Study Protocol	
Official title:	A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Non-Alcoholic Steatohepatitis
NCT Number:	NCT02912260
Document Date:	26 December 2017

CLINICAL STUDY PROTOCOL

A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Non-Alcoholic Steatohepatitis

Investigational Product: MGL-3196
Protocol Number: MGL-3196-05

Sponsor:
Madrigal Pharmaceuticals, Inc.
Four Tower Bridge, 200 Barr Harbor Drive, Suite 400
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Original Protocol: 14 July 2016
Amendment 1: 07 Sep 2016
Amendment 2: 16 Dec 2016
Amendment 3: 11 May 2017
Amendment 4: 10 August 2017
Amendment 5: 06 November 2017
Amendment 6: 26 December 2017

SIGNATURE PAGE

STUDY TITLE: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Non-Alcoholic Steatohepatitis

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
_____	_____

[redacted]
Chief Medical Officer, Executive Vice President R&D
Madrigal Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Madrigal Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Madrigal Pharmaceuticals, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Madrigal Pharmaceuticals, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, IRB and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP).

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SUMMARY OF PROTOCOL AMENDMENT 6 CHANGES

Administrative changes that may affect the content or conduct of the protocol:

Changes to dosing in the Main Study and Extension Study including changes to Inclusion Criteria #9 (Synopsis and Sections 3.1.3 and 4.1).

Rationale: Results of the 12 week MRI-PDFF primary endpoint readout of MGL-3196-05 have now been obtained in 116 patients treated with MGL-3196 or placebo who had both a baseline and Week 12 MRI-PDFF. The study remains blinded to individual patient treatment code. The primary endpoint was achieved. MGL-3196 treated patients versus placebo treated patients demonstrated [redacted] relative fat fraction reduction compared to [redacted] reduction in placebo [redacted] (see Table 1, supporting statistical data beginning on Page 8). A prespecified group of MGL-3196 treated patients [redacted] with higher MGL-3196 drug levels [redacted] demonstrated [redacted] fat reduction relative to placebo [redacted] of all MGL-3196 treated and [redacted] of the higher drug level group as compared with [redacted] of placebo patients attained >=30% liver fat reduction. Patients with lower drug exposure (MGL-3196, <2700 ng*hr/ml) had less response [redacted], significant relative to placebo [redacted]. The exposure groups were based on projected AUCs after dose adjustment, and an exposure of >=2700ng*hr/ml was chosen based on Phase 1 data that showed that there was a pharmacodynamic effect to lower lipids at this exposure.

There were statistically significant reductions in liver enzymes (ALT, AST) within the drug-treatment group that were also statistically significant relative to placebo in the group [redacted] of MGL-3196-treated patients with higher drug levels. Lipids, including LDL-cholesterol, triglycerides, apolipoprotein B and lipoprotein(a) were also significantly reduced in MGL-3196 treated compared to placebo patients. Triglyceride lowering appeared to be significantly attenuated at 12 weeks following the dose reduction at 4 weeks [redacted]
Prespecified high (>=75% increase from baseline) SHBG group (biomarker for MGL-3196 hepatic levels) showed similarly enhanced improvement in MRI-PDFF and liver enzymes relative to placebo. Overall safety has been good with mostly mild AEs and some moderate AEs which are generally balanced between placebo and treatment group. There have been 3 SAEs, blinded to treatment code, none of which are considered related to study drug by independent Medical Monitor ([redacted]) or Sponsor. More than 30 patients have now had a follow up 36 week liver biopsy; although the NASH scoring is blinded, study pathologist, [redacted], who reads the 36 week biopsies on an ongoing basis, has not reported any findings of non-NASH or biliary lesions (Page 2 of scoring sheet "Any non-NASH findings" is not blinded).

Table 1. Results of Week 12 Primary Endpoint Analysis

	ALL MGL-3196	High MGL-3196[1]	Low MGL-3196	Placebo
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]
Primary Endpoint:				
Relative change in MRI-PDFF (% change from baseline, median)	[redacted]	[redacted]	[redacted]	[redacted]
Significance relative to placebo	[redacted]	[redacted]	[redacted]	
Percentage of patients attaining ≥30% liver fat reduction	[redacted]	[redacted]	[redacted]	[redacted]
Significance relative to placebo	[redacted]	[redacted]	[redacted]	

[1] Prespecified MGL-3196 exposure groups >=2700 ng*hr/ml and <2700 ng*hr/ml

MGL-3196-05 Amendment 6 adds a minor dose adjustment (increase in dose of 20-25%) in a small percentage (~10) of patients still completing the 36 week Main study, who have low exposure on doses of 60-80 mg (low predose exposure, low SHBG response). [redacted] Several parameters and visits were assesed to assure that the data were not impacted by compliance issues (e.g. not taking drug the day before visit, taking drug prior to visit). [redacted] SHBG levels (blinded to patient ID) were reviewed because SHBG has a long half-life, and may be a marker for average drug exposure. Any dose adjustments will be made by unblinded personnel.

In patients remaining in the Main study or randomized to MGL-3196 who meet criteria and consent to Extension study:

Table 2. Doses in Main and Extension Study in Patients Assigned to MGL-3196 in the Main Study

Current dose	Main Study Week 2 PK (AUC, combined MGL-3196 plus M1 on 80 mg dose)	Main Study Predose at Week 2	Main study Predose Week 8 (post dose adjustment)	Main Study SHBG <+75% CFB at Week 12 (post dose adjustment)	Action in Main and/or Extension Study
40 mg			<5 ng/ml	Yes	Increase to 60 mg/day
60 mg	<5500ng*hr*ml[1]		< 1 ng/ml	Yes	Increase to 80 mg/day
80 mg	<4000 ng*hr/ml AND SHBG %CFB<90)			OR[2] Yes	Increase to 100 mg/day
100 mg	≤3000 ng*hr/ml	<5 ng/ml			Increase to 120 mg
120 mg					No change

[1] Recalculated 80 mg AUC based on corrected elimination rate constant for MGL-3196 and M1in patients who demonstrated average predose levels <5 ng/ml at Week 2,4,8 and had initial calculated AUC<7000 ng*hr/ml. Change from Baseline (CFB).

[2] Either exposure <4000ng*hr/ml with SHBG%CFB<+90 OR SHBG<+70%CFB qualifies for increase to 100 mg.

Table 3. Dose Adjustment During Extension Study

Extension Study Week 2 |MGL-3196 Concentration		Extension Study Week 2 SHBG	Extension Study Week 4 Action
Predose	**4 h post dose**		
>35 ng/ml	>1350 ng/ml	>200% CFB*	Downtitrate to 40 mg
Patients not meeting criteria for 40, 80, 100 or 120 mg			Downtitrate to 60 mg
<15 ng/ml	<600 ng/ml	OR <75% increase**	Remain on 80 mg or increase (see next rows)
<5 ng/ml	≤ 350 ng/ml	No rule	Increase to 100 mg
<2 ng/ml	≤ 150 ng/ml	No rule	Increase to 120 mg

*Change From Baseline, where baseline is Extension Study Day 1.
**Either predose<15ng/ml plus 4h<600ng/ml OR SHBG<+75%CFB.

Based on the Week 12 results, which are blinded to individual patient ID, the proposed predose and 4h postdose and SHBG levels as shown in Table 3 provide the primary basis for dose adjustment in the extension study. The only modification to this table from Amendment 5 is use of the SHBG algorithm for the 80 mg dose. Since the extension study is open label, it affords an opportunity to review SHBG, lipids, liver enzymes, and predose/4 h drug levels on an ongoing basis. In addition to the exploratory endpoints of the Extension study, goals will be to obtain additional dosing and PD information to supplement the data from the Main study that will be used to support dose selection for later studies, including, potentially, a pivotal NASH study. The algorithms provided in this table, which are based on current criteria, may undergo minor alterations during the extension study.

Given the overall safety, improvements in MRI-PDFF and liver enzymes in MGL-3196-treated patients at 12 weeks, a few additional patients with persistent elevations without improvement in liver enzymes >=1.5-2X (placebo or MGL-3196, Weeks 16-30, Table 4). will be eligible for the extension study.

Table 4. Modified ALT (AST) Inclusion Criteria for Extension Study

Baseline ALT	**Average of ALT at Weeks 16, 20, 24, and 30**
ALT normal (<1.5 ULN)	≥1.5 x ULN (and 30% worse than baseline)
ALT =1.5-2X	Improvement from baseline <30% and ALT =1.5-2X ULN
ALT any	ALT ≥ 2X
Note: Normal ALT male 30; female 25: 1.5 x male =45 and female=38;	Note: ALT or AST values for weeks 16, 20, 24 and 30 that are > 2 X Std Dev from mean will be excluded from the calculation of the average value. Note: When ALT does not meet criteria for inclusion, AST will be evaluated similarly to determine if criteria for inclusion are met based on AST, given normal values in men and women of 27 and 22, respectively and 1.5X of 40 and 33 respectively.

Many of these patients will have been assigned to placebo or, possibly, to an inadequate dose of MGL-3196. The baseline ALT inclusion requirement for females was increased in this Amendment, defining elevated ALT at >25 U/L rather than >19 U/L and 2X elevation at 50U/L.

Supporting Top-line Data Statistical Tables

MRI-PDFF (median change in each group)

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Table 3.1
Summary of Hepatic Fat Fraction (%) by MRI PDFF
MRI-PDFF Evaluable Population

Visit Statistic	Placebo (N= 30)	MGL-3196 (N= 78)
Week 12 [2]		
n		
Mean		
Standard deviation		
Minimum		
Median		
Maximum		
Change from Baseline to Week 12		
n [3]		
Mean		
Standard deviation		
Minimum		
Median		
Maximum		
Percent Change from Baseline to Week 12		
n [3]		
Mean		
Standard deviation		
Minimum		
Median		
Maximum		

[1] Baseline is the value at the Screening visit.
[2] Only Week 12 measurements are included. Patients without Week 12 visit are not included.
[3] n is the number of patients with valid measurements at both Baseline and this visit.

Program (Output): M011.sas (T3.1.rtf) Rundate: 2017-11-16 8:23 Database last modified: 2017-11-06 14:40

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Table 3.1.1
Summary of Hepatic Fat Fraction (%) by MRI-PDFF by Exposure Group
MRI PDFF Evaluable Population

Visit Statistic	Placebo (N= 30)	MGL 3196 AUC <2700 ng*hr/mL (N= 34)	MGL 3196 AUC >=2700 ng*hr/mL (N= 44)
Week 12 [2]			
n			
Mean			
Standard deviation			
Minimum			
Median			
Maximum			
Change from Baseline to Week 12			
n [3]			
Mean			
Standard deviation			
Minimum			
Median			
Maximum			
Percent Change from Baseline to Week 12			
n [3]			
Mean			
Standard deviation			
Minimum			
Median			
Maximum			

[1] Baseline is the value at the Screening visit.
[2] Only Week 12 measurements are included. Patients without Week 12 visit are not included.
[3] n is the number of patients with valid measurements at both Baseline and this visit.

Program (Output): M011_EXP.sas (T3.1.1.rtf) Rundate: 2017 11 17 9:36 Database last modified: 2017 11 17 6:04

Primary Endpoint

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Table 3.2
Analysis of Percent Change and Change from Baseline in Hepatic Fat Fraction by MRI-PDFF at Week 12
MRI-PDFF Evaluable Population

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 78)
% Change from Baseline to Week 12 [5]	LS Mean (SE) 95% CI p-value	[redacted]	[redacted]
Treatment Comparison of Change [4] [5]			
vs Placebo	LS Mean Difference in % Change (SE) 95% CI p-value		
(p-value of Shapiro-Wilk normality test = 0.2416)			

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Table 3.2.1
Analysis of Percent Change and Change from Baseline in Hepatic Fat Fraction by MRI-PDFF by Exposure Group at Week 12
MRI PDFF Evaluable Population
Subgroup: Exposure = AUC >= 2700 ng*hr/mL

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 44)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (%) [2]	Mean (SD)		
Week 12 (%) [3]	Mean (SD)		
% Change from Baseline to Week 12 [4]	LS Mean (SE) 95% CI p-value		
Treatment Comparison of % Change [4]			
vs Placebo	LS Mean Difference in % Change (SE) 95% CI p value		

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Table 3.2.1
Analysis of Percent Change and Change from Baseline in Hepatic Fat Fraction by MRI-PDFF by Exposure Group at Week 12
MRI-PDFF Evaluable Population
Subgroup: Exposure = AUC < 2700ng*hr/mL

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 34)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (%) [2]	Mean (SD)		
Week 12 (%) [3]	Mean (SD)		
% Change from Baseline to Week 12 [4]	LS Mean (SE) 95% CI p-value		
Treatment Comparison of % Change [4]			
vs Placebo	LS Mean Difference in % Change (SE) 95% CI p-value		

Numbers of patients with >30% Fat reduction

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Table 3.3
Analysis of Reaching Treatment Goal for Hepatic Fat Fraction by MRI-PDFF at Week 12
MRI-PDFF Evaluable Population

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 78)
Number of Patients with Week 12 [1]	N'	[redacted]	[redacted]
% Change from Baseline to Week 12 < 30% (% Reduction of 30% or more)	n (%)		
---------- Treatment Comparison [2] ----------			
vs Placebo	Odds Ratio		
	95% CI		
	p value		

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Table 3.3.1
Analysis of Reaching Treatment Goal for Hepatic Fat Fraction by MRI-PDFF by Exposure Group at Week 12
MRI-PDFF Evaluable Population
Subgroup: Exposure = AUC >= 2700 ng*hr/mL

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 44)
Number of Patients with Week 12 [1]	N'	[redacted]	[redacted]
% Change from Baseline to Week 12 <-30% (% Reduction of 30% or more)	n (%)		
---------- Treatment Comparison [2] ----------			
vs Placebo	Odds Ratio		
	95% CI		
	p-value		

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Table 3.3.1
Analysis of Reaching Treatment Goal for Hepatic Fat Fraction by MRI-PDFF by Exposure Group at Week 12
MRI-PDFF Evaluable Population
Subgroup: Exposure = AUC < 2700ng*hr/mL

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 34)
Number of Patients with Week 12 [1]	N'	[redacted]	[redacted]
% Change from Baseline to Week 12 <-30% (% Reduction of 30% or more)	n (%)		
---------- Treatment Comparison [2] ----------			
vs Placebo	Odds Ratio		
	95% CI		
	p-value		

Adverse events (study remains blinded)

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Table 11
Overview of Treatment Emergent Adverse Events
Safety Population

	Placebo (N= 41)	MGL 3196 (N= 84)	Overall (N=125)
Subjects with any treatment-emergent adverse event (TEAE)	[redacted]	[redacted]	[redacted]
Severity of TEAE			
Mild			
Moderate			
Subjects with any TEAE related to study drug			
Severity of TEAE related to study drug			
Mild			
Moderate			
Severe			

There were 3 severe AEs, originally reported as 4 severe AEs 2 in placebo 2 in MGL-3196: one was an error so the total in each group was not shown to maintain blind

Lipid Analyses

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Table 6.1
Analysis of Direct LDL
mITT Population

Category	Statistic	Placebo (N= 39)	MGL-3196 (N= 79)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (mg/dL) [2]	Mean (SD)		
Week 12 LOCF (mg/dL) [3]	Mean (SD)		
% Change from Baseline to Week 12 LOCF [4]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of % Change [4] ----------			
vs Placebo	LS Mean difference in % Change (SE)		
	95% CI		
	p-value		

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Table 6.3
Analysis of Lp(a)
mITT Population
Baseline Lipoprotein > 10

Category	Statistic	Placebo (N= 22)	MGL-3196 (N= 40)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (nmol/L) [2]	Mean (SD)		
Week 12 LOCF (nmol/L) [3]	Mean (SD)		
% Change from Baseline to Week 12 LOCF [4]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of % Change [4] ----------			
vs Placebo	LS Mean Difference in % Change (SE)		
	95% CI		
	p-value		

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Table 6.2
Analysis of Triglycerides
mITT Population

Category	Statistic	Placebo (N= 39)	MGL-3196 (N= 79)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (mg/dL) [2]	Mean (SD)		
Week 12 LOCF (mg/dL) [3]	Mean (SD)		
% Change from Baseline to Week 12 LOCF [4]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of % Change [4] ----------			
vs Placebo	LS Mean Difference in % Change (SE)		
	95% CI		
	p-value		

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Table 6.0
Analysis of Apolipoprotein B
mITT Population

Category	Statistic	Placebo (N= 39)	MGL-3196 (N= 79)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (mg/dL) [2]	Mean (SD)		
Week 12 LOCF (mg/dL) [3]	Mean (SD)		

% Change from Baseline to Week 12 LOCF [4]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of % Change [4] ----------			
vs Placebo	LS Mean Difference in % Change (SE)		
	95% CI		
	p-value		

Liver enzymes: AST, ALT

AST Treated, High exposure group, Significant decrease within group and compared with placebo

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Table 5.2.1
Analysis of AST by Exposure Group
MRI-PDFF Evaluable Population
Exposure = AUC >= 2700 ng*hr/mL

Category	Statistic	Placebo (N= 30)	MGL-3196 (N= 44)
Number of Patients	n [2]	[redacted]	[redacted]
Baseline (U/L) [2]	Mean (SD)		
Week 12 (U/L)	Mean (SD)		
Change from Baseline to Week 12 [3]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of Change [3] ----------			
vs Placebo	LS Mean Difference in Change (SE)		
	95% CI		
	p-value		

[1] Number of patients with measurements at both baseline and Week 12.
[2] Baseline is the value at the Baseline visit (Day 1). If the measurement at this visit is missing, the last measurement prior to the first dose of randomized study drug is used.
[3] The LS means, standard errors, confidence intervals, and p values come from an ANCOVA model with percent change or change from baseline as the dependent variable, treatment as a factor, and baseline as a covariate.

Program (Output): LB12.sas (t5.2.1.rtf) RunDate: 2017 11 21 5:55 Database last modified: 2017 11 20 15:41

All treated, AST, significant decrease within group

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Table 5.2
Analysis of AST
MRI-PDFF Evaluable Population

Category	Statistic	Placebo (N= 38)	MGL-3196 (N= 78)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (U/L) [2]	Mean (SD)		
Week 12 (U/L)	Mean (SD)		

Change from Baseline to Week 12 [3]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of Change [3] ----------			
vs Placebo	LS Mean Difference in Change (SE)		
	95% CI		
	p value		

ALT (defined normal values female=19, male=30; criteria, elevated at baseline >=1.5X ULN)

Significant reduction in ALT within high exposure treated group compared with placebo

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Table 5.3.1
Analysis of ALT by Exposure Group
MRI-PDFF Evaluable Population - Women with Baseline ALT >=30 U/L and Men with Baseline ALT >=45 U/L
Exposure - AUC >= 2700 ng*hr/mL

Category	Statistic	Placebo (N= 29)	MGL-3196 (N= 27)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (U/L) [2]	Mean (SD)		
Week 12 (U/L)	Mean (SD)		
Change from Baseline to Week 12 [3]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of Change [3] ----------			
vs Placebo	LS Mean Difference in Change (SE)		
	95% CI		
	p-value		

[1] Number of patients with measurements at both baseline and Week 12.
[2] Baseline is the value at the Baseline visit (Day 1). If the measurement at this visit is missing, the last measurement prior to the first dose of randomized study drug is used.
[3] The LS means, standard errors, confidence intervals, and p-values come from a linear model with percent change or change from baseline as the dependent variable and treatment as a factor. For the analysis of change from baseline, baseline is also included as a covariate in the linear model.

Program (Output): LB12.sas (T5.3.1.rtf) RunDate: 2017-11-29 20:06 Database last modified: 2017-11-20 15:41

ALL MGL-3196 treated, significant decrease in ALT within group

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Table 5.3
Analysis of ALT
MRI-PDFF Evaluable Population - Women with Baseline ALT >=30 U/L and Men with Baseline ALT >=45 U/L

Category	Statistic	Placebo (N= 29)	MGL-3196 (N= 47)
Number of Patients	n [1]	[redacted]	[redacted]
Baseline (U/L) [2]	Mean (SD)		
Week 12 (U/L)	Mean (SD)		
Change from Baseline to Week 12 [3]	LS Mean (SE)		
	95% CI		
	p-value		
---------- Treatment Comparison of Change [3] ----------			
vs Placebo	LS Mean Difference in Change (SE)		
	95% CI		
	p-value		

Administrative changes not affecting the content or conduct of the protocol:

Removed reference to serum pregnancy testing in Table B footnote 10.

SUMMARY OF PROTOCOL AMENDMENT 5 CHANGES

Administrative changes that may affect the content or conduct of the protocol:

Addition of an extension phase of the study ("Extension Study"), adding 36 weeks of treatment for patients meeting selected criteria.

Rationale: The major change in this protocol amendment is the inclusion of an extended dose study beyond 36 weeks for up to 36 weeks in a subset of enrolled patients who have persistently elevated liver enzymes, specifically defined by at least ALT ≥1.5X ULN (women ≥29; men ≥45), (Table 1) or have demonstrated worsening of liver enzymes during the first 36 weeks of the study, based on average liver enzymes between weeks 16-30, excluding outlier values (for example a transient spike in liver enzymes at a single visit). Based on the current estimate, ~25% of the total 125 enrolled patients might be eligible for the extension study. Persistently elevated liver enzymes are a good measure of NASH activity in NASH patients whose liver enzymes are elevated at baseline (many NASH patients have normal or mildly elevated liver enzymes). Approximately 36% of enrolled patients had ALT<1.5X at baseline and few of these patients showed worsening; these patients would not be eligible for the extension. Patients eligible for the extension study could include either placebo or drug-treated patients.

Table 1. ALT (AST) Inclusion Criteria for Extension Study

Baseline ALT	Average of ALT at Weeks 16, 20, 24, and 30
ALT normal (<1.5 ULN)	≥1.5 x ULN (and 30% worse than baseline)
ALT =1.5-2X	Worsened from baseline ≥ 30%
ALT any	ALT ≥ 2X
Note: Normal ALT male 30; female 19: 1.5 x male =45 and female=29	Note: ALT or AST values for weeks 16, 20, 24 and 30 that are > 2 X Std Dev from mean will be excluded from the calculation of the average value. Note: When ALT does not meet criteria for inclusion, AST will be evaluated similarly to determine if criteria for inclusion are met based on AST, given normal values in men and women of 27 and 22, respectively and 1.5X of 40 and 33 respectively.

The major rationale for the extension study is that the overall safety of the clinical study has been very good, with improvement in liver enzymes in the overall study, including a normalization of liver enzymes from baseline in a significant fraction of patients (see DSMB output, Table 4, on pages 23-12). Subsequent to the September DSMB meeting, additional patients out to 24 weeks (now 48 patients) continue to show similar average improvements in liver enzymes.

An extension study will provide

- Safety and efficacy data following extended and optimized dosing in patients previously randomized to MGL-3196
- Safety and efficacy data in patients previously randomized to placebo

Patients who may be on placebo with persistently elevated liver enzymes will have an opportunity for drug therapy during the extension. In addition, we recognize (as described below) that patients assigned to MGL-3196 who meet criteria for the extension may require longer therapy than 36 weeks or an upward adjustment in their dose if they have been on a subtherapeutic dose of MGL-3196 (<<5500 AUC). Since the study remains blinded, and the results of the liver biopsy are unknown, the patients may have shown some response to MGL-3196 but their liver enzymes may not accurately reflect their disease activity. In addition to providing a therapeutic opportunity for patients, the extension will allow Madrigal to gain a better understanding of dose and exposure response relationships that will be very important to inform dosing in a subsequent registrational NASH clinical trial. Patients in the extension study will continue to be blinded as to initial drug assignment. During the course of the extension study, the main 36-week study will complete, and it is anticipated that patient treatment assignment, including for those patients in the extension, will become unblinded at that time.

Patients in the extension study will be monitored by non-invasive tests, including an MRI-PDFF at Week 36 of the main study, which will form the baseline MRI-PDFF assessment for the extension study. Subsequent MRI-PDFFs will be performed at 12 and 36 weeks of the extension study (or at the time the patient leaves the study). Clinic visits, biomarkers and safety laboratories and procedures will be the same as the main study. The investigators are also encouraged to obtain fibroscans at 36 weeks of the main study and at the end of the extension study planned for 36 weeks later (total 72 weeks).

Dosing Groups in Patients Assigned to MGL-3196 in the Main Study

Patients in MGL-3196-05 assigned to 80 mg per day MGL-3196 had their doses adjusted so as not to exceed 5500 AUC (combined M1 and MGL-3196) after the first 4 weeks. Analysis indicates that exposure in NASH patients is generally similar to healthy volunteers. Patients who had higher exposures >5500 ng*hr/ml were successfully identified at the Week 2 PK visit resulting in downtitration of [redacted] patients to 60 mg per day and [redacted] patients to 40 mg/day. [redacted] patient ([redacted]) downtitrated to 40 mg had an exposure level that was > 2 SD above the mean at Week 2. [redacted] patients had their dose adjusted upward to 100 mg per day because of low exposure at 80 mg [redacted]).

The DSMB headed by [redacted] has evaluated the NASH study (MGL-3196-05) twice and MGL-3196-06 (Phase 2 HeFH study) once, most recently in September 2017 (NASH study fully enrolled, 63 patients completed 12 week MRI-PDFF) and recommended that both studies continue without protocol modification. The IP has been well-tolerated and a significant percentage of patients enrolled in the study have shown improvement in liver parameters, including liver enzymes and MRI-PDFF (blinded group data). There have been few SAEs and no SAEs considered related to study drug. AEs have been generally mild and unrelated.

- On approximately 10 liver biopsies evaluated after 36 weeks of treatment, no evidence of biliary hyperplasia or any non-NASH findings
- No increase in Alkaline Phosphatase (ALP) in NASH patients (see Table 4) (Note: ALP elevations were consistently observed in high dose dogs with biliary hyperplasia)
- Evidence for reduction in liver fat fraction in 63 patients (including placebos, blinded to study drug assignment) at Week 12 MRI-PDFF (see Table 4)
- Evidence for clear hepatic pharmacologic effect as evidenced by [redacted] in blinded study data(see Table 4)
- No effects on renal function, vital signs, or TSH (i.e., no central thyroid axis suppression)
- Demonstration in human, dog and rat mass balance and rat tissue distribution studies completed since the initiation of MGL-3196-05 that MGL-3196 and its metabolites are cleared without evidence of prolonged accumulation. In humans, 90% MGL-3196 and its metabolites are eliminated from plasma, urine (~10% of administered dose) largely by 24 h and gut (80-90% of administered dose) by 72 h. The M1 metabolite is the only major metabolite in humans. The M1 metabolite, which is produced at low (~1%, human) or undetectable (dog) level in hepatocytes is present at a low level in dog liver and bile duct relative to MGL-3196. (See more detailed summary of mass balance and tissue distribution studies below)

In MGL-3196-05, PK was obtained in 79 patients assigned to 80 mg MGL-3196 who completed the Week 2 visit. Careful examination of the Week 2 PK data, and serial trough drug concentrations, which are collected at each visit, indicates that the best predictors of dose reduction to 40 mg (occurred in [redacted] patients) are a high MGL-3196 predose concentration (typically > [redacted] ng/ml) and a high MGL-3196 C_{max} ([redacted] ng/ml). In addition, in all cases in which downtitration to 40 mg occurred, the patient had a SHBG [redacted] increase from baseline at Week 2. Patients meeting criteria for downtitration to 60 mg on average had [redacted] (MGL-3196 [redacted] ng/ml) and MGL-3196 C_{max} [redacted] ng/ml. Patients remaining on 80 mg or uptitrated to 100 mg on average had a predose concentration of [redacted] ng/ml and a C_{max} [redacted] ng/ml.

The major focus of dose titration in the main 36 week NASH study was to prevent high exposures >5500 AUC (combined M1 and MGL-3196). As a result, [redacted] of patients randomized to MGL-3196, including a significant percentage of those with low exposures at [redacted] and [redacted] mg per day, may have been treated with subtherapeutic or suboptimal doses of MGL-3196, based on exposures required to demonstrate lipid lowering ([redacted] ng*hr/ml MGL-3196 delivers about [redacted] of maximal LDL-C lowering in MAD and Phase 1 data). Maximal lipid lowering was observed at MGL-3196 concentrations of [redacted] ng*hr/ml in the MAD and somewhat higher concentrations in subsequent studies. M1 is [redacted] fold less potent than MGL-3196 and is not expected to contribute to activity. Potentially, NASH may respond to lower or different MGL-3196 exposures; however, animal data showed that the same doses were required to lower liver triglycerides and serum cholesterol. In the extension study, doses in patients originally randomized to MGL-3196 who meet criteria for the extension study will be further optimized while continuing to limit the total exposure to ≤ 5500 ng*hr/ml (MGL-3196 plus M1). In addition, we have now shown that most patients in

the main study who were uptitrated to 100 mg (combined MGL-3196 plus M1 AUC <3000 ng/ml at 80 mg) continue to demonstrate evidence of low exposure (undetectable trough levels on 100 mg dose) and low SHBG levels suggesting that drug exposure in these patients at 100 mg remains <<5500 ng/ml. In a few patients who are relatively early in the main study (12-24 weeks), if they meet criteria in Table 2, their dose will be increased to 120 mg during the main study, and continued on 120 mg if they meet eligibility criteria for the extension study.

Dosing algorithms for extension study. In patients randomized to MGL-3196 who meet criteria and consent to extension study:

Table 2. Dose Adjustments in Extension Study in Patients Assigned to MGL-3196 in the Main Study

Current dose	Main Study Week 2 PK (AUC, combined MGL-3196 plus M1 on 80 mg dose)	Main Study Predose at Week 2	Action in Extension Study
40-60 mg			No change
80 mg	<3500 ng*hr/ml	<5 ng/ml	Increase to 100 mg/day
100 mg	≤2500 ng*hr/ml	<5 ng/ml	Increase to 120 mg
120 mg			No change

In MGL-3196 assigned patients dose adjustments at Week 4 of the extension study will be based on Week 2 PK obtained during the main study. If patients are on 60 or 40 mg, then they will continue on that dose unchanged. For patients taking 80 or 100 mg at Week 36 of the main study, there may be an increase in dose at the 4 week Extension study visit based on criteria described in Table 2. Previously, an increase to 100 mg was based on a combined AUC of <3000 ng*hr/ml at Week 2 of the main study, and this dose adjustment to 100 mg will now be made based on patients who had an AUC<3500; patients who had a combined exposure (MGL-3196 plus M1) at Week 2 AUC ≤2500 will have their dose increased to 120 mg at Week 4 of the extension study. For each patient enrolled in the extension study who was previously assigned to MGL-3196, these calculations have been tested to assure that the combined AUC MGL-3196 plus M1 will not exceed 5500 AUC after the dose adjustment at Week 4 of the Extension study.

For patients assigned to Placebo in the main study, who meet criteria and consent to the extension study:

All former placebo patients will be randomized to receive 80 mg dose of MGL-3196 for 4 weeks. All patients will have a PK assessment predose and 4 h postdose at the extension study Week 2 visit. Algorithms have been developed that are based on the predose, 4h and SHBG levels to Week 2 PK from the main study.

Algorithms predict which patients should be downtitrated to 60 or 40 mg based on the predose level and the 4 h post dose concentration (average C_{max}). Unlike MGL-3196, MGL-3196-M1 is [redacted], and shows an average and median AUC [redacted] ng*hr/ml in patients treated with [redacted] mg that has been accounted for in the calculated AUC for MGL-3196

(Table 2 and Table 3), thus assuring that total drug exposure (MGL-3196 plus M1) in the extension study will be [redacted] AUC. Applying these algorithms accurately predicts ([redacted]) patients who were downtitrated to 60 or 40 mg in the main study.

Table 3. Dose Adjustments in the Extension Study in Patients Assigned to Placebo in the Main Study

Extension Study Week 2 |MGL-3196 Concentration		Extension Study	Extension Study
Predose	**4 h post dose**	**Week 2 SHBG**	**Week 4 Action**
>35 ng/ml	>1350 ng/ml	>125% CFB*	Downtitrate to 40 mg
Patients not meeting criteria for 40, 80, 100 or 120 mg			Downtitrate to 60 mg
<15 ng/ml	<600 ng/ml	No rule	Remain on 80 mg or increase (see next rows)
<5 ng/ml	≤ 350 ng/ml	No rule	Increase to 100 mg
<2 ng/ml	≤ 150 ng/ml	No rule	Increase to 120 mg

*Change From Baseline, where baseline is Extension Study Day 1

Additional Completed ADME and Mass Balance Studies

Further support of safety has been provided by additional completed clinical and preclinical studies. Mass balance studies in humans, dogs, and rats have been conducted (described below). In dogs, the hepatic and biliary level of M1 is low [redacted]% at the C_{max} after a 100 mg/kg oral dose (below). Additional in vitro studies have been conducted that assess hepatocyte uptake/biliary excretion in human and dog hepatocyte systems ([redacted]). We have confirmed our previous studies that little M1 is made de novo in human (<1%) or dog hepatocytes (not detected). In an in vitro hepatobiliary system (Qualyst), the uptake of M1 into human hepatocytes and, consequently, biliary excretion of M1 was lower than for MGL-3196. Taken together, these data further support a conclusion that MGL-3196 M1 is [redacted] that was observed in dogs exposed for 9 months to the highest dose of MGL-3196 (100 mg/kg, AUC [redacted] ng*hr/ml). In addition, patients in the NASH study have [redacted] ALP ([redacted] in dogs with the biliary lesion) and [redacted] of biliary hyperplasia in human liver biopsies performed at 36 weeks ([redacted]).

Summary of Mass balance in Rats, Dogs and Humans

Rat tissue distribution and mass balance studies demonstrating that radiolabel is highly concentrated in the liver, with about [redacted]% renal elimination and [redacted]% fecal elimination. MGL-3196 highly penetrates liver ([redacted] AUC over plasma), has [redacted] in bile, is [redacted] in kidney and renal elimination. Penetration of MGL-

3196 is [redacted] in brain, and heart, most other tissues and may be accounted for by blood flow to those tissues rather than penetration into tissues.

Dog mass balance shows [redacted] renal elimination, [redacted] of administered radioactivity eliminated by fecal route and [redacted] of recovered radioactivity in the feces. There was [redacted] in the liver or bile duct relative to MGL-3196.

- In **plasma**, parent MGL-3196 [redacted]
- MGL-3196 and its metabolites in **urine** accounted for [redacted] of administered dose up to [redacted] post-dose. Parent MGL-3196 was [redacted] component detected, accounted for [redacted] of administered dose. M471, and oxidation metabolites M1, and M2 were detected by mass spectrometry in minor amounts [redacted].
- MGL-3196 and its metabolites in **feces** accounted for [redacted] of administered dose up to 120 h post-dose. As the major radioactive component, parent MGL-3196 accounted for [redacted] of administered dose. Oxidation metabolites M1 and M2 accounted for [redacted] and [redacted] of administered dose, respectively.
- [redacted] post a dose of ^{14}C-MGL-3196 100 mg/kg

  At [redacted] post-dose the concentrations of M1 in liver and bile were approximately [redacted] of the concentration of MGL-3196 in liver and bile, which suggested that [redacted]. The liver to plasma ratio of MGL-3196 at [redacted] was [redacted] At [redacted] post dose, the liver to plasma ratio of MGL-3196 has been shown to be [redacted] fold at 20 mg/kg; [redacted] fold at 50 mg/kg and [redacted] fold at 100 mg/kg demonstrating more rapid clearance from plasma than liver.
- Together, the [redacted] concentration of MGL-3196, and its metabolite M1 in bile at [redacted] post-dose, and [redacted] amount of radioactivity recovered in the feces of dogs [redacted].
- Although both MGL-3196 and M1 are excreted in the bile in dogs, the level of M1 is [redacted] as a percentage of MGL-3196

Preliminary analyses of MGL-3196-07 Human Mass Balance Study with ^{14}C-MGL-3196 after 100 mg repeated doses to [redacted] male healthy volunteers.

- The elimination of an oral radiolabeled 100 mg dose in humans is [redacted] of MGL-3196 is recovered in urine and feces, almost all within [redacted] in urine and plasma most is eliminated within the first [redacted] no notable delay in elimination in any human subject including those with highest plasma exposures.
- [redacted] is the only major metabolite.
- [redacted] of total drug administered is eliminated as M1 in the urine in humans; [redacted] of the administered dose is eliminated in the urine as MGL-3196. In humans, MGL-3196 and its metabolites are [redacted] in the feces ([redacted]).

Table 4. Laboratory and MRI-PDFF Results (Blinded Group DATA, DSMB September 2017)

ALT

Parameter (unit) [range] Visit Statistic	Overall (N=125)
Alanine Aminotransferase (U/L) [6-41]	
Week 24	
n	[redacted]
mean	
SD	
minimum	
median	
maximum	
Change from Baseline to Week 24	
n'	
mean	
SD	
minimum	
median	
maximum	

ALKALINE PHOSPHATASE

Parameter (unit) [range] Visit Statistic	Overall (N=125)
Alkaline Phosphatase (U/L) [37-116]	
Week 24	
n	[redacted]
mean	
SD	
minimum	
median	
maximum	
Change from Baseline to Week 24	
n'	
mean	
SD	
minimum	
median	
maximum	

MRI-PDFF

Visit Statistic	Overall (N=125)
Screening	
n	
mean	
SD	
minimum	
median	
maximum	
Week 12	
n	
mean	
SD	
minimum	
median	
maximum	
Change from Screening to Week 12	
n'	
mean	
SD	
minimum	
median	
maximum	

Visit Statistic	Overall (N=125)
Percent Change from Screening to Week 12	
n'	
mean	
SD	
minimum	
median	
maximum	

LDL-Cholesterol

Parameter (unit) [range] Visit Statistic	Overall (N=125)
LDL-C (Direct) (mg/dL) [50-130]	
Week 24	
n	
mean	
SD	
minimum	
median	
maximum	
Change from Baseline to Week 24	
n'	
mean	
SD	
minimum	
median	
maximum	
Percent Change from Baseline to Week 24	
n'	
mean	
SD	
minimum	
median	
maximum	

SHBG (Female)

Parameter (unit) [range] Visit Statistic	Overall (N=125)
Sex Hormone Binding Globulin (nmol/L) [20.00-130.00](Female)	
Week 12	
n	[redacted]
mean	
SD	
minimum	
median	
maximum	
Change from Baseline to Week 12	
n'	
mean	
SD	
minimum	
median	
maximum	
Percent Change from Baseline to Week 12	
n	
mean	
SD	
minimum	
median	
maximum	

SHBG (Male)

Parameter (unit) [range] Visit Statistic	Overall (N=125)
Sex Hormone Binding Globulin (nmol/L) [10.00-80.00](Male)	
Week 12	
n	[redacted]
mean	
SD	
minimum	
median	
maximum	
Change from Baseline to Week 12	
n'	
mean	
SD	
minimum	
median	
maximum	
Percent Change from Baseline to Week 12	
n	
mean	
SD	
minimum	
median	
maximum	

Added additional exploratory/tertiary objectives for the extension study (Synopsis and Sections 2.3 and 7).

Added description of extension phase of the study (Synopsis and Section 3.1.3).

Addition of Inclusion Criteria #9 for eligibility to participate in the extension phase of the study (Synopsis and Section 4.1).

Added that for patients eligible to participate in the extension phase of the study, the Extension Study Informed Consent must be signed prior to any Extension Study related procedures (Sections 6.1 and 9.6).

Added that Early Termination Visit procedures could be for either Main Study or the Extension Study as indicated (Section 6.6).

Added Extension Study visits and procedures (Sections 6.7, 9.8, 9.9, 9.10, 9.11, 9.12, 9.13, 9.14, and 9.16, and Appendix B).

Added possibility of 120 mg dose in the Main Study (Section 8.1).

Added Extension Study PK assessments (Synopsis and Section 8.2).

Added new Appendix B with Extension Study Procedures.

Administrative changes not affecting the content or conduct of the protocol:

Added heading 3.1.4 for DSMB.

Added description of Extension Study treatment group (Section 5.1).

Changed headings of Section 6.4 and Appendix A to clarify that the visits and procedures where for the “Main Study”.

Added heading 8.1 for Main Study PK assessments.

References to Clinical Laboratory Analytes, Appendix B changed to Appendix C (Sections 6.2, 6.4, and 9.8, and Appendix A).

SUMMARY OF PROTOCOL AMENDMENT 4 CHANGES

Administrative changes that may affect the content or conduct of the protocol:

Change to exclusion criteria #5 – thyroxine therapy may be initiated in patients enrolled in the study. (Sections 4.2 and 5.6.1).

Rationale: The MGL-3196-05 study is now fully enrolled, and no patients with evident clinical or subclinical hypothyroidism, or taking thyroxine were enrolled. However, a few patients had elevated TPO at baseline without elevated TSH suggesting the possibility of preexisting subclinical thyroiditis. [redacted] with the highest baseline TPO level [redacted] IU/ml, has had intermittent elevations in TSH [redacted] IU/ml during the study, with one TSH [redacted] IU/ml and is asymptomatic, otherwise doing well with decreased liver enzymes from baseline. In patients enrolled in the study, patients who have elevated levels of TSH [redacted] IU/ml on at least two separate consecutive visits and are symptomatic of hypothyroidism, or TSH [redacted] IU/ml, who are indicated to be on thyroxine for clinical hypothyroidism, may initiate treatment with a low dose of thyroxine consistent with American Thyroid Association guidelines, with frequent monitoring of TSH levels at Study Visits (and within 2 weeks of initiation of thyroxine), safety labs, and monitoring of other symptoms related to hyper or hypothyroidism. Thyroxine may be administered at [redacted] to [redacted] the anticipated dose (a starting dose of [redacted] ug per day) with careful monitoring of TSH levels and symptoms related to hyper or hypothyroidism, with increments in thyroxine dose after no less than [redacted]. In most patients [redacted] ug thyroxine may suffice, and doses up to [redacted] a day are allowed. As it may take several months for the full effect of thyroxine to take place, any increase in dose should be made conservatively.

Patients' thyroid hormone indices have been carefully monitored during the study, and several patients have been treated with study drug for > 6 months. As expected, because MGL-3196 is largely restricted to the liver, [redacted] during the study (example shown for the group of [redacted] blinded patients at Week 4). Because [redacted] in TSH or FT3 have been observed, TSH [redacted] (only blinded at Weeks 2 and 4, because unblinding of the TSH data now would unblind patient identification). FT3 remains unchanged and is unblinded throughout the study. Therefore, TSH levels are now readily monitored in patients enrolled in the study.

Thyroid Stimulating Hormone (TSH) (pIU/mL)
Week 4
n
mean
SD
median

Change from Baseline to Week 4
n'
mean
SD
median

[redacted]

Some [redacted] in FT4 (monitored by individual patient for all study weeks, blinded to patient ID and treatment assignment) have been observed, consistent with the pharmacology of MGL-3196 to [redacted] the conversion of FT4 to FT3 in the liver. For virtually all patients,

FT4 [redacted], and [redacted] patients have reported symptoms consistent with clinical hyper or hypothyroidism.

There [redacted] effects of study drug on HR, [redacted] in BP have been observed, consistent with MGL-3196's [redacted] or penetration into the heart. MGL-3196 (study drug) has been [redacted] enrolled in the study have [redacted] their liver enzymes relative to baseline levels.

Given, the [redacted] of MGL-3196 on the central thyroid axis, the fact that MGL-3196 is [redacted], and that any symptoms related to hyper or hypothyroidism, safety labs and TSH levels may be closely monitored, study drug c[redacted] in the very infrequent case of a patient who becomes clinically hypothyroid during the study with persistent elevations of TSH[redacted] IU/ml.

Patients taking stable doses of lithium or other medications that may affect thyroid indices, but who have normal thyroid indices on stable lithium doses, may be included (Section 5.6.1).

Administrative changes not affecting the content or conduct of the protocol:

Added an additional exploratory/tertiary objective – [redacted]

Change in Note 2 of inclusion criteria #6 – corrected reference from exclusion #11 to #10 (Synopsis and Section 4.1).

Clarification in exclusion criteria #9 – since statins, as specified, are allowed in the study, modification or initiation of lipid therapy during the study, where indicated, is permitted using allowed doses of statins and other lipid medications. Since the lipid levels are blinded to study investigators and study personnel during the study, newly initiated statin or other lipid therapy will occur very infrequently during the study (Synopsis and Section 4.2).

Correction to measure SHBG at all Visits, now including Week 16, 20, 30 and at follow up, Week 38 (Sections 6.4.6, 6.4.7, 6.4.9, 6.5, and 9.8 and Appendix A.

Clarified that baseline MRI-PDFF only needs to be obtained as close to the randomization visit as possible. Removed the need to obtain MRI-PDFF within 3 weeks of randomization (Appendix A, Footnote 13)

Clarified that Week 36 MRI-PDFF must be obtain within 10 days prior to the Week 36 visit while patient is still on treatment (Section 6.4.10 and Appendix A, Footnote 13)

Clarified that the Week 36 liver biopsy must be conducted within a window of -10 days to +3 days relative to the Week 36 visit (Section 6.4.10 and Appendix A, Footnote 15).

Removed 30-minute rest prior to ECG (Appendix A, Footnote 19).

Added kPa to List of Abbreviations and Definition of Terms.

SUMMARY OF PROTOCOL AMENDMENT 3 CHANGES

Changes that have the potential to affect either the efficacy or safety assessments:

Change in inclusion criteria #8 – estimated glomerular filtration rate changed from ≥ 90 to ≥ 60. (Synopsis and Section 4.1).

Rationale: Over 50% of planned or approximately 59 patients are enrolled in the study with a targeted enrollment of 117. The overall safety of the study has been good, the IP is well tolerated and appears safe in patients studied as long as 24 weeks. There has been [redacted] on renal function as assessed by serial eGFR, and other renal function indices. In addition, the PK exposure of MGL-3196 is being measured and dose adjustments made based on drug exposure at steady-state. If there were any impact of mild renal impairment on the exposure to MGL-3196, dose adjustment would mitigate this effect. Moreover, only [redacted]% of total MGL-3196 is renally excreted at the 80 mg dose used in MGL-3196-05 ([redacted]% of MGL-3196 is renally excreted in humans and [redacted]% of the inactive metabolite, MGL-3196-M1, is renally excreted), and thus, mild renal impairment is unlikely to impact exposure to MGL-3196 plus MGL-3196-M1.

Other considerations: eGFR estimates, which are not validated for the Hispanic population which is overrepresented in MGL-3196-05, are known to be frequently inaccurate predictors of renal function particularly in the range of 60-90 ml/min, and are primarily used to estimate renal impairment when eGFR<60. The eGFR requirement >90 ml/min excludes a significant number of NASH patients who would otherwise be eligible for enrollment in the study, thereby impacting ability to enroll a representative NASH population.

Based on numbers enrolled, the overall safety and other considerations, patients with "mild renal failure" as determined by eGFR 60-90 ml/min are now included.

Change in exclusion criteria #9 (was original #10) – Added that stable doses of pravastatin up to 20 mg or fenofibrate are allowed. No drug interactions are predicted with these medications. (Synsopsis, Section 4.2, and section 5.6.1)

Atorvastatin up to 20 mg and rosuvastatin up to 10 mg **and *pravastatin up to 20 mg*,** on stable dose for at least six weeks prior to randomization (four weeks prior to MRI), are allowed. Stable doses of least 3 months of fenofibrate taken at night are allowed.

Added that MGL-3196 dose will be decreased from 80 to 40 mg at Week 4 if the Week 2 AUC_{inf} >11,000 (combined MGL-3196 and M1) plus SHBG>150% increase from baseline at Week 2 (indicative that average or steady-state exposure is >11,000 ng*hr/ml). The dose will be increased from 80 mg to 100 mg if AUC_{inf} at the 80 mg dose was ≤ 3000 ng*hr/mL (Synopsis, Section 3.1.2, and Section 8).

Each of these occurrences, low or high exposure to 80 mg, represents about [redacted] of patients enrolled in the study thus far.

The blinded PK exposure data from the first [redacted] enrolled patients randomized to MGL-3196 indicates, that 1) at the 80-mg dose, drug exposure in NASH patients to MGL-3196

and MGL-3196-M1 is similar to healthy volunteers, [redacted]) a few NASH patients ([redacted]) demonstrate low exposure at 80 mg [redacted] ng*hr/ml and [redacted] had high exposure [redacted] ng*hr/ml, and [redacted] the therapy is well-tolerated in patients enrolled for as long as 24 weeks in the MGL-3196-05 study.

A [redacted] of patients ([redacted]%) in the study dosed with 80 mg have shown very low exposure at 2 weeks, with exposure to active drug, MGL-3196 [redacted] ng*hr/ml, and total drug exposure [redacted] ng*hr/ml. Based on the conservative calculations their exposure at 100 mg will be significantly less than [redacted] ng*hr/ml. The rationale for the higher dose of 100 mg in a subset of patients in MGL-3196-05 is that, based on existing human data, exposures to MGL-3196 less than AUC [redacted] ng*hr/ml demonstrate limited effects on biomarkers of potential efficacy (lipid biomarkers), and preclinical data suggest a tight correlation between lipid and NASH effects of MGL-3196. MGL-3196-M1 is inactive. Therefore, for patients with exposure [redacted] ng*hr/ml at 2 weeks, the dose will be increased to 100 mg daily dose at the Week 4 visit. As with all dose adjustments, this dose adjustment will be blinded to investigators, Sponsor and study personnel.

The [redacted] with [redacted] AUC at 80 mg have been evaluated as to meeting criteria for downtitration from 60 to 40 mg and [redacted] has been downtitrated to 40 mg. No safety issues have been reported for these patients (per Unblinded Medical Monitor).

Per Amendment 1, dose adjustments in MGL-3196-05 are primarily based on the Week 2 PK determination. In Amendment 3, the language allowing further dose adjustments based on thyroid hormone levels has been clarified in Section 3.1.2. A combined MGL-3196 and MGL-3196-M1 exposure [redacted] ng*hr/ml has not demonstrated a drug-related decrease in FT4 to < LLN [redacted] ng/dL) in Phase 1 studies. Patients enrolled in MGL-3196-05 have [redacted] in TSH or FT3 (blinded data), evidence of the [redacted], and have shown [redacted] in FT4 consistent with the effect of MGL-3196 to [redacted] conversion of the prohormone FT4 to active hormone FT3 in the liver. [redacted] have reported symptoms consistent with hypo or hyperthyroidism. However, [redacted] may very occasionally have low levels of FT4, with normal FT3 and TSH, and are not clinically or subclinically hypothyroid. Low FT4 in the presence of normal FT3 (active hormone) and TSH is not consistent with hypothyroidism; for example, low <<LLN FT4 is observed in euthyroid (formerly hypothyroid) patients treated with T3 monotherapy. [20] For NASH patients with FT4< LLN (>.55 to <.7 ng/dL), if FT3 remains normal (not decreased to <LLN) and TSH remains normal, the patient may continue on the current dose unless there is evidence that the FT4 LLN is drug-related as defined in Section 3.1.2 in which case the patient may be down-titrated to the next lower dose at the next visit.

Administrative changes not affecting the content or conduct of the protocol:

Term "PDFF-MRI" corrected to "MRI-PDFF" (Synopsis and multiple Sections)

Change in inclusion criteria #2 – BMI $\geq$ 45 kg/m^2 is removed as an exclusion, because the protocol already includes other exclusions that may relate to greatly elevated body weight, such as exclusions for inability to obtain a liver biopsy, or plan to undergo bariatric surgery (Synopsis and Section 4.1).

Clarification in inclusion criteria #4 – specified quantitative ultrasound with liver fat > 10% and magnetic resonance spectroscopy consistent with significant liver steatosis (>10%).

Change in inclusion criteria #5 – added note that patients with a liver fat content >9% but < 10% on MRI-PDFF and who are highly likely to have NASH as determined by Medical Monitors on biopsy may be included in the study but the total may not exceed 10% of the total study population (Synopsis and Section 4.1).

Change in Note 2 of inclusion criteria #6 – removed weight gain as a significant change in metabolic status (Synopsis and Section 4.1).

Change in inclusion criteria #7 – clarification to use the mean of both the AST and ALT values in determining worsening liver enzymes. Patients with elevated liver enzymes at screening that improve during the screening period >50% or are improved relative to historic liver enzymes are no longer excluded, because patients are appropriately counseled on diet and exercise at the screening visit, at times, resulting in improvement in liver enzyme tests during the screening period. There is no safety risk to these patients. If there is uncertainty about the baseline, because of a marked improvement from historic to screening values, a third ALT/AST assessment will be done during the screening period to insure that liver chemistries are not >30% worse than the screening values and that the baseline is stable. (Synopsis and Section 4.1)

Removed exclusion criteria # 4 – exclusion for historic weight gain and weight loss is removed, except that patients with an eligible historic liver biopsy and with weight loss ≥5% after the time of the eligible historic liver biopsy prior to screening are excluded. (Synopsis and Section 4.2).

Renumbered exclusion criteria #5 to #29 – numbers decreased by one. (Synopsis and Section 4.2).

Exclusion Criteria #8 (was originally #9) – clarification that glucagon-like peptide analogue is permitted if stable dose ≥ 6 months prior to screening or at time of liver biopsy, and a complex oral anti-diabetic (OAD) regimen (3 or more OADs) is permitted if the OAD is stable for three months and HbA1c < 8% (Synopsis and Section 4.2).

Exclusion Criteria #13 (was originally #14) (Synopsis and Section 4.2) to clarify the assessment of hepatic decompensation

Original text:

- Clinical evidence of hepatic decompensation as defined by the presence of any of the following abnormalities:
- Serum albumin <3.5 g/dL,
- International normalized ratio >1.3 (a single retest is permitted if laboratory error is suspected),
- Total bilirubin >1.3 mg/dL, or
- History of esophageal varices, ascites, or hepatic encephalopathy;

Changed to:

Clinical evidence of hepatic decompensation which may be:

- Demonstrated by abnormalities such as platelets <140,000, serum albumin <3.5 g/dL, international normalized ratio >1.3 and/or total bilirubin >1.3 mg/dL; or
- Established by the presence or history of esophageal varices, ascites, or hepatic encephalopathy;

Note to protocol: Platelets < 140,000 remains an independent exclusion criterion.

Change in exclusion criteria #14 (was originally #15) – clarification that patients with Gilbert's syndrome are excluded if direct bilirubin is elevated and total bilirubin ≥ 2 or elevated total bilirubin is due to hemolysis to be consistent with FDA recommendation (Synopsis and Section 4.2).

Change to description of study drug administration (Section 5.5.3) – noted that dose adjustments may occur based on the process outlined in section 3.1.2.

Changes to excluded medications (Section 5.6.1):

- glipizide and tolbutamide treatment are permitted and removed as excluded medications; they had been excluded in error, no drug interaction predicted
- chronic use of oral corticosteroids is exclusionary unless discontinued 3 months before screening. Addition of oral corticosteroids during the study except short term low dose < 1 week taper is not allowed;

Note to protocol: inhaled, nasal corticosteroids, joint and muscle corticosteroid injections are allowed

Change that randomization **may** (previously "will") continue until approximately 36 patients have continued at Week 4 on the 80 mg dose (Synopsis and Section 10.2.5).

Reference #20 added (Synopsis, Section 3.1.2, and Section 14).

Sponsor Address updated (Section 13.2.1)

SUMMARY OF PROTOCOL AMENDMENT 2 CHANGES

Changes that have the potential to affect either the efficacy or safety assessments:

Clarification and revisions to inclusion criteria #4 - added "confirmed" NASH diagnosis and clarified that at least one of the listed assessments is required (Synopsis and Section 4.1).

Biopsy-proven NASH inclusion criteria #5 moved to #6 and revision to Note 2 – added "change in" (Synopsis and Section 4.1).

Exclusion Criteria #9 – HbA1c criteria changed from 9% to 9.5% (Synopsis and Section 4.2).

Exclusion Criteria #10 (Synopsis and Section 4.2):

Original text:

Use of the following lipid-modifying therapies: fibrates, niacin, proprotein convertase subtilisin/kexin type 9 inhibitors, bile acid sequestrants, and statins;

Note: Patients who require initiation on any of excluded lipid-modifying therapies at baseline or during the study must be discontinued from the study;

Changed to:

Use of the following lipid-modifying therapies: fibrates, niacin, proprotein convertase subtilisin/kexin type 9 inhibitors, **and** bile acid sequestrants. **Atorvastatin up to 20 mg and rosuvastatin up to 10 mg, on stable dose for at least six weeks prior to randomization (four weeks prior to MRI), are allowed. Other statins are excluded. Stable doses for at least three months prior to randomization of fish oils (omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid) and ezetimibe are allowed**;

Note: Patients who require initiation **of** any excluded lipid-modifying therapies at baseline or during the study must be discontinued from the study. **Statin dose increases are not allowed during the study; statin doses may be decreased during the study for tolerability or safety issues. Statin doses should be taken in the evening for at least two weeks prior to randomization**;

Exclusion Criteria #11 (Synopsis and Section 4.2):

Original text:

Use of obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), high dose vitamin E (>400 IU/day), or pioglitazone within 90 days prior to enrollment or since screening biopsy, whichever is longer;

Changed to:

Use of obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), high dose vitamin E (>400 IU/day) **unless on stable dose of vitamin E >400 IU/day for at least 6 months at the time of liver biopsy**, or pioglitazone within 90 days prior to enrollment or since screening biopsy, whichever is longer;

Change in exclusion criteria #13 – Platelet count <150,000/mm^3 changed to < 140,000 mm^3 to match the lower limit of normal of the central laboratory (Synopsis and Section 4.2).

Changes to excluded medications as described in the revised exclusion criteria #10 and #11 (Section 5.6.1).

Changes in clinical laboratory analytes including updates to testing schedule - (Sections 6.4, 6.5, 6.6, and 9.8, and Appendices A and B):

- Addition of Reverse T3, Haptoglobin, Alpha-2 macroglobulin, N-terminal pro b-type natriuretic peptide, Apolipoprotein A1, Apolipoprotein CIII, and Ferritin;
- Clarification that LDL cholesterol is both direct and calculated;
- Revisions to testing schedule for Free testosterone, thyroxine binding globulin, non-esterified fatty acid, adipose tissue insulin resistance, and adiponectin;
- Removal of Resistin, Interleukin-1β, Interleukin-33m Interleukin-6, serum cluster of differentiation 163, and Tumor necrosis factor alpha;
- Fasting Lipid parameters added to Screening Visit;
- Addition of Type 1 procollagen N-terminal propeptide and C-terminal telopeptide to Week 12;

Removed [redacted] from Exploratory Objectives (Synopsis, Section 2.3 and Section 7).

Administrative changes not affecting the content or conduct of the protocol:

Change in Sponsor address on Cover and Synopsis.

Moved PDFF-MRI inclusion criteria from #6 to #5 (Synopsis and Section 4.1).

Added TBG to List of Abbreviations and Definition of Terms.

Removed Interleukin abbreviation from List of Abbreviations and Definition of Terms. And Appendix A.

Fibrinogen moved to Other Markers (Appendix B).

Update to the DSMB meeting schedule (Synopsis, Section 3.1 and Section 10.2.4).

Removed [redacted] signatories (Signature Page).

SUMMARY OF PROTOCOL AMENDMENT 1 CHANGES

Changes that have the potential to affect either the efficacy or safety assessments:

Treatment groups changed from placebo, 80, and 120 mg to placebo and 80 mg. (Synopsis and Sections 3.1, 5.1, 5.3, and 5.5.3, 10.2.1.1, 10.2.5.).

At Week 2, added fasting PK assessments at predose and 2, 4, 6, and 8 hours postdose to compute AUC (Synopsis and Sections 3.1.2, and 8).

Possible dose reduction at Week 4 will be based on FT4 and TSH results and/or the Week 2 PK AUC > 5500 ng*hr/ml combined estimated AUC of MGL-3196 plus MGL-3196-M1. (Synopsis and Sections 3.1.2, 8, and 10.2.5).

Added exploratory objective of [redacted]

Revisions to inclusion criteria # 4 – clarification of suspected diagnosis of NASH (Synopsis and Section 4.1).

Revisions to inclusion criteria #5 – clarification of the inclusion of patients with clear ballooning fibrosis but no inflammation or patients who have clear inflammation with fibrosis but no ballooning or patients with clear NASH without fibrosis (Synopsis and Section 4.1).

Revisions to inclusion criteria #7 – clarification of AST and ALT criteria (Synopsis and Section 4.1).

Revisions to inclusion criteria #8 – Added requirement of normal renal function defined by estimated glomerular filtration rate (Synopsis and Section 4.1).

Added to exclusion criteria that unless otherwise specified repeat testing may be performed in consultation with the Medical Monitor (Synopsis and Section 4.2)

Revisions to exclusion criteria #6 – patient with subclinical hypothyroidism are excluded (Synopsis and Section 4.2).

Revisions to exclusion criteria #10 – clarification that patients require initiation on any excluded lipid-modifying therapies at baseline or during the study must be discontinued from the study (Synopsis and Section 4.2).

Change in exclusion criteria #13 – Platelet count <100,000/mm^3 changed to < 150,000 mm^3 (Synopsis and Section 4.2).

Change in exclusion criteria #14 – removed Gilbert's syndrome condition on total bilirubin (Synopsis and Section 4.2).

Revisions to exclusion #15 – added Gilbert's Syndrome (Synopsis and Section 4.2).

Added exclusion criteria #21 – history of malignant hypertension (Synopsis and Section 4.2).

Added exclusion criteria #22 – uncontrolled hypertension (Synopsis and Section 4.2).

Added exclusion criteria #23 – New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30% (Synopsis and Section 4.2).

Added exclusion criteria #24 – uncontrolled cardiac arrhythmia (Synopsis and Section 4.2).

#25 - Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to randomization (Synopsis and Section 4.2).

Clarification that the DSMB will also assess cardiovascular events (Synopsis and Sections 3.1.2, and 10.2.4).

Removed the possibility for patients who completed the 36-week Treatment Period to be eligible for an extension study (Synopsis and Section 3.1.2).

Added that cardiovascular events are possible withdrawal criteria (Section 4.3).

Add to the list of excluded medications drugs historically associated with NAFLD and drugs with known liver toxicity (Section 5.6.1).

Added to the list of excluded medications, any drugs that have the potential to affect thyroid hormone production and/or interfere with thyroid function (Section 5.6.1).

Specified fasting of at least 10 hours prior to each study visit (Section 6.4).

Addition of Cardiovascular monitoring criteria (Synopsis and 9.18).

Added CK-MB and Troponin I (Sections 6.4.1 to 6.4.10, 6.5, 6.6, and 9.8).

Added Bile Acid Levels (Sections 6.4.1, 6.4.2, 6.4.5, 6.4.10, 6.6, and 9.8).

At the Week 2 Visit, specified arriving at the study site predose after overnight fasting and collection of PK samples at predose, 2, 4, 6, and 8 hours postdose. Low fat meals permitted at 1 hr postdose and 4 hours postdose (after 4 h blood draw) (Section 6.4.2).

At the Week 4 Visit, changed the post dose PK collection to predose (Section 6.4.3).

Updates to Sample Size Estimate (Synopsis and 10.2.5).

Update to Schedule of Procedures in Appendix A to reflect protocol amendment changes (Appendix A).

Addition of CK-MB, Troponin I, and Bile Acids to Appendix B – Clinical Laboratory Analytes.

Removed Non LDL-Cholesterol from the Lipid Panel and secondary objectives (Synopsis, Sections 2.2 and 9.8, and Appendix B).

Administrative changes not affecting the content or conduct of the protocol:

Change in title for [redacted] (Signature Page).

Added CK-MB to the List of Abbreviations and Definition of Terms

Addition of [redacted] (Section 13.2.4).

Addition of [redacted] (Section 13.2.5).

SYNOPSIS

TITLE: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Non-Alcoholic Steatohepatitis

PROTOCOL NUMBER: MGL-3196-05

INVESTIGATIONAL PRODUCT: MGL-3196

PHASE: 2

INDICATION: The indication for this study is the treatment of non-alcoholic steatohepatitis (NASH).

OBJECTIVES:

The primary objective of this study is to determine the effect of once-daily oral MGL-3196 80 mg versus placebo (randomized 2:1) for 12 weeks on the percent change in hepatic fat fraction by proton density fat fraction magnetic resonance imaging (MRI-PDFF) from baseline in patients with biopsy-proven NASH.

The secondary objectives of this study are the following:

- To determine the effect of once-daily oral MGL-3196 80 mg versus placebo for 36 weeks in patients with biopsy-proven NASH on the histological improvement from baseline on:
  - Two-point reduction in non-alcoholic fatty liver disease (NAFLD) activity score (NAS);
  - Resolution of NASH (ballooning = 0; inflammation = 0 to 1); or
  - Any individual component of NASH (hepatocellular steatosis, ballooning, fibrosis, or lobular inflammation);
- To evaluate the safety and tolerability, including any changes in thyroid axis hormones, of once-daily oral MGL-3196 80 mg versus placebo after 12 and 36 weeks in patients with biopsy-proven NASH;
- To evaluate the effect of once-daily oral MGL-3196 80 mg versus placebo for 36 weeks on the percent change in hepatic fat fraction by MRI-PDFF from baseline in patients with biopsy-proven NASH;
- To evaluate the effect of once-daily oral MGL-3196 80 mg versus placebo for 12 and 36 weeks on the change in hepatic fat fraction by MRI-PDFF from baseline in patients with biopsy-proven NASH; and
- To determine the effect of once-daily oral MGL-3196 80 mg versus placebo after 12 and 36 weeks in patients with biopsy-proven NASH on:
  - High-sensitivity C-reactive protein (hsCRP);
  - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST);

- Lipid parameters including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, triglycerides, apolipoprotein B (ApoB), and lipoprotein(a) (Lp[a]) particles; and
- NASH and fibrosis biomarkers including cytokeratin-18 (CK-18), fibrosis-4 (FIB-4), and enhanced liver function (ELF) test.

The tertiary/exploratory objectives of this study are the following:

- [redacted]

[redacted]

[redacted]

POPULATION:

The population for this study is male and female patients ≥18 years of age with biopsy-proven NASH.

Inclusion Criteria:

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Must be willing to participate in the study and provide written informed consent;
2. Male and female adults ≥18 years of age;
3. Female patients of child bearing potential with negative serum pregnancy (beta human chorionic gonadotropin) tests who are not breastfeeding, do not plan to become pregnant during the study, and agree to use effective birth control (ie, condoms, diaphragm, non-hormonal intrauterine device [IUD], or sexual abstinence [only if this is in line with the patient's current lifestyle]) throughout the study and for at least 1 month after study completion; hormonal contraception (estrogens stable ≥3 months) and hormonal IUDs are permitted if used with a secondary birth control measure (eg, condoms); OR female patients of non-child bearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]); Male patients who have sexual intercourse with a female partner of child bearing potential from the first dose of study drug until 1 month after study completion must be either surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with spermicide. All male patients must agree not to donate sperm from the first dose of study drug until 1 month after study completion;
4. Suspected or confirmed diagnosis of NASH suggested by the historical data and at least <u>one</u> of the following assessments within current and/or historical data sets (and, therefore, likely to meet MRI-PDFF and liver biopsy criteria outlined in Inclusion #5 and #6):
   - Metabolic syndrome (obesity, dyslipidemia, elevated blood pressure, elevated fasting glucose) with two or more of the following: type 2 diabetes/insulin resistance, BMI ≥ 34, history of hypertension, elevated liver enzymes (ALT, AST)
   - Fibroscan, magnetic resonance elastography, or serum biomarkers (eg, AST to platelet ratio [APRI], NAFLD fibrosis score, FIB-4 or ELF) consistent with liver fibrosis
   - Controlled attenuation parameter (CAP), quantitative ultrasound (liver fat >10%), MRI-PDFF, or magnetic resonance spectroscopy consistent with significant liver steatosis (>10%)

- Previous liver biopsy consistent with NASH

Note: Assessment of the above, or other objective modalities suggested by PI, will occur. The choice of additional procedures, performed during the screening period prior to the screening MRI and liver biopsy, may include calculation of FIB-4, APRI, NAFLD fibrosis scores, and/or performance of fibroscan and/or CAP.

5. Must have confirmation of ≥10% liver fat content on MRI-PDFF;

   Note: Patients with a liver fat content >9% but <10% on MRI-PDFF and who are highly likely to have NASH as determined by Medical Monitors on biopsy may be included in the study but the total may not exceed 10% of the total study population;

6. Biopsy-proven NASH:

- Must have had prior liver biopsy within 180 days of randomization with fibrosis stage 1 to 3 and a NAS of ≥4 with at least a score of 1 in each of the following NAS components:
- Steatosis (scored 0 to 3),
- Ballooning degeneration (scored 0 to 2), and
- Lobular inflammation (scored 0 to 3)

Note 1: Patients who have clear ballooning with fibrosis but no inflammation or patients who have clear inflammation with fibrosis but no ballooning or patients with clear NASH without fibrosis may be included in the study but the total may not exceed 10% of the total study population;

Note 2: If a historical biopsy is to be used, patients must have had no significant change in metabolic status (diabetes control, lipid metabolism, and/or >5% weight loss), significant change in diabetes medication, or change in use of medications listed in Exclusion #10 since the biopsy

Note 3: If a historical biopsy is not available, patients must have confirmation of ≥10% liver fat content on MRI-PDFF prior to undergoing liver biopsy. However, if, in the opinion of the patient's physician, the patient would benefit from and be advised to obtain a liver biopsy, the patient may undergo liver biopsy prior to MRI-PDFF

7. Must have documented historical (3 weeks to 6 months prior to the study entry) ALT and AST levels consistent with the screening ALT and AST values. This consistency is established based on the following:

   - If the historical and screening ALT and AST values are both ≤1.5 × the upper limit of normal (ULN), there is no limit to the difference between the values.
   - ~~o~~ If the historic ALT/AST are >1.5 X elevated and screening ALT and AST are markedly improved (>50% decreased or normalized) relative to historic, then a third ALT/AST determination will be made during screening to assure a stable baseline, and that there is no worsening of >30% from the screening values. If the difference is >30% and the second value is greater than the first value, a third value should be determined during the screening period to confirm lack of worsening trend in ALT/AST
   - If at least 1 of the values is >1.5 × ULN and the second value is greater than the first value, the difference the mean of ALT and AST in values must be ≤30%. If the difference is >30% and the second value is greater than the first value, a third value should be determined to confirm lack of worsening trend in ALT/AST. If worsening trend is

confirmed (3 consecutive worsening values with difference from first value and second value >30%), patient will be excluded.

Note: Patients who do not have the historical ALT and AST evaluations available may have their ALT and AST repeated during the screening period (both assessments need to be 3 weeks apart);

8. Normal or minimally abnormal renal function as defined by estimated glomerular filtration rate (eGFR) ≥ 60.
9. Eligibility for extension study. Within 60 days of completion of the Week 36 Visit in the main study, patients who meet the following additional criteria will be eligible to participate in the extension phase of this study:
   - Had 36-week MRI-PDFF
   - Had 36-week liver biopsy
   - No new exclusions that would prevent the patient from participating in up to 36 weeks of additional treatment
   - Meets at least one of the following liver enzyme criteria in the table below:

Baseline ALT	Average of ALT at Weeks 16, 20, 24, and 30
ALT normal (<1.5 ULN)	≥ 1.5 x ULN (and 30% worse than baseline)
ALT =1.5-2X	Improvement from baseline <30% and ALT =1.5-2X ULN
ALT any	ALT ≥ 2X
Note: Normal ALT male 30; female 25: 1.5 x male =45 and female=38	Note: ALT or AST values for weeks 16, 20, 24 and 30 that are > 2 X Std Dev from mean will be excluded from the calculation of the average value. Note: When ALT does not meet criteria for inclusion, AST will be evaluated similarly to determine if criteria for inclusion are met based on AST, given normal values in men and women of 27 and 22, respectively and 1.5X of 40 and 33 respectively.

Exclusion Criteria

Note: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.

Patients who meet any of the following criteria will be excluded from participation in the study:

1. History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening;

   Note: Significant alcohol consumption is defined as average of >20 g/day in female patients and >30 g/day in male patients;

2. Inability to reliably quantify alcohol consumption based upon judgment of the Investigator;
3. Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) for more than 2 weeks in the year prior to screening;
4. Hyperthyroidism;
5. Patients on thyroid replacement therapy or with untreated clinical or subclinical hypothyroidism;

   Note: If TSH is up to 1.5 x ULN on screening with normal free T4, one repeat test is allowed to confirm the elevation in TSH. If TSH and free T4 are normal upon repeat testing, patient may be included. Patients with a history of thyroid hormone replacement therapy or patients who have discontinued thyroid hormone replacement therapy (including thyroxine) ≥2 months prior to randomization may be included in the study if this criterion is met;

   During the study, patients who have elevated levels of TSH >7 IU/ml on at least two separate consecutive visits and are symptomatic of hypothyroidism, or TSH >10 IU/ml, who are indicated to be on thyroxine for clinical hypothyroidism, may initiate treatment with low doses of thyroxine consistent with American Thyroid Association guidelines, with frequent monitoring of TSH levels at Study Visits (and within 2 weeks of initiation of thyroxine), safety labs, and monitoring of other symptoms related to hyper or hypothyroidism. Thyroxine may be administered at ¼ to ½ the anticipated dose (a starting dose of 25 ug per day) with careful monitoring of TSH levels and symptoms related to hyper or hypothyroidism, with increments in thyroxine dose after no less than 4-6 weeks.

   NOTE: It is anticipated that initiation of thyroxine therapy will occur very infrequently during the study and 50-75 ug thyroxine replacement will suffice for most patients requiring thyroxine treatment.
6. Prior or planned (during the study period) bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass);
7. Type 1 diabetes;
8. Uncontrolled Type 2 diabetes defined as:

- Hemoglobin A1c ≥9.5% at screening (patients with HbA1c ≥9.5% may be rescreened),
- Insulin dose adjustment >10% within 60 days prior to enrollment,
- Requirement for glucagon-like peptide analogue (unless on a stable dose ≥ 6 months prior to screening) or a complex oral anti-diabetic (OAD) regimen (3 or more OADs) (unless the OAD is stable and HbA1c < 8%), or
- History of severe hypoglycemia (symptomatic hypoglycemia requiring outside assistance to regain normal neurologic status);

  Note: Individual diabetes regimens will be reviewed by Investigator and may be adjusted based on American Diabetes Association guidelines;

9. Use of the following lipid-modifying therapies: fibrates except fenofibrate taken at night for at least 2 weeks prior to randomization and during the study, niacin, proprotein convertase

subtilisin/kexin type 9 inhibitors, and bile acid sequestrants. Atorvastatin up to 20 mg and rosuvastatin up to 10 mg and pravastatin up to 20 mg, on stable dose for at least six weeks prior to randomization (four weeks prior to MRI), are allowed. Other statins are excluded. Stable doses for at least three months prior to randomization of fish oils (omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid), fenofibrate and ezetimibe are allowed;

Note: Very infrequently, given that lipid levels are blinded to investigators and study personnel, where indicated statin and other allowed lipid therapies may be modified or initiated after enrollment in the study. Statin doses may be decreased during the study for tolerability or safety issues. Statin doses should be taken in the evening for at least two weeks prior to randomization and for the duration of the study.

10. Use of obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), high dose vitamin E (>400 IU/day) unless on stable dose of vitamin E >400 IU/day for at least 6 months at the time of liver biopsy, or pioglitazone within 90 days prior to enrollment or since screening biopsy, whichever is longer;
11. Presence of cirrhosis on liver biopsy (stage 4 fibrosis);
12. Platelet count <140,000/mm^3;
13. Clinical evidence of hepatic decompensation which may be:

- Demonstrated by abnormalities such as platelets < 140,000, serum albumin <3.5 g/dL, international normalized ratio >1.3 and/or total bilirubin >1.3 mg/dL; or
- Established by the presence or history of esophageal varices, ascites, or hepatic encephalopathy;

14. Evidence of other forms of chronic liver disease including the following:

- Hepatitis B (HepB) as defined by presence of HepB surface antigen at screening,
- Hepatitis C (HepC) as defined by presence of HepC virus (HCV) antibody (anti-HCV) and HCV ribonucleic acid (RNA). Patients with positive anti-HCV who test negative for HCV RNA at screening will be allowed to participate in the study,
- Evidence of ongoing autoimmune liver disease,
- Primary biliary cirrhosis,
- Primary sclerosing cholangitis,
- Gilbert's syndrome patients if direct bilirubin is elevated (in addition to total bilirubin ≥ 2) or there is evidence of hemolysis contributing to elevated total bilirubin
- Wilson's disease,
- Homozygous alpha-1-anti-trypsin deficiency,
- History of hemochromatosis or iron overload,
- Drug-induced liver disease,
- Known bile duct obstruction,
- Suspected or proven liver cancer, or

- Any other type of liver disease other than NASH;

15. Serum ALT or AST >5 × ULN;

    Note: Normal male and female ranges are 6 U/L to 41 U/L for ALT and 9 U/L to 34 U/L for AST at [redacted];

16. Inability to safely obtain a liver biopsy;
17. History of biliary diversion;
18. Positive for human immunodeficiency virus (HIV) infection;
19. Active, serious medical disease with likely life expectancy <2 years;
20. History of malignant hypertension;
21. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at screening;

    Note: Retest of blood pressure after establishing good blood pressure control within a reasonable period of time, up to baseline visit, is permissible at the discretion of the Investigator;

22. New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30%;
23. Uncontrolled cardiac arrhythmia, including confirmed QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females at the screening electrocardiogram (ECG) assessment;
24. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to randomization;
25. Active substance abuse, including inhaled or injected drugs, within 1 year prior to screening;
26. Use of any excluded medications listed in Section 5.6.1;
27. Participation in an investigational new drug trial in the 30 days prior to randomization; or
28. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes.

STUDY DESIGN AND DURATION:

This is a multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of MGL-3196 in patients with NASH. Patients who qualify for study inclusion will be randomized to receive one of two 36-week treatments: MGL-3196 80 mg or placebo given orally once-daily in the morning. Following 12 weeks of treatment, the primary endpoint, percent change from baseline in hepatic fat fraction measured by MRI-PDFF, will be evaluated. At 36 weeks, all patients will undergo liver biopsy.

Screening Period

Patients must provide written informed consent prior to any study procedures being performed. Patients will undergo screening procedures within 42 days of randomization. To participate in the

study, patients are required to have had a qualifying liver biopsy within 180 days of randomization. Patients must meet all of the inclusion criteria and none of the exclusion criteria to participate in the study.

Treatment Period

Following randomization, patients will begin the initial 12-week Treatment Period. Patients will undergo liver MRI-PDFF prior to the start of treatment (pre-dose), at the end of the initial 12-week Treatment Period (12 weeks after the start of treatment), and after continuing blinded treatment (MGL-3196 or placebo) for an additional 24 weeks (36 weeks after the start of treatment). A liver biopsy will be obtained prior to start of treatment (pre-dose) if the patient has not had a qualifying liver biopsy within 180 days of randomization and at 36 weeks. During the study, patients will return to the study site periodically for assessment of vital signs (temperature, pulse, respiratory rate, and seated blood pressure), 12-lead electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry, and urinalysis). During the study, patients who need to be placed on any excluded lipid lowering therapeutics will be discontinued from the study. Blood samples will be collected at specified times for the assessment of lipid parameters, thyroid hormone parameters, and other biomarkers. Patients will be evaluated for adverse events and concomitant medication use throughout the study. Patients should be monitored throughout the study for clinical signs and symptoms of hyper- or hypothyroidism.

A PK assessment will be made at Week 2 including a pre-dose fasting determination and assessments at 2, 4, 6, and 8 hours postdose. As described in PK section, patients who have a calculated $AUC_{inf} \leq$ to 5500 ng*hr/ml (combined MGL-3196 and MGL-3196-M1) will continue on 80 mg. For patients (~10%) with an $AUC_{inf} \leq 3000$ ng*hr/ml as described in Section 8 who are predicted to have exposure at 100 mg that remains AUC ≤5550 based on a conservative calculation, the MGL-3196 dose will be increased from 80 mg to 100 mg at the Week 4 visit. For patients with combined AUC >5500 ng*hr/ml, the dose of MGL-3196 will be reduced to 60 mg per day at the Week 4 visit. Patients with AUC_{inf} >11,000 (combined MGL-3196 and M1) plus SHBG>150% increase from baseline at Week 2 (indicative that average or steady-state exposure is >11,000 ng*hr/ml) will be downtitrated to 40 mg at Week 4. If SHBG ≤150%, then patient will be downtitrated to 60 mg at Week 4, and patient's 4 Week SHBG and predose concentrations will be evaluated. If at Week 4 SHBG >150% increase from baseline and predose >40ng/ml for MGL-3196 and >40ng/ml for M1 then patient will be downtitrated to 40 mg at the Week 8 visit.

A combined MGL-3196 and MGL-3196-M1 exposure ≤ 5500 ng*hr/ml has not demonstrated a drug-related decrease in FT4 to < LLN < 0.7 ng/dL) in Phase 1 studies. However, patients with NASH without symptoms of hypothyroidism may occasionally have low baseline levels of FT4, with normal FT3 and TSH, and are not clinically or subclinically hypothyroid. Low FT4 in the presence of normal FT3 (active hormone) and TSH is not consistent with hypothyroidism; low FT4 is observed in euthyroid (formerly hypothyroid) patients treated with T3 monotherapy [20]

In patients continuing on 80 mg MGL-3196 (AUC_{inf} < 5500) who have FT4 LLN (>.55 to <.7 ng/dL):

At Week 4 or later:

- If FT3 remains normal (not decreased to <LLN) and TSH remains normal, the patient does not have symptms of hypothyroidism, the patient may continue on the current dose.

- Down titration to 60 mg may be made at the next visit, Week 8 or later if FT4 <LLN (>.55 to <.7 ng/dL), FT3 and TSH are normal, and there is evidence that the decrease in FT4 <LLN (>.55 to <.7 ng/dL) is drug-related including a >30% decrease from baseline in FT4, an increase in SHBG >120% from baseline and predose exposure >40 ng/ml for MGL-3196 and > 40 ng/ml for MGL-3196-M1 that is consistent with increased drug exposure relative to the Week 2 PK assessment.

In patients downtitrated to 60 mg at Week 4 who have FT4 LLN (>.55 to <.7 ng/dL):

- At Week 8 or later, if FT3 and TSH remain normal, the patient does not have symptoms of hypothyroidism, the patient may continue on the current dose.
- Down titration to 60 or 40 mg may be made at the next visit, Week 12 or later if FT4 <LLN (>.55 to <.7 ng/dL), FT3 and TSH are normal, and there is evidence that the decrease in FT4 <LLN (>.55 to <.7 ng/dL) is drug-related including a >30% decrease from baseline in FT4, an increase in SHBG >120% from baseline and predose exposure >40 ng/ml for MGL-3196 and > 40 ng/ml for MGL-3196-M1 that is consistent with increased drug exposure relative to the Week 2 PK assessment.

If these conditions are not met, the patient will continue on current dose and thyroid indices reassessed at subsequent visits. Any randomized patients previously downtitrated based on LLN FT4 per Protocol Amendment 2 who did not meet these criteria for downtitration (Amendment 3) will be returned to the previous dose in a blinded fashion at the next visit.

If FT4 is ≤.55 ng/dL on 80 or 60 mg dose with normal FT3 and TSH (which are unblinded to study personnel for all patients), even if the decrease in FT4 is not felt to be primarily drug-related, a down titration to 60 or 40 mg, respectively, may be made at the next visit as determined by Sponsor and Medical Monitor after blinded review. If it is determined after blinded review by Sponsor and Medical Monitor that thyroid therapy should be initiated, because thyroxine cannot be initiated without breaking the blind, the patient will be discontinued from the study and Early Termination assessments will be performed.

Extension Study

Within 60 days of completion of the main study Week 36 Visit, patients who meet Inclusion Criteria #9 will be eligible to participate in an extension phase of the study for an additional 36 weeks of treatment. The extension study will initially be blinded to treatment group, but the extension study will become unblinded at the time of completion of the main study. At the extension study initiation which may be as early as the 38-week visit, (Extension study Day 1 visit), patients on placebo in the main study will begin receiving 80 mg MGL-3196 and at the Week 2 visit, all patients will have a PK assessment, and at Week 4 any dose adjustments will be made. All patients on active drug in the main study will initially receive MGL-3196 at the dose they were assigned to at the completion of the main study, and at the Week 4 visit they may have their dose adjusted up or down based on the Week 2 PK.

Dose Adjustments in Main and Extension Study in Patients Assigned to MGL-3196 in Main Study

Current dose	**Main Study Week 2 PK (AUC, combined MGL-3196 plus M1 on 80 mg dose)**	**Main Study Predose at Week 2**	**Main study Predose Week 8 (post dose adjustment)**	**Main Study SHBG <+75% CFB at Week 12 (post dose adjustment)**	**Action in Main and/or Extension Study**
40 mg			< 5 ng/ml	Yes	Increase to 60 mg/day
60 mg	<5500ng*hr*ml[1]		< 1 ng/ml	Yes	Increase to 80 mg/day
80 mg	<4000 ng*hr/ml AND SHBG %CFB<90)			OR[2] Yes	Increase to 100 mg/day
100 mg	≤3000 ng*hr/ml	<5 ng/ml			Increase to 120 mg
120 mg					No change

[1] Recalculated 80 mg AUC based on corrected elimination rate constant for MGL-3196 and M1in patients who demonstrated average predose levels <5 ng/ml at Week 2,4,8 and had initial calculated AUC<7000 ng*hr/ml. Change from Baseline (CFB).

[2] Either exposure <4000ng*hr/ml with SHBG%CFB<+90 OR SHBG<+70%CFB qualifies for increase to 100 mg.

Dose Adjustments in the Extension Study in Patients Assigned to Placebo in the Main Study

Extension Study Week 2 MGL-3196 Concentration		**Extension Study Week 2 SHBG**	**Extension Study Week 4 Action**
Predose	**4 h post dose**		
>35 ng/ml	>1350 ng/ml	>200% CFB*	Downtitrate to 40 mg
Patients not meeting criteria for 40, 80, 100 or 120 mg			Downtitrate to 60 mg
<15 ng/ml	<600 ng/ml	OR <75% CFB increase**	Remain on 80 mg or increase (see next rows)
<5 ng/ml	≤ 350 ng/ml	No rule	Increase to 100 mg
<2 ng/ml	≤ 150 ng/ml	No rule	Increase to 120 mg

*Change From Baseline, where baseline is Extension Study Day 1.

**Either predose<15ng/ml plus 4h<600ng/ml OR SHBG<+75%CFB.

No titrations will be made based on TSH which has not changed in the Main Study. TSH will be unblinded in the Extension Study. Downtitrations have not been needed for changes in FT4, but the same downtitration rules will apply in the Extension Study.

At the Extension Study Week 12 Visit, patients will have an MRI-PDFF. Within 10 days prior to or at the Extension Study Week 36 visit while the patient is still on treatment another MRI-PDFF will be performed. If available, a fibroscan may be performed at the Extension Study Week 36 visit.

DSMB

A Data Safety Monitoring Board (DSMB) will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes ALT, AST, and bilirubin), cardiovascular assessment (ie, changes in ECG, cardiac biomarkers, cardiac AEs, cardiac symptoms, arrhythmias, etc.), SAEs for trends in causality, and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews the first scheduled for when 25 patients have received 6 weeks of treatment. Additional regularly timed meetings will be held and ad hoc meetings may also occur if determined by Madrigal and the DSMB.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

MGL-3196 and matching placebo are available as hard gelatin capsules for oral administration in 40 mg and 60 mg strengths. Patients will be randomized to 1 of 2 treatments: MGL-3196 80 mg or placebo given orally once-daily in the morning for 36 weeks. Each patient will receive study drug bottles labeled as A and B. Patients will take 1 capsule from bottle A and 1 capsule from bottle B at each dosing. Each bottle will contain 32 capsules (64 capsules total), enough for 4 weeks + 4 days of dosing. Based on PK assessments and/or thyroid hormone results, the dose may be adjusted between 40 and 100 mg in intervals of 20 mg. The patient, study personnel, and Sponsor will remain blinded throughout the study.

EFFICACY VARIABLES:

The primary efficacy variable is percent change in hepatic fat fraction by MRI-PDFF from baseline at 12 weeks for MGL-3196 80 mg versus placebo.

The secondary efficacy variables include the following:

- The number and percentage of patients achieving a 2-point reduction in NAS at 36 weeks for MGL-3196 80 mg versus placebo;
- The number and percentage of patients achieving resolution of NASH (ballooning = 0; inflammation = 0 to 1) at 36 weeks for MGL-3196 80 mg versus placebo;
- The number and percentage of patients achieving a reduction in any individual component of NASH (hepatocellular steatosis, ballooning, fibrosis, or lobular inflammation) at 36 weeks for MGL-3196 80 mg versus placebo;

- The change in thyroid axis hormones from baseline at 12 and 36 weeks for MGL-3196 80 mg versus placebo;
- The percent change in hepatic fat fraction by MRI-PDFF from baseline at 36 weeks for MGL-3196 80 mg versus placebo;
- The change in hepatic fat fraction by MRI-PDFF from baseline at 12 and 36 weeks for MGL-3196 80 mg versus placebo; and
- The change in hsCRP, ALT, AST, LDL-C, HDL-C, non-HDL-C, total cholesterol, triglycerides, ApoB, Lp(a), CK-18, FIB-4, and ELF test from baseline at 12 and 36 weeks for MGL-3196 80 mg versus placebo.

The other efficacy variables include the following:

- [redacted]

PHARMACOKINETICS:

Blood samples for PK assessments will be obtained pre-dose from patients at the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 16, 24, and 36, and the Early Termination Visit. Patients will be instructed not to take study drug prior to PK sampling at these respective study weeks.

At Main Study Week 2 visit, PK assessments will be made in the clinic after over-night fast at pre-dose. An 80 mg dose of MGL-3196 or placebo will be administered and PK assessments will be made at 2, 4, 6, and 8 hours post dose. Total AUC_{inf} will be calculated for MGL-3196

and MGL-3196-M1 based on Week 2 $AUC_{(0-8)}$, exposure at 8 h and historic geometric mean elimination rate constant for MGL-3196 and MGL-3196-M1 at the 80 mg dose.

For patients eligible to participate in the extension phase of the study, at the Extension Study Week 2 visit, PK assessments at predose and 4 hours post dose will be made. See the tables on page 35 for dose adjustments.

SAFETY VARIABLES:

Safety variables to be assessed include safety laboratory tests, vital signs and anthropometrics, 12-lead ECG with rhythm strip, dual-energy x-ray absorptiometry, physical examinations, adverse events, and clinical assessments.

DRUG INDUCED LIVER INJURY MONITORING:

Close clinical monitoring must be applied to the following:

- Any patient who had normal baseline ALT, AST, and total bilirubin values and then experienced a newly treatment-emergent ALT and/or AST value >3 × ULN OR total bilirubin value >2 × ULN; or
- Any patient who had elevated ALT, AST, or total bilirubin values at baseline and then experienced a 2-fold increase above the baseline ALT and/or AST values AND/OR a 1.5-fold increase above the baseline total bilirubin values.

The patient must return to the study site within 48 to 72 hours for a confirmatory evaluation and central laboratory testing. Repeat laboratory analyses must include the following chemistries: ALP, ALT, AST, total and direct bilirubin, international normalized ratio, and lactate dehydrogenase. At the same time repeat samples are drawn, a PK sample must be taken.

CARDIOVASCULAR MONITORING

Patients will be closely monitored for signs of cardiac toxicity including assessment of CV AEs and symptoms. If any of the following abnormalities are identified, an additional clinical investigation may be appropriate:

- Onset of new (i.e. not present at baseline or documented in the medical history) and clinically significant arrhythmia which is persistent (i.e. confirmed on repeat assessment)
- Systolic hypertension (defined for the study as a SBP >160 mmHg and at least a 20 mmHg increase from baseline)
- Increase in troponin I vs. baseline and above ULN.

STATISTICAL ANALYSES:

Analysis Populations:

The Intent-to-Treat (ITT) Population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT Population will be used for all efficacy analyses. The Per Protocol Population will include all ITT patients who finish the Week 12 visit with valid MRI-PDFF measurements and do not have any major protocol deviations. Patients who are <80% compliant over the course of the initial 12-week Treatment Period will not be included in the Per Protocol Population. The Safety Population will include all patients who are randomized in the study and receive at least 1 dose of study drug and will be used for all safety analyses.

Demographics, disposition, and study populations will be summarized descriptively.

Efficacy:

The primary efficacy variable will be the percent change in MRI-PDFF from baseline to Week 12. Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change from baseline will be provided. The primary efficacy analysis will be analyzed with an analysis of covariance (ANCOVA) model with treatment as a factor. For any patients in the ITT Population with a missing primary efficacy parameter, the control (placebo)-based pattern mixture model will be used. Based on PK obtained in healthy volunteers dosed for up to two weeks on doses of MGL-3196 from 20-200 mg per day, a significant fraction of patients randomized to an 80 mg dose may have their dose reduced to 60 mg after PK assessment at Week 2. The multiplicity (MGL-3196 60 mg versus placebo and MGL-3196 80 mg versus placebo) will be controlled by Dunnett's Test. The primary efficacy analysis will be performed based on the ITT Population and repeated based on the Per Protocol Population.

For the continuous secondary efficacy variables, the same ANCOVA model will be used. Normality will be tested for the model residuals. For certain efficacy variables (such as hsCRP and triglycerides), logarithm transformation may be performed prior to fitting the ANCOVA model. For the categorical secondary efficacy variables, Fisher's exact test will be used to compare the odds ratio between MGL-3196 doses versus placebo.

The same efficacy analyses used for the secondary efficacy variables will be used for the tertiary/exploratory efficacy variables.

Subgroup analysis of the primary efficacy variable and/or selected secondary/other efficacy variables may be performed, such as gender (male/female), BMI (≥30 kg/m^2 or <30 kg/m^2), and age group (≥median or <median).

Safety:

The safety endpoints for this study include: adverse events, safety laboratory assessments, vital signs, 12-lead ECGs, concomitant medications, and clinical assessments.

The adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events (TEAEs) will be defined as adverse events that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs) will be tabulated with numbers and percentages

of patients, and repeated for severity and relationship to study drug per treatment group. The number of adverse events leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are <LLN or >ULN of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest will be summarized.

Interim Analysis:

Interim analysis is not designed for this study. However, an analysis will be performed once all patients reach Week 12 of the Treatment Period. The analysis will assess the efficacy of MGL-3196 on percent change in liver fat by MRI-PDFF.

SAMPLE SIZE DETERMINATION:

Approximately 117 patients in total will be randomized to 80 mg (2/3) or placebo (1/3) treatments. After PK assessment, a significant fraction of patients' combined AUC (MGL-3196 plus MGL-3196-M1) may exceed 5500 ng*hr/ml resulting in a dose reduction to 60 mg. In order to power the study appropriately for an efficacious dose (which may be ≥ 80 mg), randomization may continue until approximately 36 patients have continued at Week 4 on the 80 mg dose. It is estimated that the treatment difference of percent change in hepatic fat fraction from baseline to Week 12 between any dose of MGL-3196 and the placebo group is about -30%. With a common standard deviation for the percent change in hepatic fat fraction at 35%, 36 patients per group completing the Week 12 visit will provide 90% power with a 2-sample t-test. The significance level is set as 0.025 for the consideration of multiplicity in comparisons of 2 daily dosing regimens of MGL-3196 versus the placebo group. The enrollment size is designed to allow for 10% drop out before the Week 12 visit, and as such, patients who drop out of the study will not be replaced.

With the sample size of 39 patients per treatment, the power for selected secondary efficacy endpoints was calculated. The baseline hepatic fat fraction is expected to be approximately 15% to 17%, thus the change from baseline to Week 12 in hepatic fat fraction is approximately -5.5% when comparing to placebo. With common standard deviation of change in hepatic fat fraction as 6%, 36 completed patients will provide 94% power for the study when evaluating the treatment effect in change of hepatic fat fraction.

In addition, the sample size is expected to provide meaningful liver biopsy-related data.

SITES: Approximately 30 sites in the United States

SPONSOR:

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
APTT	Activated partial prothrombin time
APRI	AST to platelet ratio
AST	Aspartate aminotransferase
BMI	Body mass index
CAP	Controlled attenuation parameter
CK-18	Cytokeratin-18
CK-MB	Creatine Kinase-MB
CRA	Clinical research associate
CTA	Clinical trial authorization
CTX	C-terminal telopeptide
CYP2C8	Cytochrome P_{450} 2C8
CYP2C9	Cytochrome P_{450} 2C9
DSMB	Data Safety Monitoring Board
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver function
FIB-4	Fibrosis-4
FT3	Free triiodothyronine
FT4	Free thyroxine
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HepB	Hepatitis B
HepC	Hepatitis C
HIV	Human immunodeficiency virus
[redacted]	[redacted]

Abbreviation	Definition
hsCRP	High-sensitivity C-reactive protein
HR-QoL SF-36	Health-related quality of life short form 36
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
kPa	kiloPascals
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LLN	Lower limit of normal
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Non-alcoholic steatohepatitis
[redacted]	[redacted]
OAD	Oral anti-diabetic
MRI-PDFF	Proton density fat fraction magnetic resonance imaging
PK	Pharmacokinetic
PT	Prothrombin time
RNA	Ribonucleic acid
SAE	Serious adverse event
SHBG	Sex hormone binding globulin
T3	Triiodothyronine
T4	Thyroxine
TBG	thyroxine binding globulin
TEAE	Treatment-emergent adverse event
THR	Thyroid hormone receptor
THR-α	Thyroid hormone receptor alpha
THR-β	Thyroid hormone receptor beta
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Despite advances in treatment, approximately 70% of high-risk cardiovascular patients do not achieve low-density lipoprotein cholesterol (LDL-C) goals, and as many as 10% of hypercholesterolemic patients do not tolerate statins.[1,2] Elevated LDL-C levels are associated with cardiovascular disease, including myocardial infarctions and strokes, and drugs such as statins that lower LDL-C also reduce cardiovascular morbidity and mortality. Insulin resistant type 2 diabetics have a high incidence of atherosclerosis, and 65% to 80% of diabetics die of macrovascular cardiovascular disease.[3] Diabetes is associated with a dyslipidemia characterized by non-alcoholic fatty liver disease (NAFLD), elevated triglycerides, atherogenic low-density lipoprotein particles and reduced high-density lipoprotein cholesterol (HDL-C) that is not well treated by existing therapies.[4,5]

In large part because of the worldwide obesity and diabetes epidemic, the prevalence of NAFLD has increased dramatically with prevalence rates of approximately 25% of the US population.[6] Non-alcoholic fatty liver disease may lead to non-alcoholic steatohepatitis (NASH), a more serious liver disease that can lead to liver cirrhosis and increased cardiovascular disease. Non-alcoholic steatohepatitis was described more than 30 years ago and is characterized by findings on liver biopsy including fatty changes with lobular hepatitis (ballooning and inflammation) in the absence of history of alcoholism. The histologic components of steatosis, inflammation, and ballooning degeneration may be accompanied by various degrees of fibrosis.

MGL-3196 is a liver-directed, orally active, partial agonist for the thyroid hormone receptor (THR), with approximately 28-fold selectivity for the beta receptor compared to the active thyroid hormone, triiodothyronine (T3). Selectivity for a thyroid agonist at thyroid hormone receptor beta (THR-β) isoform, the predominant liver thyroid hormone receptor, has the potential of providing metabolic benefits of thyroid hormone that are mediated in the liver, while avoiding unwanted systemic actions of thyroid hormone in heart and bone that are largely mediated through THR alpha (THR-α).[7]

Thyroxine (T4) via its active derivative, T3, provides beneficial metabolic effects on cholesterol, triglyceride, and liver triglyceride levels, primarily through action at the THR-β, the predominant hepatocyte THR.[7,8,9,10,11] However, excessive levels of thyroid hormone can lead to adverse effects mediated by the THR-α receptor which is the major systemic thyroid hormone receptor.[12,13] MGL-3196 is a selective THR-β agonist with actions in the liver that is designed to avoid those systemic actions mediated through the THR-α and the central thyroid action suppression observed with previous analogues.

1.2 Rationale

The deficiency in THR-β activity in NASH livers cannot be corrected by treatment with thyroid hormone because 1) thyroid hormone may be rapidly metabolized in NASH livers due to the action of deiodinases, and 2) thyroid hormone has undesirable systemic actions, particularly effects on the heart and bone because of its potency at the THR-α receptor.

Thyroid hormone receptor analogs demonstrating an improved therapeutic window between beneficial lipid effects and adverse systemic effects have been developed and tested in clinical trials and demonstrated validation of cholesterol and triglyceride lowering.[14,15] However,

eprotirome and other analogs also demonstrated safety issues that resulted in discontinuation of clinical development. These include low margins relative to doses that suppress the central thyroid axis, elevated liver enzymes in Phase 1, 2, and 3 studies, and other safety issues such as formation of a nitrated mutagenic impurity at gastric pH and collagen damage in a preclinical toxicology study.[16, 17]

The oral THR-β agonist MGL-3196 was selected for clinical development based on its enhanced THR-β selectivity in functional THR assays and its greatly improved safety in preclinical animal models relative to other THR analogues and T3.[18] Unlike previous clinical analogues, MGL-3196 is highly THR-β selective in a functional coactivator recruitment assay and has virtually no THR-α activity. Liver uptake is mediated by hepatic transporters. In preclinical animal studies, MGL-3196 showed rapid and robust lowering of non-HDL cholesterol, triglycerides, and liver triglycerides, with reduction in NASH gene transcripts, differentiating MGL-3196 from statins and other lipid-lowering agents. In 14-day Phase 1 studies in healthy human volunteers, once-daily doses of MGL-3196 showed rapid, robust reduction of LDL-C and triglycerides. In these studies, there was apparent safety at all doses tested and no evidence of the liver enzyme changes or central thyroid axis suppression that were seen with T3, T4, or previous clinical thyroid analogues.[19]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the effect of once-daily oral MGL-3196 80 mg versus placebo (randomized 2:1) for 12 weeks on the percent change in hepatic fat fraction by proton density fat fraction magnetic resonance imaging (MRI-PDFF) from baseline in patients with biopsy-proven NASH.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To determine the effect of once-daily oral MGL-3196 80 mg versus placebo for 36 weeks in patients with biopsy-proven NASH on the histological improvement from baseline on:
  - Two-point reduction in NAFLD activity score (NAS);
  - Resolution of NASH (ballooning = 0; inflammation = 0 to 1); or
  - Any individual component of NASH (hepatocellular steatosis, ballooning, fibrosis, or lobular inflammation);
- To evaluate the safety and tolerability, including any changes in thyroid axis hormones, of once-daily oral MGL-3196 80 mg versus placebo after 12 and 36 weeks in patients with biopsy-proven NASH;
- To evaluate the effect of once-daily oral MGL-3196 80 mg versus placebo for 36 weeks on the percent change in hepatic fat fraction by MRI-PDFF from baseline in patients with biopsy-proven NASH;
- To evaluate the effect of once-daily oral MGL-3196 80 mg versus placebo for 12 and 36 weeks on the change in hepatic fat fraction by MRI-PDFF from baseline in patients with biopsy-proven NASH; and
- To determine the effect of once-daily oral MGL-3196 80 mg versus placebo after 12 and 36 weeks in patients with biopsy-proven NASH on:
  - High-sensitivity C-reactive protein (hsCRP);
  - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST);
  - Lipid parameters including LDL-C, HDL-C, non-HDL-C, total cholesterol, triglycerides, apolipoprotein B (ApoB), and lipoprotein(a) (Lp[a]) particles; and
  - NASH and fibrosis biomarkers including cytokeratin-18 (CK-18), fibrosis-4 (FIB-4), and enhanced liver function (ELF) test.

2.3 Exploratory Objectives

The tertiary/exploratory objectives of this study are the following:

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of MGL-3196 in patients with NASH. Patients who qualify for study inclusion will be randomized to receive one of two 36-week treatments: MGL-3196 80 mg or placebo given orally once-daily in the morning. Following 12 weeks of treatment, the primary endpoint, percent change from baseline in hepatic fat fraction measured by MRI-PDFF, will be evaluated. At 36 weeks, all patients will undergo liver biopsy.

3.1.1 Screening Period

Patients must provide written informed consent prior to any study procedures being performed. Patients will undergo screening procedures within 42 days of randomization. To participate in the study, patients are required to have had a qualifying liver biopsy within 180 days of randomization. Patients must meet all of the inclusion criteria and none of the exclusion criteria to participate in the study.

3.1.2 Treatment Period

Following randomization, patients will begin the initial 12-week Treatment Period. Patients will undergo liver MRI-PDFF prior to the start of treatment (pre-dose), at the end of the initial 12-week Treatment Period (12 weeks after the start of treatment), and after continuing blinded treatment (MGL-3196 or placebo) for an additional 24 weeks (36 weeks after the start of treatment). A liver biopsy will be obtained prior to start of treatment (pre-dose) if the patient has not had a qualifying liver biopsy within 180 days of randomization and at 36 weeks. During the study, patients will return to the study site periodically for assessment of vital signs (temperature, pulse, respiratory rate, and seated blood pressure), 12-lead electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry, and urinalysis). During the study, patients who need to be placed on any excluded lipid lowering therapeutics will be discontinued from the study. Blood samples will be collected at specified times for the assessment of lipid parameters, thyroid hormone parameters, and other biomarkers. Patients will be evaluated for adverse events and concomitant medication use throughout the study. Patients should be monitored throughout the study for clinical signs and symptoms of hyper- or hypothyroidism.

A PK assessment will be made at Week 2 including a pre-dose fasting determination and assessments at 2, 4, 6, and 8 hours postdose. As described in PK section, patients who have a calculated $AUC_{inf} \leq$ to 5500 ng*hr/ml (combined MGL-3196 and MGL-3196-M1) will continue on 80 mg. For patients (~ 10%) with an $AUC_{inf} \leq 3000$ ng*hr/ml as described in Section 8 who are predicted to have exposure at 100 mg that remains AUC ≤5550 based on a conservative calculation, the MGL-3196 dose will be increased from 80 mg to 100 mg at the Week 4 visit. For patients with combined AUC >5500 ng*hr/ml, the dose of MGL-3196 will be reduced to 60 mg per day on the Week 4 visit. Patients with AUC_{inf} >11,000 (combined MGL-3196 and M1) plus SHBG>150% increase from baseline at Week 2 (indicative that average or steady-state exposure is >11,000 ng*hr/ml) will be downtitrated to 40 mg at Week 4. If SHBG ≤150%, then patient will be downtitrated to 60 mg at Week 4, and patient's Week 4 SHBG and predose concentrations will be evaluated. If at Week 4 SHBG >150% increase from baseline and predose

>40ng/ml for MGL-3196 and >40ng/ml for M1 then patient will be downtitrated to 40 mg at the Week 8 visit.

A combined MGL-3196 and MGL-3196-M1 exposure ≤ 5500 ng*hr/ml has not demonstrated a drug-related decrease in FT4 to < LLN < 0.7 ng/dL) in Phase 1 studies. However, patients with NASH without symptoms of hypothyroidism may occasionally have low baseline levels of FT4, with normal FT3 and TSH, and are not clinically or subclinically hypothyroid. Low FT4 in the presence of normal FT3 (active hormone) and TSH is not consistent with hypothyroidism; low FT4 is observed in euthyroid (formerly hypothyroid) patients treated with T3 monotherapy [20]

In patients continuing on 80 mg MGL-3196 (AUC_{inf} < 5500) who have FT4 LLN (>.55 to <.7 ng/dL):

At Week 4 or later:

- If FT3 remains normal (not decreased to <LLN) and TSH remains normal, the patient does not have symptoms of hypothyroidism, the patient may continue on the current dose.
- Down titration to 60 mg may be made at the next visit, Week 8 or later if FT4 <LLN (>.55 to <.7 ng/dL), FT3 and TSH are normal, and there is evidence that the decrease in FT4 <LLN (>.55 to <.7 ng/dL) is drug-related including a >30% decrease from baseline in FT4, an increase in SHBG >120% from baseline and predose exposure >40 ng/ml for MGL-3196 and > 40 ng/ml for MGL-3196-M1 that is consistent with increased drug exposure relative to the Week 2 PK assessment.

In patients downtitrated to 60 mg at Week 4 who have FT4 LLN (>.55 to <.7 ng/dL):

- At Week 8 or later, if FT3 and TSH remain normal, the patient does not have symptoms of hypothyroidism, the patient may continue on the current dose.
- Down titration to 60 or 40 mg may be made at the next visit, Week 12 or later if FT4 <LLN (>.55 to <.7 ng/dL), FT3 and TSH are normal, and there is evidence that the decrease in FT4 <LLN (>.55 to <.7 ng/dL) is drug-related including a >30% decrease from baseline in FT4, an increase in SHBG >120% from baseline and predose exposure >40 ng/ml for MGL-3196 and > 40 ng/ml for MGL-3196-M1 that is consistent with increased drug exposure relative to the Week 2 PK assessment.

If these conditions are not met, the patient will continue on current dose and thyroid indices reassessed at subsequent visits. Any randomized patients previously downtitrated based on LLN FT4 per Protocol Amendment 2 who did not meet these criteria for downtitration (Amendment 3) will be returned to the previous dose in a blinded fashion at the next visit.

If FT4 is ≤.55 ng/dL on 80 or 60 mg dose with normal FT3 and TSH (which are unblinded to study personnel for all patients), even if the decrease in FT4 is not felt to be primarily drug-related, a down titration to 60 or 40 mg, respectively, may be made at the next visit as determined by Sponsor and Medical Monitor after blinded review. If it is determined after blinded review by Sponsor and Medical Monitor that thyroid therapy should be initiated, because thyroxine cannot be initiated without breaking the blind, the patient will be discontinued from the study and Early Termination assessments will be performed.

3.1.3 Extension Study

Within 60 days of completion of the main study Week 36 Visit, patients who meet Inclusion Criteria #9 will be eligible to participate in an extension phase of the study for an additional 36 weeks of treatment. The extension study will initially be blinded to treatment group, but the extension study will become unblinded at the time of completion of the main study. At the extension study initiation which may be as early as the 38-week visit, (Extension study Day 1 visit), patients on placebo in the main study will begin receiving 80 mg MGL-3196 and at the Week 2 visit, all patients will have a PK assessment, and at Week 4 any dose adjustments will be made. All patients on active drug in the main study will initially receive MGL-3196 at the dose they were assigned to at the completion of the main study, and at the Week 4 visit they may have their dose adjusted up or down based on the Week 2 PK.

Dose Adjustments in Main or Extension Study in Patients Assigned to MGL-3196 in Main Study

Current dose	**Main Study Week 2 PK (AUC, combined MGL-3196 plus M1 on 80 mg dose)**	**Main Study Predose at Week 2**	**Main study Predose Week 8 (post dose adjustment)**	**Main Study SHBG <+75% CFB at Week 12 (post dose adjustment)**	**Action in Main and/or Extension Study**
40 mg			< 5 ng/ml	Yes	Increase to 60 mg/day
60 mg	<5500 ng*hr/ml[1]		< 1 ng/ml	Yes	Increase to 80 mg/day
80 mg	<4000 ng*hr/ml AND SHBG %CFB<90)			OR[2] Yes	Increase to 100 mg/day
100 mg	≤3000 ng*hr/ml	<5 ng/ml			Increase to 120 mg
120 mg					No change

[1] Recalculated 80 mg AUC based on corrected elimination rate constant for MGL-3196 and M1in patients who demonstrated average predose levels <5 ng/ml at Week 2,4,8 and had initial calculated AUC<7000 ng*hr/ml. Change from Baseline (CFB).

[2] Either exposure <4000ng*hr/ml with SHBG%CFB<+90 OR SHBG<+70%CFB qualifies for increase to 100 mg.

Dose Adjustments in the Extension Study in Patients Assigned to Placebo in the Main Study

Extension Study Week 2 MGL-3196 Concentration		**Extension Study**	**Extension Study**
Predose	**4 h post dose**	**Week 2 SHBG**	**Week 4 Action**
>35 ng/ml	>1350 ng/ml	>200% CFB*	Downtitrate to 40 mg
Patients not meeting criteria for 40, 80, 100 or 120 mg			Downtitrate to 60 mg
<15 ng/ml	<600 ng/ml	OR <75% CFB increase**	Remain on 80 mg or increase (see next rows)
<5 ng/ml	≤ 350 ng/ml	No rule	Increase to 100 mg
<2 ng/ml	≤ 150 ng/ml	No rule	Increase to 120 mg

*Change From Baseline, where baseline is Extension Study Day 1.
**Either predose<15ng/ml plus 4h<600ng/ml OR SHBG<+75%CFB.

No titrations will be made based on TSH which has not changed in the Main Study. TSH will be unblinded in the Extension Study. Downtitrations have not been needed for changes in FT4, but the same downtitration rules will apply in the Extension Study.

At the Extension Study Week 12 Visit, patients will have an MRI-PDFF. Within 10 days prior to or at the Extension Study Week 36 visit while the patient is still on treatment another MRI-PDFF will be performed. If available, a fibroscan may be performed at the Extension Study Week 36 visit.

3.1.4 DSMB

A Data Safety Monitoring Board (DSMB) will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes ALT, AST, and bilirubin), cardiovascular assessment (ie, changes in ECG, cardiac biomarkers, cardiac AEs, cardiac symptoms, arrhythmias, etc.), SAEs for trends in causality, and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews the first scheduled for when 25 patients have received 6 weeks of treatment. Additional regularly timed meetings will be held and ad hoc meetings may also occur if determined by Madrigal and the DSMB.

3.2 Study Indication

The indication for this study is the treatment of NASH.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

The population for this study is male and female patients ≥18 years of age with biopsy-proven NASH.

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Must be willing to participate in the study and provide written informed consent;
2. Male and female adults ≥18 years of age;
3. Female patients of child bearing potential with negative serum pregnancy (beta human chorionic gonadotropin) tests who are not breastfeeding, do not plan to become pregnant during the study, and agree to use effective birth control (ie, condoms, diaphragm, non-hormonal intrauterine device [IUD], or sexual abstinence [only if this is in line with the patient's current lifestyle]) throughout the study and for at least 1 month after study completion; hormonal contraception (estrogens stable ≥3 months) and hormonal IUDs are permitted if used with a secondary birth control measure (eg, condoms); OR female patients of non-child bearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]); Male patients who have sexual intercourse with a female partner of child bearing potential from the first dose of study drug until 1 month after study completion must be either surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with spermicide. All male patients must agree not to donate sperm from the first dose of study drug until 1 month after study completion;
4. Suspected or confirmed diagnosis of NASH suggested by the historical data and at least <u>one</u> of the following assessments within current and/or historical data sets (and, therefore, likely to meet MRI-PDFF and liver biopsy criteria outlined in Inclusion #5 and #6):
    - Metabolic syndrome (obesity, dyslipidemia, elevated blood pressure, elevated fasting glucose) with two or more of the following: type 2 diabetes/insulin resistance, BMI ≥ 34, history of hypertension, elevated liver enzymes (ALT, AST)
    - Fibroscan, magnetic resonance elastography, or serum biomarkers (eg, AST to platelet ratio [APRI], NAFLD fibrosis score, FIB-4 or ELF) consistent with liver fibrosis;
    - Controlled attenuation parameter (CAP), quantitative ultrasound (liver fat >10%), MRI-PDFF, or magnetic resonance spectroscopy consistent with significant liver steatosis (>10%);
    - Previous liver biopsy consistent with NASH.

Note: Assessment of the above, or other objective modalities suggested by PI, will occur. The choice of additional procedures, performed during the screening period prior to the screening MRI and liver biopsy, may include calculation of FIB-4, APRI, NAFLD fibrosis scores, and/or performance of fibroscan and/or CAP.

5. Must have confirmation of ≥10% liver fat content on MRI-PDFF;

   Note: Patients with a liver fat content >9% but < 10% on MRI-PDFF and who are highly likely to have NASH as determined by Medical Monitors on biopsy may be included in the study but the total may not exceed 10% of the total study population;

6. Biopsy-proven NASH:

- Must have had prior liver biopsy within 180 days of randomization with fibrosis stage 1 to 3 and a NAS of ≥4 with at least a score of 1 in each of the following NAS components:
  - Steatosis (scored 0 to 3),
  - Ballooning degeneration (scored 0 to 2), and
  - Lobular inflammation (scored 0 to 3); and

  Note 1: Patients who have clear ballooning with fibrosis but no inflammation or patients who have clear inflammation with fibrosis but no ballooning or patients with clear NASH without fibrosis may be included in the study but the total may not exceed 10% of the total study population;

  Note 2: If a historical biopsy is to be used, patients must have had no significant change in metabolic status (diabetes control, lipid metabolism, and/or >5% weight loss), significant change in diabetes medication, or change in use of medications listed in Exclusion #11 since the biopsy;

  Note 3: If a historical biopsy is not available, patients must have confirmation of ≥10% liver fat content on MRI-PDFF prior to undergoing liver biopsy. However, if, in the opinion of the patient's physician, the patient would benefit from and be advised to obtain a liver biopsy, the patient may undergo liver biopsy prior to MRI-PDFF;

7. Must have documented historical (3 weeks to 6 months prior to the study entry) ALT and AST levels consistent with the screening ALT and AST values. This consistency is established based on the following:
   - If the historical and screening ALT and AST values are both ≤1.5 × the upper limit of normal (ULN), there is no limit to the difference between the values
   - If the historic ALT/AST are >1.5 X elevated and screening ALT and AST are markedly improved (>50% decreased or normalized) relative to historic, then a third ALT/AST determination will be made during screening to assure a stable baseline, and that there is no worsening of >30% form the screening values. If the difference is >30% and the second value is greater than the first value, a third value should be determined during the screening period to confirm lack of worsening trend in ALT/AST
   - If at least 1 of the values is >1.5 × ULN and the second value is greater than the first value, the difference in the mean of ALT and AST values must be ≤30%. If the difference is >30% and the second value is greater than the first value, a third value should be determined to confirm lack of worsening trend in ALT/AST. If worsening trend is confirmed (3 consecutive worsening values with difference from first value and second value >30%), patient will be excluded.

Note: Patients who do not have the historical ALT and AST evaluations available may have their ALT and AST repeated during the screening period (both assessments need to be 3 weeks apart).

8. Normal or minimally abnormal renal function as defined by estimated glomerular filtration rate (eGFR) ≥ 60.
9. Eligibility for extension study. Within 60 days of completion of the Week 36 Visit in the main study, patients who meet the following additional criteria will be eligible to participate in the extension phase of this study:
   - Had 36-week MRI-PDFF
   - Had 36-week liver biopsy
   - No new exclusions that would prevent the patient from participating in up to 36 weeks of additional treatment
   - Meets at least one of the following liver enzyme criteria in the table below:

Baseline ALT	Average of ALT at Weeks 16, 20, 24, and 30
ALT normal (<1.5 ULN)	≥ 1.5 x ULN (and 30% worse than baseline)
ALT =1.5-2X	Improvement from baseline <30% and ALT =1.5-2X ULN
ALT any	ALT ≥ 2X
Note: Normal ALT male 30; female 25: 1.5 x male =45 and female=38	Note: ALT or AST values for weeks 16, 20, 24 and 30 that are > 2 X Std Dev from mean will be excluded from the calculation of the average value. Note: When ALT does not meet criteria for inclusion, AST will be evaluated similarly to determine if criteria for inclusion are met based on AST, given normal values in men and women of 27 and 22, respectively and 1.5X of 40 and 33 respectively.

4.2 Exclusion Criteria

Note: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.

Patients who meet any of the following criteria will be excluded from participation in the study:

1. History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening;

   Note: Significant alcohol consumption is defined as average of >20 g/day in female patients and >30 g/day in male patients;
2. Inability to reliably quantify alcohol consumption based upon judgment of the Investigator;

3. Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) for more than 2 weeks in the year prior to screening;
4. Hyperthyroidism;
5. Patients on thyroid replacement therapy or with untreated clinical or subclinical hypothyroidism;

   Note: If TSH is up to 1.5 x ULN on screening with normal free T4, one repeat test is allowed to confirm the elevation in TSH. If TSH and free T4 are normal upon repeat testing, patient may be included. Patients with a history of thyroid hormone replacement therapy or patients who have discontinued thyroid hormone replacement therapy (including thyroxine) ≥2 months prior to randomization may be included in the study if this criterion is met;

   During the study, patients who have elevated levels of TSH > 7 IU/ml on at least two separate consecutive visits and are symptomatic of hypothyroidism, or TSH>10 IU/ml, who are indicated to be on thyroxine for clinical hypothyroidism, may initiate treatment with low doses of thyroxine consistent with American Thyroid Association guidelines, with frequent monitoring of TSH levels at Study Visits (and within 2 weeks of initiation of thyroxine), safety labs, and monitoring of other symptoms related to hyper or hypothyroidism. Thyroxine may be administered at ¼ to ½ the anticipated dose (a starting dose of 25 ug per day) with careful monitoring of TSH levels and symptoms related to hyper or hypothyroidism, with increments in thyroxine dose after no less than 4-6 weeks.

   NOTE: It is anticipated that initiation of thyroxine therapy will occur very infrequently during the study and 50-75 ug thyroxine replacement will suffice for most patients requiring thyroxine treatment.
6. Prior or planned (during the study period) bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass);
7. Type 1 diabetes;
8. Uncontrolled Type 2 diabetes defined as:

- Hemoglobin A1c ≥9.5% at screening (patients with HbA1c ≥9.5% may be rescreened),
- Insulin dose adjustment >10% within 60 days prior to enrollment,
- Requirement for glucagon-like peptide analogue (unless on a stable dose ≥ 6 months prior to screening) or a complex oral anti-diabetic (OAD) regimen (3 or more OADs) (unless the OAD is stable and HbA1c < 8%), or
- History of severe hypoglycemia (symptomatic hypoglycemia requiring outside assistance to regain normal neurologic status);

   Note: Individual diabetes regimens will be reviewed by Investigator and may be adjusted based on American Diabetes Association guidelines;

9. Use of the following lipid-modifying therapies: fibrates except fenofibrate taken at night for at least 2 weeks prior to randomization and during the study, niacin, proprotein convertase subtilisin/kexin type 9 inhibitors, and bile acid sequestrants. Atorvastatin up to 20 mg and

rosuvastatin up to 10 mg and pravastatin up to 20 mg, on stable dose for at least six weeks prior to randomization (four weeks prior to MRI), are allowed. Other statins are excluded. Stable doses for at least three months prior to randomization of fish oils (omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid), fenofibrate and ezetimibe are allowed;

Note: Very infrequently, given that lipid levels are blinded to investigators and study personnel, where indicated statin and other allowed lipid therapies may be modified or initiated after enrollment in the study. Statin doses may be decreased during the study for tolerability or safety issues. Statin doses should be taken in the evening for at least two weeks prior to randomization and for the duration of the study.

10. Use of obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), high dose vitamin E (>400 IU/day) unless on stable dose of vitamin E >400 IU/day for at least 6 months at the time of liver biopsy, or pioglitazone within 90 days prior to enrollment or since screening biopsy, whichever is longer.
11. Presence of cirrhosis on liver biopsy (stage 4 fibrosis);
12. Platelet count <140,000/mm^3;
13. Clinical evidence of hepatic decompensation which may be:

- Demonstrated by abnormalities such as platelets < 140,000, serum albumin <3.5 g/dL, international normalized ratio >1.3 and/or total bilirubin >1.3 mg/dL; or
- Established by the presence or history of esophageal varices, ascites, or hepatic encephalopathy;

14. Evidence of other forms of chronic liver disease including the following:

- Hepatitis B (HepB) as defined by presence of HepB surface antigen at screening,
- Hepatitis C (HepC) as defined by presence of HepC virus (HCV) antibody (anti-HCV) and HCV ribonucleic acid (RNA). Patients with positive anti-HCV who test negative for HCV RNA at screening will be allowed to participate in the study,
- Evidence of ongoing autoimmune liver disease,
- Primary biliary cirrhosis,
- Primary sclerosing cholangitis,
- Gilbert's syndrome patients if direct bilirubin is elevated (in addition to total bilirubin ≥ 2) or there is evidence of hemolysis contributing to elevated total bilirubin,
- Wilson's disease,
- Homozygous alpha-1-anti-trypsin deficiency,
- History of hemochromatosis or iron overload,
- Drug-induced liver disease,
- Known bile duct obstruction,
- Suspected or proven liver cancer, or

- Any other type of liver disease other than NASH;

15. Serum ALT or AST >5 × ULN;

    Note: Normal male and female ranges are 6 U/L to 41 U/L for ALT and 9 U/L to 34 U/L for AST at [redacted];

16. Inability to safely obtain a liver biopsy;
17. History of biliary diversion;
18. Positive for human immunodeficiency virus (HIV) infection;
19. Active, serious medical disease with likely life expectancy <2 years;
20. History of malignant hypertension;
21. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at screening;

    Note: Retest of blood pressure after establishing good blood pressure control within a reasonable period of time, up to baseline visit, is permissible at the discretion of the Investigator;

22. New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30%;
23. Uncontrolled cardiac arrhythmia, including confirmed QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females at the screening electrocardiogram (ECG) assessment;
24. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to randomization;
25. Active substance abuse, including inhaled or injected drugs, within 1 year prior to screening;
26. Use of any excluded medications listed in Section 5.6.1;
27. Participation in an investigational new drug trial in the 30 days prior to randomization; or
28. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, cardiovascular events such as new onset CHF, new onset or unstable angina or myocardial infarction, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient including

recurrent elevation of liver enzymes upon rechallenge or diagnosis of liver pathology other than NASH as described in Section 9.17;

- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment Visit. The reason for patient withdrawal must be documented in the electronic Case Report Form (eCRF). In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Patients who qualify for study inclusion will be randomized in the Main Study to receive one of two 36-week treatments: MGL-3196 80 mg or placebo given orally once-daily in the morning.

Patients who qualify for the Extension Study will receive MGL-3196. Patients previously on placebo in the Main Study will receive MGL-3196 80 mg at the start of the Extension Study. Patients previously on MGL-3196 will continue on the same MGL-3196 dose of MGL-3196 in the Extension Study that they were on at Week 36 of the main study, with a possible dose adjustment at Week 4 of the extension study as described in Section 8.2.

5.2 Rationale for Dosing

In 2 completed Phase 1 studies, MGL-3196 appeared to be safe and well tolerated at doses up to 200 mg daily for 14 days. No safety concerns were observed during either study. Lipid efficacy data suggested the therapeutic dose to be less than the highest dose of 200 mg, as this dose did not show an improved benefit over lower doses and showed more variability in pharmacokinetic (PK) levels.

5.3 Randomization and Blinding

Patients will be randomized 2:1, 80 mg or placebo treatment groups, using a computer-generated randomization schedule prepared by Medpace, Inc. prior to the start of the study. The number received during randomization will identify the patient throughout the study and will be used in the eCRF.

Patients, the Sponsor, Investigators, and all site personnel involved with dispensing study medication, carrying out study procedures, evaluating patients, entering study data, and/or evaluating study data will be blinded to treatment assignment until database lock. Blinding will be accomplished by the Sponsor providing visually indistinguishable MGL-3196 and placebo. Packaging for MGL-3196 and placebo product will be identical with the exception of a unique bottle identification number on the label.

5.4 Breaking the Blind

Until formal conclusion of the study, patients, Investigators, and all site study personnel will remain blinded as to treatment allocation, except in the event of a medical emergency which necessitates unblinding. In the event of a medical emergency when knowledge of the patient's treatment assignment would influence the patient's clinical care, the Investigator should contact the Medical Monitor to describe the emergency.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The MGL-3196 active drug substance, 2-[3,5-Dichloro-4-95-isopropyl-6-oxo-1,6-dihydro-pyridazin-3-yloxy)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4]triazine-6-carbonitrile, is a white to tan crystalline powder stable for 60 months at 25°C/60% relative humidity and 6 months at 40°C/75% relative humidity.

MGL-3196 consists of MGL-3196 active ingredient, pregelatinized starch (Starch 1500), colloidal silicon dioxide (Cab-O-Sil), and magnesium stearate encapsulated in #2 Swedish-orange hard gelatin capsules. MGL-3196 capsules are made in accordance with ICH and FDA guidelines.

MGL-3196 capsules are packaged in high-density polyethylene plastic bottles with child-resistant closures. MGL-3196 and matching placebo are available as hard gelatin capsules for oral administration in 40 mg and 60 mg strengths. Product labels will be identical except for a unique identifying code and the addition of labels of A and B. Each bottle will contain 32 capsules (64 capsules total).

5.5.2 Study Drug Preparation and Dispensing

Study drug will be bottled and labeled by [redacted] using current Good Manufacturing Practice. Study drug will be assigned by the [redacted] to study sites/patients.

5.5.3 Study Drug Administration

Study drug will be administered at each study visit and will be given in quantities sufficient to reach the next study visit. Each patient will receive study drug bottles labeled as A and B. Patients will take 1 capsule from bottle A and 1 capsule from bottle B at each dosing. Each bottle will contain 32 capsules (64 capsules total), enough for 4 weeks + 4 days of dosing. Adjustments to the dosing may occur as outlined in section 3.1.2 and the Interactive Response Web System will adjust study drug assignments accordingly.

5.5.4 Treatment Compliance

Patients will be assessed for study drug compliance at each visit. At Day 1, patients will receive a study drug journal in which to record study drug compliance. Site staff will record the number of capsules taken from each study drug bottle and record this information in the patient's eCRF. If at any visit the patient is <80% compliant, the patient will be counseled on the importance of compliance to the study regimen. If at the end of study, the patient is <80% compliant over the course of the initial 12-week Treatment Period, the patient will not be included in the Per Protocol Population.

5.5.5 Storage and Accountability

Adequate records on receipt, use, return, loss, or other disposition of medication must be maintained. Other required data includes relevant dates, quantities, unique bottle code, and patient identification for patients who receive study drug. Patients will be instructed to return all unused study medication to the Investigator in the original bottles. At the end of the study, all unused products will be collected and destroyed according to institutional pharmacy policies and procedures. The study drug will be stored according to manufacturing guidelines.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications

Excluded medications include:

- Triiodothyronine (liothyronine [Cytomel®]);
- Thyroxine (excluded at time of randomization), and very infrequently used during the study, in that thyroxine therapy may be initiated in patients who become clinically hypothyroid during the study as described in exclusion criteria #5;

  Note: Patients who discontinue thyroxine ≥2 months prior to randomization may be included in the study, as described, during the study thyroxine therapy may be initiated;
- Obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), high dose vitamin E (>400 IU/day) except as permitted in exclusion criteria #10, or pioglitazone within 90 days prior to enrollment or since screening biopsy, whichever is longer;
- Use of the following lipid-modifying therapies: fibrates except for fenofibrate taken at night for at least 2 weeks prior to randomization and during the study, niacin, proprotein convertase subtilisin/kexin type 9 inhibitors, bile acid sequestrants, and statins except as permitted in the exclusion criteria #9;
- Major inhibitors of organic anion-transporting polypeptide transporters such as gemfibrozil, cyclosporine A, or protease inhibitors;
- Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) Drugs with known liver toxicity;
- Repaglinide or a glitazone such as rosiglitazone (substrates of cytochrome P_{450} 2C8 [CYP2C8] or gemfibrozil [inhibitor of CYP2C8]);
- Chronic use of oral corticosteroids unless discontinued 3 months before screening. Addition of oral corticosteroids during the study except short term low dose < 1 week taper is not allowed. This exclusion does not include topical corticosteroids, or corticosteroid injections in muscle or joint;
- Warfarin treatment; and
- Any medications with the potential to affect thyroid hormone production and/or that may interfere with thyroid function including but not limited to methimazole, PTU, tyrosine kinase inhibitors, iodide, and glucocorticoids. Unless, for example, in the case of lithium, the medication is stably dosed and thyroid hormone levels are normal.

5.6.2 Documentation of Prior and Concomitant Medication Use

All concomitant medications must be recorded in the eCRF. Any prior medication received within 30 days of the first dose of study drug will be recorded in the eCRF. Concomitant treatments that are required to manage a patient's medical condition during the trial will also be recorded in the eCRF.

6 STUDY PROCEDURES

6.1 Informed Consent

Informed consent will be obtained at the Screening Visit (Week -6 to Week 0) of the Main Study. For patients eligible to participate in the Extension Study, obtain informed consent prior to any Extension Study Day 1 procedures.

6.2 Screening Period (Week -6 to Week 0)

The following procedures will be performed at the Screening Visit (Week -6 to Week 0):

- Determine eligibility, including assessment of ALT and AST consistency;
- Review of medical history, including substance abuse;
- Obtain informed consent;
- Collect demographic information;
- Perform 12-lead ECG;
- Perform complete physical examination;
- Collect blood sample for:
  - HepB, HepC, and HIV;
  - Hematology, fasting chemistry, fasting lipid parameters, and fasting metabolic profiles (see Appendix C for a full list of analytes to be measured);

    Note: Must have a documented historical (3 weeks to 6 months prior to the study entry) ALT and AST levels consistent with the screening ALT and AST values. Patients who do not have historical ALT and AST evaluations available may have their ALT and AST repeated during the screening period [both assessments need to be ≥3 weeks apart]);
  - Thyroid axis hormones;
  - Activated partial prothrombin time (APTT), prothrombin time (PT), and international normalized ratio (INR); and
  - Serum pregnancy test (for women of child bearing potential only);
- Collect urine sample for urinalysis;
- Collect vital signs and anthropometrics;
- Provide diet and lifestyle counseling;
- Perform MRI-PDFF;
- Perform liver biopsy only in the event that the patient does not have an available liver biopsy within 180 days of randomization, passes pre-screening procedures, and has a passing MRI-PDFF; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.3 Randomization

Patients will be randomized at the Baseline Visit (Day 1).

6.4 Main Study Treatment Period – Day 1 to Week 38

Following randomization to study medication, patients will return for visits and procedures within ±3 days of the scheduled time except where noted.

Prior to each visit, patients should fast for at least 10 hours.

If a patient requires close clinical monitoring, the patient may be asked to return to the study site for additional visits or laboratory assessments (see Section 9.17).

6.4.1 Baseline Visit (Day1)

The following procedures will be performed at the Baseline Visit (Day 1):

- Determine eligibility;
- Randomize patients;
- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug;
- Collect blood sample for:
  - Hematology, fasting chemistry, fasting metabolic profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - Thyroid axis hormones;
  - Total and free (calculated) testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol;
  - CK-MB, troponin I, Sex hormone binding globulin (SHBG);
  - Alkaline phosphatase (ALP) isoenzymes;
  - CK-18, FIB-4, and ELF;
  - PK sampling (pre-dose);
  - hsCRP;
  - Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
  - Type 1 procollagen N-terminal propeptide and C-terminal telopeptide (CTX);
  - APTT, PT, INR; and
  - Genomic sample;
  - Bile acid levels;

- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Collet vital signs and anthropometrics;
- Perform dual-energy x-ray absorptiometry (DXA) scan;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.2 Week 2 (Day 14)

The following procedures will be performed at Week 2:

- Arrive at the study site, pre-dose after overnight fasting;
- Perform 12-lead ECG pre-dose and at 5 hours post dose;
- Collect vital signs and anthropometrics;
- Collect pre-dose blood sample for:
  - Hematology, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - Pre-dose PK sampling;
  - APTT, PT, INR; and
  - Thyroid axis hormones;
  - Bile acid levels;
- Administer study drug dose;
- Collect blood for PK samples at 2, 4, 6, 8 h post dose administered in clinic;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Consume a low-fat meal at 1 hour post dose and at 4 hours post dose after the 4 hour PK sample collection;
- Perform symptom-directed physical examination;
- Assess study drug accountability;
- Provide diet and lifestyle counseling; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.3 Week 4 (Day 28)

The following procedures will be performed at Week 4:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - PK sample (pre-dose);
  - APTT, PT, INR;
  - hsCRP; and
  - Thyroid axis hormones;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.4 Week 8 (Day 56)

The following procedures will be performed at Week 8:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - PK sample (pre-dose);
  - APTT, PT, INR; and
  - Thyroid axis hormones;

- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.5 Week 12 (Day 84)

The following procedures will be performed at Week 12:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, fasting metabolic panel, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - Total testosterone, LH, FSH, and estradiol;
  - CK-MB, troponin I, SHBG;
  - ALP isoenzymes;
  - CK-18, FIB-4, and ELF;
  - hsCRP;
  - Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
  - Type 1 procollagen N-terminal propeptide and C-terminal telopeptide;
  - APTT, PT, INR; and
  - Thyroid axis hormones;
  - Bile acid levels;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment;
- Perform MRI-PDFF; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.6 Week 16 (Day 112)

The following procedures will be performed at Week 16:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - PK sampling (pre-dose);
  - APTT, PT, INR; and
  - Thyroid axis hormones;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.7 Week 20 (Day 140)

The following procedures will be performed at Week 20:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - APTT, PT, INR; and
  - Thyroid axis hormones;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.8 Week 24 (Day 168)

The following procedures will be performed at Week 24:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - PK sampling (pre-dose);
  - APTT, PT, INR;
  - hsCRP; and
  - Thyroid axis hormones;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.4.9 Week 30 (Day 210)

The following procedures will be performed at Week 30:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - APTT, PT, INR; and
  - Thyroid axis hormones;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling; and

- Review alcohol consumption, concomitant medications, and adverse events.

6.4.10 Week 36 (Day 252)

The following procedures will be performed at Week 36:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, fasting metabolic panel, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - Total and free (calculated) testosterone, LH, FSH, and estradiol;
  - CK-MB, troponin I, SHBG;
  - PK sampling (pre-dose);
  - ALP isoenzymes;
  - CK-18, FIB-4, and ELF;
  - Type 1 procollagen N-terminal propeptide and CTX;
  - Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
  - APTT, PT, INR;
  - hsCRP; and
  - Thyroid axis hormones;
  - Bile acid levels;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Perform liver biopsy (-10 days to + 3 days of the visit date);
- Perform DXA scan;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment;
- Perform MRI-PDFF (within 10 days prior to the visit date while still on treatment); and
- Review alcohol consumption, concomitant medications, and adverse events.

6.5 Follow-Up Visit (Week 38 [Day 266])

The following procedures will be performed at the Follow-Up Visit (Week 38):

- Collect blood sample for:
  - Hematology, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, Total testosterone, LH, FSH, estradiol, and SHBG;
  - ALP isoenzymes;
  - APTT, PT, INR; and
  - Thyroid axis hormones; and
- Review concomitant medications and adverse events.

6.6 Early Termination Visit and Withdrawal Procedures

Patients who are withdrawn from either the M**ain** Study or Extension Study prior to completion will return to the study site for the Early Termination Visit. The following Early Termination procedures will be completed:

Note: Completion of some procedures may depend on the guidance and discretion of the Investigators, Medical Monitors, and Sponsor taking into account factors such as why and when the patient terminated early.

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, fasting metabolic panel, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - Total and free (calculated) testosterone, LH, FSH, and estradiol;
  - CK-MB, troponin I, SHBG;
  - PK sampling (pre-dose);
  - ALP isoenzymes;
  - CK-18, FIB-4, and ELF;
  - Type 1 procollagen N-terminal propeptide and CTX;
  - Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
  - APTT, PT, INR;
  - hsCRP; and
  - Thyroid axis hormones;
  - Bile acid levels;

- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Perform liver biopsy (Main Study only);
- Perform DXA scan;
- Perform Fibroscan (if available);
- Complete HR-QoL SF-36 assessment;
- Perform MRI-PDFF; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7 Extension Study

For patients that are eligible to participate in the extension phase of the study and sign the informed consent for the extension, the following visits and procedures will be within ±3 days of the scheduled time except where noted.

Prior to each visit, patients should fast for at least 10 hours.

If a patient requires close clinical monitoring, the patient may be asked to return to the study site for additional visits or laboratory assessments (see Section 9.17).

6.7.1 Extension Study Day 1 (Extension Day1)

The Extension Study Day 1 visit should occur within 60 days inclusive of the Main Study Week 36 Visit and may occur concurrently with the Main Study Week 38 Follow-up Visit. The Extension Study Informed Consent Form must be signed prior to any Extension Study-related procedures.

The following procedures will be performed at the Extension Study Day 1 Visit:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Collect blood sample for:
  - Hematology, fasting chemistry, fasting metabolic profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - Thyroid axis hormones;
  - PK sampling (pre-dose);
  - APTT, PT, INR;
  - Total and free (calculated) testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol;
  - CK-MB, troponin I, Sex hormone binding globulin (SHBG);
  - Alkaline phosphatase (ALP) isoenzymes;

  - CK-18, FIB-4, and ELF;
  - hsCRP;
  - Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
  - Type 1 procollagen N-terminal propeptide and C-terminal telopeptide (CTX);
  - Bile acid levels;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Collect vital signs and anthropometrics;
- Dispense study drug;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7.2 Extension Study Week 2 (Extension Day 14)

The following procedures will be performed at Week 2 of the Extension Study:

- Arrive at the study site, pre-dose after overnight fasting;
- Perform 12-lead ECG pre-dose;
- Collect vital signs and anthropometrics;
- Collect pre-dose blood sample for:
  - Hematology, fasting chemistry, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - PK;
  - APTT, PT, INR;
  - Thyroid axis hormones;
  - Bile acid levels;
- Administer study drug dose;
- Consume a low-fat meal at 1 hour post dose;
- Collect blood for a PK sample at 4 h post dose;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Perform symptom-directed physical examination;
- Assess study drug accountability;

- Provide diet and lifestyle counseling; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7.3 Extension Study Weeks 4, 8, 16, 20, 28, and 32

The following procedures will be performed at Week 4, 8, 16, 20, 28, and 32 of the Extension Study:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Dispense study drug and assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect pre-dose blood sample for:
  - Hematology, fasting chemistry, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - PK (Weeks 4, 8, and 16);
  - APTT, PT, INR;
  - hsCRP (Week 4 only);
  - Thyroid axis hormones;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment (Week 4); and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7.4 Extension Study Week 12 (Extension Day 84)

The following procedures will be performed at Week 12 of the Extension Study:

- MRI-PDFF;
- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Collect vital signs and anthropometrics;
- Collect pre-dose blood sample for:
  - Hematology, fasting chemistry, fasting metabolic profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;

- Bile Acids;
- ALP isoenzymes;
- APTT, PT, INR;
- hsCRP;
- Thyroid axis hormones;
- Total and free (calculated) testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol;
- CK-18, FIB-4, and ELF;
- Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
- Type 1 procollagen N-terminal propeptide and C-terminal telopeptide (CTX);

- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Dispense study drug and assess study drug accountability;
- Administer study drug dose;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7.5 Extension Study Week 24 (Extension Day 168)

The following procedures will be performed at Week 24 of the Extension Study:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Collect blood sample for:
  - Hematology, fasting chemistry, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, SHBG;
  - Thyroid axis hormones;
  - PK;
  - APTT, PT, INR;
  - hsCRP
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Collect vital signs and anthropometrics;

- Dispense study drug and assess study drug accountability;
- Administer study drug dose;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment; and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7.6 Extension Study Week 36 (Extension Day 252)

The following procedures will be performed at Week 36 of the Extension Study:

- Perform 12-lead ECG;
- Perform symptom-directed physical examination;
- Assess study drug accountability;
- Collect vital signs and anthropometrics;
- Collect blood sample for:
  - Hematology profiles, fasting chemistry profiles, fasting metabolic panel, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - Total and free (calculated) testosterone, LH, FSH, and estradiol;
  - CK-MB, troponin I, SHBG;
  - PK sampling (pre-dose);
  - ALP isoenzymes;
  - CK-18, FIB-4, and ELF;
  - Type 1 procollagen N-terminal propeptide and CTX;
  - Fibrinogen, haptoglobin, alpha-2 macroglobulin, proBNP, apolipoprotein C-III, and ferritin;
  - APTT, PT, INR;
  - hsCRP;
  - Thyroid axis hormones;
  - Bile acid levels;
- Collect urine sample for pregnancy test (for women of child bearing potential only) and urinalysis;
- Perform DXA scan;
- Provide diet and lifestyle counseling;
- Complete HR-QoL SF-36 assessment;
- Perform Fibroscan (if available);

- Perform MRI-PDFF (within 10 days prior to the visit date while still on treatment); and
- Review alcohol consumption, concomitant medications, and adverse events.

6.7.7 Extension Study Week 38 Follow-up Visit (Extension Day 266)

The following procedures will be performed at the Extension Study Follow-Up Visit (Week 38):

- Collect blood sample for:
  - Hematology, fasting chemistry profiles, and fasting lipid parameters (see Appendix C for a full list of analytes to be measured);
  - CK-MB, troponin I, Total and free (calculated) testosterone, LH, FSH, estradiol, and SHBG;
  - ALP isoenzymes;
  - APTT, PT, INR;
  - Thyroid axis hormones; and
- Review concomitant medications and adverse events.

6.7.8 Extension Study Early Termination Visit

See Section 6.6.

7 EFFICACY ASSESSMENTS

The primary efficacy variable is percent change in hepatic fat fraction by MRI-PDFF from baseline at 12 weeks for MGL-3196 80 mg versus placebo.

The secondary efficacy variables include the following:

- The number and percentage of patients achieving a 2-point reduction in NAS at 36 weeks for MGL-3196 80 mg versus placebo;
- The number and percentage of patients achieving resolution of NASH (ballooning = 0; inflammation = 0 to 1) at 36 weeks for MGL-3196 80 mg versus placebo;
- The number and percentage of patients achieving a reduction in any individual component of NASH (hepatocellular steatosis, ballooning, fibrosis, or lobular inflammation) at 36 weeks for MGL-3196 80 mg versus placebo;
- The change in thyroid axis hormones from baseline at 12 and 36 weeks for MGL-3196 80 mg versus placebo;
- The percent change in hepatic fat fraction by MRI-PDFF from baseline at 36 weeks for MGL-3196 80 mg versus placebo;
- The change in hepatic fat fraction by MRI-PDFF from baseline at 12 and 36 weeks for MGL-3196 80 mg versus placebo; and
- The change in hsCRP, ALT, AST, LDL-C, HDL-C, non-HDL-C, total cholesterol, triglycerides, ApoB, Lp(a), CK-18, FIB-4, and ELF test from baseline at 12 and 36 weeks for MGL-3196 80 mg versus placebo.

The other efficacy variables include the following:

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

8 PHARMACOKINETIC ASSESSMENTS

8.1 Main Study

Blood samples for PK assessments will be obtained pre-dose from patients at the Baseline Visit (Day 1), Weeks 2, 4, 8, 16, 24, and 36, and the Early Termination Visit. Patients will be instructed not to take study drug prior to PK sampling at these respective study weeks.

At Week 2 visit, PK assessments will be made in the clinic after over-night fast at pre-dose. An 80 mg dose of MGL-3196 or placebo will be administered and PK assessments will be made at 2, 4, 6, and 8 hours post dose. Total AUC_{inf} will be calculated for MGL-3196 and MGL-3196-M1 based on Week 2 $AUC_{(0-8)}$, exposure at 8 h and historic geometric mean elimination rate constant for MGL-3196 and MGL-3196-M1 at the 80 mg dose. Modeling based on historic data obtained for the 80 and 100 mg doses indicate that, using this approach, AUC_{actual} ($AUC_{(0-24)}$) is estimated within 1.8%, SD 5.4% for MGL-3196 given at a dose of 80 mg and is slightly over estimated for MGL-3196-M1 AUC by 5.7% SD 8.5% at a dose of 80 mg. Similar results were obtained for a 100 mg dose. Dose adjustment will be made to 60 mg once per day for any patients whose combined estimated MGL-3196 and MGL-3196-M1 ($AUC_{(0-24)}$) at 2 weeks on the 80 mg dose exceeds 5500 ng*hr/ml. All subjects previously dosed at 50 mg MGL-3196 had combined MGL-3196 plus MGL-3196-M1 less than 5500 ng*hr/ml, geo mean= 3400 ng*hr/ml. Notably, the trough pre-dose drug levels obtained at 50 -100 mg in the MAD study are also predictive of subjects' relative AUCs at a given dose. For patients whose combined estimated $AUC_{(0-24)}$ at 2 weeks at the 80 mg dose is >11,000 ng*hr/ml plus SHBG>150% increased from baseline, the dose will be decreased to 40 mg at the 4 Week visit (or later per Synopsis), because, even given the greater than dose proportionate increase in exposure between a 60 and 80 mg dose, the exposure at 60 mg may be ≥5500 ng*hr/ml.

For patients whose combined estimated $AUC_{(0-24)}$ at 2 weeks at the 80 mg dose is ≤ 3000 ng*hr/ml the dose will be increased to 100 mg at the 4 Week visit, as based on a conservative estimates, the predicted exposure at 100 mg will be significantly ≤ 5500 ng*hr/ml. This prediction is based on data obtained in healthy volunteers in which there is greater than dose proportionate increase in MGL-3196 between 80 and 100 mg daily doses, and less than dose proportionate increases in MGL-3196-M1 between 80 and 100 mg doses. Pharmacokinetic data (blinded to patient ID) obtained from the first 21 patients randomized to MGL-3196 suggest that there are no clear differences in MGL-3196 or MGL-3196-M1 exposure at the 80-mg dose between healthy volunteers and NASH patients enrolled in this study.

For the patients who are relatively early in the Main Study (at week 24 or earlier), if their current dose is 100 mg, their Main Study Week 2 predose MGL-3196 PK value < 5 ng/mL and their Main Study Week 2 AUC ≤ 2500 ng*hr/mL, then their dose will be increased to 120 mg during the Main study and continued on 120 mg if they meet eligibility criteria for the extension study.

8.2 Extension Study

For patients participating in the extension phase of the study, PK assessments will be made at Extension Study Day 1 predose and at the Extension Study Week 2 visit at predose and 4 hours post dose.

All former placebo patients in the Main Study will be randomized to receive 80 mg dose of MGL-3196 for 4 weeks. All patients will have a PK assessment predose and 4 hours postdose at Extension Study Week 2.

Extension Study Dosing Action for Former Main Study Placebo Patients

Extension Study Week 2 MGL-3196 Concentration		**Extension Study**	**Extension Study**
Predose	**4 h post dose**	**Week 2 SHBG**	**Week 4 Action**
>35 ng/ml	>1350 ng/ml	>125% CFB*	Downtitrate to 40 mg
Patients not meeting criteria for 40, 80, 100 or 120 mg			Downtitrate to 60 mg
<15 ng/ml	< 600 ng/ml	No rule	Remain on 80 mg or increase (see next rows)
<5 ng/ml	≤ 350 ng/ml	No rule	Increase to 100 mg
<2 ng/ml	≤ 150 ng/ml	No rule	Increase to 120 mg

*Change From Baseline, where baseline is Extension Study Day 1

Extension Study Dosing Action for Former Main Study MGL-3196 Treated Patients

Any Main Study patient assigned to MGL-3196 and continuing in the Extension Study will continue on the same dose when starting Extension Study. For patients on 60 or 40 mg, they will continue on the dose unchanged. For patients taking 80 or 100 mg there may be an increase in dose if criteria as described in the table below are met.

Current dose	**Main Study Week 2 PK (AUC, combined MGL-3196 plus M1 on 80 mg dose)**	**Main Study Predose at Week 2**	**Action in Extension Study**
40-60 mg			No change
80 mg	< 3500 ng*hr/ml	< 5 ng/ml	Increase to 100 mg/day
100 mg	≤ 2500 ng*hr/ml	< 5 ng/ml	Increase to 120 mg
120 mg			No change

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning at the Screening Visit, investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

9.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

9.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

9.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes/no.

9.1.3.1 Assessment of severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

9.1.3.2 Causality assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drugs-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drug-
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
    - Note: An adverse event or adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death;
- Requires hospitalization or prolongation of existing hospitalizations;
    - Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations;
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Serious Adverse Event Reporting − Procedures for Investigators

9.3.1.1 Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to [redacted] within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] or call the [redacted] SAE hotline (phone number listed below), and fax the completed paper SAE form to [redacted] (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

9.3.1.2 Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.4 Pregnancy Reporting

If a patient or female partner of a male patient becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to [redacted] within 24 hours of being notified. [redacted] will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and Early Termination study procedures will be performed.

The patient or female partner of a male patient should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify [redacted]. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, and in any case no later than 7 days after knowledge by the Sponsor of such a case; and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

9.6 Informed Consent

All patients will be informed of the nature and purpose of the study. Patients will sign informed consent at the Screening Visit (Week -6 to 0), prior to any study procedures being performed.

For patients participating in the extension phase of the study, an informed consent for the Extension Study must be signed prior to any Extension Study-related procedures being performed.

9.7 Demographic Information

Demographic information including day, month, and year of birth; race; ethnicity; and gender will be collected at the Screening Visit (Week -6 to 0).

9.8 Clinical Laboratory Evaluations

All standard blood and urine tests will be performed by a central laboratory. For the purposes of this study, fasting will be defined as nothing by mouth except water for 10 hours. If the patient is not fasting, the Investigator will reschedule the visit as soon as possible but no later than 3 days. Laboratory certification (including expiration date) and normal reference ranges for all laboratories used during the study will be on file with [redacted] prior to study initiation. For a complete list of laboratory assessments that will be performed, see Appendix C. For blood sampling procedures, including information on blood volume, collection tubes, sample processing, storage, and shipping, see the Laboratory Manual for this study.

The Investigator must review and sign all laboratory test reports. The Investigator will be notified if laboratory values are outside of normal range and notified of alert values. In this case, the Investigator will be required to conduct clinically appropriate follow-up procedures.

The following analytes will be measured at the Screening Visit (Week -6 to 0), Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36 and 38, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 38, and the Extension Study Early Termination Visit:

- Chemistry – ALP, ALT, amylase, AST, blood urea nitrogen, calcium, carbon dioxide, chloride, creatine kinase, creatinine, direct bilirubin, eGFR (derived from creatinine), [redacted] lactate dehydrogenase, lipase, magnesium, phosphate, potassium, serum albumin, sodium, total bilirubin, total protein, and uric acid; and
- Hematology – hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration, red blood cell morphology, % differentials, and absolute differentials.

The following urinalysis analytes will be measured at the Screening Visit (Week -6 to 0), Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 38, and the Extension Study Early Termination Visit: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrate, urobilinogen, and leukocyte esterase.

Hepatitis B, HepC, and HIV will be measured at the Screening Visit (Week -6 to 0).

Total testosterone, LH, FSH, and estradiol will be measured at the Baseline Visit (Day 1), Main Study Weeks 12, 36, and 38 (Follow-Up Visit), and the Early Termination Visit, and Extension Study Day 1, Weeks 12, 36, and 38 (Follow-Up Visit). Free testosterone to be calculated from

total testosterone, SHBG, and serum albumin for the Baseline Visit (Day 1), Week 12, Week 36, the Follow-Up Visit (Week 38), and the Early Termination Visit.

Sex hormone binding globulin will be measured at the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, the Follow-Up Visit (Week 38), and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 38, and the Extension Study Early Termination Visit.

Alkaline phosphatase isoenzymes will be measured at the Baseline Visit (Day 1), Main Study Weeks 12, 36, and 38 (Follow-Up Visit), and the Early Termination Visit, and Extension Study Day 1, Weeks 12, 36, and 38 (Follow-Up Visit).

CKMB and troponin I will be measured at the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, the Follow-Up Visit (Week 38), and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 38, and the Extension Study Early Termination Visit.

Bile acids will be measured at Baseline Visit (Day 1), Main Study Weeks 2, 12, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 12, and 36, and the Extension Study Early Termination Visit.

Urine pregnancy tests will be administered for women of child bearing potential only at the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit. Serum pregnancy tests will be administered at the Screening Visit (Week -6 to 0) for women of child bearing potential only.

Thyroid axis hormones (T4, FT4, total T3, free T3 [FT3], and TSH) will be measured at the Screening Visit (Week -6 to 0), the Baseline Visit (Day 1), Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, the Follow-Up Visit (Week 38), and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit. Anti-thyroid peroxidase antibodies will be measured at the Baseline Visit (Day 1). Thyroxine-binding globulin will be measured at the Baseline Visit (Day 1), Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, the Follow Up Visit (Week 38), and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit if necessary. Reverse T3 will be measured at the Baseline Visit (Day 1), Week 12, Week 36 and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 12, and 36, and the Extension Study Early Termination Visit.

A fasting metabolic panel ([redacted]) will be measured at the Screening Visit (Weeks -6 to 0), the Baseline Visit (Day 1), Week 12, Week 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 12 and 36, and the Extension Study Early Termination Visit if necessary. [redacted] will be measured at the Baseline Visit (Day 1), Week 12, Week 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 12 and 36, and the Extension Study Early Termination Visit.

Fasting lipid parameters (triglyceride, total cholesterol, LDL-C (direct and calculated), HDL-C, and non-HDL-C) will be collected at the Screening Visit (Weeks -6 to 0), the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, the Follow-Up Visit (Week 38), and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks, 2, 4, 8, 12, 16, 20,

24, 28, 32, and 36 and the Extension Study Early Termination Visit. ApoB, Apo A1 and Lp(a) particles will be collected at the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, the Follow-Up Visit (Week 38), and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit.

Cytokeratin-18, FIB-4, ELF, fibrinogen, haptoglobin, alpha-2 macroglobulin, N-terminal pro b-type natriuretic peptide, apolipoprotein C-III, and ferritin will be measured at the Baseline Visit (Day 1), Week 12, Week 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 12 and 36, and the Extension Study Early Termination Visit.

High-sensitivity C-reactive protein will be measured at the Baseline Visit (Day 1), Weeks 4, 12, 24, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 4, 12, 24, and 36, and the Extension Study Early Termination Visit.

Bone biomarkers Type 1 procollagen N-terminal propeptide and CTX will be measured at the Baseline Visit (Day 1), Main Study Weeks 12 and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 12 and 36, and the Extension Study Early Termination Visit.

Pre-dose PK samples will be drawn at baseline (Day 1), Main Study Weeks 2, 8, 16, 24, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 16, 24, and 36, and the Extension Study Early Termination Visit. In addition, postdose PK samples will be collected at Main Study Week 2 as described in 6.4.2 and the Extension Study Week 2 as described in 6.7.2.

Coagulation markers (APTT, PT, and INR) will be measured at the Screening Visit (Week -6 to 0), the Baseline Visit (Day 1), Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, at the Follow-Up Visit (Week 38), and at the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit.

Genomic samples will be drawn at the Baseline Visit (Day 1).

9.9 Vital Signs and Anthropometrics

Vital signs and anthropometrics (weight, BMI, waist circumference, waist-hip ratio, temperature, pulse [resting], respiratory rate, and seated blood pressure [resting]) will be measured at the Screening Visit (Week -6 to 0), the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit.

Blood pressure will be measured using a standardized process:

- Patient will sit for 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Site staff will use of a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Site staff will record the arm used for measurement and use the same arm throughout the study; and
- Site staff will measure and record the blood pressure.

Blood pressure will be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on the automatic device. A blood pressure reading will be repeated 1 to 2 minutes later, and the second reading will also be recorded to the nearest 2 mmHg mark.

9.10 Electrocardiograms

Twelve-lead ECGs with rhythm strip will be performed at the Screening Visit (Week -6 to 0), the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit. Twelve-lead ECGs will be performed in triplicate in a consecutive manner after the patient has been resting in the supine position for at least 10 minutes. The ECG will include 12 standard leads and will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be recorded:

- PR interval,
- QRS interval,
- Heart rate,
- RR interval,
- QT interval,
- QTcB interval, and
- QTcF interval.

All ECGs must be evaluated by a qualified reader for the presence of abnormalities.

9.11 Physical Examinations

A complete physical examination will include documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments. A complete physical examination will be performed at the Screening Visit (Week -6 to 0), and a symptom-directed physical examination will be completed at the Baseline Visit (Day 1), Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 and the Extension Study Early Termination Visit.

9.12 Diet and Lifestyle Counseling

Patients will be counseled on maintaining a consistent diet, exercise regimen, and lifestyle at the Screening Visit (Week -6 to 0), Baseline Visit (Day 1), and Main Study Weeks 2, 4, 8, 12, 16, 20, 24, 30, and 36, and Extension Study Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36.

9.13 Health-Related Assessment-Quality of Life

Patients will undergo a HR-QoL SF-36 assessment at the Baseline Visit (Day 1), Weeks 4, 12, 24, and 36, and the Early Termination Visit, and Extension Study Day 1, Extension Study Weeks 4, 12, 24, and 36 and the Extension Study Early Termination Visit.

9.14 Proton Density Fat Fraction Magnetic Resonance Imaging

Patients will undergo MRI-PDFF at the Screening Visit (Week -6 to 0), Main Study Weeks 12 and 36, and the Early Termination Visit, and Extension Study Weeks 12 and 36 and the Extension Study Early Termination Visit. The Screening Visit MRI-PDFF will be used as baseline and should be obtained as close to randomization as possible. The MRI-PDFFs will be read by a central reader.

9.15 Liver Biopsy

Patients will undergo liver biopsy at the Screening Visit (Week -6 to 0) only in the event that the patient does not have available liver biopsy within 180 days of randomization. If a historical biopsy is to be used, patients must have had no change in metabolic status (diabetes, lipid metabolism, and/or >5% weight gain or loss) or change in diabetes medications. If a historical biopsy is not available, patients must have confirmation of ≥10% liver fat content on MRI-PDFF prior to undergoing liver biopsy. However, if, in the opinion of the patient's physician, the patient would benefit from and be advised to obtain a liver biopsy, the patient may undergo liver biopsy prior to MRI-PDFF. All patients will undergo liver biopsy at Week 36. Patients may undergo liver biopsy at the Early Termination Visit based on the discretion of the Investigator. Liver biopsies will be read by 1 central reader. Reading will include assessment of fibrosis stage, portal inflammation, and NAS.

9.16 Dual-Energy X-Ray Absorptiometry

Patients will undergo DXA scan to assess bone mineral density at the Baseline Visit (Day 1), Main Study Week 36, and the Early Termination Visit, and Extension Study Week 36 and the Extension Study Early Termination Visit.

9.17 Drug Induced Liver Injury Monitoring

Close clinical monitoring must be applied to the following:

- Any patient who had normal baseline ALT, AST, and total bilirubin values and then experienced a newly treatment-emergent ALT and/or AST value >3 × ULN OR total bilirubin value >2 × ULN; or
- Any patient who had elevated ALT, AST, or total bilirubin values at baseline and then experienced a 2-fold increase above the baseline ALT and/or AST values AND/OR a 1.5-fold increase above the baseline total bilirubin values.

The patient must return to the study site within 48 to 72 hours for a confirmatory evaluation and central laboratory testing. Repeat laboratory analyses must include the following chemistries: ALP, ALT, AST, total and direct bilirubin, INR and lactate dehydrogenase. At the same time repeat samples are drawn, a PK sample must be taken.

Close monitoring of study patients includes:

- Repeating liver enzyme and serum bilirubin tests at least once a week if abnormalities stabilize and the patient is asymptomatic;
- Obtaining a more detailed history of symptoms and prior or concomitant diseases;

- Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets;
- Ruling out acute viral hepatitis Types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease;
- Obtaining a history of exposure to environmental chemical agents;
- Considering gastroenterology or hepatology consultation; and
- Reporting to the Sponsor and Medical Monitor within 48 hours.

If close monitoring is not possible, study drug should be discontinued. If a patient lives in a remote area, they can be tested locally and the results communicated to the investigator site promptly.

Study drug must be discontinued if any of the following criteria are met:

- For patients with ALT and/or AST values ≤1.5 × ULN at baseline:
  - Post-baseline ALT or AST value is >5 × ULN, or
  - Post-baseline ALT or AST value is >3 × ULN and total bilirubin is >2 × ULN or INR is >1.5;
- For patients with ALT and/or AST values >1.5 × ULN at baseline:
  - Post-baseline ALT or AST value is >3 × the baseline value and at least 5 × ULN, or
  - Post-baseline ALT or AST value is >2 × the baseline value and is accompanied by a concomitant total bilirubin increase to >2 × the baseline value or the INR concomitantly increases by >0.2.

Study drug will be discontinued for any patient with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) and 1 of the following:

- Had normal baseline ALT and AST values and then experienced a >3 × ULN post-baseline increase; or
- Had elevated ALT and/or AST levels at baseline and then experienced a 2-fold post-baseline increase.

Study drug may be resumed once the toxicity returns to below the values prompting discontinuation. If total bilirubin, ALT, or AST elevation recurs following rechallenge with study drug, then study drug must be permanently discontinued and the patient managed according to local practice.

If acute viral hepatitis is diagnosed while the patient is on the study, study drug must be discontinued immediately and the necessary Early Termination Visit assessments will be performed (see Section 6.6).

9.18 Cardiovascular Monitoring

Patients will be closely monitored for signs of cardiac toxicity including assessments of CV AEs and symptoms.

If any of the following abnormalities are identified, an additional clinical investigation may be appropriate:

- Onset of new (i.e., not present at baseline or documented in the medical history) and clinically significant arrhythmia which is persistent (ie, confirmed on repeat assessment on a second visit), including but not limited to:
    - Sinus tachycardia (defined for the study as a HR ≥ 100 beat/min and at least a 20 bpm increase from baseline)
    - Frequent ventricular premature contractions or atrial fibrillation
- Systolic hypertension (defined for the study as a SBP >160 mmHg and at least a 20 mmHg increase from baseline)
- Increase in troponin I vs. baseline and above the ULN.

Except in cases requiring immediate action for subject protection, the Investigator should consult with the Medical Monitor on how to best further determine rate/rhythm or blood pressure changes, in light of the known day to day variability in these physiological variables. The additional investigation may include the patient return to the study site within 72 hours for a confirmatory evaluation and repeat assessment. In this case, Sponsor and Medical Monitor should be notified within 48 h of the event. At the same time repeat lab samples are drawn, a PK sample may also be collected as deemed appropriate by Investigator and medical monitor.

Confirmatory evaluations may include:

- Obtaining a more detailed history of symptoms and prior or concomitant diseases;
- Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, changes in activity, and special diets;
- Ruling out acute cardiovascular conditions, such as acute coronary syndrome, myocarditis, or acute aortic syndrome.
- Repeating ECG, troponin and CK-MB tests on at least one further occasion if abnormalities stabilize and the patient is asymptomatic;
- Considering requesting a cardiology consultation
- If immediate dose reduction or dose discontinuation is not required for concerns of subject safety, then at the Investigator's discretion more complete documentation may be obtained via, e.g. Holter monitoring or 24h Ambulatory Blood Pressure Monitoring before deciding to discontinue the subject.

If close monitoring is not possible, study drug should be discontinued temporarily, pending further evaluation by the Investigator in collaboration with the Medical Monitor and Sponsor. If a patient lives in a remote area, they can be tested locally and the results communicated to the investigator site promptly.

Study drug must be temporarily discontinued if the above abnormalities are confirmed. Frequency of subsequent repeat assessments will be determined by Sponsor and Medical Monitor.

Study drug may be resumed once abnormal results return to the normal range or to the patient's baseline values.

Study drug must be permanently discontinued if any of the following criteria are met:

1. A definite new cardiovascular diagnosis is confirmed that is considered to be probably related to study drug.
2. Abnormalities in symptoms, ECG, or laboratory biomarkers recur following re-introduction of study drug.
3. Abnormalities in symptoms, ECG, or laboratory biomarkers do not return to normal or baseline values.

The required Early Termination Visit assessments will be performed (see Section 6.6).

10 STATISTICS

10.1 Analysis Populations

The Intent-to-Treat (ITT) Population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT Population will be used for all efficacy analyses.

The Per Protocol Population will include all ITT patients who finish the Week 12 visit with valid MRI-PDFF measurements and do not have any major protocol deviations. Patients who are <80% compliant over the course of the initial 12-week Treatment Period will not be included in the Per Protocol Population.

The Safety Population will include all patients who are randomized in the study and receive at least 1 dose of study drug and will be used for all safety analyses.

Demographics, disposition, and study populations will be summarized descriptively.

10.2 Statistical Methods

10.2.1 Analysis of Efficacy

10.2.1.1 Primary efficacy analysis

The primary efficacy variable will be the percent change in MRI-PDFF from baseline to Week 12. Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change from baseline will be provided. The primary efficacy analysis will be analyzed with an analysis of covariance (ANCOVA) model with treatment as a factor. For any patients in the ITT Population with a missing primary efficacy parameter, the control (placebo)-based pattern mixture model will be used. Based on PK obtained in healthy volunteers dosed for up to two weeks on doses of MGL-3196 from 20-200 mg per day, a significant fraction of patients randomized to an 80 mg dose may have their dose reduced to 60 mg after PK assessment at Week 2. The multiplicity (MGL-3196 60 mg versus placebo and MGL-3196 80 mg versus placebo) will be controlled by Dunnett's Test. The primary efficacy analysis will be performed based on the ITT Population and repeated based on the Per Protocol Population.

10.2.1.2 Secondary efficacy analysis

For the continuous secondary efficacy variables, the same ANCOVA model will be used. Normality will be tested for the model residuals. For certain efficacy variables (such as hsCRP and triglycerides), logarithm transformation may be performed prior to fitting the ANCOVA model. For the categorical secondary efficacy variables, Fisher's exact test will be used to compare the odds ratio between MGL-3196 doses versus placebo.

10.2.1.3 Other efficacy analysis

The same efficacy analyses used for the secondary efficacy variables will be used for the tertiary/exploratory efficacy variables.

10.2.1.4 Subgroup analysis

Subgroup analysis of the primary efficacy variable and/or selected secondary/other efficacy variables may be performed, such as gender (male/female), BMI (≥30 kg/m^2 or <30 kg/m^2), and age group (≥median or <median).

10.2.2 Analysis of Safety

The safety endpoints for this study include: adverse events, safety laboratory assessments, vital signs, 12-lead ECGs, concomitant medications, and clinical assessments.

The adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be defined as adverse events that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and SAEs will be tabulated with numbers and percentages of patients, and repeated for severity and relationship to study drug per treatment group. The number of adverse events leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are <LLN or >ULN of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest will be summarized.

10.2.3 Interim Analysis

Interim analysis is not designed for this study. However, an analysis will be performed once all patients reach Week 12 of the Treatment Period. The analysis will assess the efficacy of MGL-3196 on percent change in liver fat by MRI-PDFF.

10.2.4 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes ALT, AST, and bilirubin), cardiovascular assessment (ie, changes in ECG, cardiac biomarkers, cardiac AEs, cardiac symptoms, arrhythmias, etc.), SAEs for trends in causality, and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews the first scheduled for when 25 patients have received 6 weeks of treatment. Additional regularly timed meetings will be held and ad hoc meetings may also occur if determined by Madrigal and the DSMB.

10.2.5 Sample Size Determination

Approximately 117 patients in total will be randomized to 80 mg (2/3) or placebo (1/3) treatments. After PK assessment, a significant fraction of patients' combined AUC (MGL-3196 plus MGL-3196-M1) may exceed 5500 ng*hr/ml resulting in a dose reduction to 60 mg. In order to power the study appropriately for an efficacious dose (which may be ≥80mg), randomization may continue until approximately 36 patients have continued at Week 4 on the 80 mg dose. It is estimated that the treatment difference of percent change in hepatic fat fraction from baseline to Week 12 between any dose of MGL-3196 and the placebo group is about -30%. With a common standard deviation for the percent change in hepatic fat fraction at 35%, 36 patients per group completing the Week 12 visit will provide 90% power with a 2-sample t-test. The significance level is set as 0.025 for the consideration of multiplicity in comparisons of 2 daily dosing regimens

of MGL-3196 versus the placebo group. The enrollment size is designed to allow for 10% drop out before the Week 12 visit, and as such, patients who drop out of the study will not be replaced.

With the sample size of 39 patients per treatment, the power for selected secondary efficacy endpoints was calculated. The baseline hepatic fat fraction is expected to be approximately 15% to 17%, thus the change from baseline to Week 12 in hepatic fat fraction is approximately -5.5% when comparing to placebo. With common standard deviation of change in hepatic fat fraction as 6%, 36 completed patients will provide 94% power for the study when evaluating the treatment effect in change of hepatic fat fraction.

In addition, the sample size is expected to provide meaningful liver biopsy-related data.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

11.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for adverse events and medical history, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

11.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

11.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and ICH require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is patient to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

12.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/EC, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure,

eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB, as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed ICFs, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR §54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13.2 Address List

13.2.1 Sponsor

Madrigal Pharmaceuticals, Inc.
Four Tower Bridge
200 Barr Harbor Drive, Suite 400
West Conshohocken, PA 19428
Telephone: 610-220-7260

13.2.2 Contract Research Organization

[redacted]

13.2.3 Drug Safety

[redacted]

13.2.4 Biological Specimens

[redacted]

[redacted]

13.2.5 Pharmacokinetic Samples

[redacted]

14 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES - MAIN STUDY

	Screening Period	Treatment Period											
Study Week	**Up to -6 Weeks**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 30**	**Week 36**	**Follow-Up Week 38**	**Early Term [1]**
Study Day	**Up to -42**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**210**	**252**	**266**	**n/a**
Determination of eligibility	X [2]	X											
Review of medical history [3]	X												
Obtain informed consent	X												
Demographic information	X												
12-lead ECG [4]	X	X	X	X	X	X	X	X	X	X	X		X
Complete/symptom-directed physical examination [5]	X	X	X	X	X	X	X	X	X	X	X		X
HepB, HepC, and HIV screen	X												
Randomization [6]		X											
Study drug dispensing and accountability [7]		X	X	X	X	X	X	X	X	X	X		X
Vital signs/anthropometrics [8]	X	X	X	X	X	X	X	X	X	X	X		X
Hematology profile	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting chemistry profile [9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Total and free testosterone, LH, FSH, estradiol [10]		X				X					X	X	X
SHBG		X	X	X	X	X	X	X	X	X	X	X	X
CK-MB, troponin I		X	X	X	X	X	X	X	X	X	X	X	X
Bile acids		X	X			X					X		X
ALP isoenzymes		X				X					X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X		X
Pregnancy test [11]	X	X	X	X	X	X	X	X	X	X	X		X
Thyroid axis hormones [12]	X	X	X	X	X	X	X	X	X	X	X	X	X

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APPENDIX A: SCHEDULE OF PROCEDURES - MAIN STUDY (CONTINUED)

	Screening Period	Treatment Period											
Study Week	**Up to -6 Weeks**	**Baseline Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 30**	**Week 36**	**Follow-Up Week 38**	**Early Term [1]**
Study Day	**Up to -42**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**210**	**252**	**266**	**n/a**
Diet and lifestyle counseling	X	X	X	X	X	X	X	X	X	X	X		
Health-related assessment (HR-QoL SF-36)		X		X		X			X		X		X
MRI-PDFF	X	X[13]				X					X[13]		X
Liver biopsy [14]	X [15]										X		X
Fasting metabolic panel [16]	X	X				X					X		X
Fasting lipid parameters [17]	X	X	X	X	X	X	X	X	X	X	X	X	X
CK-18, FIB-4, and ELF		X				X					X		X
Pre-dose PK sampling [18]		X	X[19]	X	X		X		X		X		X
hsCRP		X		X		X			X		X		X
Other biomarkers [20]		X				X					X		X
Bone biomarkers [21]		X				X					X		X
Coagulation markers [22]	X	X	X	X	X	X	X	X	X	X	X	X	X
DXA		X									X		X
Genomics sample		X											
Review alcohol consumption	X	X	X	X	X	X	X	X	X	X	X		X
Review concomitant medications	←----------continuous----------→												
Review adverse events	←----------continuous----------→												

Footnotes on following page

APPENDIX A: SCHEDULE OF PROCEDURES - MAIN STUDY (CONTINUED)

1. The exact Early Termination procedures to be completed, including liver biopsy, will depend on the guidance and discretion of the Investigators, Medical Monitors, and Sponsor and will include factors such as why and when the patient terminated early.
2. Includes assessment of ALT and AST consistency.
3. Includes review of substance abuse.
4. See Section 9.10 for instructions on performing 12-lead ECG.
5. Complete physical examination to be completed at screening only.
6. Patients must undergo screening procedures within 42 days of randomization.
7. Treatments include MGL-3196 80 mg or placebo. Each patient will receive study drug bottles labeled as A and B. Patients will take 1 capsule from bottle A and 1 capsule from bottle B once-daily in the morning. No study drug will be dispensed at Week 2, Week 36, or Early Termination. Study drug accountability will not be assessed at baseline.
8. Includes weight, BMI, waist circumference, waist-hip ratio, temperature, pulse, respiratory rate, and seated blood pressure. Pulse and blood pressure will be taken at rest.
9. Samples to be collected under fasting conditions (no food or drink other than water for 10 hours prior to visit). For a list of analytes to be collected, see Appendix C. Patients must have documented historical (3 weeks to 6 months prior to the study entry) ALT and AST levels consistent with the screening ALT and AST values. Patients who do not have historical ALT and AST evaluations available may have their ALT and AST repeated during the screening period [both assessments need to be ≥3 weeks apart]). If a patient requires close clinical monitoring, the patient may be asked to return to the study site for additional visits or laboratory assessments (see Section 9.17).
10. Free testosterone to be calculated from total testosterone, SHBG, and serum albumin at the Baseline Visit (Day 1), Week 12, Week 36, and the Early Termination Visit.
11. Serum HCG for women of child bearing potential at screening only. Urine pregnancy test for women of child bearing potential sufficient for subsequent visits.
12. Includes T4, FT4, total T3, FT3, TBG (not at Screening Visit), and TSH. Anti-TPO antibodies to be measured at Baseline Visit (Day 1) only. Reverse T3 at the Baseline Visit (Day 1), Week 12, Week 36, and the Early Termination Visit only.
13. Screening MRI-PDFF will be used for baseline. Screening MRI-PDFF should be obtained as close to baseline as possible. Week 36 MRI-PDFF should be obtained while on treatment within 10 days prior to the Week 36 Visit.
14. Liver biopsies to be read by 1 central reader. Includes assessment of fibrosis stage, portal inflammation, and NAS.
15. Liver biopsy to be completed at screening only in the event that the patient does not have available liver biopsy within 180 days of randomization. If a historical biopsy is to be used, patients must have had no change in metabolic status (diabetes, lipid metabolism, and/or >5% weight gain or loss) or change in diabetes medications. If a historical biopsy is not available, patients must have confirmation of ≥10% liver fat content on MRI-PDFF prior to undergoing liver biopsy. However, if, in the opinion of the patient's physician, the patient would benefit from and be advised to obtain a liver biopsy, the patient may undergo liver biopsy prior to MRI-PDFF. Week 36 liver biopsy to be completed in a window of -10 days to +3 days relative to the Week 36 visit.
16. Samples to be collected under fasting conditions (no food or drink other than water for 10 hours prior to visit). Includes [redacted] at Baseline Visit (Day 1), Week 12, Week 36, and the Early Termination Visit only.
17. Samples to be collected under fasting conditions (no food or drink other than water for 10 hours prior to visit). Includes triglyceride, total cholesterol, LDL-C (direct and calculated), HDL-C, non-HDL-C, ApoB (not at Screening Visit), Apo AI (not at Screening Visit), and Lp(a) particles (not at Screening Visit).
18. Patients will be instructed not to take study drug prior to PK sampling.
19. Patients will be instructed to fast overnight prior to predose PK sampling. PK samples will be collected at 2, 4, 6, and 8 hours postdose. Patients may have a low fat meal 1 hour postdose following any other assessments requiring fasting (eg, chemistry, hematology, SHBG, thyroid axis hormones, and fasting lipid parameters). Patients may have another low fat meal at 4 hours postdose following the 4 hour PK sample. All other study assessments will be obtained as usual.
20. Samples to be collected include fibrinogen, haptoglobin, alpha-2 macroglobulin, N-terminal pro b-type natriuretic peptide, apolipoprotein C-III, and ferritin.
21. Serum sample for Type 1 procollagen N-terminal propeptide and CTX.
22. Includes activated partial prothrombin time, prothrombin time, and international normalized ratio.

[redacted]; ALP = alkaline phosphatase; ApoB = apolipoprotein B; BMI = body mass index; CK-18 = cytokeratin-18; CK-MB = Creatine kinase-MB;CTX = c-terminal telopeptide; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; ELF = enhanced liver function test; FIB-4 = fibrosis-4; FSH = follicle stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; [redacted]; HCG = human chorionic gonadotropin; HepB = hepatitis B; HepC = hepatitis C; HIV = human immunodeficiency virus; HDL-C = high-density lipoprotein cholesterol; [redacted]; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; Lp(a) = lipoprotein(a); n/a = not applicable; NAS = non-alcoholic fatty liver disease activity score; [redacted]; non-HDL-C = non-high-density lipoprotein cholesterol; MRI-PDFF = proton density fat fraction magnetic resonance imaging; PK = pharmacokinetic; SHBG = sex hormone binding globulin; T3 = triiodothyronine; T4 = thyroxine; TBG = thyroxine-binding globulin; Term = termination; TSH = thyroid-stimulating hormone.

APPENDIX B: SCHEDULE OF PROCEDURES - EXTENSION STUDY

		Extension Study											
	Main Study Week 38 / Ext. Study Day 1 [1]	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Follow-Up Week 38**	**Early Term [3]**
Extension Study Day	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**266**	**n/a**
Determination of eligibility	X[2]												
Obtain informed consent	X												
12-lead ECG [4]	X	X	X	X	X	X	X	X	X	X	X		X
Complete/symptom-directed physical examination [5]	X	X	X	X	X	X	X	X	X	X	X		X
Study drug dispensing and accountability [6]	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs / anthropometrics [7]	X	X	X	X	X	X	X	X	X	X	X		X
Hematology profile	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting chemistry profile [8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Total and free testosterone, LH, FSH, estradiol [9]	X				X						X	X	X
SHBG	X	X	X	X	X	X	X	X	X	X	X	X	X
CK-MB, troponin I	X	X	X	X	X	X	X	X	X	X	X	X	X
Bile acids	X	X			X						X		X
ALP isoenzymes	X				X						X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X		X
Pregnancy test [10]	X	X	X	X	X	X	X	X	X	X	X		X
Thyroid axis hormones [11]	X	X	X	X	X	X	X	X	X	X	X	X	X

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APPENDIX B: SCHEDULE OF PROCEDURES - EXTENSION STUDY (CONTINUED)

		Extension Study											
	Main Study Week 38 / Ext. Study Day 1 [2]	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Follow-Up Week 38**	**Early Term [3]**
Extension Study Day	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**266**	**n/a**
Diet and lifestyle counseling	X	X	X	X	X	X	X	X	X	X	X		
Health-related assessment (HR-QoL SF-36)	X		X		X			X			X		X
MRI-PDFF					X						X[12]		X
Fibroscan											X		
DXA											X		
Fasting metabolic panel [13]	X				X						X		X
Fasting lipid parameters [14]	X	X	X	X	X	X	X	X	X	X	X	X	X
CK-18, FIB-4, and ELF	X				X						X		X
Pre-dose PK sampling [15]	X	X[16]	X	X		X		X			X		X
hsCRP	X		X		X			X			X		X
Other biomarkers [17]	X				X						X		X
Bone biomarkers [18]	X				X						X		X
Coagulation markers [19]	X	X	X	X	X	X	X	X	X	X	X	X	X
Review alcohol consumption	X	X	X	X	X	X	X	X	X	X	X		X
Review concomitant medications	←----------continuous----------→												
Review adverse events	←----------continuous----------→												

Footnotes on following page

APPENDIX B: SCHEDULE OF PROCEDURES – EXTENSION STUDY (CONTINUED)

1. The Extension Study Day 1 visit should occur within 60 days inclusive of the Main Study Week 36 Visit and may occur concurrently with the Main Study Week 38 Follow-up Visit. The Extension Study Informed Consent Form must be signed prior to any Extension Study-related procedures.
2. See Inclusion Criteria #9 for details regarding patient eligibility to participate in the extension phase of the study.
3. The exact Extensions Study Early Termination procedures to be completed will depend on the guidance and discretion of the Investigators, Medical Monitors, and Sponsor and will include factors such as why and when the patient terminated early.
4. See Section 9.10 for instructions on performing 12-lead ECG.
5. Complete physical examination to be completed at screening only.
6. Treatments include MGL-3196 40 to 120 mg. Each patient will receive study drug bottles labeled as A and B. Patients will take 1 capsule from bottle A and 1 capsule from bottle B once-daily in the morning. No study drug will be dispensed at Extension Study Week 2, Week 36, or Early Termination. Study drug accountability will not be assessed at Day 1.
7. Includes weight, BMI, waist circumference, waist-hip ratio, temperature, pulse, respiratory rate, and seated blood pressure. Pulse and blood pressure will be taken at rest.
8. Samples to be collected under fasting conditions (no food or drink other than water for 10 hours prior to visit). For a list of analytes to be collected, see Appendix C. If a patient requires close clinical monitoring, the patient may be asked to return to the study site for additional visits or laboratory assessments (see Section 9.17).
9. Free testosterone to be calculated from total testosterone, SHBG, and serum albumin at the Extension Study Day 1, Week 12, Week 36, and the Early Termination Visit.
10. Urine pregnancy test for women of child bearing potential.
11. Includes T4, FT4, total T3, FT3, TBG, and TSH. Anti-TPO antibodies to be measured at Baseline Visit (Day 1) only. Reverse T3 at the Day 1, Week 12, Week 36, and the Early Termination Visit only.
12. Extension Study Week 36 MRI-PDFF should be obtained while on treatment within 10 days prior to the visit.
13. Samples to be collected under fasting conditions (no food or drink other than water for 10 hours prior to visit). Includes [redacted] at Extension Study Day 1, Week 12, Week 36, and the Early Termination Visit only.
14. Samples to be collected under fasting conditions (no food or drink other than water for 10 hours prior to visit). Includes triglyceride, total cholesterol, LDL-C (direct and calculated), HDL-C, non-HDL-C, ApoB, Apo AI, and Lp(a) particles.
15. Patients will be instructed not to take study drug prior to PK sampling.
16. Patients will be instructed to fast overnight prior to predose PK sampling. A PK sample will also be collected at 4 hours postdose. Patients may have a low fat meal 1 hour postdose following any other assessments requiring fasting (eg, chemistry, hematology, SHBG, thyroid axis hormones, and fasting lipid parameters). All other study assessments will be obtained as usual.
17. Samples to be collected include fibrinogen, haptoglobin, alpha-2 macroglobulin, N-terminal pro b-type natriuretic peptide, apolipoprotein C-III, and ferritin.
18. Serum sample for Type 1 procollagen N-terminal propeptide and CTX.
19. Includes activated partial prothrombin time, prothrombin time, and international normalized ratio.

APPENDIX C: CLINICAL LABORATORY ANALYTES

Chemistry:

- Alkaline phosphatase
- Alkaline phosphatase isoenzymes
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Blood urea nitrogen
- Calcium
- Carbon dioxide
- Chloride
- Creatine kinase
- Creatinine
- Direct bilirubin
- Estimated glomerular filtration rate (derived from creatinine)
- Gamma-glutamyl transpeptidase
- Glucose
- Lactate dehydrogenase
- Lipase
- Magnesium
- Phosphate
- Potassium
- Serum albumin
- Sodium
- Total bilirubin
- Total protein
- Uric acid

Hematology:

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count
- Platelets
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Differentials %
- Differentials absolute
- Red blood cell morphology

Urinalysis:

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrate
- Urobilinogen
- Leukocyte esterase

Coagulation:

- Activated partial prothrombin time
- Prothrombin time
- International normalized ratio

Viral assessments:

- Hepatitis B surface antigen (qualitative)
- Hepatitis C virus antibody
- Hepatitis C virus ribonucleic acid (qualitative) (only if HCV Ab positive)
- Human immunodeficiency virus 1 and 2 antibody differentiation

Sex hormones:

- Estradiol
- Free (calculated) testosterone
- Follicle stimulating hormone
- Luteinizing hormone
- Sex hormone binding globulin
- Total testosterone

Thyroid axis hormones:

- Anti-thyroid peroxidase
- Free triiodothyronine
- Free thyroxine
- Thyroxine
- Thyroxine-binding globulin
- Total triiodothyronine
- Thyroid stimulating hormone
- Reverse T3

Metabolic panel:

- Adipose tissue insulin resistance
- Adiponectin
- Glucose
- Hemoglobin A_1c
- Homeostatic model assessment insulin resistance (calculated)
- Insulin
- Non-esterified fatty acid

Lipid panel:

- Apolipoprotein B
- High-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol (direct and calculated)
- Lipoprotein(a) particles
- Non-high-density lipoprotein cholesterol
- Total cholesterol
- Triglycerides
- Apolipoprotein A1

Bone biomarkers:

- C-terminal telopeptide
- Type 1 procollagen N-terminal propeptide

Other markers:

- Cytokeratin-18
- Enhanced liver function
- Fibrosis-4
- High sensitivity C-reactive protein
- Creatine kinase MB
- Troponin I
- Bile acids
- Fibrinogen
- Haptoglobin
- Alpha-2 macroglobulin
- N-terminal pro b-type natriuretic peptide
- Apolipoprotein C-III
- Ferritin

Other assessments:

- Urine pregnancy test (for women of child bearing potential only)
- Pharmacokinetic sample
- Genomic sample
- See Section 9.17 for possible labs and assessments for drug induced liver injury monitoring