# Gemcabene for the Treatment of Pediatric NAFLD:

# A Phase 2a Study

# GEM-IIT-601

**Protocol Number: GEM-IIT-601**

[redacted]

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**Funded by: Gemphire Therapeutics Inc.**

**Version Number: v.4.0**

**02OCT2018**

***Version 3 (27FEB2018) was never implemented.***

## Table of Contents

# STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and all applicable United States (US) Code of Federal Regulations (CFR. The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

**Title:** Gemcabene for the Treatment of Pediatric NAFLD: A Phase 2a Study

**Study Description:** This is a multicenter, prospective, open-label, Phase 2, proof of concept study to test preliminary efficacy and safety of gemcabene in children with established NAFLD incompletely treated by lifestyle changes who are ages 12-17 years. The hypothesis of the study is that 300 mg of gemcabene once a day for twelve weeks will reduce ALT, hepatic steatosis, dyslipidemia and down regulate de novo lipogenesis in children with NAFLD.

**Objectives:**

Primary Objective: To evaluate safety and preliminary efficacy using multiple biomarkers of NAFLD (ALT, AST, GGT, hepatic steatosis) in children aged 12-17 years with established NAFLD not resolved by lifestyle changes.

Secondary Objectives: To assess indices demonstrating drug response and mechanism of action.

**Endpoints:**

Primary Endpoints:

- Percent change in ALT from Baseline to Week 12

Secondary Endpoints:

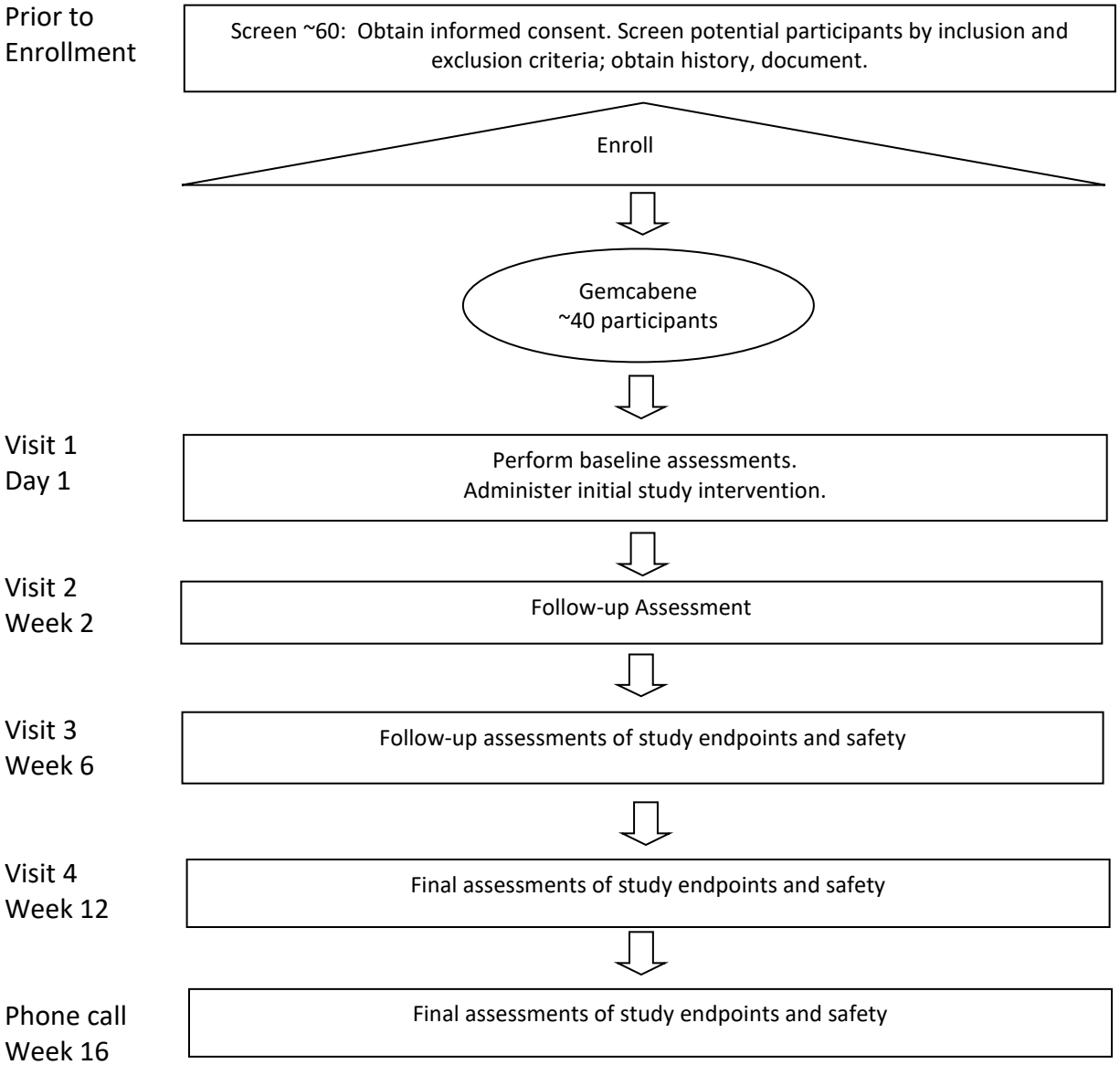
- Absolute change in ALT from Baseline to Weeks 6 and 12
- Percent change in ALT from Baseline to Weeks 6
- Percent change in ALT from Baseline to a mean of Week 6 and 12 ALT
- Absolute change and percent change in hepatic steatosis from Baseline to Week 12 as measured by MRI (volumetric fat fraction-HepaFat)
- Absolute change and percent change in pancreatic fat from Baseline to Week 12 as measured by MRI (HepaFat)
- Absolute change and percent change in AST from Baseline to Week 6 and Week 12
- Absolute change and percent change in insulin sensitivity as assessed by fasting insulin, fasting glucose, and HOMA-IR from Baseline to Week 6 and Week 12
- Absolute change and percent change in GGT from Baseline to Week 6 and Week 12
- Absolute change and percent change in serum lipids including total cholesterol, non-HDL-C, HDL-C, VLDL-C, LDL-C, and triglycerides (TG) from Baseline to Week 6 and Week 12
- Absolute change and percent change in apolipoproteins including apoA-1, apoB, apoC-II, apoE and apoCIII
- Absolute change and percent change in inflammatory markers such as hsCRP, IL-1B, IL-6 and procollagen III.
- Absolute change and percent change in lipoprotein particle sizes (VLDL, HDL, LDL, chylomicrons [NMR])
- Absolute change and percent change in post-prandial lipids (total cholesterol, non-HDL-C, HDL-C, VLDL-C, LDL-C, TG, lipoprotein particle size)
- Absolute change and percent change in rate of de novo lipogenesis using stable isotope tracers
- Absolute change and percent change in liver inflammation and fibrosis score (LIF and cT1) by MRI Liver MultiScan.
- Change in body composition measures by AMRA from Baseline to Week 12
- Absolute change and percent change in anthropometric measures including height, weight, body mass index, and waist circumference from Baseline to Week 12
- Safety related endpoints including adverse events (AEs), vital signs, clinical labs, hematology and urinalysis
- Treatment tolerance and compliance

**Study Population:** 40 enrolled (36 completers) boys and girls, aged 12-17 years, diagnosed with NAFLD

**Phase:** 2a

| | |
|---|---|
| **Sites/Facilities Enrolling Participants:** | Up to 3 US sites |
| **Study Intervention:** | 300 mg gemcabene by mouth once a day |
| **Study Duration:** | 12 months |
| **Participant Duration:** | 22 weeks |

## 1.2 SCHEMA


Prior to Enrollment
Screen ~60: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Enroll
Gemcabene
~40 participants
Visit 1
Day 1
Perform baseline assessments.
Administer initial study intervention.
Visit 2
Week 2
Follow-up Assessment
Visit 3
Week 6
Follow-up assessments of study endpoints and safety
Visit 4
Week 12
Final assessments of study endpoints and safety
Phone call
Week 16
Final assessments of study endpoints and safety

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

### Table 1. Schedule of Activities

| | Screening (-6 weeks) | Baseline (Day 1 +/- 2 days) | Week 2 (Day 15+/- 7 days) | Week 6 (Day 43+/- 10 days) | Week 12 (Day 85 +/- 10 days) | Week 16 Follow-up (phone call) Day 113 +/- 10 days | Early Termination Visit | Week 28 Long-Term Follow-up (Month 3) +/- 2 weeks | Week 36 Long-Term Follow-up (Month 6) +/- 2 weeks | Week 60 Long-Term Follow-up (Month 12) +/- 2 weeks |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent and HIPAA Authorization | X | | | | | | | | | |
| Review Inclusion/Exclusion Criteria | X | X | | | | | | | | |
| Demographics & Medical History | X | | | | | | | | | |
| Physical Exam | | X | | | X | | X | X | X | X |
| Vital Signs[A] | X | X | X | X | X | | X | X | X | X |
| Standardized lifestyle counseling | | X | | | | | | | | |
| Height, weight, (calculated BMI) waist and hip measurements[C] | X | X | X | X | X | | X | X | X | X |
| Alcohol Use Disorders Identification Test (AUDIT) | X | | | | | | | | | |
| Dietary Assessment (Food Frequency Questionnaire) | | X | | | X | | X | | | |
| MRI | | X | | | X | | X | X | X | X |
| ECG | | X | X | | | | | | | |
| PROMIS Questionnaires (fatigue, depression, anxiety) | | X | | | X | | X | | | |
| Beverage Questionnaire | | X | | | X | | X | | | |
| Tanner Staging (self-administered) | X | | | | | | | | | |
| Physical Activity Assessment (Block) | | X | | | X | | X | | | |
| Local Urine Pregnancy Test (WOCBP) | | X | X | X | X | | X | X | X | X |
| Urinalysis (UA) | X | X | X | X | X | | X | X | X | X |
| Blood Draw[B] | X | X | X | X | X | | X | X | X | X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| De novo lipogenesis (substudy) | | X | | | X | | | | | |
| Postprandial lipid (substudy) | | X | | | X | | | | | |
| Instructions for Drug Compliance | | X | X | X | | | | | | |
| Drug Dispense | | X | | X | | | | | | |
| Identify clinical follow-up plan | | | | | X | | X | | | |
| Adverse Events Review | | X | X | X | X | X | X | X | X | X |
| Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X |
| Assess Drug Accountability | | | X | X | X | | X | | | |

*A – Vital signs to include: temperature, pulse, respirations, and seated blood pressure*

*B – See details below in Table 2. Blood Draw Schedule*

*C – Measurements taken in duplicate at each timepoint and a mean will be calculated and recorded*

## Table 2. Specimen Collection Schedule

| | Screening (-6 weeks) | Baseline (Day 1) | Week 2 (Day 15+/- 7 days) | Week 6 (Day 43+/- 10 days) | Week 12 (Day 85 +/- 10 days) | Early Term Visit | Week 28 Long-term Follow-up (Month 3) | Week 36 Long-term Follow-up (Month 6) | Week 60 Long-term Follow-up (Month 12) |
|---|---|---|---|---|---|---|---|---|---|
| **Local Labs:** | | | | | | | | | |
| CMP[A] | X | X | X | X | X | X | X | X | X |
| Creatine phosphokinase (CPK) | X | X | X | X | X | X | X | X | X |
| CBC[B] | X | | | | X | X | X | X | X |
| GGT | X | X | | X | X | X | X | X | X |
| Clinical Lipid Profile[C] | X | | | | | | X | X | X |
| PT/INR | X | X | | X | X | X | X | X | X |
| HbA1c | X | X | | | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | X | X |
| **Central Labs:** | | | | | | | | | |
| Plasma & Serum (storage) [D] | X | X | X | X | X | X | X | X | X |
| Urine (storage) [D] | X | X | X | X | X | X | | | |
| Buffy coat for DNA[D] | X | | | | | | | | |
| Fasting lipids[E, F] | | X | | X | X | X | | | |
| Fasting apolipoproteins[E, G] | | X | | X | X | X | | | |
| Fasting lipoprotein particle sizes[H] | | X | | X | X | X | | | |
| Inflammation (hsCRP) [E] | | X | | X | X | X | | | |
| Liver Function panel [E,I] | | X | | X | X | X | | | |
| Diabetes Panel [E,J] | | X | | X | X | X | | | |
| Pharmacokinetics | | | X | X | X | X | | | |
| Metabolomics[D] | | X | | | X | X | | | |

*A – Comprehensive Metabolic Panel (CMP) includes: Alb, total bilirubin, Ca, CO2, Cl, Creat, Glu, Alk, Phospatase, K, TP, Na, ALT, AST, BUN (reflex to direct bilirubin if total bilirubin is elevated)*

*B – Complete Blood Count (CBC) includes: WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, neutrophils, lymphs, monocytes, eosinophils, basophils*

*C – Clinical Lipid Profile includes: cholesterol, triglyceride, HDL, LDL, VLDL*

*D – Processed locally, shipped to Emory University Biorepository*

*E – Analyzed by the Cardiovascular Research Lab at the Atlanta VA*

*F – Fasting lipids includes: TG, CHOL, HDLc, LDLc*

*G – Fasting apolipoprotein includes: apoA-I, apoB, apoC-II, apoC-III, apoE*

*H – Analyzed at LabCorp (Liposcience)*

*I – Liver Function panel includes: ALT, AST*
*J – Diabetes Panel includes: Glu, INS, NEFA*

*Note:* If the ALT at screening is more than two times the historic value, or there is no historic value available, the subject will be asked to repeat the screening ALT after four weeks. If the repeat ALT is greater than 50% increased or decreased over the screening ALT a third ALT will be obtained.

## Table 3. Blood Volume chart

| Number of mLs | Screening (-6 weeks) | Baseline (Day 1) | Week 2 (Day 15 +/- 7 days) | Week 6 (Day 43+/- 10 days) | Week 12 (Day 85 +/- 10 days) | Week 28 Long-term Follow-up (Month 3) | Week 36 Long-term Follow-up (Month 6) | Week 60 Long-term Follow-up (Month 12) | |
|---|---|---|---|---|---|---|---|---|---|
| **Local Labs:** | | | | | | | | | **TOTAL mL** |
| CMP | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | **8.5** | **8.5** | **8.5** | **68** |
| CPK | inc | inc | inc | inc | inc | **inc** | **inc** | **inc** | **-** |
| CBC | 4 | - | - | - | 4 | **4** | **4** | **4** | **20** |
| GGT | inc | inc | - | inc | inc | **inc** | **inc** | **inc** | **-** |
| Clinical Lipid Profile | inc | inc | inc | inc | inc | **inc** | **inc** | **inc** | **-** |
| PT/INR | 2.7 | 2.7 | - | 2.7 | 2.7 | **2.7** | **2.7** | **2.7** | **18.9** |
| HbA1c | 4 | 4 | - | - | 4 | **4** | **4** | **4** | **24** |
| *Safety Lab subtotal* | *19.2* | *15.2* | *8.5* | *11.2* | *19.2* | ***19.2*** | ***19.2*** | ***19.2*** | ***130.9*** |
| **Central Labs:** | | | | | | | | | |
| Plasma & Serum (storage) | 8 = 4mL Plasma and 4mL Serum | 8 = 4mL Plasma and 4mL Serum | 4 = 4mL Plasma | 8 = 4mL Plasma and 4mL Serum | 8 = 4mL Plasma and 4mL Serum | **4 ml plasma only** | **4 ml plasma only** | **4 ml plasma only** | **48** |
| Central Labs | - | 6 = 6 mL Plasma | - | 6 = 6 mL Plasma | 6 = 6 mL Plasma | **-** | | | **18** |
| PK | - | - | 3 | 3 | 3 | **-** | | | **9** |
| *Central Lab Subtotals* | *8* | *14* | *7* | *17* | *17* | ***4*** | ***4*** | ***4*** | ***75*** |
| **Totals** | | | | | | | | | |
| Total w/o substudy | 27.2 | 29.2 | 15.5 | 28.2 | 36.2 | **23.2** | **23.2** | **23.2** | **205.9** |
| PK Substudy | - | - | - | - | 9 | **-** | **-** | **-** | **9** |
| Substudy | - | 56 | - | - | 56 | **-** | **-** | **-** | **112** |
| **Total w/ substudy** | **27.2** | **85.2** | **15.5** | **28.2** | **101.2** | **-** | **-** | **-** | **327.5** |

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

Nonalcoholic fatty liver disease (NAFLD) has quickly become the most common liver disease in children in the US and is rising worldwide[1,2]. While the true prevalence and incidence are not known, estimates have placed prevalence in the US as high as 7 million children[1]. The prevalence varies greatly across race and ethnic groups with Hispanic, Asian and White children having increased rates compared to African American children[3,4].

Similar to adults, NAFLD ranges widely in severity in children. Cases of cirrhosis and end stage liver disease have been rarely reported. Most children have some fibrosis present on liver biopsy, however the majority have mild fibrosis (stages 1-2) and advanced fibrosis is less common (found in 3-15%)[5,6]. Nonalcoholic steatohepatitis (NASH) is considered the more severe form of NAFLD and is a pathologist's assessment that the biopsy has features of steatosis, inflammation and hepatocyte ballooning[7]. NASH is seen less often in children because children rarely exhibit hepatocyte ballooning; thus even with substantial levels of inflammation, the threshold of NASH is not met[8]. Children more often have a portal pattern of inflammation, called portal predominant or type 2[6,9]. This portal pattern disappears by late adolescence and is rarely seen in adults suggesting that it is simply a juvenile inflammatory response pattern[10]. The type 2 portal pattern does not appear to be predictive of future histopathology or clinical course.

ALT elevation is the most common screening test used for detecting NAFLD. A normal ALT in boys and girls is <26 U/L and <23 U/L respectively[11]. Similar to adults, very mild elevations in ALT or even normal ALT can be found in NAFLD[12]. Children with a sustained ALT ≥ 80 U/L are twice as likely to have NASH[8,13]. The typical diagnosis algorithm is complicated because NAFLD is a diagnosis of exclusion and no single test can determine it. Typically, serologic tests are sent to rule out other chronic liver diseases and including other causes of steatosis. Ruling out chronic alcohol use is critical in adults but less relevant in a pediatric cohort. After other chronic liver disease screening tests are performed, either an MRI or liver biopsy is used to detect the presence of steatosis in the liver. Ultrasound is less useful because of its low sensitivity and specificity. Magnetic resonance imaging (MRI) methods including MR spectroscopy and MR proton density fat fraction and MR volumetric fat fraction are all highly sensitive, specific and precise[14,15]. Liver biopsy has been considered the gold standard but it is less accurate for measuring fat in the liver because of the small sample size and subjective nature of the pathologist's estimate of steatosis. Liver biopsy is the best method for detecting NASH because it demonstrates all the necessary criteria (steatosis, inflammation and hepatocyte ballooning)[8]. Fibrosis is also best measured through liver biopsy at this time, although multiple non-invasive imaging methods are being developed in an attempt to replace it[8].

The pathophysiology of NAFLD is complex and mirrors the wide variety of clinical phenotypes. There is clearly a genetic background that is the basis for developing NAFLD[16,17]. However, presence of one of these polymorphisms is not sufficient to develop NAFLD. There appears to be one or more environmental triggers that induce the phenotypes of NAFLD. These environmental triggers are a subject of intense research effort. One of the top suspects in the environment is the hypercaloric diet[18]. Others include environmental toxins such as plastics, air pollution, heavy metals etc. Lastly, changes in

the nutrient content such as a high sugar diet or a diet low in antioxidant supply may contribute[19,20]. The timing of exposure may be critical and newer research points to the in utero time period as a critical time for triggering steatosis in the liver of children[21].

NAFLD is not simply a liver disease and in fact, the critical driver of NAFLD may be outside the liver. The best evidence for this is the rapid reoccurrence of NAFLD after liver transplant, suggesting that the milieu that the new liver is placed into is still NAFLD-genic. NAFLD appears to be a systemic lipid dysregulation with evidence of maladapted lipid flux throughout the body. NAFLD occurs in the setting of both hepatic and whole-body insulin resistance[22]. Adipose insulin resistance is strongly associated[23]. Within the liver, de novo lipogenesis (DNL) is inappropriately upregulated in NAFLD, resulting in increased synthesis of triglycerides from carbohydrates and other sources[24]. Increased triglycerides are exported out of the liver on large, overloaded very low-density lipoprotein (VLDL) particles resulting in dyslipidemia and resultant atherosclerosis. Increased visceral fat is closely linked to hepatic steatosis, although it appears that hepatic steatosis is more closely related to insulin resistance compared to visceral fat. Adiponectin, a beneficial hormone secreted from healthy adipose tissue is deficient in NAFLD[25].

The long term natural history of NAFLD beginning in children is not yet known because the past and current cohorts of children have not been followed long enough to assess rates of liver outcomes such as cirrhosis, hepatocellular carcinoma and portal hypertension. However, sufficient evidence exists to warrant concern. For example, rates of liver transplant for NAFLD in young adults is rapidly increasing[26]. And importantly, the incidence of type 2 diabetes in children with NAFLD is 10 x the expected rate of diabetes onset in children[27,28]. Type 2 diabetes may be the more important clinical outcome of NAFLD for children because pancreatic beta cell failure (diabetes) foretells a lifetime of morbidity including future health decline from kidney disease, vision loss, cardiovascular events and more. In children, those with NASH are more likely to have diabetes[28]. In adults with NAFLD, the most frequent cause of mortality is cardiovascular disease (CVD). Because of this, any medication developed for children with NAFLD should have long term CVD safety and/or benefit on cardiovascular risk markers.

The current standard of care for treating NAFLD in children is lifestyle changes[8]. There are not specific recommendations for a best diet or exercise goals because of the lack of randomized controlled trials in children with NAFLD, so the approach is based on an accumulation of evidence from case series, small trials and studies in obese children (not necessarily with NAFLD). Sugar reduction appears to be a potent and important component of diet improvement for treating NAFLD. Other treatments with limited evidence including metformin and vitamin E. Both were tested in a large RCT in children and did not meet the primary outcome of improved ALT, however both resulted in some significant histologic improvements in children with biopsy proven NASH[29]. A more recent trial testing cysteamine bitartrate delayed release in children with NAFLD failed to meet the primary outcome of a 2-point improvement in NAFLD activity score (NAS) although improvement was seen in ALT, particularly in younger children[30].

One of the challenges in therapeutic development for NAFLD is the lack of validated surrogate markers of clinical benefit. Because the natural history in children is not known, the target for clinical benefit is also not clear, although perhaps a case could be made for avoiding type 2 diabetes. Most trials to date in both pediatrics and adults have focused on improvement in either liver histology (a surrogate for future cirrhosis) or improvement in ALT (surrogate for improvement in liver histology). Both of these have substantial issues but have been accepted because of the lack of better alternative. ALT is associated with hepatic inflammation and a substantial decrease in ALT is likely to represent improvement in NASH and fibrosis on liver biopsy (Figure 1).

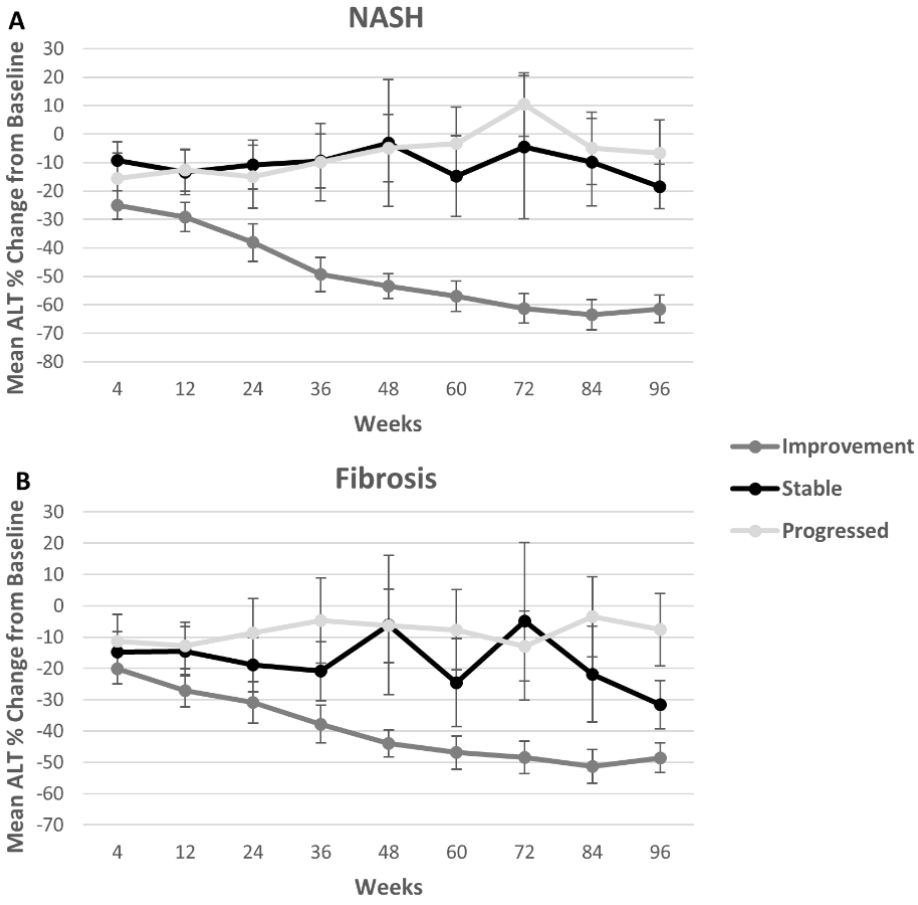



Figure 1. In 145 children who participated in the NIH sponsored "TONIC" trial testing metformin or vitamin E compared to placebo, there was significant association between improvement of ALT over time (from 0 to 96 weeks) and improvement in both NASH (1A) and Fibrosis (1B), $p<.05$ in both. At week 12, decreases in ALT of less than 20% were associated with failing to improve histology (progressed or stayed stable). Data submitted for publication.

MRI can be used to measure steatosis very precisely and is useful as a measurement in clinical trials in NAFLD. However, decrease in steatosis alone is not clearly a useful because of the lack of association of steatosis with longer term outcomes. Improvement in systemic metabolic measures such as insulin sensitivity, lipid levels, lipid particle sizes and adiponectin may be useful because of the close association of NAFLD with type 2 diabetes and CVD.

In summary, the rationale for this trial is as follows. NAFLD affects many children and is highly likely to lead to substantial morbidity and mortality, particularly from type 2 diabetes and cardiovascular disease. Lifestyle changes are the first line treatment, but many children fail to respond to these. Pharmaceutical treatments are needed for children that cure NAFLD and ideally also benefit the systemic features (dyslipidemia, insulin sensitivity, BMI). Gemcabene is a promising therapeutic that may benefit pediatric NAFLD and early phase trials are needed to support further development for this indication.

## 2.2 BACKGROUND

**Introduction to Gemcabene:** Gemphire Therapeutics Inc. (Gemphire) is developing gemcabene calcium (also denoted as CI-1027 or PD72953 and in this protocol referred to as gemcabene) for multiple indications including:

1.) As an adjunct to diet and statin therapy for the treatment of patients with dyslipidemia who require additional low-density lipoprotein cholesterol (LDL-C) lowering such as patients with homozygous familial hypercholesterolemia (HoFH) and heterozygous FH (HeFH) and atherosclerostic cardiovascular disease (ASCVD).
2.) To reduce triglycerides (TG) in patients with severe hypertriglyceridemia (TG ≥500 mg/dL),
3.) To reduce or stop progression of hepatic steatosis in patients with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH).

To date 18 clinical studies evaluating gemcabene have been conducted (17 completed and 1 terminated for business reasons) evaluating a total of 1278 healthy adult volunteers and participants with 901 exposed to gemcabene providing extensive safety data and preliminary efficacy data for triglyceride reduction. No studies have previously been conducted in NAFLD populations.

**Brief Mechanism of Action Summarized from Investigator Brochure Version 2:** Gemcabene is the monocalcium salt of a dialkyl ether dicarboxylic acid and is a new class of lipid-regulating compounds because it has 2 terminal gem-dimethyl carboxylate moieties. It has several mechanisms of action including 1) enhancing the clearance of VLDL and 2) blocking the production of hepatic TG and cholesterol synthesis.

The enhanced clearance of VLDL is through decreased apolipoprotein C-III, an apolipoprotein that when elevated can mask apoE on VLDL remnants and inhibit LPL mediated TG lipolysis. Elevated apoC-III is associated with increased CVD risk. Gemcabene decreases apoC-III through decreased expression of mRNA, likely decreasing protein production. This leads to increased VLDL-remnant clearance and enhances LPL activity with the overall effect of lowering LDL-C and TG.

Gemcabene also has effects within the hepatocytes. In primary rat hepatocytes, gemcabene markedly blocked radiolabeled acetate incorporation into both TG and cholesterol. AcetylCoA carboxylase (ACC1) is the rate limiting step in de novo lipogenesis (DNL). Gemcabene may reduce ACC1 mRNA expression as well as inhibit ACC1 enzymatic activity, suggesting that it blocks the ACC1 step during DNL.

Gemcabene may have other anti-inflammatory effects. It reduces C-reactive protein (CRP), mRNA production and decreases CRP in animal models and in humans. It down-regulates multiple markers of inflammation. It may inhibit the activation of nuclear hormone receptors (NHR) including NF-κB.

Gemcabene has a similar terminal gem-dimethyl carboxylate moiety to the widely used fibrate gemfibrozil and it also increases liver peroxisomal structures and enzymes in rodents, so it has been classified by the FDA as a peroxisome proliferator-activated receptor (PPAR) agonist. However, in 3 species (mice, rat, human) gemcabene has shown little or no direct agonist activity. It has shown weak PPAR-α and weak PPAR-γ activity *in vitro* and *in vivo*. In a 52-week safety study in monkeys no liver peroxisomal structures were noted in exposure of up to 4 times the exposure levels expected in the current study.

**Summary of Pre-Clinical Data from Investigator Brochure Version 2:**
The full details of the comprehensive program evaluating the pharmacology, absorption, distribution, metabolism, excretion, toxicokinetics, safety pharmacology and toxicology of gemcabene is available in the investigator brochure including a tabular summary of the key non-clinical safety studies. In animal models, gemcabene had the following actions:

- In LDL receptor deficient mice, gemcabene significantly reduced total cholesterol and LDL-C.
- In chow-fed Sprague-Dawley rats, gemcabene caused an increase in HDL-C and reduction of VLDL-C, LDL-C, ApoC-II, ApoC-III.
- In female, obese Zucker rats, gemcabene increased HDL-C, ApoE and decreased TG and apo-C-II.
- In transgenic lipoprotein(a) mice, gemcabene significantly reduced total cholesterol, Lp(a) and ApoB-100.
- In a mouse model of NASH, gemcabene showed anti-fibrotic effects at all tested doses and demonstrated anti-NASH and hepatoprotective effects on liver pathology of STAM mice.
- In non-human primate models, gemcabene was shown to reduce Lp(a) and total cholesterol.
- In several rodent models, gemcabene decreased inflammation and pain response.

Safety pharmacology studies in mice, Wistar rats and beagle dogs demonstrated no adverse effect on central nervous system (CNS), respiratory or cardiovascular parameters.

Oral bioavailability studies have been conducted in Wistar rats and in cynomolgus monkeys. In all studies, gemcabene was rapidly absorbed following oral administration and primarily excreted in the feces of rats and in the urine of monkeys.

Single and repeated dose toxicity studies were conducted in mice, rats and monkeys. In rats, gemcabene was well tolerated up to 100 mg/kg/day. Increased liver weight, increased hepatic peroxisomal enzymes, increased fine vacuolation of hepatocytes and hepatocellular hypertrophy were observed in rats at all doses in repeat dose studies of gemcabene. In cynomolgus monkeys, administered gemcabene at oral doses of 10, 30 and 100 mg/kg/day or up to 52 weeks there were no gemcabene related deaths, clinical signs of toxicity or ophthalmologic findings, no effects on CK and no heart related changes. Decreases in body weight gain were observed in males and females at 100 mg/kg/day. Mild, partially reversible changes in red cell mass were observed in all doses and correlated with decreased cellularity of sternal bone marrow in some animals. Reversible mild increases in creatinine and BUN were seen at all doses but without histologic changes in the kidneys. Dose related increases in liver weights were observed at 10mg/kg/day in males and >30mg/kd/day in females and were associated with histologic hepatocyte hypertrophy. In the liver, in both sexes at 100 mg/kd/day there was some single cell necrosis, mild degeneration of centrilobular hepatocytes and some oval cell hyperplasia. Findings in the liver were associated with mild to moderate increases in ALT. These were reversible at the end of the 12-week recovery period except for the increase in liver weight. Based on these findings, the no observed adverse effect level (NOAEL) at up to 52 weeks exposure is 30 mg/kg/day.

While most of the toxicity data was reassuring, there was toxicity seen in a 26 week, repeat dose oral toxicity study in rats. Body weight decreased 25-46% and hemoglobin, hematocrit and reticulocyte count decreased at all dose levels (30-300 mg/kg/day). There were increases of 85% to 4.5 fold in ALT activity at the higher doses of 100 and 300 mg/kg/day. Liver weights were increased and liver pathologic changes were seen including hepatocellular hypertrophy and vacuolation. In cynomolgus

monkeys, over 26 weeks at >30 mg/kg/day fatty changes were seen in the liver and kidneys. Carcinogenicity studies are ongoing in mice and rats. No mutagenic effects were seen in genetic toxicity studies. Developmental toxicity studies demonstrated abnormalities and teratogenicity at doses >10 mg/kg/day in rats but none in rabbits.

**Summary of clinical studies with Gemcabene from the Investigator Brochure Version 2:**
Phase 1 PK studies have demonstrated that oral gemcabene is rapidly absorbed with exposure increasing approximately linearly with dose. The primary route of elimination is renal. There is no clinically relevant effect on QT interval. There was a rapidly reversible increase in serum creatinine that is thought to be a hemodynamic change rather than a direct nephrotoxic effect because no change in protein to creatinine ration and no abnormal urine analysis was present. No effect was observed on blood pressure. There was an increase in the glucose disposal rate.

Phase 2 Efficacy studies have demonstrated benefits. In patients with dyslipidemia, monotherapy with 300 – 900 mg significantly lowered LDL-C compared to placebo in three Phase 2 studies. In patients with baseline TG ≥ 200 mg/dL (Study 1027-04), gemcabene lowered TG by 39% at the 300 mg dose compared with 5% lowering by placebo.

Human safety data is drawn from this collection of 19 clinical studies. The most frequent reported adverse events in healthy volunteers for single doses were headache, asthenia, nausea, dizziness and somnolence. The most frequent adverse events for 4 weeks were headache, infection, nausea, asthenia, photosensitivity reaction, rhinitis, diarrhea, flatulence, dizziness and pharyngitis. In patients with dyslipidemia treated for 8 weeks, headache, asthenia, dizziness and pain were more frequent with gemcabene compared to placebo at doses from 300-900 mg. Nausea, dyspepsia and flatulence were more frequent with gemcabene compared to placebo. In 1272 healthy adult volunteers and patients, only 17 discontinued due to gemcabene related adverse events. There were no treatment related serious adverse events and no deaths.

**Important Literature and Data Relevant to the Trial**
There are two publications reporting trials using gemcabene. The first was published in 2003 and reported the efficacy and tolerability of gemcabene in 161 patients with low HDL and high serum TG[31]. In this study, patients underwent a 6-week placebo, dietary lead in period and then were administered either 150, 300, 600 or 900 mg once daily for twelve weeks. At the 150 mg dose, HDL significantly improved and at both the 150 mg and 300 mg doses, TG significantly decreased compared to baseline. Gemcabene was well tolerated with adverse event rates similar to placebo. The second reported trial was published in 2016 and reported gemcabene as an additive therapy to statins in 61 stable hypercholesterolemic patients[32]. This was an 8 week, double-blind, placebo controlled, randomized, phase 2 study in men and post-menopausal women and tested Gemcabene at doses of both 300 and 900 mg. Gemcabene as an add-on to stable statin therapy demonstrated additional statistically significant reductions in LDL-C and CRP compared to placebo.

**Context of the Trial**
At this time, there is not yet an FDA approved medication for NAFLD in either children or adults. There have been two large, randomized controlled trials in children testing metformin, vitamin E and cysteamine bitartrate and both were negative for the primary outcomes. There is consensus in the NAFLD field that while patients respond to lifestyle treatment, it is not effective for all patients and may not cure or resolve the more severe forms including NASH and NAFLD with fibrosis[33,34]. Thus, medications are being sought that will not only improve the histologic features of progressive disease

(inflammation, ballooning, fibrosis) but will also improve the systemic dysmetabolic features associated with NAFLD that lead to type 2 diabetes and to cardiovascular disease. The combination of these two effects is especially important for children because simply "curing" the liver expression of the disease may not provide sufficient long term clinical benefit if the subsequent consequences are in the form of type 2 diabetes and cardiovascular disease.

**Importance of this Trial and Relevance**
Gemcabene is a novel therapeutic with substantial safety data in humans for treatment up to twelve weeks at doses as high as 900 mg daily. The mechanisms of action are highly relevant in NAFLD including reduction of de novo lipogenesis, the key lipid malfunction in NAFLD, decrease in circulating TG and LDL-C and decrease in systemic inflammation. All of these mechanisms are altered in NAFLD and Gemcabene has the potential to ameliorate hepatic steatosis, the inflammatory response to the hepatic steatosis as well as systemic inflammation and the associated dyslipidemia. The proposed trial is a phase 2a, preliminary efficacy and safety trial in children because it has not previously been tested in children and because it has not previously been tested in patients with NAFLD. This trial will provide support for future phase 2b and phase 3 trials to prove efficacy and longer term safety in this population. Critical questions to be answered in this trial include the tolerability of gemcabene at 300 mg in a pediatric population, the effect on ALT (a biomarker of hepatic inflammation), the effect on hepatic steatosis volume and the effect on circulating lipid levels. Additional mechanistic questions remain including what happens to the excess acetyl coA after interruption of the de novo lipogenesis pathway and so exploratory studies are planned to test effect of Gemcabene on DNL, ketogensis (the likely pathway for diverted acetyl CoA metabolites) and to test changes in whole body metabolite patterns (metabolomics).

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

The safety and efficacy profile of gemcabene has been developed through 18 Phase 1 and 2 studies including 1278 healthy volunteers and patients.

**Common adverse events include:**

- Headaches
- Asthenia (feeling of weakness)
- Nausea
- Dizziness
- Dyspepsia
- Abnormal bowel movements
- Myalgia (muscle pain)
- Increased BUN
- Increased creatinine

**Identified and Potential Important Risks:**
Based on the non-clinical and clinical safety data collected, important potential risks are liver findings, hemoglobin decrease, BUN and creatinine increase and myalgia. Importantly, only one patient had transaminase elevation > 3x ULN after receiving gemcabene 600 mg and atorvastatin 80 mg and the

percentage of transaminase elevations overall is similar to placebo. While hemoglobin decrease was seen in non-clinical toxicity studies, only small decreases in hemoglobin have been observed clinically and were also seen with placebo (not statistically significant). Small increases in creatinine and BUN have been observed in clinical studies with gemcabene. The effects were mild and appeared within the first 2-4 weeks of treatment, did not worsen over time and were not persistent and generally resolved within 10-14 days after discontinuation of gemcabene.

**Other risks:**

- There is a possibility of rhabdomyolysis when combined with a statin.
- Patients with a hypersensitivity to or who have a history of significant adverse reactions to any fibrate lipid lower agents should avoid gemcabene.
- Patients on potent CYP 3A4 inhibitors such as itraconazole or a macrolide antibiotic should be excluded.
- Based on non-clinical studies in rats, gemcabene should not be administered to pregnant women or women of childbearing potential not using effective methods to prevent pregnancy.
- The safety and effectiveness of gemcabene has not been established in children and juvenile toxicity studies are underway but not yet completed.
- 2-year carcinogenicity studies are ongoing and therefore potential for carcinogenic activity is still not known.

**Risks from the procedures in the protocol:**
Procedures in this protocol are minimized and include 1) blood draws 2) MRI and 3) IV placement for repeated blood draws. To minimize risk to the participants, all blood draws and IV placements will be performed by pediatric experience staff in the research centers. All MRI's will be without contrast and without any sedation as these are the two primary risks of MRI.

### 2.3.2 KNOWN POTENTIAL BENEFITS

Three Phase 2 studies have demonstrated that gemcabene is efficacious in reducing LDL-C in hypercholesterolemic patients. As many NAFLD patients have high LDL-C, this is a potential benefit for the participants.

Gemcabene has also been demonstrated to reduce TG, LDL-C, ApoB and hsCRP, all associated with cardiovascular disease risk. This is also a potential benefit to the participants.
Within the study, participants will benefit from receive lifestyle counseling, the current standard of care for pediatric NAFLD. They will also receive regular assessments of their liver disease including labs (ALT, AST and GGT) and hepatic steatosis (MRI).

Long range benefits could include satisfaction from contributing to development of treatments for NAFLD.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The rationale for the necessity of exposing participants to the risks of participating in this study is that medications for NAFLD in children are needed. Risks to children in this study are being minimized by using a low dose of the medication that has proven to be safe over twelve weeks in studies in adults. Further, risk is being minimized by using non-invasive measurement of the liver (MRI) as well as using pediatric experienced staff for the blood draws.

The value of the information to be gained outweighs the risks because the risks are minimal based on the data from the studies in adults and the potential value to improve NAFLD in children is high. Children in the study will benefit from receiving standard of care lifestyle counseling and from state of the art measurements of their liver disease.

## 3 ENDPOINTS

**Primary Endpoint**:

- Percent change in ALT from Baseline to Week 12

**Secondary Endpoints**:

- Absolute change in ALT from Baseline to Weeks 6 and 12
- Percent change in ALT from Baseline to Week 6 and the mean of Week 6 and Week 12
- Absolute change and percent change in hepatic steatosis from Baseline to Week 12 as measured by MRI (volumetric fat fraction-hepafat)
- Absolute change and percent change in pancreatic fat from Baseline to Week 12 as measured by MRI (HepaFat)
- Absolute change and percent change in AST from Baseline to Week 6 and Week 12
- Absolute change and percent change in insulin sensitivity as assessed by fasting insulin, fasting glucose, and HOMA-IR from Baseline to Week 6 and Week 12
- Absolute change and percent change in GGT from Baseline to Week 6 and Week 12
- Absolute change and percent change in serum lipids including total cholesterol, non-HDL-C, HDL-C, VLDL-C, LDL-C, and triglycerides (TG) from Baseline to Week 6 and Week 12
- Absolute change and percent change in apolipoproteins including apoA-1, apoB, apoC-II, apoE and apoCIII
- Absolute change and percent change in inflammatory markers such as hsCRP, IL-1B, IL-6 and procollagen III.
- Absolute change and percent change in lipoprotein particle sizes (VLDL, HDL, LDL, chylomicrons [NMR])
- Absolute change and percent change in post-prandial lipids (total cholesterol, non-HDL-C, HDL-C, VLDL-C, LDL-C, TG, lipoprotein particle size)
- Absolute change and percent change in rate of de novo lipogenesis using stable isotope tracers
- Change in body composition measures by AMRA from Baseline to Week 12
- Absolute change and percent change in liver inflammation and fibrosis (LIF and cT1) scores by MRI (Liver MultiScan).
- Absolute change and percent change in anthropometric measures including height, weight, body mass index, and waist circumference from Baseline to Week 12

- Safety related endpoints including adverse events (AEs), vital signs, clinical labs, hematology and urinalysis
- Treatment tolerance and compliance

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

**Hypothesis**
Gemcabene (300mg a day) for twelve weeks will be safe and will decrease ALT and percent hepatic steatosis by MRI in children with NAFLD.

**Type of trial**
- Phase 2a open label trial
- Multicenter, prospective, open label trial in 40 children (36 who complete the study) with NAFLD

**Treatment group**
- Gemcabene 300 mg once a day

**Number of clinical centers**
- 3 pediatric sites

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The scientific rationale for this phase 2a, open label trial in children with NAFLD is based on critical factors emanating from both the disease and the investigational product. NAFLD trials are challenging because of the large placebo response rate, estimated to be from 20-40%. The placebo response is likely in part due to response to lifestyle changes (improved diet and increased exercise) which is co administered in most trials. A placebo-controlled trial would require a much larger sample size (~140 subjects) in order to test response of ALT in gemcabene compared to placebo. Because this is the first study in children, a smaller study design was selected – an open label single arm study. The problem of placebo response is managed in two ways. First, the sample size was made large enough to allow detection of a greater than historical placebo response rate. Second, there will be a 4-6 week dietary lead in period between screening and initiation of gemcabene (baseline). This will moderate the effects of the dietary and exercise changes in response to counseling.

Children ages 12 years and older were selected for this study because there is not yet juvenile toxicity data to support testing in younger children.

Children diagnosed with NAFLD by either liver biopsy or by MRI will be included because routine clinical practice is quickly moving away from the use of liver biopsies with the advent of easily accessible and accurate MRI based hepatic fat measurement. To ensure that very mild cases of NAFLD are not

included, children must have an elevated ALT 2 x ULN (≥ 54 U/L for boys and ≥46 U/L for girls) at the time of screening (demonstrating increased likelihood of ongoing inflammation in the liver). To assess inflammation change in historical ALT (within three months prior to screening) will be obtained (if available). If the ALT at screening is more than two times the historic value, or there is no historic value available, the subject will be asked to repeat the screening ALT after four weeks. If the repeat ALT is greater than 50% increased or decreased over the screening ALT a third ALT will be obtained. If a third ALT is not within 50% of the previous value the subject may be re-screened at a later date.

ALT and hepatic steatosis have been selected as the two non-invasive biomarkers of response of NAFLD to gemcabene because they are non-invasive and are generally accepted as representing improvement in liver histology, which has been linked to clinical outcomes[35,36]. Importantly, both ALT and hepatic steatosis are related to NAFLD biology and are sensitive to change.

### 4.3 JUSTIFICATION FOR DOSE

The dose of 300 mg daily was selected because this was the most efficacious dose for TG reduction in adults. The drug is oral, once a day based on the previous studies. Most children in this study will be >70 kg. A minimum weight of 60 kg will be set to eliminate children receiving a higher dose/kg than intended.

### 4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study through week 12. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial for all enrolled participants.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Provision of signed and dated assent, if indicated
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. Children aged 12-17 years at the time of informed consent
5. History of clinical diagnosis of NAFLD including a, b and c below:
    a. Medical history eliminating, other chronic liver diseases (for example mitochondrial diseases, hepatotoxic drugs, anorexia nervosa)
    b. Laboratory studies: negative testing for hepatitis C and normal ceruloplasmin
    c. Either liver biopsy confirming NAFLD or MRI > 10% steatosis within the past three years
6. ALT ≥ 54 U/L for boys or ≥ 46 U/L for girls and ≤ 250 U/L at screening visit and within past three months (prior to screening). If ALT at screening is more than two times the historic value (or a historic value is not available), the subject will be asked to repeat the ALT after four weeks. If

the repeat ALT is more than 50% increased or decreased over the screening ALT a third ALT may be obtained. If a third ALT is not within 50% of the previous value then the subject is ineligible, but may be rescreened at a later date.

7. Body weight ≥ 60 kg at the time of screening
8. Able to take oral medication and be willing to adhere to the GEM-IIT-601 regimen
9. Minimum of three months of attempted lifestyle modification to treat the NAFLD and agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration

## 5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias)
2. Seizure disorder
3. Active coagulopathy (INR > 1.4)
4. Renal dysfunction with an estimated glomerular filtration rate (eGFR) <60ml/min/1.73 calculated using Schwartz Bedside GFR calculator for children
5. History of active malignant disease requiring chemotherapy or radiation
6. History of significant alcohol intake (AUDIT questionnaire) or inability to quantify alcohol consumption
7. Use of new medications or supplements with the intent to treat NAFLD/NASH during the 30 days prior to screening, including statin therapy. Medications or supplements (including metformin and vitamin E) that they have been on and are on a stable dose are acceptable
8. History of bariatric surgery or planning to undergo bariatric surgery during study duration
9. Clinically significant depression
10. Any girl nursing, planning a pregnancy, known or suspected to be pregnant, or who has a positive pregnancy screen
11. Non-compensated liver disease defined as cirrhosis and any one of the following hematologic, biochemical, and serological criteria on entry into protocol:
    - Hemoglobin < 10 g/dL;
    - White blood cell (WBC) < 3,500 cells/mm3;
    - Neutrophil count < 1,500 cells/mm3;
    - Platelets < 150,000 cells/mm3;
    - Total bilirubin > 1.3 mg/dL unless due to Gilbert's syndrome (subjects with a history of Gilbert's syndrome may be included if both direct bilirubin and the reticulocyte count do no exceed the ULN [reflexive direct bilirubin testing will be used to confirm Gilbert's syndrome])
    - Albumin < 3.2 g/dL
    - International normalized ratio (INR) > 1.3
    - Abnormal alkaline phosphatase
    - Any history of ascites, variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma (HCC)
12. Poorly controlled diabetes mellitus (hemoglobin A1c (HbA1c) > 8%) or requiring insulin
13. Patients with type I diabetes mellitus
14. Chronic liver disease other than NAFLD
15. Patients on CYP 3A4 inhibitors such as itraconazole or macrolide antibiotics are excluded
16. Patients who are on thiazolidinediones, fibrates or fish oils are excluded

17. Patients who are on daily prescription medications are excluded except for allergy medications, ADHD medications, asthma medications, or any other acceptable medication in the opinion of the investigator
18. Abnormal creatinine kinase levels at screening (may be repeated if the elevation is thought to be exercise related)
19. Sexually active female participants of childbearing potential and Tanner stage ≥ 4 or menstruating unwilling to utilize two acceptable forms of contraception from screening through completion of the study or unwilling to complete pregnancy tests throughout the study
20. Currently enrolled in a clinical trial or who received an investigational study drug within 90 days of screening
21. Participants who are not able or willing to comply with the protocol or have any other condition that would impede compliance or hinder completion of the study, in the opinion of the investigator

## 5.3 LIFESTYLE CONSIDERATIONS

All participants will be required to have attempted lifestyle changes as a treatment for their NAFLD. This will include attempting a dietary improvement and physical activity. Because of the highly variable success with this, no specific requirement for weight loss will be set.

Within the trial, all children will be given standardized lifestyle-based treatment at the Baseline visit. These will consist of the American Heart Association recommended healthy eating pattern for children (*http://www.heart.org/HEARTORG/HealthyLiving/Dietary-Recommendations-for-Healthy-Children_UCM_303886_Article.jsp#.WZx7NOmQwaY*).

It is important that participants are instructed to not undertake any form of strenuous physical activity for at least 24 hours prior to blood testing.

All clinic visit assessments except screening require the children to fast overnight. This is defined as no food or caloric beverages for a minimum of eight hours prior to sample collection. They will be permitted to have water and it will be encouraged in the evening and in the morning before the visit to promote good hydration.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a low ALT, body weight too low, other medication use or failure to meet inclusion or do meet exclusion criteria may be rescreened if in the view of the investigator there is a high likelihood that they would qualify on the rescreening. Rescreened participants will get the same screening number.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- The target study sample size is 36 completed participants and it is expected that there will be a 33% screen fail rate and a 10% drop out rate. This will require screening approximately 60 individuals, with 40 enrolled. This will allow the study to reach the target completion of 36 participants.
- Anticipated accrual rate = 2-3 participants per site per month
- Anticipated number of sites – 3 sites
- Source of participants – Well-qualified research sites with documented expertise working with this subject population
- Potential patients will be located by chart review to look for eligibility criteria or referral by the treating physician or by reviewing lists of patients who have indicated interest in NAFLD studies
- Participant retention will be enhanced by providing age appropriate activities during the visit (movies, video games, puzzles etc.), by providing transportation assistance, by reminder phone calls and through compensation for time and travel to study visits.
- Participants will receive compensation for study participation and for transportation costs. Compensation will be based on visit length and will be dispensed to the parent/legal guardian.

# 6 STUDY INTERVENTION

## 6.1 STUDY INTERVENTION(S) ADMINISTRATION

### 6.1.1 STUDY INTERVENTION DESCRIPTION

[redacted]

**USAN Name**: Gemcabene calcium

**Parent Compound**: [redacted]

**USAN Name**: Gemcabene

**CAS Registry number:** [redacted]

**Molecular Formula**

[redacted]

**Relative Molecular Mass**

[redacted]

**Manufacturer (drug substance):** [redacted]

**Gemcabene Tablets**

[redacted]

**Primary Packaging**

[redacted]

### 6.1.2 DOSING AND ADMINISTRATION

The dose is 300 mg orally once a day.

The first dose of study drug will be administered at the research site on Study Day 1. On days with a scheduled office visit with blood sample collection, subject will remain fasted and should not take gemcabene until after the blood samples are collected at the site. On all other days, the subject will self-dose: taking study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food. If a subject misses a dose prior to 6:00 PM, then the subject should take their dose. However, if past 6:00 PM, the subject should not dose and then count the dose as a "missed dose." The subject will resume normal dosing the next day (i.e., do not take two doses the following day).

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

The IP will be dispended to each site at study initiation. IP will be monitored and stored by the research pharmacy at each site. The research pharmacist will dispense to the study participants or study investigator at Baseline and at Week 6. At the end of the study, expired or unused product will be destroyed.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

[redacted]

Study drug will be prepared in bottles with 30 days of dosing contained within each bottle. The subjects will be asked to take one tablet per day. A 6-week supply (two bottles) will be dispended at Baseline

and at the Week 6 visit. This will include an extra 2 weeks of additional drug as a backup supply to account for visit windows.

### 6.2.3 PRODUCT STORAGE AND STABILITY

The study drug will be stored at controlled room temperature (15 to 30°C) in a secured location (locked) with access restricted to authorized personnel only. Storage temperature will be monitored and recorded.

Upon receipt of study drug, the Investigator or designee will conduct a complete inventory of all study drug and ensure no damage occurred during shipment.

The Investigator will maintain adequate records documenting the receipt, use, loss, or other disposition of study drug. Drug accountability logs will identify the study drug code number and account for the disposition on a subject-by-subject basis, including specific dates and quantities. The drug accountability logs will be signed by the individual who dispenses the study drug and copies will be provided to the Sponsor.

### 6.2.4 PREPARATION

No preparation is necessary.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open label, unblinded early phase study so there are no measures for blinding.

## 6.4 STUDY INTERVENTION COMPLIANCE

Subjects will be instructed to take study drug daily according to the protocol and return used and unused packaging to the site at each subsequent study visit.

Compliance with administration of study drug will be assessed at each study visit during the Treatment Period and at the Early Termination Visit, if applicable, and recorded on the appropriate eCRF and the drug accountability log.

The Investigator or designee will remind subjects at each visit of the importance of following the protocol-defined schedule for taking study drug. Reasons for not following the study drug administration schedule as described in the protocol will be clearly recorded in the source documents.

Adherence will be verified through pill counts of returned bottles, phone calls and asking parents/legal guardians. Participants will be encouraged to use a cell phone or watch alarm to remind them to take the pill each day.

## 6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

### 6.5.1 RESCUE MEDICINE

N/A

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from gemcabene does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation (Early Termination Visit) will include the following:

- Blood tests
- MRI
- Vital signs, physical measurements, and a physical examination
- Questionnaires (Food Frequency Questionnaire, PROMIS Questionnaires, Beverage Questionnaire, Physical Activity Assessment)
- Urine collection and pregnancy test (in WOCBP)
- Adverse event and concomitant medication review

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive gemcabene for ≥ 14 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, receive the study intervention for > 4 weeks, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

### 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

**Study Procedures:**

Central Lab Tests

The primary and secondary outcomes listed below will be batched and measured at a central lab. At each indicated study visit (see SOA), plasma will be collected, aliquotted and frozen within 2 hours of collection and shipped to the Cardiovascular Research Lab at the Atlanta VA. After all study visits are completed and samples are obtained for all participants, the following tests will be measured:

- Lipid panel (TG, CHOL, HDLc, LDLc)
- Apolipoprotein panel (apoA-1, apoB, apoC-II, apoC-III, apoE)
- hsCRP
- Liver function panel (AST, ALT)
- Diabetes panel (GLU, INS, NEFA)
- Pharmacokinetics (Week 2, Week 6, Week 12 and in sub-study participants at Emory 0, 2, 4 and 6 hour)

Local (safety) labs
In order to assure the safety of participants at the time of their participation in the study, the labs listed below will be performed locally at the time of the visits and reviewed by the study staff. For those labs that are measured by the local lab and by the central lab (ALT, AST, Glu, Lipids) the central lab measurements will be used for outcome analysis. In the case that a central lab is missing, this will be noted and if the local lab is available it will be used. (also see SOA).

- CMP (includes Glu, BUN, Creatinine, Lytes, Calcium, Total Protein, Albumin, Alk Phos, AST, ALT, Total Bilirubin)
- CBC (includes WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT)
- GGT
- CPK
- Lipid profile (includes cholesterol, triglycerides, HDL, LDL, and VLDL)
- HbA1c
- UA (includes chemical analysis, blood, nitrites, leukocyte esterase, protein)
- PT/INR

Imaging:
Limited MRI (no contrast) of the abdomen to measure percent hepatic steatosis and the liver multiscan. The Resonance Health (HepaFat) scan will be used for liver fat and pancreatic fat and the Perspectum Liver Multiscan (LIF and cT1 scores) will be used for inflammation and fibrosis. Body composition will be assessed by AMRA Medical AB (AMRA).

Patient reported outcomes:
PROMIS questionnaires fatigue, anxiety and depression (see Appendix B)

Study Procedures by Visit:
Please refer to Section 1.3 Schedule of Activities for additional visit details

Unscheduled Visits:

- Repeat MRI or labs
- Rescreening Visit
- Repeat ALT (for screening)
- Early Termination Visit

## 8.2 SAFETY AND OTHER ASSESSMENTS

Specific Safety Measures:

Hemoglobin decrease

For a hemoglobin decrease of > 1.5 g/dL from baseline during the study, repeat hematology studies and reflexive evaluation of reticulocyte count will be performed. The subject's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., bleeding, shortness of breath, fatigue) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

Creatinine increase

If, at any visit, a creatinine increase of > 0.3 mg/dL (27 µmol/L) from baseline, a GFR decrease of >15 mL/min from baseline is observed, a repeat chemistry/urinalysis will be performed within seven days. The subject's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., fatigue, malaise, polyuria/oliguria, or palpitations) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

Possible muscle and liver injury

For muscle injury, CPK, hepatic, and renal function laboratory data will be integrated with myopathy signs and symptoms.

For liver injury, laboratory data will be integrated with hepatic signs and symptoms. Alanine aminotransferase increases > 2 × baseline with symptoms of hepatitis or > 3 × baseline with or without symptoms of hepatitis will be evaluated and managed according to guidelines for studies in patients with pre-existing liver disease. This includes a repeat assessment as soon as possible to confirm the findings and a clinical evaluation. If the participant has signs or symptoms of hepatitis or ALT > 5x baseline, the study drug will be temporarily discontinued.

**Data to be provided to the participants** – At a minimum, the locally run clinical labs and MRI liver fat result from baseline will be provided to each patient at the end of the study and reviewed with them by a study investigator. This includes the CMP, CBC, GGT, hemoglobin A1c, insulin, glucose and fasting lipids. The investigator may choose to share other locally run clinical labs from other time points with the participant.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

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

Adverse events, which include abnormal and clinically significant clinical laboratory test variables, will be monitored and documented from the time of first dose of study drug (Study Day 1) until study participation is complete (the Follow-up Visit). Subjects should be instructed to report any adverse event that they experience to the Investigator. Beginning with the signing of the informed consent until the time of the first dose of study drug (Study Day 1), Investigators should make updates to medical history and record any pre-existing medical condition or signs or symptoms that changes in severity, frequency,

or seriousness in the medical history. Serious adverse events that occur prior to the first dose of study drug (Study Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF. Beginning with the first dose of study drug (Study Day 1), Investigators should make an assessment for adverse events at each visit and record all adverse events, non-serious and serious, on the appropriate adverse event eCRF.

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

Any medical condition already present prior to the subject taking the first dose of study drug (Study Day 1) should be reported in the medical history. Any SAEs occurring prior to the first dose of study drug (Study Day 1) should be reported as an update to medical history as well as an adverse event. Any pre-existing medical condition or signs or symptoms that changes in severity, frequency, or seriousness after the subject takes the first dose of study drug (Study Day 1) and through the Follow-up Visit should be reported as an adverse event.

Clinically significant abnormal laboratory values or other examinations (e.g., ECG) that are detected at the time of the first dose of study drug (Study Day 1) and worsen during the study should be reported as adverse events. An abnormal laboratory result that is not verified by repeat testing does not necessitate reporting as an adverse event. The Investigator will exercise his or her medical, scientific, and clinical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. Overdoses with associated symptoms are always handled as AEs and reported as such. Overdoses without associated symptoms are not reported as AEs but are documented in [specify e.g., CRF] in order to collate information for the IB regarding the level of excess dosage taken or administered without adverse effects. An overdose will be reported irrespective of outcome even if toxic effects were not observed.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using Related/Not Related. In a clinical trial, the study product must always be suspect.

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

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

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

The following factors should also be considered:

- The temporal sequence from study drug administration -
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant diseases (medical history) -

- Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug -
  - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug -
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses -
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PKs of the study drug -
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

#### 8.3.3.3 EXPECTEDNESS

The study investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

The expected adverse events are listed in the Investigators Brochure (IB).

### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

### 8.3.5 ADVERSE EVENT REPORTING

Adverse event reporting will include the following. Each AE will be reported to the study investigator and the study investigator is responsible for completing and signing off on the AE reports. Non-serious AEs will be reported to the sponsor within 30 days. The sponsor will review a summary of all AEs monthly. A summary of AEs will be provided to the DSMB as part of the quarterly reports.

NAFLD related events that are common in the study population (expected) include:

- Abdominal pain
- Hyperglycemia
- High blood pressure
- Diabetes

These and any other adverse events will be recorded on the CRF and monitored to resolution or 30 days after end of the study.

### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor and MMS Pharmacovigilance, per the SAE reporting form, any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by Emory University/[redacted] or MMS Pharmacovigilance and should be provided as soon as possible.

The study sponsor (Emory) will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of

potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

### 8.3.8 EVENTS OF SPECIAL INTEREST

N/A

### 8.3.9 REPORTING OF PREGNANCY

If a participant becomes pregnant, the study drug will be discontinued immediately while continuing to carry out safety follow-up. Permission will be requested to follow the pregnant women to pregnancy outcome. All pregnancies should be reported as an adverse event and the reporting mechanisms under that apply.

### 8.3.10 DRUG-INDUCED LIVER INJURY CLINICAL MANAGEMENT PLAN

If subjects develop elevations of AST or ALT >2x baseline or total bilirubin >1.5x baseline values during the study, repeat testing will be performed within 48 -72 hours. If there are persistent elevations (ALT or AST >2 X baseline or TBL >1.5 X baseline values) upon repeat testing, then close observation (testing and physical examination 2-3 times per week) will be implemented and discontinuation of drug will be considered.

A decision to discontinue or temporarily interrupt the study drug will be based on factors that include how much higher than baseline ALT and AST were relative to the upper limit of normal (ULN) and how much the on study ALT and AST levels have increased relative to baseline, in addition to whether there is concomitant elevation of bilirubin or INR.

The study drug will be discontinued or temporarily interrupted:

- If baseline measurements (BLM) were <2 X ULN, discontinue if ALT or AST increases to >5 X BLM.
- If BLM ≥2 X ULN but <5 X ULN, discontinue if ALT or AST increases to >3 X BLM.
- Discontinue if ALT or AST increase is >2 X BLM AND the increase is accompanied by a concomitant increase in TBL to >2 X BLM OR the INR concomitantly increases by > 0.2.
- In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

If a patient lives in a remote area, laboratory testing will be performed locally and the results will be promptly communicated to the investigator site.

### 8.3.11 LONG-TERM SAFETY FOLLOW-UP

For long-term safety follow-up of subjects there will be a Week 24, Week 36, and Week 60 safety follow-up visit. The same study procedures will be conducted at all three visits, as outlined in Table 1 (Schedule of Activities). The Month 3 Safety Follow-up Visit (Week 24 Visit) will take place 12 weeks after the Week 12 or ET visit with a two week visit window. The Month 6 Safety Follow-Up Visit (Week 36 visit) will take place 24 weeks after the Week 12 or ET visit with a two week visit window. The Month 12 Safety Follow-up Visit (Week 60) will take place a year from the Week 12 or ET visit.

## 8.4 UNANTICIPATED PROBLEMS

### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator [redacted]). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 7 calendar days of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

## 9 STATISTICAL CONSIDERATIONS

### 9.1 STATISTICAL HYPOTHESES

The primary end-point of the study and on which the statistical power is based is the percent change in ALT from Baseline to Week 12.

The hypothesis being tested is that treatment with gemcabene for twelve weeks will result in a clinically meaningful reduction in ALT, in pediatric NAFLD participants.

### 9.2 SAMPLE SIZE DETERMINATION

The sample size for this study is 36 completed participants. A percent change from baseline of approximately 20% is considered to be clinically meaningful. Assuming a two-sided test at the 5% significance level, 36 completed participants will provide 81% power to detect a percent change from baseline of 20% (effect size = 0.5), if the standard deviation is 40%. Additionally, assuming a drop-out rate of 10%, a total of 40 participants is needed for enrollment into the study to ensure an adequate number of subjects complete the trial. Power was calculated using a two-sided Wilcoxon test with a 0.05 significance level using PASS v. 14.0.8 (Kaysville, UT).

### 9.3 POPULATIONS FOR ANALYSES

- Intention-to-Treat (ITT) Analysis Set: all enrolled participants. All efficacy summaries and analyses will be performed using the ITT.
- Modified Intention-to-Treat Analysis (mITT) Set: all enrolled participants who took at least one dose of study intervention and have liver enzymes performed at Baseline and Week 12. Confirmatory efficacy analyses will be performed using the mITT.
- Safety Analysis Set (SAS): all enrolled participants who took at least one dose of study intervention. All safety summaries will be performed using the SAS.
- Per-Protocol Analysis Set (PPAS): the subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently (e.g., took at least 80% of study intervention for 80% of the days within the 12-week period) and did not have any major protocol deviations. Confirmatory efficacy and safety analyses will be performed using the PPAS.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

Statistical significance will be assessed at the 0.05 level, unless otherwise noted.

Descriptive statistics will be calculated for all variables of interest and include means and standard deviations or medians and ranges (for continuous measures) or counts and percentages (for categorical measures), as appropriate. Continuous data will be assessed for normality using histograms and normal probability plots and statistically tested using the Anderson-Darling test and/or the Shapiro Wilk test for normality. Non-normal data will be presented using medians accompanied by 25$^{th}$ and 75$^{th}$. All analyses will be conducted using SAS v. 9.4 (Cary, NC) or CRAN R v. 3.3 (Vienna, Austria).

### 9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For the primary efficacy endpoint, we will use the ITT population. The entire population, regardless of whether or not they took the study medication, will be used in the analysis.

- Percent change in ALT
  Changes in our primary continuous outcome measures (ALT) from Baseline to the primary endpoint (Week 12), will be examined as percentage change. $\left(\left(\frac{(postbasline\ value - baseline\ value)}{baseline\ value}\right) x\ 100\right)$. Statistically, percent change from Baseline to Week 12 will be tested against the null hypothesis of no change (i.e., percent change = 0) using a one-sample two-sided t-test or a Wilcoxon signed-rank test, in the event that the percent change is non-normally distributed. Output from the t-test will include the mean percent change, its 95% confidence interval and the p-value. If the data are non-normally distributed, the median percent change value and the 25$^{th}$ and 75$^{th}$ percentiles will be presented, along with the p-value from the Wilcoxon signed-rank test.

- Patients with no week 12 measurements will be excluded from the primary efficacy analysis (only observed case data will be used). In a sensitivity analysis, for subjects with missing week 12 data, we will carry forward their week 6 measurements and re-assess the primary outcomes. Similar analyses will be used to examine the mITT and the PPAS datasets.

### 9.4.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT(S)

*For each secondary efficacy endpoint:*

Similar to the primary endpoints described above, we will examine percent change in all continuous secondary outcomes measures. In addition, we will also calculate raw change from baseline (raw change = (postbaseline value – baseline value). Raw change and percent change in each continuous endpoint will be calculated in a manner analogous with described above for the

primary endpoint. Raw changes in measures from baseline will be assessed using a paired t-test or a Wilcoxon signed-rank test when data are non-normally distributed. Output for each endpoint will include the mean, its 95% confidence interval and the p-value if a t-test is performed. If the endpoint is not normally distributed, median values, and the 25$^{th}$ and 75$^{th}$ percentiles will be presented, along with the p-value from the Wilcoxon signed-rank test.

Similar analyses will be performed to examine interval changes in continuous measures from Baseline to Week 6 (when applicable).

Growth data collected during the study will be summarized descriptively at each time point and converted to age-sex specific z-scores using normative data. Raw changes in BMI and weight as well as Z-scores will be examined using the methods described above.

- Patients with no week 12 measurements will be excluded from the secondary efficacy analyses (observed case data only will be used). In a sensitivity analysis, for subjects with missing week 12 data, we will carry forward their week 6 measurements and re-assess the primary outcomes. Similar analyses will be used to examine the mITT and the PPAS datasets.

### 9.4.4 SAFETY ANALYSES

Each AE will be counted once only for a given participant in each summary table, and will be presented based on severity, frequency, and relationship of AEs to study intervention by System Organ Class (SOC) and preferred term groupings. For each AE, the severity, relationship, expectedness, outcome, and duration will be presented in a table. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table or a listing. AEs will be tabulated and described using counts and percentages with associated 95% confidence intervals.

### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics (e.g., means standard deviations, medians, counts, and percentages), will be used to describe the study cohort. No inferential statistical testing will be performed.

### 9.4.6 PLANNED INTERIM ANALYSES

No interim analysis is planned.

### 9.4.7 SUB-GROUP ANALYSES

The primary and secondary endpoints will be analyzed by sex and by presence or absence of select NAFLD genes which may alter response to the IP. Differences in the primary outcome (% change in ALT from Baseline to Week 12) will be compared among sexes and genetic subgroups using two-sample t-

tests or Wilcoxon rank sum tests, as applicable. Percent change for other continuous measures will be analyzed similarly. For subgroups with more than two levels, we will test for differences in percent change from baseline using analysis of variance (ANOVA) models with a Tukey-Kramer post-hoc multiple comparison procedure or a Kruskal Wallis test with a Dwass, Steel, Critchlow-Fligner multiple comparison procedure.

For raw changes in continuous measures (ALT, AST, etc.) subgroup analysis will be conducted using analysis of covariance (ANCOVA) models. Specifically, for each outcome of interest, we will compare the 12-week outcome measure between subgroups (e.g., sex) controlling for the baseline value of the outcome measure. Initial models will include the interaction between subgroup and baseline value to assess the homogeneity of slope assumption. If the assumption is met, the interaction will be removed and least square means with associated 95% confidence intervals will be provided for each subgroup. Differences in subgroup means will be reported and accompanied by 95% confidence intervals. If the assumption of homogeneity of slopes is violated, an alternative approach such as the Johnson-Neyman procedure, will be utilized.

#### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

#### 9.4.9 EXPLORATORY ANALYSES

Exploratory analyses are planned as described in the sub-study (appendix A).

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 10.1.1 INFORMED CONSENT PROCESS

#### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol.

The following questionnaires and handouts will be submitted with the IRB submission:

- AUDIT questionnaire
- Block physical activity questionnaire
- Bev Q survey
- Food frequency questionnaire
- TANNER screener

- PROMIS Questionnaires (Fatigue, Anxiety, Depression)
- AHA Healthy Children Handout

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. The DSMB will review all AEs and SAEs and may suspend or terminate the study for safety concerns. AEs will be reviewed quarterly and for any SAE, an ad hoc meeting of the DSMB will be convened within 10 business days to review the event.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, Gemphire, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

Patient-specific trial stopping rules include:

- In any patient who develops an AE of grade 3 that is probably or possibly related to study drug and any patient who develops a grade 4 or higher CTCAE regardless of causality assessment, investigational product will be discontinued.

- Hemoglobin will be assessed by central laboratory evaluation. For a hemoglobin decrease of > 1.5 g/dL from baseline during the study, repeat hematology studies and reflexive evaluation of reticulocyte count will be performed. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., bleeding, shortness of breath, fatigue) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

- If hemoglobin falls >3.0 g/dL without any clear cause, then the investigator should discontinue the investigational product and hemoglobin should be monitored until it returns to a level of no less than 1.0 g/dL below baseline. At this time, the investigator can consider restarting the investigational product and recheck hemoglobin levels one and two weeks after re-initiation of investigational product. If hemoglobin levels decrease >3 g/dL again, investigational product should be discontinued and the subject should continue with all other study procedures. Hemoglobin should continue to be monitored until it returns to a level of no less than 1.0 g/dL below baseline.

- If, at any visit, a creatinine increase of > 0.3 mg/dL (27 µmol/L) from baseline, a GFR decrease of > 15 mL/min from baseline, or a > 30 urinary albumin:creatinine ratio mg/g is observed, a repeat chemistry/urinalysis will be performed within one week. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., fatigue, malaise, polyuria/oliguria, or palpitations) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

- Patients with persistent serum creatinine changes of > 0.3 to < 0.5 mg/dL will be evaluated by the investigator to determine if the subject has any signs and symptoms of renal injury. If the investigator determines that the biomarkers along with the signs and symptoms are consistent with renal injury, then investigational product should be discontinued, and the subject should continue with all future protocol assessments.

- If at any time there is a doubling of serum creatinine or a decrease > 50% in GFR from baseline, then investigational product should be discontinued immediately. The patient will be followed until renal parameters return to baseline or normal levels. The investigator can determine based on signs, symptoms and laboratory data whether or not to reinitiate investigational product and continue with scheduled monitoring. Regardless of whether or not investigational product is reinitiated subjects should continue with all future protocol assessments.

### 10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Emory University. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Emory University research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Emory University.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Emory University. After the study is completed, the de-identified, archived data will remain at Emory and will be made available for use by other qualified researchers including those outside of the study with the consent of the steering committee and Gemphire. Permission to transmit data to the outside investigators for the purpose of improving human health will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at Emory with the same goal as the sharing of data. These samples may be shared with other qualified researchers after permission from the steering committee and Gemphire.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| Principal Investigator | Medical Monitor |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

Steering Committee:

[redacted]

### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including pediatric hepatology, pediatric nephrology and pediatric endocrinology. Members of the DSMB are independent from the study conduct and free of potential/perceived conflict of interest with Gemphire, [redacted] and the study investigators. The DSMB will meet at least quarterly to assess summary safety and efficacy data for the study. If requested, the summary data tables may be shared with regulatory agencies. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to [redacted] and the steering committee.

**DSMB Members:**

[redacted]

[redacted]

[redacted]

[redacted]

**DSMB Statistician:**

[redacted]

### 10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by an appointed CRA on behalf of Gemphire. The study monitor will perform on-site monitoring every 4-8 weeks, or as needed, depending on data quality, enrollment and other factors. 100% SDV will be performed, with particular attention of monitoring time to eligibility and safety assessments.
- To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, management of investigational product, and the procedure for reporting adverse events such as SAEs.
- A detailed follow-up letter will be provided to the Principal Investigator following visits and will be acknowledged and filed in the Trial Master File.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted by QACV Consulting or a similar vendor to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

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

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### 10.1.9 DATA HANDLING AND RECORD KEEPING

#### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by Gemphire Therapeutics Inc. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

#### 10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

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

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

### 10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

### 10.1.11 PUBLICATION AND DATA SHARING POLICY

**Publication Policy**

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

**Insurance and Indemnity**

In accordance with the relevant national regulations, Gemphire has taken out clinical trial insurance. This insurance provides coverage to the sites through Gemphire in the event of physical injury or death related to the study drug or any procedure related to the protocol.

### 10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. All study group members will disclose all conflicts of interest every 12 months during the study and the sponsor (Emory University) will establish a mechanism for the management of all reported dualities of interest.

## 10.2 ADDITIONAL CONSIDERATIONS

N/A

## 10.3 ABBREVIATIONS

*The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).*

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |

| | |
|---|---|
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CPK | Creatine phosphokinase |
| CRF | Case Report Form |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| DRE | Disease-Related Event |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GWAS | Genome-Wide Association Studies |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| ISO | International Organization for Standardization |
| ITT | Intention-To-Treat |
| LSMEANS | Least-squares Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMC | Safety Monitoring Committee |
| SOA | Schedule of Activities |
| SOC | System Organ Class |

| | |
|---|---|
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| US | United States |

## 10.4 PROTOCOL AMENDMENT HISTORY

*Summary of changes from previous version of protocol.*
*Version 4.0 02OCT2018*

| Section(s) Affected by Change | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis<br>3. Endpoints<br>8.1 Efficacy Assessments | Addition of cT1 score by Liver Multiscan as secondary endpoint | LIF score is a categorical descriptor of cT1 measurements. This was inadvertently left out of the original protocol. Both measures will be included as secondary endpoints. |
| 1.3 Schedule of Activities | Removed description of MRI details in the table. | These procedures are detailed later in the protocol. |
| 10.1.6 Safety Oversight | Change cardiology to endocrinology | Correction of initial error regarding DSMB member specialty |
| 14. Sub-study Methods | Added Week 12 only for PK collection | Clarification that PK was only collected at Week 12 during the sub-study (not during baseline) |
| 1.3 Schedule of Activities | Updated Table 1, 2, and 3 to reflect details of the three additional long-term safety visits. | To clarify which study procedures will take place at the additional three long-term safety follow-up visits. |
| 8.3.11 Long-term safety follow-up | Addition of long-term safety follow-up visits | To clarify the long-term safety follow-up plan |

*Summary of changes from previous version of protocol.*
*Version 3.0 – 31JUL2018*

| Section(s) Affected by Change | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Synopsis<br>3. Endpoints<br>8.1 Efficacy Assessments | Addition of cT1 score by Liver Multiscan as secondary endpoint | LIF score is a categorical descriptor of cT1 measurements. This was inadvertently left out of the original protocol. Both measures will be included as secondary endpoints. |
| 1.1 Synopsis<br>4.1 Overall Design<br>5.5 Strategies for Recruitment and Retention<br>10.1 Key Roles and Study Governance | Study population increased from 40 to 50 subjects due to the addition of a 4$^{th}$ site. | Addition of UCSD (PI: Dr. Jeff Schwimmer) to increase the study population by 10 subjects. |
| 1.3 Schedule of Activities | Removed description of MRI details in the table. | These procedures are detailed later in the protocol. |

| | | |
|---|---|---|
| Table 2. Specimen Collection Schedule<br>Table 3. Blood Volume Chart | Addition of clinical lipid profile at Baseline, Week 2, Week 6, and Week 12 | To get clinical lipid profiles run in real time for investigator review |
| 5.1 Inclusion Criteria | Changed language regarding *historic* ALT requirement to be within 50% of the screening visit ALT but not necessarily within the other set range of girl ≥ 46 boy ≥ 54 but < 250. | To improve clarity surrounding historic ALT requirements |
| 5.2 Exclusion Criteria | Addition of timing criteria of taking fish oil, fibrates, or thiazolidinediones – must be at least 30 days prior to screening | To improve clarity for subjects previously taking these medications |
| 8.3.10 Drug-Induced Liver Injury Clinical Management Plan | Changed definition of close observation from 2-3 times weekly to at least weekly | To give more flexibility to subjects in scheduling multiple unscheduled visits |
| 10.1.6 Safety Oversight | Change cardiology to endocrinology | Correction of initial error regarding DSMB member specialty |
| 12.1 Meal Challenge Sub-study and Deuterated Water Tracer Sub-study | Changed until 10 have completed sub-study | To improve clarity |
| 14. Methods | Clarified that PK labs are only to be drawn at Week 12 in the sub-study and not at baseline | To improve clarity and consistency throughout protocol |
| 14. Methods | Clarified when drug is administered at the Week 12 visit for the substudy. | To improve clarity |

*Summary of changes from previous version of protocol.*
Version 2.0 – 27FEB2018

| **Section(s) Affected by Change** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Section 1.1 Synopsis<br><br>Section 3 Endpoints | Added “absolute change and percent change in pancreatic fat from Baseline to Week 12” | Pancreatic fat protocol added to Hepafat scan (MRI) |
| Section 1.1 Synopsis<br><br>Section 3 Endpoints | Added “change in body composition measures by AMRA from Baseline to Week 12” | Addition of body composition acquisition (MRI) |
| Section 1.3 Schedule of Activities (Table 1) | Moved standardized lifestyle counseling from Screening to Baseline | Correction of an oversight on the timing of the counseling |
| Section 1.3 Schedule of Activities (Table 1) | Added visit window for Baseline Visit activities (+/- 2 days) | Allow for flexibility in scheduling the baseline MRI and completing other visit activities |
| Section 1.3 Schedule of Activities (Table 1) | Added Early Termination Visit | To improve clarity of study procedures for an ET visit |
| Section 1.3 Schedule of Activities (Table 1) | Moved “Metabolomics” from Table 1 to Table 2 | To improve clarity |
| Section 1.3 Specimen Collection Schedule (Table 2) | Added specimen collection details for Early Termination visit | To improve clarity of study procedures for an ET visit |

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|---|---|---|
| Section 1.3 Specimen Collection Schedule (Table 2) | Clarified which labs are included within CMP, CBC, and Lipid Profile | To improve clarity |
| Section 1.3 Specimen Collection Schedule (Table 2) | Added note regarding the possibility of an additional lab draw during screening for subjects with no historic ALT available | To improve clarity |
| Section 1.3 Blood Volume Chart (Table 3) | Updated entire table to reflect the blood volume changes from switching vendors and combining draw tubes. | To reflect the changes made to the labs |
| Section 7.1 Discontinuation of Study Intervention | Defined which activities will take place at the Early Termination visit | To improve clarity |
| Section 7.2 Participation Discontinuation/Withdrawal from the study | Clarified the timing of when subjects should be replaced | To improve clarity |
| Section 8.1 Efficacy Assessments | Added pancreatic fat and body composition | To reflect additional MRI protocols |
| Section 8.1 Efficacy Assessments | Added to Unscheduled visits: repeat ALT during screening and the Early Termination visit | To improve clarity |
| Throughout protocol | Renaming “12 weeks” and “6 weeks” to “Week 12” and “Week 6” | To improve clarity |
| Throughout protocol | Minor changes to format and correction of typographical errors | To improve clarity |

*Summary of changes from previous version of protocol.*
Version 1.1 – 01DEC2017

| **Section(s) Affected by Change** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Title Page | Removed NCT number and summary of changes | To avoid need for future amendment and redundancy |
| Table 1. Schedule of Activities | Added calculated BMI at each visit | To address request by FDA |
| Table 1. Schedule of Activities | Added footnote C in regards to obtaining physical measurements | To improve clarity |
| Table 1. Schedule of Activities | Added ECG to Baseline and Week 2 visits | To address request by FDA |
| Table 1. Schedule of Activities | Added pregnancy test at Week 2 and Week 6 visits | To improve safety |
| Table 2. Specimen Collection Schedule | Added urinalysis and urine collection for storage | To improve clarity |
| Table 2. Specimen Collection Schedule | Added pharmacokinetic studies | To address request by FDA |
| Table 2. Specimen Collection Schedule | Added CBC at Week 12 | To address request by FDA |
| Table 3. Blood Volume Chart | Added Table 3 to show blood volume amounts throughout study | To address request by FDA |

| | | |
|---|---|---|
| Section 4.2 Scientific Rationale for Study Design<br><br>Section 5.1 Inclusion Criteria | Added language regarding assessment of inflammation change in ALT at screening: obtain historical and/or repeat ALT measure | To address request by FDA |
| Section 5.1 Inclusion Criteria | Added inclusion criteria of ALT ≤ 250 at screening | To address request by FDA |
| Section 5.1 Inclusion Criteria | Entry criteria clarification of clinical diagnosis of NAFLD | To address request by FDA |
| Section 5.1 Inclusion Criteria | Added inclusion requirement of attempted lifestyle modification to treat NAFLD for at least three months | To address request by FDA |
| Section 5.2 Exclusion Criteria | Entry criteria clarification regarding Gilbert's syndrome lab requirements | To address request by FDA |
| Section 5.2 Exclusion Criteria | Addition of abnormal alkaline phosphatase to exclusion criteria | To address request by FDA |
| Section 5.2 Exclusion Criteria | Addition of any history of ascites, variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma (HCC) to exclusion criteria | To address request by FDA |
| Section 5.2 Exclusion Criteria | Changed HbA1c exclusion criteria to < 8% at screening | To address request by FDA |
| Section 5.2 Exclusion Criteria | Addition of exclusion criteria for patient with type 1 diabetes mellitus | To address request by FDA |
| Section 5.2 Exclusion Criteria | Change in exclusion of elevated creatinine kinase elevations to allow for repeat test if thought to be related to exercise | To address request by FDA |
| Section 5.3 Lifestyle Considerations | Fasting requirement changed from 12 hours to 8 hour minimum, clarified that fasting is not required for the screening visit | To make fasting requirements easier on participants |
| Section 8.2 Safety and Other Assessments | Addition of 7 day window for obtaining repeat creatinine levels | To improve clarity |
| Section 8.3.10 Drug-Induced Liver Injury Clinical Management Plan | Addition of Section 8.3.10 Drug-Induced Liver Injury Clinical Management Plan | To address request by FDA |
| Section 10.1.2 Study Discontinuation and Closure | Addition of Patient-specific trial stopping rules | To address request by FDA |
| Section 10.1.6 Safety Oversight | Addition DSMB Statistician | To improve clarity |
| Appendix B. PROMIS Questionnaires | Addition of PROMIS questionnaires to protocol | To address request by FDA |
| Throughout protocol | Minor changes to format and correction of typographical errors | To improve clarity |

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# APPENDIX A. POST PRANDIAL LIPIDS AND DE NOVO LIPOGENESIS SUB-STUDIES

**Purpose and Background**

While fasting lipids reflect steady state and remnants from the previous day's diet, the patterns of lipids following a meal reflects important aspects of metabolic health (or dysfunction) especially in patients with NAFLD. Gemcabene is proposed to improve postprandial lipids in several ways. First, it is a dual inhibitor of both cholesterol synthesis and fatty acid synthesis. In addition, it decreases plasma levels of apoC-III, which then leads to increased clearance of VLDL particles, lowering circulating TG levels. The mechanism of apoC-III lowering is thought to be through inhibition of the expression of apoC-III.

## 12 SUB-STUDY SUMMARY

### 12.1 MEAL CHALLENGE SUB-STUDY & DEUTERATED WATER TRACER SUB-STUDY

**Title:** Meal Challenge Sub-Study

**Study Description:** Provides measurement of postprandial lipids in 10 participants

**Endpoints:**

Primary Endpoint:

- Incremental area under the curve for TG concentration in plasma, chylomicrons and VLDL

Secondary Endpoint:

- Incremental AUC for apoB and apoC-III in plasma, chylomicrons and VLDL

**Title:** Deuterated Water Tracer Sub-Study

**Study Description:** Provides measurement of postprandial lipids and will be performed simultaneously in the same 10 participants who are participating in the Meal Challenge Sub-Study

**Endpoints:**

Primary Endpoint:

- Change in fractional hepatic De Novo Lipogenesis (DNL) and fractional cholesterol synthesis (DNC) after twelve weeks of gemcabene

Secondary Endpoint:

- Change in absolute hepatic De Novo Lipogenesis (DNL) and absolute cholesterol synthesis (DNC) after twelve weeks of gemcabene

**Study Population:** The sample for this study will include n=10 participants with NAFLD (~50% boys and ~50% girls) who are participating in the GEM-IIT-601 study. The

| | |
|---|---|
| | sub-study will only be conducted at Emory. All Emory site participants will be invited to participate in the sub-study until 10 have been enrolled . |
| **Description of Sites/Facilities Enrolling Participants:** | Emory University |
| **Description of Study Intervention:** | No intervention; only blood collection will occur |
| **Study Duration:** | 12 months |
| **Participant Duration:** | 12 weeks |

## 13 STUDY POPULATION

The sample for this study will include n=10 participants with NAFLD (~50% boys and ~50% girls) who are participating in the GEM-IIT-601 study. The sub-study will only be conducted at Emory. All Emory site participants will be invited to participate in the sub-study until 10 have been enrolled.

### 13.1 INCLUSION CRITERIA * *ADDITIONAL INCLUSION AND EXCLUSION CRITERIA (IN ADDITION TO THE MAIN STUDY CRITERIA)*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

10. Willing to participate in the sub-study and complete all sub-study procedures at Baseline and Week 12 visits
11. History of hypertriglyceridemia

### 13.2 EXCLUSION CRITERIA * *ADDITIONAL INCLUSION AND EXCLUSION CRITERIA (IN ADDITION TO THE MAIN STUDY CRITERIA)*

An individual who meets any of the following criteria will be excluded from participation in this study:

22. Food allergies including gluten sensitivities
23. Known reaction to deuterated water

## 14 METHODS

After consent and assent to the main study, participants at Emory University will be informed of the sub-study at the Screening visit. Consent and assent for the sub-study will be obtained through providing details of the sub-study and procedures and through discussion. The postprandial lipid study will take place at the Baseline and Week 12 visit. Prior to the day of the visit, the participants will have a standardized meal provided for their evening meal. They will be asked not to consume any sugar

containing beverages including juice. The meal will be identical at Baseline and Week 12 and will consist of a commercially prepared frozen dinner that can be microwaved at the time of consumption. It will be shipped frozen to the participant's home along with instructions.

*Deuterated water:* De novo lipogenesis and cholesterol synthesis can be studied by measuring the incorporation of deuterium from deuterated water into VLDL-TG palmitate and plasma free cholesterol. Two 60 ml bottles of deuterated water (D, 70%) will be provided the evening prior to the DNL and DNC assessments. One bottle will be consumed with the standardized evening meal and one bottle 3 hours later around bedtime.

No food or flavored drinks will be allowed after 7 pm the day prior to the visit to ensure 8 hours of fasting. Participants will be asked to consume one glass of water in the morning prior to driving to the research center to ensure good hydration at the time of the sub-study.

On the morning of the visit, at the pediatric research unit, participants will have an IV placed during the initial blood draw to make repeated blood draws more comfortable. After fasting labs are completed, a standardized breakfast will be provided (approximately 30% fat [~12% polyunsaturated, 8% saturated, and 10% monounsaturated], 15% protein and 55% carbohydrates consumed in combination with a juice beverage). The standardized breakfast will be enriched with fructose to stimulate DNL and will be identical at Baseline (Week 0) and Week 12 assessments. It will be a fixed meal and not calorie-adjusted for body weight.

Blood samples will be drawn at 0, 2, 4, and 6 hours to assess the biological measures of interest. At each timepoint, 14 mL of blood will be collected in spray-dried K2 EDTA vacutainers and immediately placed on ice. Blood samples will be transported to the lab within 30 minutes, spun and the plasma aliquoted. At each blood collection timepoints, four (4) mL of plasma will be stored at 4◦C and transported to the Biomarker Core Laboratory, Atlanta VAMC (Dr. Ahn Le's lab) on the same day for lipoprotein fractionation by density ultracentrifugation. Two (2) plasma aliquots from each timepoint will be stored at -80 ◦C.

| **Timepoint (hours)** | **0** | **2** | **4** | **6** | **Total amount of blood per assessment** |
|---|---|---|---|---|---|
| **K2 EDTA** | 14 ml | 14 ml | 14 ml | 14 ml | 56 ml |
| **PK Sampling (Week 12 only)** | 3 ml | 3 ml | 3 ml | 3 ml | 12 ml |

## 14.1 PART 2: DE NOVO LIPOGENESIS

**Study Subjects:** 10 adolescents (as described above)

**Study Design:** Hepatic de novo lipogenesis will be measured in the fasting state (0 HR) and during the fructose enriched meal challenge (0, 2, 4 and 6 HRS) before Gemcabene treatment begins (Week 0) and after treatment is complete (Week 12).

**Sample Collection and Processing:**

(1) VLDL (Sf20-400) particles will be isolated from 1 mL of plasma at the Biomarker Core Laboratory, split in two equal VLDL aliquots (one primary and one back-up sample), frozen at -80 °C and shipped to Metabolic Solutions, Inc. for triglyceride isolation and deuterium enrichment of VLDL-TG palmitate by IRMS.

(2) Plasma (250 µL) will be collected at 0, 2, 4 and 6 HRS and frozen at -20 °C for body water enrichment analyses (Metabolic Solutions, Inc.). Spray-dried K2 EDTA vacutainers will be used to collect plasma for body water enrichment analyses.

(3) VLDL-TG palmitate concentration

**Data Analysis:** Deuterium enrichment in VLDL-TG palmitate and plasma water will be determined by IRMS. Fractional DNL will be calculated from body water and VLDL-TG-palmitate deuterium enrichment using precursor-product relationships. Absolute DNL will be calculated as Fractional DNL x VLDL-TG palmitate pool size.

**Endpoints:**

Primary Endpoint:

- Fractional hepatic DNL in the fasting state (0 HR) and during meal stimulation (2 HR, 4 HR, 6 HR)

Secondary Endpoint:

- Absolute hepatic DNL in the fasting state (0 HR) and during meal stimulation (2 HR, 4 HR, 6 HR)

## 14.2 PART 3: CHOLESTEROL SYNTHESIS

**Study Subjects:** 10 adolescents (as described above)

**Study Design:** Cholesterol synthesis will be measured in the fasting state (0 HR) and during the meal challenge (6 HR) before Gemcabene treatment begins (Week 0) and after treatment is complete (Week 12).

**Sample Collection and Processing:**

(1) Plasma (250µL) will be collected at 0, and 6 HRS and frozen at -20 °C for deuterium enrichment analyses of free cholesterol (Metabolic Solutions, Inc.) by IRMS.
(2) Plasma free cholesterol concentration

**Data Analysis:**

Deuterium enrichment in plasma free cholesterol and plasma water will be determined by IRMS. The fraction of newly synthesized cholesterol (DNC) will be calculated from body water and cholesterol deuterium enrichment using precursor-product relationships. Absolute cholesterol synthesis will be calculated as DNL (%) x plasma (free) cholesterol concentration.

**Endpoints:**

Primary Endpoint:

- Fractional cholesterol synthesis in the fasting state (0 HR) and during meal stimulation (6 HR)

Secondary Endpoint:

- Absolute cholesterol synthesis in the fasting state (0 HR) and during meal stimulation (6 HR)

Measurements for DNL and DNC endpoints:

| **Measurement** | **0 HR** | **2 HR** | **4 HR** | **6 HR** |
|---|---|---|---|---|
| Deuterium enrichment in VLDL-TG palmitate (1 mL of plasma to isolate VLDL-TG for IRMS analyses) | X (in duplicate) | x | x | x |
| Deuterium enrichment in plasma water (0.25 mL of plasma for IRMS or Cavity Ringdown Spectrometer analyses) | x | x | x | x |
| Deuterium enrichment in plasma free cholesterol (0.25 mL of plasma for IRMS analyses) | x | | | x |
| VLDL-TG palmitate concentration (GCMS) | x | | | x |
| Plasma free cholesterol concentration (Enzymatic Method) | x | | | x |

## 15 ADVERSE EVENT REPORTING

## 15.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 15.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Please refer to the main protocol.

### 15.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Please refer to the main protocol.

### 15.1.3 ADVERSE EVENT REPORTING

Please refer to the main protocol.

### 15.1.4 SERIOUS ADVERSE EVENT REPORTING

Please refer to the main protocol.

# 16 STATISTICAL CONSIDERATIONS

## 16.1 STATISTICAL ANALYSIS

Data will be examined to identify missing data from one or more timepoints. Paired-sample t-tests will be conducted for comparison between Baseline and Week 12, and p-values will be considered as significance when <0.05. Missing data imputation methods will be used for the small number of missing data points (<1%). If there is a clear linear pattern, the mean of the previous and subsequent data points will be used. If there is a lack of linear pattern over time, the average change plus the average mean of the outcome at its adjacent timepoints will be used to replace the missing data. For lipid and glucose metabolism variables, comparisons of the 6-hour response will be made using the incremental area under the curve (IAUC) using the trapezoidal method and paired analysis comparing individual timepoints at Baseline (0 hour, fasting) and post-prandially. Since the response variables will be measured repeatedly throughout the 6-hr period, the linear mixed model analysis will be utilized to compare the effects of the two different beverages, as well as the influence of sex. Specifically, a random intercept model will be assumed for each individual to incorporate the within-subject correlation with those random effects representing the influence of the repeated observations from the same subject.

# APPENDIX B. PROMIS QUESTIONNAIRES

PROMIS® Pediatric Item Bank v.1.0 - Fatigue - Short Form 10a

## Pediatric Fatigue - Short Form

**Please respond to each item by marking one box per row.**

**In the past 7 days.....**

| | | Never | Almost Never | Sometimes | Often | Almost Always |
|---|---|---|---|---|---|---|
| 4212R1 | Being tired made it hard for me to play or go out with my friends as much as I'd like. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4213R1 | I felt weak. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 2876R1 | I got tired easily. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4239aR2 | Being tired made it hard for me to keep up with my schoolwork. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4221R1 | I had trouble finishing things because I was too tired. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4220R1 | I had trouble starting things because I was too tired. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4210R2 | I was so tired it was hard for me to pay attention. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4241R2 | I was too tired to do sports or exercise. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4208bR2 | I was too tired to do things outside. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 4196R1 | I was too tired to enjoy the things I like to do. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |

PROMIS® Pediatric Item Bank v.1.1 - Depressive Symptoms - Short Form 8b

**Pediatric Depressive Symptoms - Short Form**

**Please respond to each item by marking one box per row.**

| | **In the past 7 days.....** | **Never** | **Almost Never** | **Sometimes** | **Often** | **Almost Always** |
|---|---|---|---|---|---|---|
| 488R1 | I could not stop feeling sad. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 461R1 | I felt alone. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 5041R1 | I felt everything in my life went wrong. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 5035R1 | I felt like I couldn't do anything right. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 711R1 | I felt lonely. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 228R1 | I felt sad. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 712R1 | I felt unhappy. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 3952aR2 | It was hard for me to have fun. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |

PROMIS® Pediatric Item Bank v.1.1 - Anxiety - Short Form 8b

**Pediatric Anxiety - Short Form**

**Please respond to each item by marking one box per row.**

| | **In the past 7 days…..** | **Never** | **Almost Never** | **Sometimes** | **Often** | **Almost Always** |
|---|---|---|---|---|---|---|
| 2220R2 | I felt like something awful might happen. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 713R1 | I felt nervous. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 2276R1 | I felt scared. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 5044R1 | I felt worried. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 3459bR1 | I worried when I was at home. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 2230R1 | I got scared really easy. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 231R1 | I worried about what could happen to me. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| 3150bR2 | I worried when I went to bed at night. | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |