CLINICAL STUDY PROTOCOL

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

Study Number: CPI-1103-002

Protocol Version

Version Number: 03
Final: 04 SEPTEMBER 2019
Amendment: Replacing protocol amendment, version 02, dated 11Mar2019

CONFIDENTIALITY STATEMENT

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1 INVESTIGATOR'S STATEMENT

I have read and agree to the Protocol CPI-1103-002, Amendment 03, "Phase II, dose-ranging study to evaluate the efficacy dose response and pharmacokinetics of intravenous atorvastatin in hypercholesterolemic patients previously controlled with oral atorvastatin". I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

Principal Investigator

Signature: _____ 06 Sep 2019

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(201) 678-0288

Sponsor Signature

Signature: _____ September 5, 2019

Todd Rice, MD — Date of Signature
Director, Medical Affairs

Signature: _____

Leo Pavliv, R.Ph — Date of Signature
Executive Vice President, Operations & Chief Development Officer

1 INVESTIGATOR'S STATEMENT

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Principal Investigator

Signature:

Gregory Tracey, MD Frontage Clinical Services 200 Meadowland Parkway Secaucus, NJ 07094 (201) 678-0288	Date of Signature

Sponsor Signature

Signature:

Todd Rice, MD Director, Medical Affairs	Date of Signature

Signature:

Leo Pavliv, R.Ph Executive Vice President, Operations & Chief Development Officer	4/Sep/19 Date of Signature

2 SYNOPSIS

Name of Sponsor: Cumberland Pharmaceuticals Inc.	**Finished Product:** Atorvastatin injection	**Active Ingredient:** Atorvastatin Calcium
Title of Study: Phase II, dose-ranging study to evaluate the efficacy dose response and pharmacokinetics of intravenous atorvastatin in hypercholesterolemic patients previously controlled with oral atorvastatin		
Study Center: Frontage Clinical Services, Inc.		
Expected Study Duration: 9 months	**Phase of Development:** II	
Objectives: • To propose intravenous doses of atorvastatin injection that adequately replace each dose level of oral atorvastatin • To describe the pharmacokinetic profile of atorvastatin injection administered by the intravenous route • To explore the pharmacokinetic profile of atorvastatin administered by the subcutaneous route • To assess the safety of the study drug administered by either the intravenous or subcutaneous route		
Methodology: Cohorts of thirteen subjects, composed from each of the commercially-prescribed levels of daily oral atorvastatin dosing (10, 20, and 40 mg), are treated for 15 days with open-label injectable atorvastatin. Dosing for each cohort is adjusted, if necessary as determined by the Sponsor based on either the Day 8 or Day 15 LDL-C values. Any cohort that does not remain below 125% of baseline LDL-C may be repeated at a dose level to be determined by the protocol. Pharmacokinetic profiles are summarized for multiple doses via the intravenous or subcutaneous routes and for a single dose via a subcutaneous route (sub-study). Safety is assessed by standard adverse event reporting and monitoring of serum levels of liver and muscle enzymes.		
Number of subjects (planned): Approximately 40 in the main study; estimated 26 in the sub-study		

Name of Sponsor: Cumberland Pharmaceuticals Inc.	**Finished Product:** Atorvastatin injection	**Active Ingredient:** Atorvastatin Calcium

Main criteria for inclusion:

1. Adult between 18 and 65 years, inclusive.
2. On a stable dose of oral atorvastatin for at least 5 weeks prior to investigational treatment.
3. LDL-C value taken immediately at baseline is ≥ 75% and ≤ 125% of LDL-C taken one week prior.

Main criteria for exclusion:

1. A history of myopathy or rhabdomyolysis
2. Any hepatic impairment in the Investigator's judgement, including active gall bladder or biliary disorders
3. Screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than two times the upper limit of normal
4. Uncontrolled hypothyroidism or diabetes mellitus
5. Alcohol consumption of more than two drinks per day, on average

Investigational Medicinal Product (IMP), dose and mode of administration:
Subjects taking 10 mg daily of oral atorvastatin at baseline start by receiving replacement treatment with 2 mg of intravenous atorvastatin daily. Based on monitoring of LDL-C levels, dosing in that group and subsequent groups may be adjusted in order to target an intravenous or subcutaneous dose for each baseline oral-dose level that controls LDL-C.

A sub-study collects pharmacokinetic data following a single subcutaneous dose of atorvastatin injection.

Duration of treatment: 15 days (+1 day for the sub-study)

Criteria for evaluation:

SAFETY EVALUATION

- Adverse events
- Changes in creatine phosphokinase, ALT and AST

EFFICACY EVALUATION

- Changes in LDL-C and high-density lipoprotein cholesterol (HDL-C)

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition or Term
AE	Adverse Event
AUC_{inf}	area under the curve to infinity
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	Blood urea nitrogen
^{o}C	Celsius, degrees
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CK	Creatine Kinase
Cl	Clearance
C_{max}	maximum serum concentration
CMP	Comprehensive metabolic profile (serum biochemistry profile)
CPI	Cumberland Pharmaceuticals Inc.
CRF	Case Report Form
dL	deciliter
eCRF	Electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis Virus B
HCV	Hepatitis Virus C
HDL-C	high density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	intravenous
K_{el}	elimination rate constant
kg	kilogram
LDH	Lactate dehydrogenase
LDL-C	low density lipoprotein cholesterol
Mg	milligram

Abbreviation	Definition or Term
MI	myocardial infarction
mL	milliliter
mmHg	millimeters of mercury
N	*Number*
NPO	*Nil per os* (nothing by mouth)
NOAEL	no observed adverse effect level
PK	pharmacokinetics
PO	*Per os* (by mouth)
q.d.	Once daily
SAE	Serious Adverse Event/Experience
SC	Subcutaneous
SCr	Serum creatinine
$T_{1/2}$	elimination half-life
TEAE	Treatment-emergent adverse event
ULN	upper limit of normal
VDss	Volume of distribution at steady state
WD	withdrawn

5 INTRODUCTION

This study is to be performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations Parts 50, 56 and 312, and the International Conference on Harmonization E6.

5.1 Background Information

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

Oral 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 (Lipitor Package Insert 2018). 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 (Endres 2008, Daskalopoulou 2008, Schouten 2007). 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* (NPO) 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 (MI) 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 Cumberland Pharmaceuticals Inc. (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 (NOAEL) of 20 mg/kg/day atorvastatin injection.

In a Phase 1 clinical trial in healthy volunteers, a preliminary pharmacokinetic profile for the parent compound and the two active metabolites was established for the intravenous 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 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 04Sep2019, subjects taking oral atorvastatin change to a subcutaneous route for the treatment phase rather than an intravenous route.

5.2 Stage of Development

This is a Phase II study to determine the efficacy dose response and pharmacokinetics of injectable atorvastatin in hypercholesterolemic subjects.

5.3 Subject Population

Subjects already taking statins to control elevated low-density lipoprotein cholesterol (LDL-C), or subjects not taking statins that currently have elevated LDL-C.

5.4 Trial Rationale

This study is designed to propose non-inferior intravenous and subcutaneous doses of atorvastatin injection to temporarily replace stable, oral doses of 10, 20, and 40 mg. As expected and confirmed by the Phase I results, the systemic ratios of parent compound to active metabolites are altered with intravenous dosing as compared to oral. The pharmacokinetic profiles of each are further studied in this trial at the level of the individual patient to support both the dosing regimen and the safety profile of atorvastatin when administered parentally.

5.5 Risk-Benefit Assessment

Atorvastatin was first approved by the Food and Drug Administration (FDA) in December 1996 as an oral tablet under the trade name Lipitor®. Expected risks associated with the administration of atorvastatin injection can in part be anticipated because of the longstanding and widespread use of oral atorvastatin. The most commonly reported adverse reactions in subjects treated in clinical

trials with Lipitor, when having a higher incidence than with placebo and regardless of causality were nasopharyngitis, arthralgia, diarrhea, pain in extremity and urinary tract infection (Lipitor Package Insert 2018). Although rare, cases of rhabdomyolysis have been reported with use of Lipitor and other drugs in the class. This marks a serious potential risk with the drug class and one that needs to be monitored during statin treatment. Lipitor is indicated for extended dosing; however, this study will evaluate a two-week treatment period with atorvastatin injection. The Phase 1 study with atorvastatin injection did not detect any additional risks with the formulation or intravenous administration route.

6 STUDY OBJECTIVES

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

- To propose intravenous doses of atorvastatin injection that adequately replace each dose level of oral atorvastatin
- To describe the pharmacokinetic profile of atorvastatin injection administered by the intravenous route
- To explore the pharmacokinetic profile of atorvastatin administered by the subcutaneous route
- To assess the safety of the study drug when administered either intravenously or subcutaneously

7 STUDY ENDPOINTS

- To support a dose of atorvastatin injection that adequately replaces oral atorvastatin, the following primary endpoint will be evaluated for each of the three, labelled oral doses of atorvastatin (10, 20, and 40 mg daily); endpoints are assessed using the subjects' levels of (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 pharmacokinetic profile of atorvastatin administered by the intravenous 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 three final IV treatment cohorts (See Study Design for description of the three 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 pharmacokinetic profile of atorvastatin administered by the subcutaneous route, the following parameters of atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin will be calculated for each of the three final treatment cohorts (See Study Design for description of the three cohorts):
  - C_{max}
  - AUC_{inf}
  - AUC_{0-24}
  - $T_{1/2}$
  - VD_{ss}
  - K_{el}
  - Cl/F
  - Cl
- 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.

8 STUDY DESCRIPTION

8.1 Study Design

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

- Three treatment cohorts of 13 subjects each are planned, potentially for each of the routes of administration (intravenously and subcutaneously). The different cohorts are composed of subjects taking three of the four commercially-prescribed levels of daily oral dosing: 10, 20, and 40 80 mg. Subjects are treated with daily doses of injectable atorvastatin intended to be non-inferior to the efficacy of their stable oral dose during the Lead-in Period.

- Enrollment of subjects into any one of the cohorts that does not prove to meet the primary endpoint, or otherwise shows a lack of efficacy, 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 Section 9.3.6.2.2.

- 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 (PK) profile evaluation .of both the oral and IV dosing and, starting with Amendment 3, the SC dosing regimen.
    - Cholesterol (LDL-C) levels to assess efficacy
    - Safety assessment, including markers of rhabdomyolysis

- **Sub-study (Amendments 1 and 2 only)**: If remaining on oral atorvastatin in the follow-up period, subjects that individually meet the study objective (Day 15 LDL-C $\leq$ 125% of baseline level) may substitute a daily oral dose of atorvastatin for a subcutaneous dose of the same volume as the intravenous dose to which they were assigned. Plasma levels of atorvastatin and the two metabolites are measured for a 24-hour period to assess the pharmacokinetic parameters of the subcutaneous route.

- Schedules of assessments are summarized in Table 9-1A and Table 9-1B depending on the medication history of the subject when they entered the study.

8.2 Randomization and Blinding Conditions and Methods

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.

8.3 Drugs and Dosages

8.3.1 Identification and Description of Test Agent

Atorvastatin injection is available for investigational use only. Atorvastatin injection is packaged as a clear, colorless to slightly yellow liquid in a glass vial containing 40 mg atorvastatin in a total volume of 4 mL (10mg/mL). Atorvastatin injection contains the following inactive ingredients: hydroxypropyl beta cyclodextrin, L-cysteine monohydrochloride monohydrate, dibasic sodium phosphate, sodium hydroxide and water for injection. Ingredients in the formulation meet current Pharmacopeia standards. A copy of the vial investigational label is included as Figure 8-1.

Figure 8–1 Investigational Labeling

Atorvastatin Injection, 40 mg (40 mg/4 mL) Lot: Store at room temperature. Instructions: Use as directed Caution: New Drug – Limited by United States Law to Investigational Use Cumberland Pharmaceuticals Inc., Nashville, TN

For subjects that were taking oral atorvastatin prior to their study involvement, it will continue to be obtained according to the subject's standard methods. Oral atorvastatin will be supplied by the study for subjects that were not taking it prior to study involvement.

8.3.2 Investigational Medicinal Product (IMP) Preparation and Dosing Instructions

8.3.2.1 Intravenous Route

Atorvastatin injection is administered intravenously over 5 - 10 seconds into an antecubital or forearm vein. Following the Investigator's standard technique and equipment for preparing the injection site, the open-label study drug is administered without dilution. The dose is determined as directed in Section 8.3.2.4. If any IV tubing is utilized, normal saline is used to flush the line immediately following the injection of IMP to clear the line of any residual drug and ensure complete dosing. The location of the injection is captured in the source documents, but not the CRF.

8.3.2.2 Subcutaneous Route

Atorvastatin injection is administered subcutaneously as an injection into the abdominal area. The Investigator's center uses their standard technique and equipment to prepare the injection site and

to administer the injection. The location of the injection is captured in the source documents, but not the CRF.

8.3.2.3 Study Drug Product

Atorvastatin injection is administered at its full 10 mg/mL strength without dilution. For doses of 10 mg or less, 1.0 mL or insulin syringes are used so that small volumes can be drawn up and administered accurately.

A new vial of Atorvastatin injection (40 mg/4 mL) is used each calendar day. Sterile technique is utilized to draw individual subject doses; the same 10 mL vial can be used to dose multiple subjects on the same calendar day, but partially-used vials must not be used on a subsequent day. Drug accountability is documented at the level of each 40 mg vial of Atorvastatin injection.

8.3.2.4 Dose

The daily dose of IMP to be administered to each subject by both the intravenous route and the subcutaneous route is provided by the sponsor when the enrollment decision is made by the Investigator. It is based on the stable dose of oral atorvastatin taken by the subject during the lead-in phase. The initial dose for patients entering the treatment phase on 10 mg of daily oral atorvastatin is 2 mg IV daily. Corresponding initial target doses for the other levels of oral dosing are listed in Table 9-4. Dose adjustments for all follow the guidance listed in Section 9.3.6.2.2. In all cases, the Investigator will adhere to the dosing assignment documented by the Sponsor for each individual subject.

8.3.3 Drug Accountability Procedures

Atorvastatin injection, labeled for investigational use, will be provided by Cumberland Pharmaceuticals Inc. The investigator is required to keep complete and accurate records of the receipt, dispensation, disposal and return of all clinical trial drugs provided during the conduct of the study.

For subjects entering the study already taking oral atorvastatin, the product will continue to be obtained according to the subjects' standard methods through the lead-in and follow-up periods. Accountability is not formally documented in these cases; however, in determining each subject's eligibility, the Investigator assures to the best of his or her knowledge that the subject has been on a stable dose of oral atorvastatin.

Subjects that were not taking oral atorvastatin when entering the study are provided it by the study at the assigned dose. Drug accountability for these subjects is calculated during the five-week lead-in period so that compliance for that patient is understood and eligibility can be confirmed.

8.4 Selection of Study Population

Eligible subjects ultimately enter a baseline lead-in period where they take daily oral atorvastatin prior to converting to the investigational atorvastatin injection in the treatment phase. There are two main classifications of patients, and two sub-classifications, that may be eligible for screening and entry into the lead-in phase and the specific eligibility criteria differ for each:

a) Subjects that are taking a daily statin prior to their study involvement
   i. Subjects taking oral atorvastatin
   ii. Subjects taking a statin other than atorvastatin
b) Subjects that are not taking a daily statin prior to their study involvement

Determination of study eligibility will be made by the Investigator on the basis of the inclusion and exclusion criteria listed below.

8.4.1 Main Study Screening Phase

After a subject provides written consent to participate in the study, they may enter the screening phase by meeting one of the two following groups of inclusion criteria, depending on their pre-study medication history.

a) Subjects that are already taking a statin prior to their study involvement:
   1a. Male or female, between 18 and 65 years of age, inclusive.
   2a. Have been taking a commercially-labelled (U.S.), daily, stable dose of an oral statin for at least 28 days prior to consent.
   3a. Point-of-care* LDL-C level $\geq$ 65 mg/dL (measured on CardioChek® PA Analyzer, or equivalent)
   4a. Ability to make daily office visits, including weekends, during the two-week treatment period.
b) Subjects that are not taking a statin prior to their study involvement:
   1b. Male or female, between 18 and 65 years of age, inclusive.
   2b. No statin use in the 6 weeks prior to consent
   3b. Point-of-care* LDL-C level $\geq$ 120 mg/dL (measured on CardioChek® PA Analyzer, or equivalent)
   4b. Ability to make daily office visits, including weekends, during the two-week treatment period.

**If there are occurrences where the point-of-care analyzer gives an error message rather than a numerical result, it may be possible to substitute LDL-C from the local laboratory. See Section 9.4.1.*

8.4.2 Main Study_Lead-in Phase

After a subject has completed the screening phase assessments, they may enter the lead-in phase by meeting the following eligibility criteria.

Please note that the structure of the Lead-in Phase is different depending on the pre-study medication history of the individual patient, as described in Section 9.4.2.

8.4.2.1 Inclusion Criteria_Lead-in Phase

1. Female subjects must have a negative pregnancy test at screening AND
    - be surgically sterile (with documentation of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation/tubal occlusion),
    - OR be post-menopausal (no menstruation for a minimum of 12 months), As evaluated by Investigator,
    - OR if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or two forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months. All females must agree to continue to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle.

8.4.2.2 Exclusion Criteria_Lead-in Phase

1. A history of myopathy or rhabdomyolysis or an Investigator assessment that subject may have experienced myopathy with previous statin use

2. Screening AST or ALT > 2x the upper limit of normal (ULN)

3. Any hepatic impairment in the Investigator's judgement, including active gall bladder or biliary disorders. Previous cholecystectomy is allowable if the subject is stable.

4. Positive status for Human Immunodeficiency Virus (HIV) virus, Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV).

5. Alcohol consumption of more than two drinks per day, on average. Or any abuse of alcohol or non-prescribed drugs based on Investigator opinion and/or study screening.

6. Current known unstable angina or uncontrolled cardiac arrhythmias or a known cardiac event in the three months before screening (e.g., myocardial infarction, cerebral vascular event, percutaneous coronary intervention, coronary bypass surgery, etc.)

7. Uncontrolled hypothyroidism or diabetes mellitus, as determined by Investigator opinion based on subject health or medication records, and/or verbal report.

8. Uncontrolled hypertension (e.g., systolic pressure >160 mmHg or diastolic pressure>110 mmHg)

9. Concurrent treatment with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors, etc.)

10. Poor venous access for intravenous injections or blood draws

11. Pregnant, nursing, or planning to become pregnant.

12. A history of allergy or hypersensitivity to oral atorvastatin

13. Have taken investigational drugs within 30 days before IMP administration.

14. Inability to understand the requirements of the study.

15. Be otherwise unsuitable for the study, in the opinion of the Investigator.

8.4.3 Main Study_Treatment Phase

Subjects are eligible to enter the Treatment Phase and receive IMP after completing the Lead-in period and meeting one of the two following groups of inclusion criteria, depending on their pre-study medication history, and not meeting any exclusion criteria.

8.4.3.1 Inclusion Criteria_Treatment Phase

a) Subjects that were already taking oral atorvastatin prior to their study involvement:

   1a. LDL-C value from Lead-in End Visit is ≥ 75% and ≤ 125% of Screening Visit LDL-C measured by the point-of-care tests*.

   2a. Female subjects must have a negative pregnancy test at screening AND, if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or two forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months. All females must agree to continue

to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle.

b) Subjects that were NOT taking oral atorvastatin prior to their study involvement (includes subjects not taking any statin and those taking statins other than atorvastatin)

1b. LDL-C value from Lead-in End Visit is ≥ 75% and ≤ 125% of Lead-in Interim Visit LDL-C measured by the point-of care tests*.

2b. Female subjects must have a negative pregnancy test at screening AND, if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or two forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months. All females must agree to continue to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle.

**If there are occurrences where the point-of-care analyzer gives an error message rather than a numerical result, it may be possible to substitute LDL-C from the local laboratory. See Section 9.4.2.*

8.4.3.2 Exclusion Criteria_Treatment Phase

1. Clinically-significant elevation of ALT, AST, or CK during the Lead-in Period, as determined by the Investigator.

2. Known compliance for oral atorvastatin <90% during the Lead-in Period.

3. Failure to complete the pharmacokinetic blood draws (See Section 9.3.4.1) during the Lead-in Period.

8.4.4 Sub-study: Subcutaneous Pharmacokinetics

Please note that the Sub-study is no longer active or available under Protocol Amendment 3.

A subject must first meet all the eligibility criteria in Sections 8.4.1, 8.4.2 and 8.4.3 to qualify for the Sub-study.

In addition, the following criteria must be met:

8.4.4.1 Sub-study Inclusion Criteria

1. Ability to present to clinic for IMP dosing and PK assessment timepoints.

2. Approval to participate granted by sponsor based on review of each subject's Day 15 LDL-C level, baseline dose of oral atorvastatin and current enrollment numbers.

8.4.4.2 Sub-study Exclusion Criteria

1. Study Day 15 LDL-C > 125% of baseline LDL-C

2. Cohort to which subject belongs has three or more subjects with Day 15 LDL-C > 125% of baseline LDL-C

8.5 Prior and Concomitant Therapy

8.5.1 Excluded Medications/Procedures/Therapy

Concomitant medications and treatments that may directly or indirectly affect cholesterol levels are not to be initiated, discontinued, or otherwise changed during the lead-in and treatment phases of the study. Subjects that enter screening on a statin other than atorvastatin will replace that drug with oral atorvastatin during the Lead-in Period.

Use of St. John's Wort or grapefruit juice is prohibited 24 hours prior to IMP administration and throughout the conduct of the study.

Caution should be used with concurrent use of fibrate products or lipid-modifying doses (≥1 g/day) of niacin as this may increase the risk of adverse skeletal muscle effects while taking atorvastatin. Patients on digoxin should be monitored appropriately (Lipitor Package Insert 2018).

8.5.2 Dietary and Fasting Requirements

During the study, subjects maintain the dietary practices that they followed prior to study participation. Changes in nutritional or dietary behavior during the study, if deemed significant by the Investigator, are recorded in the Case Report Forms.

All lipid panel lab draws will be performed in a fasting state.

9 STUDY PROCEDURES

9.1 Study Overview

A schematic of the overview of the study is shown below in Figure 9-1. Three types of patient populations, categorized by statin use prior to study participation, are all potentially eligible for the study as shown below, and their progression through the screening and lead-in periods follows the pathway determined by their pre-study use of statins:

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

The study consists of a screening visit that determines a subject's eligibility to enter a lead-in phase where they will start or continue taking daily oral atorvastatin. Specific eligibility requirements are dependent on their pre-study statin use.

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 or subcutaneous 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.

Subjects eligible for the Sub-study and willing to participate receive a subcutaneous injection of atorvastatin on Day 22 and complete PK sampling the following day. The follow-up phone call, as noted above, is completed on Day 29.

9.2 Schedule of Time and Events

A detailed schedule of events is found below which lists the assessments required by the study at the corresponding timepoints. The type of statin use of the individual subject prior to study involvement determines which schedule to follow:

- Table 9-1A is to be followed for patients that entered the study having been taking a daily oral dose of atorvastatin.

- Table 9-1B is followed for patients that are not taking oral atorvastatin on their entry into the study. Two sub-classifications of patients comprise this group:
    - Patients that were not taking ANY statin at the time of study entry, and

- Patients that were taking a statin other than atorvastatin at the time of study entry.

Figure 9-1 Study Overview

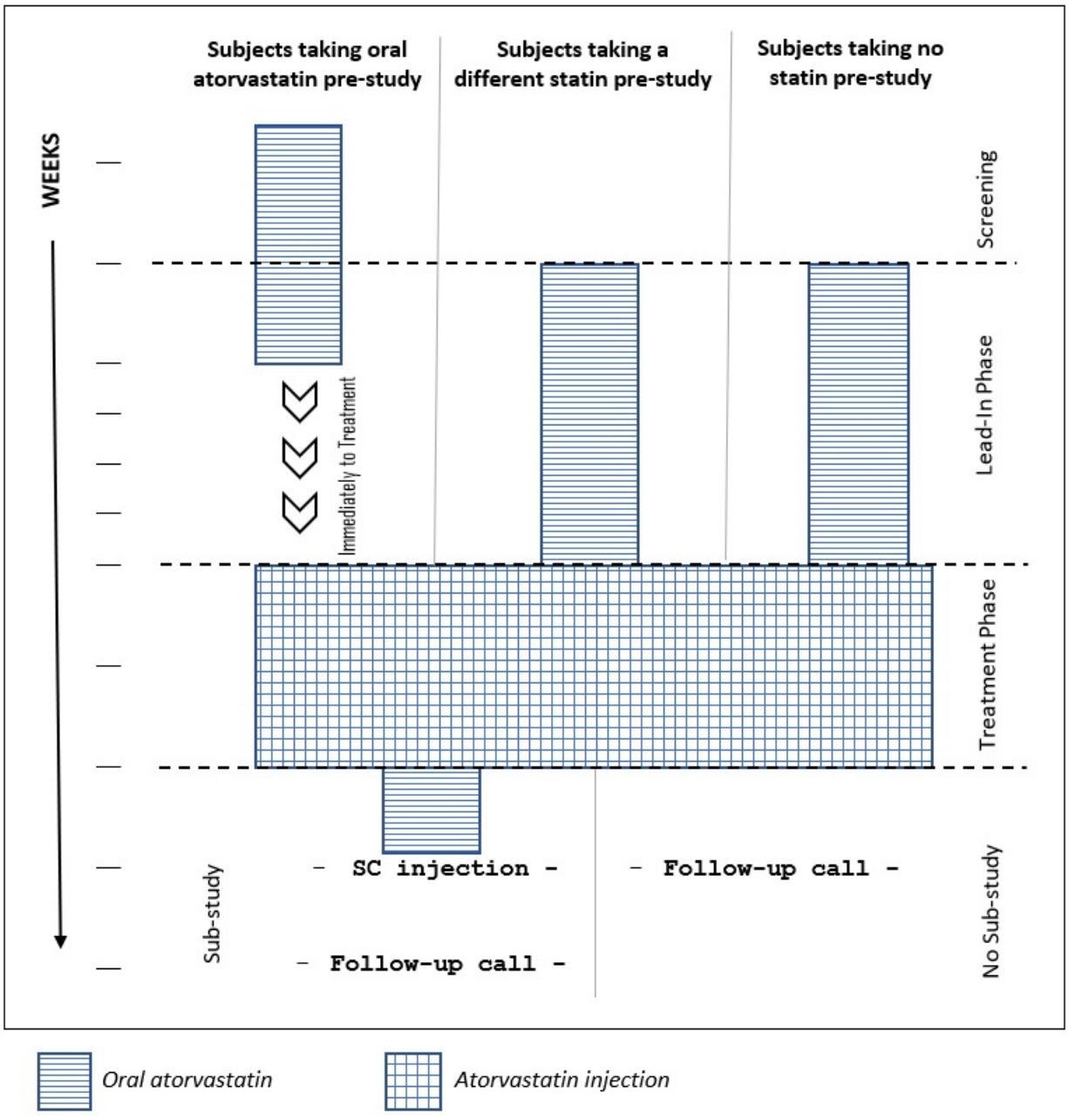

Table 9–1A Schedule of Events

For subjects that ARE taking oral atorvastatin 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 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 SCIMP			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 Section 9.3.4.1. The pre-dose sample serves as the Hour 24 level.

‖ 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 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 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 9-1B Schedule of Events
for subjects NOT taking oral atorvastatin 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△	
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 Section 9.3.4.1. The pre-dose sample serves as the Hour 24 level.

‖ 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 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 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.

9.3 Key Study Procedures

9.3.1 Clinical Laboratory Assessments

Blood sample collection for routine laboratory assessments will be performed within protocol-specified time periods and according to the site's standard practices for drawing and processing samples. The analytes listed here in Table 9-2 are measured by the site's local laboratory and evaluated by the investigator for safety monitoring with respect to reference ranges provided by that lab:

Table 9–2a. Clinical Lab Analytes to be Measured at Screening, Lead-in End Visit and Day 15

Complete blood count (CBC) with differential	
Hematocrit	Neutrophils, absolute count
Hemoglobin	Lymphocytes, absolute count
Total white blood cell count	Monocytes, absolute count
Platelet count	Eosinophils, absolute count
	Basophils, absolute count
Comprehensive Metabolic Panel (CMP)	
Sodium	Albumin
Potassium	Total protein
Chloride	Aspartate aminotransferase (AST)
Total carbon dioxide (serum biocarbonate)	Alanine aminotransferase (ALT)
Glucose	Alkaline phosphatase (ALP)
Blood urea nitrogen (BUN)	Total bilirubin
Serum creatinine (SCr)	Creatine Kinase (CK)
Calcium	Lactate Dehydrogenase (LDH)
Lipid Profile	
Low-density lipoprotein cholesterol (LDL-C)	Total cholesterol
High-density lipoprotein cholesterol (HDL-C)	Triglycerides

b. Clinical Lab Analytes to be Measured at Day 3 and Day 8

Basic Metabolic Panel	
Blood urea nitrogen (BUN)	Aspartate aminotransferase (AST)
Serum creatinine (SCr)	Alanine aminotransferase (ALT)
Creatine Kinase (CK)	Alkaline phosphatase (ALP)
LDL-C (Day 8 only)	

9.3.2 LDL-C, Point of Care

A point-of-care analytical device (CardioChek® PA Analyzer, or equivalent) is used for the measurement of LDL-C levels when immediate results are required in order to make study-related

decisions. Table 9-1A and Table 9-1B designated the timepoints where a point-of-care LDL-C is measured. In each occurrence, a skin lancet is used to collect 1-2 drops of blood from the subject's finger. The instructional manual for the device will be followed for the assessment and LDL-C values will be documented, as required, in the source and/or the CRF.

9.3.3 Drug, Alcohol, and Viral Screening

During the screening visit, all subjects receive a urine drug screen and a saliva alcohol (ethanol) test. Subjects confirmed or suspected, in the Investigator's opinion, as abusing alcohol or non-prescription drugs are not eligible for the study.

Serology is performed to detect active infections of HIV, HBV, and HCV; positive subjects are not eligible to participate in the study treatment.

9.3.4 Pharmacokinetic Assessments

Allowable time windows for PK draws are shown below in Table 9-3. Sampling taken outside of the allowable windows still contribute to building the pharmacokinetic profile, but minor deviations are captured in the Case Report Form (CRF).

Blood samples are taken by either direct venipuncture or via an indwelling catheter; however, samples must not be taken from the same catheter or any device used for administering the study drug.

Pharmacokinetic blood samples are collected for analyzing atorvastatin and metabolite concentrations in plasma.

If blood samples are obtained from an indwelling catheter rather than direct venipuncture, the catheter must be kept patent with saline flushes. A blood sample of approximately 1 mL will be drawn and discarded prior to each saved collection.

The samples are frozen in a -20°C freezer within 120 minutes of being drawn.

The actual sample collection date and time is entered in the eCRFs. Any issues with the sampling process will be noted.

Table 9–3 Allowable Time Windows for Pharmacokinetic Draws

Route being studied	Target time of blood draw	Allowable time window
Oral (screening period)	Pre-dose	-60 to -1 minutes before a dose of oral atorvastatin is taken

	Hour 0.5	± 5 minutes
	Hours 1, 2, 4, 6, and 8	± 10 minutes
Intravenous or Subcutaneous (Day 15)	Prior to the IV or SC dose	-60 to -1 minutes before the dose of IV or SC atorvastatin is taken
	Immediately after the IV or SC dose	3 to 7 minutes following the end of the administration
	Hour 0.5	± 5 minutes
	Hours 1, 2, 4, 6, and 8	± 10 minutes
Subcutaneous (Day 22)	Hour 0.5	± 5 minutes
	Hours 1, 2, 4, 6, 8	± 10 minutes
	Hour 24	± 60 minutes

9.3.4.1 Pharmacokinetics for Oral Dosing

Samples will be drawn from all participating subjects at the Lead-in End Visit in order to define the steady-state pharmacokinetic profile of the respective, stable dosing regimen on oral atorvastatin.

The subject is directed to refrain from taking their daily oral dose of atorvastatin at home, but then to bring the dose to the clinic for the PK visit. The visit is scheduled such that the dose is taken in the clinic at a time of day as close as possible to the time that the subject typically takes their oral dose.

At the oral PK visit, samples are drawn and processed per the procedure detailed above in Section 9.3.4 at the following times; allowable windows are listed in Table 9-3:

- Within 60 minutes prior to taking the oral dose of atorvastatin.
- At the following times after taking the oral dose:
  - 30 minutes
  - 1 hour
  - 2 hours
  - 4 hours
  - 6 hours
  - 8 hours

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

9.3.4.2 Pharmacokinetics for Multi-dose Intravenous or Subcutaneous Dosing (Treatment Phase)

Subjects receive their last dose of injectable atorvastatin at their Day 15 visit. Following the sampling and processing procedure detailed in Section 9.3.4, samples are drawn at the following times relative to their last injectable dose; allowable windows are listed in Table 9-3:

- Within 60 minutes prior to the start of the dose.
- At the following times after completing the dose:
  - Immediately after completion (**IV dose only;** subjects taking the SC dose under Amendment 03 omit this timepoint.)
  - 30 minutes
  - 1 hour
  - 2 hours
  - 4 hours
  - 6 hours
  - 8 hours

9.3.4.3 Pharmacokinetics for Subcutaneous Dosing (Sub-Study)

Subjects must first meet the eligibility criteria listed in Section 8.4.4 before participating in the subcutaneous PK sub-study. The Investigator ensures the subject has given and documented their consent to participate in the sub-study before performing related procedures.

As a result of the review of real-time, open-label LDL-C values, the sponsor informs the Investigator as to which subject(s) qualify for the sub-study. This determination is made following the subject's Day 15 visit and the subsequent reporting of the LDL-C level from the visit. The Investigator inquires of the subject's ability and continued consent to participate in the sub-study (Inclusion Criteria).

Eligible subjects that have consented to the sub-study will have resumed taking daily oral atorvastatin at their lead-in dose since Day 16. They then return to the study center on Day 22 $\pm$ 2 days after being instructed by the Investigator to refrain from taking their daily oral dose of atorvastatin at home on the day of the visit.

Subjects receive a subcutaneous dose of atorvastatin injection (Section 8.3.2.2), then samples are drawn at the following times after the time of the SC dose; allowable windows are listed in Table 9-3:

- 30 minutes
- 1 hour

- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 24 hours

9.3.5 Pharmacodynamic Assessments

The main efficacy objectives of the study are assessed through the lipid profile measured at Lead-in End Visit, Day 8 and Day 15. (See Tables 9-1A and 9-1B).

9.3.6 Dose Assignments

Subjects are assigned to one of three lead-in cohorts based on their daily dose of oral statin on which they entered the study, if applicable, and their screening value for LDL-C. Lead-in cohorts are categorized by the amount of daily, oral atorvastatin the corresponding subject will take (10, 20, or 40 mg). Following the completion of the Lead-in Period, subjects are assigned a daily intravenous or subcutaneous (Amendment 3) dose on which they remain during their complete treatment period, including the sub-study, if they participate. The dose for each cohort is determined by the sponsor and may be adjusted while the study is ongoing based on the continual monitoring and evaluation of safety and efficacy parameters.

9.3.6.1 Lead-in Period Dosing

Subjects that pass screening and enter the Lead-in Period are assigned an oral dose by the sponsor. Subjects enter one of the three possible Lead-in cohorts: 10, 20, and 40 mg. The sponsor will communicate the dosing assignment for each individual subject to the Investigator in writing.

9.3.6.2 Intravenous Dosing

The goal of the intravenous dosing and any associated dose adjustments is to fill all three cohorts and meet the primary study endpoint for each while utilizing the lowest possible daily dose of intravenous atorvastatin injection.

Primary study endpoint (See Section 7): 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.

9.3.6.2.1 Initial Cohort (10 mg PO Atorvastatin)

Subjects belonging to the 10-mg *per os* (PO) baseline cohort group (those that were taking 10 mg oral atorvastatin per day during Lead-in) are the first to be enrolled on the study. As shown below in Table 9-4, the initial subject in the 10 mg cohort is assigned to 2 mg IV atorvastatin injection as their daily dose. Subsequent subjects from the 10 mg PO Lead-in group are enrolled and treated with 2 mg IV daily while LDL-C values from their Day 8 and Day 15 study visits are reported and compared to baseline values in real time.

Table 9–4 Intravenous Dosing by Lead-in Cohort

Lead-in Daily Dose of Oral Atorvastatin	Initial Targeted, Daily Intravenous Dose	Maximum Daily Intravenous Dose, after escalations
10 mg	2 mg	5 mg
20 mg	4 mg	10 mg
40 mg	8 mg*	20 mg

*Targeted starting doses for the cohort are shown; however actual starting doses may be adjusted pending findings from earlier cohorts.

LDL-C values are monitored by the sponsor in real time and, if consistent and significant trends are seen to suggest that a cohort is not receiving an adequate dose, a dose adjustment for the cohort is warranted. Ongoing subjects in the treatment period of the affected cohort at the time of the decision to adjust the dose are contacted by the Investigator and directed to immediately discontinue the intravenous dosing and withdraw from the treatment period. The subjects are then not eligible for the sub-study.

9.3.6.2.2 Dose Adjustments

Following are two criteria that may initiate a dose adjustment:

- Three or more subjects have a Day 8 and/or a Day 15 LDL-C $\geq$ 125% of their baseline LDL-C. The dose is then increased for subsequent subjects.
- Three or more subjects have a Day 8 and/or Day 15 LDL-C $\leq$ 75% of their baseline LDL-C AND the mean of the lowest available post-treatment values is $\leq$ 85% of the mean of the baselines

In all scenarios, additional enrollment into the cohort is immediately stopped if the dose for the cohort is adjusted following an open-label review by the sponsor's clinical and medical teams. Enrollment into that cohort is then re-started at a new dose with the intention to enroll thirteen subjects. Doses will be adjusted by an amount not to exceed 25% of the preceding dose for that cohort.

The final dose will not exceed the maximum for that group as listed in Table 9-4. The maximum intravenous or subcutaneous dose to be administered to any cohort level will not exceed 50% of the oral dose for that same cohort. Prior to increasing a dose, the sponsor's medical monitor reviews a listing of serum biochemical values from all subjects in the current cohort and determines if there are any concerns of safety issues. Subsequent investigational treatment can proceed at the increased dose once any safety concerns have been eliminated.

In the opposite scenario, where three or more subjects report an LDL-C $\leq$ 75% of their baseline LDL-C and the mean of the lowest available post-treatment values is $\leq$ 85% of the mean of the baselines, the dose will be decreased following review of all treated subjects from that baseline group.

If subsequent dose adjustments are needed, the guidelines above continue to be followed.

Once a full cohort of 13 subjects have been enrolled and treated and the primary study objective has been met, the current dose is considered the established dose for that cohort and the next cohort initiates enrollment.

9.3.6.2.3 Subsequent Cohorts (20and 40 mg PO Atorvastatin)

Once two or more subjects from the 10 mg Lead-in group complete the study, the other cohorts can be opened to enrollment.

LDL-C results from completed subjects in the 10 mg PO atorvastatin cohort provide information on the dose-response efficacy for the injectable route for atorvastatin that is helpful toward dosing the other Lead-in groups.

The targeted initial dose for each of the subsequent Lead-in cohorts is listed in Table 9-4. However, any adjustments that were ultimately required for the dosing of the 10 mg PO cohort suggest that a similar adjustment is needed from the targeted doses for the other cohorts. Therefore, the starting dose for each subsequent cohort is adjusted accordingly by the sponsor prior to dosing the first enrolled subject of that treatment cohort.

With the activation of Protocol Amendment 3, dated 04Sep2019, one additional cohort is to be enrolled: Ten subjects that qualify for treatment following a lead-in period taking 20 mg oral atorvastatin are assigned to a daily dose of subcutaneous atorvastatin for the 15-day treatment phase.

9.3.6.3 Subcutaneous Dosing (Sub-Study)

Those subjects that are participating in the sub-study resume their Lead-in daily oral dose of atorvastatin beginning on Day 16. Their oral dose is withheld on the day of their Day 22 Visit while they return to the clinic for a subcutaneous injection given as close as possible to the time of day at which they take their oral dose. The dose amount administered is the same as that which was taken intravenously during the treatment period.

Subjects that are not participating in the sub-study resume their standard of care treatment, if any, for hypercholesterolemia while they await their Day 22 follow-up call.

9.4 Measurements and Evaluations

9.4.1 Description of Screening Visit

Before the initiation of study-specific screening assessments, the subject or legal authorized representative must be given a complete explanation of the purpose and conduct of the study. Subsequently, the subject or legal authorized representative must sign and receive a copy of an Informed Consent Form that was approved by the center's governing Institutional Review Board (IRB).

During this consenting process, the Investigator or designee has a preliminary discussion with the subject about participation in the sub-study. The subject's initial consent or refusal to participate in the sub-study is documented; however, this decision by the subject can be re-evaluated and changed prior to the end of the study treatment period.

Subjects that enter the study taking oral statins remain on their prescribed dose during the screening process.

After consent is obtained, the inclusion criteria in Section 8.4.1 are confirmed, including the measurement of LDL-C by the point-of-care test (CardioChek® PA Analyzer, or equivalent). In the event that the point-of-care analyzer gives an error message rather than a numerical result at the Screening Visit, a blood sample may be submitted to the site's local laboratory for the eligibility determination. Subjects that do not meet the eligibility requirement are deemed screen failures; others continue to complete the full screening visit to determine the subject's eligibility to enter the Lead-In Period and to document their baseline disease state. Allowable time windows are described in Table 9-1A and Table 9-1B:

- Collection of demographic data, including age, gender, race and ethnicity

- Review and documentation of medical history. Resolved diseases or past procedures that are not significant to the disease under study should be captured only if they occurred or were present in the previous five years. Other history (diagnoses, major signs or symptoms) should be recorded in the CRF regardless of time reference.

- A serum and/or urine pregnancy test is performed on all women.

- A serum FSH and estradiol test may be performed by Investigator on subjects to confirm postmenopausal status.

- Serology for HIV, HBV, and HCV.

- Urine Drug Screen and Saliva Alcohol Test

- A baseline physical examination is performed on all significant body systems.

- Blood samples are analyzed for hematology and serum biochemical levels, including a lipid profile. Labs are drawn and processed according to standard local processes and analyzed at the Investigator's local clinical laboratory. Analytes to be measured are listed in Table 9-2a.

- Vital signs are measured to include heart rate, respiration rate, body temperature, and seated blood pressure.

9.4.2 Description of Lead-in Period

Subjects that meet all screening requirements enter the Lead-in Period. The Investigator notifies the sponsor that a subject is eligible for Lead-in and the sponsor assigns a dose of oral atorvastatin:

a. Subjects already on oral atorvastatin stay on their current dose.
b. Subjects not on oral atorvastatin are prescribed and dispensed oral atorvastatin at the assigned dose.

During the Lead-in Period, oral atorvastatin is to be taken in the morning. Subjects are also instructed to bring their medication vials to their study visits so that drug compliance can be calculated. Finally, subjects are instructed to refrain from taking a dose at home on the morning of their Lead-in End Visit.

The remainder of the Lead-in Period transpires according to one of two schedules depending on the pre-study medication history of the individual subject:

a. Subjects that were already taking oral atorvastatin prior to their study involvement (See Table 9-1A):

- There is no Lead-in Interim Visit.
- The Lead-in End Visit occurs 7 to 10 days after the Screening Visit.
- A point-of-care LDL-C value is obtained and compared to the value from the screening visit as per Inclusion Criterion 1a in Section 8.4.3.1. If the comparison between values meets eligibility, the Lead-In End Visit continues including the oral pharmacokinetic assessments per Section 9.3.4.1.
- In the event that the point-of-care analyzer gives and error message rather than a numerical result at the Lead-in End Visit, a blood sample may be submitted to the site's local laboratory and be compared to the Screening LDL-C value, also measured by the local lab. Values taken by one method may not be compared to values taken by the other method.
- Other assessments are completed as per Table 9-1A.

b. Subjects that were not taking oral atorvastatin prior to their study involvement (See Table 9-1B):

- Subjects are dispensed oral atorvastatin at the dose assigned by the sponsor and instructed to initiate their daily dosing on Lead-in Day 0, as defined by the Investigator.
- Twenty-eight (+/- two) days following the first dose of oral atorvastatin (defined as Lead-in Day 0), the subject returns to the clinic for a Lead-in Interim Visit that includes a point-of-care LDL-C measurement and a review of drug compliance. Any compliance other than 100% prompts re-training of the subject. The subject is reminded to refrain from taking their oral atorvastatin at home on the day of the Lead-in End Visit.
- The Lead-in End Visit occurs 7 to 10 days after the Lead-in Interim Visit:
- A point-of-care LDL-C value is obtained and compared to the value from the Lead-in Interim Visit as per Inclusion Criterion 1b in Section 8.4.3.1. If the comparison between values meets eligibility, the Lead-In End Visit continues including the oral pharmacokinetic assessments per Section 9.3.4.1.

- In the event that the point-of-care analyzer gives an error message rather than a numerical result at the Lead-in Interim Visit, a blood sample may be submitted to the site's local laboratory and be available for comparison to a LDL-C value measured by the local lab at the Lead-in End Visit. Values taken by one method may not be compared to values taken by the other method.

- Other assessments are completed as per Table 9-1B.

9.4.3 Eligibility Confirmation and Treatment Assignment

The Investigator reviews all eligibility criteria that are assessed in the subject's history and screening period, then confirms whether the subject will enter study treatment. All subjects are assigned to open-label atorvastatin injection; however, the Investigator must obtain from the Sponsor the daily amount of IMP to be administered to each individual subject. This daily dose will be provided by the sponsor in writing based on 1) the oral dose of atorvastatin taken during the Lead-in Period, and 2) the most recent dosing assignment given by the protocol or medical review committee (See Section 9.3.6).

The Day 1 Visit occurs within two days following the Lead-in End Visit and the subject is instructed to continue their daily oral atorvastatin but to refrain from taking it on Treatment Day 1.

9.4.4 Description of Treatment Period

The subject presents to the clinic for daily outpatient visits during the 15-day treatment period. The subject is monitored in the clinic for a minimum of approximately 15 minutes after any injection to ensure there are no issues with bleeding or other adverse reactions.

Spontaneously-reported adverse events are recorded in addition to any changes in concomitant treatments.

9.4.4.1 Day 1

Vitals are taken between 30 and 0 minutes before the start of the first IMP injection.

The Investigator's standard technique and equipment are used to prepare the injection site and delivering the injection. If any IV tubing is utilized, normal saline is used to flush the line immediately following the injection of IMP.

Vital sign measurements are repeated at 15 ($\pm$ 5) minutes after the time of the IMP administration.

9.4.4.2 Days 2, and 4 through Day 7

The subject returns to the clinic each day at the approximate same time of day for an outpatient visit. The subject receives an injection of atorvastatin at the same amount and by the same route and method as at the Day 1 visit.

9.4.4.3 Day 3

Blood is drawn prior to the daily injection of study drug and submitted to the site's local laboratory to measure the analytes listed in Table 9-2b. Levels of liver and muscle enzymes are reviewed against baseline values to assess safety.

9.4.4.4 Day 8

Prior to administration of the daily injection of atorvastatin, a blood sample is collected, processed and analyzed at the Investigator's local laboratory to provide an LDL-C level. Additionally, the analytes listed in Table 9-2b are measured. Levels of liver and muscle enzymes are reviewed against baseline values to assess safety.

LDL-C levels are transmitted to the sponsor as soon as available.

9.4.4.5 Days 9 through 14

The subject returns to the clinic each day at the approximate same time of day for an outpatient visit. The subject receives an injection of atorvastatin at the same amount and by the same method as at the Day 1 visit

9.4.4.6 Day 15

Unless withdrawn early from the treatment period (See Section 9.4.4.7), the subject presents to the clinic on Study Day 15 for their final injection with atorvastatin.

Prior to administration, blood samples are drawn for analysis of hematology and serum biochemical levels, including a lipid profile. Labs are drawn and processed according to standard local processes and analyzed at the Investigator's local clinical laboratory. Analytes to be measured are listed in Table 9-2a. The Investigator reviews reported values in comparison to those reported at the screening and treatment visits and any changes that are deemed undesirable and clinically significant are reported as adverse events. Subjects with clinically-significant changes in lab values are monitored at unscheduled visits until values return to normal or until a cause other than the study drug is determined.

LDL-C and HDL-C levels are transmitted to the sponsor as soon as available.

Samples for Pharmacokinetic profiling of intravenous atorvastatin are taken per Section 9.3.4.2.

A urine pregnancy test is administered for all women of child-bearing potential.

Subjects that entered the study taking oral atorvastatin are directed to resume taking their oral atorvastatin on the day following the Day 15 (or withdrawal) visit at the same dose level as that taken during the Lead-in Period.

Subjects that did not enter the study taking oral atorvastatin but continue to participate in the Sub-study are dispensed oral atorvastatin at the same dose as that taken during the Lead-in Period. Patients that are in the Sub-study are directed to refrain from taking their oral dose at home on the day of their Day 22 Visit.

9.4.4.7 Withdrawal

Subjects may be withdrawn from the treatment on any day during the 15-day period by subject, Investigator or sponsor decision. Withdrawn subjects are not eligible to participate in the sub-study that would immediately follow their treatment period.

If the sponsor determines that a cohort will not meet the primary endpoint (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), any subjects currently being treated in that cohort are to be withdrawn. In such a case, there is no benefit to the subject or the study data for the subject to continue taking an investigational drug at a non-efficacious dose. The Investigator is notified by the sponsor in writing that the cohort is closed.

For patients that were taking oral atorvastatin prior to the study, the investigator contacts the subject and instructs them to resume taking their normal dose of oral atorvastatin on the day following their last injected dose. Other subjects return to their standard of care treatment. The subject returns to the clinic as previously planned according to the daily visit schedule but does not receive an injection of study drug or undergo pharmacokinetic sampling. Labs are drawn and processed according to standard local processes and analyzed at the Investigator's local clinical laboratory. Analytes to be measured are listed in Table 9-2a. Also, a urine pregnancy test is administered for all women of child-bearing potential. Following the visit, the subject enters the follow-up period and receives a phone call 6-8 days later.

9.4.5 SUB-STUDY to Evaluate Subcutaneous Pharmacokinetics

Please note that the Sub-study is no longer active or available under Protocol Amendment 3.

Participation in the sub-study is initially discussed between the Investigator and subject during the original consenting process for the main study. The subject's decision regarding participation is discussed again at the end of the 15-day treatment period. Any change to their consent is documented by both the subject and the Investigator or designee.

Final approval for an individual subject to participate in the sub-study is made by the sponsor following review of their Day 15 LDL-C levels. The Investigator is immediately made aware of this decision and informs the subject to confirm their participation and schedule of events.

Subjects participating in the sub-study proceed according to the process described in Section 9.3.4.3. Subjects that decline participation or are not eligible per sponsor decision continue to be monitored until their Follow-up call.

9.4.6 Follow-up Call

The Investigator or designee contacts all subjects 7 days (± 2 days) after their last exposure to study drug. For subjects participating in the sub-study, this occurs at approximately Study Day 29. Subjects that do not participate in the sub-study receive follow-up contact at approximately Study Day 22.

A phone call is the desired method of communication; however, alternate methods can be utilized by the Investigator if deemed appropriate and effective.

During the contact, the subject is asked about any changes in their medical condition or concomitant medications and responses are recorded and/or monitored further as appropriate.

9.4.7 Rescreening

Individual subjects may be rescreened one time each if the Investigator obtains sponsor approval. This applies to subjects that previously screen fail, lead-in fail and those that initiate investigational treatment. In such cases, the subject will begin with a new screening visit.

10 SUBJECT DISCONTINUATION

10.1 Subject Discontinuation

Subjects will be encouraged to complete the study; however, they may voluntarily discontinue at any time and for any reason. Also, the sponsor directs the Investigator to withdraw subjects if they belong to a treatment cohort that will not meet the primary endpoint (See Section 9.4.4.7). The Investigator will describe in the CRF the reason for discontinuation.

A subject may be removed from the study for the following additional reasons; in each case, the decision to discontinue should be confirmed following consultation between the Investigator and Sponsor:

- Adverse event (AE): If a subject experiences an AE for which continued study participation presents an unacceptable consequence or risk to the subject, the subject may be discontinued.

- Subject non-compliance: A subject's past, current, or anticipated inability to comply with study visits, clinical trial medication or other processes required by the protocol may lead to the decision to discontinue the subject from the study.

- Enrollment violation: If it is realized after the initiation of investigational treatment that a subject did not meet all eligibility requirements, the Sponsor and Investigator will discuss whether it is safe, ethical, and scientifically sound to keep the subject in the study or to discontinue the subject.

- Concurrent Treatment: If a subject initiates a procedure or medication that may interfere with their study conduct or for which study involvement may pose a significant risk to the prescribed therapy, the subject may be discontinued.

- Other reasons: Following discussion between the Sponsor and Investigator, subjects may be discontinued from the study for reasons other than those listed above.

10.2 Procedures for Subject Discontinuation

If a subject is discontinued or withdrawn for any reason prior to completion of the full treatment period, a withdrawal visit plus follow-up, as described above should be performed. Following the visit, reasonable efforts should be made to monitor the subject for AEs, as appropriate.

Subjects that do not complete the full treatment period do not undergo the Day 15 PK assessments. They are also not eligible to participate in the sub-study.

Subjects that are discontinued may be replaced, as needed. The decision will be made on a case-by-case basis by the study sponsor.

10.3 Study or Site Termination

If conditions arise during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Medical Monitor, and Study Monitor.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

A study conducted at a single study site or a single study site in a multicenter study may also warrant termination under the following conditions:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization (ICH) sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

11 ADVERSE EVENTS

Information about AEs, whether spontaneously reported by the subject, discovered by the Investigator by questioning/review of records or detected through physical examination, laboratory test or other means, will be collected and recorded on the adverse event form and followed-up as appropriate. Information about serious adverse events should be reported to the Sponsor within 24 hours of obtaining knowledge of the event.

11.1 Definitions

11.1.1 Adverse Event Definitions

Adverse events are defined according to ICH Harmonized Tripartite Guideline E2A.

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a trial product whether it has a causal relationship with the study treatment or not.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

None of the following are considered an AE:

- Pre-planned procedure (documented as concomitant illness on the CRF at screening) unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent form.
- Pre-existing conditions found as a result of screening procedures.

Serious adverse event (SAE)

An AE that meets any of the following criteria:

- results in death
- is immediately life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is judged medically important in the opinion of the Investigator (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed).

Non-serious adverse event

Any adverse event that does not meet the definition of an SAE.

Unexpected adverse event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.2 Adverse Event Assessment Definitions

Anticipated

Anticipated events include known consequences of an underlying disease or the condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline.

Severity

The maximum severity of an adverse event is assessed by the investigator using the following guidelines:

Mild: Transient symptoms, no interference with the subject's daily activities.

Moderate: Marked symptoms, moderate interference with the subject's daily activities.

Severe: Considerable interference with the subject's daily activities.

Relationship/Relatedness

The causal relationship between an adverse event and the trial product is assessed by the investigator using the following definitions:

Related: No reasonable support to believe that the event was caused by something other than the study drug.

Probably Related: There is good reason to assume a causal relationship.

Unlikely Related: A causal relationship is doubtful but cannot be fully dismissed.

Not related: The Investigator cannot suggest any reasonable relationship between the event and the study drug.

Outcome

The outcome of an adverse event is assessed by the investigator using the following definitions:

Recovered: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the subject's study baseline.

Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial.

Ongoing: The subject's condition has not improved and the symptoms are unchanged.

Fatal: The event resulted in death.

Unknown: The subject's condition is unknown. This term should only be used when no other definition is possible e.g., the subject is lost to follow-up.

11.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an adverse event must be collected and reported from the first trial-related activity after the subject signs the informed consent and until last subject contact/visit/end of post-treatment follow-up period.

At each contact with the trial center, the subject must be asked about adverse events in an objective manner like: "Have you experienced any problems since the last contact?"

Adverse events according to the definition, either observed by the investigator or reported by the subject, must be recorded by the investigator and evaluated. Adverse events must be recorded in the case report forms. For serious adverse events, the SAE form must also be filled in.

The investigator should record the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual adverse events.

Serious Adverse Events

The investigator must report initial information on all serious adverse events within 24 hours of obtaining knowledge of the event.

Furthermore, the investigator must complete and transmit, as applicable, the adverse event and SAE forms within five days of obtaining knowledge of the SAE. The monitor must be informed accordingly.

The Investigator will inform the health authorities and IRBs in accordance with local requirements in force and the International Conference on Harmonization (ICH) guidelines for GCP and the European Union (EU) Directive 2001/20/EC / Food and Drug Administration (FDA) Title 21 Code of Federal Regulations, Part 312.32 (5).

Adverse Events Starting after Trial Completion

Adverse events occurring after trial completion, which the investigator considers to be related to the investigational medicinal product must be reported to the sponsor.

11.3 Follow-up of Adverse Events

Follow-up of Non-Serious Adverse Events

All adverse events classified as non-serious adverse events that are both severe and related or probably related to the investigational medicinal product should be followed until the event has recovered or, in cases where recovery is not expected, until the event is stabilized and well defined and understood by the investigator.

Follow-up of Serious Adverse Events

All serious adverse events should be followed until resolved, or until stabilized and understood or a non-IMP reason is determined to be the most probable cause.

12 STATISTICAL METHODS AND DATA ANALYSIS

12.1 Sample Size Determination

The clinical goal of replacing stable oral dosing of atorvastatin with temporary intravenous or subcutaneous 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 intravenous or subcutaneous 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.

12.2 Subject Population(s) for Analysis

The safety population consists of all subjects who were enrolled and received at least a partial dose of IMP; no treated subjects will be excluded from the safety analysis population.

For the efficacy analyses, subjects will be stratified by their lead-in dose of oral atorvastatin. Defined by each of the three lead-in cohorts (10, 20, and 40 mg oral atorvastatin), the completed groups of thirteen subjects that 1) finish the two-week treatment period with intravenous atorvastatin, 2) provide a Day 15 LDL-C level, and 3) took the final targeted dose for that cohort comprise the three intravenous efficacy populations.

With the activation of Protocol Amendment 3, dated 04Sep2019, one additional efficacy population is defined. Ten subjects that qualify for treatment following a lead-in period taking 20 mg oral atorvastatin are assigned to a daily dose of subcutaneous atorvastatin for the 15-day treatment phase. Efficacy and pharmacokinetic outputs are calculated individually for this population.

12.3 Statistical Methods

To assess efficacy endpoints related to changes in cholesterol, the expected biological variabilities of LDL-C (9%) and HDL-C (7%) in a standard population (Marcovina 1994) were factored into the statistical calculations. Additional data are available in the literature to understand the rate of cholesterol changes when statin dosing is inadequate. A population that discontinued their stable dosing of statins showed significant elevations of LDL-C after 5 days (Fadini 2015). A dosing duration of 15 days was chosen to allow adequate time to detect changes in LDL-C resulting from inadequate intravenous dosing.

In the evaluation of all pharmacokinetics except for the single-dose subcutaneous PK of the sub-study, levels of atorvastatin and 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 imputation will relieve subjects from making an extra clinic visit.

12.3.1 General Considerations

Data collected in this study will be presented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically n (number of subjects), mean, median, standard deviation (SD), minimum and maximum. Categorical variables will be summarized by frequencies and percentages.

Statistical calculations will be done using SAS software (Version 9.3 or higher, SAS Institute, Cary, North Carolina, USA).

Baseline is considered the last assessment prior to the date and time of first dose of study drug.

Change from Baseline is defined as: post baseline assessment value – baseline assessment value.

12.3.2 Efficacy Analyses

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

- 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 subjects and summarized. A dosing cohort will be considered successful if eleven or more subjects have a Day 15 HDL-C not less than 75% of their baseline HDL-C and if eleven or more subjects have a Day 15 LDL-C not more than 125% of their baseline LDL-C.

12.3.3 Pharmacokinetics

Plasma concentrations will be listed at each time point by subject, and summarized by treatment at each time point using descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum and maximum values). PK calculations will be performed based on actual time of blood sample collection, using non-compartmental methods with WinNonlin Version 6.3.1 or higher (Certara Corporation, Princeton, New Jersey, USA). PK parameters will be listed by subject and summarized by cohort. In addition to the descriptive statistics listed above, geometric means will be reported for the PK parameters.

All plasma concentrations below the lower limit of quantitation (BLOQ) for the assay that occur prior to the first or after the last quantifiable timepoint will be treated as “0” in the PK analyses and summary statistics. Plasma concentrations that are BLOQ but occur between quantifiable timepoints will be set to missing.

The PK endpoints will be listed and summarized for each dosing route and cohort. The arithmetic means, geometric means, medians, minimums and maximums, CV% will be displayed.

Plots of mean concentration levels and individual subject concentrations versus time will also be prepared.

12.3.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects using descriptive statistics. The current medical condition and/or other significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1, or higher. Conditions will be listed, including reported term, System Organ Class (SOC) and Preferred Term (PT).

12.3.5 Prior/Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced Dictionary (September 2014 or later). 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 subject including Anatomical Therapeutic Class (ATC) classification, preferred term and reported term; the start and end dates (or ongoing status). Medications taken by subjects from 15 days prior to Screening until the end of treatment will be included in the listing.

12.3.6 Safety Analyses

The safety and tolerability of Atorvastatin IV and SC will be assessed by the evaluation of treatment-emergent adverse events (TEAEs), study discontinuation information, laboratory test results, vital signs and physical examination findings.

Safety variables will be tabulated and presented for all subjects in the Safety Population. Data will be summarized by route and cohort. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for preferred term and system organ class, and will be listed by subject. Treatment-emergent AEs (TEAEs) will be summarized by treatment, where treatment-emergent is defined as any event with a start date on or after the date and time of the first dose date and time of study drug. All TEAEs will be summarized by relationship to study drug and by intensity.

Deaths, SAEs, and AEs resulting in study discontinuation will be listed.

12.4 Interim Analysis

No interim analyses are planned.

13 STUDY MANAGEMENT AND DATA COLLECTION

13.1 Confidentiality

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on CRFs and other study documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the subject (e.g., the

signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

13.2 Source Documents

Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. The Monitor, representatives of the Sponsor and the applicable regulatory authority will be allowed access to source documentation.

13.3 Case Report Forms

CRF forms will be available for data entry by the site through Medrio, a web-based, electronic data entry and reporting platform. Cases will be monitored remotely and on-site by the sponsor according to a written Monitoring Plan and data will be retrieved by the monitor for data analysis by the sponsor.

13.4 Records Retention

According to 21CFR312.62, all CRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of two years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted.

14 STUDY MONITORING, AUDITING, AND INSPECTING

14.1 Study Monitoring Plan

The investigator will permit study-related monitoring, audits and inspections by the IRB, the Sponsor and any applicable regulatory authority.

The sponsor will adhere to a written Monitoring Plan in fulfilling the requirements of ICH/GCP guidelines and the CFR to monitor the execution of the study and the collection of data. In general, the progress of the study will be monitored by using the following methods:

- Periodic onsite visit(s) by the sponsor representative
- Telephone communications among the Investigator, Clinical Monitor and/or Medical Monitor, as needed
- Remote and on-site review by the sponsor representative of CRFs, clinical records and regulatory documents

15 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of ICH, GCP Guidelines, IRB regulations, any applicable government regulations and procedures. This protocol and any amendments will be submitted to a properly constituted IRB for approval of the study conduct.

15.1 Informed Consent

Written informed consent must be obtained from each subject (or the subject's legal guardian/representative) before performing any Screening/Baseline Period evaluations. The signed informed consent document will be retained by the Investigator, and a signed copy will be given to the subject or subject's legal guardian/representative. The informed consent document, which is prepared by the sponsor, must have been reviewed and approved by the Sponsor and the Investigator's IRB before the initiation of the study. The document must contain the 20 elements of informed consent described in 21CFR50.25 and ICH E6 4.8. In addition, subjects of appropriate intellectual maturity should provide written informed assent, as determined by the institution's IRB or local legal requirement.

15.2 Protocol Compliance

Investigators must follow the IRB-approved protocol. If the Investigator intends to deviate from the protocol, the IRB and Sponsor should be informed prior to the deviation.

In cases where the Investigator decides to deviate from the protocol in order to avoid an apparent immediate risk to a specific subject, the Investigator may proceed with emergency and appropriate treatment at his discretion and the IRB and Sponsor will be notified as soon as possible afterward. In addition, the Investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by the Sponsor. A protocol amendment must receive IRB approval before implementation.

In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be approved by the Sponsor, Study Monitor, and the IRB prior to its use in consenting potential subjects.

15.3 Financial Disclosure

Each clinical site investigator will provide the Sponsor with sufficient, accurate financial information in accordance with local and federal regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory health authorities. Investigators are responsible for providing information on financial interest during the study and for one year after completion of the study in accordance with FDA policy (Title 21 CFR – PART 54 FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS Revised as of April 1, 2015).

15.4 Study Files

Documentation verifying the Investigator's legal and regulatory authority and acceptable scientific background to conduct the trial will be available at both the site and the sponsor before shipments of IMP are sent to the investigative center.

Following study initiation, the Investigator will maintain adequate records to re-create and justify the complete conduct of the trial at a later date. Document inventory will adhere to ICH/GCP and CFR requirements and will include those pertaining to the Investigator's qualifications, inventory and handling details of investigational products, and detailed medical and study histories for all subjects.

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