MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Version/Date:	Version 1.0 / 01 July 2019 Version 2.0 / 09 Sept 2019 Version 3.0 / 14 Nov 2019
Investigational Product:	CIVI 007
Sponsor:	CiVi Biopharma, Inc. 200 Four Falls Corporate Center Suite 107 West Conshohocken, PA 19428 USA
SAP Version/Date:	Version 2.0 / 19 February 2020

SIGNATURE PAGE

Protocol 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
SAP Version/Date:	Version 2.0 / 19 February 2020

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature **Date**

VERSION HISTORY

Version	Version Date	Description
1.0	09 July 2019	Original signed version
2.0	19 February 2020	Updated per Amendment 1 and Amendment 2

TABLE OF CONTENTS

1 Introduction 8
2 Study Overview 8
2.1 Study Objectives 8
2.1.1 Primary Objective 8
2.1.2 Secondary Objectives 8
2.1.3 Exploratory Objectives 8
2.2 Study Design 8
2.2.1 Overview 8
2.2.2 Randomization and Blinding 10
2.2.3 Study Drug 10
2.2.4 Sample Size Determination 10
2.3 Study Endpoints 10
2.3.1 Primary Safety/Tolerability Endpoints 10
2.3.2 Secondary Endpoints 11
2.3.3 Exploratory Endpoints 11
2.3.4 Safety Variables 12
3 Statistical Methodology 12
3.1 General Considerations 12
3.1.1 Analysis Day 12
3.1.2 Analysis Visits 12
3.1.3 Definition of Baseline 12
3.1.4 Summary Statistics 13
3.2 Analysis Populations 13
3.2.1 Intent-to-Treat (ITT) Population 13
3.2.2 Per-Protocol (PP) Population 13
3.2.3 Safety Analysis Population 13
3.2.4 Pharmacokinetic Population 13
3.3 Subject Data and Study Conduct 13
3.3.1 Subject Disposition 13
3.3.2 Protocol Deviations 13
3.3.3 Analysis Populations 13
3.3.4 Demographic and Baseline Characteristics 13
3.3.5 Medical History 14
3.3.6 Concomitant Medications 14
3.3.7 Study Exposure and Compliance 14
3.4 Efficacy and Pharmacodynamics Assessments 15
3.4.1 Secondary Efficacy Endpoints Analyses 15
3.4.2 Exploratory Efficacy Endpoints Analyses 16

3.5 Pharmacokinetic Assessment 16
3.5.1 Handling Missing Data or Concentration Below the Lower Limit of Quantification 17
3.5.2 Pharmacokinetic Concentrations 17
3.5.3 Pharmacokinetic Parameters 18
3.6 Safety Assessment 18
3.6.1 Adverse Events (AEs) 18
3.6.2 Clinical Laboratory Tests 19
3.6.3 Vital Signs 20
3.6.4 Electrocardiograms 21
3.6.5 Physical Examinations 21
3.6.6 Other Safety Assessments 21
4 Interim Analysis 21
5 Programming Specifications 21

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
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_{0-168}	Area under the plasma concentration-time curve from time 0 to 168 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
BLQ	Below the lower limit of quantification
BMI	Body mass index
CRF	Case report form
CL/F	Apparent clearance
CSR	Clinical Study Report
C_{max}	Maximum observed plasma concentration
C_{trough}	Concentration observed at pre-dose
CTCAE	Common Terminology Criteria for Adverse Events
Ecrf	Electronic Case Report Form
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
hsCRP	High-sensitivity C-reactive protein
ITT	Intent-to-treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
NCA	Non-compartmental analyses
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-Protocol
Q4W	Every 4 weeks
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SC	Subcutaneous(ly)
SD	Standard deviation
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSH	Thyroid-stimulating hormone
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
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods and pharmacokinetic (PK) methodology to be implemented for the analysis of data from the study with CiVi Biopharma, Inc. protocol number CIVI 007-2-01. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be substantiated by sound statistical/PK rationale and will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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.

2.1.2 Secondary Objectives

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

2.1.3 Exploratory Objectives

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

2.2 Study Design

2.2.1 Overview

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) across approximately 7 sites in the United States.

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

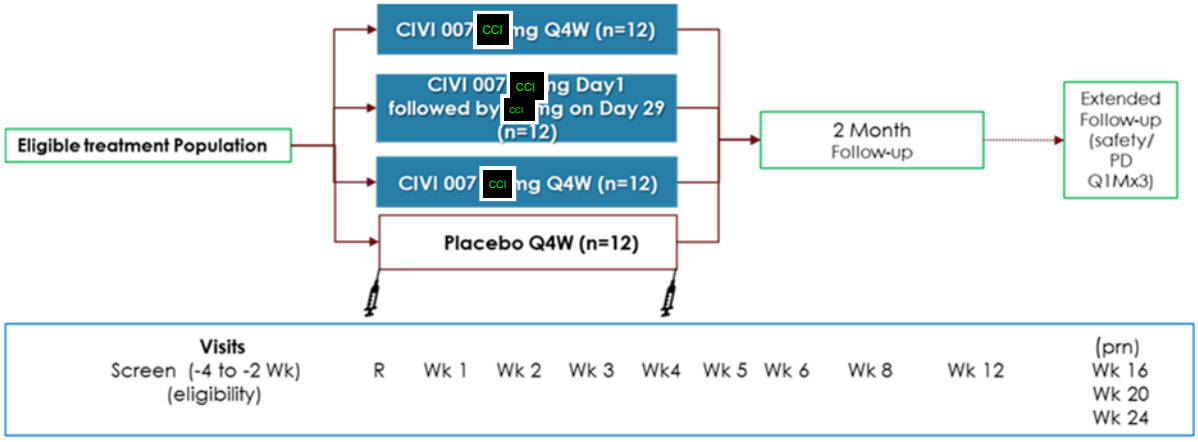
The Treatment Period will be approximately 28 days from Day 1 to Day 29; each treatment group will receive 2 administrations of study drug. Eligible patients will be randomized on Day 1 in a 1:1:1:1 ratio to one of the following treatment groups:

- Group 1: [redacted] mg CIVI 007 administered SC on Days 1 and 29
- Group 2: [redacted] mg CIVI 007 administered SC on Day 1 followed by [redacted] mg CIVI 007 administered SC on Day 29
- Group 3: [redacted] 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 of the protocol: measurements will be taken as detailed in Appendix A (schedule) and Appendix B (clinical laboratory analytes).

2.2.2 Randomization and Blinding

Approximately 48 patients will be assigned randomly to placebo, [redacted] mg CIVI 007, [redacted] mg CIVI 007 followed by [redacted] mg CIVI 007 or [redacted] 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.

2.2.3 Study Drug

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 fast:

- 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 [redacted] mg Q4W x2, [redacted] mg on Day 1 followed by [redacted] mg on Day 29 and [redacted] 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.

2.2.4 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.

2.3 Study Endpoints

2.3.1 Primary Safety/Tolerability 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 haematology, clinical safety chemistry, and urinalysis test results.

2.3.2 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

2.3.3 Exploratory Endpoints

The exploratory endpoints include the following:

2.3.3.1 Lipid/Pharmacodynamic (PD) Endpoints

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

2.3.3.2 Pharmacokinetic (PK) Endpoints

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}) (Day 29 only)

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 168 hours (AUC_{0-168})

- percentage of $AUC_{0-\infty}$ that is due to extrapolation ($\%AUC_{extrap}$)
- apparent terminal 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)

2.3.4 Safety Variables

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.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). Unscheduled and early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 8	8	2	11
Day 15	15	12	18
Day 22	22	19	25
Day 29	29	26	32
Day 36	36	33	39
Day 43	43	40	46
Day 57	57	47	71
Day 85	85	72	85 or End of Study (if Last Observation > Day 85)

Within an analysis visit window, the measurement from the visit closest to the defined target analysis day will be used. If there is more than one measurement with equal distance to the defined target analysis day, the latter will be used. If no visits occur within a visit window, the measurement for this visit will be treated as missing.

3.1.3 Definition of Baseline

Baseline for all efficacy and safety variables will be defined as the last scheduled value obtained prior to the first dose of study drug. If the measurement at this visit is missing, the last measurement prior to the first dose of study drug will be used as baseline. The scheduled baseline visit for all efficacy and safety variables is Day 1 pre-dose.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population will include all patients who are randomized to the study and will be used to assess efficacy.

3.2.2 Per-Protocol (PP) Population

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

A list of patients with major protocol deviations leading to exclusion from the PP Population will be finalized prior to unblinding the randomized treatment assignments.

3.2.3 Safety Analysis Population

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

3.2.4 Pharmacokinetic Population

The Pharmacokinetic Population will include all patients who receive any amount of investigational product and have at least one measurable CIVI 007 concentration.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened patients. Reasons for early discontinuation will also be summarized.

Counts and percentages of patients who were randomized, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized patients. Reasons for early discontinuation will also be summarized.

3.3.2 Protocol Deviations

Protocol deviations will be defined in the Protocol Deviation Plan. Counts and percentages of patients with CSR reportable protocol deviations by deviation category will be summarized by treatment and in total based on all randomized patients.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment and in total based on all randomized patients.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline Body mass index (BMI) (kg/m^2) and Baseline BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Baseline PCSK9 (mg)
- Baseline fasting LDL-C (mg/dL)
- Background statin therapy

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment and in total for all randomized patients and each defined analysis population if the analysis population composition is different than all randomized patients.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version 22.0 (or the most recent version available). Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized patients.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary version 2019G B3 (or the most recent version available). For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

Counts and percentages of patients taking concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Analysis Population. The use of any prior medication or concomitant medication will be listed for all randomized subjects.

3.3.7 Study Exposure and Compliance

Days of exposure to study will be calculated as date of last visit – date of first dose of study drug + 1. Days of exposure to study will be summarized by treatment based on the Safety Analysis Population with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- <= 14 days
- 15 - 28 days
- 29 - 56 days
- 57 - 84 days
- >= 85 days

The total number of injections administered will be calculated for each patient. A contingency table will be provided to display the number and percentage of patients in each treatment group with the number of injections.

3.4 Efficacy and Pharmacodynamics Assessments

PCSK9 will be collected at Day 1, Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Day 57 and Day 85 or early termination. Fasting lipid panel (including LDL-C, non-HDL-C, total cholesterol, triglycerides, HDL-C, and VLDL-C) will be collected at each study visit. Fasting apolipoproteins (including apolipoproteins B and A-I, and lipoprotein (a)) and β-Q LDL-C will be collected at Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, Day 57 and Day 85 or early termination.

All the secondary and exploratory efficacy endpoints will be summarized descriptively and analyzed by planned treatment based on ITT Population. All the individual data will be listed.

3.4.1 Secondary Efficacy Endpoints Analyses

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

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 approximately 28 days after the first injection (Day 29) and approximately 28 and 56 days after the second injection of study drug (Day 57 and Day 85) between treatment groups with placebo. This ANCOVA model will include treatment as a factor and baseline level as a covariate. The missing values will be imputed by last observation carried forward (LOCF) method.

Normality will be tested for the model residuals and the p-value from the Shapiro-Wilk test will be provided. If the residuals of this model are not normal, then non-parametric analyses (Wilcoxon rank- sum test) will be explored to compare the difference in median percent change between treatment groups.

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 SAS sample code is listed:

```
**********************************************************************
  TREATMENT: 0 (Placebo), 1 (CIVI 007 cci mg Q4W x2),
             2 (CIVI 007 cci mg on Day 1 followed by cci mg on Day 29), or
             3 (CIVI 007 cci mg Q4W x2)
  BASE: Baseline PCSK9 or LDL-C
  CHG: Change from baseline to the specified visit in PCSK9 or LDL-C
**********************************************************************;
proc glm;
  class TREATMENT;
  model CHG = TREATMENT BASE / p;
  lsmeans TREATMENT / stderr pdiff cl;
  estimate "CIVI 007 cci mg Q4W x2: Placebo" TREATMENT -1 0 0 1;
  estimate "CIVI 007 cci mg on Day 1 followed by cci mg on Day 29: Placebo"
           TREATMENT -1 0 1 0;
  estimate "CIVI 007 cci mg Q4W x2: Placebo" TREATMENT -1 1 0 0;
run;
```

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 PP Population.

Mixed-Effect Model Repeated Measure (MMRM) method may be used to test the robustness of the results with baseline value, treatment and visit as factors, and treatment by visit interaction. An unstructured covariance matrix will be used (TYPE=UN). The treatment difference will be estimated from the MMRM. No imputation will be performed. The SAS sample code is listed:

```
**********************************************************************
  USUBJID: Unique subject identifier
  TREATMENT: 0 (Placebo), 1 (CIVI 007 [CCI] mg Q4W x2),
             2 (CIVI 007 [CCI] mg on Day 1 followed by [CCI] mg on Day 29), or
             3 (CIVI 007 [CCI] mg Q4W x2)
  BASE: Baseline PCSK9 or LDL-C
  VISIT: Visits
  CHG: Change from baseline to the specified visit in PCSK9 or LDL-C
**********************************************************************;
proc mixed;
  class USUBJID TREATMENT VISIT;
  model CHG = TREATMENT BASE VISIT TREATMENT*VISIT;
  Repeated VISIT / TYPE=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT / cl pdiff slice=VISIT;
run;
```

3.4.2 Exploratory Efficacy Endpoints Analyses

The exploratory lipid/PD endpoints are listed in the section 2.3.3.1 excluding hsCRP. All the endpoints will be listed and summarized using descriptive statistics by treatment group over the study period to describe absolute and percent changes from baseline.

For continuous variables, the ANCOVA model specified for the secondary efficacy endpoints analysis will be used. The missing values will be imputed by LOCF method. For certain efficacy endpoints like the percent change in triglycerides, logarithmic transformation may be performed prior to fitting the ANCOVA model.

For certain efficacy endpoints, the MMRM method may be used to test the robustness of the results with baseline value, treatment and visit as factors, and treatment by visit interaction. An unstructured covariance matrix will be used (TYPE=UN). The treatment difference will be estimated from the MMRM. No imputation will be performed.

3.5 Pharmacokinetic Assessment

Sparse PK sampling will be conducted for all consenting patients. 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.

3.5.1 Handling Missing Data or Concentration Below the Lower Limit of Quantification

For non-compartmental analyses (NCA), missing or concentration below the lower limit of quantification (BLQ) data will be handled based on the current knowledge of the study drug.

If the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged and the scheduled time point may be used for the calculation of PK parameters.

In cases of missing pre-dose values on Day 1, the missing components will be assumed as zero. In cases of a missing pre-dose value on Day 29, the individual minimum observed concentration during the dosing interval will be used as pre-dose concentration values. For the other cases, the missing data will not be imputed.

The following rules will be used to handle BLQ data for individual plot and PK parameter calculation:

- If BLQ values occur in a profile before the first measurable concentration, it is assigned as zero for Day 1 and as LLOQ for Day 29.
- If BLQ values occur between measurable concentrations or after the last measurable concentration, it is treated as missing.

The following rules will be used to handle BLQ data for mean plot and concentration summary:

- Mean concentration at any individual time point are only calculated if at least half (50%) of the patients have valid values (i.e., measurable and not missing) at this time point for each treatment.
- In cases where a mean value is not calculated due to the criterion above not met, the value will be set to missing
- BLQ will be set as zero. The only exception is that the pre-dose BLQ on Day 29 will be set as LLOQ
- Missing values are excluded from the calculation of these means.

3.5.2 Pharmacokinetic Concentrations

Plasma concentrations for CIVI 007 will be summarized over scheduled time using descriptive statistics. Actual sampling times that are outside the scheduled sampling time window will be excluded from summary statistics but will still be used in the calculation of PK parameters. Individual plasma concentration data versus actual time points will be listed.

For each of the dosing days, the sampling time windows are as follows:

- Pre-dose: -1 hour,
- 3 hours post-dose: ±1 hour, and
- 8 hours post-dose: ±1 hour.

For each study visit, the sampling time window is ±3 days.

Individual concentrations of CIVI 007 will be plotted on a linear and semi-log scale against actual sampling time points for each treatment. Mean (±SD) CIVI 007 concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by treatment.

3.5.3 Pharmacokinetic Parameters

Where possible, standard non-compartmental analyses will be used to calculate the PK parameters of interest for CIVI 007 in section 2.3.3.2. The actual collection times will be used for PK parameter calculation. The Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin® Professional) will be used in the computation of AUCs.

The elimination constant rate, λ_z, will not be presented for patients who do not exhibit a terminal elimination phase in their concentration-time profiles. In order to estimate λ_z, linear regression of concentration in logarithm scale versus time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λ_z.

Generally, λ_z will not be assigned if one of the following happens:

1. T_{max} is one of the 3 last data points,

2. The adjusted regression coefficient (R-squared) is less than 0.80,

3. The estimated λ_z indicates a positive slope, or

4. The terminal elimination phase is not linear (as appears in a semi-logarithmic scale) based on visual inspection.

If the λ_z is not assigned, the values of associated PK parameters will not be calculated. In the cases where AUC_{extrap} exceeds 20%, the λ_z will be assigned and the λ_z and the corresponding λ_z-related PK parameters will be flagged but still included to the summary statistics with an explanatory footnote.

Pharmacokinetic parameters of CIVI 007 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 analysis of variance model, as appropriate.

3.6 Safety Assessment

Safety data will be summarized descriptively by actual treatment received (and in total for selected analyses) based on the Safety Analysis Population. All the individual data will be listed.

3.6.1 Adverse Events (AEs)

AEs 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. All AEs will be coded to system organ class and preferred term using MedDRA terminology version 22.0 (or the most recent version available).

Treatment-emergent adverse events (TEAEs) are defined as AEs that worsen in severity or relationship to study drug or start on or after the time of start of first study drug administration.

Adverse events of special interest (AESIs) include CTCAE Version 5.0 Grade 2 or higher ALT measurements, and injection site reactions (ISRs).

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any AEs (overall and by maximum severity)

- Any drug related AEs (overall and by maximum severity)
- Any AEs of special interest (ALT and injection site reactions)
- Any serious AEs (SAEs)
- Any AEs leading to discontinuation of study treatment
- Any AEs leading to discontinuation of study
- Any AEs leading to death

The primary endpoint is the incidence and severity of any drug-related AEs. The number and percentage of patients who experience 1 or more drug-related (possibly, probably, or definitely related) AEs will be presented by system organ class and preferred term by overall and by maximum severity. In addition, summaries will be provided by system organ class, preferred term, and maximum severity.

Listings of patients with drug-related AEs will be presented.

Counts and percentages of patients (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented for all AEs, specifically for AESIs, SAEs and AEs leading to death.

3.6.2 Clinical Laboratory Tests

Clinical safety chemistry, hematology, coagulation, and urinalysis will be collected at each study visit. Fibrinogen, cytokine and complement activation sampling will be collected at Day 1, Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Day 57 and Day 85 or early termination. hsCRP will be collected at Day 1, Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Day 57 and Day 85 or early termination. Thyroid-stimulating hormone (TSH), hemoglobin A1c (HbA1c), and serology will be collected in the Screening Visit.

Observed values and changes from baseline will be presented at each scheduled visit and baseline by laboratory test.

The primary endpoint is the incidence of clinically significant laboratory abnormalities, based on changes from baseline in hematology, clinical safety chemistry, and urinalysis test results. The incidence of abnormalities will be summarized with counts and percentages of patients for selected parameters grading by Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 if appropriate.

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
	Blood bilirubin increased	Total Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Total Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	Total Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	Total Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
	CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
	Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L	Potassium >6.0 - 7.0 mmol/L	Potassium >7.0 mmol/L
	Chronic kidney disease	eGFR <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5'.	eGFR 59 - 30 ml/min/1.73 m2	eGFR 29 - 15 ml/min/1.73 m2	eGFR <15 ml/min/1.73 m2
Hematology	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L	
	Hemoglobin increased	Hemoglobin > ULN & Increase in >0 - 2 g/dL	Hemoglobin > ULN & Increase in >2 - 4 g/dL	Hemoglobin > ULN & Increase in >4 g/dL	
	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L

For the other parameters, the incidence of abnormalities (as defined by normal ranges) prior to the first dose of study drug and after the first dose of study drug will be summarized with counts and percentages of subjects.

3.6.3 Vital Signs

Vital signs including supine blood pressure, supine heart rate, respiration rate, oral body temperature and weight will be measured at each study visit. Height will be measured only at the participant's Screening Visit.

Observed values and changes from baseline in vital signs will be summarized.

3.6.4 Electrocardiograms

12-lead ECGs will be performed in triplicate and measured at Screening, Day 1 pre-dose (- 1 hour), Day 1 post-dose (2.5 hours ±0.5 hour), Day 15, Day 29 pre-dose (-1 hour), Day 29 post-dose (2.5 hours ±0.5 hour), Day 57 and Day 85 or early termination.

Observed values and changes from baseline in quantitative ECG parameters (heart rate, PR interval, QRS Interval, QT interval, QTcB interval, QTcF interval and RR interval) and overall interpretation will be summarized by scheduled timepoint. The number and percentage of patients with absolute QTc interval values in the pre-specified categories (>450, >480, and >500 msec), and QTc interval change (>30 and >60 msec) will be summarized. Triplicate measurements will be averaged prior to summary.

3.6.5 Physical Examinations

Physical examination findings will be listed.

3.6.6 Other Safety Assessments

ADA will be listed and summarized using descriptive statistics by treatment group. All other safety data will be listed.

4 INTERIM ANALYSIS

No formal interim analyses are planned for this study other than descriptive analyses required for the Safety Review Committee (SRC) to review accumulating safety information. The reviews and analyses will be defined in the SRC Charter.

5 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.