by the Safety Review Committee.

4.7 Determination of the Maximum Feasible Dose (Part 1) or Maximum Tolerated Dose/Maximum Feasible Dose/Optimal Efficacious Dose/Recommended Phase 2 Dose (Part 2)

The selection of 100 mg or 30 mg NGM120 as the expansion dose will be based on the safety profiles, PK, PD, and additional considerations of the doses in the dose-finding cohorts. Following completion of the final dose-finding meeting, another dose level of NGM120 may be selected, by the Safety Review Committee, for further investigation.

If the 100 mg dose is not safe and well-tolerated, and the 30 mg dose selected by the Safety Review Committee is deemed safe (defined as DLTs ≤33% within the 21-day window for Part 1

and 28-day window for Part 2) and well tolerated, the 30 mg dose will be the MTD and expanded thereafter.

If both the 100 mg and 30 mg doses are deemed safe (defined as DLTs ≤33% within the 21-day window for Part 1 and 28-day window for Part 2) and well tolerated, the OED will be selected based on PK/PD correlation in the consideration of PD activity and adequate drug exposure. If the OED is identified, the OED will be the recommended Phase 2 dose (RP2D). If the 30 mg dose is chosen as the expansion dose, a loading dose of 100 mg could be used to accelerate the time to steady-state drug concentrations.

All available data will be reviewed according to a separately prepared Cohort Management Plan.

In subjects who are tolerating the study treatment and have not experienced disease progression, study treatment may be continued after Medical Monitor and Principal Investigator approval. The study treatment will continue until disease progression, intolerable toxicity, the need for other anticancer therapy, pregnancy, or a physician or the subject's decision to withdraw from the study. Subjects will continue with their assigned NGM120 monotherapy or NGM120/placebo with gemcitabine+Abraxane combination therapy.

4.8 Study Stopping Criteria

4.8.1 Stopping Criteria for Individual Subjects

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment, see Section 7.2. The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, the case will be reviewed by the Medical Monitor, and the severity of the deviation from eligibility criteria will be determined. The Medical Monitor will determine whether the subject may remain on study treatment or not.

Treatment for any individual subject may be stopped if the subject experiences unacceptable toxicity, disease progression (see Section 8.5.2), symptomatic deterioration (e.g., performance status deterioration to Eastern Cooperative Oncology Group [ECOG] rating 3), withdrawal of consent, Investigator decision, or other reasons specified by the Investigator, study physician, or the Sponsor's medical representative that warrants discontinuation of the study for that subject's well-being.

Beyond the aforementioned, the Investigator may remove a subject from the study for the following reasons after discussion with the Medical Monitor:

- Noncompliance with study procedures.
- Need of treatment with medications not allowed by the study protocol.
- Intercurrent illness that interferes with study assessments.

- Incidence or severity of AEs in this study indicates a potential health hazard to the subject.
- Cancellation of the drug development program by the Sponsor.

The treatment will also be stopped immediately for any female subject who reports a pregnancy during study participation.

In the case of premature withdrawal from the study, the assessments scheduled for the end of treatment visit should be performed. The subject should be asked whether any study specimens for future testing may be retained, and this should be documented.

In the dose-finding cohorts, only subjects who do not complete the DLT observation period (Cycle 1) for reasons other than a DLT, will be replaced. Subjects who are withdrawn because of a DLT will not be replaced.

4.8.2 Criteria for Stopping Dose-Finding Cohorts

Dose-finding cohorts will be stopped if any of the criteria detailed in Section 4.5 are met.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Males and females (Part 1 and Part 2) and males (Part 3) at least 18 years of age who are able to comprehend and willing to sign an informed consent form.
2. Part 1 and Part 2 Only: Have at least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 guidelines.Have an ECOG performance status of 0 to 1 at Screening.
4. The following additional laboratory parameters must be met at Screening:
   a) Serum albumin >30 g/L
   b) Absolute neutrophil count ≥1.5 × 10^9/L (without growth factors for >21 days)
   c) Platelets >100 × 10^9/L (without platelet transfusion for >21 days)
   d) Hemoglobin ≥9 g/dL
   e) Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault formula
   f) Total bilirubin ≤1.5 × ULN. Total bilirubin ≤3 × ULN in the presence of liver metastases. Subjects with Gilbert's disease may be included.
   g) ALT ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN
1. Have a life expectancy of at least 12 weeks.
2. Male subjects must agree to use contraception as detailed in Appendix 7 of this protocol during the treatment period and for at least 90 days after the last study treatment administration and refrain from donating sperm during this period.
3. Male subjects with a female partner of childbearing potential have to agree to use consistent and adequate birth control from Screening to 90 days after the last study treatment administration.
4. Female subjects will be eligible to participate if she is not pregnant (see Appendix 7), not breastfeeding, and at least 1 of the following conditions applies:
   i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 7.
   OR
   ii) A WOCBP, defined as a woman <55 years of age with <2 years of amenorrhea (absence of menstruation) who agrees to follow the contraceptive guidance in Appendix 7 during the treatment period and for at least 90 days after the last study treatment administration.
5. Able and willing to comply with the dosing instructions for study treatment administration and able to complete the study schedule of assessments.

6. Provision of an archival tumor sample (within 5 years). If an archival sample is unavailable, a fresh biopsy can be obtained during Screening. If archival tissue or biopsy sample is unavailable, the subject is ineligible.

Part 1 Specific Criteria

1. Have histologically confirmed advanced or metastatic castration-resistant prostate cancer, bladder cancer, melanoma, non-small cell lung cancer, pancreatic cancer, colorectal cancer, gastric cancer, esophageal cancer, ovarian cancer, and head neck squamous cell carcinoma.
2. Have exhausted all standard therapies for underlying cancer.
3. Have progressive disease (PD) for which no effective therapies are available.
4. Have serum GDF15 level [redacted].

Part 2 Specific Criteria

5. Have histologically confirmed metastatic pancreatic adenocarcinoma. Recurrent unresectable pancreatic cancer is acceptable as long as the treatment is first line for recurrent disease.
6. Have not received any chemotherapy other than chemotherapy given with neoadjuvant or adjuvant intent as specified below:
   a) For dose-level cohorts (dose-finding portion), if subjects received prior gemcitabine + Abraxane, they are only eligible when they did not discontinue this therapy for excess toxicity.
   b) For dose-expansion (randomized portion):
      i) In neoadjuvant setting, FOLFIRINOX is allowed. Those receiving gemcitabine and Abraxane are required to have had a best radiographic (RECIST v1.1) response of partial response and/or complete pathologic response in order to be eligible.
      ii) In adjuvant setting, FOLFIRINOX, gemcitabine and Xeloda combination therapy, or gemcitabine monotherapy is allowed.
   c) For all Part 2 subjects, subjects can only have received 2 separate regimens maximum adjuvant and/or with neoadjuvant intent.
7. Serum GDF15 levels [redacted]. For the 45 subjects in the Phase 2 expansion cohort, up to 12 subjects (20%) can be enrolled with [redacted] Lowering of the cutoff will allow the testing a broader range of pancreatic cancer patients and take into the consideration that GDF15 levels are typically increased 2-3-fold with gemcitabine and Abraxane treatment.

Part 3 Specific Criteria

1. Metastatic, castrate resistance, histologically confirmed prostate cancer; continuous medical castration for ≥8 weeks prior to screening.
2. Effective castration with serum testosterone levels <0.5 ng/mL (50 ng/dL; 1.7 nmol/L).
3. Have serum GDF15 levels [redacted].

8. Have experienced PSA progression under 1 or more lines of ADT in the absence or presence of radiographic and/or clinical progression, who decline or are not eligible to receive chemotherapy.
   a) PSA progression is defined as an increase of 25% and an absolute increase of ≥2 ng/mL from nadir, confirmed by a second value obtained ≥3 weeks later (as defined by PCWG2). The confirmatory PSA should be taken within 4 weeks prior to enrollment and analyzed at a central laboratory.

   b) Subjects are required to be on at least 1 line of ADT and are allowed to be on combination of 2 or more lines of ADT. Lines of ADT include: 1) Luteinizing hormone-releasing hormone (LHRH) agonists, e.g., leuprolide (Lupron), goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas); 2) LHRH antagonists, e.g., degarelix (Firmagon) and relugolix (Orgovyx); 3) Androgen receptor antagonists, e.g., flutamide, bicalutamide (Casodex), nilutamide (Nilandron), and the second-generation drugs enzalutamide (Xtandi), apalutamide (Erleada), and darolutamide (Nubeqa); 4) Androgen synthesis inhibitors, e.g., abiraterone (Yonsa, Zytiga).
9. Have had PSA doubling time of >3 months.

5.2 Exclusion Criteria

Subjects are to be excluded from the study if any of the following criteria apply:

1. Subject was using immunosuppressive medications within 14 days before Cycle 1 Day 1 with the exception of topical (intranasal, inhaled, and local injection), systemic (prednisone equivalent 10 mg/day or less), or as needed for hypersensitivity reactions such as computed tomography (CT) scan premedication.
2. Subject has active infections or other serious underlying significant medical illness, abnormal and clinically significant laboratory findings, or psychiatric illness/social situation.
3. Subject is using a pacemaker, implantable cardiac defibrillator, neurostimulator, cochlear implants, cochlear implants, or other electronic medical equipment.
4. Subject has an allergy to elastomer/rubber.
5. Subject has documented immunodeficiency or organ transplant.
6. Subject is currently planning to use, or has used, any live vaccines within 28 days before Cycle 1 Day 1.
7. Subject is planning to, or has undergone, major surgery within 28 days before Cycle 1 Day 1.
8. Subject initiated concurrent cancer therapies (chemotherapy, radiotherapy, surgery, immunotherapy, biologic, or hormonal therapy) within 28 days before Cycle 1 Day 1.
9. Subject received concurrent treatment with an investigational agent or participated in another clinical study within 28 days or 2 half-lives, whichever is longer, before Cycle 1 Day 1.
10. Subject has a history of cerebral vascular accident, transient ischemic attack, or subarachnoid hemorrhage within 3 months before Cycle 1 Day 1.

11. Subject has a history of clinically significant hemorrhage within 3 months before Cycle 1 Day 1.
12. Subject has an untreated central nervous system disease.
13. Subject has a history, or presence, of significant cardiovascular diseases; including uncontrolled hypertension, clinically relevant cardiac arrhythmia, unstable angina, or myocardial infarction within 6 months before randomization, congestive heart failure > New York Heart Association Class II, severe peripheral vascular disease, corrected QT (QTc) prolongation >470 msec, clinically significant pericardial effusion.
14. Female subjects who are pregnant or currently breastfeeding.
15. Presence of persistent clinically relevant therapy-related toxicity from previous anticancer therapy (any Grade 3 to 4 toxicity or Grade ≥2 neuropathy), except alopecia or fatigue.
16. Subject has a history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Principal Investigator.
17. Subject has a history or presence of autoimmune disease within the 2 years before Cycle 1 Day 1 with the exceptions of vitiligo, Hashimoto's thyroiditis, Grave's disease, and/or psoriasis not requiring systemic treatment.
18. Subject has a history or presence of documented inflammatory bowel disease.
19. Subject has a history or presence of gastric or duodenal obstruction within 6 months before Cycle 1 Day 1.
20. Subject has a history or presence of clinically significant pleural effusion and ascites requiring paracentesis within 6 months before Cycle 1 Day 1.
21. Subject has a current and active tuberculosis infection at Screening. For eligibility purposes, it is acceptable for Investigators to confirm through clinical symptoms, or radiographic signs to rule out an active tuberculosis infection.
22. Subject is known to be positive for human immunodeficiency virus infection.
23. Subject is (a) not currently diagnosed with or being treated for a malignant cancer other than castration-resistant prostate cancer, bladder cancer, melanoma, non-small cell lung cancer, pancreatic cancer, colorectal cancer, gastric cancer, esophageal cancer, ovarian cancer, or head neck squamous cell carcinoma or (b) if the subject was diagnosed with a malignant cancer in the past, it must have been effectively treated (no residual disease) at least 5 years prior to Screening.
24. Subject has central nervous system metastatic disease from castration-resistant prostate cancer, bladder cancer, melanoma, non-small cell lung cancer, pancreatic cancer, colorectal cancer, gastric cancer, esophageal cancer, ovarian cancer, and head neck squamous cell carcinoma.

    Active central nervous system (CNS) metastasis is defined as metastases involving either brain or cord/leptomeninges in which:

    - The metastases are untreated (surgery and/or radiotherapy); OR
    - The subject is on corticosteroids of > 10 mg/day prednisone or equivalent; OR

- The subject is not neurologically stable for 28 days prior to enrollment.

NOTE: For subjects with known brain metastases, it is expected that brain MRI is performed within 6 weeks of enrollment. Subjects without known CNS metastases are NOT required to have brain MRI during Screening unless clinically indicated. Also note that any therapy for CNS metastases (surgery or radiation) is complete > 28 days from enrollment.

24. In the opinion of the Principal Investigator, the subject is not acceptable to participate in the study.
25. Subject is related to the Investigator, is an employee of the study center, related to an employee of the study center, or involved in the conduct of the study in any way.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

The following restrictions will apply:

1. Subjects will be required to fast overnight for at least 8 hours before each visit. After laboratory sample collection, no other restrictions regarding food are required.
2. Water is allowed ad libitum.
3. Part 2 only: Subjects should refrain from consumption of grapefruit or similar substances (Seville oranges or marmalade, grapefruit juice, grapefruit hybrids, pomelos, exotic citrus fruits, or grapefruit/orange juices) within 7 days before Cycle 1 Day 1 and throughout the study.

5.3.2 Caffeine, Alcohol, and Tobacco

The following restrictions will apply:

1. Throughout the study, consumption of alcohol should be moderate and limited to no more than 1 drink on any single day and no more than 7 drinks per week.
2. Subjects are not permitted to consume alcohol for 3 days before Cycle 1 Day 1 and must refrain from any alcohol consumption for at least 2 days before each study visit throughout study participation.

5.3.3 Activity

The following restrictions will apply:

1. Subjects may continue with their regular exercise regimen with which they are comfortable; however, anything outside of ordinary activities should be approved by the treating physician. Subjects should abstain from strenuous exercise outside of that approved by the treating physician for 3 days before each scheduled visit.

2. Subjects will be advised not to donate blood or plasma while on the study and for at least 6 months after the last study treatment administration.
3. Subjects are to be informed that they must apply highly effective contraceptive methods. The contraceptive method should still be used for at least 6 months following the last study treatment administration. For details on the acceptable contraception methods and follow-up in case of a pregnancy, see Appendix 7.

5.4 Screening and Rescreening Criteria

Patients will undergo all screening evaluations to confirm that they meet all study eligibility criteria. Screen failures are defined as subjects who consent to participate in the study but are subsequently not entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographic data, screen failure details, eligibility criteria, and any SAE.

Subjects who do not meet the criteria for participation (i.e., screen failure) may be rescreened 1 time only within a 60-day period prior to Cycle 1 Day 1. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine patient eligibility. The Sponsor's Medical Monitor should be consulted for approval of subject rescreening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatments Administered

Study treatment details are presented in Table 6-1.

Table 6-1 Study Treatment Details

Study Treatment Name:	NGM120	Placebo	Abraxane (Paclitaxel protein-bound particles for injectable suspension)	GEMZAR (Gemcitabine)
Applicable Study Part (Cohort):	Part 1 and Part 2 (dose-finding and expansion) and Part 3	Part 2 (dose expansion only)	Part 2 (dose-finding and expansion)	Part 2 (dose-finding and expansion)
Dosage Formulation:	Injection solution provided at a concentration of 100 mg/mL	Injection solution	Lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution	200 or 1000 mg lyophilized powder in single-dose vials for reconstitution
Unit Dose Strength/Dosage Level:	Dose-finding cohorts: 100 mg or 30 mg [a] Dose-expansion cohorts: To be determined as detailed in Section 4.6. Part 3: 100 mg	Not applicable	125 mg/m^2	1000 mg/m^2
Route of Administration:	Subcutaneous injection Part 1: Once every 3 weeks Part 2: Once every 4 weeks Part 3: Once every 3 weeks	Subcutaneous injection Part 2 only: Once every 4 weeks	Intravenous infusion over 30-40 minutes. Weekly administration for the first 3 weeks of a 4-week cycle	Intravenous infusion over 30-40 minutes. Weekly administration for the first 3 weeks of a 4-week cycle
Use:	Experimental	Placebo-comparator	Concurrent therapy	Concurrent therapy

Study Treatment Name:	NGM120	Placebo	Abraxane (Paclitaxel protein-bound particles for injectable suspension)	GEMZAR (Gemcitabine)
Dosing Instructions:	Part 1, Part 2, and Part 3: NGM120 administration will occur after all other study assessments have been completed. Part 2: study treatment administration will occur in the following sequential order: 1. NGM120 or placebo 2. Abraxane 3. Gemcitabine All study treatment administration will occur under supervision at the study center.			
Packaging and Labeling:	Supplied in a 2R Type 1 glass vial with a rubber stopper. Each container will be labeled as required per country requirement.	Supplied in a 2R Type 1 glass vial with a rubber stopper. Each container will be labeled as required per country requirement.	Supplied as single-dose vials individually packaged in a carton. Each container will be labeled as required per country requirement.	Supplied as single-dose vials individually packaged in a carton. Each container will be labeled as required per country requirement.
Manufacturer:	NGM Biopharmaceuticals, Inc.	NGM Biopharmaceuticals, Inc.	Celgene Corporation	Eli Lilly

[a] Following completion of the final dose-finding meeting, another dose level of NGM120 may be selected, by the Safety Review Committee, for further investigation.

6.2 Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatments.

Only subjects enrolled in the study may receive the study treatments and only authorized study center staff may supply or administer the study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, study center, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

The gemcitabine and Abraxane treatments will be reconstituted as per the product label.

6.3 Measures to Minimize Bias: Randomization and Blinding

At Screening, potential study subjects will be assigned a Screening number. Following confirmation of eligibility, before study treatment administration, subjects will be assigned a subject number in the order in which they are enrolled in the study.

Part 1 (dose-finding and dose-expansion cohorts) and Part 2 (dose-expansion cohort) are open-label with all subjects receiving the same dose of study treatment depending on their enrolled cohort. Part 3 is open-label will all subjects receiving NGM120 100 mg Q3W.

Part 2 (dose-expansion cohort) will be single-blind (Sponsor-unblinded) with respect to the NGM120 and placebo administration, with limited access to the randomization code.

All subjects will be centrally assigned to randomized study treatment using an [redacted] Before the study is initiated, the log-in information and directions for the [redacted] will be provided to each study center.

On Cycle 1 Day 1 (before study treatment administration) subjects will be assigned a unique number (randomization number) in ascending numerical order at the study center.
The randomization number encodes the subject's assignment to 1 of 2 treatments (either NGM120 or placebo), according to the randomization schedule generated prior to the study by the Sponsor-appointed vendor. Each subject will receive the study treatment labeled with his/her unique randomization number, throughout the study. The randomization schedule will start with number 1001 and increment sequentially as subjects are assigned.

In order to maintain the blind, the NGM120 and placebo injections will be provided to the study center already blinded with the NGM120 and placebo injections identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center staff, the subject, or study vendors. The Sponsor will be unblinded.

In the event of a quality assurance audit, the auditor(s) will be allowed access to the study treatment records at the study center(s) to verify that randomization/dispensing has been done accurately.

[redacted] will be programmed with blind-breaking instructions. In case of an emergency, the Investigator should contact the Medical Monitor to determine if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If it is decided that unblinding is warranted, the Medical Monitor is responsible for unblinding a subject's treatment assignment. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report forms (eCRFs), as applicable.

6.4 Study Treatment Compliance

The administered dosage, timing, and mode of administration may not be changed, except as defined in Section 6.6. Any departures from the intended regimen must be recorded in the eCRF.

All study treatment administrations will be performed in the study center under the supervision of appropriately trained staff.

6.4.1 Treatment Strategy

The study center staff is responsible for the ongoing safety and well-being of the subjects while they are in the study center. Appropriate equipment and emergency drugs should be available to treat common medical emergencies that might occur in a Phase 1 study, and a physician should be available to manage the subject at all times.

6.4.2 Warnings and Precautions

As this is only the second study with administration of NGM120 to man, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

See Section 6.4.2.1 and Section 6.4.2.2 for more details regarding the risks and precautions for gemcitabine and Abraxane, respectively.

For Part 3, please refer to the product labels for any concomitant therapy for the treatment of mCRPC (see Section 5.1 for allowed therapies) for more details regarding the warning and precautions for those therapies.

6.4.2.1 Gemcitabine

The following warnings and precautions have been noted for gemcitabine, see the product label for more details.[33]

- Schedule-dependent toxicity:
  In clinical studies evaluating the MTD of gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of gemcitabine is influenced by the length of the infusion.
- Myelosuppression:
  Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent and the risks are increased when gemcitabine is combined with other cytotoxic drugs. In clinical studies, Grade 3 to 4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively, of the 979 subjects who received single agent gemcitabine. The frequencies of Grade 3 to 4 neutropenia, anemia, and

thrombocytopenia varied from 48%-71%, 8%-28%, and 5%-55%, respectively, in subjects receiving gemcitabine in combination with another drug.

- Pulmonary toxicity and respiratory failure:
  Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome, has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite the discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last administration of gemcitabine.
- Hemolytic-uremic syndrome:
  Hemolytic uremic syndrome, including fatalities from renal failure or the requirement for dialysis, can occur with gemcitabine. In clinical studies, hemolytic uremic syndrome occurred in 0.25% of 2429 subjects. Most fatal cases of renal failure were due to hemolytic uremic syndrome.
- Hepatic toxicity:
  Drug-induced liver injury, including liver failure and death, has been reported in subjects receiving gemcitabine alone or with other potentially hepatotoxic drugs. Administration of gemcitabine in subjects with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency.
- Embryo-fetal toxicity:
  Based on animal data and its mechanism of action, gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits.
- Exacerbation of radiation therapy toxicity:
  May cause severe and life-threatening toxicity when administered during or within 7 days of radiation therapy.
- Capillary leak syndrome:
  Capillary leak syndrome with severe consequences has been reported in subjects receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents.
- Posterior Reversible Encephalopathy Syndrome:
  Posterior reversible encephalopathy syndrome has been reported in subjects receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Posterior reversible encephalopathy syndrome can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of posterior reversible encephalopathy syndrome with magnetic resonance imaging (MRI).

For the recommended monitoring and treatment refer to the product label.[33]

6.4.2.2 Abraxane

The following warnings and precautions have been noted for Abraxane, see the product label for more details. [34]

- Myelosuppression:
  Bone marrow suppression (primarily neutropenia) is dose-dependent and a DLT of Abraxane. In clinical studies, Grade 3 to 4 neutropenia occurred in 34% of subjects with metastatic breast cancer, 47% of subjects with non-small cell lung cancer, and 38% of subjects with pancreatic cancer.
- Sensory neuropathy:
  Sensory neuropathy is dose and schedule dependent. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If ≥ Grade 3 sensory neuropathy develops, withhold Abraxane treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for non-small cell lung cancer and pancreatic cancer followed by a dose reduction for all subsequent courses of Abraxane.
- Sepsis:
  Sepsis occurred in 5% of subjects with or without neutropenia who received Abraxane in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis.
- Pneumonitis:
  Pneumonitis, including some fatal incidences, occurred in 4% of subjects receiving Abraxane in combination with gemcitabine. Monitor subjects for signs and symptoms of pneumonitis and interrupt Abraxane and gemcitabine during evaluation of suspected pneumonitis.
- Severe hypersensitivity:
  Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Subjects who experience a severe hypersensitivity reaction to Abraxane should not be rechallenged with this drug. Cross-hypersensitivity between Abraxane and other taxane products has been reported and may include severe reactions such as anaphylaxis. Subjects with a previous history of hypersensitivity to other taxanes should be closely monitored during initiation of Abraxane therapy.
- Hepatic impairment:
  Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of Abraxane in subjects with hepatic impairment should be performed with caution. Subjects with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such subjects should be closely monitored for development of profound myelosuppression. Abraxane is not recommended in subjects who have total bilirubin >5 × ULN or AST >10 × ULN. In addition, Abraxane is not recommended in subjects with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin >1.5 × ULN and AST ≤10 × ULN). The starting dose should be reduced for subjects with moderate or severe hepatic impairment.

- Risk of viral transmission:
  Abraxane contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease also is considered extremely remote. No cases of transmission of viral diseases or Creutzfeldt-Jakob Disease have ever been identified for albumin.
- Fetal harm:
  Based on mechanism of action and findings in animals, Abraxane can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

For the recommended monitoring and treatment refer to the product label.[34]

6.5 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of Screening or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Supportive care for the subject would be at the Investigator's discretion.

A list of excluded medications/therapy is provided in Appendix 6. Paclitaxel is a CYP2C8 and CYP3A4 substrate. Caution should be exercised when administering Abraxane concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

Significant therapeutic interventions should be recorded in the eCRF as part of the subject's medical history (see Section 8.2).

6.5.1 COVID-19 Vaccination Recommendation

- Part 1 and Part 3: Subjects should avoid vaccination in the first cycle and schedule the vaccination during the second weeks (i.e., Day 8 to Day 15) of any subsequent cycles.
- Part 2: Subjects should avoid vaccination in the first cycle and schedule the vaccination for Day 20 to Day 22 of any subsequent cycle.

6.5.2 Sepsis Prophylaxis Recommendation

Due to the significant safety risk of chemotherapy-induced neutropenia and sepsis, at the first occurrence of fever >38.5ºC, it is recommended to start antibiotic treatment immediately regardless of neutrophil count. On Cycle 1 Day 1, subjects can be prescribed antibiotics, such as ciprofloxacin (500 mg orally twice daily) or amoxicillin clavulanate (500 mg orally 2-3 times daily; for subjects with allergy to fluroquinolones) or as per Institutional practice.

6.5.3 Prevention of Chemotherapy-Induced Nausea and Vomiting

To make the gemcitabine and Abraxane combination more tolerable and reduce COVID-19 exposure (due to potential emergency room/clinic visits), the following regimen is recommended:

- 5-hydroxytryptamine (5-HT3) receptor antagonist, 30 minutes before chemotherapy: Palonosetron 0.25 mg intravenously, granisetron 1 mg intravenously or 2 mg orally, or ondansetron 8 mg intravenously or orally
- Neurokinan 1 (NK1)-receptor antagonist, 30 minutes before chemotherapy: aprepitant or fosaprepitant
- Olanzapine: 10 mg orally once daily on Days 1-4 if chemotherapy is administered

Dexamethasone is not recommended due to its anti-inflammatory effect. The antitumor mechanism of action for NGM120 is to activate myeloid and T cells, which could be neutralized by dexamethasone.

6.6 Dose Modifications

The details of dose-selection, dose-finding, and study stopping criteria are described in Section 4.0 of this protocol. Two doses of NGM120 are planned to be administered in the study: 100 mg and 30 mg in Part 1 and Part 2 and 1 dose of NGM120 is planned to be administered in Part 3: 100 mg. Following completion of the final dose-finding meeting, another dose level of NGM120 may be selected, by the Safety Review Committee, for further investigation.

The decision to proceed to the next dose level of NGM120 will be made by the Safety Review Committee based on safety, tolerability, and preliminary PK and/or PD data obtained in all subjects enrolled at the prior dose level.

Dose modifications of NGM120 are not planned or allowed in this study.

Dose modifications for gemcitabine and Abraxane are the presented in the following sections. Deviations from the dose modifications require review and approval by the Medical Monitor.

6.6.1 Dose Modifications for Hematologic Toxicity

Dose modifications for neutropenia and/or thrombocytopenia are outlined in Table 6-2 and dose levels are outlined in Table 6-3. Dose modifications can be implemented at the start of a cycle or within a cycle. Dose re-escalation is not permitted after dose modification.

Table 6-2 Dose Modifications for Neutropenia and/or Thrombocytopenia

Cycle Day	Absolute neutrophil count (cells/mm^3)		Platelet count (cells/mm^3)	Nab-paclitaxel Dose and Gemcitabine Dose
Day 1	≥1500	AND	≥100,000	Treat on schedule at current dose levels
	<1500	OR	<100,000	Delay dose until recovery
Day 8	≥1000	AND	≥75,000	Treat on schedule at current dose levels
	≥500 to <1000	OR	≥50,000 to <75,000	Reduce to Dose Level -1
	<500	OR	<50,000	Withhold doses
Day 15: If Day 8 doses were given without dose modification				
Day 15	≥1000	AND	≥75,000	Treat on schedule at current dose levels
	≥500 to <1000	OR	≥50000 to <75000	Reduce to Dose Level -1
	<500	OR	<50000	Withhold doses
Day 15: If Day 8 doses were reduced				
Day 15	≥1000	AND	≥75,000	Treat with same dose as Day 8
	≥500 to <1000	OR	≥50,000 to <75,000	Reduce 1 dose level from Day 8
	<500	OR	<50,000	Withhold doses
Day 15: If Day 8 doses were withheld				
Day 15	≥1000	AND	≥75,000	Reduce 1 dose level from Day 1
	≥500 to <1000	OR	≥50,000 to <75,000	Reduce 2 dose levels from Day 1
	<500	OR	<50,000	Withhold doses

Table 6-3 Dose Levels

Dose Level	Nab-Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Study dose	125	1000
-1	100	800
-2	75	600

Recommendation for G-CSF Support

Consider G-CSF use for the treatment of neutropenic fever or infections associated with neutropenia and the prevention of febrile neutropenia in subjects with absolute neutrophil count (ANC) <500 cells/mm^3.

Types of granulocyte colony-stimulating factor (G-CSF) and timing:

- Neupogen: given at the nadir of ANC, which is typically on Day 16 and Day 17 after the third dose during early cycles.
- Neulasta: given typically on Day 16 after the third dose during early cycles
- Based on institutional guidelines

6.6.2 Dose Modifications for Bilirubin

For Grade 2 increased blood bilirubin, delay Abraxane until bilirubin improves to ≤ Grade 1, then resume Abraxane at 100 mg/m^2 for this and all subsequent administrations.

For Grade 3 increased blood bilirubin, decrease gemcitabine to 800 mg/m^2 for this and all subsequent administrations and delay Abraxane until bilirubin improves to ≤ Grade 1, then resume Abraxane at 100 mg/m^2 for this and all subsequent doses.

For Grade 4 increased blood bilirubin on Day 1, delay gemcitabine until bilirubin improves to ≤ Grade 3, then resume gemcitabine at 800 mg/m^2 for this and all subsequent administrations and discontinue Abraxane.

For Grade 4 increased blood bilirubin on Days 8 or 15, skip gemcitabine. Skipped doses are not to be made up. Resume gemcitabine at 800 mg/m^2 for this and all subsequent administrations and discontinue Abraxane.

6.6.3 Dose Modifications for Transaminitis

For AST or ALT >10 × ULN on Day 1, delay gemcitabine and Abraxane until <5 × ULN and then resume gemcitabine and Abraxane.

For AST or ALT >10 × ULN on Days 8 or 15, delay gemcitabine and Abraxane until <5 × ULN and resume gemcitabine at 800 mg/m^2 for this and all subsequent administrations and Abraxane at 100 mg/m^2 for this and all subsequent administrations.

6.6.4 Dose Modifications for Kidney Function

For Grade 3 or 4 creatinine increased, decrease gemcitabine to 800 mg/m^2 and Abraxane to 100 mg/m^2 for this and all subsequent administrations.

6.6.5 Dose Modifications for Neurologic Disorders

For Grade 3 or 4 neuropathy, delay Abraxane until neuropathy improves to ≤ Grade 1, then resume Abraxane at 100 mg/m^2.

Permanently discontinue gemcitabine for posterior reversible encephalopathy syndrome.

6.6.6 Dose Modifications for Pneumonitis

Permanently discontinue gemcitabine and Abraxane for pneumonitis.

6.6.7 Dose Modifications for Other Non-Hematologic Toxicity

For Grade 3 other non-hematologic toxicities considered at least possibly related to gemcitabine/Abraxane, delay (Day 1) or skip (Days 8 or 15) gemcitabine/Abraxane until toxicity improves to ≤ Grade 1, then resume gemcitabine at 800 mg/m^2 for this and all subsequent administrations.

For Grade 4 other non-hematologic toxicities considered at least possibly related to gemcitabine/Abraxane, discontinue gemcitabine/Abraxane.

6.7 Treatment after the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for subjects with advanced solid tumors (Part 1) or metastatic pancreatic adenocarcinoma (Part 2).

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The process for dose-finding and the stopping criteria for the study are described in Section 4.5 and Section 4.8, respectively.

See Section 4.8.1 for more details on stopping of the study treatment administration for individual subjects.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. See Section 4.8.1 for more details on stopping of the study treatment administration for individual subjects.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

See Section 1.3 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Subjects who discontinue study treatment for reasons other than PD will be assessed per RECIST/PCWG2 at a minimum of every 12 weeks until documentation of PD, start of new anticancer therapy, subject withdraws consent, death, or study termination by the Sponsor, whichever comes first.

The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the study center for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Section 1.3.

Protocol waivers or exemptions may be allowed but would need to be discussed and agreed on with the Sponsor and Medical Advisor. Any protocol waiver or exemption would need to be documented along with the discussion and agreement of all parties involved.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

8.1 Demographic Assessments

During Screening, each subject's date of birth, gender, race, height, and ethnicity will be recorded. Reporting of race and ethnicity is mandatory. Additionally, the subject's medical history (see Section 8.7.1 for more details) and prior medications (see Section 6.5 for more details) will be checked.

8.2 Medical History

The following medical history items will be collected to determine subject eligibility at Screening:

- Prior cancer therapies and procedures.
- Assessment of current signs and symptoms.
- Current disease status, including a complete assessment of malignancy using disease-specific criteria.
- Significant past and current conditions.
- Recent significant therapeutic interventions (surgery, radiation therapy) and all medications within 28 days before Cycle 1 Day 1 or as necessary to determine eligibility for study entry.

Medical history should be captured in the eCRFs as well as any prior radiotherapy including the extent of radiotherapy and the body parts that were radiated.

8.3 Diagnosis of the Primary Tumor

The subject's disease history will be recorded, see the study specific entry criteria in Section 5.1 for more details. The subject's diagnosis and stage of cancer should be recorded in the eCRF.

An archival tumor sample (collected within 5 years before Screening) is to be collected as part of the Screening process. If an archival sample is unavailable, a fresh biopsy can be obtained during Screening. If archival tissue or biopsy sample is unavailable, the subject is ineligible. Details on the sample collection, handling, and analysis will be provided in the Laboratory Manual.

8.4 Survival Follow-up

To evaluate overall survival, subjects should be called by phone every 3 months for at least 24 months after the last study treatment administration. The subject's survival status, including the date of the call and details as per Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3), should be documented. In case of death, the primary and, if applicable, the secondary cause of death should also be documented. For subjects who withdraw from the study during the treatment period or the follow-up period, consent to ongoing survival follow-up should be checked and documented.

The overall survival follow-up is to continue for at least 24 months after the last study treatment administration as defined in Section 4.4.

8.5 Assessment of Anticancer Activity

8.5.1 Response Evaluation Criteria in Solid Tumors/PCWG2

Within 28 days before the first study treatment administration, a CT scan or MRI scan will be performed to document the subject's baseline status using the RECIST criteria (Part 1 and Part 2) and PCWG2 (Part 3). In addition, a bone scan will be performed to document the subjects baseline status using PCWG2 for Part 3. A CT/MRI will be performed at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3). A bone scan will be performed at the time points specified in Table 1-5 and Table 1-6 (Part 3).

Eligibility Review: It is required to provide images for central review during Screening. The central radiologist will confirm that the subject has measurable disease and meets eligibility criteria. The subject will NOT be able to be enrolled until the central radiology review is complete and eligibility is confirmed. The screening scan results will be turned around within 3 business days from receipt of a query-free scan at the central imaging vendor.

On Study Review: For real-time therapy decisions, sites will utilize their local radiology read and local RECIST or PCWG2 measurements to determine subjects' response and treatment decision. Note that target and non-target lesions should be selected by the site Investigator at baseline, and followed on subsequent scans, as per RECIST Version 1.1 or PCWG2. After obtaining the screening central read, align with local radiology on the target and non-target lesions, which can be a common reason for discrepancies between local and central reads. Scans must be uploaded for central review within 24 to 48 hours of being obtained (see imaging manual for upload instructions). If the local read shows 11%-30% tumor growth, contact the Sponsor/IQVIA to alert that an expedited review (4 business days from receipt of a query free scan) is required. Given that there is a ±3-day window for the scan; this would require that the scan should be completed early in that window. In these cases, central reads will determine whether treatment should be continued. Inform your subjects to wait for central reads and set appropriate expectations accordingly. If the local read falls outside of the 11%-30% range (i.e., <11% or >30%), treatment decisions can be made without waiting for the central read.

Enter local measurements on RECIST or PCWG2 worksheet in the EDC within 10 business days of each scan being performed and keep corresponding source documentation (radiology report). If the central review notes a different response than is noted in the EDC by local review (i.e., there is imaging discordance), the site will receive communication from the Medical Monitor regarding the central review and what action should be taken with the subject. The central review will trump the local review (e.g., if the central review shows PD but the local imaging review does not, the subject MUST come off study drug as soon as the discordance is identified). If there is concordance (local and central review agree on the response of the subject), there will be no communication from the Medical Monitor regarding the central review.

The Investigator should contact the Medical Monitor or Sponsor before discontinuing a subject due to PD.

Computed tomography scans of the neck, chest, abdomen, and pelvis are the preferred imaging method for tumor assessment. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. The target and nontarget lesions will be selected based on the initial scan, and all subsequent scans should use the same methodology.

Anticancer activity and staging will be assessed using the RECIST Version 1.1 or PCWG2 criteria. However, confirmation of response will not be required.

Anticancer activity parameters to be assessed include determination of the following:

- Best overall response (complete response, partial response, stable disease, or PD)
- Overall response rate (complete response + partial response).
- Disease control
- Duration of response

- Progression-free survival
- Overall survival
- PSA response (Part 3)
- Symptomatic skeletal events (SSE) rate (Part 3)
- 24 month overall survival (Part 3)

For Part 3, a radionucleotide bone scan will be performed to document the subject's bone lesion status using the PCWG2 within 28 days before the first study treatment administration and at the time points specified in Table 1-5 and Table 1-6. This will also be part of the anticancer activity parameters.

8.5.2 Disease Progression

8.5.2.1 Part 1 and Part 2

Subjects with stable disease, complete response, or partial response may continue in the study.

In Part 2, subjects will discontinue all study treatment upon definitive signs of disease progression. Progression does not have to be confirmed before discontinuation of the study treatments.

Disease progression: An initial baseline assessment of the subject's tumor will be done at Screening using RECIST Version 1.1 (see Section 8.5.1). Repeat evaluations will be done at the next tumor assessment time point as per the schedule of assessments, but no sooner than 4 weeks later. If any subsequent post baseline tumor assessment shows a ≥20% increase in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared with the initial baseline assessment (the sum of diameters of target lesions and new lesions), then disease progression would be confirmed.

In Part 2, if the principal investigator believes the subject is experiencing clinical benefit from treatment, the subject may be treated beyond potential progression, and another disease assessment should be performed (at the next visit ±3 days).

Only subjects meeting the following criteria will be allowed for study drug continuation:

1. No deterioration in ECOG performance status;
2. Investigator assessment of clinical benefit;
3. Tolerating study drug;
4. Continued treatment will not prevent or delay treatment that may prevent serious complications of disease.

On the follow-up scan, if the subject is proven to have further progression, the subject should be discontinued. If the subject has subsequent regression, the subject may continue in the study.

Symptomatic deterioration: Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of radiographic disease progression, and

not due to study treatment or other medical conditions, should be reported as subject discontinuation due to "symptomatic deterioration." For example, a decline in ECOG performance status to ≥3.

The following would also be considered progression of the subject's disease:

- The subject has clinical symptoms or signs indicating significant disease progression such as the benefit/risk ratio of continuing therapy is no longer justified.
- Threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention.

8.5.2.2 Part 3

Criteria established by PCWG2 will be used to define disease progression on the basis of changes in PSA, bone metastases, and measurable disease.[44]

- PSA progression
    - An increase of 25% and an absolute increase of ≥2 ng/mL from nadir, confirmed by a second value obtained ≥3 week later
- Target lesions progression
    - Use RECIST to record soft-tissue (nodal and visceral) lesions as target. Only lymph nodes ≥ 2 cm in diameter should be used to assess for a change in size. Record presence of nodal and/or visceral disease separately
    - Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later
- Bone progression
    - The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesion Progression = appearance of 2 or more new lesions
    - Continue therapy during new lesion confirmation.

Only subjects meeting the following criteria will be allowed for study drug continuation:

1. No deterioration in ECOG performance status;
2. Investigator assessment of clinical benefit;
3. Tolerating study drug;
4. Continued treatment will not prevent or delay treatment that may prevent serious complications of disease.

8.5.3 Changes in Body Weight, Body Composition, and Lean Body Mass

8.5.3.1 Body Weight and Body Composition

The subjects' weight will be measured and the body mass index calculated at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3). The subjects' waist circumference will be measured at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2).

The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

8.5.3.2 Lean Body Mass

Within 28 days before the first study treatment administration, a CT scan will be performed to document the subject's baseline lean body mass.[41] Subsequently, a CT scan will be performed at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

A CT scan of the abdomen is the preferred imaging method. Lean body mass and adipose tissue mass will be calculated at the level of L3. MRI scans may be used instead of CT scans in case of hypersensitivity to CT contrast media or for medical reasons, but the same method must be used consistently throughout the study. All subsequent scans should use the same methodology. Scans should be submitted to imaging within 5 business days of obtaining them.

The lean body mass will be read centrally.

8.5.4 Patient Reported Outcomes

The following PROs will be completed at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

8.5.4.1 Part 1 and Part 2

- [redacted]
- [redacted]

Subjects should be instructed on the manner in which to complete each of the PROs. The PROs should be completed under supervision of a qualified individual at the study center. Once completed, the PRO should be reviewed for completeness. The completed PROs will be collected and entered into the database.

8.5.4.2 Part 3

[redacted]).

[redacted]

8.5.5 Tumor Archival Tissues

An archival tumor sample (collected within 5 years before Screening) is to be collected as part of the screening process. If an archival sample is unavailable, a fresh biopsy can be obtained during Screening. If archival tissue or biopsy sample is unavailable, the subject is ineligible. Details on the sample collection, handling, and analysis will be provided in the Laboratory Manual.

8.5.6 Cancer Antigen 19-9

Cancer antigen 19-9 is a type of antigen released by pancreatic cancer cells. It can also be referred to as a tumor marker. Changes in cancer antigen 19-9 levels is useful to determine if the pancreatic tumor is growing, staying the same or getting smaller.

Blood samples for radioimmunoassay blood test will be collected at the time points specified in Table 1-3 (Part 2).

8.5.7 Prostate Specific Antigen (Part 3 Only)

PSA levels will be obtained within 8 days prior to enrollment and at the times specified in Table 1-5 and Table 1-6 (Part 3). The PSA sample will be analyzed in a designated central laboratory.

8.5.8 Symptomatic Skeletal Events (Part 3 Only)

Symptomatic skeletal events are defined as:

- The occurrence of new symptomatic pathological fracture
- The use of external beam radiation to relieve bone pain
- The occurrence of spinal cord compression
- Tumor-related orthopedic surgical intervention

The occurrence of symptomatic skeletal events will be collected within 8 days before enrollment, at each cycle, and at the end of treatment.

8.6 Safety Assessments

Planned time points for all safety assessments are specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

8.6.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

Height will be measured and recorded at Screening. Weight, waist circumference, and body mass index will also be measured and recorded as detailed in Section 8.5.3.1. The subject will be allowed to wear indoor, daytime clothing with no shoes during the assessments.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.6.2 Local Injection-Site Symptom Assessments

Assessments will occur at the time points indicated in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

Local injection-site symptom assessments may be performed if necessary and as clinically indicated by the Principal Investigator or delegate to capture injection-site reactions outside of the routine scheduled assessment time points.

The 2007 United States Food and Drug Association Toxicity Grading Scale will be used to assess any injection-site reactions.[42] 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 study center staff. The results will be documented in the subject's eCRF.

8.6.3 Vital Signs

Temperature, pulse rate, blood pressure, and respiratory rate will be assessed. The method of temperature measurement will be recorded in the eCRF.

Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded in the eCRF.

8.6.4 Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be obtained at Screening and triplicate ECGs will be obtained at all subsequent assessments using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Measurements of ECG and heart rate will be recorded in a supine position after the subjects have been resting for at least 5 minutes. Heart rate will be measured via ECG.

The ECG will be recorded by means of a 12-lead ECG system over 10 seconds while the subjects rest in a supine position. The chart speed will be set at 50 mm/second. The ECG patterns will be analyzed qualitatively with particular emphasis on changes in the T-wave morphology. Heart rate and time intervals of the ECG such as PQ, QRS, and QT interval will be computed automatically by the ECG system, while the heart rate corrected QT interval will be calculated by the system according to the Fridericia formula. In case of prevalence of automatically computed pathological ECG intervals, the ECG has to be manually reanalyzed by the Investigator.

The ECG printouts will be signed by the study center staff collecting the recording and will be signed and dated by the Investigator after being assessed.

8.6.5 Clinical Safety Laboratory Assessments

See Appendix 4 for the list of clinical laboratory assessments to be performed, and see Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3), for the timing and frequency. All laboratory samples should be collected in a fasted state as detailed in Section 5.3.1.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.
The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the subject's underlying disease/health status, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a time period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the Laboratory Manual and the timepoints indicated in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).
- If laboratory values from non-protocol specified laboratory assessments performed at the study center's local laboratory require a change in subject management or are considered

clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.7 Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver or, surrogate).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatments or study procedures, or that caused the subject to discontinue the study treatment administration or the study (see Section 7.0).

8.7.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be assessed beginning from the start of the first injection of study drug(s) and throughout study participation. AEs will continue to be assessed until the follow-up visit at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3). After this period, the Investigator should only report SAEs that are believed to be related to study drug treatment.

Only SAEs caused by a protocol-mandated procedure (e.g., invasive procedures such as biopsies, discontinuation of medications) that occur after informed consent has been obtained but prior to initiation of the study drug, should be reported as SAEs.

AEs reported by the subject or noted by study personnel after obtaining informed consent but prior to initiation of study drug will be captured as part of medical history in the eCRF, including those events that are related to a protocol-mandated procedure but do not meet serious criteria.

In the event the subject is a screen failure, no AEs will be recorded in the eCRF.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 5. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatments or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 5.

8.7.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 5.

8.7.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.7.5 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until 4 weeks after the last NGM120 administration.

The Investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The Investigator will provide this information in a follow-up report. The reason(s) for an induced abortion should be specified. A report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

If a pregnancy is reported, the Investigator should inform the Sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

If a pregnancy is reported for a female subject participating in the study, the subject should be discontinued from the study immediately.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.8 Treatment of Overdose

For this study, any dose of any study treatment greater than those described in Section 6.1 will be considered an overdose.

There is no known antidote for NGM120. In the case of an overdose, the subject should receive the standard treatment for overdose and supportive therapy based on the subject's signs and symptoms.

There is no known antidote for an Abraxane overdose. The primary anticipated complications of an overdose would consist of bone marrow suppression, sensory neurotoxicity, and mucositis. See the product label for more details.[34]

There is no known antidote for an overdose of gemcitabine. Myelosuppression, paresthesia, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by intravenous infusion over 30 minutes every 2 weeks to several subjects in a dose-finding study. In the event of suspected overdose, the subject should be monitored with appropriate blood counts and be provided supportive therapy, as necessary. See the product label for more details.[33]

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until the study treatment can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within any period from the date of the last study treatment administration if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.9 Pharmacokinetics

8.9.1 Collection of Samples

Predose blood samples will be collected for measurement of serum concentrations of NGM120 at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

Instructions for the collection and handling of biological samples will be provided in a separate Laboratory Manual.

Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein or from a central line or port. Sites must follow appropriate guidelines for flushing, aspirating, and drawing from a central line or port to collect blood samples appropriately as required for the study. The actual date and time (24-hour clock time) of each blood sample will be recorded in the eCRF. The time and date of study treatment administration will also be recorded. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.9.2 Determination of Drug Concentration

Samples for the determination of NGM120 in serum will be analyzed on behalf of the Sponsor by a Sponsor selected vendor using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Remaining serum samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence of other biomarkers. Samples collected for analyses of NGM120 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.9.3 Calculation of Derivation of Pharmacokinetic Variables

Details on the PK parameters to be calculated are presented in Section 9.5.

8.10 Pharmacodynamics

8.10.1 Metabolic Parameters (Part 1 and Part 2 Only)

Blood samples will be collected for measurement of the following variables at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2). The metabolic parameters to be assessed will include, but not be limited to the following:

- [redacted]

- [redacted]

8.10.2 Other Pharmacodynamic Assessments

Additionally, the following PD assessments will be performed at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3):

- [redacted]

8.11 Biomarkers

[redacted]

[redacted]

8.12 Immunogenicity Assessments

Antibodies to NGM120 will be evaluated in blood samples collected from all subjects at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

Additionally, blood samples should also be collected at the final visit from subjects who discontinued the study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or a designee.

The collected blood samples will be screened for antibodies binding to NGM120 and the titer of confirmed positive samples will be reported. Any potentially positive results in the Screening assay will have a confirmation assay performed on the sample to confirm the positive status of the sample. In confirmed positive samples, the relative titer of the antibody will be determined as well as whether the confirmed positive samples represent a neutralizing antibody. All neutralizing antibody samples will be collected as scheduled but will be analyzed only, if necessary, based on confirmed positive samples.

Other analyses may be performed to verify the stability of antibodies to NGM120 and/or further characterize the immunogenicity of NGM120.

The detection and characterization of antibodies to NGM120 will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to NGM120.

8.13 Immunophenotyping

Samples collected from all subjects in Part 1 at the time points specified in Table 1-1 and Table 1-2 (Part 1) will be used to perform immunophenotyping using a validated assay methodology. The following cells will be profiled:

[redacted]

8.14 Eastern Cooperative Oncology Group Performance Status

Subject performance status will be assessed by using ECOG performance status scale (see Appendix 2) at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2), Table 1-5 and Table 1-6 (Part 3).

8.15 Skeletal Muscle Index (Part 1 and Part 2 Only)

The CT scans performed during the study (see Section 8.5.1) will be used to determine the skeletal muscle index and adiposity of the subjects.[43]

8.16 Biometric Activity (Part 1 and Part 2 Only)

Biometric activity would be assessed at the time points specified in Table 1-1 and Table 1-2 (Part 1), Table 1-3 and Table 1-4 (Part 2). Data will be extracted by a trained individual at the indicated time points and the data will be entered in the eCRF.

[redacted]

[redacted]

l.

8.17 [redacted]

[redacted]

8.18 Pharmacogenetics

[redacted]

s.

Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

See Appendix 9 for information regarding genetic research.

9.0 STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) will be provided and finalized prior to the study database lock or unblinding. No discrepancies are expected between the SAP and the protocol. However, if there are discrepancies between this section of the protocol and the final SAP, the SAP will override the protocol.

In general, descriptive statistics including the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum will be presented for continuous variables. Frequency and percentage distribution will be presented for categorical variables. Kaplan-Meier estimates will be presented for time-to-event variables.

9.1 Sample Size Determination

For Part 1, a standard sample size of 3 to 6 subjects will be entered per 3+3 dose level. This number of subjects is considered sufficient to proceed to another dose level. An additional 12 subjects will be enrolled for the dose-expansion cohorts and the total sample size for Part 1 will be approximately 15 to 21 subjects.

Part 2 will use the 3+3 design with 2 dose levels (100 mg and 30 mg) followed by an additional 60 subjects enrolled for the dose-level expansion. A standard sample size of 3 to 6 subjects will be entered per 3+3 dose level. Protocol version 5.0 expanded the NGM120 30 mg cohort to add 6 subjects based on emerging data (see Section 4.3).

Based on a sample size of 30 subjects, the 95% Clopper-Pearson (Exact) CI for Part 2 are presented in Table 9-1.

Table 9-1 Confidence Intervals Based on Response (Part 2)

# of Response	Response Rate	95% Lower Confidence Limit	95% Upper Confidence Limit
6	0.2	0.0771	0.3857
7	0.23333	0.0993	0.4228
8	0.26667	0.1228	0.4589
9	0.3	0.1473	0.494
10	0.33333	0.1729	0.5281
11	0.36667	0.1993	0.5614
12	0.4	0.2266	0.594

For Part 3, 10 patients will be initially accrued before expansion to 25 subjects. At least 2 subjects with a 50% or higher magnitude of PSA reduction from baseline level and maintained

for at least 3 weeks are required within the initial 10 subject cohort to continue the patient accrual, with a planned enrollment of 25 patients.

Based on N of 25, the 95% Clopper-Pearson (Exact) CI for Part 3 are presented in Table 9-2.

Table 9-2 Confidence Intervals Based on Response (Part 3)

# of Responses	Response Rate	95% Lower Confidence Limit	95% Upper Confidence Limit
5	0.2	0.0683	0.407
6	0.24	0.0936	0.4513
7	0.28	0.1207	0.4939
8	0.32	0.1495	0.535
9	0.36	0.1797	0.5748
10	0.4	0.2113	0.6133

9.2 Analysis Sets

Safety Analysis Set: All subjects who receive at least 1 dose (full or partial) of study treatment and have at least 1 postdose safety assessment.

PD/Efficacy Analysis Set: [redacted].

PK Analysis Set: [redacted]

9.3 Demographics and Other Baseline Characteristics

Demographics (e.g., age, sex, race, body weight, height, etc.) and other baseline characteristics will be summarized with descriptive statistics by treatment/dose group for each analysis set.

9.4 Pharmacodynamic/Efficacy Analyses

[redacted].

9.5 Pharmacokinetic Analyses

[redacted]

9.6 Immunogenicity Analyses

All immunogenicity analyses will be summarized with descriptive statistics by treatment/dose group using the Safety Analysis Set.

9.7 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) will be summarized by primary System Organ Class and Preferred Term. Actual values and change from baseline values for vital signs, ECGs, clinical laboratory (hematology and chemistry) tests, and other continuous safety variables will be summarized with descriptive statistics. Dose limiting toxicity, concomitant medications, physical examinations, local injection-site symptom assessment, and other categorical safety variables will be summarized with frequency and percentage distribution.

All safety analyses will be performed using the Safety Analysis Set.

9.8 Exploratory Analyses

[redacted]

9.9 Interim Analyses

No formal interim analysis will be performed.

9.10 Safety Review Committee

The Safety Review Committee will be responsible for reviewing and evaluating the safety, PK, and PD data collected after completion of the first treatment cycle in each dose-finding cohort and at regularly scheduled meetings during the subsequent dose-expansion cohorts. The Safety Review Committee may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. The Safety Review Committee will be responsible for making recommendations as to whether it is scientifically and ethically appropriate to continue

enrollment to additional dose-finding cohorts and the dose-expansion cohorts, or to stop the study.

The Safety Review Committee will include, at a minimum, the Sponsor's responsible physician, the Medical Monitor, and the Principal Investigator. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, e.g., PK scientists, statisticians, clinical specialists, etc.

For the dose-expansion cohorts, the Safety Review Committee will meet quarterly, or as needed (ad hoc).

10.0 REFERENCES

1. Unsicker K, Spittau B, Krieglstein K. The multiple facets of the TGF-β family cytokine growth/differentiation factor-15/macrophage inhibitory cytokine-1. Cytokine Growth Factor Rev. 2013 Aug;24(4):373-84.
2. Winand FJ, Boegemann M, Gallitz I, et al. GDF15 and hepcidin as prognostic factors in patients with prostate cancer. J Mol Biomark Diagn. 2014 Oct 27;5(6):199.
3. Brown DA, Ward RL, Buckhaults P, et al. MIC-1 serum level and genotype: associations with progress and prognosis of colorectal carcinoma. Clin Cancer Res. 2003 Jul;9(7):2642-50.
4. Fisher OM, Levert-Mignon AJ, Lord SJ. MIC-1/GDF15 in Barrett's oesophagus and oesophageal adenocarcinoma. Br J Cancer. 2015 Apr 14;112(8):1384-91.
5. Staff AC, Bock AJ, Becker C, et al. Growth differentiation factor-15 as a prognostic biomarker in ovarian cancer. Gynecol Oncol. 2010 Sep;118(3):237-43.
6. Altena R, Fehrmann RS, Boer H, et al. Growth differentiation factor 15 (GDF-15) plasma levels increase during bleomycin- and cisplatin-based treatment of testicular cancer patients and relate to endothelial damage. PloS One. 2015 Jan 15;10(1):e0115372.
7. Johnen H, Lin S, Kuffner T. Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1. Nat Med. 2007 Nov;13(11):1333-40.
8. Hsu JY, Crawley S, Chen M, et al. Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. Nature. 2017 Sep 27. Doi: 10.1038/nature24042.
9. Emmerson PJ, Wang F, Du Y, et al. The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. Nat Med. 2017 Aug 28. Doi: 10.1038/nm.4393.
10. Mullican SE, Lin-Schmidt X, Chin CN, et al. GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. Nat Med. 2017 Aug 28.
11. Yang L, Chang CC, Sun Z, et al. GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. Nat Med. 2017 Oct;23(10):1158-66.
12. Contreras RJ, Fox E, Drugovich ML. Area postrema lesions produce feeding deficits in the rat: effects of preoperative dieting and 2-deoxy-D-glucose. Physiol Behav. 1982 Nov;29(5):875-84.
13. Kott JN, Ganfield CL, Kenney NJ. Area postrema/nucleus of the solitary tract ablations: analysis of the effects of hypophagia. Physiol Behav. 1984 Mar;32(3):429-35.
14. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and Therapeutic relevance of neuroimmune communication. Immunity. 2017 Jun 20;46(6):927-42.
15. Qiao G, Chen M, Bucsek MJ, et al. Adrenergic signaling: A targetable checkpoint limiting development of the antitumor immune response. Front Immunol. 2018 Feb 6;9:164.
16. Sloan EK, Priceman SJ, Cox BF, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res. 2010 Sep 15;70(18):7042-52.
17. Le CP, Nowell CJ, Kim-Fuchs C, et al. Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. Nat Commun. 2016 Mar 1;7:10634.
18. De Giorgi V, Grazzini M, Benemei S, et al. Propranolol for off-label treatment of patients with melanoma: results from a cohort study. JAMA Oncol. 2018 Feb 8;4(2):e172908.
19. Pasquier E, André N, Street J, et al. Effective management of advanced angiosarcoma by the synergistic combination of propranolol and vinblastine-based metronomic chemotherapy: A bench to bedside study. EBioMedicine. 2016;6:87-95.
20. Choi CH, Song T, Kim TH, et al. Meta-analysis of the effects of beta blocker on survival time in cancer patients. J Cancer Res Clin Oncol. 2014 Jul;140(7):1179-88. doi: 10.1007/s00432-014-1658-7. Epub 2014 Mar 27
21. Grytli HH, Fagerland MW, Fosså SD, Taskén KA. Association between use of β-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol. 2014 Mar;65(3):635-41. doi: 10.1016/j.eururo.2013.01.007. Epub 2013 Jan 14.

22. Breit SN, Johnen H, Cook AD, et al. The TGF-β superfamily cytokine, MIC-1/GDF15: a pleotrophic cytokine with roles in inflammation, cancer and metabolism. Growth Factors. 2011 Oct;29(5):187-95.
23. Abulizi P, Loganathan N, Zhao D, et al. Growth differentiation factor-15 deficiency augments inflammatory response and exacerbates septic heart and renal injury induced by lipopolysaccharide. Sci Rep. 2017 Apr 21;7(1):1037. doi: 10.1038/s41598-017-00902-5.
24. Estrada LD, Ağaç D, Farrar JD. Sympathetic neural signaling via the β2-adrenergic receptor suppresses T-cell receptor-mediated human and mouse CD8(+) T-cell effector function. Eur J Immunol. 2016 Aug;46(8):1948-58.
25. Bucsek MJ, Qiao G, MacDonald CR, et al. β-Adrenergic signaling in mice housed at standard temperatures suppresses an effector phenotype in CD8(+) T cells and undermines checkpoint inhibitor therapy. Cancer Res. 2017 Oct 15;77(20):5639-51.
26. Brown IS. Pathology of perineural spread. J Neurol Surg B Skull Base. 2016 Apr;77(2):12430.
27. Magnon C, Hall SJ, Lin J, et al. Autonomic nerve development contributes to prostate cancer progression. Science. 2013 Jul 12;341(6142):1236361.
28. Ratnam NM, Peterson JM, Talbert EE, et al. NF-κB regulates GDF-15 to suppress macrophage surveillance during early tumor development. J Clin Invest. 2017 Oct 2;127(10):3796-3809.
29. Corre J, Hébraud B, Bourin P. Concise review: growth differentiation factor 15 in pathology: a clinical role? Stem Cells Transl Med. 2013 Dec;2(12):946-52.
30. Wollert KC, Kempf T, Wallentin L. Growth differentiation factor 15 as a Biomarker in cardiovascular disease. Clin Chem. 2017 Jan;63(1):140-151.
31. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol. 2010 Oct;7(10):564-75.
32. Putt M, Hahn VS, Januzzi JL, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem. 2015 Sep;61(9):1164-72.
33. Prescribing Information, GEMZAR®, revised November 2018.
34. Prescribing Information, ABRAXANE®, revised August 2018.
35. Glare, P., et al., A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ, 2003;327(7408):195-8.
36. Christakis, N.A. and E.B. Lamont, Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. BMJ, 2000;320(7233):469-72.
37. Pal, S.K., V. Katheria, and A. Hurria, Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin, 2010;60(2):120-32.
38. Bassett, D.R., Jr., et al., Pedometer-measured physical activity and health behaviors in U.S. adults. Med Sci Sports Exerc, 2010;42(10):1819-25.
39. Fried, L.P., et al., Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci, 2001;56(3):M146-56.
40. Turner DC, Kondic AG, Anderson KM, et al. Pembrolizumab exposure–response assessments challenged by association of cancer cachexia and catabolic clearance. Clin Cancer Res; 2018:24(23):5481-9.
41. Mourtzakis M, Prado CMM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008 Oct;33(5):997-1006.
42. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007.
43. Choi Y, Oh D-Y, Kim T-Y, Lee K-H, et al. Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. PloS One. 2015; 10(10): e0139749.

44. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M; Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008 Mar 1;26(7):1148-59.

11.0 APPENDICES

Appendix 1. Abbreviations

Abbreviation	Definition
[redacted]	[redacted]
5-HT3	5-hydroxytryptamine
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AP	area postrema
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}28d}$	area under the concentration–time curve from time zero to 28 days
$AUC_{0\text{–}t}$	area under the concentration–time curve from time zero to the last measurable time point
CACS	cancer anorexia cachexia syndrome
CFR	code of Federal Regulations
[redacted]	[redacted]
C_{max}	maximum observed concentration
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DLT	dose limiting toxicities
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
EW	early withdrawal
FAACT	[redacted]
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GDF15	growth differentiation factor 15
GFRAL	glial cell line-derived neurotrophic factor receptor alpha-like
HRT	hormonal replacement therapy
ICH	International Council for Harmonisation
IRB	Institutional Review Board
LHRH	luteinizing hormone-releasing hormone
LISSA	local injection-site symptom assessment
MedDRA	Medical Dictionary for Regulatory Activities
MAD	multiple ascending dose
mCRPC	metastatic castration resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	norepinephrine
NK-1	neurokinan 1
NOAEL	no-observed-adverse-effect level
NTS	nucleus of the solitary tract
OS	overall survival

Abbreviation	Definition
PCWG2	Prostate Cancer Working Group 2
PD	pharmacodynamic(s) or progressive disease
PK	pharmacokinetic(s)
PRO	patient reported outcomes
PSA	prostate specific antigen
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
Q6W	once every 6 weeks
Q8W	once every 8 weeks
QTc	corrected QT
RECIST	response evaluation criteria in solid tumors
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SNS	sympathetic nervous system
SSE	symptomatic skeletal events
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed concentration
TTPE	time to PSA progression
ULN	upper limit of normal
Wk	week
WOCBP	woman of childbearing potential

Appendix 2. Eastern Cooperative Oncology Group Performance Status Scale

Eastern Cooperative Oncology Group Performance Status [a]	
Grade	**Eastern Cooperative Oncology Group**
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, such as light house work or office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed/chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed/chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Appendix 3. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 11). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual, or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.
- Subjects must be reconsented to the most current version of the informed consent form(s) during their participation in the study.
- A copy of the informed consent form(s) must be provided to the subject.
- The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. Subjects will indicate (via initials or signature) their agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Administrative Structure

The Safety Review Committee will include, at a minimum, the Sponsor's responsible physician, the Medical Monitor, and the Principal Investigator. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, e.g., PK scientists, statisticians, clinical specialists, etc.

Table 11-1 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring Study Master File Data Management Safety Management	IQVIA Biotech
Clinical Supply Management Quality Assurance Auditing Safety Review Committee (see Section 9.10)	Sponsor
Biostatistics Randomization Code	Sponsor-appointed vendor
Medical Writing	IQVIA/IQVIA Biotech
Laboratory Assessments (Safety)	Q2 central laboratory
Pharmacokinetic/Pharmacodynamic Sample Testing	Sample management: Q2 Central Laboratory Analysis: Sponsor-appointed vendor
Central CT/MRI reading	Sponsor-appointed vendor

Medical Monitor

[redacted]

Dissemination of Clinical Study Data

A clinical study report, compliant with the requirements of ICH E3, will be prepared once the study has been completed.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further NGM120 development.

Publication Policy

- NGM Biopharmaceuticals, Inc. will retain ownership of all data. All proposed publications based on this study will be subject to Sponsor's approval requirements.

Appendix 4. Clinical Laboratory Tests

The tests detailed in Table 11-2 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered in the eCRF.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Subjects should be fasted overnight (for at least 8 hours) before sample collections as detailed in Section 5.3.1.

Table 11-2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean cell hemoglobin concentration %Reticulocytes	White Blood Cell Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Blood urea nitrogen Creatinine Gamma glutamyl transferase Urea Magnesium Potassium Sodium Calcium Lactate dehydrogenase Uric acid C-reactive protein Cortisol Albumin Creatine kinase muscle-brain fraction to be performed if clinically indicated	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Creatine kinase Chloride Globulin Amylase Total and direct bilirubin Total protein Phosphate Carbon dioxide (bicarbonate) Conjugated and unconjugated bilirubin will be performed if clinically indicated.
[redacted]	[redacted]	[redacted]s
Urinalysis	Leukocytes Protein Bilirubin Urobilinogen Ketones Microscopy (if clinically indicated)	Red blood cells pH Nitrite Specific gravity Glucose
Drugs of abuse and alcohol	Amphetamine Ethanol Cannabinoids Cocaine metabolites Urine creatinine Cotinine Tricyclic antidepressants	Opiates Benzodiazepines Methadone metabolites Barbiturates Phencyclidine Ecstasy (3,4-methylenedioxymethamphetamine)
Other Screening tests	Serum human chorionic gonadotropin pregnancy test (for women of childbearing potential) at Screening. Subsequently, the pregnancy test is to be performed per institutional standards. Tuberculosis: QuantiFERON-TB Gold test will be performed in Part 1 and Part 2 as part of the Screening assessments. Tuberculosis testing may be performed locally when a 37°C incubator is not available on site. Local testing results must be entered in the eCRF.	

Investigators must document their review of each laboratory safety report.

Appendix 5. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). Clinically significant includes an abnormal laboratory or other finding that indicates new disease or worsening of an existing disease or requires intervention. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): The condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per the definitions above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF and when applicable, sending the paper SAE Report Form to IQQVIA Biotech Safety. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the requestor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and classify it to according to the NCI-CTCAE Version 5.0, available online at https://evs.nci.nih.gov/ftp1/CTCAE/.

The NCI-CTCAE is a descriptive terminology that can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. The CTCAE displays Grade 1 through Grade 5 with unique clinical descriptions of severity for each AE based on this general guideline. If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life.
- Grade 3: Severe; significant but not immediately life-threatening; hospitalization, or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Note: The maximum severity of an AE is to be considered for classification.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, definitely related, or unknown (unable to judge).
    - "Definitely related" conveys it certainly related.
    - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
    - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.

- "Unlikely to be related" suggests that only a remote connection exists between the study treatments and the AE. Other conditions, including chronic illness, progression, or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
- "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
- All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is mandatory that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor and any other institutions (as required by local regulations) with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF and the paper SAE Report Form, when applicable.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Sponsor or designee via Paper SAE Report Form

- The preferred method for transmission of the SAE report form is via email to Safety-Inbox.Biotech@IQVIA.com) or facsimile utilizing the study-specific SAE Report Form that is filed in the site Study Reference Binders.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Appendix 6. Excluded Medications/Therapy

Excluded medications/therapy is listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

- Immunosuppressive medications within 14 days of Screening with the exception of topical (intranasal, inhaled, and local injection), systemic (prednisone equivalent 10 mg/day or less), or as needed for hypersensitivity reactions such as CT scan premedication.
- Use, or planned used, of any live vaccines within 28 days before Cycle 1 Day 1.
- Concurrent cancer therapies (chemotherapy, radiotherapy, surgery, immunotherapy, biologic, or hormonal therapy) within 28 days before Cycle 1 Day 1.
- Paclitaxel is a CYP2C8 and CYP3A4 substrate. Caution should be exercised when administering Abraxane concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

This list of excluded medications/therapies is not an inclusive list. Investigator judgement must be used to justify initiating any study medication during the study.

Appendix 7. Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for 90 days after the last study treatment administration.
  - Agree to use a male condom and have their partner use of a contraceptive method with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 90 days after study completion or the last study treatment administration.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study treatment.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening; subsequently, urine pregnancy test is to be performed.
- Additional pregnancy testing should be performed at the times specified in the schedule of assessments during the treatment period and as required locally.

Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

- Screening serum pregnancy testing will be performed and assayed in the central laboratory.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive NGM120.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

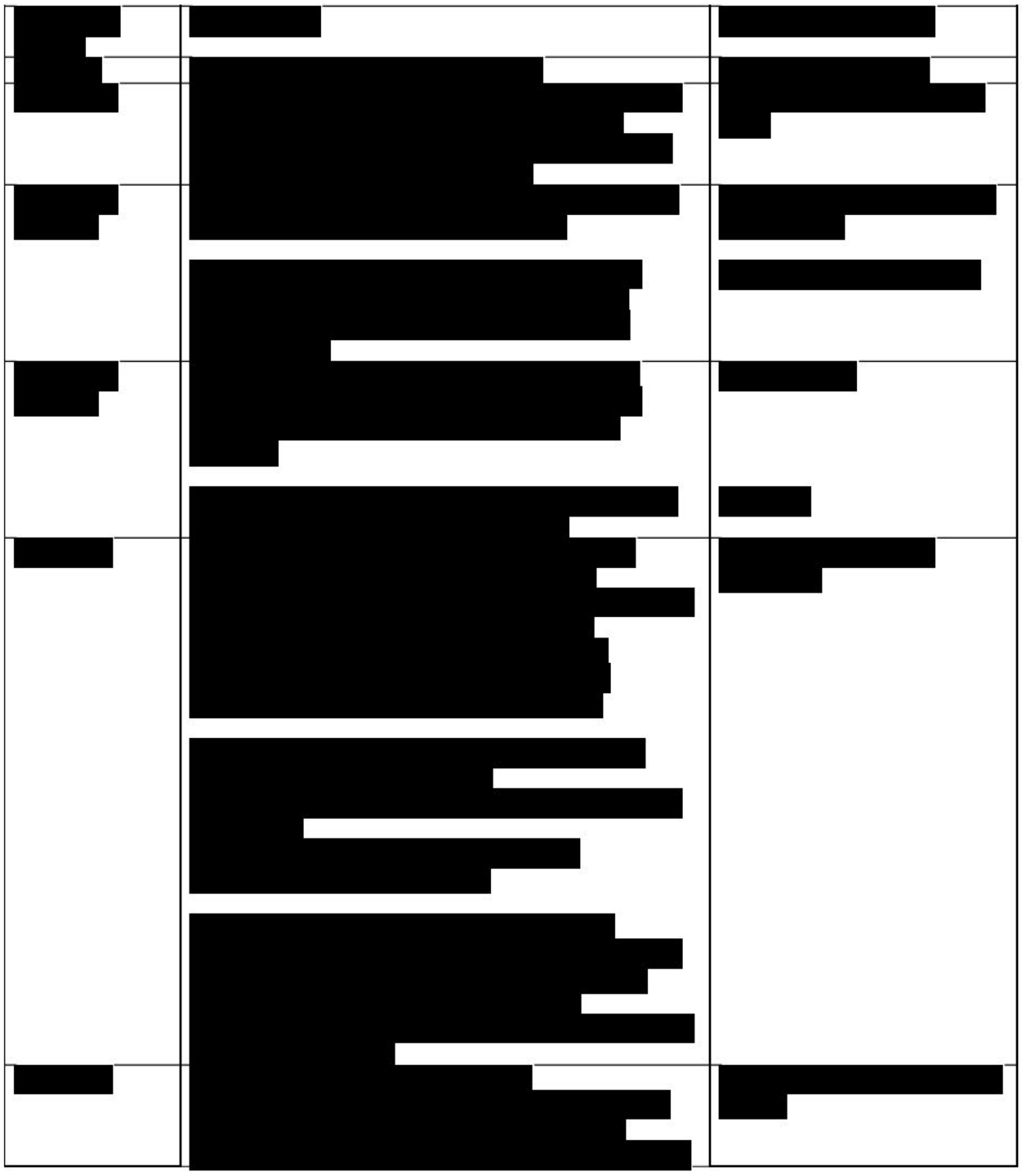
- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

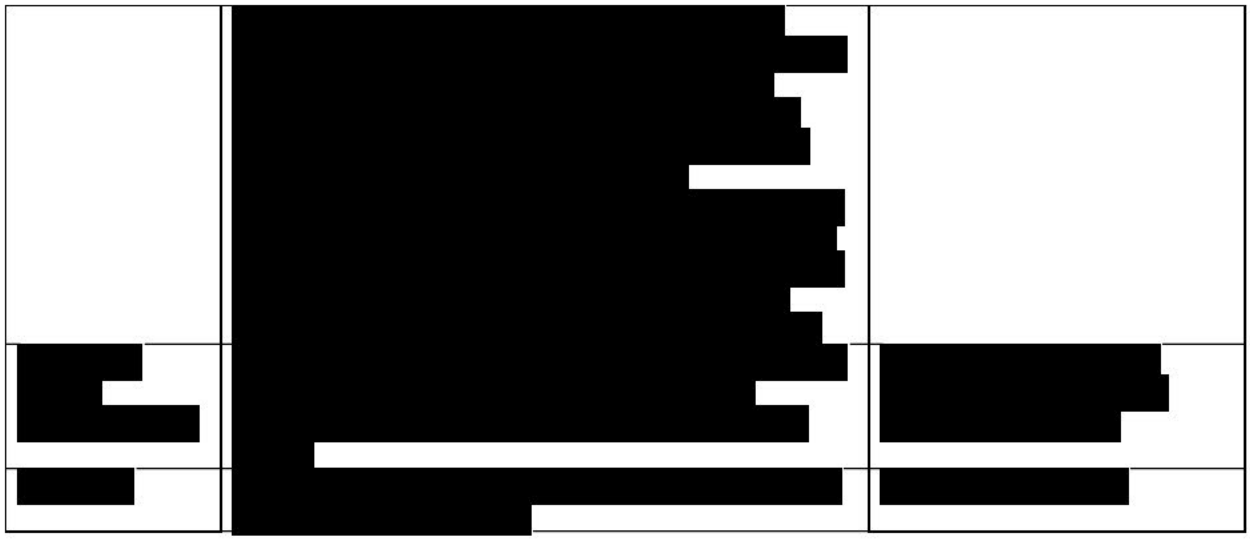
- Any poststudy pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.7.4. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

Appendix 8. Protocol Amendment History

Original Protocol - Version 1.0, 04 March 2019

[redacted]





Amendment 2 – Version 3.0, 24 June 2020

Location of Change	Change Made	Justification of Change
[redacted]	[redacted]	[redacted]

Location of Change	Change Made	Justification of Change
[redacted]	[redacted]	[redacted]

Location of Change	Change Made	Justification of Change
	4	

Location of Change	Change Made	Justification of Change
[redacted]	[redacted]	[redacted]

Amendment 3 – Version 4.0, 12 March 2021

[redacted]

[redacted]	[redacted]	[redacted] y

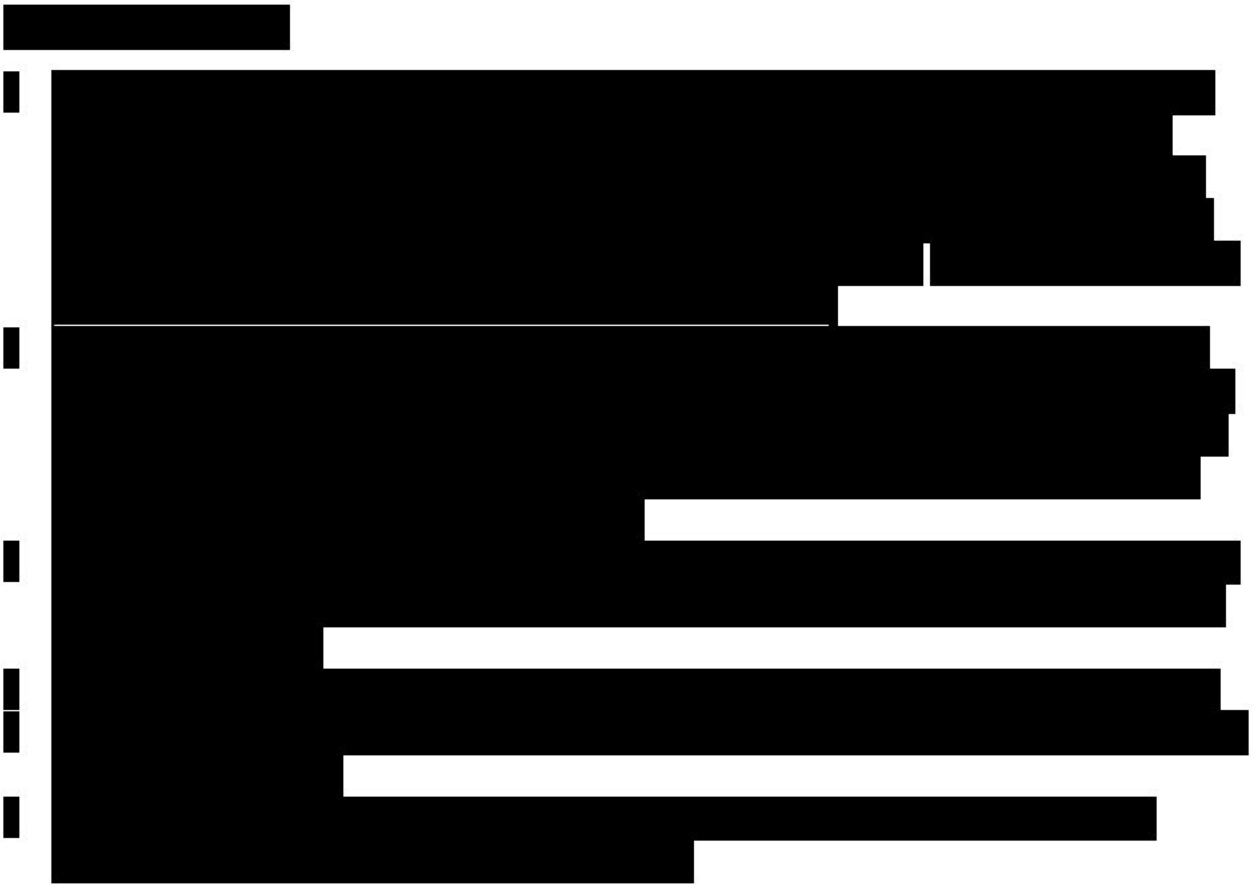
Location of Change	Change Made	Justification of Change
[redacted]	[redacted]	[redacted]

Location of Change	Change Made	Justification of Change
[redacted]	[redacted]	[redacted]

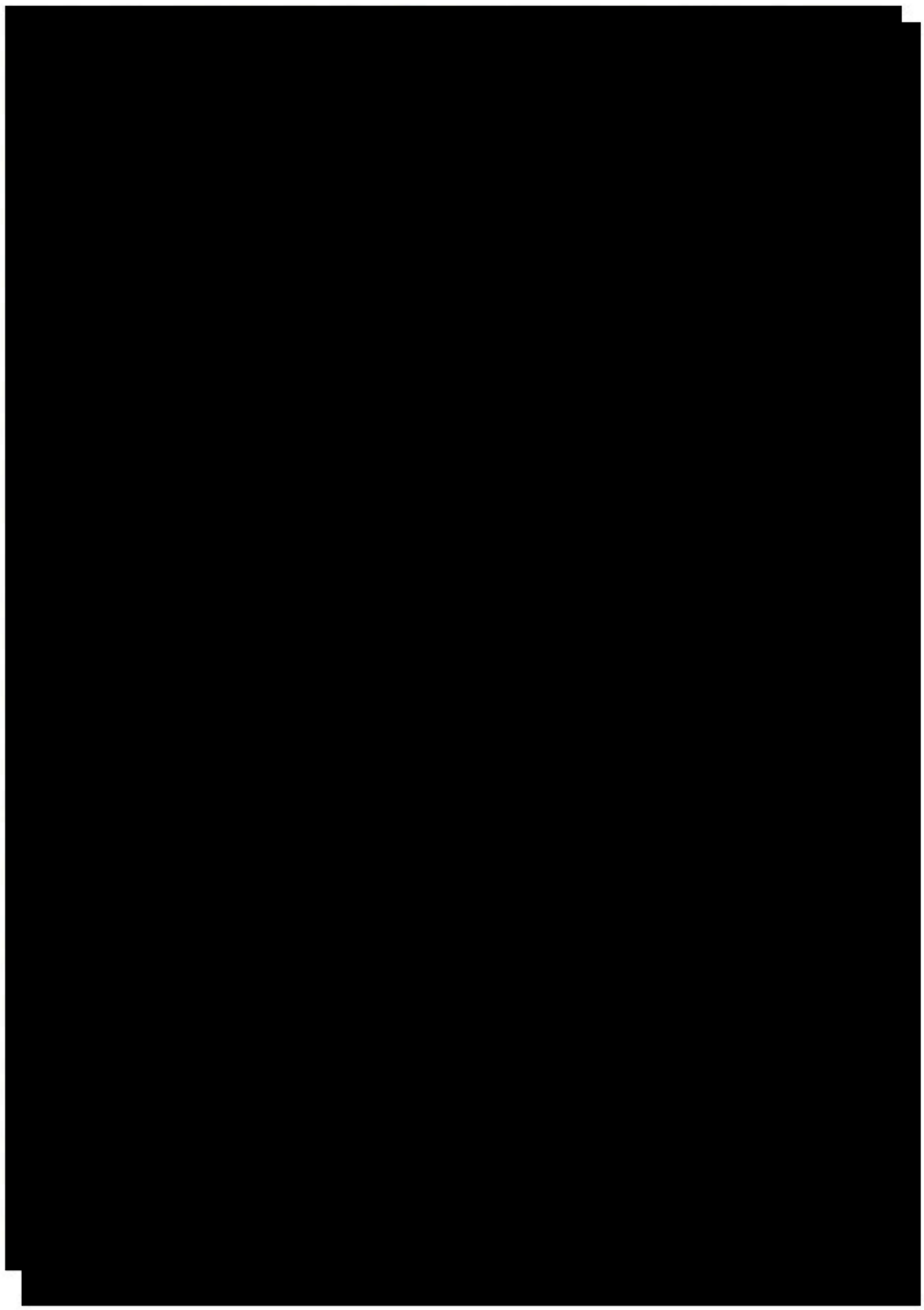
Amendment 4 – Version 5.0, 20 December 2021

Location of Change	Change Made	Justification of Change
[redacted]	[redacted]	[redacted]

Appendix 9. Genetics



Appendix 10. [redacted]



© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Appendix 11. Signature of Investigator

PROTOCOL TITLE: A Phase 1/2 Dose-Finding Study Followed by Expansion Cohorts of NGM120, a GFRAL Antagonist Monoclonal Antibody Blocking GDF15 Signaling, in Subjects With Advanced Solid Tumors and Pancreatic Cancer Using Combination Therapy

PROTOCOL NO: 18-0402

VERSION: Amendment 6 - Version 7.0, 07 April 2022

This protocol is a confidential communication of NGM Biopharmaceuticals, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my; agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Signature Page for VV-CLIN-000594 v1.0

Approval	[redacted]

Signature Page for VV-CLIN-000594 v1.0