A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy, Safety, and Tolerability of Three Doses of NGM282 Administered for 24 Weeks for the Treatment of Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)

PROTOCOL NUMBER 18-0108
For
NGM Biopharmaceuticals, Inc.

MRI Manual July 5, 2019

STUDY IDENTIFICATION

Sponsor:	NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: (650) 243-5555 Fax: (650) 583-1646
Central Radiology Core:	Center for Advanced Magnetic Resonance Development Department of Radiology Duke University Medical Center 200 Trent Dr., Box 3808 Durham, NC 27710, USA
Medpace Core Laboratories	Tamara Davis Project Manager Medpace Core Laboratories 5365 Medpace Way Cincinnati, OH 45227
Sponsor Study Contact:	William Chang, JD Executive Director, Clinical Operations NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080 Office: (650) 416-5254
Sponsor Medical Monitor:	Millie Gottwald, PharmD Sr. Director, Clinical Development NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080 Phone: (650) 392-1779 Mobile: (650) 830-1514 Fax: (650) 583-1646

Table of Contents

1. Brief Study Summary and Imaging Endpoints

Protocol 18-0108 is a phase 2b multicenter, randomized, double blind, placebo-controlled trial of the safety, efficacy, and tolerability of NGM282. It is a 24-week treatment trial with primary endpoints based on liver histology. A secondary objective of protocol 18-0108 is to evaluate changes in liver fat content as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) between baseline and at end-of-treatment (EOT) or end-of-study (EOS).

This trial also includes exploratory measures related to MRI.

2. Central Radiology Core and Contact Information

MRI qualification and image analysis will be performed at the Center for Advanced Magnetic Resonance Development at Duke University Medical Center, in Durham, North Carolina, USA. Queries regarding imaging for Protocol 18-0108 should be directed to:

a. Tamara Davis
Project Manager
Medpace Core Laboratories
5365 Medpace Way
Cincinnati, OH 45227, USA
Phone: +1(513)579-9911 ext. 11365
Fax: +1(513) 579-0444

b. Millie Gottwald, PharmD
Sr. Director, Clinical Development
NGM Biopharmaceuticals, Inc.
333 Oyster Point Boulevard
South San Francisco, CA 94080
Phone: (650) 392-1779
Mobile: (650) 830-1514
Fax: (650) 583-1646

3. MRI Overview

MR Imaging for Protocol 18-0108 will include baseline, 12-week, 24-week (end-of-treatment), and 30-week scans (end-of-study). Scans should be performed at high field strength (3T preferred, 1.5T acceptable), without the administration of oral or intravenous contrast material. MRI examinations will include a six-echo gradient recalled echo (2D GRE) sequence, abdominal adiposity (using a single echo 3D T1-weighted sequence), and a multi-echo acquisition for lipid composition assessment.

4. MRI Procedures

The baseline MRI examination will be performed during the screening period prior to randomization. A PDFF value of ≥10%, as assessed by the central radiology core, is one of the inclusion criteria for the study. Therefore, for patients who are to undergo liver biopsy as part of the trial (for whom no recent liver biopsy is available), it is recommended that liver biopsy be scheduled no sooner than 7 business days after (electronic) transmission of the baseline MRI examination to the central radiology core, to allow adequate time for processing and reporting of the result. Baseline MRI results will be reported to the individual site (as a PDFF % value) no more than 5 business days after the MRI examination is received. In general, it is preferable that a new liver biopsy for the trial should not be performed until and unless a "qualified" result has been received based on the baseline MRI. However, this should be based on scheduling availability for both procedures. Note that none of the on-treatment or post-treatment PDFF time-point results nor other MRI results (besides incidental findings that may be clinically relevant) will be provided to sites.

For all MRI examinations, patients should consume nothing by mouth (NPO) for four hours prior to their MRI appointment. Medications and small amounts of water are acceptable.

The MRI examination protocol is described in detail in Section 8 of this manual. Prior to MRI, all patients and volunteers should undergo safety assessment per institutional protocols and per the guidelines of the site's Institutional Review Board. Patients should be questioned regarding claustrophobia, pregnancy or potential pregnancy, size or weight exceeding the capabilities of the MRI system, metal implants, and other potential safety issues.

5. MRI Site Questionnaire

This questionnaire is designed to collect information regarding site contacts, equipment, and ability to perform MRI activities for this trial. The questionnaire is shown below:

NGM Protocol 18-0108
MRI Site Questionnaire

Site name:	
Site number:	

Contact Information

Site Radiologist

Name:	
Academic Title:	
Address:	
E-mail address:	
Contact phone number:	
Fax Number:	

Technical Contact (typically MRI Technologist)

Name:	
Academic Title:	
Address:	
E-mail address:	
Contact phone number:	
Fax Number:	

Other Center Personnel (if needed)

Name:	
Academic Title:	
Address:	
E-mail address:	
Contact phone number:	
Fax Number:	

MRI Center Technical Information

MRI Hardware

MRI Scanner Manufacturer:	
MRI Scanner Model:	
MRI Scanner Field Strength (1.5T or 3T):	
MRI Scanner Software Version:	
Local abdominal receive coil channel count (anterior + posterior arrays):	

Liver Fat Quantification		
Name of six-echo pulse sequence* to be used:		
*typical sequences:		
Siemens: fl2d (2D FLASH) with 6 contrasts		
GE: StarMap		
Philips: mFFE (multi-echo Fast Field Echo)		
Verify that this can be run as a 2D sequence:	Yes	No

Scan Identification		
Confirm that your center is able to:		
Register subjects using only study identifiers, using no PHI	Yes	No
and/or		
Remove all PHI from images and their DICOM headers		
(except examination date) prior to transfer	Yes	No

Scan Data Transfer		
Confirm that your center is able to:		
Access Box.com via internet browser for image data transfer	Yes	No
and/or		
Burn image data to CD/DVD for transfer via FedEx	Yes	No

Please provide at least 2-3 e-mail addresses for individuals who will be responsible for electronic image data transfer so that we may set up their system access:

If you have any questions completeing this questionnaire, please contact Mustafa R. Bashir, MD, at mustafa.bashir@duke.edu or 919-684-7366.

Thank you.

6. Qualification Scan

Each imaging site must submit at least one qualification MRI to the central radiology core for review and quality assurance. This MRI can be obtained from a volunteer or patient scanned for other reasons, subject to the guidelines of the site's Institutional Review Board. Qualification scans should be submitted through the usual data transfer protocol outlined in Section 9 below. The central radiology core will assess image quality and adherence to study protocol parameters and will issue a determination of "pass" or "fail" for each qualification scan. Sites must have at least one qualification scan with a determination of "pass" prior to performing any MRIs on patients for Protocol 18-0108. The passing scan protocol should be saved on the MRI scanner and used for all MRIs performed for Protocol 18-0108.

Please note that scans for Protocol 18-0108 should ideally be performed by a single MRI technologist/operator per study site. If a site desires to use more than one technologist/operator, each technologist/operator must use the scan protocol that passed the qualification process above for all MRIs performed for Protocol 18-0108.

7. MRI De-identification

All Protected Health Information (PHI), with the exception of examination date and location, must be removed from all MRI images submitted, including the images themselves (if applicable) and DICOM headers. Please note that each site MUST inform study patients in their informed consent documents that the MRI examination dates and locations will be retained with the examination, since these are considered potential identifiers.

Each MRI examination will be identified by a "NGM06_" followed by a three-part study identifier, with the parts connected by an underscore ("_") character.

Part 1: Study site number
Part 2: Subject number (if this is a qualification scan, the subject number will be "qq"); note that subject numbers for 18-0108 are three digits beginning with "2".

Part 3:

For the original submission of a regular study scan, this will be:

- "A" for the baseline scan
- "B" for the 12-week scan
- "C" for the 24-week scan (end-of-treatment) scan
- "D" for the 30-week (end-of-study) scan
- "EW" for any early withdrawal scan.

For resubmitted regular study scans, this will be "A2" or "B2" for a first resubmission, "A3" or "B3" for second resubmission, and so on.

For qualification scans, this will be "Q" followed by a number counting the number of qualification scans submitted to date. For example, the first qualification scan will be "Q1", a second will be "Q2", and so on.

Examples:

- For site 807's second qualification scan: NGM06_807_qq_Q2
- For site 805's third subject's screening scan (not a resubmission: NGM06_805_203_A
- For a first resubmission of the end-of-study (30 week) scan for the tenth patient from site 802: NGM06_802_210_D2

This identifier should be entered into the "Last Name" field, and the "First Name" should be left blank. The "Medical Record Number" and "Accession Number" fields should be left blank. In addition, the "Date of Birth" field should be completed using the date of January 1, with the patient's birth year. So, for a patient born on June 20, 1961, the "Date of Birth" should be entered as 1/1/61.

a. Check for Protected Health Information (PHI)

Please note that as part of the initial quality assurance step, the central radiology core will check several DICOM header fields as well as the images themselves for PHI. With the exception of the MRI examination date and location, if any PHI is found associated with an MRI examination, the copy of the data received by the central radiology core will be destroyed, and the site will be asked to resubmit the examination following de-identification per study protocol.

8. MRI Examination Protocol

Prior to undergoing MRI, patients should complete a safety assessment as described in Section 4 above. Patients should be dressed in MRI-compatible clothing and empty their bladders prior to MRI. Breathing instructions should be explained to the patient's satisfaction prior to MRI. The patient should be positioned supine with pillows/blankets etc. in order to maintain comfort for the examination.

The MRI pulse sequences should be performed in the order below, although it is permissible to reorder or repeat sequences as the needs of the individual patient and examination dictate (for example in order to obtain adequate coverage or rescan due to motion). All sequences should be obtained using at least one set of anterior and posterior phased array coils.

a. General Sequence Guidelines

All pulse sequences should be acquired with respiration suspended at end-inspiration. The field-of-view should be prescribed in order to include the entire peritoneal cavity and abdominal wall on every image, with no phase wrap; partial phase field-of-views are allowed. For sequences that are repeated (e.g. multi-echo fat quant to ensure full liver coverage), number the sequences sequentially (e.g. Multi-echo fat quant 1, Multi-echo fat quant 2, etc.) No fat suppression should be used for any of the pulse sequences. Please do NOT use any in-plane interpolation techniques. Partial Fourier/partial NEX is allowed. For all pulse sequences, parallel acceleration factors up to 2 are allowed.

b. MRI Scan Protocol

1) 3-plane localizer
2) Coronal SSFSE liver
3) Axial SSFSE liver
4) Multi-echo fat quant
5) Coronal SSFSE abdomen/pelvis
6) Adiposity
7) Multi-echo fat composition liver (Siemens systems only)
8) Multi-echo fat composition abdomen (Siemens systems only)

c. Specific Pulse Sequence Parameters

Sequence Name	Plane	Coverage	Flip Angle (°)	TR (ms)	TE (ms)	Base Matrix	Slice Thickness (Gap)
Coronal SSFSE liver	Coronal	Whole liver	90[a]	Min	Min	256 x 128-192	8 (0)
Axial SSFSE liver	Axial	Whole liver	90[a]	Min	Min	256 x 128-192	10 (0)
Multi-echo fat quant[b]	Axial	Whole liver	10	175	Six TEs[c]	192 x 96	10 (0)
Coronal SSFSE abdomen/pelvis	Coronal	Abdomen/ pelvis[d]	90[a]	Min	Min	256 x 128-192	8 (0)
Adiposity[e]	Axial	Abdomen/ pelvis[d]	12	Min	Min	256 x 192	5-10 (0)
Multi-echo fat composition[f]	Axial	Liver and below kidneys	12	Min	[g]	128 x 96[h]	5-10 (0)

[a] Hyperechoes/variable flip angles for reduction of the specific adsorption rate are allowed.

[b] Include at least one slice above the liver and at least one slice below the liver. Pulse sequences should be performed in 2D mode withOUT fat suppression:

Siemens systems: FLASH sequence (fl2d)
GE systems: StarMap is preferred; multi-echo fgre or mgre sequences are acceptable if StarMap is not available.
Philips systems: multi-echo Fast Field Echo sequence (mFFE)

[c] Six echo times:

At 3T: TEs = 1.19, 2.38, 3.57, 4.76, 5.95, and 7.14 ms.
At 1.5T: TEs = 2.38, 4.76, 7.14, 9.52, 11.9, and 14.28 ms.
Note that it may not be possible to precisely match the below echo times, particularly with the StarMap sequence. After setting up the rest of the sequence parameters, the receiver bandwidth should be manipulated to provide a range of six evenly spaced echo times between 0-8 ms at 3T, or 0-16 ms at 1.5T.

[d] Coverage should include the entire abdomen/pelvis from the level of the highest part of the diaphragm to the level of the urinary bladder base.

[e] The Adiposity series is acquired using a standard 3D T1-weighted pulse sequence withOUT fat suppression. This can be acquired using:

Siemens systems: VIBE sequence
GE systems: LAVA or LAVA-XV sequence
Philips systems: eTHRIVE sequence

[f] The Multi-echo fat composition sequence is acquired only on Siemens systems and using the 2D FLASH sequence (fl2d).

[g] Use the maximum number of echo times allowed by the pulse sequence (typically 12-20 echoes will be allowed). Echoes should be evenly spaced as follows:

At 3T, spacing is 1.2 msec; therefore, TEs may be:
1.2, 2.4, 3.6, 4.8, 6, 7.2, 8.4, 9.6, 10.8, 12.0, 13.2, 14.4… msec
At 1.5T, spacing is 2.4 msec, therefore TEs may be:
2.4, 4.8, 7.2, 9.6, 12.0, 14.4, 16.8, 19.2, 21.6, 24.0, 26.4, 28.8… msec

[h] Attempt to obtain a matrix of 128 x 96; many sequences will not allow this, if this matrix cannot be achieved, use the lowest possible matrix for the sequence.

e. Other Technical Guidelines

For the **Coronal and Axial SSFSE liver** sequences:

- Ensure that the entire liver is imaged. If multiple series are needed to cover the liver, ensure at least 2 cm of overlap between each series.
- For the coronal sequences, ensure that at least one image is obtained in front of the liver, and at least one is obtained behind the liver
- For the axial sequences, ensure that at least one image is obtained above the liver, and at least one is obtained below the liver.

For the **Multi-echo fat quant** sequence(s):

- Ensure that the entire liver is imaged. If multiple series are needed to cover the liver, ensure at least 2 cm of overlap between each series.
- Ensure that at least one image is obtained above the liver, and at least one is obtained below the liver.

For the **Coronal SSFSE abdomen/pelvis** sequence(s):

- Ensure that the entire abdomen/pelvis is included, from the diaphragm to the base of the urinary bladder. If multiple series are needed to cover the entire abdomen/pelvis, ensure at least 2 cm of overlap between each series.
- If the MRI system's phased array coils do not allow for adequate coverage of the entire abdomen and pelvis (without distortion at the edges of the field of view), switch to the intrinsic body coil.

For the **Adiposity** sequence(s):

- Ensure that the entire abdomen/pelvis is included, from the diaphragm to the base of the urinary bladder. If multiple series are needed to cover the entire abdomen/pelvis, ensure at least 2 cm of overlap between each series.
- Use the same coil configuration as that used for the **Coronal SSFSE abdomen/pelvis** sequence(s) (whether phased array coils or intrinsic body coil).

For the **Multi-echo fat composition** sequence(s):

- This sequence requires the generation of complex (magnitude and phase) images, which is available for the routine fl2d sequence on Siemens scanners, but may not be possible on other scanners without a research agreement or specialized software. As a result, it should only be performed at sites using Siemens scanners; sites using a non-Siemens scanner, are asked NOT to perform this sequence.
- This sequence is performed in two stations: one axial station through the liver, and one axial station through the abdomen just below the kidneys.
- Complete coverage is not necessary for this sequence, and due to the relatively long time associated with the maximum echo time, it may only be possible to obtain 3-5 images in one acquisition. Please obtain the first acquisition through the thickest portion of the right hepatic lobe, and the second acquisition through the fat just below the kidneys, including the mesenteric fat and subcutaneous fat.
- It is very important that the receiver bandwidth be set as low as possible for this sequence in order to maximize signal-to-noise, while maintaining an echo spacing of no more than 1.4 msec at 3T and 2.8 msec at 1.5T.
- For Siemens scanners, please set this sequence to produce both magnitude and phase images. Under the "Contrast" card, "Dynamic" tab, the "Reconstruction" option should be set to "magnitude and phase". Both the magnitude and phase images should be sent with the image transfer.
- Please be careful that there is no phase wrap for this acquisition, particularly from the abdominal wall. A large field of view may be necessary.

9. MRI Data Transfer

After de-identification, MRI data will be transferred to the central radiology core for analysis. Electronic data transfer is strongly preferred over physical media (CD/DVD) transfer. Sites will retain a copy of each MRI examination locally per the protocol-defined retention of records requirements.

All MRI study scans should be submitted via the Medidata Image Management System within 1-2 business days. All images must be de-identified and in DICOM format. For sites that are unable to perform electronic data transfer, the MRI examination and MRI CRF can submitted to the central radiology core via courier service.

Detailed instructions for electronic or manual image submission can be found in the Image Submission Manual.

a. MRI Case Report Form

NGM Protocol 18-0108
MRI Case Report Form

Center for Advanced
Magnetic Resonance Development

Identifiers	
Site name:	
MRI identifier (NGM06_aaa_2bb_c):	
Date of MRI:	
Name of MRI system:	
Initials of MRI technologist/operator:	

Adverse Events		
Did any adverse events occur during the MRI?	Yes	No
If "yes", please describe in detail:		

Scan Deidentification		
Are any PHI (except for scan date) present within the image data or DICOM headers?	Yes	No
If "yes", please remove PHI prior to data transmission.		

Scan Data Transfer		
Have all image data been uploaded via electronic data transfer system?	Yes	No