PROTOCOL NO. MN-001-NATG-201

Title of Study: An Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of MN-001 (tipelukast) on HDL (High Density Lipoprotein) Function and Serum Triglyceride Levels in Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD) Subjects with Hypertriglyceridemia

IND Number:	123659
Study Phase:	2a
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ORIGINAL PROTOCOL	28 May 2015
AMENDMENT 1	20 November 2015
AMENDMENT 2	06 June 2016
AMENDMENT 3	14 August 2017

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PROTOCOL SIGNATURE PAGE

Study No: MN-001-NATG-201

MediciNova Approval:

Signature: _____ Date: August 14, 2017

Name: Kazuko Matsuda, MD PhD MPH

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: MN-001-NATG-201

I have read the foregoing protocol and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by MediciNova, Inc. in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by MediciNova, Inc. will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____
Investigator Name (Print)

_____ _____
Investigator Signature Date

1. SYNOPSIS

Name of Sponsor: MediciNova Inc.

Name of Investigational Product: MN-001

Protocol Number: MN-001-NATG-201

Title of Study: An Open–label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of MN-001 (tipelukast) on HDL (high density lipoprotein) Function and Serum Triglyceride Levels in Non-Alcoholic Steatohepatitis (NASH) and Non-alcoholic Fatty Liver Disease (NAFLD) Subjects with Hypertriglyceridemia

Study Center: Multiple centers

Phase of Development: 2a

STUDY OBJECTIVES

Primary Objectives:

- To evaluate the effects of MN-001 on Cholesterol Efflux Capacity in NASH and NAFLD subjects with hypertriglyceridemia
- To evaluate the effects of MN-001 on triglyceride levels in NASH and NAFLD subjects with hypertriglyceridemia

Secondary Objectives:

- To evaluate the safety and tolerability of MN-001
- To evaluate PK profile of MN-001/MN-002 (metabolite)
- To evaluate the effect of MN-001 on lipid profile
    - HDL-C, LDL-C, total cholesterol level
- To evaluate the effect of MN-001/002 on liver enzymes
- To evaluate the effect of MN-001/002 on percentage of fat in the liver assessed using MRI at Week 12

METHODOLOGY

This is a multi-center, proof-of-principle, open-label study designed to evaluate the efficacy, safety, and tolerability of MN-001 in subjects diagnosed with non-alcoholic steatohepatitis (NASH) or NAFLD with hypertriglyceridemia. Subjects will receive MN-001 250 mg qd for the first 4 weeks and will take 250 mg bid for 8 weeks. Subjects will receive MN-001 for a total of 12 weeks. A total of forty (40) subjects will be enrolled. Eligible subjects will consist of males and females ≥ 18 of age. To be eligible, subjects must have a histologically confirmed diagnosis of NASH within 36 months prior to baseline visit or NAFLD confirmed by imaging studies and an elevated serum triglyceride (> 150 mg/dL) during the Screening Phase.

The study will consist of a Screening Phase (up to 4 months) followed by a Treatment Phase (12 weeks), and a Follow-up visit (within 1 week after the last dose).

Screening Phase (Day -120 to -7)

During the Screening Phase, subjects will be assessed for study eligibility. After signing the informed consent form, the following assessments will be performed: medical history including review of prior medications, physical examination including height and body weight, waist circumference, vital signs and an electrocardiogram (ECG). Clinical labs, chemistry (including CPK, liver enzymes and fasting lipid profile), hematology, coagulation profile, urinalysis and a serum pregnancy test will be collected as well as cytokeratin-18 (CK-18), a serum biomarker for NASH diagnosis. An alcohol consumption questionnaire will be administered and a MRI scan of the liver will be performed.

Treatment Phase (12 weeks)

Subjects who complete all of the screening assessments will return to the clinic on Treatment Day 1 (Baseline) to repeat laboratory tests and physical assessments. Subjects who continue to be eligible will be enrolled to receive MN-001 250 mg qd (250 mg/day) for 4 weeks and will take 250 mg bid (500 mg/day) for 8 weeks.

Subjects will receive their first dose of study medication on Day 1 at the clinic. The first 6 subjects will have the option to stay at the study center overnight on Day 1 or return to the clinic the following day for the last/final blood draw. Blood samples for MN-001 /MN-002 (major metabolite) concentrations will be collected at the following timepoints:

- Day 1
    - Baseline: prior to the first dose
    - post dose hour 0.5, 1.5, 3, 6, 9, 12, 24* (*Day 2)

PK parameters will be calculated and results will be reviewed prior to increasing the dose to 250 mg bid after Week 4.

Subjects will return to the clinic at Weeks 4, 8, and 12. After Week 4, subjects will start taking 250 mg bid. During these visits, subjects will undergo safety and efficacy assessments. ECGs will be conducted at T_{max} at hour 1.5 (± 30 minutes) after drug ingestion at each clinic visits: See Table 1 for visit schedule and procedures for all assessments.

Throughout the Treatment Phase, safety parameters will be assessed and concomitant medications will also be documented. The safety and tolerability of MN-001 will be evaluated by an Independent Safety Monitor during this phase.

Follow-up Visit (Week 13)

All subjects who complete the study will return for a follow-up visit at Week 13. At the last visit a physical examination including body weight, vital signs, and safety labs will be done. Adverse events and concomitant medications will be collected.

Individual Stopping Criteria

Subjects who experience an adverse event of Grade 2 nausea and/or diarrhea for greater than 3 consecutive days or Grade 3 nausea and/or vomiting for greater than 1 day thought to be related to study drug will be discontinued from the study. Additionally, subjects who experience an adverse event of Grade 3 abdominal pain lasting for greater than 1 day thought to be related to study drug will be discontinued from the study.

Additionally, study drug will be discontinued or temporarily interrupted under the following

conditions:

- When the baseline values were <2X ULN, discontinue if ALT or AST increases to >5X baseline value (BLM).
- When the baseline values were ≥2X ULN but <5X ULN, discontinue if ALT or AST increases to >3X BLM
- When the baseline values were ≥5X ULN, discontinue if ALT or AST increases to >2X BLM
- Discontinue if ALT or AST increase >2X BLM AND the increase is accompanied by a concomitant total bilirubin (TBL) increase to >2X BLM OR the INR concomitantly increases by >0.2

Study Stopping Rules

The study will be stopped if two subjects experience a Grade 4 adverse event thought to be related to study drug.

Number of Subjects (Planned): The number of subjects planned for enrollment is 40.

STUDY ENTRY CRITERIA:

Inclusion Criteria:

- Written informed consent is obtained and willing and able to comply with the protocol in the opinion of the Investigator.
- Male or female subjects age ≥18 years of age
- Histologically proven NASH (NAFLD activity score of 3 or greater with at least 1 point being ballooning) based on liver biopsy performed within the last 36 months or NAFLD confirmed by imaging studies.
- Fasting serum triglyceride level > 150 mg/dL (confirmed at screening)
- Serum ALT, AST, ALP and total bilirubin levels at Screening (- 120 days to – 30 days) and Lab Visit values (- 1 week ± 5 days) are stable or changes at the Lab visit are < 20% of the values from Screening.
- Subjects on the following medications can be enrolled if these medications are necessary, cannot be stopped, and the dose has been stable for 3 months or more prior to baseline:
  - Stable doses of anti-diabetic medications
  - Stable doses of fibrates, statins, niacin, ezetimibe
  - Stable doses of Vitamin E for at least 8 weeks
- Less than 21units of alcohol/week for men and 14 units of alcohol/week for women over a 2-year time frame
- Females of child-bearing potential must have a negative serum ß-hCG at screening and must be willing to use appropriate contraception (as defined by the investigator) for the duration of study treatment and 30 days after the last dose of study treatment
- Males should practice contraception as follows: condom use and contraception by female

partner

- Subject is in good physical health on the basis of medical history, physical examination, and laboratory screening, as defined by the investigator
- Subject is willing and able to comply with the protocol assessments and visits, in the opinion of the study nurse/coordinator and the Investigator

Exclusion Criteria:

- Diagnosis of other known cause of liver disease (autoimmune, viral, genetic, drug- or alcohol-induced, or storage disease)
- Decompensated or severe liver disease defined by one or more of the following:
    1) biopsy-proven cirrhosis
    2) INR >1.5
    3) Total bilirubin (TBL) > 1.5x ULN, or > 2 x ULN for unconjugated bilirubin
    4) serum albumin < 2.8 g/dL
    5) ALT or AST > 10 x ULN
    6) evidence of portal hypertension including splenomegaly, ascites, encephalopathy and/or esophageal varices
- Current diagnosis of hepatocellular carcinoma (HCC) or suspicion of HCC clinically or on ultrasound
- Uncontrolled diabetes mellitus Type 2
- Recent heart attack, coronary artery intervention, coronary bypass surgery, or stroke.
- Patients with class 3 or 4 heart failure
- History of bariatric surgery
- Greater than 10-pound weight gain or loss in the last 6 months
- Clinically significant cardiovascular/cerebrovascular disease, including myocardial infarction within last 6 months, coronary artery intervention, coronary artery bypass, unstable ischemic heart disease, heart failure Class III or IV, angina or cerebral vascular accident
- Resting pulse < 50 bpm, SA or AV block, uncontrolled hypertension, or QTcF > 450 ms
- History of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug
- Any significant laboratory abnormality which, in the opinion of the Investigator, may put the subject at risk
- History of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer
- History of HIV (human immunodeficiency virus), HBV, HCV (cured HCV is not excluded), EBV CMV or other active infection.
- Currently has a clinically significant medical condition including the following: neurological,

psychiatric, metabolic, immunologic, hematological, pulmonary, cardiovascular (including uncontrolled hypertension), gastrointestinal, urological disorder, or central nervous system (CNS) infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study

*Note***:** Active medical conditions that are minor or well-controlled are not exclusionary if, in the judgment of the Investigator, they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Safety Monitor should be consulted.

- CYP2C8 substrates with a narrow therapeutic index (e.g., paclitaxel) within 15 days prior to study, and throughout the study are prohibited
- CYP2C9 substrates with a narrow therapeutic index (e.g., phenytoin, S-warfarin, tolbutamide) within 15 days prior to study and throughout the study are prohibited
- Macrolide or quinolone class antibiotics within 15 days of Screening and throughout the study are prohibited
- Steroids within 30 days prior to study drug dosing and throughout the study unless administered for a short term treatment course during the study are prohibited
- History of alcohol or substance abuse (DSM-IV-TR criteria) within 3 months prior to screening or alcohol or substance dependence (DSM-IV-TR criteria) within 12 months prior to screening. The only exceptions include caffeine or nicotine abuse/dependence
- Poor peripheral venous access that will limit the ability to draw blood as judged by the Investigator
- Currently participating, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent
- Unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator, or was planning to relocate during the study

Investigational Product, Dosage and Mode of Administration: MN-001 tablets (250 mg) to be administered orally for a total of 12 weeks (250 mg qd for 4 weeks and 250 mg bid for 8 weeks).

Duration of Treatment: Total 12 weeks

Reference Therapy, Dosage, and Mode of Administration: N/A

Pharmacokinetics: Plasma samples for analysis of MN-001 and its metabolite MN-002 will be collected from the first 6 subjects at the following timepoints:

- Baseline: prior to the first dose
- Post first dose at hours: 0.5, 1.5, 3, 6, 9, 12, 24

Statistical Methods

Analysis Populations:

Safety Analysis Set: The group of subjects who received at least one dose of study drug and had at least one post dose safety assessment.

Per Protocol Set: The group of subjects who received at least one dose of study drug and who did not

have any major protocol deviations.

Safety Analysis

Safety analyses will be conducted on the Safety Analysis Set.

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of study medication), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness.

Changes from baseline in laboratory values will be summarized by treatment groups for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed by treatment groups. Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed.

Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated by treatment group.

Changes in vital signs from baseline to each visit will be summarized by treatment groups.

Plasma MN-001 concentrations and its metabolite will be measured.

Sample Size Justification:

The sample size is not based on hypothesis testing. The selected sample size is considered adequate to provide a preliminary evaluation of efficacy and safety.

Table 1: Schedule of Assessments

Phase	**Screening**		**Treatment**					**Follow-up**
Tests and Evaluations	**Day -120 to Day -7**	**– 1 week ± 5 days**	**Baseline Day 1-2***	**Week 2 ± 3 days**	**Week 4 ± 5 days**	**Week 8 ± 5 days**	**Week 12/ET** ± 5 days**	**Week 13 ± 5 days**
Type of Visit	**Clinic**	**Lab**	**Clinic**	**Tel**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
Inclusion/exclusion criteria review	X		X					
Medical history	X							
Physical examination	X		X		X	X	X	X
Body height	X							
Body weight/Waist circumference	X		X		X	X	X	X
Vital signs	X		X		X	X	X	X
Alcohol consumption questionnaire	X						X	
Pregnancy test (serum /urine)	X (serum)	X (serum)			X	X	X	
12-lead ECG	X		X		X	X	X	
Clinical labs (chemistry, incl CPK, hematology, lipid panel coagulation profile including INR, urinalysis)	X	X			X	X	X	X
CK-18 biomarker	X						X	
Fib-4 Index calculation	X							
NAFLD fibrosis score	X							
Blood Sample for Cholesterol Efflux			X				X	
MN-001 plasma concentration ***			X					
Liver MRI[a]	X****						X****	
Adverse event review			X	X	X	X	X	X
Concom med review	X		X	X	X	X	X	
Study Drug Dispensing			X					
Study Drug Accountability				X	X	X	X	

* Baseline visit will be overnight stay for selected 6 subjects from whom PK samples will be obtained
** ET: Early termination visit
*** PK sample for MN-001/002 will be also obtained when subjects experience SAE
**** Liver MRI can be scheduled on different day of each lab/clinic visit
[a] Pre-treatment Liver MRI may be performed between Day -120 and Day -1prior to Baseline Day 1

2. TABLE OF CONTENTS

List of Figures and Tables

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Terms

Abbreviation	Term
AE	adverse event
Alb	albumin
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
aPTT	activated partial prothrombin time
AST (SGOT)	aspartate aminotransferase
AV	atrioventricular
β-hCG	beta-subunit of human chorionic gonadotropin
bid	twice daily
BLM	Baseline values
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CK-18	cytokeratin-18
C_{max}	Maximum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CTCAE	Common terminology criteria for adverse events
CVD	cardiovascular disease

Abbreviation	Term
CYP	cytochrome
DDI	drug-drug interaction
DILI	drug-induced liver injury
dL	deciliter
DM	Diabetes mellitus
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition-Text Revision
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
ET	Early Termination
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HV	Healthy volunteer
IC_{50}	inhibition constant 50%
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMM	independent medical monitor
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
L	liter

Abbreviation	Term
LDL	low-density lipoprotein
LO	lipoxygenase
LT	leukotriene
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MRI	magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NAS	Non-alcoholic fatty liver disease activity score
NASH	Non-alcoholic steatohepatitis
NDA	new drug application
NSAID	Non-steroidal anti-inflammatory drug
PK	pharmacokinetics
PI	Principal Investigator
PTT	prothrombin time
qd	once-daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SA	sinoatrial
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SOC	system-organ-class
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
tid	three times daily
T_{max}	time maximum plasma concentration
TRAE	Treatment-related adverse event
ULN	Upper limit of normal
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

4. BACKGROUND AND RATIONALE

4.1. Introduction

In the United States, non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease. Population based studies in the United States estimate that the prevalence of NAFLD ranges between 17% and 30% in the general population and as high as 80% in obese individuals undergoing weight loss surgery. NAFLD represents a histopathologic spectrum ranging from steatosis alone, to necroinflammation - an entity described as nonalcoholic steatohepatitis (NASH). Less than 1% - 4% of patients with simple steatosis progress to a more advanced fibrosis while NASH has an increased risk for the progression to advanced fibrosis and cirrhosis. The prevalence of NASH is between 12%-17%. Despite the high prevalence of this disease, the natural history of NAFLD/NASH remains unclear.

There is sufficient clinical and epidemiological evidence supporting the assertion that NAFLD/NASH is strongly associated with an increased prevalence and incidence of cardio-vascular disease (CVD) (Ballestri et al 2014). Patients with NAFLD/NASH often have dyslipidemia along with other features of metabolic syndrome such as obesity, diabetes mellitus, and hypertension. The presence of dyslipidemia (hypercholesterolemia, hypertriglyceridemia or both) has been reported in 20-80% of cases associates with NAFLD (Souza et al 2012). The dyslipidemia is characterized by increased serum triglycerides, increased small, dense low-density lipoprotein (LDL nontype A) particles, and low high-density lipoprotein (HDL) cholesterol. The pathogenesis of dyslipidemia in NAFLD/NASH is not well understood (Chatrath et al 2012).

A low level of high-density lipoprotein (HDL) cholesterol has been considered a major independent risk factor for atherosclerotic cardiovascular disease. HDL has numerous anti-atherosclerotic actions that are not readily reflected by HDL cholesterol levels (deGoma et al 2008). A key function of HDL is to promote reverse cholesterol transport from the periphery to the liver, and the critical initial step in reverse cholesterol transport is cholesterol efflux from macrophages to HDL (Rader et al 2009). Macrophage-specific cholesterol efflux capacity has been directly and causally linked to the prevention of atherosclerosis in animal models (Rader et al 2009). In a recent population-based cohort study, cholesterol efflux capacity, a key step in reverse cholesterol transport, was inversely associated with the incidence of cardiovascular events (Rohatgi et al 2014) and is considered to be a new biomarker to assess cardiovascular risk.

MN-001

MN-001 (4-[6-acetyl-3-[3-[(4-acetyl-3-hydroxy-2-propylphenyl)thio]propoxy]-2-propylphenoxy]butanoic acid), formerly KCA-757 (Kyorin Pharmaceutical Co., Ltd.) is a novel, orally bioavailable small molecule compound which demonstrates anti-inflammatory activity in preclinical models. The 5-lipoxygenase (5-LO) pathway, which generates leukotrienes (LT) from arachidonic acid, is one of the major inflammatory systems in mammals (Samuelsson et al

1987; Funk 2001). It has been shown that 5-LO expression and LT formation were increased in livers in animals with induced cirrhosis (Titos et al 2000), suggesting that 5-LO plays an important role in Kupffer cell survival and in the pathogenesis of liver inflammation and fibrosis (Titos et al 2004). Kupffer cells are known as the predominant primary inflammatory effector cells to promote tissue remodeling and fibrosis (Titos et al 2004). MN-001 is thought to exert an inhibitory effect on 5-LO and the 5-LO/LT pathway and, therefore, may have potential utility for the treatment of fatty liver disease, including non-alcoholic steatohepatitis (NASH).

4.1.1. Rationale of the MN-001 for treatment of NASH and NAFLD Subjects with hypertriglyceridemia

Rationale for the use of MN-001 in NASH and NAFLD with hypertriglyceridemia is based on preclinical studies and previous clinical studies.

The safety pharmacology of MN-001 and its major metabolite MN-002 was examined *in vitro* and *in vivo*. Effects on serum lipids were evaluated in rats with both MN-001 and MN-002 as single doses at 0, 30, 100 and 300 mg/kg. With MN-001, a significant decrease was observed in the [total cholesterol - free cholesterol]/free cholesterol ratio in some approximate dose-dependent manner 2-6 hours after dosing. At 100 mg/kg, MN-002 caused significant decreases in triglycerides and 300 mg/kg led to significant decreases in triglycerides and β-lipoprotein. In a 52- week oral toxicity study in dogs treated with MN-001, a reduction in triglycerides and ß-lipoprotein was evident in both sexes at dose 180 mg/kg (Study Report #K93CD02).

The *in vivo* effects of MN-001 on fatty liver disease were directly evaluated using a mouse model for NASH. In this mouse model of NASH, treatment with MN-001 significantly reduced fibrosis as compared with vehicle in a dose dependent manner demonstrating the anti-fibrotic effect of MN-001. High dose of MN-001 tended to reduce liver hydroxyproline content supporting its anti-fibrotic property. Treatment with high dose of MN-001 significantly decreased the NAS. The improvement in NAS was attributable to the reduction in lobular inflammation and hepatocyte ballooning. Notably, high dose of MN-001 significantly reduced ballooning score. Since hepatocyte ballooning is derived from oxidative stress-induced hepatocellular damage and is associated with disease progression of NASH (Fujii et al 2009; Rangwala et al 2011), the data strongly suggest that MN-001 improved NASH histopathology by inhibiting hepatocyte damage and ballooning. Treatment with low dose of MN-001 significantly reduced the area of inflammation compared with vehicle; demonstrating anti-inflammatory effect of MN-001

In a Phase 2 trial with asthma patients (Protocol #MN-001-CL-001), an interesting observation was the change in the fasting lipid profiles from screening to the end of the study. Mean total cholesterol decreased 8 mg/dL in the combined MN-001 treatment groups while increasing 3.7 mg/dL in the placebo group. Mean low density lipoprotein cholesterol (LDL) decreased 6.5 mg/dL in the combined MN-001 treatment groups while increasing 1.7 mg/dL in the placebo group. Mean triglycerides decreased 16.4 mg/dL in the combined MN-001 treatment groups while increasing 1.1 mg/dL in the placebo group. Similar trends were also observed in the Phase 2 trial with Interstitial Cystitis patients and a Phase 1 trial with healthy volunteers.

With these preclinical and clinical studies data, we hypothesized that MN-001 is beneficial to improve lipid profile and to protect liver damage in patients with NASH and NAFLD with elevated serum triglyceride level.

4.2. Prior Clinical Experience

4.2.1. Clinical Study Overview

To date, a total of 11 clinical trials have been conducted with MN-001 and over 600 subjects have been dosed. Doses of MN-001 ranging from 80 mg to 2000 mg for up to 12 weeks in 6 Phase 1 studies, 4 Phase 2 studies and 1 Phase 3 study have been studied in healthy subjects and patients with asthma and interstitial cystitis. A summary of completed studies is listed in Table 3.

Phase 1 Studies

In the single dose studies of 80 mg to 600 mg, there appeared to be few adverse events. The most common treatment emergent adverse events (TEAEs) were mild diarrhea, sensation of borborygmus, and heavy headedness. No clinically significant changes in vital signs, ECGs, and safety labs were observed.

In two multiple dose studies (study KCA-757 and study 478-02), MN-001 250 mg to 1000 mg bid was administered for approximately 7 days in healthy volunteers and subjects with mild bronchial hypersensitivity. No serious adverse events were reported and no subjects discontinued the study due to an adverse event. The most common AEs experienced in study 478-02 were upper abdominal pain (reported by 1 subject each in the 500 mg and 750 mg groups), loose stools (reported by 1 subject each in the 500 mg and 1000 mg groups), and nausea (reported by 1 subject each in the 750 mg and 1000 mg groups). The Investigator considered the following treatment-emergent AEs to be possibly or probably related to study drug (treatment group in parentheses): abdominal pain (placebo), upper abdominal pain (500 mg and 750 mg), dyspepsia (1000 mg), fatigue (placebo), loose stools (500 mg and 1000 mg), nausea (750 mg and 1000 mg), somnolence (750 mg), urine odor abnormal (500 mg).

In study 478-02, vital signs were within normal limits. All mean ECG measurements remained within normal limits. At Hour 359.67 mean QTc for the 750 mg group increased 27.66 ms from baseline for a mean QTc of 395.83 ms and mean heart rate increased 14.50 bpm from baseline for a mean heart rate of 70.67 ms. No other marked mean changes from baseline were noted. The Investigator did not consider any of the ECG abnormalities in this study to be adverse events.

All treatment groups, including the placebo group, exhibited notable mean increases in CPK (ranging between 22 to 135 U/L) at Hour 360. No other marked mean changes from baseline were noted for the remaining serum chemistry parameters.

High Doses of MN-001 (1500 mg)

Study MN-001-CL-003 was another multiple dose study in healthy volunteers testing doses of 1500 mg for 5 days. In this study, no SAEs occurred and no subjects discontinued the study due

to a TEAE. Two subjects reported a TEAE during the study. Both subjects experienced dizziness (mild, possibly related), one on Day 2 and the other on Day 3 of dosing with MN-001 750 mg bid.

Mean serum chemistry and hematology results showed transient fluctuations between screening and follow-up on Day 11, 8 hours after the last dose, but no apparent treatment-related trends were observed for any of the serum chemistry or hematological parameters evaluated. None of the abnormal laboratory values observed during the study was considered a clinically significant treatment-related change, and no AEs related to abnormal laboratory values were reported. No clinically significant changes in vital sign parameters and ECGs were noted during the study.

The mean triglyceride (mg/dL) changes from baseline at Day 11 are listed below.

Time point	**MN-001 1500 mg/day (N=11)**
Screening	145.4
Day 11	87.5 (-39.8%)

Phase 2 Studies

Study KCA-757-T201

MN-001 100 mg, 200 mg, 400 mg and 600 mg was evaluated in 112 asthma patients over 6 weeks. No serious adverse events occurred and 11 subjects discontinued due to a TEAE. Seven subjects experienced 20 adverse reactions.

Study MN-001-CL-001

MN-001 (500 mg tid, 750 mg bid, or 750 mg qd) or placebo was evaluated for 4 weeks in 147 asthma patients. AEs within the Gastrointestinal Disorders system organ class were the most commonly observed, reported by 18.2% of the combined MN-001 subjects and 10.8% of those receiving placebo. These AEs appeared to demonstrate a dose relationship, and the most frequent AEs among the combined MN-001 treatment groups were diarrhea, nausea, and vomiting. Each of these individual events occurred in less than 10% (with only diarrhea exceeding 5%) of all MN-001-treated subjects. No severe gastrointestinal AEs were reported, and none led to discontinuation from the study.

The mean triglyceride (mg/dL) changes from baseline at Week 4 are listed below.

Time point	Placebo (N=36)	500mg tid (N=36)	750mg bid (N=36)	750mg qd (N=36)
Screening	132.3	109.5	125.5	112.2
Week 4	126.9 (-4.1%)	91.6 (-16.3%)	98.5 (-21.5%)	117.2 (+4.5%)

Study MN-001-CL-002

MN-001 500 mg bid and 500 mg qd were evaluated in 305 patients with interstitial cystitis. The TEAE most frequently reported by all the patients in the MN-001 group was diarrhea, which was higher in both MN-001 groups compared with placebo and higher in the MN-001 500 mg bid group compared with the MN-001 500 mg qd group. Although the incidence of loose stools was lower than the incidence of diarrhea, similar comparisons as seen with diarrhea among the treatment groups were also observed for loose stools.

The mean triglyceride (mg/dL) changes from baseline at Week 4 are listed below.

Time point	Placebo (N=100)	500mg qd (N=94)	500mg bid (N=106)
Baseline	144.3	136.1	135.7
Week 4	144.5 (+0.1%)	109.5 (-19.5%)	106.7 (-21.3%)

Phase 3 Study

MN-001 (500 mg tid or 750 mg bid) or placebo was evaluated for 12 weeks in patients with asthma. This study was stopped early by sponsor in June 2007 due to strategic reasons unrelated to the safety or efficacy of study drug. (MediciNova, Inc.'s business decision to discontinue further development of MN-001 in its current immediate-release formulation for asthma indication was based on the competitive landscape at that time.)

There were total 154 subjects enrolled, 152 subjects were randomized (108 in MN-001 groups and 44 in placebo group). The study was terminated before planned enrollment was achieved. In the all MN-001 groups, the system organ class (SOC) categories with the most reported TEAEs were gastrointestinal disorders (19% vs. 5% in the placebo group), infections and Infestations (11% vs. 18% in the placebo group) and respiratory, thoracic and mediastinal disorders (8% vs. 7% in the placebo group). In the placebo group, the SOC category with the most reported TEAEs

(incidence of ≥ 10%) was infections and infestations (18%). The only AE that was reported in > 2 subjects in each treatment group was diarrhea, which occurred at a higher frequency in the 750 mg bid group than the 500 mg tid group (21% vs. 9% respectively). The TEAEs experienced by > 2 subjects in the all MN-001 group were nasopharyngitis (4%), urinary tract infection (3%), asthma (3%), and joint sprain (3%).

The mean triglyceride (mg/dL) changes from baseline at Week 4 are listed below.

Time point	**Placebo (N=44)**	**500 mg tid (N=54)**	**750 mg bid (N=53)**
Baseline	135.4	159.4	117.0
Week 4	123.1 (-9.1%)	112.5 (-29.4%)	94.1 (-19.6%)

Additional safety information is reported in the Investigator Brochure.

Table 3: Clinical Studies

Phase	Study Number	Title	Design	Dosage	Treatment Duration	Target Population	# of Subjects Enrolled
1	2254	Ascending dose tolerance study of KCA-757 (MN-001) in healthy volunteers with preliminary pharmacokinetic assessment	Open-label, single-dose	80 mg, 160 mg	single-dose	Healthy Volunteers	5
1	151408	The disposition of 14C-KCA-757 (MN-001) in man	Open-label, single oral dose to investigate the rates and routes of excretion and the plasma kinetics of total radioactivity following [^{14}C]-KCA-757 (MN-001)	80 mg	single-dose	Healthy Volunteers	4
1	Kyorin	Phase 1 Trial of KCA-757 (MN-001) Single-dose study	Ascending, single-dose to evaluate safety and PK	100 mg to 600 mg	single-dose	Healthy Volunteers	29
1	Kyorin	Phase 1 Trial of KCA-757 (MN-001) Repeated-dose study	Safety and PK	300 mg bid	7 days	Healthy Volunteers	6
1	478-02	A Randomized, Double-Blind, Placebo-Controlled, Ascending Dose Study to Assess the Safety and Tolerability of MN-001 When Given in Multiple Doses to Healthy Volunteers and the Pharmacodynamic Effect of MN-001 When Given in Multiple Doses to Volunteers with Mild Bronchial Hypersensitivity	Randomized, double-blind safety and tolerability	250, 500, 750, 1000 mg bid	6 days	Healthy Volunteers and bronchial hypersensitive subjects	32
1	MN-001-CL-003	A Phase I, Randomized Single-blind study to Determine the Relative Pharmacokinetics of Two Dosing Regimens of MN-001 Administered Orally to Normal, Healthy Male and Female Subjects	Single-Blind, Randomized 1:1, Crossover	500mg tid and 750mg bid	5 days of dosing for each regimen	Healthy Volunteers	11 subjects randomized and completed
2	KCA-757-T201	Early Phase 2 Study of KCA-757 (MN-001)	Open-label	50 mg bid, 100 mg bid, 200 mg bid, 300 mg bid	6 weeks	Bronchial asthma	108 subjects
2	4204	A standard antigen challenge study of KCA-757 (MN-001) in 10	Cross-over	300 mg bid	single-dose	Asthma	3

Phase	Study Number	Title	Design	Dosage	Treatment Duration	Target Population	# of Subjects Enrolled
		patients with asthma					
2	MN-001-CL-001	A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of MN-001 in Subjects with Mild to Moderate Asthma	Double-Blind, Randomized	500mg tid, 750mg bid, 750mg qd, or placebo	4 weeks	Mild to Moderate Asthma pts	147 subjects randomized with 131 completing, placebo N=37, 500mg tid N=37, 750mg bid N=37, 750mg qd N=36
2	MN-001-CL-002	A Phase II, Randomized, Double-blind, Placebo-Controlled Multi-Center Study to Evaluate the Efficacy and Safety of Two Dosing Regimens of MN-001 in Patients with Interstitial Cystitis	Double-Blind, Randomized 1:1:1	500mg bid 500mg qd, or placebo	8 weeks	Interstitial Cystitis pts	305 subjects randomized with 251 completing, placebo N=102, 500mg qd=95, 500mg bid N=108
3	MN-001-CL-004	A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of MN-001 in Subjects with Mild to Moderate Asthma	Double-Blind, Randomized 1:1:1	500mg tid 750mg bid, or placebo	12 weeks	Mild to Moderate Asthma pts	152 subjects randomized 108 MN-001 44 Placebo

4.3. Potential Drug-Drug Interactions

From the *in vitro* CYP enzyme study, both MN-001 and MN-002 were found to be highly bound to human serum albumin.

- MN-001 and MN-002 directly inhibit CYP2C enzymes in a Michaelis-Menten manner, and do so with a relatively high degree of potency according to the following rank order: CYP2C8 > CYP2C9 > CYP2C19. The IC_{50} values for MN-001 and MN-002 are 1.5 and 1.4 μM for CYP2C8; 3.8 and 8.1 μM for CYP2C9; and 25 and 28 μM for CYP219, respectively. As an inhibitor of these CYP2C enzymes, MN-001 tended to be slightly more potent than MN-002 and neither compounds exhibited evidence of metabolism- or time-dependent inhibition of CYP2C8, CYP2C9 or CYP2C19.
- MN-001 and MN-002 directly inhibited several CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 and CYP3A4/5) in a non-Michaelis-Menten manner whereby they caused little or no inhibition up to a certain concentration, after which they caused marked inhibition of these CYP enzymes by an unknown mechanism.

  Based on data from single and repeat oral dose PK study, with the proposed dose of MN-001 250 mg/day (250 mg qd), plasma concentrations may peak at ~ 575 ng/ml (~ 1.1 μM) for MN-001 and ~ 5200 ng/mL (~ 9.8 μM). These results suggest that MN-001 and MN-

002 could potentially inhibit the metabolism of concomitantly administered drugs, particularly the concomitant drugs that are substrates of CYP2C8 and CYP2C9.

5. TRIAL OBJECTIVES AND PURPOSE

This is a multi-center, proof-of-principle, open-label study designed to evaluate the efficacy, safety, and tolerability of MN-001 in non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) subjects with hypertriglyceridemia.

5.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the effects of MN-001 on Cholesterol Efflux Capacity in NASH and NAFLD subjects with hypertriglyceridemia

- To evaluate the effects of MN-001 on triglyceride levels in NASH and NAFLD subjects with hypertriglyceridemia

5.2. Secondary Objectives

The secondary objectives are:

- To evaluate the safety and tolerability of MN-001
- To evaluate PK profile of MN-001/MN-002
- To evaluate the effect of MN-001 on Lipid profile
    - HDL-C, LDL-C, Total cholesterol level
- To evaluate the effect of MN-001/002 on liver enzymes
- To evaluate the effect of MN-001/002 on the percentage of fat in the liver assessed using MRI at Week 12

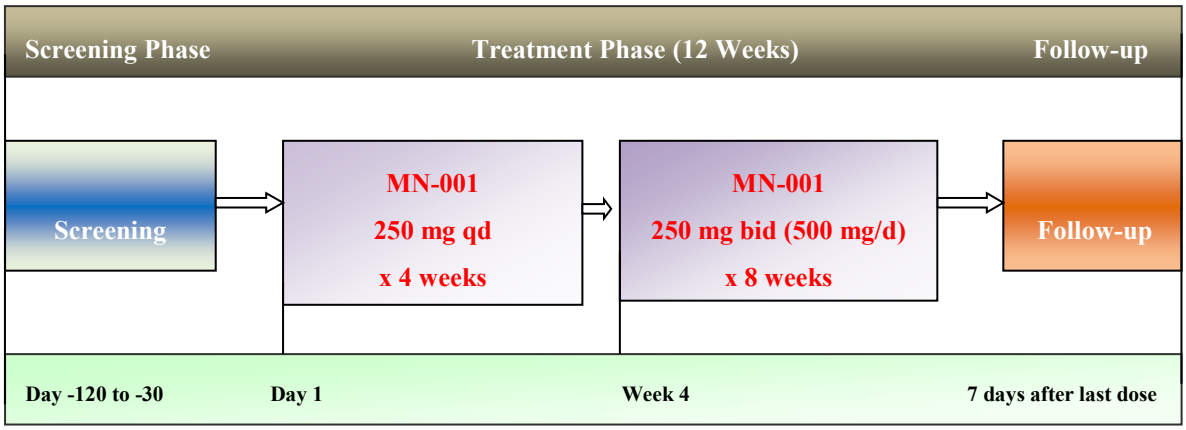
6. OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

The study will consist a Screening Phase (up to 4 months) followed by a Treatment Phase (12 weeks), and a Follow-up visit (within 1 week after the last dose).

A total of 40 male and female subjects ≥18 years of age are planned to be enrolled.

The study phases are described below and displayed in Figure 1 and the Schedule of Assessments is displayed in Table 1.

Figure 1: Study Design



6.1. Screening Phase (up to - 4 months to – 7 days)

A total of up to 4 months will be allowed to complete the screening assessments. During the Screening Phase, subjects will be assessed for study eligibility. After signing the informed consent form, the following assessments will be performed: medical history including review of prior and current medications, physical examination including height and body weight, waist circumference, vital signs and an electrocardiogram. Clinical labs, routine chemistries (including CPK, liver enzymes and fasting lipid profile), hematology, coagulation profile, urinalysis and a serum pregnancy test will be collected as well as cytokeratin-18 (CK-18), a biomarker for NASH diagnosis. An alcohol consumption questionnaire will be administered and a MRI scan of the liver will be performed. Serum fibrosis markers, the Fib-4 index (age, AST, ALT, PLT) and NAFLD fibrosis score (age, BMI, AST/ALT ratio, IFG/DM, PLT, Albumin) will be calculated.

Detailed information on permitted and excluded concomitant medications is provided in Section 8.2 and Section 8.3 of the protocol.

6.1.1. Diagnosis at Screening

Subjects must have a histologically confirmed diagnosis of NASH (NAS of ≥ 3 with at least 1 point being ballooning) by liver biopsy within the past 36 months or NAFLD confirmed by imaging studies. The diagnosis must be noted in the source documents and a copy of the report must be obtained.

6.1.2. Treatment Phase

Subjects who complete all of the screening assessments will repeat laboratory tests around 1 week prior to Treatment Day 1 (Baseline) to confirm their eligibility. Subjects who continue to be eligible will return to the clinic on Treatment Day 1 (Baseline) and be enrolled to receive MN-001 250 mg qd for 4 weeks and will take MN-001 250 mg bid (500 mg) for 8 weeks. Subjects will receive MN-001 for a total of 12 weeks. Subjects will receive their first dose of study medication on Day 1 in the clinic.

Thereafter, subjects will return to the clinic at Weeks 4, 8 and 12. During these visits, subjects will undergo safety and efficacy assessments. ECGs will be conducted at T_{max} at hour 1.5 (± 30 minutes) at each clinic visit: See Table 1 for visit schedule and procedures for all assessments.

Throughout the Treatment Phase, safety parameters will be assessed and concomitant medications will also be documented. An independent safety monitor will review the data on a regular basis during the Treatment Phase.

6.1.2.1. Pharmacokinetics

The first 6 subjects who are eligible to be dosed will stay at the clinic overnight or return to the clinic the following day for last/final blood draw. Blood samples for MN-001/002 serum concentration will be collected at the following timepoints:

- Day 1 (Baseline): prior to the first dose
- Post dose hour 0.5, 1.5, 3, 6, 9, 12, 24* (*Day2)

PK parameters will be calculated and reviewed prior to increasing the dose to 250 mg bid (500 mg/d) after Week 4.

6.1.3. Follow-up Phase

All subjects who complete the study will return for their final visit at Week 13 for safety assessments and to assess adverse event status and document concomitant medications.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Clinical Trial Population

The population for this trial will include male and female subjects ≥ 18 years of age with elevated serum triglycerides and a diagnosis of NASH by liver biopsy or NAFLD confirmed by abdominal ultrasound.

7.2. Inclusion/Exclusion Criteria

7.2.1. Inclusion Criteria

- Written informed consent is obtained and willing and able to comply with the protocol in the opinion of the Investigator.
- Male or female subjects ≥ 18 years of age
- Histologically proven NASH (NAFLD activity score of 3 or greater with at least 1 point being ballooning) based on liver biopsy performed within the last 36 months or NAFLD confirmed by imaging studies.
- Fasting serum triglyceride level > 150 mg/dL (confirmed at screening)
- Serum ALT, AST, ALP and total bilirubin levels at Screening (- 120 days to -30 days) and Lab Visit values (- 1 week ± 5 days) are stable or changes at the Lab visit are < 20% of the values from Screening.
- Subjects on the following medications can be enrolled if these medications are necessary, cannot be stopped, and the dose has been stable for 4 months or more prior to baseline:
    - Stable doses of anti-diabetic medications
    - Stable doses of fibrates, statins, niacin, ezetimibe.
    - Stable doses of Vitamin E for at least 8 weeks
- Less than 21 units of alcohol/week for men and 14 units of alcohol/week for women over a 2-year time frame
- Females of child-bearing potential must have a negative serum ß-hCG at screening and must be willing to use appropriate contraception (as defined by the investigator) for the duration of study treatment and 30 days after the last dose of study treatment.
- Males should practice contraception as follows: condom use and contraception by female partner.
- Subject is in good physical health on the basis of medical history, physical examination, and laboratory screening, as defined by the investigator.
- Subject is willing and able to comply with the protocol assessments and visits, in the opinion of the study nurse/coordinator and the Investigator.

7.2.2. Exclusion Criteria

- Diagnosis of other known cause of liver disease (autoimmune, viral, genetic, drug- or alcohol-induced, or storage disease)
- Decompensated or severe liver disease defined by one or more of the following:
    - biopsy-proven cirrhosis
    - INR >1.5
    - Total bilirubin (TBL) > 1.5 x ULN, or > 2 x ULN for unconjugated bilirubin
    - serum albumin <2.8 g/dL
    - ALT or AST > 10 x ULN
    - evidence of portal hypertension including splenomegaly, ascites, encephalopathy and/or esophageal varices
- Current diagnosis of hepatocellular carcinoma (HCC) or suspicion of HCC clinically or on ultrasound
- Uncontrolled diabetes mellitus Type 2
- History of bariatric surgery
- Greater than 10-pound weight gain or loss in the last 6 months
- Clinically significant cardiovascular/cerebrovascular disease, including myocardial infarct within last 6 months, coronary artery intervention, coronary artery bypass, unstable ischemic heart disease, heart failure class III or IV, angina or cerebral vascular accident.
- Resting pulse < 50 bpm, SA or AV block, uncontrolled hypertension, or QTcF > 450 ms
- History of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug.
- Any significant laboratory abnormality which, in the opinion of the Investigator, may put the subject at risk
- History of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer.
- History of HIV (human immunodeficiency virus), HBV, HCV (cured HCV is not excluded), EBV CMV or other active infection.
- Currently has a clinically significant medical condition including the following: neurological, psychiatric, metabolic, immunologic, hematological, pulmonary, cardiovascular (including uncontrolled hypertension), gastrointestinal, urological disorder, or central nervous system (CNS) infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study.

    *Note***:** Active medical conditions that are minor or well-controlled are not exclusionary if, in the judgment of the Investigator, they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Safety Monitor should be consulted.

- CYP2C8 substrates with a narrow therapeutic index (e.g., paclitaxel) within 15 days prior to study and throughout the study are prohibited.
- CYP2C9 substrate with narrow therapeutic index (e.g., phenytoin, S-warfarin, tolbutamide) within 15 days prior to study and throughout the study are prohibited.
- Macrolide or quinolone class antibiotics within 15 days of Screening Visit and throughout the study are prohibited.
- Steroids within 30 days prior to study drug dosing and throughout the study unless administered for a short-term treatment course during the study are prohibited.
- History of alcohol or substance abuse (DSM-IV-TR criteria) within 3 months prior to screening or alcohol or substance dependence (DSM-IV-TR criteria) within 12 months prior to screening. The only exceptions include caffeine or nicotine abuse/dependence.
- Poor peripheral venous access that will limit the ability to draw blood as judged by the Investigator.
- Currently participating, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent.
- Unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator, or was planning to relocate during the study.

7.3. Subject Withdrawal/Discontinuation Criteria

Subjects may request to be withdrawn from the study at any time for any reason.

The Investigator may interrupt the treatment of any subject whose health or well-being may be compromised by continuation in the study. The following instances require subjects to be withdrawn from the study:

- Subject fails to adequately comply with the dosing, evaluations, or other requirements of the study at the discretion of Investigator.
- Subjects who have adverse events or abnormal laboratory tests that require discontinuation of study medication;
- Subjects who, in the opinion of the Investigator, should be discontinued for their well-being;
- Subjects who are no longer able to understand task instructions or to perform tests adequately.
- Subject becomes pregnant during the study. See section 12.7 for reporting requirements and follow-up of the pregnancy.

If a subject withdraws or is removed from the study for any reason, the reason and date of discontinuation of study medication should be recorded in the appropriate section of the Case Report Form (CRF). At the time of study discontinuation, every effort should be made to ensure all Early Termination (ET) procedures and evaluations are performed.

The study sponsors reserve the right to discontinue the study at any time for medical or administrative reasons.

7.3.1. Individual Stopping Criteria

Subjects who experience an adverse event of Grade 2 nausea and/or diarrhea for greater than 3 consecutive days, or Grade 3 nausea and/or vomiting for greater than 1 day thought to be related to study drug will be discontinued from the study. Additionally, subjects who experience an adverse event of Grade 3 abdominal pain lasting for greater than 1 day thought to be related to study drug will be discontinued from the study.

Subjects with abnormal laboratory tests should be discontinued or study drug temporarily interrupted. Please see section 8.6.2 and 8.6.3 for details.

7.3.2. Study Stopping Rules

The study will be stopped if two subjects experience any Grade 4 (i.e., life-threatening consequences; urgent intervention indicated) adverse event thought to be related to study drug. The medical monitor will review the cases with the PI prior to the decision to terminate the study is made.

7.3.3. Follow-up Procedures Upon Discontinuation/Withdrawal

A termination CRF page should be completed for every subject who received study medication whether or not the subject completed the study. The reason for discontinuation should be indicated on the CRF. Any AEs that are present at the time of discontinuation/ withdrawal should be followed in accordance with the safety requirements outlined in Section 11.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

MN-001 will be provided in bottles and will be stored at room temperature.

8.2. Concomitant Medications

Concomitant medications required for the treatment of symptoms and signs of baseline disease (e.g., hypercholesterolemia, Type 2 diabetes) are permitted except as excluded below.

Concomitant medications for treatment of adverse events may be allowed. Subjects will be instructed to contact a member of the study staff prior to taking any medication.

Based on data *in vitro* CYP enzyme studies, MN-001 and MN-002 could potentially inhibit the metabolism of concomitantly administered drugs, particularly the concomitant drugs that are substrates of CYP2C8 and CYP2C9.

8.3. Prohibited Medications

The following medications are **prohibited** prior to and during study participation:

- CYP2C8 substrate with narrow therapeutic index (e.g., paclitaxel) within 15 days prior to study drug dosing and throughout the study
- CYP2C9 substrate with narrow therapeutic index (e.g., phenytoin, S-warfarin, tolbutamide) within 15 days prior to study drug dosing and throughout the study
- Macrolides and other antibiotics within 15 days prior to study drug dosing and throughout the study unless administered for a short-term treatment course during the study.
- Steroids within 30 days prior to study drug dosing and throughout the study unless administered for a short-term treatment course during the study

The medical monitor should be consulted prior to administration of a prohibited concomitant medication.

8.4. Treatment Compliance

Compliance will be monitored closely at each visit. Subjects will be instructed to bring all unused study medication with them to each visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study medication for the effectiveness of treatment and for the successful outcome of the study. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant and may be discontinued from the study per investigator's judgment.

8.5. Randomization and Blinding

This study is an open-label study; randomization and blinding are not applicable.

8.6. Dosing Guidelines

8.6.1. Treatment Phase

On Day 1, once baseline assessments are completed, subjects will be administered their first dose (one MN-001 250 mg tablet) of study drug in the clinic. Subjects will continue to take study drug once daily for 4 weeks and will increase the dose to 250 mg bid (500 mg/d) for 8 weeks.

8.6.2. Abnormal Laboratory Values

Laboratory tests should be repeated within 48 hours* after any of the following laboratory values are met:

- Develop elevations of AST or ALT greater than 2 times baseline values (BLM) or total bilirubin (TBL) is greater than 1.5 X BLM

If there are persistent elevations in ALT or AST > 2 X BLM or TBL > than 1.5 X BLM, then close observation by a hepatologist, repeat further laboratory tests, and physical examination 2-3 times per week should be initiated in order to identify the cause of liver function deterioration (i.e. potential of drug-induced liver injury (DILI).

*(*If a patient resides in a remote area, they can be tested locally and the results be communicated to the investigator site promptly)*

8.6.3. Dosing Interruption for Abnormal Laboratory Values

If the laboratory values are any of the following, then the **subjects should stop study medication**. When baseline values were:

- < 2X ULN, discontinue if ALT or AST increases to >5X BLM.
- ≥ 2X ULN but <5X ULN, discontinue if ALT or AST increases to >3X BLM
- ≥ 5X ULN, discontinue if ALT or AST increases to >2X BLM
- Discontinue if ALT or AST increase >2X BLM AND the increase is accompanied by a concomitant TBL increase to >2X BLM OR the INR concomitantly increases by >0.2.

While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in the protocol (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects must have the abnormal laboratory result rechecked at least every 2 weeks (rechecks will be run at the local laboratory if a patient lives remote area) until resolution or stabilization of the laboratory value.

After laboratory values return within normal limits, resumption of blinded study treatment is to be considered on a case by case basis and must be discussed with the Independent Medical Monitor.

8.7. Written Informed Consent

Each subject is required to provide written informed consent prior to undergoing any study procedures. A copy of the signed and dated informed consent (in a language in which the subject is fluent) is required to be given to the subject. If a subject withdraws consent, data collected up to the time of discontinuation will be used to evaluate study results.

8.8. Assessments

The Schedule of Assessments is presented in Table 1.

Clinical laboratory evaluations will be performed by a central laboratory. All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or performed during treatment must be reviewed, initialed and dated by the Principal Investigator or appropriate designee listed on Form FDA 1572.

8.8.1. Study Assessments by Visit

The following is a summary of assessments by study visit.

8.8.1.1. Screening Phase (up to – 120 to – 7 days)

Visit 1: Screening

During the Screening Phase, once the informed consent form is signed, the following assessments will be performed/collected:

- Inclusion/Exclusion review
- Medical history
- Body height/weight
- Waist circumference
- Vital signs
- Physical examination
- Electrocardiogram (12-lead)
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, coagulation profile, and urinalysis labs
- CK-18 biomarker
- Liver MRI (can be scheduled on separate date)
- Serum β-hCG (pre-menopausal females)
- Fib-4 Index
- NAFLD fibrosis score
- Prior/concomitant medication review
- Alcohol consumption questionnaire

Visit 2: Laboratory visit (-1 week ± 5 days)

Fasting safety labs and serum β-hCG (for pre-menopausal females) will be repeated around 1 week prior to Day 1 Baseline visit.

8.8.1.2. Treatment Phase (12 weeks)

Subjects who complete all of the screening assessments will return to the clinic on Treatment Day1 (Baseline) to repeat laboratory tests and physical assessments. Subjects who continue to be eligible will be enrolled to receive MN-001 250 mg qd for 4 weeks and then increase their dosage to 250 mg bid (500 mg/d) for the remaining 8 weeks (total dosing of 12 weeks). Subjects will receive their first dose of study medication on Day 1 at the clinic.

Subjects will enter the clinic in the morning prior to breakfast. Once the pre-dose fasting labs have been completed, subjects will be given breakfast.

Visit 3: Baseline Day 1

- Inclusion/Exclusion review
- Body weight/waist circumference
- Vital signs
- Physical Examination
- 12-lead ECG at hour 1.5 (± 30 minutes) post dose
- Blood sample for Cholesterol efflux capacity test
- MN-001 blood concentration sample will be collected at the following timepoints: prior to the first dose and at Hour 0.5, 1.5, 3, 6, 9, 12 and 24 (± 30 minutes) post dose for the first 6 subjects only*
- Concomitant medication review
- Adverse event review
- Dispense study drug

Once the pre-dose assessments have been completed, the subject will be administered a single dose of MN-001 with room temperature water.

* The first 6 subjects enrolled in the study will have the option to remain in the clinic overnight until the last PK blood sample is drawn or return the following day for the last/final blood draw.

Visit 4: Telephone Visit Week 2 ± 3 days

The study nurse/coordinator will telephone the subject to review adverse events and concomitant medications.

Visit 5: Week 4 ± 5 days

The following assessments will be conducted:

- Body weight /waist circumference
- Vital signs
- Abbreviated physical examination

- 12-lead ECG at hour 1.5 (± 30 minutes) post dose
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, coagulation profile, and urinalysis labs
- Urine pregnancy test (pre-menopausal female)
- Adverse event review
- Concomitant medication review
- Study drug accountability
- Subjects will be instructed to increase their dose to 250 mg bid.

Visit 6: Week 8 ± 5 days

- Body weight/waist circumference
- Vital signs
- Abbreviated physical examination
- 12-lead ECG at hour 1.5 (± 30 minutes) post dose
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, coagulation profile, and urinalysis labs
- Urine β-hCG (in pre-menopausal females)
- Adverse event review
- Concomitant medication review
- Study drug accountability

Visit 7: Week 12 ± 5 days

- Body weight/waist circumference
- Vital signs
- Abbreviated physical examination
- 12-lead ECG at hour 1.5 ± 30 minutes) post dose
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, coagulation profile, and urinalysis labs
- CK-18 biomarker
- Blood sample for Cholesterol efflux capacity test
- Liver MRI
- Urine β -hCG (in pre-menopausal females)

- Alcohol consumption questionnaire
- Adverse event review
- Concomitant medication review
- Study drug accountability/return of study drug

8.8.1.3. Follow Up Phase

Visit 8: Week 13 ± 3 days

- Body weight/waist circumference
- Vital signs
- Physical examination
- Adverse event review

Early Termination visit

Subjects who discontinued study medication will undergo the following assessments:

- Body weight/waist circumference
- Vital signs
- Abbreviated physical examination
- 12-lead ECG
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, coagulation profile, and urinalysis labs
- CK-18 biomarker
- Blood sample for cholesterol efflux
- Liver MRI
- Urine β-hCG (in pre-menopausal females)
- Alcohol consumption questionnaire
- Adverse event review
- Concomitant medication review
- Study drug accountability /return of study drug

Laboratory Re-test visit

Subjects who have an abnormal lab finding will return for a laboratory re-test visit and will have the following assessments performed:

- Fasting chemistry, hematology, or urinalysis lab, as indicated
- Adverse event review

- Concomitant medication review

8.8.2. Procedures/Assessment Details

8.8.2.1. Informed Consent

The Principal Investigator or a qualified designee (e.g., a licensed, qualified medical practitioner such as a physician's assistant or a nurse practitioner) listed on Form FDA 1572 will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent before performing any study-related procedure. Informed Consent should be conducted in accordance with local requirements. Subjects should be able to verbally describe the benefits and risks associated with this study and what other treatment alternatives are available (as described in the consent form). Only subjects who provide informed consent, as assessed and documented by the Investigator, will be enrolled.

8.8.2.2. Medical History

A medical history obtained by the PI or qualified designee as listed on the Form FDA 1572.

8.8.2.3. Prior/Concomitant Medication Review

Site study staff will record all medications taken within 1 month prior to screening visit in the CRF. Also, the following parameters will be recorded for all concomitant medications: drug name, route of administration, total daily dose, unit, frequency, start/stop dates, indication, and whether the medication was started after last dose of study medication. The concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

8.8.2.4. Physical Examination

The physical exams must be performed by the PI or qualified designee (physician, physician's assistant or nurse practitioner) listed on the Form FDA 1572. Clinically significant changes from the signing of the informed consent form (ICF) should be captured as AEs in the CRF.

A complete physical examination includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, and musculoskeletal. If the subject is discontinued for any reason, every attempt should be made to perform a final physical examination.

8.8.2.5. Vital Signs, Height, and Weight

Blood pressure (BP), heart rate (HR) measurements will be taken in a supine position. Respiratory rate and temperature will also be measured and all measurements will be recorded in the CRF. Clinically significant changes from baseline should be captured as AEs in the CRF.

Weight will be measured in pounds. Height will be recorded only at Visit 1 (screening). Waist circumference will also be recorded.

8.8.2.6. Electrocardiogram (12-Lead ECG)

All subjects will have standard resting 12-lead ECGs performed and interpreted. Subjects are to be supine for at least 5 minutes prior to ECG assessments. The time the ECG is performed will be recorded (using a 24-h clock).

The PI or a qualified designee listed on Form Food and Drug Administration (FDA) 1572 must review, initial, and date the report, which must be filed in the subject's study chart. Clinically significant findings at screening must be captured in the medical history. Any clinically significant changes compared post study drug administration must be captured as an adverse event in the CRF.

8.8.2.7. Fib-4 Index

The Fib-4 index is a non-invasive method for identification of patients with advanced fibrosis. The Fib-4 is a simple formula based on age, AST, ALT and platelets that corresponds with fibrosis stage (Martinez et al 2011).

8.8.2.8. Nonalcoholic fatty liver disease (NAFLD) Fibrosis Score

The NAFLD Fibrosis Score is a validated method of noninvasively estimating the fibrosis stage in a patient with NAFLD. This score calculates a patient's risk of fibrosis based on age, body mass index (BMI), presence of impaired fasting glucose/diabetes, platelets, albumin, ALT and AST (Angulo et al 2007).

8.8.2.9. Cytokeratin-18 (CK-18)

Cytokeratin 18 (CK-18) fragment levels correlate with the magnitude of hepatocyte apoptosis and independently predict the presence of NASH.

8.8.2.10. Adverse Event (AE) Monitoring

The PI or a qualified designee listed on Form FDA 1572 must assess the severity and relationship to study medication for all AEs (see Section 12.2).

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be recorded on the AE page(s) of the CRF.

Each PI and research team are responsible for identifying adverse events and reporting them.

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see Section 12.2) requiring immediate notification to the Sponsor or its designated representative.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality and indicate that assessment on the CRF. For AEs with a causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Sponsor concurs with that assessment.

Adverse events (serious and non-serious) including all suspected unexpected serious adverse reactions (SUSARs) should be recorded on the CRF from the date of informed consent until the

end of their participation in the study (i.e., the subject has discontinued or completed the follow-up visit).

8.8.2.11. Laboratory Evaluations

Laboratory evaluations will include the tests listed in Appendix 1.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Table 4: Study Dug Information

Investigational Drug:	MN-001
Formulation:	250 mg tablet
Frequency:	250 mg qd or 250 mg bid
Storage Conditions:	Store at room temperature

9.2. Study Drug Packaging and Labeling

At a minimum the following information will be included on each bottle:

- Name of Sponsor
- Study number/Acronym/IND number
- Route of administration
- Quantity of dosage unit
- Directions for use
- Storage conditions
- Space for information to be completed by Investigator/designee:
  - Name and telephone number of Investigator
  - Dispensing date
  - Subject number
- Statement "Caution: New Drug – Limited by federal law to investigational use"
- Statement: "Keep out of reach of children"

9.3. Study Drug Storage

The clinical study drug MN-001 should be stored at room temperature (preferably 18-23^{0}C, but 15-25^{0}C is acceptable).

9.4. Study Drug Administration

The study drug will be dispensed by appropriately qualified site study staff as indicated on the delegation of authority log. Subjects will self-administer the study drug at home except on scheduled visits to the clinic. On those days, subjects will wait until they come to the clinic to take their study medication. The subject will be instructed to return all unused study drug to the clinical trial site at each visit.

9.5. Study Drug Accountability

Investigational clinical supplies must be received by the PI or a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and/or designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol.

The PI or designee is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. At the end of the study, all clinical supplies must be returned to the Sponsor, or designee, after confirmation with the CRA (Clinical Research Associate) or destroyed at the clinical site. Study drug will not be destroyed until written documentation is received from the study sponsor or designee. Proper documentation of the destruction of study drug must be provided by the site.

The following information is to be included in the CRF: visit medication dispensed, dosing start/stop dates, dosage level, number of tablets dispensed and number of tablets returned.

10. ASSESSMENT OF EFFICACY

10.1. Primary Endpoints

The primary endpoint, cholesterol efflux, will be calculated as the percent of cholesterol removed from the cells and appearing in the culture medium normalized to a reference serum pool. The ability of serum HDL to remove cholesterol from cultured cells will be assessed as an *in vitro* method to evaluate functional changes in HDL mediated by changes due to MN-001 treatment.

Cholesterol efflux with HDL will be measured by Cholesterol Efflux Fluorometric Assay Kit (BioVision, Inc.). Detailed protocol is attached in Appendix 3.

An additional primary endpoint is will evaluate the effects of MN-001 on triglyceride level in subjects with NAFLD or NASH. The primary endpoint will be decreased triglycerides measured as the difference after 12 weeks of treatment from baseline levels. The data are expressed as the percent change from the baseline value and calculated using he equation: Change = [100%*(Endpoint value - Baseline Value)/Baseline Value]

10.2. Secondary Endpoints

Safety will be assessed by the monitoring and recording of all AEs and serious adverse events (SAEs), regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs, electrocardiograms (ECGs), and the performance of physical examinations.

Other secondary measures, lipid profile including HDL-C, LDL-C, total cholesterol level, liver enzymes and percentage of fat in the liver assessed, will be measured by the change from baseline to Week 12.

Pharmacokinetic parameters of MN-001 and its metabolite, MN-002 will be calculated in a subset of 6 subjects.

11. ASSESSMENT OF SAFETY

Safety will be assessed by the proportion of subjects with the following events:

- clinical and laboratory treatment emergent adverse events (TEAEs)
- discontinuations due to TEAEs
- treatment emergent serious adverse events (TESAEs)

Safety (relationship and severity) and tolerability will further be assessed by statistical and clinical review of AEs, laboratory values, ECGs, physical examinations, vital signs and weight.

12. ADVERSE EVENTS

12.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Adverse events may include the onset of a new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs, (e.g., those occurring during treatment-free periods, including screening or post-treatment follow-up periods), in association with study-related procedures and assessments.

12.2. Assessment of Adverse Events

The PI or an authorized physician will assess all AEs for severity, relationship with study medication, and whether it meets the criteria for classification as a SAE, requiring immediate notification to the Sponsor or designee (see Section 12.5). These assessments will be made in accordance with the standard ratings detailed in the following sections.

12.2.1. Severity Assessment

The severity of AEs will be determined as described in Table 5.

Table 5: Adverse Events Severity Definition

Mild Grade 1	Ordinarily transient symptoms that do not influence performance of subject's daily activities. Treatment is not ordinarily indicated.
Moderate Grade 2	Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary.
Severe Grade 3	Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary.
Life-threatening Grade 4	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization probable.
Death Grade 5	Death.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

12.2.2. Relationship to Study Drug

One of the following categories in Table 6 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 6: Adverse Event Causality Definition

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which cannot be explained by concurrent disease or other medications or chemicals. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other medications or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly related	A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other medications or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, occurs with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other medications, chemicals, or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, occurs with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other medications or chemicals).

[a] Dechallenge is when a medication suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from medication discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the medication, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the medication, yet medication-relatedness clearly exists (e.g., as in bone marrow suppression, fixed medication eruptions, or tardive dyskinesia)

[b] Rechallenge is when a medication suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

12.3. Recording Adverse Events

Adverse events should be collected and recorded for each subject from the date that the first study dose was taken until the end of their participation in the study (i.e., the subject has discontinued or completed the study). Only those AEs that occurred while on study drug that have not been resolved will be followed until resolution or stabilization.

Following the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Adverse events may be volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as, "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded in the subject's source documentation and transcribed onto the appropriate CRF page for the study period indicated. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be documented together with the PI or an authorized physician's assessment of the seriousness of the AE and causal relationship to study medication and/or study procedure (at the time of assessment).

All AEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the PI or an authorized physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the MedDRA.

12.4. Treatment and Follow-Up of AEs

Appropriate measures should be taken to treat AEs as necessary, and the response of the study subject should be monitored and recorded. Clinical, laboratory, and diagnostic measures should be obtained as needed, and the results of which should be recorded in the subject's source documentation and transcribed onto the appropriate CRF page.

All SAEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

12.5. Serious Adverse Events (SAEs)

An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening (i.e., a subject is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is another important medical event (see below).

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject 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 in a physician's office, blood dyscrasias or seizures that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse. A distinction should be drawn between serious and severe AEs.

Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity, but would probably not be considered an SAE.

A blood sample for MN-001 concentration will be obtained when a subject experiences a SAE.

12.5.1. SAE Reporting Requirements

The PI or an authorized delegate is responsible for faxing the requested information to the Sponsor or designee within 24 hours or as soon as possible after learning of the event. Following the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Notification should be made by emailing a completed SAE Report Form to the Sponsor. Study sites in the US should email a completed SAE Report Form to: Safetymonitors@medicinova.com.As a minimum requirement, the initial notification should provide the following information:

- Study number
- Subject number
- Gender
- Date of birth
- PI's name and full study site address
- Details of SAE
- Criterion/criteria for classification as "serious"
- Study medication name, or code if blinded, and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification).

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports, etc.), with the study subject's personal identifiers removed. All relevant information obtained by the PI or an authorized delegate through review of these documents will be recorded on the AE eCRF page and/or a new SAE Report Form and faxed to the Sponsor or designee within 24 hours of receipt of the information. If a new SAE Report Form is faxed, the PI must sign and date the form. The Sponsor may also request additional information on the SAE, which the PI or an authorized delegate must fax to the Sponsor or designee within 24 hours of the request using a new SAE Report Form, bearing the PI's signature and date.

Any AE fulfilling the criteria for expedited reporting will be reported by the Sponsor to regulatory authorities and Investigators and IEC(s) in accordance with the Sponsor's standard operating procedures (SOPs) and local regulatory requirements.

PIs should report all Investigational New Drug Application safety alerts received from the Sponsor to their local IRB/IECs.

12.6. Guidance for Overdose

There is no clinical experience with MN-001 overdose in humans and there is no available specific antidote to the effects of MN-001. Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose.

12.7. Reporting and Follow-up of Pregnancies

If any study subject or subject's partner becomes pregnant after receiving the first dose of study medication (MN-001) and until the follow-up period specified in the protocol, the PI or an authorized delegate should submit a Pregnancy Report Form to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the pregnancy. If a pregnancy is to be terminated, the anticipated date of termination should also be provided in the "Additional Information/Comments" field of the Pregnancy Report Form. If a maternal SAE is reported for the study subject during the initial notification of pregnancy, a separate SAE Report Form should also be completed and submitted to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the SAE.

Subjects who become pregnant while in the study should be followed for the duration of their pregnancy. If the pregnancy is discovered between regularly scheduled study visits, subjects should return for an unscheduled visit to return their study medication. A quantitative β-hCG should be obtained and subjects should be encouraged to return for follow-up visits. If follow-up visits are not possible, then the principal investigator should collect information about the pregnancy such as spontaneous or elective termination, details of birth, and presence or absence of birth defects, congenital abnormalities, or maternal and newborn complications.

The Sponsor will request that the PI follow the progress of the study subject's pregnancy with the doctor medically responsible for the pregnancy. A new Pregnancy Report Form should be submitted within 24 hours of the PI or an authorized delegate first becoming aware of any new information.

If additional information on the outcome of the pregnancy and/or the details of the birth/delivery is received "spontaneously" by the study site, the PI or authorized delegate should also submit a Pregnancy Report Form within 24 hours of becoming aware of the information. If the outcome of the pregnancy is reported as premature birth, or as elective termination due to a medical reason or as spontaneous or accidental miscarriage, the details of the outcome should be described in the "Additional Information/Comments" field of the Pregnancy Report Form. The pregnancy outcome will generally be reported as a follow-up report.

Complete an SAE Report Form if the delivery outcome meets the criteria for a SAE (e.g., congenital anomaly/birth defect, stillbirth, some other sickness, etc.). The SAE Report Form should be completed with the study subject's details (e.g., subject number, initials, date of birth, investigational product information, etc.) and the details of the fetal SAE and maternal complications should be described in the "Narrative" field of the SAE Report Form.

If a pregnancy is reported for the study subject's partner, the sponsor will provide instructions on how to collect pregnancy information in accordance with local requirements.

12.8. Preplanned Hospitalizations or Procedures

During the study, if a subject has a hospitalization or procedure (e.g., elective surgery) that was scheduled prior to the subject entering the study (i.e., before the subject signed the ICF) for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of an SAE. However, if the event/condition worsens during the study, it must be reported as an AE or SAE (if the event/condition results in a serious outcome such as prolongation of hospitalization.)

13. STATISTICS

The Statistical Analysis Plan (SAP) will provide comprehensive details on the statistical methods and sensitivity analyses for dealing with dropouts, planned for this study prior to database lock.

13.1. Data Analysis

13.1.1 Analysis Populations

Safety Analysis Set (SAS) will include all subjects who received at least one dose of study drug and had at least one post dose safety assessment.

Per Protocol Set: The group of subjects who received at least one dose of study drug and who did not have any major protocol deviations.

13.1.2 Statistical Analysis Plan

A statistical analysis plan will outline the efficacy analysis and safety analysis prior to database lock.

13.1.3 Sample Size Justification

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 40 subjects is deemed to be appropriate for this purpose.

13.1.4 Safety Analysis

Safety analyses will be conducted on the Safety Analysis Set.

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of study medication), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness.

Changes from baseline in laboratory values will be summarized for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed. Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed.

Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated.

Changes in vital signs from baseline to each visit will be summarized by treatment groups.

13.2. Direct Access to Source Data/Documents

By signing this protocol, the PI agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The PI also agrees to allow monitoring, audits, and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The PI shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor, or its designee, as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor, or its designee, by the PI upon request and shall also be made available at the PI's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The PI agrees to promptly take any reasonable steps that are requested by the Sponsor, or its designee, as a result of an audit to address deficiencies in the study documentation and worksheets/CRFs.

The PI will promptly inform the Sponsor or its designee of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The PI will immediately disclose in writing to the Sponsor or its designee if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

13.3. Study Monitoring

Monitoring will include on-site monitoring to assure that the investigation is conducted according to protocol, to protect subject rights and safety, and to confirm data integrity and quality.

This study will be monitored through all phases of study conduct by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Investigators will be required to store all source documents.

13.4. Audits and Inspections

The PI and appropriate personnel may be periodically requested to attend meetings organized by the Sponsor or its designee to assure acceptable protocol execution. The study may be subject to audit by the Sponsor/designee or by regulatory authorities. If such an audit occurs, the PI must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate. The PI has to inform the Sponsor if he/she is approached for a regulatory audit.

13.5. Institutional Review Board (IRB)

Before initiation of the study, the PI must obtain approval of the research protocol, informed consent form (ICF), and any advertisement for subject recruitment from the IRB complying with the provisions specified in the Code of Federal Regulations (CFR) 21 Part 56 and applicable government regulations. A copy of written IRB approval of the protocol, ICF, and advertising (if applicable) must be provided to the Sponsor or their designee prior to initiation of the study.

13.6. Study Documentation

By signing a copy of Form FDA 1572, the Investigator acknowledges that he/she has received a copy of the investigational drug brochure on MN-001 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the Sponsor's written approval.

The Investigator will supply the Sponsor with the following:

1. Original, signed Form FDA 1572
2. Curricula vitae for all Investigators listed on Form FDA 1572
3. Copy of the Investigator's medical licensure/medical registration number
4. Signed protocol signature page
5. Signed IB signature page
6. Financial disclosure forms for all study staff listed on the FDA 1572.

14. QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the Sponsor and Clinical Study Sites Principal Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) reviewed and approved by the sponsor to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

15. ETHICS

15.1. Ethics Review

Documented approval from the IRB will be obtained for all participating centers prior to clinical trial start, according to ICH (International Conference on Harmonisation) GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

15.2. Ethical Conduct of the Study

The procedures set out in this clinical trial protocol pertaining to the conduct, evaluation, and documentation of this clinical trial, are designed to ensure that the Sponsor and Principal Investigator abide by Good Clinical Practice Guidelines (GCP in the appropriate current version). The clinical trial will also be carried out in accordance with applicable local law(s) and regulation(s). This may include an inspection by representatives from MediciNova Inc. and/or Regulatory Authority representatives at any time. The PI must agree to the inspection of clinical trial-related records by MediciNova, Inc. representatives, and must allow representatives direct access to source documents.

15.3. Written Informed Consent

An information and consent form will be provided to the subject. The process of obtaining informed consent must be in accordance with applicable regulatory requirements, and must adhere to GCP and ethical principles in the Declaration of Helsinki. Written informed consent must be obtained and documented before any clinical trial-specific procedure takes place. Participation in the clinical trial and date of informed consent given by the subject must be documented in the subject files.

15.4. Confidentiality

15.4.1. Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

16. DATA HANDLING AND RECORDKEEPING

16.1. Review of Records

The results from Screening and data collected during the study will be recorded in the subject's CRF, which will be designed and provided by the sponsor or a designee. The Investigator will review all CRFs. The CRFs will be signed by the PI or a sub-Investigator who is listed on the Form FDA 1572 if the PI is unavailable. In order to maintain confidentiality, the subject will be identified only by his/her subject number and initials.

16.2. Retention of Records

The PI must arrange for retention of study records at the site for at least two years after the New Drug Application (NDA) is approved or Investigational New Drug (IND) is withdrawn, as required by the US Food and Drug Administration (FDA) regulations, or in accordance with local and/or national requirements, whichever is longer. The PI should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the PI when the destruction of documents is permitted.

17. ADMINISTRATIVE AND REGULATORY DETAILS

17.1. Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing from the Sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

17.2. Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at site(s) for safety or administrative reasons at any time. For example, a site that does not recruit at an acceptable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

17.3. Compliance with Financial Disclosure Requirements

By signing this protocol, the PI agrees to provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The PI further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by MediciNova Inc. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study. This requirement also extends to sub-Investigators. The PI also consents to the transmission of this information to MediciNova Inc. for these purposes.

18. REFERENCES

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19. APPENDICES

Appendix 1: Laboratory Safety Tests for MN-001

Blood Chemistry Tests
aspartate aminotransferase (AST)
alanine aminotransferase (ALT)
albumin
alkaline phosphatase
bicarbonate
blood urea nitrogen
calcium
chloride
creatinine
creatine phosphokinase (CPK)
gamma-glutamyl transferase
phosphorous
potassium
sodium
total bilirubin[a]
total protein
lactate dehydrogenase
triglyceride
serum cholesterol
serum high-density lipoprotein cholesterol
serum low-density lipoprotein cholesterol
glucose
Endocrine Tests
serum beta-human chorionic gonadotropin (for females of childbearing potential)
urine beta-human chorionic gonadotropin
Hematology Tests
white blood cell count
white blood cell differential
eosinophilic leukocyte count
basophilic leukocyte count
neutrophil count
lymphocyte count
monocyte count
platelet count
hemoglobin
blood hematocrit
red blood cell count
red cell distribution width
red blood cell indices:
mean corpuscular volume
mean corpuscular hemoglobin concentration
mean corpuscular hemoglobin
Coagulation Tests
INR
PT
APTT

Urinalysis Tests
color
appearance
total ketones
urobilinogen
bilirubin
red blood cells
leukocyte esterase
nitrite
pH
protein
specific gravity
glucose
microscopic evaluation[b]

[a] Bilirubin will be fractionated (direct serum bilirubin test/indirect serum bilirubin test) if elevated 2.0 times the upper limit of the normal range.

[b] Microscopic evaluation will be performed if dipstick analysis indicates the presence of any significant abnormality.

Appendix 2: Informed Consent Form

"MODEL" INFORMED CONSENT

This is a "Model" informed consent provided by MediciNova, Inc., only as a guide for the convenience of the Principal Investigator and the affiliated institution. It is the responsibility of each Investigator and institution to draft and obtain IRB approval of an Informed Consent that complies with Regulatory guidelines and ethical standards for their particular site. Any use, in whole or in part, of this "Model" Informed Consent shall be at the sole discretion of said Investigator and institution, and MediciNova, Inc., shall have no liability for the form or content of the Informed Consent adopted for actual use by said Investigator and institution.

Informed Consent

Protocol Number:	MN-001-NATG-201
Protocol Title:	An Open-Label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of MN-001 (tipelukast) in Non-alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD) Subjects with Hypertriglyceridemia
Protocol Date:	June 6, 2016
Investigator:	{*Investigator Name/Address}*

1. General Information

You are being asked to participate in a research project to study MN-001 (tipelukast) because you are diagnosed with Non-alcoholic steatohepatitis (NASH) or Non-Alcoholic Fatty Liver Disease (NAFLD) and your blood triglyceride level is high. Before agreeing to participate in this research study sponsored by MediciNova, Inc, it is important that you read and understand this document. It describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. If you are not completely truthful with your doctor regarding your health history, you may harm yourself by participating in this study. If this form contains any words that you do not understand, please ask your study doctor or member of the study staff to explain them to you.

2. About the Study

The purpose of this research study is to evaluate the effectiveness and safety of MN-001 on subjects with NASH or Non-Alcoholic Fatty Liver Disease (NAFLD) and high triglyceride level. This will be assessed by looking at how the drug affects your blood cholesterol function and triglyceride level.

The name of the investigational drug that you may take in this study is MN-001. "Investigational" means that the drug has not been approved by the Food and Drug Administration (FDA). Animal

and human studies have shown that MN-001 may be useful for treating the NASH and blood lipid profile.

Approximately 40 subjects will participate in this research study. Your participation in this study will last for approximately 13 weeks. You can expect a total of 7 study visits (including 1 telephone visit) during this time, although more visits may be required if your Study Doctor decides they are needed for medical reasons.

3. Study Eligibility

To participate in this study,

- Male or female and must be at least 18 years of age
- Diagnosis of NASH by liver biopsy or NAFLD confirmed by imaging studies with elevated blood triglyceride level
- All females must not be pregnant or nursing, and must be practicing an acceptable method of birth control
- All males should practice contraception for the duration of study treatment and 30 days after the last dose of study treatment as follows: condom use and contraception by female partner
- You must currently not be participating in another clinical study and not have participated in another clinical study in the previous 3 months to signing this informed consent
- No other significant diseases, such as heart attack within 6 months, unstable ischemic heart disease, etc.

During your study participation there are certain medications that you will not be allowed to use. These medications are listed under *Prohibited Medications* in Section 10 of this form. Please discuss any new medication that you would like to take during study participation with your study doctor **prior to starting** this study and discuss the medication you are currently taking.

4. Description of the Procedures

This is an open-label study. This means that you will receive the active drug (MN-001 tablets). You will be instructed to take MN-001 250 mg tablet once a day for first 4 weeks. After 4 weeks, you will start taking a MN-001 250 mg tablet twice a day for the next 8 weeks.

If you qualify to participate, you will receive study medication at Baseline Visit and continue for total of 12 weeks. Study medication will be taken once a day for first 4 weeks. After the Week 4 visit, you will start to take study drug 2 times per day, morning, and evening (for example, 7 AM and 9 PM).

On Baseline visit (Day 1 of study), you may be asked to stay overnight at the study center and blood samples will be collected before and after taking medication. Blood samples will be used to evaluate the study drug concentration.

After baseline visit, this study requires 4 more visits (Week 4, Week 8, Week 12, and Week 13/Follow-up) to the clinic over a period of approximately 13 weeks. The clinic visits will require you to be in the clinic for approximately 2-3 hours for a physical exam, ECG test, and blood test.

You must fast (no food or liquid intake) after midnight before each clinic visit. You must not drink alcoholic beverages for at least 6 hours prior to each visit. No caffeinated food, beverages, or medications will be allowed for at least 6 hours before each visit.

5. Study Visits and Procedures

During your regular follow-up clinical visit, your doctor will ask you if you are interested in participating in the study. If you are interested in the study, your doctor will give you "Informed consent" (this form) to review. After reading the form carefully and if you are interested in the study, your doctor can determine whether you are eligible to participate in the study when you return for your next clinic visit. You will receive no study drug at pre-treatment visits.

Screening Phase

Screening Visit (This Visit will last approximately 2-3 hours)

If you read the informed consent form and are still interested in participating study, the tests listed below will be conducted to evaluate your eligibility

- Vital signs, physical exam, body weight, height and waist circumference.
- Review your medical history and medication you are taking
- 12 lead- ECG test
- Blood test and Urine test
- Liver MRI (MRI may be scheduled on different day)

Treatment Phase

Baseline visit: This Visit will last approximately 1 hour

If you are eligible for the study, you will be asked to return to the clinic later. During this visit, the Study Doctor will

- Check vital signs
- Perform a blood pregnancy test (if you are pre-menopausal female)
- Review your other medications
- Provide you with study medication. The first dose will be taken at the clinic. (Selected patients will stay at the research center overnight and blood samples will be collected multiple times before and after taking study drug)
- Perform a 12-lead ECG after about 1.5 hour after first dose
- Schedule next visit for 4 weeks later

Telephone visit

At Week 2, you will be called by a study team member (for example, a study coordinator or nurse) to collect information regarding your health status. Your medications and any adverse events will be documented.

Clinic Visits (Week 4, 8 and 12): These Visits will last approximately 2-3 hours

- Vital signs, physical exam, body weight / waist circumference
- Review your medication
- 12 lead- ECG test
- Blood draw
- Urine pregnancy test (if you are pre-menopausal female)

If you decide to discontinue from the study early, you need to come back to the clinic to complete evaluations for an "Early termination" visit.

Follow-up visit

You will be asked to come back to the clinic about 1 week after your last dose.

This visit will last approximately 1 hour and the following assessments will be performed:

- Physical examination
- Vital signs
- Adverse event review
- Concomitant medication review

6. Subject Responsibilities

As a subject in this study, you have certain responsibilities to help ensure your safety. These responsibilities are listed below:

Complete all required visits.

- Take the study medication as prescribed. You will be asked to withhold your morning dose of study medication on the day of each clinic visit. On the day of your appointment, the morning dose of study medication will be administered at the clinic.
- Report all side effects and medical problems to your doctor or the study coordinator.
- Inform the study doctor or staff if you decide to discontinue your participation at which time you will be required to complete a close-out visit.

7. Potential Benefits

There is no guarantee that you will benefit from study participation. The study treatment may result in an improvement in your blood lipid profile or you may have no improvement at all.

8. Potential Risks and/or Discomforts

Tipelukast is an investigational drug that has been evaluated in clinical trials in the U.S. and other countries. More than 600 individuals have been exposed to tipelukast to date.

Based on past experience, common side effects of MN-001 are the following:

- diarrhea /loose stools
- headache
- nausea

Other side effects associated with tipelukast are vomiting and dizziness. The majority of side effects was mild and reversible.

Additionally, in a MN-001 study of subjects with interstitial cystitis, there was one event that was serious and considered possibly related to MN-001 by the treating physician: an infant, whose mother became pregnant during her study participation, was born with a birth defect in the right eye.

9. Cautions and Warnings

Serious allergic reactions that can be life-threatening may occur.

All study medication must be taken only by the person for whom it has been prescribed. The study medication is not in a package that is resistant to opening by children.

10. Pregnancy/Birth Control

Female subjects

The risks of taking MN-001 to pregnant women on an unborn baby are unknown. For this reason, females must have a negative pregnancy test before the study starts and again at

Visit 3. You must not become pregnant during this study. If you are a female of childbearing potential, you must use an effective form of birth control during this study. Acceptable methods of birth control include

- consistent use of an approved oral contraceptive (birth control pill)
- an implantable contraceptive (such as Norplant®)
- an injectable contraceptive (Depo-Provera®)

Note: If your primary birth control method is one of these first three methods (that is, hormonal) you are encouraged to add the use of a barrier method and spermicide since the effect MN-001 may have on hormonal methods has not yet been determined.

- a double-barrier method (diaphragm with spermicide, condom with spermicide)
- abstinence

Oral, implantable, or injectable contraceptives are only considered effective if used properly and started at least 30 days prior to the screening visit. Some drugs (e.g., antibiotics) may interact with hormonal contraceptives, making them not work properly. Please inform your Study Doctor of all other medications you are taking. If you suspect that you may have become pregnant during the study, you must contact the study doctor immediately. Your study doctor may want to follow you and the progress of your pregnancy until the baby is born. The effect of MN-001on a nursing infant is also unknown; if you are breastfeeding, you cannot participate in the study.

Male subjects

Male subjects should be advised that the effects of the study drug on the male reproductive system are not known at this time, and contraceptive methods should be used throughout the study and for 30 days after completion of the study. It is recommended that both partners use contraception. If you suspect your partner may be pregnant you must contact the study doctor immediately. Your study doctor may want to follow the progress of your partner's pregnancy until the baby is born.

Prohibited Medications

During your study participation there are certain medications that you will not be allowed to use. Please discuss any new medication that you would like to take during study participation with your Study Doctor prior to starting this study and discuss the medication you are currently taking.

- CYP2C8 substrate with narrow therapeutic index (for example, paclitaxel) within 15 days prior to starting study drug and throughout the study
- CYP2C9 substrate with narrow therapeutic index (for example, phenytoin, S-warfarin, tolbutamide) within 15 days prior to starting study drug dosing and throughout the study
- Macrolides and other antibiotics within 15 days prior to starting study drug dosing and throughout the study unless administered for a short-term treatment course during the study
- Steroids within 30 days prior to starting study drug dosing and throughout the study unless administered for a short term treatment course during the study.

11. Compensation for Research-Related Injury

You can obtain medical treatment for an injury related to treatment with MN-001 at the

[Insert Institution's Name Here]. Please ask your Study Doctor for more details. If you believe you have been injured as a result participating in this study, please contact your study doctor immediately.

If you have any injury that is related to treatment with study drug, MediciNova will pay for the reasonable cost of necessary medical care to the extent the cost is not paid by your commercial medical insurance, or another party. You may not be compensated for uninsured medical care if you do not follow instructions regarding proper use of the study drug. If you have an injury related to treatment with the study drug, your doctor will decide what medical care you need. MediciNova will not pay for the normal progress of your disease, or any injury or complication due to the medical condition you already have. MediciNova will not provide any other kind of compensation such as compensation for lost wages, disability or discomfort. You do not give up any of your legal rights by signing this consent form.

Neither the sponsor nor the study doctor has a program in place to provide other compensation in the event of an injury.

12. Alternative Treatments

If you do not wish to participate in this study, you will continue to be treated by your doctor and your care will not be jeopardized in any way. Your doctor may continue with your current treatment regimen with modifications that you and your doctor agree are appropriate.

13. Publication of Information and Confidentiality of Subject's Name

All reasonable measures to protect the confidentiality of your study records and your identity will be taken to the extent permitted by the applicable laws and/or regulations, and will not be made publicly available. ***U.S. Federal Privacy Regulations require that you authorize the release of any health information that may reveal your identity. The persons and entities that you are authorizing to use or disclose your individually identifiable health information may include the study doctor, the study staff, the Institution, and the Sponsor. In order to analyze the data collected during this research study, all of the health***

information generated or collected about you during the study may be inspected by MediciNova, Inc. or the authorized agents of MediciNova, the FDA, the Department of Health and Human Services (DHHS) other government regulatory agencies from other countries, the study center ethics committee (Internal Review Board).

The results of this study may be presented at meetings or in publications; however, your identity will not be disclosed in these presentations. By signing this informed consent form, you are authorizing such access to your medical records. ***This authorization will not have an expiration date.***

14. Voluntary Participation and Termination of Participation

Your participation in this research study is voluntary. You can choose not to participate in this study either at the beginning or at any time during the study. Your choice will not have an adverse impact on your present or future health care. There will be no penalty or loss of benefits to which you are otherwise entitled. To ensure your safety, you will be asked to undergo a final evaluation visit. If you wish to withdraw from the study, you should contact:

(*Insert name of study doctor*) or study personnel at (*insert phone no*.).

You may also revoke the authorization to use or disclose personal information about your health. If you choose to withdraw your authorization, you must notify the study doctor in writing and you will be withdrawn from the study. The study doctor's mailing address is:

(Insert Principal Investigator's name and mailing address)

The study doctor will still be able to use the information collected about you prior to your withdrawal from the study. Information that has already been sent to the study sponsor cannot be withdrawn.

Your participation in this study may be discontinued without your consent by the investigator or the sponsoring company if you fail to follow the investigator's instructions. You may also be withdrawn from the study if, in the investigator's opinion, the study drug is ineffective, harmful, or has medically unacceptable side effects, or for other reasons at the discretion of the sponsor or investigator. If you are withdrawn from the study, you will be asked to have the appropriate medical tests and follow-up to evaluate your health and safety.

15. Who to Contact to Ask Questions about Your Rights as a Research Subject

This research project has been reviewed by *the (insert name of board) or* institutional review board (IRB)/ independent ethic committee (IEC). This committee or board is a group of individuals from the community responsible for the review and approval of research proposals to be conducted. If you have questions about your rights as a research subject, you may contact:

The *(insert name of IRB/IEC)*, at *(insert phone number).*

16. Subject's Consent to Participate

I have read the above information, have been given the opportunity to ask questions, and my questions have been answered to my satisfaction. By signing this form, I voluntarily consent to participate in the research study***. I am also authorizing the use and disclosure of my personal health information. I cannot participate in this research study without this authorization. If I refuse to give my authorization, my medical care will not be affected.*** I will be given a copy of this signed consent form. I hereby elect to participate in this research study.

Signature Page

Subject Name (Print)	
Subject Name (Signature)	Date
Legally Authorized Representative (Print) (If Applicable)	Relationship to Subject
Legally Authorized Representative (Signature) (If Applicable)	Date
Name of Person Conducting Consent Discussion (Print)	
Person Conducting Consent Discussion (Signature)	Date
Investigator Name (Print)	
Investigator Name (Signature)	Date

Appendix 3: Cholesterol Efflux Study Protocol

Cholesterol Efflux Assay Protocol

The procedure described below is for macrophage cell line J774.1. This procedure can also be used with macrophage cells derived from THP-1 monocytes, by addition of 100 nM phorbol 12-myristate 13-acetate (PMA) for 48 h.

1. Label Cells:

Grow J774.1 cells in RPMI 1640 media containing 10% FBS in cell culture flask till ~90% confluency (37°C incubator containing 5% CO2). Split cells under sterile conditions using basic cell culture techniques & plate approximately 1 x 105 J774.1 cells/well in a 96-well plate (white plate with clear bottom) using 100 2l media/well. Grow for 2 h in a 37°C incubator containing 5% CO_2. After 2 hours, when the cells are attached to the plates, wash the cell monolayer with RPMI 1640 media (no serum added). Premix 50 2l of Labeling Reagent and 50 2l of Equilibration Buffer containing Reagent A and B/well just before use. Add 100 2l mix/well. Incubate the plate overnight (16 hrs.) in a 37°C incubator containing 5% CO_2.

Notes:

a. To test the background fluorescence, add 100 2l of Equilibration Buffer containing Reagent A and B to the cell monolayer. Don't add labelling reagent to the background control well(s).

b. For accurate assay, we recommend each treatment and control to be performed in triplicates.

2. Treat Cells:

After 16 h, remove the Labeling Reagent. Wash the cells gently by adding 200 2l of RPMI media (no serum) to all the wells. Remove the media. Treat cells with desired cholesterol acceptors in RPMI media. If using human serum as cholesterol acceptor, pre-treat the serum with Serum Treatment Reagent. Add 2 parts of Serum Treatment Reagent to 5 parts of human serum (Ratio 2:5).

Incubate for 20 min. on ice. Centrifuge the mixture at 9,000 x g, for 10 min. at 4°C. Use the supernatant to treat the cells as desired and make up the volume to 100 2l by RPMI media. For Positive Control, add 20 2l of Positive Control & make up the volume to 100 2l by

RPMI media. For no treatment control, add 100 2l RPMI media (no serum) to no treatment control well(s). Incubate cells for 4-6 h. in a 37°C incubator containing 5% CO_2.

3. Measurement:

At the end of incubation, transfer supernatant to a 96-well plate (white plate). Measure the fluorescence (Ex/Em = 482/515 nm). Solubilize the cell monolayer by adding 100 2l of Cell Lysis Buffer and shaking on a plate shaker for 30 min at room temperature. Pipette up and down to dissolve any cell debris. Measure the fluorescence (Ex/Em = 482/515 nm).

4. Calculations:

Cholesterol efflux of the treatments is calculated by dividing the fluorescence intensity of the media by total fluorescence intensity of the cell lysate of the same treatment & media. This value is multiplied by 100 to obtain % Cholesterol Efflux. Subtract %

Cholesterol Efflux obtained from no treatment control from the treatment groups to determine the final % Cholesterol Efflux.

$$\% \text{ Cholesterol Efflux} = \frac{\text{Fluorescence intensity of the media}}{\text{Fluorescence intensity of the cell lysate + media}} \times 100$$

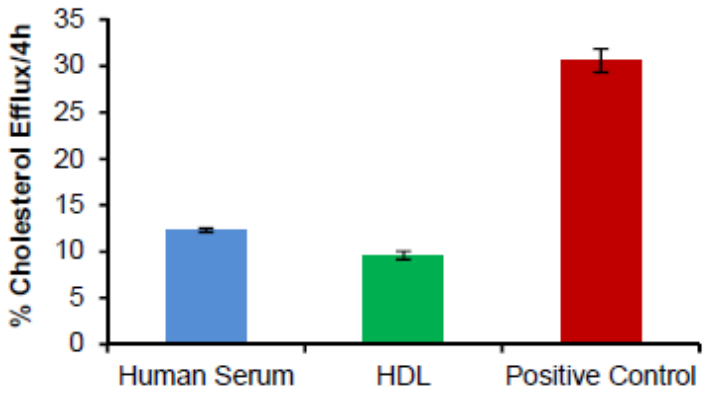

Figure: Percentage (%) Cholesterol Efflux: J774.1 cells were labeled with the Labeling Media and treated with various cholesterol acceptors like Human Serum, HDL (50 2g) or Positive control known to cause cholesterol efflux. Cholesterol efflux is expressed as % efflux elicited by cells in 4h.

1 STATISTICAL ANALYSIS PLAN

STUDY TITLE	An Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of MN-001 (tipelukast) on HDL (High Density Lipoprotein) Function and Serum Triglyceride Levels in Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD) Subjects with Hypertriglyceridemia
SPONSOR	MediciNova, Inc. 4275 Executive Square, Suite 300 La Jolla, California 92037
PREPARED BY	Kazuko Matsuda, M.D., Ph.D., M.P.H. Chief Medical Officer MediciNova, Inc. Malath Makhay, Ph.D., MWC Director, Medical Writing, MediciNova, Inc.
SAP VERSION	2.0, July 23, 2020
PREVIOUS SAP VERSION AND DATE	1.0, August 12, 2019
IND NO.	123659
PHASE OF STUDY	Phase 2a
PROTOCOL NO.	MN-001-NATG-201
PROTOCOL VERSION AND DATE	Amendment 3, August 14, 2017
NCT NO.	02681055
REVISIONS	Signature Page added Background, Rationale sections added General Statistical Considerations section added List of Tables and Listings was split into 2 Tables: Table of Tables, Table of Listings

CONFIDENTIALITY STATEMENT

The information being provided in this protocol is considered confidential, proprietary trade secret information as defined by the Federal Trade Secrets Acts and is thus protected from disclosure to unauthorized parties under the Freedom of Information Act. This protocol shall be considered a confidential document that provides information for the sole use of clinical Investigators for the referenced study, their teams, and the study site Institutional Review Boards/Ethics Committees (IRB/EC).

2 SIGNATURES

I give my approval for the Statistical Analysis Plan v2.0, for the study entitled, "An Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of MN-001 (tipelukast) on HDL (High Density Lipoprotein) Function and Serum Triglyceride Levels in Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD) Subjects with Hypertriglyceridemia."

Kazuko Matsuda, M.D., Ph.D., M.P.H.	Chief Medical Officer, MediciNova, Inc.
Name	Title
	
	23 July 2020
Signature	Date

3 TABLE OF CONTENTS

4 ABBREVIATIONS AND DEFINITIONS

ABBREVIATION

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
$AUC_{0\rightarrow t}$	Area Under the Concentration vs. Time Curve
$AUC_{0\rightarrow\infty}$	Area Under the Concentration Versus Time Curve, from Time 0 to Infinity
Bid	Twice Daily
Cmin	Minimum Concentration
C_{max}	Maximum Concentration
Clast	Concentration at the time of the last measurable concentration
CRF	Case Report Form
CSS	Concentration Steady-State
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ER	Extended-Release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H	Hour
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IR	Intermediate-Release
IRB	Institutional/independent Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
QD	Once Daily
QT	Time Between the Beginning of the QRS Complex and the End of the T-Wave
QTcB	QT interval using Bazette's correction
QTcF	QT interval using Fridericia's correction
SAE	Serious Adverse Event
SD	Standard Deviation
SAP	Statistical Analysis Plan
$t_{1/2}$	Terminal Elimination Half Life
t_{max}	Time to Maximum Measured Concentration
Tid	Three Times Daily
λz	Terminal Elimination Rate Constant

DEFINITIONS

Adverse Event	An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of causality assessment.
Full Analysis Set Population	Group of randomized subjects who received at least 14 days of study drug and had at least one post-dose efficacy measurement.
Safety Analysis Set Population	Group of subjects who received at least one dose of study drug and had at least one post-dose safety assessment.
PK population	PK sample collection of the first 6 subjects enrolled in the study.
Serious AE	An AE occurring at any dose that: results in death; is a life-threatening experience; requires inpatient hospitalization or prolongation of an existing hospitalization; results in a persistent or significant disability/incapacity; or is a congenital anomaly/birth defect in the offspring of a patient who received study drug.
Treatment-emergent AE	AEs occurring from the time of first dose through 7 days after the last dose or that is already present prior to the first dose of study drug and becomes more severe post-dose

5 INTRODUCTION

5.1 Background

The purpose of this statistical analysis plan (SAP) is to outline in detail the statistical methods, data derivations, and presentations of data so that valid conclusions can be reached to address the study objectives outlined in the MN-001-NATG-201 protocol Amendment 3, dated 14 August 2017.

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

5.2 Rationale

Preclinical and clinical studies have shown that MN-001 treatment improves lipid profile and protects the liver in patients with comorbidities of NASH or NAFLD and elevated serum triglyceride levels.

In an in vivo NASH mouse model, MN-001 (10, 30 and 100 mg) or placebo was administered to male mice for 3 weeks. MN-001 significantly reduced fibrosis in a dose-dependent manner ($P <$ .01) as demonstrated by a reduction in liver hydroxyproline content, supporting MN-001's anti-fibrotic properties. MN-001 improved NASH pathology by inhibiting hepatocyte damage ($P <$ .01) and ballooning ($P <$ .01).

In a Phase 1 trial (Protocol no. MN-001-CL-003), the pharmacokinetics, safety, and tolerability of MN-001 at 750 mg BID vs 500 mg TID were evaluated in healthy volunteers. Additionally, sponsor conducted two Phase 2 trials to evaluate MN-001 in patients with asthma (Protocol no. MN-001-CL-001) and in patients with interstitial cystitis (MN-001-CL-002). Results from clinical laboratory assessments throughout these clinical trials , MN-001 showed a decrease in serum triglyceride levels, i.e., improvement, while subjects given placebo showed unchanged or increased serum triglyceride levels. These findings warranted a closer examination of MN-001's potential utility as a treatment for hypertriglyceridemia.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

Co-Primary Objectives:

- To evaluate the effects of MN-001 on triglyceride levels in NASH and NAFLD subjects with hypertriglyceridemia;
- To evaluate the effects of MN-001 on Cholesterol Efflux Capacity in NASH and NAFLD subjects with hypertriglyceridemia.

Secondary Objectives:

- To evaluate the safety and tolerability of MN-001;

- To evaluate PK profile of MN-001/MN-002 (metabolite) in first 6 enrolled subjects;
- To evaluate the effect of MN-001 on lipid profile
  - HDL-C, LDL-C, total cholesterol level;
- To evaluate the effect of MN-001/002 on liver enzymes;
- To evaluate the effect of MN-001/002 on percentage of fat in the liver assessed using MRI at Week 12.

6.2 Study Endpoints (Outcome Variable)

Co-Primary Outcome Variables

- Mean change from baseline on serum triglyceride levels at Week 8

The primary endpoint is to evaluate the effects of MN-001 on serum triglyceride level in NASH and NAFLD with hypertriglyceridemia. The serum triglycerides will be measured as the difference after 8 weeks of treatment from pre-treatment serum triglyceride levels. Pre-treatment triglyceride level will be defined as the highest value of serum triglyceride at screening visit or baseline visit. The data are expressed as the percent change from the baseline value and calculated using he equation: Change = [100%*(Endpoint value - Baseline Value)/Baseline Value]

- Mean change from baseline on cholesterol efflux capacity at Week 12

Cholesterol efflux capacity in the subjects will be quantified at National Institute of Biomedical Innovation, Osaka, Japan using the method previously reported (Ogura et al 2016). Percent efflux will be calculated by the following formula: [(μCi of 3H-cholesterol in mediums containing 2.8% apolipoprotein B–depleted serum –μCi of 3H-cholesterol in serum-free mediums)/μCi of 3H-cholesterol in cells extracted before the efflux step] × 100. All assays will be performed in duplicate. To correct for inter-assay variation across plates, a pooled serum control from eleven healthy volunteers was included on each plate, and values for serum samples from patients were normalized to the value of the pooled sample in subsequent analyses.

Secondary Outcome Variables

- Treatment-emergent adverse events (TEAEs) and Treatment-emergent serious adverse events (SAE);
- Discontinuations of treatment for any reason;
- Treatment discontinuations due to TEAEs;
- Treatment discontinuations due to treatment-related AEs or SAEs;
- Changes from baseline for safety clinical laboratory tests;
- Changes from baseline in vital signs and 12-lead ECG;
- Lipid profile (serum HDL-C, LDL-C, total cholesterol level), liver enzymes (ALT and AST) changes from baseline;
- Changes of liver fat content (%) assessed by MRI from baseline to post treatment MRI.

7 STUDY DESIGN

7.1 General Study Design and Plan

This is a multi-center, proof-of-principle, open-label study designed to evaluate the efficacy, safety, and tolerability of MN-001 in subjects diagnosed with non-alcoholic steatohepatitis (NASH) or NAFLD with hypertriglyceridemia. Subjects will receive MN-001 250 mg qd for the first 4 weeks and will take 250 mg bid for an additional 8 weeks. Subjects will receive MN-001 for a total of 12 weeks. Anticipated enrollment is 20-40 subjects.

7.2 Inclusion-Exclusion Criteria and General Study Population

Eligible subjects will consist of males and female participants ≥18 years of age. To be eligible, subjects must have a histologically confirmed diagnosis of NASH within 36 months of baseline visit or NAFLD confirmed by imaging studies and an elevated serum triglyceride (>150 mg/dL) at screening. Diagnosis of other known cause of liver disease, current diagnosis or suspicion of hepatocellular carcinoma, decompensated or severe liver disease, and uncontrolled diabetes mellitus Type 2, are major exclusionary criteria.

7.3 Randomization and Blinding

This is an open-label study; therefore, randomization and blinding are not applicable.

7.4 Study Assessments

Please see Schedule of Events in Table 1.

Table 1 Schedule of Events

Phase	**Screening**		**Treatment**					**Follow-up**
Tests and Evaluations	**Day -120 to Day -7**	**– 1 week ± 5 days**	**Baseline Day 1-2***	**Week 2 ± 3 days**	**Week 4 ± 5 days**	**Week 8 ± 5 days**	**Week 12/ET** ± 5 days**	**Week 13 ± 5 days**
Type of Visit	**Clinic**	**Lab**	**Clinic**	**Tel**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
Inclusion/exclusion criteria review	X		X					
Medical history	X							
Physical examination	X		X		X	X	X	X
Body height	X							
Body weight/Waist circumference	X		X		X	X	X	X
Vital signs	X		X		X	X	X	X
Alcohol consumption questionnaire	X						X	
Pregnancy test (serum /urine)	X (serum)	X (serum)			X	X	X	
12-lead ECG	X		X		X	X	X	
Clinical labs (chemistry, incl CPK, hematology, lipid panel coagulation profile including INR, urinalysis)	X	X			X	X	X	X
CK-18 biomarker	X						X	
Fib-4 Index calculation	X							
NAFLD fibrosis score	X							
Blood Sample for Cholesterol Efflux			X				X	
MN-001 plasma concentration ***			X					
Liver MRI[a]	X****						X****	
Adverse event review			X	X	X	X	X	X
Concom med review	X		X	X	X	X	X	
Study Drug Dispensing			X					
Study Drug Accountability				X	X	X	X	

* Baseline visit will be overnight stay for selected 6 subjects from whom PK samples will be obtained
** ET: Early termination visit
*** PK sample for MN-001/002 will be also obtained when subjects experience SAE
**** Liver MRI can be scheduled on different day of each lab/clinic visit
[a] Pre-treatment Liver MRI may be performed between Day -120 and Day -1prior to Baseline Day 1

8 GENERAL STATISTICAL CONSIDERATIONS

8.1 Determination of Sample Size

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 20 subjects is deemed to be appropriate for this purpose.

8.2 Statistical Software

Statistical analyses will be performed using SAS (SAS Institute, NC, USA). Cholesterol efflux capacity and percent (%) fat in liver assessed by MRI will be reported and calculated by EXCEL.

Summary Statistics

Data will be summarized with respect to disposition, demographics, pre-treatment characteristics, safety outcomes, tolerability, and efficacy outcomes. Summary statistics for continuous variables will include the number of subjects, the mean, median, standard deviation, and range. For categorical data, summaries will include counts and percentages.

Biomarkers and clinical outcomes will be summarized longitudinally from baseline to Week 8 or Week 12, with means and standard deviations at each timepoint.

8.3 Precision

Results will be reported to 3 significant figures. Percentages will be reported to 0.1 percentage points. *P*-values will be reported to two digits when ≥ .095, to three digits when ≥ .00095 and < .095, and as < .001 for all smaller values.

9 ANALYSIS POPULATION

For purposes of analysis, the following sets are defined:

Population	Description
All Subjects	All subjects enrolled
Safety Analysis Set	All subjects who received at least one dose of study drug and had at least one post dose safety assessment.
Intent-to-treat Set	All randomized subjects in the groups to which they are randomly assigned, regardless of their adherence to the inclusion-exclusion criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.
Per Protocol Set	All subjects who received at least one dose of study drug and no major protocol deviations.
PK population	All subjects who received at least 1 dose of study drug (MN-001) and have evaluable PK data, and complete scheduled post-dose PK measurements without protocol deviations, violations, or events include, but may not be limited to, vomiting occurring within 30 minutes following oral dosing, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK sampling. In the case of a significant protocol deviation, PK data collected during the affected treatment period will be excluded from summary statistics but will be included in individual subject listings.

10 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Two listings will be presented for Subject Disposition and Major Protocol Deviations as defined below.

10.1 Subject Disposition

All enrolled subject disposition will be presented.

Number of subjects in the following categories will be summarized as appropriate:

- Enrolled
- Safety Population
- PK Population

Additionally, a summary on study completion status will be presented:

- Completed study among subjects enrolled;
- Prematurely discontinued the study and the reasons for discontinuations as follows:
    - Adverse Event
    - Informed Consent Withdrawn
    - Lost to Follow-Up
    - Other reason, specify

10.2 Protocol Deviations

The following will be considered as major protocol violations:

Protocol deviations are collected and will further be evaluated by the sponsor to determine whether the violation affects the efficacy and/or safety measurements for the subject.

Major deviations will be defined as the following:

- Eligibility Criteria not met – any deviation from the inclusion / exclusion criteria in the protocol will be considered major
- Informed consent – missing consent
- Dose administration errors
    - Incorrect (high, low) dose administered to subject
- Unreported SAEs
- Any other instance in the opinion of the sponsor and investigator that adversely affects the safety of the subject or the integrity of the study data

10.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects, including age, sex, race, ethnicity, Fib-4 Index score, and NAFLD score. Summary statistics (e.g., number of subjects, mean, median, standard deviation, and range) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for

categorical variables (e.g., gender, ethnicity, and race). Age will be presented as captured in the Screening visit CRF.

10.4 Medical History

Medical and surgical history will be coded according to the latest version of MedDRA and summarized by system organ class and preferred term.

10.5 Prior and Concomitant Medication

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced and categorized as follows:

Prior medication is any medication that started before initial dosing of study drug, regardless of when it ended.

Concomitant medication is any medication received at or after the dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

A given medication can be classified as a prior medication or a concomitant medication or both. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial dosing or concomitantly, it will be considered as both prior and concomitant.

11 EFFICACY ANALYSIS

11.1 Serum Triglyceride Level

The primary endpoint is to evaluate the effects of MN-001 on serum triglyceride level in NASH and NAFLD with hypertriglyceridemia. The serum triglycerides will be measured as the difference after 8 weeks of treatment from pre-treatment serum triglyceride levels. Pre-treatment triglyceride level will be defined as the highest value of serum triglyceride at screening visit or baseline visit. The data are expressed as the percent change from the baseline value and calculated using the equation: Change = [100%*(Endpoint value - Baseline Value)/Baseline Value].

11.2 Cholesterol Efflux Capacity

Cholesterol efflux capacity in the subjects will be quantified at National Institute of Biomedical Innovation, Osaka, Japan using the method previously reported (Ogura et al 2016). Percent efflux will be calculated by the following formula: [(μCi of 3H-cholesterol in mediums containing 2.8% apolipoprotein B–depleted serum –μCi of 3H-cholesterol in serum-free mediums)/μCi of 3H-cholesterol in cells extracted before the efflux step] × 100. All assays will be performed in duplicate. To correct for inter-assay variation across plates, a pooled serum control from eleven healthy volunteers will be included on each plate, and values for serum samples from patients will be normalized to the value of the pooled sample in subsequent analyses.

11.3 Other Secondary Efficacy Analysis

Other secondary measures, lipid profile including serum HDL-C, LDL-C, total cholesterol level, liver enzymes (ALT and AST) will be measured by the change from baseline to Week 8 and Week 12. The percentage (%) of fat in the liver assessed by MRI will be measured by the changes from baseline MRI to post treatment MRI.

12 PHARMACOKINETICS ANALYSIS

Pharmacokinetic parameters of MN-001 and its metabolite, MN-002 will be calculated in a subset of 6 subjects. The following parameters are to be calculated from MN-001/MN-002 plasma concentrations:

Parameter	Description of Parameter
t_{max}	Time from the start of dosing at which the maximum concentration was observed.
C_{max}	Maximum observed concentration.
AUC_{0-t}	Area under the concentration versus time curve from the start of dose administration to the last quantifiable point within the dosing interval.
λ_z	Terminal rate constant calculated from the terminal slope of the log-linear regression of concentration with time.
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$
$AUC_{0-\infty}$	Area under the concentration versus time curve from time 0 to infinity calculated as $AUC_{0-t} + C_{last}/\lambda_z$ where C_{last} is the last quantifiable concentration.

13 SAFETY ANALYSIS

Safety analyses will be based on the Safety Analysis Set.

13.1 Adverse Events

All AEs occurring after the subject signed Informed Consent Form (ICF) will be reported and will be coded using the latest version of MedDRA dictionary.

An overall summary of the number and percentage of subjects with AEs, subjects that lead to discontinuation of study drug, AEs related to study drug (the relationship will be categorized as “related” or “unrelated”, where “related” includes investigator terms of “Possibly Related” and “Probably Related”), SAEs, and SAEs related to study drug will be presented by treatment. Also, the AEs will be presented by SOC, PT and treatment. In addition, subjects with AEs in various severity categories (mild, moderate, severe, and life-threatening) will be presented based on the maximum severity of a specific AE for a subject.

Listings of individual by-subject data for any subject experiencing an SAE will be provided separately. All AEs will also be presented in individual by-subject data listings.

13.2 Clinical Laboratory Assessments

For each subject, clinical laboratory parameters including hematology, chemistry will be listed by visit.

13.3 Vital Signs

Vital signs will include systolic and diastolic blood pressure, respiration rate and pulse rate. Pre-dose values, the values at the final visit, and changes from pre-dose will be summarized for each of the quantitative laboratory assessments.

13.4 Electrocardiogram (ECG)

For standard 12-lead ECG, the summary statistics results for heart rate, QT interval, PR interval, QRS interval, QTcB, and QTcF, the values will be listed by subject, along with the overall clinical interpretation.

14 DATA PRESENTATION

Tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the “footer” or bottom of each table and listing will include the following information:

- Date and time of output generation;
- Program name;
- Any other output specific details that require further elaboration.

15 TABLES AND LISTINGS

15.1 Table of Tables

Table Number	Table Description
14.1	**Demographic Data**
14.1.1	Subject Disposition (including discontinued subjects)
14.1.2	Summary of Protocol Deviations
14.1.3	Demographics and Baseline Characteristics
14.1.4	Summary of Medical History
14.1.5	Prior and Concomitant Medications (Safety Population)
14.1.6	Study Drug Exposure
14.2	**Efficacy**
14.2.1	Summary of Serum triglyceride – Mean Change from Baseline to Week 8
14.2.2	Summary of Serum Lipid Panel – Mean Change from Baseline to Week 8
14.2.3	Summary of Liver Enzymes (ALT, AST) – Mean Change from Baseline to Week 8
14.3	**Safety Data**
14.3.1	**Display of Adverse Events**
14.3.1.1	Number of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)
14.3.1.2	Number of Subjects with Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)
14.3.1.3	Number of Subjects with Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Intensity (Safety Analysis Set)
14.3.1.4	Number of Subjects with Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Relationship (Safety Analysis Set)
14.3.1.5	Number of Subjects with Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)
14.3.1.6	Number of Subjects with Treatment-emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term (Safety Analysis Set)
14.3.2	**Listings of Serious and Significant Adverse Events**
14.3.3	**Narratives of Serious and Certain Other Significant Adverse Events**
14.3.4	**Abnormal Laboratory Value Listing (Each Subject)**
14.3.4.1	Summary of Hematology by Visit (Safety Analysis Set)
14.3.4.2	Hematology – Shift from Baseline by Visit (Safety Analysis Set)
14.3.4.3	Summary of Serum Chemistry by Visit (Safety Analysis Set)
14.3.4.4	Serum Chemistry – Shift from Baseline by Visit (Safety Analysis Set)
14.3.4.5	Summary of Vital Signs by Visit (Safety Analysis Set)
14.3.4.6	Summary of Electrocardiogram Results by Visit (Safety Analysis Set)
14.3.4.7	Shift from Baseline in Electrocardiogram Finding and Overall Impression by Visit (Safety Analysis Set)
14.3.4.8	Abnormal QTc Interval (ms) by Visit (Safety Analysis Set)

15.2 Table of Listings

Listing Number	Listing Description
16.2	**Subject Data Listings**
16.2.1	Discontinued Subjects
16.2.1.1	Disposition
16.2.2	Protocol Deviations
16.2.2.1	Major Protocol Deviations
16.2.3	Subjects Excluded from the Efficacy Analysis
16.2.3.1	Subject Eligibility
16.2.4	Demographic Data
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2.1	Medical History
16.2.4.2.2	Alcohol Consumption
16.2.4.3.1	Serum Pregnancy
14.2.4.3.2	Urine Pregnancy
16.2.4.4	Prior and Concomitant Medications
16.2.5	Study Drug Exposure
16.2.6	Individual Efficacy Response Data
16.2.6.1	Triglyceride Levels – Change from Baseline to Week 8
16.2.6.2	Cholesterol Efflux Capacity – Change from Baseline to post treatment
16.2.6.3	Lipid Profile (serum HDL-C, LDL-C, total cholesterol, Liver Enzymes (ALT, AST) – Changes from Baseline to Week 8 and to Week 12
16.2.6.4	Percent (%) fat in Liver – Change from Baseline to Post-treatment MRI
16.2.7	Adverse Event Listings (by Subject)
16.2.7.1	Treatment-emergent AEs
16.2.7.2	Treatment-emergent SAEs
16.2.7.3	Treatment-emergent AEs leading to study discontinuation, study drug interruption, or death
16.2.7.5	Treatment-related AEs
16.2.7.6	Treatment-related SAEs
16.2.8	Listing of Individual Laboratory Measurements by Subject, when Required by Regulatory Authorities
16.2.8.1	Hematology (all subjects)
16.2.8.2	Serum Chemistry (all subjects)
16.2.8.3	Vital Signs (all subjects)
16.2.8.4	Physical Examination (all subjects)
16.2.8.6	12-lead ECG (all subjects)
16.3	**Case Report Forms**
16.3.1	CRFs for Serious Adverse Events and Withdrawals for AE
16.3.2	Other CRFs Submitted
16.4	**Individual Subject Data Listings (U.S. Archival Listings)**

16 REFERENCE

Ogura M, Hori M, Harada-Shiba M. Association between cholesterol efflux capacity and atherosclerotic cardiovascular disease in patients with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2016; 36:181-8.