CLINICAL STUDY PROTOCOL

A Placebo-controlled, Randomized, Phase 2a, Study to Assess the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of CIVI 007 in Patients on a background of Stable Statin Therapy

Investigational Product: CIVI 007
Protocol Number: CIVI 007-2-01

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Version Number: 3.0
Original Protocol Date: 01 July 2019
Amendment 1 Date: 09 Sept 2019
Amendment 2 Date: 14 Nov 2019

SIGNATURE PAGE

STUDY TITLE: A Placebo-controlled, Randomized, Phase 2a, Study to Assess the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of CIVI 007 in Patients on a background of Stable Statin Therapy

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

Signature Date

INVESTIGATOR AGREEMENT

By signing below I agree that:

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

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Placebo-controlled, Randomized, Phase 2a, Study to Assess the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of CIVI 007 in Patients on a background of Stable Statin Therapy

PROTOCOL NUMBER: CIVI 007-2-01

INVESTIGATIONAL PRODUCT: CIVI 007

PHASE: 2

INDICATION: Treatment of hypercholesterolemia

OBJECTIVES:

The primary objective of the study is to assess the safety and tolerability of CIVI 007 following multiple subcutaneous (SC) doses in patients on a background of a stable dose of statin therapy.

The secondary objective is to assess the pharmacodynamic (PD) effect of CIVI 007 on total plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) and LDL-C levels in the study population.

The exploratory objectives include the following:

- To assess the effect of CIVI 007 on other lipid and lipoproteins including triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), total cholesterol, apolipoproteins B, A-I and lipoprotein(a)
- To assess the effect of CIVI 007 on high-sensitivity C-reactive protein (hsCRP)
- To collect antidrug antibody (ADA) samples for potential future assessments of immunogenicity
- To further inform the population pharmacokinetic (PK) model of CIVI 007 with sparse PK sampling in patients on a background of statin therapy

POPULATION:

The population for this study includes male and female patients aged 18-70 currently on standard of care treatment for high blood cholesterol consistent with 2018 ACC/AHA guidelines (Appendix C) that includes a stable dose of background statin therapy with or without ezetimibe.

INCLUSION CRITERIA:

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

1. Willing and able to provide written and signed informed consent prior to any study-specific procedures.
2. Males or females, 18-70 years of age at the time of consent.
3. Body mass index (BMI) between 18.0 and 40.0 kg/m^2, inclusive, and a body weight of ≥60 kg at screening.
4. Currently on a stable (>4 weeks prior to the Screening Visit) dose of statin therapy (with or without ezetimibe).

5. Fasting low-density lipoprotein cholesterol (LDL-C):

   a. ≥100 mg/dL for those without any evidence of established ASCVD at the Screening Visit

   or,

   b. ≥70 mg/dL for those with evidence of established ASCVD at the Screening Visit.

   - Established ASCVD is defined as a history of at least 1 of the following occurring no more recently than 3 months prior to screening:
     - Acute coronary syndrome
     - Myocardial infarction
     - Stroke or transient ischemic attack presumed to be of atherosclerotic origin
     - Coronary revascularization (Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention)
     - Peripheral vascular disease or revascularization
     - In the absence of an above event, ASCVD as diagnosed >3 months prior to the Screening Visit based on invasive or noninvasive imaging such as angiography, coronary artery calcium (CAC) score >75th percentile, or >50% stenosis in any arterial bed.

   Note: Retesting will be allowed once at Screening Visit for LDL-C that is in the range of 65-69 mg/dL.

6. Fasting TGs <400 mg/dL at the Screening Visit.

   Note: Retesting will be allowed once at Screening Visit for TGs in the range of 401-450 mg/dL.

7. Women of childbearing potential (i.e., not postmenopausal [documented amenorrhea for ≥1 year in the absence of other biological or physiological causes] or surgically sterile including tubal ligation) must have a negative serum pregnancy test at the Screening Visit and a negative urine dipstick prior to dosing on Day 1. Postmenopausal status will be confirmed with a Screening Visit serum follicle-stimulating hormone (FSH) level >40 mIU/mL. Women aged >60 years whose FSH values are not >40 mIU/mL may be included at the discretion of the Investigator and in consultation with the Sponsor. Participating women of childbearing potential must agree to use 2 acceptable methods of contraception throughout the duration of the study and for 30 days after the last dose of study drug. Acceptable methods of contraception include condom, indwelling intrauterine device, or a vasectomized partner.

8. Male patients must be willing to use condoms during sexual intercourse from the Screening Visit until at least 90 days after administration of the last dose of study drug.

EXCLUSION CRITERIA:

Patients who meet any of the following medical history, concurrent medication or laboratory abnormality criteria will be excluded from participation in the study:

1. Women who are pregnant, nursing or breast feeding.
2. Currently prescribed a lipid lowering agent other than a statin or ezetimibe.
3. Abnormal liver function test at the Screening Visit (aspartate aminotransferase or alanine aminotransferase >1.5 × the upper limit of normal [ULN], total bilirubin >1.5 × ULN, or alkaline phosphatase >1.5 × ULN, based on appropriate age and gender normal values). Participants with bilirubin >1.5 × ULN and a history of Gilbert's syndrome may be included.
4. Active liver disease as defined by the investigator (e.g., cirrhosis, alcoholic liver disease, hepatitis B virus, hepatitis C virus, autoimmune hepatitis, liver failure, and/or liver cancer) or history of liver

transplant. NASH is considered exclusionary while non-alcoholic fatty liver (NAFL) is not exclusionary.

5. Known diagnosis of human immunodeficiency virus.
6. Mild, moderate or severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration eGFR formula), at the Screening Visit.
7. Uncontrolled thyroid disease: hypothyroidism or hyperthyroidism, as defined by thyroid-stimulating hormone below the lower limit of normal or >1.5 × ULN, respectively, based on results from the Screening Visit. If controlled, treatment should be stable for at least 3 months prior to the Screening Visit.
8. Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus, defined as hemoglobin A1c value >9%, based on results from the Screening Visit.
9. New York Heart Association Class II, III, or IV heart failure.
10. Myocardial infarction, severe or unstable angina pectoris, coronary revascularization, or other major cardiovascular event(s) resulting in hospitalization within 3 months of the Screening Visit.
11. Uncontrolled cardiac arrhythmia or prolonged QT interval on the Screening Visit electrocardiogram (ECG) (QT corrected using Fridericia's formula >450 msec for men and >470 msec for women), or known family history of prolonged QT interval or unexplained sudden cardiac death.
12. Currently receiving cancer treatments or, in the Investigator's opinion, is at risk of relapse for recent cancer within the study period.
13. A history of autoimmune disorder(s).
14. A history of hematologic or coagulation disorders.
15. Abnormal PT, aPTT, or INR at the screening visit.
16. Concomitant antiplatelet or anticoagulation medication. Allowable are low-dose aspirin (81 mg or less, daily) for CVD risk reduction, or PRN for occasional pain relief. Other antiplatelet drugs (e.g., P2Y12 inhibitors) and all anticoagulants are exclusionary.
17. Except as noted above, patients who have a clinically significant disorder that, in the opinion of the Investigator, could contraindicate the administration of study drug, affect compliance, interfere with study evaluations, or confound the interpretation of study results.
18. History of drug or alcohol abuse within the past year.
19. Previous treatment with CIVI 007.
20. Participation in another clinical study of an investigational agent or device concurrently or within 1 month prior to the Screening Visit or use of an investigational agent within 1 month or 5 half-lives (if known), whichever is longer, prior to the Screening Visit.
21. Donation of blood from 3 months prior, plasma 2 weeks prior, and platelets 6 weeks prior to the Screening Visit.
22. Any other findings that, in the opinion of the Investigator, would compromise the participant's safety or participation in the study.

STUDY DESIGN AND DURATION:

This is a Phase 2a, randomized, double-blind (investigator/subject), sponsor-open, parallel-group, multicenter study to evaluate the early clinical profile (safety, tolerability, pharmacodynamics and

pharmacokinetics) of CIVI 007 in patients on a background of statin therapy with or without ezetimibe. Patients are required to be on standard of care treatment for high blood cholesterol consistent with 2018 ACC/AHA guidelines that includes a stable dose of statin therapy (with or without ezetimibe) for at least 4 weeks prior to the Screening Visit. The study will enroll approximately 48 patients who will be randomized to 1 of 3 active treatment groups or the placebo reference group (12 patients per active treatment group and 12 in the placebo treatment group).

All potentially eligible patients will partake in the Screening Visit up to 21 days prior to Day 1. The Screening Visit will be the first study visit.

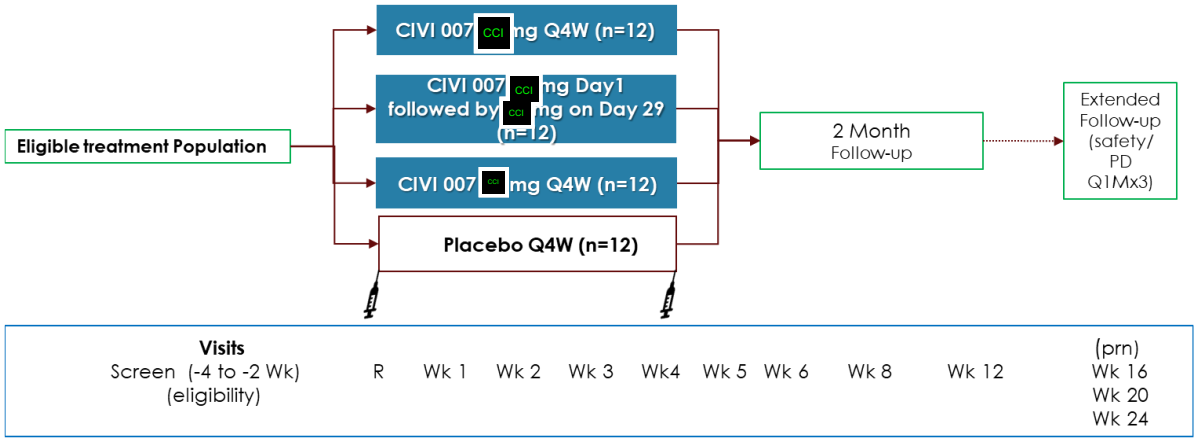
The Treatment Period will be approximately 28 days from Day 1 to Day 29; each treatment group will receive 2 administrations of study drug. Eligible patients will be randomized on Day 1 in a 1:1:1:1 ratio to one of the following treatment groups:

- Group 1: CCI mg CIVI 007 administered SC on Days 1 and 29
- Group 2: CCI mg CIVI 007 administered SC on Day 1 followed by CCI mg CIVI 007 administered SC on Day 29
- Group 3: CCI mg CIVI 007 administered SC on Days 1 and 29
- Group 4: Placebo for CIVI 007 administered SC on Days 1 and 29

The Follow-up Period will be approximately 8 weeks and begin following the last dose of study drug, unless extended follow-up is required based on the Day 85 LDL-C assessment or other Investigator determined safety considerations.

Extended follow-up visits will be conducted on a monthly basis for up to 3 months if Day 85 LDL-C levels are <80% of their baseline level; extended follow-up will end within the 3-month period if LDL-C levels are ≥80% of baseline. Extended follow-up visits (frequency and assessments will be at the discretion of the Investigator) to monitor Investigator determined safety considerations may extend beyond 3 months, if deemed appropriate by the Investigator, and will continue until there are no safety observations requiring further follow-up. The total duration of the study for each patient will be approximately 3 to 6.5 months, depending on the length of the screening, and follow up periods.

The study design is graphically summarized below.



Patients will be routinely monitored for safety, tolerability and pharmacodynamic effects. The schedule of procedures and clinical laboratory analytes are detailed in Appendices: Measurements will be taken as detailed in Appendix A (schedule) and Appendix B (clinical laboratory analytes).

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

CIVI 007 and placebo are sterile solutions to be administered by SC injection. Placebo for CIVI 007 will be commercially available sterile saline for injection. An unblinded pharmacist will prepare the study drug for blinded administration by the investigator site as detailed in the protocol's Pharmacy Manual.

Dosing is to be in the morning following an overnight fasting.

- CIVI 007 is to be administered SC into the abdomen (or thigh or upper arm, if necessary) from a solution at 150 mg/mL .
- Doses of CIVI 007 are CCI mg Q4W x2, CCI mg on Day 1 followed by CCI mg on Day 29 and CCI mg Q4W x2.
- Placebo is to be administered SC into the abdomen (or in thigh or upper arm, if necessary) on Day 1 and Day 29. The volume of injection will be randomly assigned to match the active CIVI 007 dose.

SAFETY/EFFICACY/PK VARIABLES AND ENDPOINTS:

Primary Endpoints

The primary safety/tolerability endpoints for this study are as follows:

- incidence and severity of any drug-related AE
- incidence of clinically significant laboratory abnormalities, based on drug-induced changes from baseline in hematology, clinical safety chemistry, and urinalysis test results

Secondary Endpoints

The secondary efficacy endpoints include the following changes from baseline measured approximately 28 days after the first and 28 and 56 days after the last injection of study drug:

- percent change in total plasma PCSK9 and LDL-C

Exploratory Endpoints

The exploratory PD endpoints are the absolute and % changes from baseline (except where indicated) in the levels of the following in serum or plasma over the time course of the treatment period and follow-up:

- PCSK9 (absolute only)
- LDL-C (absolute only)
- VLDL-C
- triglycerides
- HDL-C
- Non-HDL-C
- total cholesterol
- lipoprotein (a)
- apolipoproteins B and A-I
- hsCRP

The following PK parameters will be calculated for CIVI 007, where possible:

- C_{max}
- time of the maximum observed plasma concentration (t_{max})
- AUC_{0-t}
- concentration observed at pre-dose (C_{trough})

Additional exploratory PK parameters, which may include but are not limited to the following, may be calculated:

- area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24})
- area under the plasma concentration-time curve from time 0 to 48 hours (AUC_{0-48})
- percentage of $AUC_{0-\infty}$ that is due to extrapolation ($\%AUC_{extrap}$)
- apparent termination elimination rate constant (λ_z)
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- apparent total plasma clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)

SAFETY VARIABLES:

The safety variables include adverse events, clinical safety laboratory parameters (including clinical safety chemistry, hematology, coagulation parameters including fibrinogen, complement activation, cytokines

and urinalysis), 12-lead ECGs, physical examinations, and vital signs. Samples will also be collected for the potential future assessment of anti-drug antibodies.

PHARMACOKINETICS:

Sparse PK sampling will be conducted for all consenting patients in each active treatment group. Sampling will be performed on dosing days, and at each study visit during the Treatment and Follow-up Periods. For each of the dosing days, a PK sample will be drawn pre-dose (-1 hour), 3 hours (±1 hour) post-dose, and at 8 hours (±1 hour) post-dose.

The population PK model created based on data from the ongoing Phase 1 study will be refined to evaluate the relationship of CIVI 007 PK to demographics and background statin therapy. The model will be periodically refined as new and broader datasets emerge to include the covariates of special populations, concomitant medications, and disease state.

STATISTICAL ANALYSES:

All adverse events (AEs) will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and by association with the study drug (CIVI 007 or placebo) as determined by the Investigator (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities. Injection site reactions will be listed (those recorded as AEs will also be included in the AE outputs).

Observed values and clinically important changes from baseline for clinical laboratory test data, 12 lead ECGs, and vital signs will be listed and summarized. CTCAE grading (using the most recent version available) summaries will be provided as appropriate. All other safety data will be listed.

Plasma concentrations of CIVI 007 will be listed; PK parameters (where possible) of CIVI 007 after each dose will be listed and summarized using descriptive statistics. Individual and mean CIVI 007 plasma concentration time profiles for each treatment cohort will also be presented graphically.

The PD data will be listed and summarized using descriptive statistics by cohort.

The Intent-to-Treat (ITT) Population will include all patients who are randomized to the study and will be used to assess efficacy. The change from baseline measures in lipids and lipoproteins will be analyzed using an analysis of covariance (ANCOVA) model to compare the mean percent change from baseline in PCSK9 and LDL-C 28 days after the first injection and 28 and 56 days after the second injection of study drug between treatment groups with placebo. This ANCOVA model will include treatment as a factor and baseline LDL-C level as a covariate.

The Per-Protocol Population will include all patients who are randomized to the study and do not have any major protocol deviations. Analysis of the primary efficacy endpoint will be repeated with the Per-Protocol Population.

Further details will be specified in the Statistical Analysis Plan (SAP).

SAMPLE SIZE DETERMINATION:

Approximately 48 patients (12 patients per active treatment group, 12 per placebo treatment) will be randomized into 1 of 4 treatment groups.

The sample size chosen for this study was not based on power calculations. However, the number of participating patients in each part of the present study is common in early clinical studies and is considered sufficient to achieve the objectives of the study without exposing undue numbers of patients to study drug.

Following discussion between the Investigator and the Sponsor, additional patients may be enrolled to replace patients who do not complete the study.

SITES: Approximately 7 sites in the United States.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
λ_z	apparent termination elimination rate constant
ADA	antidrug antibody
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
apo	apolipoprotein
aPTT	activated Partial Thromboplastin Time
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-48}	area under the plasma concentration-time curve from time 0 to 48 hours
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration
AUC_{extrap}	extrapolation of area under plasma concentration
BP	blood pressure
CAC	coronary artery calcium
CFR	Code of Federal Regulations
CiVi	CiVi Biopharma, Inc.
CL/F	apparent total plasma clearance
C_{max}	maximum observed plasma concentration
C_{trough}	concentration observed at pre-dose
CRA	Clinical Research Associate
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CYP	cytochrome
eCRF	electronic Case Report Form
EDC	electronic data capture
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EIU	exposure in utero
FIH	first in human
FSH	follicle-stimulating hormone
GalNAc	Galactose/N-Acetylgalactosamine

Abbreviation	Definition
Gb3	globotriaosylceramides
GCP	Good Clinical Practice
Glc/GalCer	glucosyl/ galactosylceramides
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HEK	human embryonic kidney
hERG	human ether-à-go-go-related gene
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IC_{50}	concentration of drug required to produce 50% inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Investigational Review Board
ISR	injection site reaction
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous(ly)
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDL-R	low-density lipoprotein receptor
LFT	liver function test
LNA	locked nucleic acid
mAb	monoclonal antibody
MAD	multiple ascending dose
mRNA	messenger ribonucleic acid
NAFL	non-alcoholic fatty liver
NASH	non-alcoholic steatohepatitis
NOAEL	no observed adverse effect level
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QT	measure between Q wave and T wave in heart's electrical cycle
QTcF	heart-rate corrected QT interval using Fridericia's formula
Q4W	every 4 weeks
SAD	single ascending dose

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent plasma terminal elimination half-life
TG	triglyceride
t_{max}	time to maximum observed plasma concentration
TSH	thyroid-stimulating hormone
UGT	uridine glucuronyl transferase
ULN	upper limit of normal
VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein cholesterol
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cell

1 INTRODUCTION AND BACKGROUND INFORMATION

Refer to the Investigator's Brochure (IB)[1] for additional detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1 Overview

CIVI 007 [redacted] is an antisense oligonucleotide under development as an adjunct to diet with or without concurrent hypolipidemic agents for treatment of adults who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

Consistent evidence from experimental, clinical and genetic studies unequivocally establishes that low-density lipoprotein (LDL) causes atherosclerotic cardiovascular disease (ASCVD).[2] First-line drug treatment for hypercholesterolemia is with statins, which inhibit 3 hydroxy-3-methyl-glutaryl-coenzyme A reductase, a key step in cholesterol synthesis. They decrease plasma levels of cholesterol by increasing its hepatic clearance through the upregulation of LDL receptors (LDL-R) on hepatocytes. As a result, statins are effective in preventing ASCVD occurrence, the effectiveness of which is dependent on the patient's baseline ASCVD risk, absolute degree and length of cholesterol lowering achieved.[3] However, there are important limitations to statin therapy, including muscular intolerance to therapy,[4] dose limiting side effects including transaminitis[5] as well as limitations on their LDL-C lowering capacity and the ability to achieve recommended LDL-C target levels.[6] An important factor limiting statin's LDL-C lowering capacity is the result of the upregulation of proprotein convertase subtilisin/kexin type 9 (PCSK9) that occurs concurrently with the intended upregulation of LDL-R. This statin mediated PCSK9 upregulation counteracts LDL-R upregulation by enhancing LDL-R degradation which limits the hepatic uptake of cholesterol, and therefore paradoxically limits the level of plasma cholesterol reduction that can be achieved.[7] Thus, there remains an unmet medical need beyond statin therapy for novel pharmaceutical agents to reduce cardiovascular (CV) morbidity and mortality caused by elevated LDL-C, particularly for patients with inadequate response of LDL-C to statin therapy, those intolerant to it and those with very high LDL-C levels caused by genetic mutations, such as familial hypercholesterolemia.

The inhibition of PCSK9 is one novel approach being taken to overcome the residual shortcomings of statin therapy. As PCSK9 acts to inactivate LDL-R, its inhibition reverses this process and has been shown to cause a decrease in plasma LDL levels of up to 60% in humans. Currently, 2 monoclonal antibodies (mAbs) to PCSK9 have been approved for clinical use, and 2 outcomes trials have shown reductions in CV events, thus validating the clinical benefit of inhibiting the PCSK9 target.[8,9] The PCSK9 mAbs (evolocumab, alirocumab) target only the circulating levels of PCSK9 and have the potential for production of antidrug antibodies. Common side effects include injection site reactions, common cold, and influenza. Serious allergic reactions have also been reported.

An alternative approach to reducing the impact of PCSK9 on LDL-C is blocking its production at the level of messenger ribonucleic acid (mRNA) using an antisense inhibitor complementary and specific to human PCSK9 mRNA. Compared to mAb therapy, this mode of action will have the advantage of blocking both intra- and extracellular PCSK9 levels, reducing the potential for antidrug antibody formation and impacting novel ASCVD risk biomarkers such as ceramides.[10] In addition, due to its high potency and long half-life in liver administration of CIVI 007 to human subjects, CIVI 007 treatment is expected to lead to stable reductions in LDL-C when dosed

monthly at a single low volume dose ([redacted]mg), thus improving patient convenience and compliance and potentially reducing local pain at the injection site compared to mAbs that can require 3 injections of each 1.5ml or an on-body infusor when dosed monthly.

CIVI 007 is currently under development by CiVi Biopharma, Inc. (CiVi, hereinafter). CIVI 007 is an antisense inhibitor complementary to human PCSK9 mRNA and is based on the Locked Nucleic Acid (LNA) drug platform, which was pioneered by Santaris Pharma. The LNA oligonucleotide is designed to specifically bind to, and degrade, the mRNA encoding PCSK9, using the endogenously expressed enzyme, ribonuclease H, to cleave the mRNA. To facilitate optimal delivery of the drug to the intended target organ (liver), the LNA oligonucleotide is conjugated to a galactose/N-acetylgalactosamine (GalNAc) moiety that facilitates functional uptake by hepatocytes through binding to the surface expressed asialoglycoprotein receptor.

In summary, treatment with CIVI 007, through its degradation of PCSK9 mRNA, is designed to increase the number of LDL-R on the surface of hepatocytes leading to a reduction in circulating LDL-C. Ultimately, this therapeutic approach may be a useful addition to currently available drug therapy for hypercholesterolemia either as a monotherapy or as combination therapy with existing LDL-C lowering drugs, such as statins.

1.2 Summary of Preclinical Pharmacology

1.2.1 Primary Pharmacodynamics

In monkeys administered CIVI 007 at 0.5 and 1.5 mg/kg once weekly for 4 weeks via the subcutaneous (SC) route, the PCSK9 protein in serum was reduced by [redacted] compared to the baseline level, respectively. The maximum effect was achieved on Day 29, and PCSK9 levels did not fully return to pre-study values during the 8-week recovery phase. The effects were substantially greater than those seen with [redacted] (the oligonucleotide moiety of CIVI 007, without GalNAc conjugate), underpinning the ability of the GalNAc moiety to drive effective liver delivery.

In the same study, CIVI 007 caused dose responsive LDL-C reductions of 53% and 70% compared to baseline, respectively, with maximum effect on Day 29; the half-life for reversal of the LDL-C reductions was [redacted] days, respectively. As expected, LDL reductions were tracked by apolipoprotein (apo) B reductions. On Day 29, apoB levels were down dose dependently by [redacted], respectively, and apoB levels did not return fully to baseline during the 7 weeks of recovery in either of the 2 dose groups. Weak or no effects on high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides were observed.

The administration route seemed to have an effect on the intended pharmacology (serum PCSK9, plasma apoB, and LDL-C), with the intravenous (IV) route being significantly less effective than the SC route. Receptor saturation differences might account for an apparent greater effect with the more protracted distribution phase associated with SC administration than with the shorter distribution phase associated with IV administration.

1.2.2 Effect on Plasma Ceramide Levels in Monkeys

To investigate the potential effect of CIVI 007 on ceramides in monkeys, samples were drawn from 6 animals receiving 1.5 mg/kg/week for 4 weeks, on pretreatment Day -8, Day -1, and Day 29, one week after the final dose. Compared to both pretreatment days, treatment with CIVI 007 significantly decreased the levels of ceramides [redacted]

[redacted]. In these lipid classes, the total levels and practically all molecular species within the class were decreased by approximately [redacted] when compared to the pre-dose levels. This is quite similar to the effect of the PCSK9 loss of function mutation (R46L) in humans, suggesting that treatment with CIVI 007 may recapitulate the known CV benefit of this mutation. For some reason, the [redacted] levels varied considerably between pre-dose samples, obscuring any potential effect of the treatment on this class of ceramides.

1.3 Summary of Safety Pharmacology and Toxicology

1.3.1 Safety Pharmacology

[redacted]

1.3.2 Toxicology

In the pivotal GLP toxicology studies (2-week and 13-week studies in both rats and monkeys), doses of CIVI 007 were administered SC at either weekly (2-week studies) or biweekly (13-week studies) intervals at 0, 5, 20, or 50 mg/kg/dose (rats) and 0, 3, 10, or 30 mg/kg/dose (monkeys).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Based on the combined observations in the 2 and 13-week studies, the no observed adverse effect level (NOAEL) was considered to be 20 mg/kg/dose in the rat, which corresponds to a C_{max} of [redacted] and an AUC_{0-336} of [redacted] (mean of both sexes on Day 85), and 30 mg/kg/dose in the monkey, which corresponded to CIVI 007 exposures (mean of both sexes on Day 85) of [redacted] for AUC0.5-24 and [redacted] for Cmax.

The genotoxic and mutagenic potential of CIVI 007 was evaluated in GLP in vitro bacterial mutagenicity and chromosomal aberrations studies and were found to be negative at maximum "limit" doses specified in regulatory guidelines.

[redacted]

[redacted]

In conclusion, it is considered that the available safety information supports the administration of CIVI 007 to volunteers in this study.

[redacted]

[redacted]

1.7 Clinical Summary

The first in human (FIH) study is a placebo controlled, single blind, randomized, Phase 1, single ascending dose (SAD) and multiple ascending dose (MAD) study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of CIVI 007 SC administered in otherwise healthy male and female subjects with an elevated LDL-C level. This study is currently ongoing

[redacted]

1.8 Rationale

The purpose of this study is to further investigate the early clinical profile of lower doses of CIVI 007 in patients with hypercholesterolemia and on a stable dose of background statin therapy. The principal objective of this study is to obtain safety and tolerability data when CIVI 007 is administered SC given twice over a 28-day dosing interval. This information, together with the PK and PD data, will help establish the doses and dosage regimen suitable for administration to larger groups of patients in Phase 2b and 3 clinical development.

1.9 Risk/Benefit

Patients in the current study are not expected to receive any significant, long-term health benefit (beyond that of an assessment of their medical status) from participating in the study.

The risks of participation are primarily those associated with adverse reactions to the study treatment as previously described. Based on initial observations in the ongoing Phase 1 trial, CIVI 007 has a favorable clinical profile at lower doses and number of injections to justify advancement of CIVI 007 to Phase 2a clinical development. The proposed Phase 2a study will provide robust information to determine advancement of the program to Phase 2b/3 testing.

There may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated adverse events associated with CIVI 007 may be found in the IB[1].

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the safety and tolerability of CIVI 007 following multiple SC doses in patients on a background of a stable dose of statin therapy.

2.2 Secondary Objective

The secondary objective is to assess the PD effect of CIVI 007 on total PCSK9 and LDL-C levels in the study population.

2.3 Exploratory Objectives

The exploratory objectives include the following:

- To assess the effect of CIVI 007 on other lipid and lipoproteins including triglycerides (TG), HDL-C, non-HDL-C, very low density lipoprotein-cholesterol (VLDL-C), total cholesterol, apolipoproteins B, A-I and lipoprotein(a)
- To assess the effect of CIVI 007 on high-sensitivity C-reactive protein (hsCRP)
- To collect antidrug antibody (ADA) samples for potential future assessments of immunogenicity
- To further inform the population PK model of CIVI 007 with sparse PK sampling in patients on a background of statin therapy

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2a, randomized, double-blind (investigator/subject), sponsor open, parallel-group, multicenter study to evaluate the early clinical profile (safety, tolerability, PD, and PK) of CIVI 007 in patients on a background of statin therapy with or without ezetimibe. Patients are required to be on standard of care treatment for high blood cholesterol consistent with 2018 ACC/AHA guidelines[14], that includes a stable dose of statin therapy for at least 4 weeks prior to the Screening Visit. The study will enroll approximately 48 patients who will be randomized to 1 of 3 active treatment groups or the placebo reference group (12 patients per active treatment group and 12 in the placebo treatment group).

All potentially eligible patients will partake in the Screening Visit up to 21 days prior to Day 1. The Screening Visit will be the first study visit.

The Treatment Period begins with the first administration of study drug on Day 1 where eligible patients will be randomized in a 1:1:1:1 ratio to one of the following treatment groups:

- Group 1: CCI mg CIVI 007 administered SC on Day 1 and Day 29
- Group 2: CCI mg CIVI 007 administered SC on Day 1 followed by CCI mg CIVI 007 administered SC on Day 29
- Group 3: CCI mg CIVI 007 administered SC on Day 1 and Day 29
- Group 4: Placebo for CIVI 007 administered SC on Day 1 and Day 29

Patients will receive an initial dose of CIVI 007 or placebo at the study site on Day 1. For convenience, eligible patients will have the option to be admitted to the study site the day prior to Day 1. Patients will be discharged from the study site after completing the 8-hour post-dose follow-up assessments and will attend scheduled outpatient visits at Days 8, 15 and 22 to assess safety, tolerability, PK, and PD prior to their second dose. These visits and associated lab results will be used to assess eligibility to receive the second study drug administration. All doses will be administered in the fasted state in the morning, in accordance with a randomization schedule.

The second administration of study drug ends the Treatment Period and is to occur 4 weeks later on Day 29. Patients will again be discharged from the study site after completing the 8-hour post dose follow-up assessments. This will end the Treatment Period.

The Follow-up Period then begins and patients will attend scheduled follow-up visits at Days 36, 43, 57 and 85 to assess safety, tolerability, PK, and PD. The duration of the Follow-up Period will therefore be approximately 2 months from the last dose of study drug, unless extended follow-up is required based on Day 85 LDL-C assessments or other Investigator determined safety considerations.

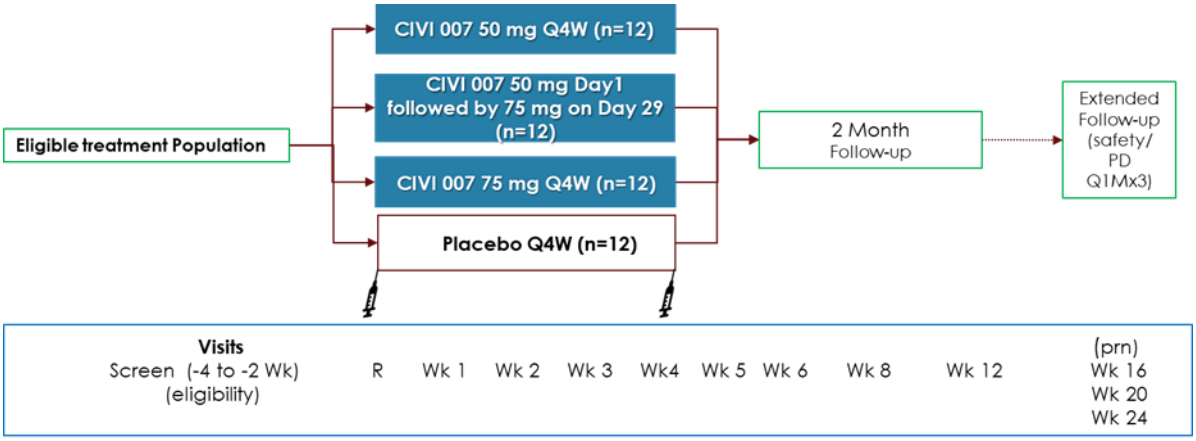
Extended follow-up visits will be conducted on a monthly basis for up to 3 months if Day 85 LDL-C levels are <80% of their baseline level; extended follow-up will end within the 3-month period if LDL-C levels are ≥80% of baseline. Extended follow-up visits (frequency and assessments will be at the discretion of the Investigator) to monitor Investigator determined safety considerations may extend beyond 3 months, if deemed appropriate by the Investigator, and will continue until there are no safety observations requiring further follow-up. The total duration of

the study for each patient will be approximately 3 to 6.5 months, depending on the variable length of the screening, and follow up periods.

A Safety Review Committee (SRC) will perform interim unblinded reviews of safety, tolerability, and available PK and PD data collected for the purposes of protecting subject safety as well as providing guidance to the Sponsor on the evolving clinical profile of CIVI 007. The SRC will comprise, at a minimum, the Sponsor's clinical development contact, the study Medical Monitor, a gastroenterologist not involved in study conduct and a pharmacokineticist. A separate document will detail the SRC's operating procedures.

The study design is graphically summarized in Figure 1:

Figure 1. Summary of the Study Design



Mo = month; Q4W = Every 4 weeks; Wk = week; R = randomization;

A visit window of ±3 days will be permitted for each study visit except for the first day of study drug administration.

Appendices A and B define the detailed Schedule of Procedures and Clinical Laboratory Analyte measures, respectively, to be performed during the study.

3.2 Study Design Rationale

Based on initial data from the ongoing FIH study and within the context of a limited experience, CIVI 007 appears to provide the expected pharmacologic profile associated with PCSK9 inhibition. CIVI 007 shows PCSK9 knockdown that begins around 12.5 mg with maximal inhibition of approximately 90% at CCI mg. The efficacy profile includes robust, dose-dependent reductions in atherogenic lipoproteins and lipids that appear to peak within a week following administration and are stable out to 4 weeks after administration. Changes in lipoproteins and lipids after multiple doses are consistent with those after single doses.

[redacted] CCI

CIVI 007 therefore appears to have a favorable clinical profile [redacted] and [redacted] justify advancement to Phase 2 testing in this study. The Phase 2a study will provide robust information to determine advancement of the program to Phase 2b/3 testing. A forced up-titration dosing group ([redacted]mg) will provide an initial understanding of this dosing strategy on CIVI 007's clinical profile.

A parallel group design, as opposed to an ascending dose design, has been chosen as initial Phase 1 observations have demonstrated safety in the study dose range. Subcutaneous dosing has been chosen as this is the intended clinical route of administration.

Dosing and follow-up will occur in a double-blind state for the Investigator and clinical staff in order to avoid bias in the collection of data.

Conducting the study in patients with LDL-C levels in the study range and on a background of a stable dose of statin therapy (with or without ezetimibe) will enable safety, tolerability, PK, and PD data to be collected in the intended clinical population in whom additional drug treatment may be warranted to optimize their LDL-C levels.

Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

3.3 Study Start and End of Study Definitions

The start of the study is defined as the date the first patient who is subsequently enrolled to the study signs an Informed Consent Form (ICF). The end-of-the study is defined as the date of the last patient's last assessment (scheduled or unscheduled).

3.4 Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients and execution of the study
- Cancellation of drug development

3.5 Study Indication

Treatment of hypercholesterolemia.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Willing and able to provide written and signed informed consent prior to any study-specific procedures.
2. Males or females, 18-70 years of age at the time of consent.
3. Body mass index (BMI) between 18.0 and 40.0 kg/m^2, inclusive, and a body weight of ≥60 kg at screening.
4. Currently on a stable (>4 weeks prior to the Screening Visit) dose of statin therapy (with or without ezetimibe).
5. Fasting LDL-C:
   a. ≥100 mg/dL for those without any evidence of established ASCVD at the Screening Visit

      or,

   b. ≥70 mg/dL for those with evidence of established ASCVD at the Screening Visit.
      - Established ASCVD is defined as a history of at least 1 of the following occurring no more recently than 3 months prior to screening:
        - Acute coronary syndrome
        - Myocardial infarction
        - Stroke or transient ischemic attack presumed to be of atherosclerotic origin
        - Coronary revascularization (Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention)
        - Peripheral vascular disease or revascularization
        - In the absence of an above event, ASCVD as diagnosed >3 months prior to the Screening Visit based on invasive or noninvasive imaging such as angiography, coronary artery calcium (CAC) score >75th percentile, or >50% stenosis in any arterial bed.

   Note: Retesting will be allowed once at Screening Visit for LDL-C that is in the range of 65-69 mg/dL.
6. Fasting TGs <400 mg/dL at the Screening Visit.

   Note: Retesting will be allowed once at Screening Visit for TGs in the range of 401-450 mg/dL.
7. Women of childbearing potential (i.e., not postmenopausal [documented amenorrhea for ≥1 year in the absence of other biological or physiological causes] or surgically sterile including tubal ligation) must have a negative serum pregnancy test at the Screening Visit and a negative urine dipstick prior to dosing on Day 1. Postmenopausal status will be confirmed with a Screening Visit serum follicle-stimulating hormone (FSH) level >40 mIU/mL. Women aged >60 years whose FSH values are not >40 mIU/mL may be included at the discretion of the Investigator and in consultation with the Sponsor.

Participating women of childbearing potential must agree to use 2 acceptable methods of contraception throughout the duration of the study and for 30 days after the last dose of study drug. Acceptable methods of contraception include condom, nonhormonal intrauterine device, or a vasectomized partner.

8. Male participants must be willing to use condoms during sexual intercourse from the Screening Visit until at least 90 days after administration of the last dose of study drug.

4.2 Exclusion Criteria

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

1. Women who are pregnant, nursing or breast feeding.
2. Currently prescribed a lipid lowering agent other than a statin or ezetimibe.
3. Abnormal liver function test at the Screening Visit (aspartate aminotransferase or alanine aminotransferase >1.5 × the ULN, total bilirubin >1.5 × ULN, or alkaline phosphatase >1.5 × ULN, based on appropriate age and gender normal values). Participants with bilirubin >1.5 × ULN and a history of Gilbert's syndrome may be included.
4. Active liver disease as defined by the investigator (e.g., cirrhosis, alcoholic liver disease, hepatitis B virus, hepatitis C virus, autoimmune hepatitis, liver failure, and/or liver cancer) or history of liver transplant. NASH is considered exclusionary while non-alcoholic fatty liver (NAFL) is not exclusionary.
5. Known diagnosis of human immunodeficiency virus.
6. Mild, moderate or severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration eGFR formula), at the Screening Visit.
7. Uncontrolled thyroid disease: hypothyroidism or hyperthyroidism, as defined by thyroid-stimulating hormone below the lower limit of normal or >1.5 × ULN, respectively, based on results from the Screening Visit. If controlled, treatment should be stable for at least 3 months prior to the Screening Visit.
8. Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus, defined as hemoglobin A1c (HbA1c) value >9%, based on results from the Screening Visit.
9. New York Heart Association Class II, III, or IV heart failure.
10. Myocardial infarction, severe or unstable angina pectoris, coronary revascularization, or other major cardiovascular event(s) resulting in hospitalization within 3 months of the Screening Visit.
11. Uncontrolled cardiac arrhythmia or prolonged QT interval on the Screening Visit or the pre-dose Day 1 ECG (QT corrected using Fridericia's formula [QTcF] >450 msec for men and >470 msec for women), or known family history of prolonged QT interval or unexplained sudden cardiac death.
12. Currently receiving cancer treatments or, in the Investigator's opinion, is at risk of relapse for recent cancer within the study period.
13. A history of autoimmune disorder(s).

14. A history of hematologic or coagulation disorders.
15. Abnormal PT, aPTT, or INR at the screening visit.
16. Concomitant antiplatelet or anticoagulation medication. Allowable are low-dose aspirin (81 mg or less, daily) for CVD risk reduction, or PRN for occasional pain relief. Other antiplatelet drugs (e.g., P2Y12 inhibitors) and all anticoagulants are exclusionary.
17. Except as noted above, patients who have a clinically significant disorder that, in the opinion of the Investigator, could contraindicate the administration of study drug, affect compliance, interfere with study evaluations, or confound the interpretation of study results
18. History of drug or alcohol abuse within the past year.
19. Previous treatment with CIVI 007.
20. Participation in another clinical study of an investigational agent or device concurrently or within 1 month prior to the Screening Visit or use of an investigational agent within 1 month or 5 half-lives (if known), whichever is longer, prior to the Screening Visit.
21. Donation of blood from 3 months prior, plasma 2 weeks prior, and platelets 6 weeks prior to the Screening Visit.
22. Any other findings that, in the opinion of the Investigator, would compromise the participant's safety or participation in the study.

4.3 Retesting

Laboratory values can be retested once during screening for LDL-C that is in the range of 65-69 mg/dL, or for triglycerides in the range of 401- 450 mg/dL.

4.4 Rescreening

Participants may be rescreened on one occasion only, following consultation with the Medical Monitor, after a minimum of 5 days have elapsed from a patient's last screening visit.

4.5 Withdrawal Criteria

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

- The patient withdraws consent or requests discontinuation from the study for any reason.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient. Specific guidance for monitoring of patients and the withdraw of study drug is found in Section 8.1.
- Pregnancy.
- Requirement of prohibited concomitant medication.
- Patient failure to comply with protocol requirements or study-related procedures.

- Termination of the study by the Sponsor or the regulatory authority.

Patients are encouraged not to change their statin dose or use of ezetimibe during the study. If such occurs, they should not be withdrawn from the study.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the end of follow-up visit (Day 85). The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study site. In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

5 STUDY TREATMENTS

5.1 Treatment Groups

All eligible patients will participate in the Screening Visit up to 21 days prior to Day 1. The Screening Visit will be their first study visit.

The Treatment Period will consist of two administrations of study drug. Eligible patients will be randomized on Day 1 in a 1:1:1:1 ratio to one of the following treatment groups:

- Group 1: CCI mg CIVI 007 administered SC on Days 1 and 29
- Group 2: CCI mg CIVI 007 administered SC on Day 1 followed by CCI mg CIVI 007 administered SC on Day 29
- Group 3: CCI mg CIVI 007 administered SC on Days 1 and 29
- Group 4: Placebo for CIVI 007 administered SC on Days 1 and 29

5.2 Rationale for Dosing

Standard antisense molecules have been demonstrated to scale allometrically between the mouse, monkey, and human based on body weight.[15] Accordingly, with a NOAEL in monkeys of 30 mg/kg, the doses of CCI and CCI mg/patient (based on an average body weight of 60 kg) is >CCI-fold below the NOAEL.

More importantly, based on initial data from the ongoing FIH study and within the context of a limited experience, CIVI 007 appears to provide the expected pharmacologic profile associated with PCSK9 inhibition. CIVI 007 shows PCSK9 knockdown that begins around 12.5 mg with maximal inhibition of approximately 90% at CCI mg. The efficacy profile includes robust, dose-dependent reductions in atherogenic lipoproteins and lipids that begin within 1 week of administration and are stable out to 4 weeks after administration. Changes in lipoproteins and lipids after multiple doses are consistent with those after single doses.

There were no obvious drug-related safety findings in the dose range of 12.5 to CCI mg. Grade 1 ALT elevations appeared in both placebo and active doses with similar frequency. At higher doses, and based on higher levels of ALT increase, a signal of hepatotoxicity was apparent at 300 mg with a potential signal in one subject at 150 mg that was confounded with alcohol intake at the time of liver testing.

CIVI 007 therefore appears to have a favorable clinical profile at lower doses and these justify advancement to Phase 2a testing in this study.

5.3 Randomization and Blinding

Approximately 48 patients will be assigned randomly to placebo, CCI mg CIVI 007, CCI mg CIVI 007 followed by CCI mg CIVI 007 or CCI mg CIVI 007 in a 1:1:1:1 allocation ratio.

Throughout the study, study treatment will be administered in a double-blinded fashion for the Investigator, clinical staff, and patients. Only where required will key site staff (such as pharmacist) be unblinded throughout the study.

The following controls will be employed to maintain the double-blind execution of the study:

- The placebo solution will be identical in appearance to the CIVI 007 solution.

- The Investigator and other members of staff involved with the study will remain blinded.
- Lipid levels after randomization will be blinded to the study site.
- Appropriate firewalls will exist to prevent communication between the unblinded SRC and personnel involved in study execution.

5.4 Breaking the Blind

In order to manage patient safety (in the event of possible treatment-related SAEs or severe adverse events), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the patient, the Investigator will discuss the intended code-break with the study Medical Monitor. If it becomes necessary to break the code it will be done using the IRT and the date, time, and reason will be recorded in the patient's source data.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

CIVI 007 for SC administration will be supplied by the Sponsor in vials packaged in a study drug kit (2 vials per kit). The placebo study drug (commercial grade sterile saline solution for SC administration) will also be supplied by the Sponsor.

Study drug will be packaged according to current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

Study drug will be labeled according to the requirements of local law and legislation, as well as current GMP and GCP guidelines. Proof labels, detailing actual label text, will be available in the study files.

An unblinded pharmacist will prepare the appropriate study drug or placebo for blinded administration by the Investigator site.

5.5.2 Study Drug Preparation and Dispensing

The study drugs will be transferred from the pharmacy to the area where patients will be dosed by qualified clinical staff who will remain blinded to the treatment group.

5.5.3 Study Drug Administration

CIVI 007 and placebo are sterile solutions to be administered by SC injection.

Dosing is to be in the morning following an overnight fast:

- CIVI 007 (cci or cci mg) is to be administered SC into the abdomen (or thigh or upper arm, if necessary) from a solution at 150 mg/mL (cci mg per cci mL vial).
- Placebo is to be administered SC into the abdomen (or in thigh or upper arm, if necessary). The volume of injection will be randomly assigned to match one of the two active CIVI 007 doses.

  Note: For the second dose of CIVI 007 or placebo administration, the investigators should try to avoid using the same injection site area as the first dose. For other permitted concomitant

medications administered subcutaneously, do not administer in same injection site area as the study drug, for at least 2 weeks after the last dose of study drug.

5.5.4 Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered by and under the supervision of suitably qualified study site staff.

5.5.5 Storage and Accountability

Both CIVI 007 and placebo will be stored at the study site, according to the instructions on the label, in a location that is locked with restricted access.

The unblinded pharmacist will maintain an accurate record of the receipt of CIVI 007 and placebo vials received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each patient and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

Used and empty dose kits will be discarded upon satisfactory completion of the compliance and accountability procedures by study CRO personnel monitoring the study. Any unused or partially used kits will be retained until completion of the study.

At the completion of the study, all unused CIVI 007 kits and vials will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Once eligibility is determined, and until study completion, patients are to be counseled from use of any new, or change in dose, of any prescription or nonprescription medications/products. Specific attention is to be paid to maintaining the concurrent dose of statin/ezetimibe therapy during the course of the study.

5.6.2 Restricted Medications and/or Procedures

Patients are restricted from using any new prescription or over-the-counter cholesterol lowering medication. In addition, until completion of follow-up, change in the concurrent dose or discontinuation of statin/ezetimibe medication during the course of the study is prohibited unless deemed medically necessary by the Investigator (or designee) or the patient's medical care provider.

5.6.3 Allowed Medications and/or Procedures

Except as noted in restricted medications, and if medically warranted and deemed necessary by the Investigator (or designee) or the patient's medical care provider, concurrent medication is to be added or doses changed as needed given the patient's prior consent to its use.

5.6.4 Documentation of Prior and Concomitant Medication Use

Any medication taken by a patient during the course of the study and the reason for its use will be documented in the source data. For patients not taking a lower than recommended statin therapy, the reason should be documented in the CRF.

5.7 Dietary and Lifestyle Restrictions

5.7.1 Diet

Most study visits require measurement of fasting lipids. Those study visits requiring lipid measurement should be following an overnight fast by the patient (10 hours ±2 hours).

In addition, on Day 1 and Day 29, patients will be fasted overnight (10 ±2 hours) prior to study drug administration and until 3 hours post-dose, after which a meal will be provided by study staff (lunch times will be staggered as needed between patients to ensure this 3-hour interval in each case). Patients may consume water ad libitum during the days of study drug administration.

At all other times during the study, patients are to follow their normal dietary pattern and may consume water ad libitum.

Consumption of alcohol will not be permitted the day immediately prior to and days of study drug administration. Alcohol intake will be limited to a maximum of 2 units/day on all other days, from screening through the final Follow-up Visit.

5.7.2 Smoking

Smoking will not be permitted on days of study drug administration until after lunch, and for 1 hour before each BP and pulse rate measurement outside these periods. Patients will otherwise be permitted to smoke their normal daily number of cigarettes.

5.7.3 Exercise

Patients are required to refrain from strenuous exercise from the screening visit until the final Follow-up Visit and will otherwise maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

5.7.4 Blood Donation

Patients are required to refrain from donation until 3 months after the final Follow-up Visit.

5.7.5 Contraception

Female patients who are of non-childbearing potential will not be required to use contraception. Women of non-childbearing potential are defined as permanently sterile (i.e., due to hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or postmenopausal (defined as at least 1-year post cessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum FSH level >40 mIU/mL. FSH testing will be conducted in all postmenopausal females who are not surgically sterile regardless of age. Women aged >60 years whose FSH values are not >40 mIU/mL may be included at the discretion of the Investigator and in consultation with the Sponsor.

Female patients of childbearing potential must be willing to use a highly effective method of birth control (i.e., contraceptive measure with a failure rate of <1% per year) in conjunction with male barrier contraception (i.e., male condom with spermicide) from the time of signing the ICF until 30 days after the last dose of study drug. Highly effective methods of contraception include the following:

- Intrauterine device (IUD; e.g., Mirena®). Steel or copper IUDs are acceptable.
- Established use of oral, implanted, transdermal, or injectable hormonal method of contraception associated with inhibition of ovulation.
- Male sterilization (performed at least 90 days prior to the Screening Visit), with verbal confirmation of surgical success (for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Bilateral tubal ligation or occlusion (performed at least 90 days prior to the Screening Visit).

Male patients with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners, from Day 1 until 90 days after the last dose of study drug. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception for the female partner include the following:

- Established use of progesterone-only oral contraception, where inhibition of ovulation is not the primary mode of action.
- Diaphragm, cap, or sponge in conjunction with spermicide.

For male patients, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the last dose of study drug. Male patients are required to refrain from donation of sperm from Day 1 until 90 days after the last dose of study drug.

Patients who practice true abstinence, because of the patient's lifestyle choice (i.e., the patient should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. If a patient who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For patients who are exclusively in same sex relationships, contraceptive requirements do not apply. If a patient who is in a same sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as previously described.

The contraceptive method(s) being employed by patients should be reviewed with the patient during the course of the trial.

6 STUDY PROCEDURES

6.1 Screening Visit (Up to Day -21)

The following procedures will be performed at the Screening Visit:

- Obtain informed consent.
- Review inclusion/exclusion criteria.
- Record medical/surgical history and demographics.
- Perform full physical examination
- Record vital signs, height and weight (height will only be collected at the screening visit).
- Collect urinalysis assessment.
- Perform serum pregnancy test.
- Perform FSH testing.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for TSH, HbA1c, and serology measurements.
- Collect blood samples for drugs of abuse.
- Collect blood for fasting lipid panel assessment.
- Perform 12-lead ECG measurements.
- Record adverse events.
- Record concomitant medications.

6.2 Treatment Period (Days 1 to 29)

6.2.1 Day 1

The following procedures will be performed at Day 1:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment and statin PK.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.

- Collect blood samples for anti-drug antibody analysis
- Perform 12-lead ECG measurements.
- Randomize patients.
- Administer study drug.
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Record adverse events including injection site reactions.
- Record concomitant medications.

6.2.2 Day 8

The following procedures will be performed at Day 8:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Record adverse events.
- Record concomitant medications.

6.2.2 Day 15

The following procedures will be performed at Day 15:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.

- Collect blood samples for anti-drug antibody analysis
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Perform 12-lead ECG measurements.
- Record adverse events.
- Record concomitant medications.

6.2.3 Day 22

The following procedures will be performed at Day 22:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Record adverse events.
- Record concomitant medications.

6.2.4 Day 29

The following procedures will be performed at Day 29:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment and statin PK.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Determine eligibility to receive 2nd study drug injection.
- Administer study drug.
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.

- Collect blood samples for anti-drug antibody analysis.
- Perform 12-lead ECG measurements.
- Record adverse events including injection site reactions.
- Record concomitant medications.

6.3 Follow-Up Period (Days 30 to 85 or End of Treatment)

6.3.1 Day 36

The following procedures will be performed at Day 36:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Record adverse events.
- Record concomitant medications.

6.3.2 Day 43

The following procedures will be performed at Day 43:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for anti-drug antibody analysis
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Record adverse events.

- Record concomitant medications.

6.3.3 Day 57

The following procedures will be performed at Day 57:

- Perform symptom-directed physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment and statin PK.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for anti-drug antibody analysis
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Perform 12-lead ECG measurements.
- Record adverse events.
- Record concomitant medications.

6.3.4 Day 85 or Early Termination

The following procedures will be performed at Day 85 or early termination:

- Perform full physical examination.
- Record vital signs and weight.
- Collect urine urinalysis assessment.
- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for anti-drug antibody analysis
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Perform 12-lead ECG measurements.
- Record adverse events.

- Record concomitant medications.

6.4 Extended Follow-up Visits

Extended follow-up visits will be conducted based on either LDL-C level at Day 85 or for safety considerations at the Investigator's discretion.

- If Day 85 LDL-C levels are <80% of their baseline level; extended follow-up will occur monthly for 3 months and end earlier if LDL-C levels are ≥80% of baseline. The fasting lipid panel will be assessed and occur monthly for up to 3 months or until LDL-C returns to within 80% of its baseline level (whichever is sooner). Those visits will also record AEs and concomitant medication.
- Extended Follow-up visits for safety considerations (frequency and assessments will be at the discretion of the Investigator) to monitor Investigator determined safety considerations may also occur and extend beyond 3 months, if deemed appropriate by the Investigator, and will continue until there are no safety observations requiring further follow-up. Those visits will also record AEs and concomitant medication.

For extended follow-up Visits due to LDL-C <80% of the baseline level. The procedures need to be performed will include the following:

- Record vital signs and weight.
- Collect blood samples for fasting lipid panel assessment.
- Record adverse events.
- Record concomitant medications.

For extended follow-up Visits for safety considerations, the procedures need to be performed will be consideration specific and may include but not be limited to the following:

- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Perform 12-lead ECG measurements.
- Record adverse events.
- Record concomitant medications.

6.5 Early Termination Visit and Withdrawal Procedures

The end of treatment for patients completing the study is the Day 85 visit. For patients who are withdrawn from the study prior to completion, all Day 85 procedures will be performed at an early termination visit. These procedures include the following:

- Perform full physical examination.
- Record vital signs and weight.
- Collect urine sample for urinalysis assessment.

- Perform urine pregnancy test.
- Collect blood samples for clinical safety chemistry panel, coagulation, and hematology assessments.
- Collect blood samples for fasting lipid panel assessment.
- Collect blood samples for fasting apolipoproteins and LDL-C (beta-quant).
- Collect blood samples for hsCRP, PCSK9, and fibrinogen analysis.
- Collect blood samples for anti-drug antibody analysis
- Collect blood samples for sparse PK, cytokine panel and complement activation analysis.
- Perform 12-lead ECG measurements.
- Record adverse events.
- Record concomitant medications.

7 EFFICACY ASSESSMENTS

7.1 Primary Endpoints

The primary safety/tolerability endpoints for this study are as follows:

- incidence and severity of any drug-related AE
- incidence of clinically significant laboratory abnormalities, based on drug-induced changes from baseline in hematology, clinical safety chemistry, and urinalysis test results.

7.2 Secondary Endpoints

The secondary efficacy endpoints include the following changes from baseline measured approximately 28 days after the first and 28 and 56 days after the last injection of study drug:

- The percent change in PCSK9 and LDL-C

7.3 Exploratory Endpoints

The exploratory endpoints include the following:

PD endpoints are the absolute and % changes from baseline (except where indicated) in the levels of the following in serum or plasma over the time course of the treatment period and follow-up:

- PCSK9 (absolute only)
- LDL-C (absolute only)
- VLDL-C
- triglycerides
- HDL-C
- Non-HDL-C
- total cholesterol
- lipoprotein (a)
- apolipoproteins B and A-I
- hsCRP

The following PK parameters will be calculated for CIVI 007, where possible:

- C_{max}
- time of the maximum observed plasma concentration (t_{max})
- Area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (AUC_{0-t})
- concentration observed at pre-dose (C_{trough})

Additional exploratory PK parameters, which may include but are not limited to the following, may be calculated:

- area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24})
- area under the plasma concentration-time curve from time 0 to 48 hours (AUC_{0-48})
- percentage of $AUC_{0-\infty}$ that is due to extrapolation ($\%AUC_{extrap}$)
- apparent termination elimination rate constant (λ_z)
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- apparent total plasma clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)

7.4 Pharmacokinetics

Sparse PK sampling will be conducted for all consenting participants. Sampling will be performed on dosing days, and at each study visit during the Treatment and Follow-up Periods. For each of the dosing days, a PK sample will be drawn pre-dose (- 1 hour), 3 hours (±1 hour) post-dose, and at 8 hours (±1 hour) post-dose.

The population PK model created based on data from the ongoing Phase 1 study will be refined to evaluate the relationship of CIVI 007 PK to demographics and background statin therapy. The model will be periodically refined as new and broader datasets emerge to include the covariates of special populations, concomitant medications, and disease state.

8 SAFETY ASSESSMENTS

The safety variables include adverse events, safety laboratory parameters (including clinical safety chemistry, hematology, coagulation parameters including fibrinogen, complement activation, cytokines, and urinalysis), 12-lead ECGs, physical examinations, and vital signs. Samples will also be collected for the potential future assessment of anti-drug antibodies.

8.1 Individual Patient Safety Monitoring and Criteria For Discontinuation of Study Drug

When any the following criteria are met, patients will be monitored for safety and discontinuation of study drug considered using the following guidance.

- Liver (as per FDA guidance on drug-induced liver injury[16])
    - Patients with signs or symptoms consistent with liver injury (such as nausea, vomiting, anorexia, fatigue, right upper abdominal pain or discomfort) should undergo immediate testing of ALT, AST, GGT, bilirubin, ALP, PT, and INR.
    - In the absence of clinical symptoms, patients with ALT or AST > 3xULN (if normal at baseline) or >2-fold change (if abnormal at baseline) should be retested within 48 to 72 hours for the usual serum measures (ALT, AST, ALP, and bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms at the time of follow-up.
    - If the above abnormalities are confirmed,
        - repeat liver enzyme and serum bilirubin tests two or three times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
        - Obtain a more detailed history of symptoms and prior or concurrent diseases.
        - Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
        - Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
        - Obtain a history of exposure to environmental chemical agents.
        - Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
        - Considering gastroenterology or hepatology consultations.
    - Study drug discontinuation should occur if:
        - ALT or AST >8xULN
        - ALT or AST >5xULN for more than 2 weeks
        - ALT or AST >3xULN and (bilirubin >2xULN or INR >1.5)
        - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Platelet Count

- Patients whose platelet count decreases to <140,000 mm^3 should begin weekly platelet monitoring, and patient whose platelet count decreases to <75,000 mm^3 should have platelets monitored every 2 to 3 days. Patients whose platelet count decreases to <50,000 mm^3 should discontinue drug and undergo daily platelet monitoring; consultation with a hematologist is also recommended.

- Renal
  - Patients with concern for renal toxicity, spot urine UPCR and/or spot UACR should be obtained. Patients with UPCR >50% from baseline or 1.5x ULN should be monitored at least every 2 weeks.
  - Study drug should be discontinued if patients experience an unexplained, confirmed increase in serum creatinine of 0.3 mg/dL above baseline; unexplained, confirmed 25% decline in eGFR from baseline; or new-onset hematuria, albuminuria (UACR ≥250 mg/g), or proteinuria (≥UPCR 500 mg/g) confirmed on repeat testing.

8.2 Adverse Events

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

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of screening until completion of the Day 85 Visit, early termination visit or extended Follow-up, whichever is later. Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at screening, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

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

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

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at Screening, and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should

not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

8.2.1 Adverse (Drug) Reaction

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

8.2.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For CIVI 007 the reference safety information is included in the IB currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.2.3 Assessment of Adverse Events by the Investigator

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

Assessment of severity:

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

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

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

Causality assessment:

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

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

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

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

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

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

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

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

8.2.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for adverse events of special interest (AESIs) throughout the patient's participation in this study as defined below.

The Investigator will assess and record any additional information on the AESI in detail on an adverse event form which must be submitted within 24 hours of awareness of the event.

For this study, AESIs include the following:

- CTCAE (current version) Grade 2 or higher ALT measurements confirmed on repeat measurement
- Severe or serious injection site reactions (ISRs), ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), recurrent ISRs that are increasing in severity, or ISRs that lead to temporary dose interruption or permanent discontinuation of study drug.
- An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (e.g., as may occur with swelling or hematoma). A systemic reaction which includes the injection site (e.g., generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR

Adverse events of special interest must be recorded in the eCRF.

8.3 Serious Adverse Events

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

- Death.
- A life-threatening adverse event.

  Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Hospitalization or prolongation of existing hospitalizations.

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.4 Serious Adverse Event Reporting - Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until completion of the follow-up period must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-

safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.7) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

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

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

8.5 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), Health Canada, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, Health Canada, and to the Central Ethics Committee, as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to IMP.

8.7 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of patients missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situations Report form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situations Report forms should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
email: medpace-safetynotification@medpace.com

8.8 Injection Site Assessment

The SC injection site may be marked and mapped for later observation. Visual assessment of the injection site will be conducted by an Investigator (or designee) at the times indicated in the

Schedule of Procedures in Appendix A. Categorical scales will be used to score injection site reaction severity, pain, induration, erythema and edema. If a local reaction around the injection site occurs, photographs may be obtained.

8.9 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical safety chemistry; hematology; coagulation parameters including fibrinogen; cytokine; complement activation; urinalysis; and serology) at the times indicated in the Schedule of Procedures in Appendix A. Clinical laboratory analytes are listed in Appendix B.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

8.10 Vital Signs

Sitting BP, heart rate, respiration rate, and oral body temperature will be assessed at the times indicated in the Schedule of Procedures in Appendix A. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Patients must be sitting for at least 5 minutes before vital signs measurements.

8.11 12-Lead Electrocardiograms

Resting 12-lead ECGs will be performed in triplicate and recorded using the automatic data generated by the ECG as the source data. Recordings are to occur after the patient has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Procedures in Appendix A**.**

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

8.12 Physical Examinations

A full physical examination or symptom-directed physical examination will be performed at the time points specified in the Schedule of Procedures in Appendix A.

8.13 Pharmacokinetic Assessments

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Procedures in Appendix A. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

Plasma concentrations of CIVI 007 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in a separate document.

8.14 Pharmacodynamic Assessments

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Procedures in Appendix A. Procedures for collection, processing, and shipping of PD blood samples will be detailed in a separate document.

Concentrations of PCSK9, apolipoproteins, circulating lipids (LDL-C, triglycerides, HDL-C, non-HDL-C [calculation], lipoprotein(a), and total cholesterol), and inflammatory biomarkers, will be determined using validated analytical procedures in serum or plasma. Specifics of the analytical methods will be provided in a separate document.

9 STATISTICS

9.1 Analysis Populations

The Intent-to-Treat (ITT) Population will include all patients who are randomized to the study and will be used to assess efficacy.

The Per-Protocol Population will include all patients who are randomized to the study and do not have any major protocol deviations.

The Safety Analysis Population will include all patients who receive any amount of study drug.

9.2 Statistical Methods

9.2.1 Analysis of Primary Safety/Tolerability Data

Analysis of safety will be descriptive.

The number and percentage of patients who experience 1 or more adverse events will be summarized by dose, relationship to study drug, and severity by descriptive statistics. Adverse events will be coded using Medical Dictionary for Regulatory Activities terminology. Listings of patients with SAE or discontinuations due to an adverse event will be presented.

Laboratory parameters will be summarized by dose using descriptive statistics; data listings of clinically significant abnormalities will be presented. Individual results of vital signs will be listed and summarized. Observed values and changes from baseline in vital signs will be summarized by dose. Individual results of quantitative safety ECG parameters from the 12-lead safety ECGs will be listed. Observed values and changes from baseline in quantitative ECG parameters will be summarized by dose. Abnormal ECGs will be summarized for each dose level. Physical examination findings will be listed.

Where appropriate, safety findings will be graded using the CTCAE version available at the time of analysis.

9.2.2 Secondary and Exploratory Efficacy Analysis

The PCSK9, LDL-C, and exploratory lipid/PD endpoints will be listed and summarized using descriptive statistics by treatment group over the study period to describe absolute and percent changes from baseline.

The presentation of results will be the observed data and include the estimated means by treatment group, their standard errors, and the estimated differences in means between the patient treatments and corresponding 95% confidence intervals and p-values.

The treatment comparisons between each active dose versus placebo will be tested following a fixed sequence step-down procedure to control the multiplicity.

Analysis of the secondary efficacy endpoints will be repeated with the Per Protocol Population. Further details will be specified in the Statistical Analysis Plan (SAP).

9.2.2.1 Secondary efficacy analysis

The secondary endpoints of the study will be analyzed using analysis of covariance (ANCOVA) models to compare the mean percent change from baseline in LDL-C and PCSK9 28 days after the first injection and 28 and 56 days after the second injection of study drug between treatment

groups with placebo. This ANCOVA model will include treatment as a factor and baseline level as a covariate.

9.2.2.2 Pharmacokinetic analysis

Plasma concentrations of CIVI 007 will be determined for patients randomized to active drug; samples for placebo patients will not be analyzed unless required (e.g., to help explain anomalous results). Plasma concentrations of CIVI 007 will be listed. Individual and mean CIVI 007 plasma concentration-time profiles for each treatment cohort will also be presented graphically.

Where possible, plasma PK parameters of CIVI 007 after each dose will be calculated using standard non-compartmental methods and will be listed and summarized using descriptive statistics.

Where sufficient data are available, CIVI 007 fold increase in exposure will be examined between the dose cohorts. The PK parameters may be analyzed for dose proportionality using a variance model approach or analysis of variance model as appropriate.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other details and data handling procedures will be detailed in the SAP.

9.2.3 Interim Analysis

No formal interim analyses are planned for this study other than descriptive analyses required for the SRC to review accumulating safety information. Interim safety reviews and lipid analyses (sponsor only) will initially occur when approximately 12 patients have received their first study drug injection and have two weeks of follow-up data available. Subsequent analyses will occur with the accrual of each 12 new patients who have two week follow-up data available with a final review when the last 12 patients have two week follow-up data available.

Guidelines for interim study stoppage by the SRC will be based on safety parameters and the cumulative evidence of treatment group imbalances as follows:

- Clinically relevant signs or symptoms of similar nature occur in 3 or more patients in a treatment group that, in the opinion of the Investigator, warrants stopping based on concerns of patient safety.
- Two or more patients experiencing a non-cardiovascular SAE or 4 or more patients experience severe AEs.
- There is evidence of clinically significant increases in the following:
    - liver tests, defined as 3 × ULN (confirmed with repeat testing) in either ALT or AST; or 2 × ULN in either ALP or bilirubin, in 3 or more patients in a treatment group.
    - confirmed platelet count decreases to <140,000 mm^3
    - confirmed increases in serum creatinine of 0.3 mg/dL above baseline

9.2.4 Sample Size Determination

Approximately 48 patients (12 patients per active treatment group, 12 patients per placebo treatment) will be randomized into 1 of 4 treatment groups.

The sample size chosen for this study was not based on power calculations. However, the number of patients in each part of the present study is common in early clinical studies and is considered sufficient to achieve the objectives of the study without exposing undue numbers of patients to study drug.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

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

10.1.2 Computer Systems

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

10.1.3 Data Entry

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

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest version) for medical history and adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications
- CTCAE (current version)

10.1.5 Data Validation

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

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

10.2 Record Keeping

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

destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

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

11.2 Institutional Review Board

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

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

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

11.3 Informed Consent

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

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

11.4 Study Monitoring Requirements

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

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

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

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

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

11.5 Disclosure of Data

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

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

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, 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 the Sponsor before disposing of any records, even if retention requirements have been met.

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

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor and share their proposed publication with Medpace and the Sponsor at least 60 days prior to submitting for publication, upon which, the Sponsor has 60 days to review and propose edits or additional delay. 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.

11.8 Financial Disclosure

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

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

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

13 REFERENCES

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APPENDICIES

Appendix A: Schedule of Procedures

Procedure/Visit	Screening[a]	Treatment Period[b]					Follow-up Period[c]			
	Up to Day -21	Day 1[d]	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 57	Day 85 or ET
Visit #	1	2	3	4	5	6	7	8	9	10
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical/surgical history and demographics	X									
Full physical examination	X									X
Symptom-directed physical examination		X	X	X	X	X	X	X	X	
Vital signs[e], height[f], and weight	X	X	X	X	X	X	X	X	X	X
Urinalysis[g]	X	X	X	X	X	X	X	X	X	X
FSH/Serum/Urine pregnancy test[h]	X	X	X	X	X	X	X	X	X	X
Clinical safety chemistry panel, coagulation, and hematology	X	X	X	X	X	X	X	X	X	X
Drug Screen/ TSH, HbA1c, and serology[i]	X									
Fasting lipid panel[j]	X	X	X	X	X	X	X	X	X	X
Fasting apolipoproteins & beta quant LDL-C[k]		X	X	X		X	X	X	X	X
hsCRP, PCSK9, and fibrinogen		X	X	X	X	X	X	X	X	X
Randomization		X								
Study drug/Placebo administration		X				X				
Sample for antidrug antibodies		X		X		X		X	X	X
Sparse PK, cytokine and complement activation sampling[l]		X	X	X	X	X	X	X	X	X
12-lead ECG[m]	X	X		X		X			X	X
Concurrent statin PK[n]		X				X			X	
Adverse events (including injection site reactions)	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Footnotes are on the next page.

[a] All eligible patients will partake in the Screening Visit up to 21 days prior to Day 1.

[b,c] Study assessments will be completed within ±3 days of the given time point for all study visits other than Day 1. Extended follow-up beyond day 85 for below baseline LDL-C will assess the fasting lipid panel and occur monthly for up to 3 months or until LDL-C returns to within 80% of its baseline level. Those visits will also record AEs and concomitant medication.

[d] The Investigator will query the participant on Day 1 to determine if there have been any changes in the participant's health that would affect eligibility or require an update to his/her medical/surgical history.

[e] Vital signs include pulse rate, blood pressure, respiration rate, and temperature. Blood pressure should be obtained in a seated position after the participant has been sitting or at least 5 minutes. Blood pressure at the Screening Visit should be obtained in both arms, and the arm with the highest value should be used for ongoing monitoring throughout the rest of the study. If an automated assessment is performed, the same machine should be used for the participant throughout the study whenever possible. Care should be taken to ensure an appropriate cuff size is utilized.

[f] Height will be measured only at the participant's Screening Visit.

[g] A urine microscopic examination will be performed when the dipstick result is abnormal (i.e., positive for blood, leukocyte esterase, or nitrites).

[h] Pregnancy tests are for women of childbearing potential only. A serum pregnancy test will be performed at screening. Urine pregnancy test will be conducted at all other visits. Unscheduled serum pregnancy testing will be performed for confirmation of positive urine pregnancy testing. FSH tests are for all postmenopausal women who are not surgically sterile; FSH testing will be performed once at screening.

[i] Drugs of abuse along with thyroid-stimulating hormone, HbA1c, and serology (HBsAg, HBV, HCV, and HIV) will be measured at the participant's Screening Visit. Serology testing will be HBsAg, HCV, and HIV, with confirmatory testing for positive HCV and HIV Ab screens.

[j] The fasting lipid panel includes LDL-C, non–HDL-C, TC, TGs, HDL-C, and VLDL-C. Fasting will be defined as no food or caloric beverage for at least 10 hours (±2 hours) prior to sample collection. Patients will be permitted to have water. LDL-C will be estimated.

[k] Fasting apolipoproteins include apoB, apoA1, and Lp(a). Beta quant LDL is beta-quantification measurement of LDL-C. Fasting will be defined as no food or caloric beverage for at least 10 hours (±2 hours) prior to sample collection. Patients will be permitted to have water.

[l] PK, cytokine panel, and complement activation sampling will be performed on dosing days and at each study visit during the Follow-up Period. For each of the dosing days, samples will be drawn at pre-dose (-1 hour), 3 hours (±1 hour) post-dose, and at 8 hours (±1 hour) post-dose.

[m] Patients should be at rest for at least 5 minutes lying quietly in a fully supine position prior to each triplicate 12-lead ECG. The triplicate measurements should be taken approximately one minute apart. ECGs on Days 1 and 29 should be performed twice: the first should be pre-dose (-1 hour) and the second at 2.5 hours post-dose (±0.5 hours) which is about 30 min prior to the 3-hour PK draw.

[n] Statin PK blood sample will be taken for measurement of their steady state levels/major components when validated assays are available for such measurements.

apo = apolipoprotein; CV = cardiovascular; ECG = electrocardiogram; ET = Early Termination; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); non–HDL-C = non–high-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetic(s); TC = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone; VLDL-C = very low-density lipoprotein cholesterol.

Appendix B: Clinical Laboratory Analytes

Clinical Safety Chemistry Panel

Aspartate aminotransferase	Inorganic phosphate
Alanine aminotransferase	Glucose
Alkaline phosphatase	BUN
Gamma glutamyl transferase (GGT)	Bilirubin (direct)
Sodium	Bilirubin (total)
Potassium	Creatinine
Chloride	Total protein
Calcium	Albumin
Creatine Kinase (CK)	Cystatin C
	eGFR (CKD-EPI)

Endocrinology

Thyroid-stimulation hormone	Serum pregnancy test (human chorionic gonadotropin) (females at screening only)
Follicle-stimulating hormone [1](females only)	
Urine pregnancy test (females only)	Hemoglobin A1c

[1] Follicle-stimulating hormone in peri-menopausal women who have not had a menstrual period for <12 months at Screening.

Hematology

Hematocrit	Hemoglobin
Mean cell volume	Mean cell hemoglobin concentration
Mean cell hemoglobin	Platelets
Red blood cell count	White blood cell count and differential [1]

[1] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	Spot Urine: Albumin, Creatine, Protein, Albumin-to-Creatine Ratio (UACR), and Protein-to-Creatine Ratio (UPCR).

[1] Microscopy is performed only as needed based on positive dipstick test results for hematuria or proteinuria.

Serology

Hepatitis B surface antigen (HBsAg)
Hepatitis C antibody
HIV antibodies
HBV

Drug Screen

Drugs of abuse in urine:

- Tetrahydrocannabinol (THC)
- Heroin
- Methamphetamine
- Ecstasy
- Methadone
- Alcohol
- Cocaine
- Amphetamines
- Phencyclidine (PCP)
- Barbiturates
- Oxycodone

Cytokine Panel

IL-1β
IFNγ
TNFα
IL-2
IL-6
IL-12
MCP-1

Coagulation

Activated partial thromboplastin time (aPTT)
Prothrombin time (PT)
International normalized ratio (INR)

Pharmacodynamic Assessments

PCSK9

Lipid profile:

- Low-density lipoprotein cholesterol (β quantification and estimated by Friedewald equation)
- Very low-density lipoprotein cholesterol
- High-density-lipoprotein cholesterol
- Total cholesterol
- Triglycerides
- Non-high-density lipoprotein cholesterol (calculated)
- Lipoprotein (a)

Apolipoproteins:

- Apolipoprotein B
- Apolipoprotein A-I

Complement Activation

C3a
C5a
Split product Bb

Inflammatory/ Other Biomarkers	
C-reactive protein	Fibrinogen
Concurrent Statin PK	
Atorvastatin parent; ortho- para- hydroxy metabolite concentrations Other statin PK levels based on availability of validated assays	

Appendix C: 2018 Guideline on the Management of Blood Cholesterol

American Heart Association.

Top Ten Things to Know
2018 Guideline on the Management of Blood Cholesterol

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
2. In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.
3. In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy.
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL (≥4.9 mmol/L)), begin high-intensity statin therapy without calculating 10-year ASCVD risk.
5. In patients 40 to 75 years of age with diabetes mellitus and an LDL-C level of ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statins without calculating 10-year ASCVD risk.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5%–19.9%, risk-enhancing factors favor initiation of statin therapy.
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL– 189 mg/dL (≥1.8–4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5%– 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC).
10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

Other highlights:

1. For secondary prevention, at mid- 2018 list prices PCSK9 inhibitors have a low-cost value [>$150,000 per QALY (quality-adjusted life-year)] compared to good cost value [<$50,000 per QALY]. The guideline provides a full discussion of the dynamic interaction of different prices and clinical benefit.
2. This guideline provides recommendations for children and adolescents with lipid abnormalities.
3. Substantial advances in estimation of risk with CAC scoring have been made in the past 5 years. One purpose of CAC scoring is to reclassify risk identification of patients who will potentially benefit from statin therapy. This is especially useful when the clinician and patient are uncertain whether to start a statin.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print November 10, 2018]. *Circulation*. DOI: 10.1161/CIR.0000000000000625.