Clinical Trial Protocol: MSDC-0602K-C009NASH

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 12-Month, Multiple-Dose Study to Evaluate the Safety, Tolerability and Efficacy of Three Dose Levels of MSDC-0602K in Patients with NASH (EMMINENCE™)
Study Number	MSDC-0602K-C009NASH
Study Phase:	Phase 2
Product Name:	MSDC-0602K Tablets
Indication:	Non-alcoholic steatohepatitis (NASH)
Sponsor:	Cirius Therapeutics, Inc.
Medical Monitor:	Bill Welder, MD Chiltern International Inc. Phone: +1 (423) 990-0471
Chief Medical Officer and After Hours Medical Monitor:	Howard C. Dittrich, MD Cirius Therapeutics, Inc. Phone: +1 (858) 333-6274, ext. 508

	Date
Original Protocol:	04 March 2016
Amendment 1	22 May 2016
Amendment 2	23 June 2016
Amendment 3	11 October 2016
Amendment 4	31 July 2017

SPONSOR SIGNATURE

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 12-Month, Multiple-Dose Study to Evaluate the Safety, Tolerability and Efficacy of Three Dose Levels of MSDC-0602K in Patients with NASH (EMMINENCE™)
Study Number:	MSDC-0602K-C009NASH
Amendment Number:	Amendment 4
Amendment Date:	31 July 2017

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed:_____ Date:_____

Howard Dittrich, MD
Chief Medical Officer
Cirius Therapeutics, Inc.

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 12-Month, Multiple-Dose Study to Evaluate the Safety, Tolerability and Efficacy of Three Dose Levels of MSDC-0602K in Patients with NASH (EMMINENCE™)
Study Number:	MSDC-0602K-C009NASH
Amendment Number:	Amendment 4
Amendment Date:	31 July 2017

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with Good Clinical Practice guidelines. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in this protocol. I also agree to handle all clinical supplies provided by the sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information.

It is obligatory that the Investigator become familiar with all the sections of the MSDC-0602K Investigator's Brochure prior to initiation of the study.

Signed:_____ Date:_____
Principal Investigator Signature

_____
Principal Investigator Name (print)

SYNOPSIS

Sponsor:	Cirius Therapeutics, Inc.
Name of Finished Product	MSDC-0602K Tablets
Name of Active Ingredient	MSDC-0602K
Study Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 12-Month, Multiple-Dose Study to Evaluate the Safety, Tolerability and Efficacy of Three Dose Levels of MSDC-0602K in Patients with NASH (EMMINENCE™)
Study Number	MSDC-0602K-C009NASH
Study Phase	Phase 2
Study Design	This is a randomized, double-blinded study of three doses of MSDC-0602K (62.5, 125 and 250 mg) or placebo given orally once daily to subjects with biopsy proven NASH with fibrosis and no cirrhosis. Subjects will be stratified by presence of T2DM (Yes/No), use of Vitamin E ≥ 400 IU (Yes/No) and fibrosis score (F1 or ≥ F2) to ensure equal representation across all groups. The primary efficacy endpoint will be assessed at 12 months. Visits to the clinic will be at baseline, 1, 2, 3, 6, 9, and 12 months, with one 2-week follow-up visit.
Subject Population	Subjects with biopsy proven NASH (NAS ≥ 4; at least one point in each category) with F1 to F3 fibrosis score. Subjects with demonstrated cirrhosis, or evidence of other chronic liver diseases to include active hepatitis, excess alcohol consumption, documented hemochromatosis or other metabolic liver diseases, or autoimmune hepatitis will be excluded from the trial. Females should be postmenopausal or surgically sterilized. Subjects must have signed an informed consent.
Planned Number of Subjects	Approximately 380 subjects will be randomized with the intent to have 340 subjects complete the 12-month assessment (4 groups; approximately 85 subjects/group) at approximately 50 to 75 sites in the US. Sites in other regions may be added. Subjects who do not complete the study will not be replaced.

Test Product, Dose, and Mode of Administration	Size #00 opaque gelatin capsules will be prepared using MSDC-0602K tablets or matching placebo capsules containing micro-crystalline cellulose. All doses will be taken orally with about 8 ounces (one glassful) of room temperature water at least 30 minutes before each morning meal Dose levels for MSDC-0602K will be 62.5, 125, and 250 mg. Each subject will self-administer one capsule per day.
Duration of Treatment	This study will be comprised of a maximum 42-day Screening period, a treatment period of 360 days and a 14-day follow-up period. The total duration of the study for each subject will be up to 416 days, including follow-up.
Pharmacokinetic Variables	Blood samples for trough PK analysis of MSDC-0602 and MSDC-0597 (the hydroxymetabolite) will be taken at Study Visits 2, 4, 5, 6 and 7 (Days 30, 90, 180, 270 and 360).
Efficacy Variables	
Primary Efficacy Endpoint	Hepatic histological improvement in NAS defined as a decrease of at least 2 points with no worsening of fibrosis stage at 12 months. The reduction in NAS must include at least a 1 point reduction in either ballooning or inflammation. No worsening of fibrosis is defined as no increase in CRN fibrosis score.
Secondary Efficacy Endpoints	1. Proportion of subjects with resolution of NASH with no worsening of fibrosis at 12 months. Resolution of NASH is defined as a ballooning score of 0 and an inflammation score of 0-1. No worsening of fibrosis is defined as no increase in CRN fibrosis score. 2. Proportion of subjects with improvement of fibrosis (CRN staging score) by at least 1 stage with no worsening of NASH at 12 months. 3. Mean change from baseline in NAFLD activity score (NAS) and each one of its components (steatosis, inflammation and ballooning) at 12 months. 4. Mean change from baseline in fibrosis score at 12 months.

Exploratory Efficacy Endpoints	1. Mean change in liver stiffness as measured by transient elastography (FibroScan) (change from baseline relative to placebo at 12 months). 2. Change from baseline relative to placebo for liver function tests (ALT, AST, ALP, GGT, bilirubin, albumin, PT and INR) at 6 and 12 months, and biomarkers and indirect measures of apoptosis and liver fibrosis (CK-18 [M30 and M65], Fibrosure, APRI, FIB-4 index, Pro C_3-C3 and ELF score and its individual components (HA, PIIINP, TIMP-1) at 12 months. 3. Changes from baseline relative to placebo in circulating inflammatory markers (HMW adiponectin and hsCRP) and markers of bone metabolism (osteocalcin and serum CTX) at 6 and 12 months. 4. Changes from baseline relative to placebo in FFA, serum triglycerides and fasting cholesterol (total, HDL, LDL, VLDL) at 6 and 12 months and changes from baseline of NMR analysis of lipoprotein particle size at 12 months. 5. Changes from baseline relative to placebo in markers of insulin sensitivity: HOMA-IR, HbA1c, fasting plasma glucose, and fasting insulin at 6 and 12 months. 6. Changes from baseline relative to placebo in blood pressure (systolic and diastolic), heart rate, weight, and abdominal girth at 6 and 12 months. 7. Changes from baseline relative to placebo at the 12 month endpoint in the pathologist's general impression as to the three categories of diagnosis: 1) NASH, 2) Simple/isolated steatosis with no steatohepatitis (NASH), or 3) No fatty liver disease (no NAFLD). 8. Changes from baseline relative to placebo in subjects with PNPLA3 variants and other genotypes.
Eligibility Criteria	
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Adult subjects at least 18 years of age. 2. Histological evidence of NASH, based on biopsy, with a NAS (NASH CRN scoring) ≥ 4 with a score of at least 1 in each component of NAS 3. Histological evidence of liver fibrosis defined as NASH CRN System fibrosis score of F1 to F3

	4. Qualifying liver biopsy must be within 9 months prior to or during Screening. If no usable liver biopsy is available within 9 months prior to Screening, a liver biopsy must be performed during Screening after the following criteria are confirmed: a. AST ≥ 20 U/L b. FibroScan with CAP score ≥ 270 db/m and kPa ≥ 8.5
	5. Subjects with type 2 diabetes mellitus (DM) must be under stable and reasonable control, defined as under a healthcare provider's care for DM with glycosylated hemoglobin [HbA1c] ≤ 9.5%. Subjects taking permitted anti-diabetic therapies (metformin, GLP-1 agonists, SGLT2 inhibitors, sulfonylureas or DPP4 inhibitors) must be on stable doses for a period of at least 3 months prior to randomization. Refer to Section 6.4 for additional clarification about the use of antidiabetics.
	6. Subjects taking Vitamin E must be on a stable dose (if ≥ 400 IU) for a period of at least 3 months prior to randomization.
	7. Females must be either postmenopausal (at least 12 months since last menses) or surgically sterilized (bilateral tubal ligation, bilateral oopherectomy and/or hysterectomy) verified by a follicle-stimulating hormone (FSH) test result ≥ 40 mIU/mL. Those with FSH <40 or with bilateral tubal ligation must use a barrier method of birth control. In addition, all females must have a negative pregnancy test at Screening and Day 1 regardless of childbearing potential. For postmenopausal women only, if FSH levels are above 40 mIU/mL and serum pregnancy results are indeterminant, the subject will be assessed as not pregnant. Males with female partners of child-bearing potential must agree to use adequate contraceptive methods (including a condom, plus one other form of contraception) if engaging in sexual intercourse.
	8. Body Mass Index (BMI) ≤ 50 kg/m^2.
	9. Willing and able to sign an informed consent document indicating understanding of the purpose of and procedures required for the study and willingness to participate in the study.
	10. Willing and able to attend all study visits and undergo all protocol-specified procedures including liver biopsies at baseline and at the end of study treatment (one year).

Subject Exclusion Criteria	1. Known history of HIV. 2. Prior liver transplantation. 3. Other well-documented causes of active chronic liver disease, including, but not restricted to: history of positive hepatitis B surface antigen (HBsAg) or HCV RNA (subjects must be viremia free for a minimum of 2 years), suspicion of drug-induced liver disease, alcoholic liver disease and auto-immune hepatitis, Wilson's disease hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, genetic hemochromatosis, known or suspected HCC, history of planned liver transplant or current MELD score > 12. 4. History of cirrhosis and/or hepatic decompensation including ascites, hepatic encephalopathy or variceal bleeding. Platelet count < 100,000/μL of blood at Screening. 5. AST or ALT > 5 times the upper limit of normal at Screening. 6. Total bilirubin > 1.8 mg/dL unless diagnosis of Gilbert's disease or serum albumin < 2.5 gms/dL at Screening. 7. INR ≥ 1.5 times ULN at Screening or other evidence of impaired coagulation. 8. History of alcohol abuse or drug abuse within 6 months of Screening. 9. Inability to safely obtain a liver biopsy. 10. Current or history of Type 1 diabetes mellitus. 11. Current or history of recent (≤ 6 months) use of ursodeoxycholic acid. 12. Current use of any diabetes medications other than metformin, GLP-1 agonists, SGLT2 inhibitors, sulfonylureas or DPP4 inhibitors three months prior to the baseline diagnostic liver biopsy or during the study unless as specified in the protocol. Current use of insulin or PPARγ agonists (pioglitazone or rosiglitazone) is not allowed for the duration of the study. Refer to Section 6.4 for additional clarification about the use of antidiabetics. 13. Use of concomitant medications with a known significant metabolism by CYP2C8 or CYP2C9 including paclitaxel, phenytoin, warfarin, celecoxib, tolbutamide, or replaglinide for the duration of the study.

	14. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma within the 6 months prior to randomization. 15. History of heart failure (including CHF) or previous cardiovascular event (acute coronary syndrome, myocardial infarction, coronary by-pass surgery, or catheter based coronary intervention) within the 6 months prior to randomization. 16. Serum creatinine >2 mg/dL at Screening. 17. Current or recurrent disease that may affect the action, absorption or disposition of the study treatment, or clinical or laboratory assessments. 18. Current or history of severe or unstable disorder (medical or psychiatric) requiring treatment that may make the subject unlikely to complete the study. 19. Blood pressure greater than 160/100 mmHg. Subjects with elevated BP (but < 160/100 mmHg) with or without current treatment are allowed at the discretion of the Investigator and primary care physician. Individuals with hypertension must have been stabilized to the current treatment regimen for at least 6 weeks prior to randomization. 20. Known or suspected intolerance or hypersensitivity to the study drugs, closely related compounds or any of their stated ingredients. 21. Participation in an investigational study (other than a non-treatment registry study) or received an investigational drug within 30 days or 5 half-lives (whichever is longer) prior to randomization. 22. Blood donation of 1 unit or more within 56 days of randomization. 23. Plasmapheresis or plasma donation within 30 days of randomization. 24. Single 12-lead ECG demonstrating a screening QTc > 450 msec in men and > 470 msec in women. A single repeat ECG may be done at the Investigator's discretion. 25. Any surgical or medical condition which may significantly alter the absorption of the study drug including, but not limited to the following: history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling, or gastric banding, currently active inflammatory bowel syndrome. Subjects

	with reversal of gastric sleeve or banding are allowed. 26. Evidence of clinically relevant pathology that could interfere with the study results or put the patient's safety at risk. 27. Malignancy, including leukemia and lymphoma (excluding basal cell and squamous cell skin cancers and localized prostate cancer) not treated within the last 2 years.
Safety Assessments	Safety will be assessed by periodic measurement of vital signs, 12-lead electrocardiogram (ECG), physical examinations and the occurrence of adverse events (AEs). Fasting blood samples for central lab analyses of clinical chemistries and hematology will be collected at each study visit (Screening and Study Visits 1-8). Samples for urinalysis will be collected at Screening and all Study Visits except Visits 2 and 3.
Statistical Plan and Methods	Sample Size Each of the three MSDC-0602K dose groups will be compared to the placebo group at the two-sided 0.05 significance level; 85 subjects per arm provides approximately 80% power to detect a difference in response rates of 39.5% in any MSDC-0602K dose group versus 20% response rate in the placebo group. Assuming 10% of subjects will not complete the 12-month assessment due to early discontinuation, approximately 380 subjects will be randomized to the study. The randomization ratio is 1:1:1:1. Plan for statistical analysis The modified Intent-to-Treat analysis set (mITT, see Section 11.2 for details), including treated subjects in the treatment group to which randomized, will be used in the analysis of the primary endpoint. The other key efficacy response related endpoints will also use mITT for the main analysis. A responder with respect to the primary endpoint will be defined as having a 2 point reduction in NAS (NASH CRN scoring) with no concurrent worsening of fibrosis defined as progression of at least one stage (using the NASH Clinical Research Network (CRN) fibrosis staging system). The reduction in NAS must include at least a 1 point reduction in either ballooning or inflammation. Comparisons between each active treatment group and the placebo group with respect to the primary efficacy endpoint will be evaluated using appropriate contrasts from a logistic regression model that includes adjustments for randomization stratification factors and baseline NAS. Model-adjusted odds ratios and their 95% confidence intervals (CI) will be provided. In addition, the stratum-

	adjusted response rate differences between each dose group and the placebo group and their associated 95% CIs will be provided. An exploratory evaluation of the homogeneity of comparisons across the randomization stratification factors will be provided. The secondary response-related, binary efficacy endpoints will also be analyzed using logistic regression adjusting for the randomization stratification factors. Model-adjusted odds ratios and their associated 95% confidence intervals will be provided. The mean change from baseline secondary endpoints will be analyzed using Analysis of Covariance (ANCOVA) models adjusted for the stratification factors and the baseline score**.** An interim analysis of exploratory and safety endpoints is planned after all subjects have been randomized into the study and 6-month data are available on a minimum of 300 randomized subjects.

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LIST OF TABLES

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine transaminase (SGPT)
ANCOVA	Analysis of covariance
APRI	Aspartate aminotransferase-to-platelet ratio index
AST	Aspartate transaminase (SGOT)
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration-time curve calculated over the dosing interval
B-hCG	Beta human Chorionic Gonadotropin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CHF	Congestive Heart Failure
CK-18	Cytokeratin-18
Cmax	Maximum plasma concentration
CRN	Clinical Research Network
CPRU	Clinical Pharmacology Research Unit, Investigational Site
(e)CRF	(electronic) Case Report Form
CRO	Contract Research Organization
CTX	C-terminal telopeptide
DM	Diabetes Mellitus
DBP	Diastolic Blood Pressure
DPP4	Dipeptidyl peptidase-4
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELF	Enhanced liver fibrosis score
FFA	Free fatty acids
FIB-4	Fibrosis 4 score
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating hormone

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practices
GLP-1	Glucagon-like peptide-1
HA	Hyaluronic acid
hERG	Human ether-a-go-go
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HEENT	Head Ears Eyes Nose and Throat
HIV	Human Immunodeficiency Virus
HMW	High molecular weight
HOMA-IR	Homeostasis model assessment-insulin resistance
hsCRP	High-sensitivity C-reactive protein
HR	Heart Rate
IATA	International Air Transport Association
IC20	Inhibitory Concentration 20%
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IXRS	Interactive Response System
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
miRNA	Micro RNA
MedDRA	Medical Dictionary for Regulatory Authorities
MELD	Model for End-Stage Liver Disease
MRS	Magnetic resonance spectroscopy
MSDC	Metabolic Solutions Development Company
mTOR	Mechanistic Target of Rapamycin
mTOT	Mitochondrial Target Of the Thiazolidinediones
NAFLD	Non-alcoholic fatty liver disease
NAS	Non-alcoholic fatty liver disease (NAFLD) activity score (Sum of scores for steatosis, lobular inflammation and

	ballooning, ranging from 0 to 8)
NASH	Non-alcoholic steatohepatitis
NMR	Nuclear magnetic resonance
NOAEL	No-Observable Adverse Effect Level
OTC	Over the counter
PIIINP	Amino-terminal peptide of type III collagen
PD	Pharmacodynamic
PI	Principal Investigator
PIC	Powder in Capsule
PK	Pharmacokinetic
PNPLA3	Patatin-like phospholipase domain-containing protein 3
PP	Per Protocol
PPARγ	Peroxisome proliferator-activated receptor gamma
Pro-C3	N-terminal type III collagen propeptide
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
QTc	Corrected QT interval
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGLT2	Sodium-glucose linked transporter member 2
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TEAEs	Treatment emergent adverse events
TG	Triglycerides
TIMP-1	Tissue inhibitor of metalloproteinases
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1 STUDY ADMINISTRATION STRUCTURE

1.1 Medical Monitors

Bill Welder, MD
Chiltern International Inc.
Phone: +1 (423) 990-0471

1.2 Chief Medical Officer and After Hours Medical Monitor:

Howard C Dittrich, MD
Cirius Therapeutics, Inc.
Phone: +1 (858) 333-6274, ext. 508

1.3 SAE Reporting Contact Information

Serious adverse events (SAEs) should be reported by completing the AE eCRF in the EDC system and completing and submitting the SAE report form by e-mail (GlobalSAEInbox@chiltern.com) or by fax (1-888-726-8416) within 24 hours after the Investigator becomes aware of their occurrence. Section 9.1.7 contains details regarding reporting of SAEs.

2 BACKGROUND AND RATIONALE FOR THE STUDY

2.1 Background

MSDC-0602K is a novel insulin sensitizer that interacts with a newly identified mitochondrial target (mTOT, **m**itochondrial **T**arget **O**f the **T**hiazolidinediones), while sparing direct activation of the PPARγ receptor believed to be associated with side effects of volume expansion and weight gain related to the first generation of insulin sensitizers which were marketed as PPARγ agonists (1-3). As an mTOT modulating insulin sensitizer, MSDC-0602K has a favorable pharmacological profile to treat fatty liver disease including non-alcoholic steatohepatitis (NASH). The effects of MSDC-0602K have been evaluated in two animal models of fatty liver disease. In the first model, C57B1/6J mice were fed a diet providing 60% of its calories as fat for 10 weeks (C57 DIO mice) and then administered a high fat diet containing either no drug or MSDC-0602K 30 mg/kg for 2 to 4 weeks. Treatment of these mice resulted in a number of positive effects associated with the insulin-sensitizing pharmacology, including a complete clearance of fat from the liver once the high fat diet was removed. Consistent with the proposed mechanism of action, MSDC-0602K treatment reduced the activation of mTOR in the liver and resulted in changes that favored lipid oxidation over lipid storage (4). Since the C57 DIO mouse model does not develop liver lesions that are representative of NASH, similar studies were repeated in C57 mice fed a diet containing a high content of trans fat (40% of calories, mainly trans-oleic and trans-linoleic acids) together with cholesterol (2%) and fructose (22%). This diet produces scarring of the liver and a liver pathology with ballooning that is characteristic of NASH. Treatment of these mice with MSDC-0602K after 4 weeks of this diet through 16 weeks of age produced a significant reduction in the portal tract pathology even though the mice were retained on the diet throughout the 16 week period. These data suggest that MSDC-0602K should be effective in the treatment of NASH.

2.2 Summary of Preclinical Safety of MSDC-0602

2.2.1 Safety Pharmacology

MSDC-0602 did not induce adverse neurofunctional (5) or pulmonary effects (6) in rats at doses up to the limit dose of 2000 mg/kg/day. *In vitro*, MSDC-0602 inhibited the hERG-mediated potassium current with an IC_{20} (unbound drug concentration) of 20.2 μM (7490 ng/mL). However, the hydroxymetabolite MSDC-0597 inhibited the hERG-mediated potassium current by only 7.62% at 33 μM (12,300 ng/mL), the highest concentration that could be tested based on solubility (7). Given the high degree of binding of MSDC-0602 and MSDC-0597 to plasma proteins in humans (>98%) (8), free concentrations associated with hERG inhibition *in vitro* are unlikely to be achieved *in vivo*. In the cardiovascular safety study in monkeys given up to the limit dose of 1000 mg/kg/day, no effects on heart rate, blood pressure, or ECG parameters including QT interval were noted (9).

2.2.2 Toxicology

The nonclinical safety profile of non-micronized MSDC-0602 was evaluated in rats and monkeys given once daily oral doses for up to 28 days (10,11). Pharmacokinetic studies of the micronized MSDC-0602 in the vehicle used in toxicology studies indicated that systemic exposures to both MSDC-0602 and MSDC-0597 were approximately 2.5-fold higher in rats and approximately 6-fold higher in monkeys than after administration of non-micronized compound. Consequently, the nonclinical safety profile of micronized MSDC-0602 was also evaluated in mice, rats and monkeys given once daily oral doses for up to 15 days. Subsequent pharmacokinetics studies demonstrated that even higher systemic exposure to both MSDC-0602 and MSDC-0597 was achieved following administration of MSDC-0602K (12,13). Since MSDC-0602K was selected for continued development, the nonclinical safety profile of MSDC-0602K was also evaluated in mice, rats and monkeys in repeated dose studies up to 52 weeks.

In 13-week studies, there were no MSDC-0602K-related deaths in mice given up to 2000 mg/kg/day (14) or in monkeys given up to 1000 mg/kg/day for 13 weeks (15). In the 13-week study in rats, 2 females given 2000 mg/kg/day had drug-related deaths; the highest nonlethal dose was 300 mg/kg/day (16). Decreases in red cell mass, and increases in liver and heart weight were observed in all 3 species; these effects were reversible. In rodents, the organ weight increases were accompanied by hepatocellular and cardiac myofiber hypertrophy. Increased adipocytes were seen in bone marrow in all 3 species, but hematopoietic cells were unaffected. Macrovesiculation of brown adipose tissue was noted in monkeys. There was biochemical and ultrastructural evidence of peroxisome proliferation in rats but not in monkeys. The NOAEL in the primary toxicology species, rats and monkeys, were 30 and 100 mg/kg/day, respectively. The mean combined-sex steady-state $AUC_{0\text{-}24}$ of pharmacologically active species (MSDC-0602 + MSDC-0597) at the NOAEL was 1,040,000 ng·hr/mL in rats and 549,000 ng·hr/mL in monkeys.

The chronic toxicity of MSDC-0602K was evaluated in rats given up to 60 mg/kg/day for 26 weeks (17) and in monkeys given up to 300 mg/kg/day for up to 52 weeks, including a 26-week interim sacrifice group (18). There were no MSDC-0602K-related deaths in rats treated for 26 weeks or in monkeys treated for up to 52 weeks. Body weight and food consumption were increased in rats but not in monkeys. Decreases in red cell mass were noted in both species.

Heart weights were increased in rats but there were no accompanying histopathologic or histomorphometric changes. No effects on heart weight or histopathology or histomorphometry of the heart were observed in monkeys. Echocardiographic examinations did not identify any drug-related changes in heart chamber size, systolic performance, or hemodynamics in monkeys after 26 or 52 weeks. Liver weights were increased in monkeys but there were no associated histopathologic changes. Increased adipocytes in bone marrow were seen in rats and monkeys but hematopoietic cells were unaffected in all but a few rats. Macrovesiculation of intrascapular brown adipose tissue was observed in monkeys at ≥30 mg/kg/day. Urothelial vacuolation in urinary bladder and/or renal pelvis was observed in monkeys at ≥30 mg/kg/day. None of these changes were considered adverse. Therefore, the NOAEL was 60 mg/kg/day in rats and 300 mg/kg/day in monkeys. The mean combined-sex steady-state $AUC_{0\text{-}24}$ of pharmacologically active species (MSDC-0602 + MSDC-0597) at the NOAEL was 1,380,000 ng·hr/mL in rats and 901,000 ng·hr/mL in monkeys.

As described above, some findings typically observed with other insulin-sensitizing agents were observed in mice, rats, and monkeys given high doses of MSDC-0602 or MSDC-0602K in sub-chronic studies. However, in chronic studies with MSDC-0602K, findings similar to those of other insulin-sensitizing agents that were noted were not considered adverse based on the low magnitude of the changes and lack of adverse physiologic consequences. Importantly, key effects such as edema, fluid volume expansion, body weight (in monkeys), pericardial/thoracic fluid accumulation, heart weight increase (in monkeys), fatty change in liver, adipose tissue proliferation, and effects in ovary and lymphoid tissue reported with other insulin-sensitizing agents were not observed in chronic studies in rats or monkeys at exposures 7 to 11 times those in humans given 250 mg doses of MSDC-0602K (free acid equivalents). The diminished effects of MSDC-0602 and MSDC-0602K in toxicology studies completed to date may reflect a reduced ability to directly activate the nuclear transcription factor PPARγ, particularly at the lower dose levels evaluated, compared to typical PPARγ agonists. This supposition is supported by recent evidence indicating that PPARγ activation is not necessary for insulin sensitization, but it is responsible for dose-limiting side effects of pioglitazone, including increased plasma volume (19, 20).

MSDC-0602 was not mutagenic in bacteria, was not clastogenic in human peripheral blood lymphocytes *in vitro*, and was not genotoxic in bone marrow of mice. The hydroxymetabolite MSDC-0597 was also not mutagenic in bacteria.

Two-year carcinogenicity studies in mice and rats with MSDC-0602K have been completed (21, 22), and neoplastic findings were limited to an increased incidence of hemangiosarcoma in male mice at 100 mg/kg/day (only when compared to the upper range of historical control incidence) and an increased, albeit low incidence of transitional cell carcinoma in the urinary bladder in male rats at ≥10 mg/kg/day. Published mechanistic studies with other compounds inducing similar tumors suggest that such tumors are not indicative of human risk (23-26).

2.3 Clinical Summary and Dose Selection

2.3.1 Early Clinical Data for MSDC-0602

Three Phase 1 clinical studies in healthy volunteers have been completed (27-29). Study MSDC-0602-C001 evaluated the safety and pharmacokinetics of single and multiple doses of non-micronized and micronized unformulated bulk drug given as powder in capsule (PIC). Study MSDC-0602-C003 was a pharmacokinetics and relative bioavailability study of 100 mg and 250 mg tablets made with micronized bulk drug that were administered at doses of 100 mg, 250 mg, and 500 mg (2 x 250 mg tablets) in hard gelatin capsules. The bioavailability was determined relative to micronized MSDC-0602 bulk drug powder in a gelatin capsule similar to what was dosed in Study MSDC-0602-C001. Study MSDC-0602K-C004 was a pharmacokinetics and relative bioavailability study of 125 mg, 250 mg and 500 mg (2 x 250 mg tablets) (free acid equivalents) of MSDC-0602K tablets in hard gelatin capsules. The bioavailability was determined relative to micronized MSDC-0602 free acid tablets (250 mg) in a gelatin capsule similar to what was dosed in Study MSDC-0602-C002.

Two Phase 2 clinical studies in subjects with type 2 diabetes mellitus have been conducted (30, 31). MSDC-0602-C002, a completed Phase 2a study, was conducted to assess the efficacy and safety of once daily oral doses of micronized MSDC-0602 free acid compressed tablets at 100, 250 and 500 mg in subjects with type 2 diabetes. Daily treatment with MSDC-0602 250 mg and MSDC-0602 500 mg for 4 weeks resulted in clinically meaningful median reductions in fasting plasma glucose (FPG) from baseline that reached borderline statistical significance relative to placebo and were comparable in magnitude to those observed in a parallel group with pioglitazone 45 mg. Treatment with MSDC-0602 500 mg resulted in a small, statistically significant mean reduction in HbA1c, and in statistically significant reductions in fasting plasma insulin and HOMA-IR when compared with placebo. Overall male and female mean steady state Cmax of MSDC-0602 and MSDC-0597 for the 100, 250 and 500 mg doses were 2360, 4650 and 7740 ng/mL, respectively, and overall male and female steady state AUC (0-24) of MSDC-0602 and MSDC-0597 were 34,700, 80,100 and 112,000 ng·hr/mL, respectively.

MSDC-0602 treatment was safe and well tolerated. The incidences of treatment emergent adverse events (TEAEs) and drug-related TEAEs were similar among the treatment groups. There were no serious adverse events (SAEs) and no deaths during this study. There were no clinically meaningful differences between the MSDC-0602 dose groups and placebo with respect to safety laboratory parameters, heart rate, physical examination results, ECG parameters, or edema.

These data confirm that MSDC-0602 has insulin-sensitizing pharmacology similar to pioglitazone 45 mg. The full insulin-sensitizing potential of MSDC-0602 will be further evaluated in larger clinical studies of longer duration.

A pilot, three month mechanistic study is ongoing in type 2 diabetic subjects given once daily 250 mg doses of MSDC-0602K (MSDC-0602K-C007UT). Results from three subjects who have completed this study to date confirmed the ability of this treatment to increase insulin sensitivity in a hyperinsulinemic euglycemic glucose clamp (80 mU/m^2/min Insulin) by 40% and also resulted in an average reduction in hemoglobin A1c of 1.4%. There was also a 50% reduction in intramyocellular fat content in skeletal muscle and a similar reduction in hepatic fat.

2.3.2 **Rationale for Dose Selection**

The choice of doses that will be explored in the NASH Phase 2 dose ranging study with MSDC-0602K have been established from an ongoing program connecting AUC to clinical results for MSDC-0602 (free acid, micronized acid, and eventually potassium salt), together with historical results using earlier generation compounds including pioglitazone and the prototype mTOT modulating insulin sensitizer, MSDC-0160 (also known as oxopioglitazone and Mitoglitazone).

Clinical development in Phase 1 for MSDC-0602 began with the free acid as powder-in-capsule (PIC). These studies showed that the target AUCs could not be easily achieved with free acid, but that adequate exposures could be reached with the micronized free acid (27-29). A tablet formulation of the micronized free acid was developed for evaluation in the first Phase 2a trial. The Phase 2a trial then confirmed that the targeted AUCs would have anti-diabetic pharmacology similar to 45 mg pioglitazone with the reduced PPARγ side effects as predicted from the clinical comparison with the pilot compound, MSDC-0160 (20). The micronized free acid of MSDC-0602 was able to produce pharmacology similar to pioglitazone 45 mg in a 28 day study, again with less effect on body weight and adiponectin (30).

The sodium and the potassium salts of MSDC-0602 were considered as possible replacements for the micronized free acid and both were compared in the cynomolgus monkey, which proved to be a good predictor of the kinetics in man. The potassium (K) salt proved to be most effective (13). Therefore, the development program was shifted to the K salt for all long-term preclinical work and for subsequent clinical development. The use of the K salt simplified the production of drug product, allowed much higher exposures in the preclinical models to expand the exploration of safety margins, and allows for lower tablet strengths for drug product. A cross-over relative bioavailability study was conducted in normal volunteers to directly compare the pharmaco-kinetics for micronized free acid tablets that were used in the Phase 2a trial to the new formulation of MSDC-0602K tablets (29). In contrast to the Phase 2a 250 mg micronized free acid tablet formulation that produced exposures of 101,000 ng.hr/ml and the 500 mg micronized free acid tablets that produced exposures from 126,000 to 151,000 ng.hr/ml, the 250 mg MSDC-0602K tablet produced an AUC of over 130,000 ng.hr/ml. These results suggest that 250 mg MSDC-0602K should be more than sufficient to produce the maximum insulin sensitizing pharmacology based on available data with this compound, as well as the prototype mTOT insulin sensitizer, MSDC-0160. Importantly, exploring doses up to this exposure allows for a direct comparison to pioglitazone (45 mg), which along with its active metabolites achieves an AUC of 60,000 ng.hr/ml. Cusi demonstrated effective resolution of NASH with treatment of 45 mg/day of pioglitazone (32).

To confirm that the 250 mg MSDC-0602K dose would produce significant insulin sensitizing pharmacology in man, a small, 3-month mechanistic study was conducted in 3 subjects with type 2 diabetes. This dose was capable of producing a 1.4% reduction in hemoglobin A1c, a 40% improvement in insulin sensitivity, and a 50% reduction in intramyocellular lipids in skeletal muscle. Measurement of hepatic lipid by MRS demonstrated a similar reduction in the one subject who has been evaluated for this parameter. Therefore, the effects of MSDC-0602K are at least as large, if not larger, than what has ever been observed with 45 mg pioglitazone in such subjects (31,33).

In summary, the choice of doses that will be explored in the Phase 2 NASH dose-ranging study with MSDC-0602K, 62.5, 125 and 250 mg, have been established from an ongoing program connecting AUC to clinical results for MSDC-0602 (free acid, micronized acid, and eventually potassium salt) together with historical results using earlier generation compounds including pioglitazone and the prototype mTOT modulating insulin sensitizer, MSDC-0160. An ongoing, small, 3-month mechanistic study of MSDC-0602K in 3 subjects with type 2 diabetes confirmed that the 250 mg MSDC-0602K dose would produce significant insulin sensitizing pharmacology in man. The effects of MSDC-0602K are expected to be at least as significant as what was observed with 45 mg pioglitazone in such subjects. Data available from the trial of Cusi (32) that evaluated the effects of 45 mg pioglitazone in subjects with NASH have been used to power this trial.

All preclinical and clinical data regarding the development of MSDC-0602K are summarized in the MSDC-0602K Investigator's Brochure.

3 STUDY OBJECTIVES

To assess the preliminary safety and efficacy of 3 doses of MSDC-0602K (62.5, 125, or 250 mg) as compared to placebo in subjects with non-alcoholic steatohepatitis (NASH).

4 ENDPOINTS

4.1 Safety

Safety will be assessed by periodic measurement of vital signs, 12-lead electrocardiogram (ECG), physical examinations and the occurrence of adverse events (AEs). Fasting blood samples for central lab analyses of clinical chemistries and hematology will be collected at each study visit (Screening and Study Visits 1-8). Samples for urinalysis will be collected at Screening and all Study Visits except Visits 2 and 3.

4.2 Efficacy

4.2.1 Primary Efficacy Endpoint

Hepatic histological improvement in NAS defined as a decrease of at least 2 points with no worsening of fibrosis stage at 12 months. The reduction in NAS must include at least a 1 point reduction in either ballooning or inflammation. No worsening of fibrosis is defined as no increase in CRN fibrosis score.

4.2.2 Secondary Efficacy Endpoints

1. Proportion of subjects with resolution of NASH with no worsening of fibrosis at 12 months. Resolution of NASH is defined as a ballooning score of 0 and an inflammation score of 0-1. No worsening of fibrosis is defined as no increase in CRN fibrosis score.
2. Proportion of subjects with improvement of fibrosis (CRN staging score) by at least 1 stage with no worsening of NASH at 12 months.
3. Mean change from baseline in NAFLD activity score (NAS) and each one of its components (steatosis, inflammation and ballooning) at 12 months.

4. Mean change from baseline in fibrosis score at 12 months.

4.2.3 Exploratory Efficacy Endpoints

1. Mean change in liver stiffness as measured by transient elastography (FibroScan) (change from baseline relative to placebo at 12 months).
2. Change from baseline relative to placebo for liver function tests (ALT, AST, ALP, GGT, bilirubin, albumin, PT and INR) at 6 and 12 months, and biomarkers and indirect measures of apoptosis and liver fibrosis (CK-18 [M30 and M65], Fibrosure, APRI, FIB-4 index, Pro-C3 and ELF score and its individual components (HA, PIIINP, TIMP-1) at 12 months.
3. Changes from baseline relative to placebo in circulating inflammatory markers (HMW adiponectin, and hsCRP) and markers of bone metabolism (osteocalcin and serum CTX) at 6 and 12 months.
4. Changes from baseline relative to placebo in FFA, serum triglycerides and fasting cholesterol (total, HDL, LDL, VLDL) at 6 and 12 months and changes from baseline of NMR analysis of lipoprotein particle size at 12 months.
5. Changes from baseline relative to placebo in markers of insulin sensitivity: HOMA-IR, HbA1c, fasting plasma glucose, and fasting insulin at 6 and 12 months.
6. Changes from baseline relative to placebo on blood pressure (systolic and diastolic), heart rate, weight, and abdominal girth at 6 and 12 months.
7. Changes from baseline relative to placebo at the 12 month endpoint in the pathologist's general impression as to the three categories of diagnosis: 1) NASH, 2) Simple/isolated steatosis with no steatohepatitis (NASH), or 3) No fatty liver disease (no NAFLD).
8. Changes from baseline relative to placebo in subjects with PNPLA3 variants and other genotypes.

4.3 Pharmacokinetics

Steady-state trough measurements will be made for MSDC-0602 and MSDC-0597 (a major metabolite) at Study Visits 2, 4, 5, 6, and 7 (Days 30, 90, 180, 270, 360).

5 SUBJECT SELECTION

Approximately 380 subjects will be randomized with the intent to have 340 subjects complete the 12-month assessment (4 groups; approximately 85 subjects/group) at approximately 50 to 75 sites in the US. Sites in other regions may be added. Subjects who do not complete the study will not be replaced.

5.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Adult subjects at least 18 years of age.

2. Histological evidence of NASH, based on biopsy, with a NAS (NASH CRN scoring) ≥ 4 with a score of at least 1 in each component of NAS.
3. Histological evidence of liver fibrosis defined as NASH CRN System fibrosis score of F1 to F3.
4. Qualifying liver biopsy must be within 9 months prior to or during Screening. If no usable liver biopsy is available within 9 months prior to Screening, a liver biopsy must be performed during Screening after the following criteria are confirmed:
    a. AST ≥ 20 U/L
    b. FibroScan with CAP score ≥ 270 db/m and kPa ≥ 8.5
5. Subjects with type 2 diabetes mellitus (DM) must be under stable and reasonable control, defined as under a healthcare provider's care for DM with glycosylated hemoglobin [HbA1c] ≤ 9.5%. Subjects taking permitted anti-diabetic therapies (metformin, GLP-1 agonists, SGLT2 inhibitors, sulfonylureas or DPP4 inhibitors) must be on stable doses for a period of at least 3 months prior to randomization. Refer to Section 6.4 for additional clarification about the use of antidiabetics.
6. Subjects taking Vitamin E must be on a stable dose (if ≥ 400 IU) for a period of at least 3 months prior to randomization.
7. Females must be either postmenopausal (at least 12 months since last menses) or surgically sterilized (bilateral tubal ligation, bilateral oopherectomy and/or hysterectomy) verified by a follicle-stimulating hormone (FSH) test result ≥40 mIU/mL. Those with FSH < 40 or with bilateral tubal ligation must use a barrier method of birth control. In addition, all females must have a negative pregnancy test at Screening and Day 1 regardless of childbearing potential. For postmenopausal women only, if FSH levels are above 40 mIU/mL and serum pregnancy results are indeterminant, the subject will be assessed as not pregnant.

    Males with female partners of child-bearing potential must agree to use adequate contraceptive methods (including a condom, plus one other form of contraception) if engaging in sexual intercourse.
8. Body Mass Index (BMI) ≤ 50 kg/m^2.
9. Willing and able to sign an informed consent document indicating understanding of the purpose of and procedures required for the study and willingness to participate in the study.
10. Willing and able to attend all study visits and undergo all protocol-specified procedures including liver biopsies at baseline and at the end of study treatment (one year).

5.2 Subject Exclusion Criteria

1. Known history of HIV.
2. Prior liver transplantation.

3. Other well-documented causes of active chronic liver disease, including, but not restricted to: history of positive hepatitis B surface antigen (HBsAg) or HCV RNA (subjects must be viremia free for a minimum of 2 years), suspicion of drug-induced liver disease, alcoholic liver disease and auto-immune hepatitis, Wilson's disease hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, genetic hemochromatosis, known or suspected HCC, history of planned liver transplant or current MELD score > 12.
4. History of cirrhosis and/or hepatic decompensation including ascites, hepatic encephalopathy or variceal bleeding. Platelet count < 100,000/μL of blood at Screening.
5. AST or ALT >5 times the upper limit of normal at Screening.
6. Total bilirubin > 1.8 mg/dL unless diagnosis of Gilbert's disease or serum albumin < 2.5 gms/dL at Screening.
7. INR ≥ 1.5 times ULN at Screening or other evidence of impaired coagulation.
8. History of alcohol abuse or drug abuse within 6 months of Screening.
9. Inability to safely obtain a liver biopsy.
10. Current or history of Type 1 diabetes mellitus.
11. Current or history of recent (≤ 6 months) use of ursodeoxycholic acid.
12. Current use of any diabetes medications other than metformin, GLP-1 agonists, SGLT2 inhibitors, sulfonylureas or DPP4 inhibitors three months prior to the baseline diagnostic liver biopsy or during the study unless as specified in the protocol. Current use of insulin or PPARγ agonists (pioglitazone or rosiglitazone) is not allowed for the duration of the study. Refer to Section 6.4 for additional clarification about the use of antidiabetics.
13. Use of concomitant medications with a known significant metabolism by CYP2C8 or CYP2C9 including paclitaxel, phenytoin, warfarin, celecoxib, tolbutamide, or replaglinide for the duration of the study.
14. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma within the 6 months prior to randomization.
15. History of heart failure (including CHF) or previous cardiovascular event (acute coronary syndrome, myocardial infarction, coronary by-pass surgery, or catheter based coronary intervention) within the 6 months prior to randomization.
16. Serum creatinine >2 mg/dL at Screening.
17. Current or recurrent disease that may affect the action, absorption or disposition of the study treatment, or clinical or laboratory assessments.
18. Current or history of severe or unstable disorder (medical or psychiatric) requiring treatment that may make the subject unlikely to complete the study.
19. Blood pressure greater than 160/100 mmHg. Subjects with elevated BP (but < 160/100 mmHg) with or without current treatment are allowed at the discretion of the Investigator and primary care physician. Individuals with hypertension must have been stabilized to the current treatment regimen for at least 6 weeks prior to randomization.

20. Known or suspected intolerance or hypersensitivity to the study drugs, closely related compounds or any of their stated ingredients.
21. Participation in an investigational study (other than a non-treatment registry study) or received an investigational drug within 30 days or 5 half-lives (whichever is longer) prior to randomization.
22. Blood donation of 1 unit or more within 56 days of randomization.
23. Plasmapheresis or plasma donation within 30 days of randomization.
24. Single 12-lead ECG demonstrating a screening QTc > 450 msec in men and > 470 msec in women. A single repeat ECG may be done at the Investigator's discretion.
25. Any surgical or medical condition which may significantly alter the absorption of the study drug including, but not limited to the following: history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling, or gastric banding, currently active inflammatory bowel syndrome. Subjects with reversal of gastric sleeve or banding are allowed.
26. Evidence of clinically relevant pathology that could interfere with the study results or put the patient's safety at risk.
27. Malignancy, including leukemia and lymphoma (excluding basal cell and squamous cell skin cancers and localized prostate cancer) not treated within the last 2 years.

6 STUDY DESIGN

6.1 Summary of Study Design

This is a double-blind, randomized, placebo-controlled study of three oral dose levels of MSDC-0602K. Subjects will be screened for eligibility up to 42 days in advance of randomization (between Days -42 and -1). Subjects will be randomized into 1 of 4 treatment groups based on a stratification criteria of presence Type 2 DM (Yes/No), use of Vitamin E ≥ 400 IU (Yes/No), and fibrosis score (F1 or ≥ F2) and will receive single daily doses of MSDC-0602K (62.5, 125 or 250 mg), or placebo for one year (360 days). Approximately 380 subjects will be randomized to achieve 85 completed subjects in each of the 4 treatment groups. The number of subjects who have a fibrosis score of F1 will be no greater than 50% of each group in order to best inform the design of the Phase 3 clinical trial.

- Male or female subjects with NASH and fibrosis should have an interpretable liver biopsy within 9 months prior to randomization and at the end of study treatment at Visit 7. Double-blind study drug will be dispensed for daily administration starting at Study Visit 1. Subsequent study visits will occur on Days 30 (1 month), 60 (2 months), 90 (3 months), 180 (6 months), 270 (9 months), 360 (12 months) and a 14-day follow-up visit on Day 374. Subjects will self-administer study drug once daily throughout the treatment period through the Day 360 visit. Site personnel will contact subjects every month to inquire about safety, adverse events and serious adverse events.

Blood samples will be collected for trough level assay of MSDC-0602 and major metabolite MSDC-0597 concentrations. Fasting blood samples will also be collected for analysis of

biomarkers and for safety chemistry/hematology laboratory testing at all outpatient visits. Urine samples will be collected for urinalysis quarterly throughout the study.

Subjects will return to the clinic for a Follow-Up visit approximately 2 weeks after the final dose (Day 374, Visit 8) for blood sampling. A complete physical examination will be performed at Screening and at the Follow-up visit on Day 374, and a limited physical examination will be performed at all other study visits.

6.1.1 **Schedule of Activities**

A schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

	Screen[1]	Treatment							Follow-up
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Months		**Randomization**	**1**	**2**	**3**	**6**	**9**	**12**	
Study Day	**-42 to -1**	**1**	**30**	**60**	**90**	**180**	**270**	**360**	**374**
Window		**N/A**	**± 7 days**						**± 3 days**
General Activities									
Informed Consent	X								
Medical History	X								
Complete Physical Examination[2]	X								X
Limited Physical Examination[2]		X	X	X	X	X	X	X	
Vital signs[3]	X	X	X	X	X	X	X	X	X
12-lead ECG	X					X		X	X
Pregnancy test (females only)	X	X							X
FSH (post-menopausal females only)	X								
FibroScan[4]	X							X	
Liver Biopsy[5]	X							X	
Randomization		X							
Dietary guidance and assessment of alcohol intake[6]	X	X	X	X	X	X	X	X	
Adverse event review	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	
Monthly phone assessment[7]					X	X	X		
Study drug dispensing[8]		X			X	X	X		
Central Lab Evaluations									
Hematology & serum chemistry [9, 10]	X	X	X	X	X	X	X	X	X
Liver function tests	X	X	X	X	X	X	X	X	
Urinalysis	X	X			X	X	X	X	X
HMW adiponectin, hsCRP, CK-18 [M30 & M65], osteocalcin, and CTX		X				X		X	
Fibrosure, ELF score, APRI, FIB-4 index, Pro-C3		X				X		X	
Serum sample for NMR analysis		X						X	
Blood sample for genotyping analyses (optional)[11]		X							
Plasma samples for future miRNA and biomarker testing[12]		X				X		X	
Trough PK sample[13]			X		X	X	X	X	

1. ICF may be obtained before the 42-day screening window. Re-testing is allowed within the 42-day Screening period if, in the opinion of the Investigator, the subject may become eligible upon repeat testing
2. Height and body weight are collected at Screening only; body weight, waist circumference measured midway between the lowest rib and the iliac crest, and signs of peripheral edema are collected at all study visits.
3. Vital sign measurements including seated BP and heart rate are collected at every visit; oral temperature is collected at screening, pre-dose on Day 1 and Visit 8.
4. FibroScan is required within 90 days prior to or during Screening.
5. A qualifying liver biopsy is required within 9 months prior to Screening. If a historical liver biopsy result is not available within this period, a liver biopsy must be performed during Screening for eligible subjects who meet all other entry criteria. A liver biopsy is also performed at Visit 7.
6. Non-diabetic subjects are provided the NCEP dietary guidance at Screening and diabetic subjects are provided the ADA dietary guidance at Screening. Guidance regarding alcohol consumption is also provided to all subjects at Screening. All subjects are assessed for compliance with dietary guidelines and alcohol consumption at each visit.
7. Study staff will contact the subjects by phone every month between Visits 4-7 to inquire about adverse events and serious adverse events.
8. 3 bottles dispensed at Visits 1, 4, 5, and 6.
9. Minimum 10-hour fasting blood sample collected pre-dose.
10. FPG and HbA1c will also be measured at Visits 1, 5 and 7.
11. A separate genotyping informed consent is required to enable collection of blood sample for genotyping analyses.
12. At each timepoint, plasma samples will be split into two separate vials and stored for biomarker testing, including miRNA, to be determined at a later date.
13. Pre-dose trough PK sample collected for analysis of MSDC-0602 and MSDC-0597.

6.2 Study Activities

6.2.1 Method of Assigning Subjects to Treatment

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be allocated centrally by an IXRS to one of the four treatment groups in a 1:1:1:1 allocation ratio, according to a central randomization scheme stratified by the presence of T2DM (Yes/No), use of Vitamin E ≥ 400 IU (Yes/No), and fibrosis score (F1 or ≥ F2), each enrolled subject will be sequentially assigned the next available randomization number and be allotted the specified treatment corresponding to that randomization number.

6.2.2 Screening Period (Days -42 to -1)

Prior to conducting any study-related procedures, written informed consent must be obtained from the subject. Participation in this study is voluntary. The nature of the study will be fully explained to each subject during the informed consent process and the subject will have the opportunity to ask questions. An informed consent document will then be signed by the subject and the person performing the consent discussion, and retained by the Investigator. A copy of the informed consent form will be given to the subject. Informed consent may be obtained before the 42-day screening window.

After obtaining a signed informed consent form, study site personnel will access the IXRS to assign a subject identification (ID) number to a potential study subject. This number will be used to identify the patient for the remainder of the study. Screening evaluations to determine subject eligibility will be conducted within 42 days prior to randomization (Day 1) in the study. Subjects must fast for at least 10 hours prior to the following Screening procedures.

- Medical history
- Complete physical examination
- Vital sign measurements
- 12-lead ECG
- Pregnancy test (serum, females only)
- FSH (post-menopausal females only)
- Transient elastography measure of liver fibrosis (FibroScan) within 90 days prior to or during Screening
- Qualifying liver biopsy within 9 months prior to Screening. If a usable liver biopsy is not available, a liver biopsy must be performed during Screening for eligible subjects who meet all other entry criteria after the following criteria are confirmed:
    a. AST ≥ 20 U/L
    b. FibroScan with CAP score ≥ 270 db/m and kPa ≥ 8.5
- Documentation of any AEs
- Assessment of alcohol use

- Provide and discuss the recommended standard of care diet program, the NCEP step 1 diet for subjects who are not diabetic and the ADA diet recommended for subjects with diabetes (Appendix 2 and Appendix 1)
- Clinical chemistry and hematology laboratory evaluations
- Liver function tests
- Urine sample for urinalysis
- Concomitant medication review

Re-testing is allowed within the 42-day Screening period if, in the opinion of the Investigator, the subject may become eligible upon repeat testing.

Eligible subjects will be scheduled to return to the clinic for the start of the 12-month treatment period. Male subjects will be advised to inform female partners of their participation in the study and to use adequate contraceptive methods (including a condom plus another form of contraception) if engaging in sexual intercourse with a woman who could become pregnant.

6.2.3 **Study Visit 1**

Day 1 is the day of randomization, which is usually the day of the first dose of randomized study drug treatment.

Continued eligibility based on exclusion criteria relating to safety and concomitant medications will be reassessed. Eligible subjects will be instructed to report to the clinic for a study visit on Day 1 following a minimum 10-hour fast. The following procedures will be performed for all subjects at Study Visit 1 (Day 1):

- Limited physical examination
- Vital sign measurements
- Pregnancy test (dip-stick, females only)
- Randomization
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Clinical chemistry and hematology laboratory evaluations
- Liver function tests
- HMW adiponectin, hsCRP, and CK-18 [M30 & M65], osteocalcin and serum CTX
- Calculation of Fibrosure, APRI, FIB-4 index, ELF score and its indivudual components (TIMP-1, PIIINP and HA), and Pro-C3
- NMR analysis of lipoprotein particle size
- Genotyping analyses (provided subject has signed the ancillary informed consent for genotype testing, which is optional)
- Future miRNA and additional biomarkers of interest testing

- Urine sample for urinalysis
- Documentation of any AEs
- Notation of any change in concomitant medication use
- Study drug (3 bottles of 33 capsules from the assigned kit) will be dispensed

6.2.4 **Study Visit 2, Month 1**

Subjects will be instructed to report to the clinic for a study visit on Day 30 following a minimum 10-hour fast and without having taken their morning dose of study drug. The following procedures will be performed for all subjects at Study Visit 2 (Day 30 ± 7 days):

- Limited physical examination
- Vital sign measurements
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Clinical chemistry and hematology laboratory evaluations
- Liver function tests
- Trough PK analysis of MSDC-0602 and MSDC-0597
- Notation of any change in concomitant medication use
- Documentation of any AEs

6.2.5 **Study Visit 3, Month 2**

Subjects will be instructed to report to the clinic on Day 60 following a minimum 10-hour fast and without having taken their morning dose of study drug. The following procedures will be performed for all subjects at Study Visit 3 (Day 60 ±7 days):

- Limited physical examination
- Vital sign measurements
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Clinical chemistry and hematology laboratory testing evaluations
- Liver function tests
- Documentation of any AEs
- Notation of any change in concomitant medication use

6.2.6 **Study Visit 4, Month 3**

Subjects will be instructed to report to the clinic on Day 90 following a minimum 10-hour fast and without having taken their morning dose of study drug. Subjects should return the unused study drug. The following procedures will be performed for all subjects at Study Visit 2 (Day 90 ±7 days):

- Limited physical examination
- Vital sign measurements
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Clinical chemistry and hematology laboratory evalations
- Liver function tests
- Urine sample for urinalysis
- Trough PK analysis of MSDC-0602 and MSDC-0597
- Documentation of any AEs
- Notation of any change in concomitant medication use
- Monthly phone calls to inquire about adverse events and serious adverse events
- Study drug (3 bottles of 33 capsules from the assigned kits) will be dispensed

6.2.7 **Study Visit 5, Month 6**

Subjects will be instructed to report to the CPRU for an outpatient study visit on the morning of Day 180 following a minimum 10-hour fast and without having taken their morning dose of study drug. Subjects should return the unused study drug. The following procedures will be performed for all subjects at Study Visit 5 (Day 180 ±7 days):

- Limited physical examination
- Vital sign measurements
- 12-lead ECG
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Clinical chemistry and hematology laboratory evaluations
- Liver function tests
- Urine sample for urinalysis
- HMW adiponectin, hsCRP, and CK-18 [M30 & M65], osteocalcin and serum CTX
- Calculation of Fibrosure, APRI, FIB-4 index, ELF score and its indivudual components (TIMP-1, PIIINP and HA), and Pro-C3
- Future miRNA and additional biomarkers of interest testing
- Trough PK analysis of MSDC-0602 and MSDC-0597
- Notation of any change in concomitant medication use
- Documentation of any AEs
- Monthly phone calls to inquire about adverse events and serious adverse events
- Study drug (3 bottles of 33 capsules from the assigned kits) will be dispensed

6.2.8 **Study Visit 6, Month 9**

Subjects will be instructed to report to the clinic on the morning of Day 270 following a minimum 10-hour fast and without having taken their morning dose of study drug. Subjects should return the unused study drug. The following procedures will be performed for all subjects at Study Visit 6 (Day 270 ±7 days):

- Limited physical examination
- Vital sign measurements
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Blood sample for clinical chemistry and hematology laboratory testing
- Liver function tests
- Blood sample for trough PK analysis of MSDC-0602 and MSDC-0597
- Urine sample for urinalysis
- Monthly phone calls to inquire about adverse events and serious adverse events
- Notation of any change in concomitant medication use
- Documentation of any AEs
- Study drug (3 bottles of 33 capsules from the assigned kits) will be dispensed

6.2.9 **Study Visit 7, Month 12**

Subjects will be instructed to report to the clinic on the morning of Day 360 following a minimum 10-hour fast before taking their morning dose of study drug. Subjects should return the unused study drug. The following procedures will be performed for all subjects at Study Visit 7 (Day 360 ± 7 days):

- Limited physical examination
- Vital sign measurements
- 12-lead ECG
- Assess compliance to diet (Y/N) and alcohol intake (Y/N)
- Transient elastography of liver fibrosis (FibroScan)
- Liver biopsy
- Clinical chemistry and hematology laboratory testing
- Liver function tests
- Urine sample for urinalysis
- HMW adiponectin, hsCRP, CK-18 [M30 & M65], osteocalcin and serum CTX

- Calculation of Fibrosure, ELF score, and its individual components (HA, PIIINP, TIMP-1), APRI, FIB-4 index, and Pro-C3
- NMR analysis of lipoprotein particle size
- Future miRNA and additional biomarkers of interest testing
- Trough PK analysis of MSDC-0602 and MSDC-0597
- Notation of any change in concomitant medication use
- Documentation of any AEs

6.2.10 **Study Visit 8, Day 374 (Follow-Up Visit)**

The following procedures will be performed for all subjects at the Follow-Up Visit (Study Visit 8, Day 374 ±3 days):

- Complete physical examination
- Vital sign measurements
- 12-lead ECG
- Pregnancy Test (females only)
- Clinical chemistry and hematology laboratory evaluations
- Urine sample for urinalysis
- Documentation of any AEs

6.2.11 **Additional Follow-Up Visits**

In the event of an AE that has not resolved by the follow-up visit, additional follow-up visits may be scheduled until the event resolves or is deemed to be a permanently continuing event. At the Investigator's discretion, minor AEs may be followed until resolution via a telephone contact.

6.3 **Discontinuation of Study Drug and Study Termination**

Subjects are free to discontinue participation in the study at any time and for any reason without prejudice to future medical care; however, prior to randomization, it should be made clear to potential subjects that early withdrawal from the study including loss to follow up can be extremely damaging to the scientific research and may pose some risk to the subject. If a subject withdraws consent to be treated with study drug prior to receiving any dose of study drug, the subject should be discontinued from the study. Once a subject has been randomized, the investigator will make every reasonable effort to keep the subject in the study.

Subjects may withdraw from study for the following reasons:

- Withdrawal of informed consent: A subject should be considered to have withdrawn consent when the subject no longer wishes to participate in any aspect of the study, and

does not want any further assessments, visits, or contact. A subject's refusal to participate in specific aspects of the study, such as a refusal to continue taking study drug or to provide blood samples, will NOT constitute withdrawal of consent. Investigators should make every effort to facilitate the subject's continued participation in remaining aspects of the study.

- Subject is lost to follow-up: A subject will not be considered lost to follow-up until just prior to database lock and after all efforts to contact the subject have been exhausted.

If a subject withdraws from study for any reason above, vital status as of Day 374 may be obtained through pubic registries as permitted by local regulations.

Subjects who wish to withdraw consent from the study, to the extent possible, will undergo an End of Study evaluation equivalent to Visit 8 (Day 374) (see Table 1).

The appropriate case report forms (eCRFs) should be completed, including an explanation as to why the subject participation in the study is being discontinued. Subjects who do not complete the study will not be replaced.

The Investigator and Cirius Therapeutics, Inc. have the right to discontinue study drug dosing from any subject in the event of an intercurrent illness, AE, protocol violation, or other reason including, but not limited to:

- Need for any treatment not allowed by the protocol
- Subject's inability to comply with protocol-specified procedures
- Sites with serious GCP or quality concerns
- Adverse event that in the opinion of the Investigator requires discontinuation of study drugDevelopment of symptoms of CHF that in the opinion of the Investigator requires immediate treatment.

6.4 **Type 2 Diabetes Mellitus**

Refer to subject's healthcare provider for diabetic care; however, note that no change in dose is allowed for GLP1 agonists or SGLT2 inhibitors during the study and these drugs cannot be added as rescue medications during the study if the subject had not been on a previous stable dose of either drug 3 months prior to randomization. Use of PPARγ agonists (pioglitazone or rosiglitazone) or insulin are prohibited during the study.

Subjects being treated with therapeutic agents for diabetes should be on stable dose(s) of the following antidiabetic medications at least 3 months prior to randomization and for the full duration of the trial: metformin, GLP1 agonists, SGLT2 inhibitors, sulfonylureas and DPP4 inhibitors.

If, during the study, a measurement of HbA1c exceeds 9.5% at two consecutive visits, the following suggested rescue approach may be followed:

1. Start metformin or uptitrate metformin if the subject is already taking it

2. Start a DPP4 inhibitor or uptitrate the DPP4 inhibitor if the subject is already taking a DPP4 inhibitor
3. Start careful titration of a sulfonylurea or titrate sulfonylurea if the subject is already taking it.

If no reversible cause is identified or hyperglycemia persists despite counseling and all permitted co-therapies, subject should be discontinued from study drug, referred for treatment, and continue in the study and complete the required study visits.

If a measurement of fasting plasma glucose (FPG) during the study is lower than 60 mg/dL, an alert will be sent to the investigational site and confirmatory FPG should be performed at the site within 7 days. In case of a symptomatic hypoglycemic event and if the subject is on a sulfonylurea, the sulfonylurea dose should be reduced by 50% or discontinued. Severe hypoglycemia is defined as any hypoglycemia requiring the assistance of a third party, hospitalization or associated with seizures or coma. Refer to Section 9 Adverse Events for reporting instructions.

6.5 **Liver Function Tests**

If subjects demonstrate an increase in AST, ALT or total bilirubin (TB) greater than 2 times their baseline values (mean of Screening & Visit 1), there should be repeat tests of transaminases (AST and ALT), bilirubin, and physical exam performed within 48-72 hours. If the levels then decrease, the subjects will be under close observation (repeat testing 2-3x weekly) until the levels return toward the individual's baseline values. Should these levels continue to be elevated, the drug should be discontinued.

Subjects should be discontinued for elevations of transaminases (AST or ALT) or TB above baseline associated with symptoms of right upper quadrant abdominal pain, fatigue, anorexia, nausea or vomiting, or eosinophilia. Subjects should be discontinued for persistent (> 1 month) increases of AST and ALT and/or TB > 2 times baseline.

Subjects may be rechallenged with study drug and closely monitored with repeat testing at least weekly. Re-elevation of values after re-challenge necessitate permanent discontinuation of study drug (but continuation of study visits).

If a new concomitant medication with known hepatotoxicity is started and liver function tests rise to meet the above criteria, the known hepatotoxin should be discontinued (replaced) if possible and liver function tests be followed in the same manner as outlined above. If liver function tests remain elevated or increase further, then the study drug should be discontinued (and subjects should continue with the study. visits).

6.6 **PT/INR Tests**

If subjects demonstrate an increase in PT or INR > 2 times the baseline value (mean of Screening & Visit 1), repeat tests of PT or INR and eosinophil counts should be performed within approximately 48-72 hours. If the PT or INR elevation is associated with changes in liver biochemistries, the subject should be followed closely per Investigator judgement with repeat testing at least weekly until levels return toward baseline values. Subjects should be discontinued

from study drug (and continue with study visits) and be referred for treatment if they show signs of spontaneous, serious or persistent bleeding.

7 STUDY PROCEDURES AND EVALUATIONS

7.1 Vital Signs

Vital signs will be measured at every study visit including Screening and Follow-Up visits . Vital sign measurements will include blood pressure and heart rate, will be taken pre-dose.

For all subjects, oral temperature (in degrees Celsius) will be measured at Screening and pre-dose on Day 1 (Study Visit 1) and at the Follow-up visit on Day 374 (Study Visit 8).

7.2 Physical Examinations

A complete physical examination will be performed at Screening and at the Follow-Up Visit (Day 374, Study Visit 8); a limited physical examination will be performed at all other study visits (Study Visits 1-7). Information regarding body weight, waist circumference and assessment for the presence of edema will be collected at all study visits and height will be recorded only at Screening. Subjects are to be weighed in similar attire without shoes on the same scale at each visit. Measure waist circumference as follows:

Locate the lowest rib and the iliac crest. Place the tape measure evenly around the bare abdomen at the midpoint between the lowest rib and the iliac crest. Read the tape measure and record the waist circumference in centimeters.

The complete physical examination will be comprised of the following general categories of parameters: General Appearance, Dermatological, Head Ears Eyes Nose and Throat (HEENT)/Neck, Pulmonary, Cardiovascular, Gastro-Intestinal, Neurological, Extremities, Lymphatic, and Other.

The limited physical examination will be comprised of at least the following categories of parameters: Pulmonary, Cardiovascular, and Extremities. The presence or absence of edema will be recorded as “yes“ or “no“ at each complete and limited physical examination. If “yes,“ a grade will be recorded for the edema. Peripheral edema will be assessed as follows:

Place your index finger over the participant's tibia, 10 cm above the lateral malleolus. Exert pressure for 5 seconds. Any depression that does not resume its original contour almost immediately is a sign of pitting edema. Record if there is no edema observed. The following scale should be used to grade any edema that is observed.

Grade	Physical Characteristics
1+	No visible change in shape of the extremity, pitting ≤ 2 mm, pit disappears rapidly
2+	No marked change in the shape of the extremity, 2 mm < pitting ≤ 5 mm, pit usually disappears in 10-15 seconds
3+	Noticeably swollen extremity, 5 mm < pitting ≤ 10 mm, pit may persist for about a minute
4+	Very swollen and distorted extremity, very deep pit > 10 mm, pit may persist 2 - 5 minutes

7.3 **Electrocardiograms**

Twelve-lead ECGs will be performed at Screening, Study Visit 5 (Day 180), Visit 7 (Day 360) and Visit 8 (Day 374). The ECG obtained at the Screening visit will serve as the baseline measurement. All scheduled ECGs will be performed after the subject has rested quietly for at least 10 minutes in a supine position. The QT correction derived by the ECG machine or computed manually should be recorded.

To ensure safety of the subjects, a qualified individual at the Investigator site will make comparisons with baseline measurements. If the QTc is >60 msec from the baseline; or an absolute QTc value is >500 msec for any scheduled ECG, the ECG will be repeated 2 more times, approximately 2-4 minutes apart.

If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality such as readings of ischemia, T wave changes, or infarct.

7.4 **Laboratory Assessments**

For all subjects, blood samples for safety laboratory assessments will be drawn at every visit (Table 1). All blood samples for clinical chemistry and hematology should be drawn in a fasted state (approximately 10 hours). A certified central clinical laboratory will be used to perform all routine hematology, clinical chemistry and urinalysis. Table 2 provides a summary of safety laboratory tests performed during the study.

All clinical laboratory tests will be performed by the central laboratory specified in Form FDA 1572 Section 4. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments.

Local laboratory assessments may be used to manage patient care during the conduct of the study (eg, routine care, unscheduled visits, urgent care). Such laboratory data will not be entered into the study database and local laboratories will not be included on the FDA 1572 form.

Table 2. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Albumin	Bilirubin, Blood	
Hematocrit	Alkaline phosphatase	Glucose, Ketones, pH, creatinine,	
Platelets, RBC with indices	ALT, AST, BUN, Bicarbonate	Protein, Specific gravity	Pregnancy test[b,c] FSH[b,c]
WBC with differential	Calcium, Chloride, Creatinine, Fasting Plasma Glucose, Fasting Insulin, FFA	Microscopic exam[a]	hsCRP CK-18 [M30 & M65]
HbA1c	LDH, Phosphorus		HMW adiponectin
INR, PT	Potassium, Sodium		osteocalcin
	Gamma-glutamyl transpeptidase		Serum CTX
	Total Bilirubin		TIMP-1
	Total Protein, Uric acid		PIIINP
	Cholesterol (total, HDL, LDL, VLDL)		HA
	Triglycerides		Pro-C3

[a] Only if positive for blood or protein

[b] Only at Screening (β-hCG), Day 1 (urine dipstick), and Day 374 (urine dipstick)

[c] Females only.

7.5 **Efficacy and Pharmacokinetic Assessments**

For all subjects, blood samples for pharmacologic (efficacy and safety) assessments will be drawn at all visits except Screening (Table 1). All blood samples should be drawn in a fasted state (approximately 10 hours). Instructions for collecting, processing, storing and shipping of blood samples for pharmacologic and pharmacokinetic analyses will be provided in the Laboratory Manual.

Blood samples for trough PK analysis of MSDC-0602 and MSDC-0597 will be collected pre-dose at Study Visits 2, 4, 5, 6 and 7 (Days 30, 90, 180, 270 and 360).

Blood samples for analysis of FPG and HbA1c will be collected at Screening.

Blood samples for analysis of insulin, HOMA-IR, FPG, HbA1c, TG, FFA and fasting cholesterol (total, HDL, LDL, VLDL) will be collected as part of the standard chemistry profile at Study Visits 1, 5, and 7 (Days 1, 180 and 360).

Blood samples for analysis of liver function tests (AST, ALT, bilirubin, PT/INR, ALP, GGT and albumin) will be collected at Study Visits 1, 2, 3, 4, 5, 6 and 7 (Days 1, 30, 60, 90, 180, 270 and 360).

Blood samples for analysis of HMW adiponectin, hsCRP, osteocalcin, serum CTX concentrations will be collected at Study Visits 1, 5, and 7 (Days 1, 180, and 360).

Blood samples for biomarkers of liver apoptosis (CK-18 [M30 and M65]) will be collected at Visits 1, 5 and 7 (Days 1, 180, and 360), whereas blood samples for TIMP-1, PIIINP, HA will be collected at Visits 1 and 7 (Days 1 and 360).

Serum samples for NMR analysis of lipoprotein particle size will be collected at Study Visits 1 and 7 (Days 1 and 360).

Blood samples will be collected at Visit 1 (Day 1) to be analyzed for genotyping.

Plasma samples for future miRNA measurements and additional biomarkers of interest will be collected at Study Visits 1, 5 and 7 (Days 1, 180 and 360).

Data obtained from the circulating liver function tests and other biomarkers will be used to calculate composite scores that may provide an indirect measure of changes in fibrosis from baseline to the 12 month endpoint (Days 1 and 360).

It is estimated that approximately 226 mL of blood for the safety, pharmacokinetic, and pharmacodynamic parameters will be drawn from each subject who completes the trial.

7.6 **Transient elastography (FibroScan) measurement of liver fibrosis**

Vibration-Controlled Transient Elastography or FibroScan is a non-invasive methodology that assesses liver fibrosis/steatosis by measuring liver stiffness using ultrasonographic elastometry. The measures are expressed in kilopascals (kPa) and db/m, and values increase with greater fibrosis/steatosis. FibroScan will be conducted at Days 1 and 360 using M or XL probe as

needed. Averages of ten measurements for kPa and CAP scores will be recorded as suggested by the manufacturer for the baseline and end of study measurements. FibroScan values of CAP ≥ 270 db/m and kPa ≥ 8.5 will be used to qualify subjects for liver biopsy if no historical liver biopsy is available.

7.7 **Liver Biopsies**

All subjects will have a liver biopsy at screening/baseline and at Visit 7. Qualifying liver biopsy must be within 9 months prior to Screening. If no usable liver biopsy is available within 9 months prior to Screening, a liver biopsy must be performed during Screening after the following criteria are confirmed:

a. AST ≥ 20 U/L

b. FibroScan with CAP score ≥ 270 db/m and kPa ≥ 8.5

The primary clinical diagnosis to enter the study will be performed by a central clinical pathologist. Slides/paraffin blocks will be shipped to the central laboratory where slides will be digitized using a Scanscope™ XT (Aperio Technologies, Inc.) ultra-fast, high-capacity slide scanner. Digitized slides will be sent to a single expert histopathologist who is a member of the NASH Clinical Research Network. The expert pathologist reader will provide individual scores for both NAS components and fibrosis scores.

At the completion of the study, the liver biopsy slides at Visit 7 will be used for diagnosis by the local pathologist and then scanned, digitized and sent for blinded reading by the expert histopathologist.

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the subject should not outweigh the potential benefits.

The subject's platelet count and PT (or INR) may be checked prior to the liver biopsy according to local standards. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count > 60,000/μL, a PT > 60% or longer by no more than 4 seconds over the control or INR < 1.3, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a subject that has stopped taking any antiaggregant therapy for > 5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by trans-jugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gauge needle
- A tissue core ≥ 2 cm long (≥ 10 portal tracts) represents optimal biopsy length

- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the subject should remain in the hospital consistent with the standard of care of that institution.

The biopsies will be sent to the central laboratory and then to a central reader who will read the biopsies to determine the eligibility to the study according to the fibrosis stage and consistency with NASH diagnosis. Biopsy slides will be blinded for subject and visit identification prior to central reading.

7.8 **Concomitant Medications and Other Therapy**

For diabetic subjects, use of any diabetic medication other than metformin (generic or Glucophage®), GLP-1 agonists, SGLT2 inhibitors, sulfonylureas or DPP4 inhibitors 3 months prior to the diagnostic liver biopsy or during the study is prohibited. Subjects on metformin, GLP1 agonists, SGLT2 inhibitors, sulfonylureas or DPP4 inhibitors must have been stabilized on their current dose for a period of 3 months prior to diagnostic liver biopsy and the doses should not be altered during the study except as provided in the rescue medication instructions (Section 6.4).

Use of other prescription or over-the-counter (OTC) medications or herbal remedies is allowed during the study, as long as the subject has been stabilized on a dose for 6 weeks prior to study entry. Antiaggregants are allowed but should be discontinued for at least 5 days prior to the liver biopsy. Any concomitant medication taken during the study must be recorded in the eCRF.

Use of ursodeoxycholic acid is prohibited as there is insufficient knowledge of its effects in this subject population.

MSDC-0602K is metabolized to its hydroxymetabolite by a carbonyl reductase. This is a ubiquitous enzyme and there is no prior evidence to indicate that any concomitant medications would interfere with this metabolism. There is minimal interaction of MSDC-0602K or its metabolite with CYP P450 systems, either by direct inhibition or induction. However, there is a potential for inhibition of CYP2C8 and CYP2C9 particularly with the active metabolite, which is the predominant moiety in circulation. For these reasons, the following medications are also prohibited in this trial: paclitaxel, phenytoin, warfarin, celecoxib, tolbutamide and repaglinide.

7.9 **Alcohol, Caffeine and Tobacco**

Use of alcohol should be consistent with Exclusion Criterion 5 (no substance abuse within the past 6 months). If change in use of alcohol, caffeinated products or tobacco, as reported by the subject (not solicited by site at each visit), results in an adverse event, note this change in event term (e.g., headache from caffeine reduction, jittery from quitting or reducing tobacco use).

7.10 **Physical Activity**

Subjects will abstain from strenuous exercise other than normal activity (e.g., heavy lifting, weight training, calisthenics, or aerobics) for 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

7.11 **Dietary Guidance**

Beginning at Visit 1, subjects who are not diabetics will be counseled to follow the NCEP Step 1 diet (Appendix 2). Subjects who are diabetic who have been following a diet consistent with ADA recommendations for type 2 diabetics (Appendix 1) should be counseled to continue that diet.

7.12 **Meals and Fluid Intake**

Subjects must abstain from all food and drink (except water) at least 10 hours prior to any safety laboratory evaluations and 10 hours prior to the start of PK sample collections.

7.13 **Contraception**

Only females who are postmenopausal (verified by FSH) or are surgically sterilized (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) will be included in the study population; those with bilateral tubal ligation must use a barrier method of birth control during the study. Male subjects must use a condom, plus another form of contraception (e.g., spermicide, intrauterine device, birth control pills taken by female partner, diaphragm with spermicide) if engaging in sexual intercourse with a woman who could become pregnant. Male subjects must also be willing to abstain from sexual intercourse or use a condom during sexual intercourse with pregnant or lactating females. Male subjects must adhere to these contraceptive criteria from administration of study drug through the follow up visit on Day 374.

7.14 **Premature Termination of Study/Closure of Site**

The study may be terminated prematurely if new toxicological findings, or results affecting the safety of the subjects, become available. The sponsor reserves the right to terminate the study at any time for any reason.

A site may be closed based on issues identified with subject recruitment, GCP compliance, poor quality data, evidence of attempted or proven fraud, or for any reason at the sponsor's discretion.

In the event the sponsor prematurely terminates a particular study site, the site staff will promptly notify the Institutional Review Board (IRB).

8 STUDY DRUG

8.1 **Investigational and Control Drugs**

The sponsor will provide the following double blind study drugs:

- MSDC-0602K 62.5 mg capsules
- MSDC-0602K 125 mg capsules
- MSDC-0602K 250 mg capsules
- Matching Placebo #00 capsules

MSDC-0602K Tablets were manufactured by USV Limited, Daman, India. MSDC-0602K Capsules and Placebo Capsules were prepared, packaged and labeled by TEAM Pharmaceuticals, Kalamazoo, Michigan. All medication will be over-encapsulated in matching opaque capsules

and supplied to the Investigator as double-blind study drug in high-density polyethylene bottles (HDPE) with child resistant caps. Each bottle will contain medication for 31 days + 2 additional days of treatment. Three bottles/kit will be assigned and dispensed to each subject at each of Visits 1, 4, 5 and 6. Medication labels will include storage conditions for the drug and the subject's initials.

8.2 **Treatments**

At Visit 1 (Day 1), all eligible subjects will be equally randomized to one of the 4 treatment arms listed below:

- MSDC-0602K 62.5 mg capsules
- MSDC-0602K 125 mg capsules
- MSDC-0602K 250 mg capsules
- Matching Placebo #00 capsules

8.3 **Randomization Code Creation and Storage**

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 **Study Drug Blinding**

The study is double-blind in that neither the subjects nor the Investigator will be aware of the treatment or dose administered. Blinding will be maintained throughout the study by use of active and placebo capsules of similar appearance. The series of random numbers from which the randomization algorithm operates will be created by personnel who will have no other involvement with analysis or statistical decision making for the study. The random number series will be sequestered from all blinded study personnel, assuring there will be no unblinding information available to them until the study completes.

8.5 **Study Drug Assignment and Dispensing Procedures**

At Visit 1 (Day 1), subjects who fulfill all the inclusion/exclusion criteria will be randomized to one of the 4 treatment arms using a stratification criterion based on presence of T2DM (Yes/No), use of Vitamin E ≥ 400 IU (Yes/No) and fibrosis score (F1 or F≥2). The Investigator or his/her delegate will confirm that the subject fulfills all the inclusion/exclusion criteria prior to randomization. Treatment will be comprised of a 360-day double-blind period, followed by a 14-day safety follow-up period. Each subject is uniquely identified in the study by a combination of his/her center number and subject number. Only the assigned subject number should be entered in the field labeled "subject ID" on the electronic data capture (EDC) form. Once assigned to a subject, the subject number will not be reused.

Subjects, Investigator staff, and persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the conduct of the study (except for emergency unblinding as noted in Section 8.9).
2. The identity of the treatments will be concealed by the use of study drugs that are identical in packaging, labeling, and schedule of administration, appearance, taste and odor.

Data analysts, who are not directly involved with data management and monitoring of the trial, will remain blinded to individual treatment assignments until the interim analysis (see Section 11.3.4); an unblinded statistician may monitor the randomization process during the trial. The Interactive Response System (IXRS) will maintain a record that identifies each subject and the treatment/study drug of an individual subject's treatment assignment. Unblinding of all subjects' treatment assignments will occur at the conclusion of the trial following final database lock.

8.5.1 **Dispensing the Study Drug**

Each study site will be supplied by Sponsor or Designee with study drug in identically appearing packaging. The clinical supplies will be packaged and labeled in a double blind fashion. Medication will be supplied to the site in kits (containing 3 bottles per kit) for each subject. Each bottle will contain medication for 31 days + 2 additional days of treatment, and will have a total of 33 capsules per bottle. Three bottles will be packaged in a kit. A three bottle kit will be dispensed to subjects at Visits 1, 4, 5, and 6. Instructions will be provided in order to advise the site on the proper method of randomizing the subject and selecting the correct medication ID numbered kit/bottles for dispensing to a given subject at a specific visit. Sites will be resupplied additional kits as supplies diminish.

On Day 1, site personnel will administer the first dose of drug with approximately 240 mL of water following a minimum 10-hour overnight fast. The study drug kit will then be dispensed to the subject (1 kit containing 3 bottles each that will be dispensed at Visits 1, 4, 5 and 6). Subjects will be instructed to self-administer study drug once daily in the morning at least 30 minutes before the morning meal. They will be instructed to swallow the drug whole and not to chew or open the contents of the capsule.

One component of the packaging (kit) has a 2-part label. Each part of this label contains a medication ID number that will correspond to one of the treatment arms. Investigator staff will be informed which study drug package to dispense to the subject by contacting and obtaining the medication number via IXRS. Immediately before dispensing study drug to the subject, Investigator staff will detach the outer part of the label from the kits and affix them to the source document (Drug Label Form).

8.6 **Study Drug Interruptions**

Treatment interruptions should be avoided. A drug interruption occurring at any time during any period will be considered a protocol deviation. An occasional missed tablet is not considered treatment interruption. All changes will be recorded in the study records.

8.7 **Compliance**

Treatment compliance will be assessed using capsule counts conducted at Visits 4, 5, 6, and 7.

8.8 **Study Drug Supply, Storage and Tracking**

Study drugs must be received by 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 designated site staff have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Study drug must be kept in a secure cabinet or room with access restricted to only necessary study site personnel until it is used. Unused medication may be destroyed onsite with sponsor's approval or returned to the sponsor or designee for destruction. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will comply with the legal requirements of the U.S. They will include storage conditions for the drug, but no information about the subject. The Investigator must maintain an accurate record of the receipt of shipments and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all used and unused study drug to the Sponsor or designee.

8.9 **Emergency Unblinding**

Unblinding is restricted to emergency situations and should be used only under circumstances where knowledge of the treatment is necessary for the proper management of the subject. When possible, the investigator should attempt to contact the medical monitor at Sponsor or designee before unblinding a subject's treatment assignment. The randomization code can only be broken if an emergency situation arises that, in the Investigator's opinion, requires knowledge of the drug product dosed for management of the emergency medical condition. To unblind a subject's treatment assignment, the investigator will access the unblinding module within the interactive response system. Instructions for breaking the blind will be provided to the site. Unless discontinued for a safety reason, study drug may be continued following unblinding of the subject's treatment assignment.

Copies of the randomization code will be made available to the analytical laboratory performing the PK analysis of plasma samples at the end of the study.

9 ADVERSE EVENTS

9.1 **Adverse Events**

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the subject using concise medical terminology. In addition, each subject will be questioned, in a non-directed manner about AEs at times specified in Table 1.

The AE reporting period for this trial begins upon signing of the informed consent form and ends at the final study visit (Visit 8).

All AEs that occur in subjects during the AE reporting period specified in the protocol, whether reported in response to a query, observed by site personnel, or reported spontaneously by the subject, must be recorded on the eCRF in the EDC system regardless of whether or not the event is considered medication related. Information to be collected and reported includes severity of the AE, relationship to study drug, duration of the AE, the treatment the subject is receiving at the time of the AE, and the outcome of the AE. The Investigator should attempt, if possible, to establish a diagnosis. For any AE which remains unresolved after completion of the study, the Investigator is responsible for following the AE to resolution or until a reasonable explanation for its persistence is found. In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the Investigator assesses as possibly related to the investigational medication/product should also be reported as an adverse event.

9.1.1 **Adverse Event Definitions**

An AE is any untoward medical occurrence in a subject or trial subject that is administered a drug or biologic (medicinal product) or that is using a medical device; the event does not necessarily have a causal relationship with that treatment or usage. Adverse events include the following:

- All suspected adverse reactions
- All reactions from overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness or orthostasis), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. The outcome of the accident (e.g., hip fracture secondary to the fall) should be recorded in source documents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a subject with jaundice) should be captured in the source documents.

Each adverse event is to be classified by the Investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed.

9.1.2 **Serious Adverse Event Definition**

An AE that meets one or more of the following criteria/outcomes is classified as an SAE:

- Death
- Life-threatening (i.e., at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important AEs that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they

may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious also includes any other event that the Investigator or sponsor company judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred.

A ***life-threatening AE*** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization is to be considered only as an overnight admission with observation for a minimum of 24 hours. Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization as an SAE. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study site (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the course of the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt whether the information constitutes an AE or SAE, the information is to be treated as a SAE.

9.1.3 **Pre-existing Condition Definition**

In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

9.1.4 **Procedures**

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the AE and the resulting appendectomy should be recorded in the source documents. If a subject undergoes a surgical procedure that was planned prior to entry into the trial, and the surgery is not performed due to a worsening of a baseline (at the time of informed consent) condition, this should not be reported as an AE.

9.1.5 **Grading of Adverse Event Severity**

If required on the AE CRFs, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function
MODERATE	Interferes to some extent with subject's usual function
SEVERE	Interferes significantly with subject's usual function

Note the distinction between the gravity and the intensity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity but would not be classified as serious unless it met one of the criteria for serious events listed above.

9.1.6 **Relationship to Study Drug**

The causal relationship of the AE to study drug will be assessed by both the Investigator and the sponsor. The following definitions will be used in assessment.

- Probably Related: The AE follows a reasonable temporal sequence from the time of drug administration. It follows a known response pattern to the study drug. The AE cannot be reasonably explained by other factors such as the subject’s clinical state, therapeutic interventions or concomitant drugs.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the subject’s clinical state, other therapeutic interventions or concomitant drugs.
- Unrelated: An AE does not follow a reasonable temporal sequence from administration of the product or the AE is clearly related to other factors such as the subject’s clinical state, other therapeutic interventions or concomitant drugs administered to the subject.

9.1.7 **Reporting Serious Adverse Events**

All SAEs, regardless of causal relationship, occurring from the time of signing the informed consent through the final study visit (Visit 8), must be reported within 24 hours after the Investigator becomes aware of the SAE. SAEs will be reported by completing the AE eCRF in the EDC system. The SAE information must be entered into the eCRF within 24 hours. Upon

completion of the eCRF, Chiltern Clinical Safety will be notified and receive the form electronically. In addition, the clinical site is to report the SAE using a SAE report form. The contact information for submission of SAEs is as follows:

E-mail: GlobalSAEInbox@chiltern.com
Facsimile: 1-888-726-8416

Clinical safety personnel are available for SAE reporting on a 24-hour basis. Reports are reviewed during normal business hours. The Investigator is required to submit SAE reports to the IRB/EC in accordance with local requirements.

Follow-up information relating to an SAE must be updated in the EDC system and SAE form within 24 hours of awareness of the SAE. Chiltern Clinical Safety will be notified via email when the information has been updated in the EDC system.

The subject should be observed and monitored carefully until the condition resolves or stabilizes.

Any emergency event deemed related to study drug must be reported to the Chiltern Clinical Safety (within 24 hours of the site's awareness of the event).

All deaths are to be thoroughly investigated and reported. Autopsy reports are to be obtained, if possible.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (for example, if an outpatient trial subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document his/her first awareness of the AE.

Any SAE brought to the attention of the Investigator after cessation of the investigational medication/product and considered to be caused, with a reasonable possibility, by the investigational product should be reported to Cirius Therapeutics, Inc. or its designee.

The Sponsor and/or its Contract Research Organization (CRO) designee is responsible for reporting SAEs to all applicable regulatory agencies and the central ethics committees within the required timeline.

The Investigators are responsible for submitting to their local Institutional Review Board (IRB) the required safety information including any safety alert letter received from the Sponsor as well as any SAEs occurring at their site.

Exposure *in Utero* during Clinical Trials

Any pregnancy diagnosed in a female subject or a male subject's partner while receiving or within 30 days of discontinuing the investigational study drug, must be reported to Cirius Therapeutics, Inc. or its designee within 24 hours of learning of the pregnancy. The Investigator should contact the SAE hotline and report information related to the pregnancy on an Exposure in Utero form provided by Cirius Therapeutics, Inc. or its designee. If a female subject who is

enrolled in the study does become pregnant during the course of the study, the study drug will be discontinued immediately, and the subject will continue to be followed throughout the study.

The Investigator is also responsible for a telephone contact with the subject to assess the outcome of the pregnancy. These findings must be reported on the Exposure *in Utero* form and transmitted to Cirius Therapeutics, Inc. or its designee.

10 STUDY DURATION

The total duration of the study will be approximately 416 days; comprised of a Screening period of up to 42 days, maximum, a treatment period of 360 days and a 14-day follow-up period.

11 STATISTICS

This section outlines the statistical analysis strategy and procedures. A separate statistical analysis plan (SAP) that details the statistical methods for the study will be finalized prior to any unblinded analysis of the study.

11.1 **Sample Size and Power Calculations**

Each active treatment group will be compared with the placebo group at the two-sided 0.05 significance level; 85 subjects per arm provides approximately 80% power to detect a difference in the proportions of subjects achieving the primary efficacy endpoint of 39.5% in any MSDC-0602K group versus 20% response rate in the placebo group. These response rates are similar to effects reported after 18 months daily treatment with 45 mg pioglitazone (58% response) or placebo (17% response) in subjects with pre-diabetes or T2DM (32); after 96 weeks daily treatment with 30 mg pioglitazone (34% response) or placebo (19%) in non-diabetic adults with NASH in the PIVENS study (34); and in the GOLDEN study, after 52 weeks daily treatment with 120 mg elafibranor (32% response) or placebo (21%) in the subset of NASH subjects with a baseline NAS ≥ 4 (35). Assuming 10% of subjects will not complete the 12-month assessment due to early dropout, 380 subjects will be randomized to the study.

11.2 **Analysis Set**

Final decisions regarding the assignment of subjects to analysis sets will be made during the Validity Review Meeting and documented in the Validity Review Report. Data from sites with serious GCP or quality concerns may be excluded from the analyses.

Enrolled Set

All subjects who signed informed consent.

Modified Intent-to-Treat Analysis Set

The modified Intent-to-Treat (mITT) analysis set includes all subjects who are randomized and who receive at least one dose of study drug. Pre-treatment baseline measures and post-baseline assessments through 14 days after the last dose of study drug will be included in the analyses. Subjects in the mITT will be analyzed as randomized regardless of treatment received. This means that subjects who are randomized who receive the incorrect study drug (i.e., not the study drug to which they were randomized) will be analyzed for efficacy under mITT as in the

treatment group to which the subject was randomized. The primary population for efficacy analyses is the mITT.

Safety Analysis Set

Safety analysis set (SAF) includes all subjects who are randomized and received at least one dose of study drug. SAF will be used in the analyses of all safety endpoints. Subjects will be included in the analyses according to the actual treatment they received. If a subject incorrectly receives more than one dose of study drug, the subject will be analyzed in the treatment group corresponding to the highest dose received. Pre-treatment baseline measures and post-baseline assessments through 14 days after the last dose of study drug will be included in the analyses.

Per-Protocol Analysis Set

The per-protocol analysis set (PPS) includes all subjects in the mITT population without major protocol deviations. Identification of all subjects in the PPS will be determined before the database lock and unblinding. Post-baseline measures during follow-up periods where the subject was < 80% compliant with study drug dosing may be excluded from the PPS. The PPS will be used as an additional sensitivity analysis for key efficacy endpoints.

11.3 **Planned Methods of Analysis**

The principal analysis for the primary endpoint will employ the mITT analysis set and the per-protocol approach will be considered supportive. Safety analyses will be performed using the safety analysis set**.**

Continuous variables will be summarized using mean, median, standard deviations, 25th and 75th percentiles, min, and max. Categorical variables will be summarized using number and percentages. All statistical tests and confidence intervals are two-sided unless otherwise stated.

11.3.1 **Analysis of Key Study Endpoints**

11.3.1.1 Efficacy Analysis

Primary Endpoint

The primary efficacy endpoint is hepatic histological improvement in NAS (NASH CRN scoring). A responder (subjects with hepatic histological improvement) is defined as having all of followings:

(1) At least 2 point reduction in NAS at 12 months. The reduction in NAS must also include at least a 1 point reduction in either ballooning or inflammation.
(2) No worsening of fibrosis, defined as no increase in CRN fibrosis score.

Each MSDC-0602K dose group will be compared with the placebo group at the two-sided 0.05 significance level. For each comparison, the null hypothesis is that there is no difference in response rates between the MSDC-0602K dose and placebo. The alternative hypothesis is that there is a difference in response rates between the MSDC-0602K dose and placebo. The primary analysis of the primary efficacy endpoint will be performed in the mITT, with supportive analysis

in the PPS. The number and percentage of responders will be summarized by treatment group. The primary analysis will be conducted using observed data included in the analysis dataset. Sensitivity analyses will be conducted where missing values are multiply imputed, and where subjects with missing data will be treated as non-responders. Comparisons between each active treatment group and the placebo group will be evaluated using appropriate contrasts from a logistic regression model that includes adjustments for the randomization stratification factors (presence of diabetes mellitus, Vitamin E use ≥ 400 IU, and baseline fibrosis 1 versus ≥ 2) and baseline NAS. Model-adjusted odds ratios for each active dose group relative to placebo and their associated 95% confidence intervals (CIs) will be provided. In addition, stratification-adjusted differences in response rates between each active dose group and placebo and their associated 95% CIs will be provided.

Supportive analyses of the primary endpoint will include comparisons of each active dose group with placebo using Cochran-Mantel-Haenszel (CMH) tests adjusting for the randomization stratification factors. Sensitivity analysis for primary endpoint will be performed using a logistic regression model adjusting for treatment, gender, presence of diabetes mellitus, Vitamin E use ≥ 400 IU, baseline fibrosis and baseline NAS. Adjusted odds ratios relative to placebo and the corresponding 95% CIs and p-values will be provided.

Further details will be provided in the SAP.

Secondary Endpoints

Primary analyses of the secondary efficacy endpoints will be conducted in the mITT with supportive analyses in the PPS.

Proportion of subjects with resolution of NASH

Resolution of NASH is defined as a ballooning score of 0 and an inflammation score of 0-1 without worsening of fibrosis at month 12. No worsening of fibrosis is defined as no increase in CRN fibrosis score.

The incidence rate of resolution of NASH will be summarized by treatment group. Each active treatment group will be compared to the placebo group using appropriate contrasts from a logistic regression model that includes adjustments for the randomization stratification factors and baseline NAS. Model-adjusted odds ratios for each active dose group relative to placebo and their associated 95% CIs will be provided. In addition, stratification-adjusted rate differences and their associated 95% CIs will be provided. Supportive analyses will include comparisons of each active dose group with placebo using Cochran-Mantel-Haenszel (CMH) tests adjusting for the randomization stratification factors. A logistic regression model adjusting for treatment, gender, presence of diabetes mellitus, Vitamin E use ≥ 400 IU, baseline fibrosis and baseline NAS will be used as sensitivity analysis. Adjusted odds ratios relative to placebo and the corresponding 95% CIs and p-values will be provided.

Proportion of subjects with improvement of fibrosis by at least 1 stage with no worsening of NASH at 12 months

Reduction of fibrosis is measured by CRN staging score. All subjects with CRN staging score ≥ 1 decrease from baseline will be considered as responders. Worsening of NASH is defined as an increase of either ballooning or inflammation.

The incidence rate of the responders will be summarized by treatment group. Each active treatment group will be compared to the placebo group using appropriate contrasts from a logistic regression model that includes adjustment for the randomization stratification factors and baseline NAS. Adjusted odds ratios relative to placebo and their associated 95% CIs will be provided. In addition, stratification-adjusted rate differences and their associated 95% CIs will be provided. A logistic regression model adjusting for treatment, gender, presence of diabetes mellitus, baseline fibrosis and baseline NAS will be used as sensitivity analysis. Adjusted odds ratios relative to placebo and the corresponding 95% CIs and p-values will be provided.

Mean change from baseline in NAS and each one of its components (steatosis, inflammation and ballooning) at 12 months.

For each of these outcomes separately, the change from baseline to 12 months will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, Vitamin E ≥ 400 IU, gender, fibrosis stage, baseline NAS and the baseline value of the component score where applicable. Least square mean treatment differences relative to placebo and associated 95% CIs will be presented.

Mean change from baseline in fibrosis score at 12 months

Mean change in fibrosis score will be analyzed similarly as the mean change in NAS above.

Exploratory Endpoints

For change from baseline endpoints, the mean change will be summarized by treatment groups at each evaluation time point. Highly skewed variables will be log-transformed for analysis, and geometric mean changes presented. Comparisons between each active dose and placebo will be done using ANCOVA models, similarly as for secondary endpoints.

11.3.1.2 Safety Analysis

Adverse Events

Safety data will be summarized in the Safety analysis set. All AEs will be coded using the Medical Dictionary for Regulatory Authorities (MedDRA). Treatment-emergent AEs are those with an onset after the first dose of study drug or any event already present that worsens in either intensity or frequency following exposure to the study treatment. Adverse events with an onset between signing of informed consent and study drug initiation, and those with an onset more than 14 days after the last dose of study drug will be listed separately. The incidence of treatment-emergent AEs, serious AEs, AEs resulting in study drug discontinuation, AEs at least possibly related to study drug, and fatal SAEs will be summarized by system organ class and AE preferred term in each treatment group. A summary of treatment-emergent AEs by preferred term and severity, using the worst reported severity grade for each event for a given subject, will be presented.

Clinical Laboratory

Descriptive statistics for laboratory parameter values, and for values of changes from baseline, by treatment group and visit, will be provided. The occurrence of significantly abnormal changes in laboratory values from baseline will be summarized by treatment group. Graphical representations may also be presented.

11.3.2 Demographic and Baseline Characteristics

Summary statistics will be provided by treatment group for demographics (e.g. age, sex, race, and ethnicity) and for baseline characteristics including medical history and randomization stratification factors.

11.3.3 Study Drug Exposure, Compliance, and Concomitant Therapies

Overall percent compliance to study drug dosage regimen, calculated as percent of doses taken relative to doses scheduled to be taken, will be summarized by treatment group. Extent of exposure in days will be evaluated and summarized from the first dose date to the last dose date of randomized study drug.

Study drug capsule count will be conducted at Visit 2 (1 month), Visit 3 (2 months), Visit 4 (3 months), Visit 5 (6 months), Visit 6 (9 Months), and Visit 7 (12 months). For the periods of Visit 1 to Visit 4, Visit 4 to Visit 5, Visit 5 to Visit 6, and Visit 6 to Visit 7, percent compliance with study drug during each period will be calculated as the actual number of capsules taken divided by the number of capsules required, then multiplied by 100. The required number of capsules will be calculated as the number of capsules per day (1) times the number of treatment days in the period, which will be determined using the start date and the end date of the period. For example, the number of treatment days for Visit 4 to Visit 5 will be calculated by the date of Visit 5 minus the date of Visit 4. If a subject's study drug or study participation is discontinued early during any of the periods, last dose date +14 days will be used as the end of period. If the date of last dose is missing, the last clinic visit date during the period will be used to estimate the end of the period. As a summary, the following formula will be used to calculate the compliance:

$$100 \times \frac{(\text{total no. of capsules dispensed - total no. of capsules returned})}{(\text{total no. of days in the period})}$$

At the end of each period, efficacy measurements with a compliance less than 80% will be considered for exclusion from per-protocol analyses. The subjects with a compliance less than 80% will be reviewed by the medical monitor and Cirius Therapeutics, Inc. Efficacy measurements to be excluded from the per-protocol analyses will be pre-specified prior to unblinding treatment codes for analyses.

Overall compliance of the 12-month double-blind treatment period will also be calculated and summarized. In addition, counts and percents will be produced to show in each treatment group with exposure in the following categories: $1 - \leq 90$ days, $91 - \leq 180$ days, $181 - \leq 270$ days, and $271 - \leq 360$ days. Similarly to the compliance at each period, overall compliance will be calculated as the total number of capsules taken divided by the total number of capsules required,

then multiplied by 100. The required number of capsules will be calculated as the number of capsules per day (1) times the number of treatment days, which will be determined using the randomization date and clinic visit date for Visit 7/Day 360. For subjects who discontinue the study or who discontinue study drug early, the last clinic visit date during period when the subject was on double-blind treatment will be used.

Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary. The number and percentage of subjects taking concomitant medications will be summarized by Anatomic & Therapeutic Chemical classification and preferred term for each treatment group.

No formal statistical tests are planned for all of the variables stated above.

11.3.3.1 Subgroup Analysis

Subgroup analysis will be performed for the primary and key secondary efficacy endpoints.

The subgroups examined will include diabetics vs. non-diabetics, use of Vitamin E ≥ 400 IU (Yes v. No), F2+3 vs. F1, and by PNPLA3 genotype. The homogeneity of the effect of each active dose relative to placebo across each subgroup will be assessed using appropriate contrasts in a logistic regression model that includes terms for the treatment groups, the subgroup under consideration, and their interaction, together with the randomization stratification factors. Additional subgroup analyses will be described in the SAP.

11.3.3.2 Other endpoints

Vital signs, physical exam and ECG QTc intervals will also be summarized descriptively.

11.3.3.3 Pharmacokinetic Analysis

Plasma concentrations will be summarized by treatment group using descriptive statistics. Individual subject and mean plasma MSDC-0602 and MSDC-0597 concentrations will be plotted vs. time. Additional details for pharmacokinetic analysis will be specified in the pharmacokinetic analysis plan.

11.3.4 **Interim Analysis**

An interim analysis of exploratory and safety endpoints is planned after all subjects have been randomized into the study and 6-month data are available for a minimum of 300 randomized subjects. Changes in serum biomarkers from baseline to 6 months will be assessed. Biomarkers include:

- Liver function tests (ALT, AST, ALP, GGT, bilirubin, albumin, PT and INR)
- Circulating inflammatory markers (HMW adiponectin and hsCRP)
- Markers of bone metabolism (osteocalcin and serum CTX), FFA, serum triglycerides and fasting cholesterol (total, HDL, LDL, VLDL),)
- Markers of insulin sensitivity (HOMA-IR, HbA1c, fasting plasma glucose and fasting insulin). Markers of insulin sensitivity will be analyzed separately in subjects with and without T2DM.

- CK-18 [M30 & M65]
- Fibrosure, ELF score, APRI, FIB-4 index, Pro-C3

Statistical methods similar to those employed for mean changes in secondary efficacy endpoints will be employed. Only summary statistics by treatment group will be presented and results shared with a limited group of people to be identified by the Sponsor. The treatment assignments of individual subjects will not be presented, i.e., data listings will not be included for this interim analysis. Details will be provided in a SAP for the interim analysis.

12 BIOLOGICAL SPECIMENS

Blood and urine samples will be collected, processed, stored, and shipped as outlined in respective Study Manuals or instructions provided by responsible assay laboratories for clinical chemistry, hematology, PK, pharmacodynamics (PD) and urinalysis.

It is the responsibility of the Investigator to ensure that all personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

13 CLINICAL AND LABORATORY DATA COLLECTION

13.1 **Case Report Forms**

An electronic version of the CRF data collection form (eCRFs) for each subject will be provided. All appropriate subject data gathered during the study will be recorded in English on these forms.

Whenever possible, all information requested on a CRF sheet or entered directly into an eCRF should be completed. If information is not available, it should be documented as such. Paper based forms should be filled out with a black or blue ballpoint pen. All deletions and corrections must be made by drawing a single line through the error and writing the correct information next to the change. All corrections must be initialed and dated. Correction fluid must not be used. A tracking system for changes to the eCRFs (i.e., an audit system) will be available.

The completed CRFs or completed print out and/or electronic copy of the eCRFs for this study are the property of Cirius Therapeutics, Inc. and should not be made available to third parties, except for authorized representatives of appropriate health/regulatory authorities, without written permission from Cirius Therapeutics, Inc.

13.2 **Laboratory Results**

Laboratory tests (clinical chemistry and hematology) will be analyzed by a central laboratory and reported to the clinical site as results are generated. The Investigator will review and comment on any laboratory value reported outside the normal range provided by the central laboratory. The laboratory report must be signed and kept in the study subject file at the site for the Sponsor. The electronic copies of the laboratory data will represent the clinical chemistry and hematology source data.

14 STUDY DOCUMENTATION AND RECORDS RETENTION

14.1 **Access to Records**

As required by the International Conference on Harmonization (ICH)-Good Clinical Practice (GCP) guidelines and regulatory authorities, the Investigator will allow sponsor's representative(s) direct access to all pertinent medical records in order to allow for the verification of data gathered in the CRFs or the electronic data forms and for the review of the data collection process. The records, including source documentation, must also be available for inspection by relevant regulatory health authorities.

14.2 **Source Documents**

Source documents may include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, biopsy slides or reports, ultrasound photographs, clinic notes or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol. Source documents may also include CRFs or electronic devices when information is recorded directly onto such forms or devices.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

14.3 **Record Retention (Investigator's Study File)**

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical study must be retained by the Investigator. They shall be retained until at least 2 years after the last approval of a marketing application in an ICH region. The Investigator may neither assign archiving of the files to someone else nor remove them to another location, without previously obtaining written approval from the sponsor. The sponsor will notify the Investigator in writing when retention is no longer necessary.

15 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE

The Investigator is responsible for obtaining an approval for conduct of the study from the Institutional Review Board (IRB) / Ethics Committee (EC), as well as approval of all subsequent major changes to the study, in compliance with local law. These approvals must be forwarded to the sponsor. The IRB/EC will comply with all federal, state, and local laws.

The Investigator shall also obtain from the IRB/EC and submit to the sponsor, a signed statement indicating that it complies with GCP.

16 ETHICAL CONDUCT OF THE STUDY

The study will be performed according to the Declaration of Helsinki, seventh edition (Edinburgh, Scotland, 2013) with approval from the IRB.

17 INFORMED CONSENT

It is the responsibility of the Investigator to give each potential study subject, prior to inclusion into the study, full and adequate verbal and written information regarding the objectives and procedures of the study. The study subjects must be informed about their right to withdraw from the study at any time. It is the responsibility of the Investigator (who may delegate this task to other members of the study team) to obtain signed informed consent from all study subjects before any study related assessments are performed. Consent must be documented by the subject's dated signature on an informed consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form and any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use.

18 CONFIDENTIALITY

18.1 **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 and regulatory agency, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication as provided in Section 21, Publications.

18.2 **Confidentiality of Subject Records**

By signing this protocol, the Investigator agrees that the Sponsor (or Sponsor representative), IRB or regulatory agency representatives may consult and/or copy study documents in order to verify case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by subject number only, full names/initials will be masked prior to transmission to the Sponsor, IRB or regulatory agency.

19 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the Investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable 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 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 by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to correct deficiencies in the study documentation and case report forms.

International Conference on Harmonization's GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The Investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study and provide the final results (i.e., final observations and responses).

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 study. The Investigator will immediately disclose in writing to the Sponsor 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.

In the event the sponsor prematurely terminates a particular study site, the Sponsor will promptly notify the IRB.

20 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the Sponsor agrees to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP under quality assurance systems with written standard operating procedures, and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

21 PUBLICATIONS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the sponsor as confidential must be deleted prior to submission.

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4. Chen Z, Vigueira PA, Chambers KT, *et al*. Insulin resistance and metabolic derangements in obese mice are ameliorated by a novel peroxisome proliferator-activated receptor γ-sparing thiazolidinedione. J Biol Chem (2012) 287:23537-48.

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APPENDIX 1 - ADA DIABETIC DIET GUIDELINES

- **Meal plans are balanced**
  - They include breakfast, lunch, dinner, and two snacks.
  - Each one-day plan includes about 8 servings of fruits and vegetables.
  - Fruits and vegetables are included at almost every meal and snack.
- **1550-1650 calories per day**
  - Your calorie level may vary based on your age, gender, activity level and whether or not you need to lose weight.
  - Calories are spaced throughout the day between meals and two snacks.
  - We also include tips each month to add or cut total calories by 200.
- **Moderate-carbohydrate (about 45% of calories come from carbohydrate)**
  - Carbohydrate intake is spread throughout the day.
  - Most meals have 45-60 grams of carbohydrate.
  - Most snacks have 10-25 grams of carbohydrate.
  - We also provide tips on how to adjust each meal plan to make it lower in carbohydrates.
- **Limit trans-fat as much as possible, <10% of calories from saturated fat, and focus on healthy or "good" fat sources**
  - People with diabetes have a higher-than-average risk of having a heart attack or stroke. Due to their connection with heart disease risk, the amount of saturated and trans-fats in our meal plans is limited. Trans fat and saturated fats are sometimes referred to as "bad fats."
  - "Good fats" include monounsaturated and polyunsaturated fats and may promote heart health. Meal plans include these over "bad fats" as much as possible.
- **300 mg of cholesterol per day**
  - Your body makes some cholesterol on its own but you also get cholesterol from food. People with diabetes should have 300 mg or less per day.
  - Some foods, like shrimp and eggs, are fairly nutritious foods but are somewhat high in cholesterol. Meal plans may include these foods because they provide other benefits or help to balance the plan.
- **>25 grams of dietary fiber per day**
  - You get fiber from plant-based foods like whole grains, fruit, vegetables, nuts, seeds and beans.
  - People with diabetes should consume at least the recommended amount of fiber for the general population: about 25 grams per day for women and 38 grams per day for men. Many Americans only get about half of what is recommended.
- **2300 mg of sodium or less per day**
  - Watching sodium is important for blood pressure control.
  - The American Diabetes Association recommends 2300 mg of sodium or less per day.
  - If you have diabetes and hypertension, you should work with your health care team to see if further reduction of sodium intake is necessary.
  - The current food supply is packed with hidden sources of sodium, and most Americans are consuming closer to 3400 mg of sodium per day. You can take some simple steps to reducing the sodium in your diet by learning what foods are major sources of sodium, making smart food choices, and controlling portion sizes.

APPENDIX 2 - THE NCEP DIETARY GUIDELINES

- Less than 7% of the day's total calories from saturated fat.
- 25-35% of the day's total calories from fat.
- Less than 200 milligrams of dietary cholesterol a day.

TLC diet tips

Meat, Poultry, Fish, Dry Beans, Eggs, and Nuts

- Limit the total amount of meat to 5 ounces or less per day
- Choose chicken and turkey without skin or remove skin before eating
- Eat fish, like cod, that has less saturated fat than either chicken or meat
- Dry peas and beans and tofu (bean curd) are great meat substitutes
- Limit egg yolks to no more than 2 yolks per week, including egg yolks in baked goods
- Substitute egg whites for whole eggs

Milk, Yogurt, and Cheese

- Eat 2 to 3 servings per day of low-fat or nonfat dairy products
- Choose varieties that have 3 grams of fat or less per ounce, including low-fat (1%) or nonfat cottage cheese
- Buy frozen desserts that are lower in saturated fat, like ice milk, low-fat frozen yogurt, sorbet
- Try low-fat or nonfat sour cream or cream cheese blends

Fats and Oils

- Replace saturated fats with unsaturated fat and limit the total amount of fats or oils
- Use liquid vegetable oils that are high in unsaturated fats (canola, corn, olive, peanut, safflower, sesame, soybean, sunflower oils)
- Use margarine made with unsaturated liquid vegetable oils as the first ingredient
- Limit butter, lard, fatback, and solid shortenings
- Buy light or nonfat mayonnaise and salad dressing

Fruits and Vegetables

- Eat at least 3 to 5 servings of fruits and vegetables each day
- Buy fruits and vegetables to eat as snacks, desserts, salads, side dishes, and main dishes