Statistical Analysis Plan

Protocol No. CPI-1103-002, Version 3.0, 04 September 2019

PHASE II, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY DOSE RESPONSE AND PHARMACOKINETICS OF INTRAVENOUS ATORVASTATIN IN HYPERCHOLESTEROLEMIC PATIENTS PREVIOUSLY CONTROLLED WITH ORAL ATORVASTATIN

Sponsor: Cumberland Pharmaceuticals Inc.
2525 West End Avenue, Suite 950
Nashville, TN 37203, USA

Prepared by: Frontage Clinical Services, Inc.
200 Meadowlands Parkway
Secaucus, NJ 07094, USA
Tel: (201) 678-0288
Fax: (201) 552-2597

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Authors:	
Ruth E. Swanton, MPH Director of Biostatistics Frontage Clinical Services, Inc. 101 Carnegie Center, Suite 102 Princeton, NJ 08540	Signature:_____ Date:_____
Ken Yin, PhD Director, Clinical Pharmacology Frontage Clinical Services, Inc. 200 Meadowlands Parkway Secaucus, NJ 07094	Signature:_____ Date:_____
Frontage Representative:	
Annie Li, MD Associate Director, Project Management Frontage Clinical Services, Inc. 200 Meadowlands Parkway Secaucus, NJ 07094	Signature:_____ Date:_____
Sponsor Representative:	
Jerry Fox, DVM Sr. Manager, Clinical Operations Cumberland Pharmaceuticals Inc. 2525 West End Avenue, Suite 950 Nashville, TN 37203 Tel.: 615-255-0068 Fax.: 866-438-2372 Email: jfox@cumberlandpharma.com	Signature:_____ Date:_____

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Glossary and Abbreviations

Abbreviation	Term
AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
BLQ	Below the lower limit of quantification
CBC	Complete blood count
CI(s)	Confidence Interval(s)
CL(/F)	(Apparent) clearance of drug from plasma
C_{max}	Maximum plasma concentration
CMP	Comprehensive metabolic panel
CPI	Cumberland Pharmaceuticals Inc.
CPK	Creatine phosphokinase
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
eCRF	Electronic Case Report Form
h or hr	Hour(s)
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IV	Intravenous
K_{el}	Elimination rate constant
Kg	Kilogram(s)
L	Liter
LDL-C	Low-density lipoprotein cholesterol
Ln	Natural logarithm

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
max	Maximum
mg	Milligram(s)
min	Minimum
mL	Milliliter
n or N	Number of subjects
OTC	Over the counter
PK	Pharmacokinetic(s)
PO	Per os
PT	Preferred Term
SC	Subcutaneous
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
TEAE(s)	Treatment Emergent Adverse Event(s)
TLFs	Tables, Listings, and Figures
T_{max}	Time to reach maximum plasma concentration
$T_{½}$	Elimination half-life
Vd_{ss}	Volume of distribution at steady state for intravenous dosing
V_z/F	Apparent volume of distribution
WHO	World Health Organization

1 Introduction

Cumberland Pharmaceuticals Inc. (CPI) is developing atorvastatin injection for use in patients where an injectable route of atorvastatin administration is preferred.

Oral (PO) atorvastatin is currently approved for a number of indications, including the treatment of hyperlipidemia and the reduction of risk of myocardial infarction, stroke, revascularization procedures and angina. Atorvastatin injection is initially under study for treatment of hypercholesterolemia in patients where the intravenous (IV) or subcutaneous (SC) route is preferable to the oral route.

Statins, i.e., 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are a class of drugs to treat patients with hypercholesterolemia and for secondary prevention of coronary artery disease and stroke. Statins are among the most potent cholesterol lowering drugs available, yet only commercially available in oral formulations.

An injectable formulation of atorvastatin would allow for continuation of atorvastatin therapy in patients whenever enteral administration is not possible. There is evidence that abrupt discontinuation of statin therapy in patients with acute vascular disease results in adverse outcomes like cardiac events and higher mortality. Patients that may potentially benefit from injectable statin administration include: (1) individuals on an established statin regimen who are hospitalized and listed as *nil per os* such as those who are intubated, sedated, unconscious, or perioperative; (2) classes of acutely vulnerable patients such as those experiencing stroke, acute coronary syndrome, and certain types of myocardial infarction who may obtain protective effects from immediate statin administration; and (3) patients at high-risk of vascular events prior to and immediately following surgery.

Atorvastatin injection is being developed by CPI. The current formulation of atorvastatin injection is a 10 mg/mL (40 mg/4mL) liquid for injection, available in a glass vial.

Several Cumberland-sponsored nonclinical studies of atorvastatin injection have been conducted. No adverse trends were seen in a repeat-dose canine toxicity study, a rabbit-ear venous irritation study, or hemolysis and flocculation studies with human plasma/serum. The highest doses of atorvastatin injection caused elevated liver enzymes, a result consistent with high dose oral atorvastatin. The dog toxicity study determined a no observed adverse effect level of 20 mg/kg/day atorvastatin injection.

In a Phase 1 clinical trial in healthy volunteers, a preliminary pharmacokinetic (PK) profile for the parent compound and the two active metabolites was established for the IV delivery route. No major safety concerns were identified.

The current study is intended to further define the pharmacodynamic properties of atorvastatin and metabolites when delivered intravenously or subcutaneously, and to propose a dosing regimen to meet efficacy and safety objectives in changing from an oral to an injectable route. A single dose of atorvastatin will also be given by the subcutaneous

(SC) route in a sub-study and initial pharmacokinetic data will be collected for subjects enrolling under Amendments 1 or 2 of the study protocol. In Protocol Amendment 3, dated 03Sep2019, subjects taking oral atorvastatin change to a subcutaneous route for the treatment phase rather than an intravenous route.

This statistical analysis plan (SAP) covers the detailed procedures for performing statistical analyses and for producing Tables, Figures, and Listings (TLFs) for this study.

2 Study Objectives

The objectives of this study apply to hypercholesterolemic subjects currently being maintained on a stable dose of oral atorvastatin:

- To propose IV doses of atorvastatin injection that adequately replace each dose level of oral atorvastatin
- To describe the PK profile of atorvastatin injection administered by the IV route
- To explore the PK profile of atorvastatin administered by the SC route
- To assess the safety of the study drug administered by either the IV or SC route.

3 Study Endpoints

- To support a dose of atorvastatin injection that adequately replaces oral atorvastatin, the following primary endpoint will be evaluated for three of the four labelled oral doses of atorvastatin (10, 20, and 40 mg daily); endpoints are assessed using the subjects' levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C):
    - Eleven or more subjects in a dosing cohort of thirteen with a Day 15 LDL-C not more than 125% of their baseline LDL-C.

  Secondary endpoints that contribute to the same objective are as follows:
    - Eleven or more subjects in a dosing cohort of thirteen with a Day 15 HDL-C not less than 75% of their baseline HDL-C.
    - The mean change in LDL-C at Day 15 for each treatment cohort (N=13)
- To compare the PK profile of atorvastatin administered by the IV route to that of oral administration, the following parameters of atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin will be calculated for each of the four final multiple dosing injectables (IV and SC) treatment cohorts:
    - Maximum serum concentration (C_{max})
    - Area under the curve to infinity (AUC_{inf})
    - Area under the curve to 24 hours (AUC_{0-24})
    - Elimination half-life ($T_{1/2}$)
    - Volume of distribution at steady state (Vd_{ss})
    - Elimination rate constant (K_{el})
    - Clearance (CL)
- To explore the PK profile of a single dose of atorvastatin administered by the SC route, the following parameters of atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin will be calculated for each of the three final treatment cohorts:
    - C_{max}
    - AUC_{inf}
    - AUC_{0-24}
    - $T_{1/2}$
    - Vd_{ss}

- K_{el}
- Apparent clearance (CL/F)

- To assess the safety of the study drug, the following will be evaluated:
  - Adverse events
  - Mean change (baseline to Day 15) for creatine phosphokinase (CPK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in each dosing cohort.

4 Study Design and Methods

This is a Phase II, open-label, single-center dose-ranging study.

Three treatment cohorts of 13 subjects each are planned for intravenous route of administration. The different cohorts are composed of subjects taking three of the four commercially-prescribed levels of daily oral dosing: 10, 20, and 40 mg. The 4th Cohort for 80 mg oral dosing did not proceed with enrollment (per Amendment 3). Instead a 4th Cohort of 10 subjects (Amendment 03 of the protocol (Sections 9.3.6.2.3 and 12.2)) following the daily oral dosing of 20 mg will receive 15 days of subcutaneous treatment with atorvastatin**.** Subjects are treated with daily doses of injectable atorvastatin intended to be non-inferior to the efficacy of their stable oral dose at baseline.

Enrollment of subjects into any one of the cohorts that does not prove to meet the primary endpoint is terminated as soon as this determination is made, and a new cohort intended for 13 subjects is opened at an adjusted dose with intentions to meet the primary endpoint (See Table 1).

Table 1: Treatment Assignment – Main Study

Cohort	Lead-in Daily Dose of Oral Atorvastatin	Initial Targeted, Daily IV or SC Atorvastatin Dose	Maximum Daily IV or SC Atorvastatin Dose, after Escalations	Subjects
1	10 mg	2 mg IV	5 mg IV	13
2	20 mg	4 mg IV	10 mg IV	13
3	40 mg	8 mg*IV	20 mg IV	13
4	20 mg	5 mg SC**		10

*Targeted starting doses for the cohort are shown; however actual starting doses may be adjusted pending findings from earlier cohorts **4th Cohort received 5 mg (0.5mL Atorvastatin) SC q 24 for 15 days.

Subjects remain on the replacement treatment with atorvastatin for injection for 15 days, followed by a one-week follow-up period.

Assessments include the following:

- Pharmacokinetic profile evaluation of both the oral and IV dosing
- Cholesterol levels to assess efficacy
- Safety assessment, including markers of rhabdomyolysis

Sub-study: For those subjects that are participating in the sub-study (only Cohorts 1, 2 and 3) will resume their Lead-in visit oral dose of atorvastatin on Day 16. On Day 22, subjects that individually meet the study objective (Day 15 LDL-C ≤ 125% of baseline level) may replace a daily oral dose of atorvastatin by a SC dose of the same quantity as the IV dose to which they were assigned (see Table 2). Plasma levels of atorvastatin and the two metabolites are measured for a 24-hour period to assess the PK parameters of the SC route.

Table 2: Treatment Assignment – Sub-study

Cohort	Baseline Daily Dose of Oral Atorvastatin	Daily SC Atorvastatin Dose	Subjects*
1	10 mg	Same as daily final dose of IV Atorvastatin	≤13
2	20 mg	Same as daily final dose of IV Atorvastatin	≤13
3	40 mg	Same as daily final dose of IV Atorvastatin	≤13

* Subjects are from those meeting the study objective (Day 15 LDL-C < 125% of baseline level) in the main study.

Per protocol amendment, version 02, subjects eligible for enrollment in the main study will include:

- Subjects taking oral atorvastatin prior to the study
- Subjects taking statins other than atorvastatin prior to the study
- Subjects not taking any statins prior to the study.

Based on the subject's prior use of atorvastatin, another statin, or no prior use of a statin, their progression through the screening and lead-in periods will follow the pathway as described in the following Study Procedures and description in the protocol (Section 9.1). For those subjects with prior oral atorvastatin use refer to Table 3A for the procedures. For subjects on a different statin or whom do not have prior use of a statin refer to Table 3B for the procedures.

During the Lead-in Period, daily dosing of oral atorvastatin allows the determination of baseline LDL-C levels and also provides PK data from steady-state oral administration that will be compared to that from the intravenous administration.

The treatment period consists of an open-label treatment of 15 daily intravenous doses of atorvastatin injection. A 7-day follow up period follows and concludes with a phone call

from the Investigator or designee to the subject to collect information on any possible adverse events or changes in concomitant treatments.

The schedule of study procedures is presented in Table 3 below. For a detailed description of study procedures, please refer to protocol Section 9 “STUDY PROCEDURES”.

Table 3A: Schedule of Study Procedures for Subject's with Prior Oral Atorvastatin Use

Study Phase	**Screen -ing**	**Lead-in**	**Treatment**							**Follow-up call**	**Optional SUB-STUDY**	
Study Day	Day -3 to 0 from LI Day 0	LI End Visit (Screening visit + 7 to 10 days) AND (0 to -2 days before Day 1)	Day 1	Day 2	Day 3	Days 4–7	Day 8	Days 9-14	Day 15/ WD**	Day 22	Day 22 ± 2 days	Day 29 ± 3 days (Phone call)
LDL-C, Point of care	X*	X†										
LDL-C, Local laboratory							X					
Demographic Data	X											
Medical History	X											
Pregnancy Test, if needed	X	X							X			
Drug, Alcohol, Viral screen	X											
Physical Exam	X											
CBC, CMP, lipid profile	X	X‡							X			
Basic Metabolic Panel					X		X					
Vital Signs	X		X‖									
Review of Eligibility	X	X										
PK Blood Draws		X§							X¶		X△	
Daily oral atorvastatin dosing (standard of care).	X									Resume on Day 16, if in sub-study		
Daily IV or SC IMP			X									
Single injection SC											X	
Con Med monitoring	X										X	
Adverse Event monitoring		X									X	

* Point of care LDL-C is the first procedure done after the subject gives consent. If the value does not meet eligibility, the subject screen fails and receives no other assessments. Otherwise, the subject continues into the full screening phase.

† On LI End Visit, the Point of Care LDL-C is performed first and, if the subject does not qualify for treatment, they are a screen fail and no other assessments are done.

‡ The CMP, including liver enzymes and CK results must be reviewed by an Investigator before the subject is deemed eligible for treatment. The LDL result from this panel will not weigh in on the eligibility determination. Only the point of care result from LI End Visit determines eligibility.

§ PK sampling (oral PK) is performed at the Lead-in End visit. Samples are taken per protocol Section 9.3.4.1. The pre-dose sample serves as the Hour 24 level.

ǀ On Day 1, vitals are measured twice: 1) between 30 and 0 minutes before the start of IMP, and 2) 15 (± 5) minutes after the start of IMP

ǁ PK sampling (multi-dose PK) is performed on subjects that complete a Day 15 visit. Samples are taken per protocol Section 9.3.4.2. The pre-dose sample serves as the Hour 24 level.

Δ PK sampling (SC PK) is performed On Day 22 for those subjects participating in the sub-study. A subcutaneous injection of IMP is administered on a day that oral atorvastatin is withheld, then samples are taken per protocol Section 9.3.4.3.

** If a subject withdraws (WD) from the treatment period before Day 15, the following assessments should be completed: Physical exam, CBC, CMP, lipid profile, vital signs. Withdrawn subjects do not have PK blood draws and are not eligible for the SC sub-study.

Table 3B: Schedule of Study Procedures for Subject's without Prior Oral Atorvastatin Use at Study Entry

Study Phase	**Screen-ing**	**Lead-in**			**Treatment**							**Follow-up call**	**Optional SUB-STUDY**	
Study Day	Day -3 to 0 from LI Day 0	LI Day 0	LI Interim Visit (LI Day 28 +/-2 days)	LI End Visit (Interim visit + 7 to 10 days AND 0 to -2 days before Day 1)	Day 1	Day 2	Day 3	Days 4–7	Day 8	Days 9-14	Day 15	Day 22	Day 22 ± 2 days	Day 29 ± 3 days (Phone call)
LDL-C, Point of care	X*		X	X[†]										
LDL-C, Local									X					
Demographic Data	X													
Medical History	X													
Pregnancy Test, if	X			X							X			
Drug, Alcohol, Viral	X													
Physical Exam	X													
CBC, CMP, lipid profile	X			X[‡]							X			
Basic Metabolic Panel							X		X					
Vital Signs	X				X[‖]									
Review of Eligibility	X			X										
PK Blood Draws				X[§]							X[¶]		X[Δ]	
Dispense oral		X												
Daily oral atorvastatin dosing		X										Resume on Day 16, if in sub-study		
Drug accountability			X	X										
Daily IV or SC IMP					X									

Single injection SC													X	
Con Med monitoring	X												X	
Adverse Event		X											X	

* Point of care LDL-C is the first procedure done after the subject gives consent. If the value does not meet eligibility, the subject screen fails and receives no other assessments. Otherwise, the subject continues into the full screening phase.

† On LI End Visit, the Point of Care LDL-C is performed first and, if the subject does not qualify for treatment, they are a screen fail and no other assessments are done.

‡ The CMP, including liver enzymes and CK results must be reviewed by an Investigator before the subject is deemed eligible for treatment. The LDL result from this panel will not weigh in on the eligibility determination. Only the point of care result from LI End Visit determines eligibility.

§ PK sampling (oral PK) is performed at the Lead-in End visit. Samples are taken per protocol Section 9.3.4.1. The pre-dose sample serves as the Hour 24 level.

ǁ On Day 1, vitals are measured twice: 1) between 30 and 0 minutes before the start of IMP, and 2) 15 (± 5) minutes after the start of IMP

¶ PK sampling (multi-dose PK) is performed on subjects that complete a Day 15 visit. Samples are taken per protocol Section 9.3.4.2. The pre-dose sample serves as the Hour 24 level.

Δ PK sampling (SC PK) is performed On Day 22 for those subjects participating in the sub-study. A subcutaneous injection of IMP is administered on a day that oral atorvastatin is withheld, then samples are taken per protocol Section 9.3.4.3.

** If a subject withdraws (WD) from the treatment period before Day 15, the following assessments should be completed: Physical exam, CBC, CMP, lipid profile, vital signs. Withdrawn subjects do not have PK blood draws and are not eligible for the SC sub-study.

4.1 Study Measurements

4.1.1 Efficacy Measurements

The main efficacy measurements are the assessments of the LDL-C and HDL-C levels and the mean change in LDL-C in the injectable atorvastatin administration for each dosing cohort.

To assess the main efficacy objectives of the study, the lipid profile (including LDL-C and HDL-C) will be measured at the Screening Visit and Day 15, and the LDL-C level will be measured at Day 8.

4.1.2 Pharmacokinetic Measurements

The PK measurements in each dosing cohort are the assessments of plasma concentrations of atorvastatin and its metabolites (2-hydroxy atorvastatin and 4-hydroxy atorvastatin) in the oral administration and the administrations by the injectable route.

At the oral PK visit (Screening Period), serial PK blood samples to measure plasma concentrations of atorvastatin and its metabolites will be collected within 60 minutes prior to taking the oral dose of atorvastatin, at 30 minutes (± 5 minutes), 1, 2, 4, 6, and 8 h (± 10 minutes) after taking the oral dose.

Levels of atorvastatin and metabolites measured from the pre-dose (oral) timepoint are imputed as 24-hour levels since the subject is on daily, constant dosing.

In the last dose of injectable atorvastatin at Day 15 visit, serial PK blood samples to measure plasma concentrations of atorvastatin and its metabolites will be collected within 60 minutes prior to the start of the dose, immediately after completion of IV dose (within 3 to 7 minutes), at 30 minutes (± 5 minutes), 1, 2, 4, 6, and 8 h (± 10 minutes) after completing the injected dose.

Levels of atorvastatin and metabolites measured from the pre-dose (IV) timepoint are imputed as 24-hour levels since the subject is on daily, constant dosing.

In the sub-study for the single SC atorvastatin dose, serial PK blood samples to measure plasma concentrations of atorvastatin and its metabolites will be collected at 30 minutes (± 5 minutes), 1, 2, 4, 6, 8 (± 10 minutes) and 24 h (± 60 minutes) after the SC dose.

4.1.3 Safety Measurements

The safety and tolerability of study drug in each dosing cohort will be evaluated through:

- Incidence of treatment-emergent adverse events (TEAEs)
- Study discontinuation information
- Changes in clinical laboratory tests (CPK, ALT and AST)
- Vital signs (clinically significant changes in a subject will be recorded as AEs)

Adverse events (AEs) will be collected from the signing of informed consent form (ICF) to last subject contact/visit/end of post-treatment follow-up period.

Clinical laboratory tests including complete blood count (CBC), comprehensive metabolic panel (CMP), and lipid profile will be conducted at the Screening and, End Lead-in Visits, and at Day 15 or withdrawal.

Vital signs, including seated systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, respiration rate and body temperature, will be measured at the Screening Visit, between 30 and 0 minutes before the start of investigational medicinal product (IMP) and at 15 (+ 5) minutes after the start of IMP on Day 1.

4.2 Randomization

There is no randomization planned in the study.

4.3 Blinding

This is an unblinded study. All subjects will be openly assigned atorvastatin injection and their daily dose will be known by the Investigator and the subject.

4.4 Sample Size Justification

The clinical goal of replacing stable oral dosing of atorvastatin with temporary injectable dosing is to maintain constant LDL-C levels during and following the replacement therapy window. Therefore, the target mean change in LDL-C is zero. Utilizing the standard biological variabilities of LDL-C and an associated, estimated standard deviation of 0.15, a sample size of 13 would provide 80% power to show that the mean change in LDL-C after switching to injectable dosing is less than 10% of baseline levels if the true mean change for the group is zero. A mean change in LDL-C of up to 10% is not considered to be clinically significant over a short, two-week period.

4.5 Data Handling

All subject data used for analysis will be displayed in listings.

Summaries for continuous variables will include the descriptive statistics for number of subjects (n), mean (arithmetic and geometric), standard deviation (SD), minimum (min), median, and maximum (max). Summaries for categorical (discrete) variables will include the number and/or percentage of subjects in a particular category.

Conventions for presentation of numerical data:

Minimum and maximum values will be presented to the same number of decimal places as the electronic Case Report Form (eCRF) data. Means and medians will be presented to one more decimal place than the eCRF data. Standard deviations will be presented to two more decimal places than the eCRF data.

Plasma concentration and PK parameters in tables and listings will be displayed with 3 significant figures as follows:

(1) Values > = 0.0001 and < 1 will be reported with 3 significant figures (e.g., 0.0123).

(2) Values >= 1 and < 10 will be reported with 3 significant figures (e.g., 1.02).

(3) Values > = 10 and < 100 will be reported with 3 significant figures (e.g., 10.2).

(4) Values >= 100 and < 1000 will be reported with 3 significant figures (e.g., 102).

(5) Values >= 1000 will be reported with 3 significant figures (e.g., 1020).

(6) Values = 0 will be reported as 0.

Values for T_{max} will be reported to 2 significant figures.

In the evaluation of both oral and injectable, multiple-dose PK, levels of atorvastatin and its metabolites measured from the pre-dose timepoint are imputed as the Hour 24 levels since the subject will have been on at least a two-week period of daily, constant dosing, and the pre-dose value will essentially be the Hour 24 level from the previously administered dose. This will relieve subjects from making an extra clinic visit.

Baseline is defined as the last value measured prior to the first dose of study drug.

Change from Baseline is defined as [Post-baseline Value – Baseline Value].

5 Data Analysis

5.1 Analysis Populations

The following analysis populations will be used to summarize the results from this study.

- **Enrolled Population**: All subjects who were eligible, signed informed consent and were assigned IMP.
- **Safety Population**: All subjects who received at least a partial dose of IMP. No treated subjects will be excluded from the safety population.
- **Efficacy Population**: A completed group of subjects that 1) finished the two-week treatment period, 2) provided a Day 15 LDL-C level, and 3) took the final targeted dose for that cohort comprise the four efficacy populations.
- **Pharmacokinetic Population**: All subjects in the Efficacy Population who have no major protocol deviations and who have sufficient plasma atorvastatin concentration data for reliable estimates of the key PK variables for each of the four baseline cohorts.
- **Bioavailability Population**: All subjects in the PK Population who have complete PK profiles for either the IV or the SC multiple-dose treatment. This population will be used for the bioavailability analysis of PO/IV and PO/SC, respectively.

The frequency and percentage of subjects in each population will be summarized by cohort. Subjects who are excluded from the analysis populations will be listed by cohort, subject and treatment.

5.2 Study Subjects

Subject Disposition

Subject disposition will be summarized by cohort, using the number and percent of subjects who complete the study, the number and percent of subjects who discontinue the study, and the reasons for discontinuation.

Subject disposition and completion status will be listed for all enrolled subjects.

Protocol Deviations

Protocol deviations will be identified prior to database lock and may include but are not limited to: significant violations of inclusion/exclusion criteria, noncompliance of the trial treatment taken, conditions such as vomiting and diarrhea or use of prohibited medications, and not following clinical trial protocol procedures that may affect evaluation of the PK profile.

Protocol deviations will be listed by subject, cohort, and treatment for all enrolled subjects.

Subject Eligibility

Following protocol amendment, version 01 the eligibility for enrollment included subjects taking oral atorvastatin prior to the study, subjects taking statins other than atorvastatin prior to the study, and subjects not taking any statins prior to the study. A summary of these groups and cohort, final intravenous treatment, and final subcutaneous treatment will be produced. A listing by subject and cohort will be produced.

5.3 Subject Demographics

Demographics will be summarized by cohort and by IV or SC treatment in the safety population. The demographic consist of age, gender, race, and ethnicity. Individual demographics for the safety population will be listed by cohort, subject and treatment.

The age is a calculated parameter. Age will be calculated using the subject's date of birth and the subject's informed consent date.

Continuous variables (age) will be summarized by n, mean, SD, min, median, and max. Number of subjects and percentages will be used to describe categorical (discrete) variables (gender, race and ethnicity).

5.4 General Medical/Surgical History and Procedures/Non-Drug Therapies

The presence/absence of any current medical condition and/or other significant medical/surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. Any procedures/non-drug therapies that are incurred during the course of the study will also be coded using MedDRA or World Health Organization (WHO) Drug Enhanced Dictionary (version Global B3 March 2019), as appropriate.

Medical/surgical history and procedures/non-drug therapies will be listed by cohort, subject and treatment, respectively.

5.5 Prior and Concomitant Medications

All prescription medications and over-the-counter (OTC) products, including herbal products, taken from 30 days prior to Screening until the end of treatment will be documented in the subject's source documentation and the eCRF.

Prior and concomitant medications will be recorded and coded using the current version of WHO Drug Enhanced Dictionary (version Global B3 March 2019). Prior medications will be those that start and end prior to first dose of study drug. Concomitant medications will be those that have a known end date after the first dose of study drug or have a missing end date. Medications will be listed by cohort, subject, treatment, preferred term (PT) and Anatomical Therapeutic Chemical (ATC) classification, including the start and end dates and times, dose, unit and indication.

5.6 Efficacy Analysis

Efficacy will be determined by evaluating the final cohorts for each dosing level and the ability to meet the targets of

- 11 of 13 subjects with a Day 15 LDL-C not more than 125% of their baseline LDL-C
- 11 of 13 subjects with a Day 15 HDL-C not less than 75% of their baseline HDL-C
- The mean change at Day 15 in LDL-C for each treatment cohort

The dose required to meet the targets for each cohort will be listed by subject and summarized. A dosing cohort will be considered successful if eleven or more subjects have a Day 15 LDL-C not more than 125% of their baseline LDL-C. The responders for LDL-C and HDL-C and LDL-C change from baseline in each dosing cohort will be summarized for final IV daily dose as well as each IV daily dose.

5.7 Pharmacokinetic Analysis

The PK analysis will be conducted using WinNonlin Version 8.1 or higher (Certara, Princeton, NJ). In the PK analyses and summary statistics, all plasma concentrations below the lower limit of quantification (BQL) for the assay will be treated as "0" if they occur before the first measurable or after the last measurable concentration, and will be set as missing for data points in between two measurable concentrations.

5.7.1 Plasma Concentrations

Plasma concentrations of atorvastatin and its metabolites will be listed at each time point by cohort, subject and treatment, and summarized by route and final treatment cohort at each time point using descriptive statistics (n, arithmetic mean, SD and coefficient of variation (CV), geometric mean, geometric CV%, min, median and max).

Plots of individual concentrations of atorvastatin and its metabolites versus time, and mean plasma concentrations of atorvastatin and its metabolites versus the planned sampling time, will be presented on linear and semi-logarithmic scales.

5.7.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived for atorvastatin and its metabolites for subjects in the PK population.

Pharmacokinetic parameters are defined in Table 4.

Table 4: Pharmacokinetic Parameters

Parameter	Description
C_{max}	Maximum plasma concentration
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
T_{max}	Time to reach maximum plasma concentration
$T_{½}$	Elimination half-life
K_{el}	Elimination rate constant
Cl(/F)	(Apparent) clearance of drug from plasma for extravascular dosing
VD_{ss}	Volume of distribution at steady state for intravenous dosing
V_z/F	Apparent volume of distribution for extravascular dosing

Pharmacokinetic parameters will be calculated using noncompartmental methods and actual blood sampling times. In case of missing actual time, planned (or nominal) time will be used.

Concentration listed as below the limit of quantitation will be set to zero for the calculations. If a sample is missing or the value is not reportable and is between two measurable concentrations, the value at that time point will be left blank for the analysis and reported as either Not Reportable (NR) or No Sample (NS).

The PK timepoint at 24-hour post oral dosing is the pre-dose concentration due to reaching steady state. The first timepoint immediately following IV bolus dosing is set as 0.0055 hour (assume 20 seconds bolus dosing). The 24-hour post-dose concentration is set as pre-dose concentration before IV and multiple-dose SC dosing. For the single dose SC (sub-study) the pre-dose concentration is the 24-hour post-oral dose concentration.

No value of K_{el}, AUC_{inf} or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. If the adjusted R-squared value (Rsq_adjusted) is < 0.8, the analyst may evaluate if other time points are more appropriate and use those for the calculation of K_{el}, or no value of K_{el}, AUC_{inf} or $t_{½}$ will be reported.

For determination of AUC_{inf}, if calculated AUC from last to infinity is greater than 20% of the calculated AUC from 0 to infinity, then AUC_{inf} will not be reported.

Summary statistics for PK parameters except for T_{max} will be described by n, arithmetic mean (mean), arithmetic mean SD, arithmetic CV%, geometric mean, geometric CV%, min, median, inter-quartile range (Q1:Q3) and max. For T_{max}, summary statistics will be described by n, median, Q1:Q3, min and max. All PK parameters will be listed by cohort, subject and treatment.

5.7.3 Relative Bioavailability Analysis

To compare the PK profile of atorvastatin and metabolites administered by the IV or SC route to that of oral administration, the relative bioavailability analysis will be performed for each cohort using key PK parameters (C_{max}, AUC_{0-24} and AUC_{inf}) of atorvastatin and, if data allow, its metabolites. Dose-normalized key PK parameters of the oral and IV (or SC) routes of administration will be log-transformed and analyzed using an analysis of variance (ANOVA) model including terms for treatment route as a fixed effect and subject as a random effect. The least squares geometric means ratio of atorvastatin oral vs IV (or SC) will be calculated. A 90% CI on the ratio of untransformed PK parameters will be derived through reverse transformation of the 90% CI for the difference in the log scale to the 90% CI for the ratio in the original scale.

When appropriate, the same analysis may be performed to compare the PK profile of the atorvastatin SC vs oral (Cohort 4).

The least-squares geometric means, ratio of the geometric means and 90% CIs on the ratio will be displayed.

5.7.4 Exploratory Dose Response

An exploratory dose response analysis may be conducted if the efficacy data vs the dose indicates a trend. Summary of the baseline, Day 8 and Day 15 for LDL-C and HDL-C by IV dose will be produced. A dose-response plot (mean change from baseline in LDL-C and HDL-C for Day 8 and Day 15 vs. IV dose) may be produced. If the efficacy over time vs IV dose indicates a trend then a plot of percent change from baseline for LDL-C and HDL-C at Days 8 and 15 vs IV dose may be produced.

5.8 Safety Analysis

The safety and tolerability of IV and SC atorvastatin will be assessed by the evaluation of TEAEs, study discontinuation information, laboratory test results, and vital signs.

Safety variables will be tabulated and presented for all subjects in the Safety Population. Data will be summarized by cohort and by route. Adverse events will be summarized by MedDRA system organ class (SOC), preferred term (PT) and treatment. Mean change (baseline to Day 15) for CPK, ALT and AST in each dosing cohort, changes from baseline in other clinical laboratory parameters and vital signs parameters will be summarized.

5.8.1 Study Product Exposure

Exposure to study drug will be listed by cohort, subject and treatment received, indicating dose date and time. Any deviations will be documented.

5.8.2 Adverse Events

Adverse events will be collected from the ICF signing to last subject contact/visit/end of post-treatment follow-up period.

All AEs will be coded and classified according to MedDRA (Version 22.0). The intensity of adverse events is judged by the Investigator as mild, moderate or severe, and a causal relationship to study drug is judged by the Investigator as related, probably related, unlikely related or not related. Adverse events occurring prior to the date and time of first dose of study drug are considered non-TEAEs. Events occurring on or after the date and time of the first dose of study drug through last contact/visit of follow-up are considered treatment emergent if they are not listed in the subject's history.

A summary table of AEs will be created containing: number of AEs, number of subjects experiencing AEs, number of TEAEs, number of subjects experiencing TEAEs, severe TEAE, serious AEs, serious TEAEs, AEs causing discontinuation and AEs causing death.

All TEAEs will be summarized as the number and percentage of subjects by SOC, PT and treatment. Separate summaries will be created by intensity and by relationship to study drug. If the same AE (PT) is reported more than once for the same subject, it will only be counted once in the summary table. For summary tables by intensity and relationship to study drug, if the same AE (PT) is reported more than once for the same subject, the highest intensity grade (severe > moderate > mild) or the strongest relationship to treatment (related > probably related > unlikely related > not related) will be counted in the summary table.

All AEs will be listed, and a flag will indicate if the AE is treatment emergent.

All serious AEs (SAEs) will be listed, and a flag will indicate if the SAE is treatment emergent.

All adverse events leading to study discontinuation will be listed by subject.

All adverse events leading to death will be listed by subject.

5.8.3 Clinical Laboratory Assessments

Clinical laboratory tests (CBC, CMP, and/or lipid profile) will be performed at the Screening Visit and at Day 15 or withdrawal. Per the protocol amendment, version 02, basic metabolic panels will be performed at Day 3 and Day 8.

Clinical laboratory test parameters, with associated reference ranges provided by the laboratory, will be listed by cohort, subject and treatment. Clinical laboratory test results will be indicated as normal or abnormal (high, low). Mean change (baseline to Day 15) for CPK, ALT and AST in each dosing cohort will be summarized by cohort and by final IV treatment. For other clinical laboratory test parameters, observed values change from baseline will be also summarized for cohorts and final IV treatments.

5.8.4 Vital Signs Assessments

Vital signs (seated SBP, DBP, heart rate, respiration rate and body temperature) will be measured at the Screening Visit, between 30 and 0 minutes before the start of IMP and at 15 (+ 5) minutes after the start of IMP on Day 1.

Vital signs results will be listed by cohort, subject and treatment. Observed values and change from baseline to the one time point for vital signs will be summarized for cohort and final IV treatments.

5.8.5 Physical Examinations

A physical examination will be performed at the Screening Visit.

Physical examination results will be listed by cohort, subject and treatment.

5.9 Interim Analysis

No interim analysis is planned for this study.

5.10 Statistical Programming and Deliverables

All statistical analyses, tables and listings will be generated in SAS (version 9.3 or later) with appropriate documentation and programming validation. The table of contents of all tables, figures, and listings will be presented in a TFLs shell supplemental document.

5.11 Changes from Pre-Specified Analyses

5.12 Changes to the Planned Analysis

Any deviation(s) of consequence from the SAP during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document, as appropriate.

6 Revision History

Version	Date	Comments
2.0	3/16/20	Updated per Amendment 3 04 September 2019.