CSC01: High Intensity Lipid Lowering for Coronary Artery Disease Prevention for Persons Living with Human Immunodeficiency Virus (HILLCLIMBER)

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HILLCLIMBER
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CONTENTS

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ABBREVIATIONS

ACS	Acute coronary syndrome
AE	adverse event
ALT	alanine aminotransferase
ART	Antiretroviral Therapy
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CHD	Coronary Heart Disease
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CRF	case report form
CRP	C-reactive protein
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HDL-c	High-density lipoprotine cholesterol
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LDL-C	Low-density lipoprotein cholesterol
LFTs	Liver Function Tests
Lp-PLA2	Lipoprotein-associated phospholipase A2
LVEF	Left Ventricular Ejection Fraction
mEq	Milliequivalents
MI	Myocardial Infarction
PAI-1	Plasminogen Activator Inhibitor-1
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PT	Prothrombin time
SAE	serious adverse experience
TSH	Thyroid-stimulating hormone

SCHEMA

DESIGN

HILLCLIMBER is a randomized, controlled, open-label phase II trial of moderate dose statin therapy versus high-dose statin therapy in HIV-infected persons taking antiretroviral therapy (ART) who have coronary heart disease (CHD) or are at high risk for atherosclerotic cardiovascular disease. All subjects will have an initial two-week run-in period with pravastatin 40mg daily. Subjects not demonstrating significant toxicity at week 2 will then be randomized to rosuvastatin 20mg versus continuing pravastatin 40mg daily. At week 6; those in the rosuvastatin arm who do not demonstrate significant clinical or laboratory safety/toxicity issues will then have doses increased to rosuvastatin 40mg (high intensity dose group). The group randomized to pravastatin 40mg daily at week 2 will not have their dose increased at the end of week 6 (moderate intensity group).

- The primary endpoint is percent change in low-density lipoprotein cholesterol (LDL-c) from Week 2 to 14 of high versus moderate intensity lipid-lowering statin therapy

DURATION — Total duration of the study is 14 weeks: 2 weeks for the initial run-in, 12 weeks on therapy as per randomization (weeks 6-14 with possible dose increase).

SAMPLE SIZE — 40 subjects

POPULATION — HIV-infected subjects not already on high dose statin therapy who have coronary heart disease (CHD) or are at high risk for atherosclerotic cardiovascular disease (ASCVD, which includes myocardial infarction and stroke) as evidenced by 10-year ASCVD risk of 15.0% or greater.

REGIMEN — The following treatment regimens will be used:

Stage One (Run-in): Pravastatin 40mg daily (Weeks 0-2),

Stage Two (Randomization in 1:1 ratio):

- Moderate intensity group: Pravastatin 40mg daily (Weeks 2-14)

OR

- High intensity group: Rosuvastatin 20mg daily (Weeks 2-6), titrated to Rosuvastatin 40mg daily (Weeks 6-14).

1.0 STUDY OBJECTIVES

1.1 Primary Objectives

- To evaluate the lipid-lowering efficacy, as measured by percent change in low-density lipoprotein cholesterol (LDL-c) from Week 2 to 14 of high versus moderate intensity lipid-lowering statin therapy in HIV-infected persons taking antiretroviral therapy (ART)

who have coronary heart disease (CHD) or are at high risk for atherosclerotic cardiovascular disease (ASCVD).

1.2 Secondary Objectives

To determine mean changes from week 2 to week 14 for patients randomized to high versus moderate intensity statins in the following:

- Lipid parameters (HDL-c, triglycerides, and total cholesterol)
- Inflammatory biomarkers (soluble CD163, ST2, high sensitivity troponin I, and high-sensitivity C-reactive protein)
- Immunologic markers (T cell reactivity) and viral reservoir persistence

To evaluate safety, as measured by treatment-emergent clinical and laboratory adverse events, of high versus moderate intensity statin therapy in HIV-infected persons taking ART who have coronary heart disease (CHD) or are at high risk for ASCVD.

2.0 Background

This study is a phase II investigation of the efficacy of high intensity versus moderate intensity lipid lowering statin therapy for HIV-infected persons with coronary heart disease (CHD) and/or high risk for atherosclerotic cardiovascular disease (ASCVD) not already on high intensity lipid lowering therapy. This is a pilot study for potential future studies that would be adequately powered to evaluate the safety – in addition to efficacy – of high-intensity versus moderate-intensity statin regimens for HIV-infected persons with CHD and/or high risk for ASCVD. The study drugs (rosuvastatin and pravastatin) are approved and in regular clinical use, but rosuvastatin is being repurposed in this study for a new population in which there are no data for the higher intensity therapy under study.

2.1 Rationale

Over the past two decades, antiretroviral therapy (ART) has dramatically improved longevity among persons living with human immunodeficiency virus (HIV), who are increasingly at risk for non-communicable comorbidities such as cardiovascular disease (CVD). (1-5) Compared with uninfected persons, persons living with HIV are at 50% or greater risk for myocardial infarction (MI), even after adjustment for CVD risk factors, and over fourfold greater risk for sudden cardiac death. (6-13) Standard care for persons with coronary heart disease (CHD), which includes previous acute coronary syndromes (ACS) and MI, in the general population includes intensive lipid lowering with high dose statin therapy, such as rosuvastatin 20-40mg daily or atorvastatin 40-80mg daily, due to high-quality clinical trial data demonstrating significant net clinical benefits of intensive lipid lowering with high dose statins compared with less intensive lipid lowering with lower dose statins. (14-16) The importance of intensive lipid lowering following coronary events has been re-affirmed by a recent trial in which patients hospitalized for ACS randomized to a statin plus ezetimibe versus a statin alone achieved lower LDL-c levels (median LDL-c 53.7 mg/dl versus 69.5 mg/dl) and experienced improved cardiovascular outcomes without excess adverse events. (17) Furthermore, the most recent American College of Cardiology (ACC)/American Heart Association (AHA) evidence-based guidelines recommend that persons with predicted 10-year ASCVD risks of 7.5% or greater be prescribed moderate-to-high-intensity statins; the absolute net benefit of intensifying statin

therapy becomes even greater and thus favors high intensity statin therapy at higher ASCVD risk levels. (18)

Despite these convincing data in the general population, it remains unknown whether intensive lipid lowering with high dose statins for HIV-infected persons with known CHD and/or high risk for ASCVD confers clinical benefit. Trials of lipid-lowering therapy among persons living with HIV on ART have generally tested lower dose statins due to safety concerns related to theoretical and observed drug-drug interactions between ARTs, particularly protease inhibitors (PIs), and statins. Some of this is warranted; simvastatin is contraindicated with concomitant PI use and should generally be avoided in patients on ART, as simvastatin levels increase more than fivefold with concomitant PI use. (18) However, most other statins have proven safe and efficacious in numerous small trials of HIV-infected persons on ART, albeit at relatively low doses. (19) The most potent statin doses tested in these trials have generally been rosuvastatin 10mg daily or atorvastatin 10mg daily (20-24); a lone exception is a recent trial in which 19 HIV-infected persons were started on atorvastatin 20mg daily and titrated up to 40mg daily, which revealed similar safety profiles of atorvastatin 40mg daily and placebo. (25) No trials of any size have evaluated HIV-infected persons on ART taking atorvastatin 80mg daily or rosuvastatin 20-40mg daily, which are the standard of care for persons with CHD, particularly previous ACS, as well as persons with high ASCVD risk, in the general population.

In this study, we intend to evaluate high intensity rosuvastatin (20mg daily uptitrated to 40mg daily) rather than atorvastatin 80mg daily because rosuvastatin 40mg daily has somewhat greater LDL-lowering efficacy and fewer pharmacological interactions with common HIV medications, particularly protease inhibitors. Rosuvastatin is not lipophilic, absorbed rapidly, and minimally (<10%) metabolized by the CYP450 system, resulting in negligible pharmacokinetic interactions with protease inhibitors or other CYP450-metabolized medications; meanwhile, atorvastatin is more lipophilic and metabolized extensively by the CYP450 system, resulting in potential toxicity due to accumulation in the setting of co-administration with protease inhibitors and other CYP450-metabolized medications. (26) Thus, although rosuvastatin and atorvastatin both appear to be safe based on limited data in HIV-infected persons taking ART, we anticipated that the safety margin would be greater for high-dose rosuvastatin compared with atorvastatin in this population. This a randomized, controlled, open-label Phase II study of a known approved drug re-purposed for a unique population.

Full prescribing information for rosuvastatin, which is an approved drug with tablets of doses 5mg, 10mg, 20mg, and 40mg, may be found at: http://www1.astrazeneca-us.com/pi/crestor.pdf. Full information for pravastatin, which is an approved drug with tablets of doses 10mg, 20mg, 40mg, and 80mg, may be found at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019898s062lbl.pdf.

3.0 STUDY DESIGN

This is a single center, randomized, controlled, open-label phase II trial. Up to 40 subjects not already on high dose statin therapy who have documented CHD and/or calculated 10-year ASCVD risk >15% will be included and started on moderate dose statin therapy (pravastatin 40mg daily) for an initial two-week run-in period. Subjects not demonstrating significant toxicity at week 2 will then be randomized to rosuvastatin 20mg versus continuing pravastatin 40mg daily. Subjects will return at week 6; those in the rosuvastatin arm who do not demonstrate significant safety or toxicity concerns will then have doses increased to rosuvastatin 40mg (high dose group). The group randomized to pravastatin 40mg daily at week 2 will not have their dose increased at the end of week 6.

The following treatment regimens will be used:

Stage One (Run-in): Pravastatin 40mg daily (Weeks 0-2),

Stage Two (Randomization in 1:1 ratio):

- Moderate intensity group: Pravastatin 40mg daily (Weeks 2-14)

OR

- High intensity group: Rosuvastatin 20mg daily (Weeks 2-6), potentially titrated to Rosuvastatin 40mg daily (Weeks 6-14).

Total duration of the study is 14 weeks: 2 weeks for the initial run-in, 6 weeks following randomization, and 6 weeks following dose increase.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by: any licensed rapid HIV test or HIV enzyme or chemoiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load. OR HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating >1000 RNA copies/mL

4.1.2. HIV RNA below the lower limit of assay detection within 12 months of study entry

NOTE: one detectable HIV RNA (<400 copies/ml) is allowed.

4.1.3 (1) Documented coronary heart disease (CHD): nonfatal MI, unrecognized MI, unstable angina pectoris, and/or stable angina pectoris, as defined by the American Heart Association Case Definitions for Acute Coronary Heart Disease in Epidemiology and Clinical Research Studies (Luepker R et al., Circulation 2003. 108(20):2543-9. URL: http://circ.ahajournals.org/content/108/20/2543).

Or (2) Documented 10-year ASCVD risk of 15% or greater based on the ACC/AHA ASCVD Risk Estimator (http://tools.acc.org/ASCVD-Risk-estimator/).

4.1.4 Negative serum or urine pregnancy test within 48 hours of study entry for women with reproductive potential (defined as women who have not been postmenopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone surgical sterilization [e.g., hysterectomy, bilateral oophorectomy, or salpingectomy]) .The urine test must have a sensitivity of ≤50 mIU/mL.

4.1.5 If participating in sexual activity that could lead to pregnancy, female subjects with reproductive potential must use one form of contraceptive as listed below while receiving protocol-specified medications. At least one of the following methods MUST be used appropriately:

- Condoms (male or female) with or without a spermicidal agent. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission.
- Diaphragm or cervical cap with spermicide

- IUD (intrauterine device)
- Hormone-based contraceptive. Subject-reported history is acceptable documentation of sterilization, other contraception methods, menopause, and reproductive potential.

4.1.6 Men and women age 18 to 75 years of age

4.1.7 Ability and willingness of subject to provide informed consent

4.2. Exclusion Criteria

4.2.1 Serious illness or AIDS-related complication within 21 days of screening requiring systemic treatment and/or hospitalization until candidate either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least 7 days prior to study entry. Need for systemic therapy for malignancy currently or anticipated during the study period.

4.2.2 No coronary heart disease (CHD) and 10-year ASCVD risk <15.0%.

4.2.3 Not currently receiving antiretroviral therapy or taking any of the following antiretroviral agents: atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir.

4.2.4 Not currently receiving any of the following agents: cyclosporine or rifampin.

4.2.5 History of statin intolerance leading to discontinuation, dose decrease, or change to less potent dose equivalent

4.2.6 Statin absolute contraindication

4.2.7 Current use of atorvastatin 20mg daily or greater or rosuvastatin 10mg daily or greater

4.2.8 Chronic kidney disease stage 4 or greater (including dialysis)

4.2.9 Systolic heart failure with last documented LVEF <35%

4.2.10. Pregnant or breastfeeding

4.2.11. Laboratory values obtained within 45 days prior to study entry:

LDL-c <80 mg/dl while not on statin or LDL-c <60 mg/dl while on statin

ALT > 3 x Upper Limit of Normal (ULN)

AST > 3 x ULN

Creatinine kinase (CK) > 10 x ULN

Calculated creatinine clearance (CrCl) <50 mL/min, as estimated by the Cockcroft-Gault equation

4.2.12. Life expectancy <12 months

4.2.13. Prior organ transplant

4.2.14. Active malignancy

4.2.15. Inflammatory muscle disease

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, sites must have the protocol and the protocol consent form approved by their local institutional review board (IRB).

Once a candidate for study entry has been identified, details will be carefully discussed with the subject. The subject will be asked to read and sign the approved protocol consent form.

Candidates for study entry will be identified using an existing IRB-approved data repository of HIV-infected persons in the Northwestern Medicine Enterprise Data Warehouse (NMEDW). These candidates will be identified by querying this NMEDW data repository for any living HIV-infected persons aged 18 to 75 who have no HIV viral RNA values of 400 copies/ml or greater anytime in the previous 12 months from the time of screening and who have any diagnosis of coronary heart disease (CHD) based on any documented ICD-9-CM codes 410-414 and/or ICD-10-CM codes I21-I25. Candidates will also be identified by calculating the 10-year ASCVD risk of patients referred by primary care providers. Once these candidates are identified, participants will be excluded if they are noted to be prescribed atorvastatin 20mg daily or greater, rosuvastatin 10mg daily greater, atazanavir/ritonavir (at any dose), lopinavir/ritonavir (at any dose), simeprevir.(at any dose), or are not currently taking antiretroviral therapy. Of the remaining candidates, persons with an active primary care provider and/or infectious disease provider at Northwestern Medicine will be eligible to be contacted for enrollment via telephone. The order of contacting patients will be by those with the most recent new diagnoses of CHD first, with the plan to continue contacting patients (those with the earlier CHD diagnosis dates would be contacted later, then patients with no known CHD but with 10-year ASCVD risk of 15% or greater) until the target enrollment is achieved.

4.3.2 Randomization

Subjects who meet enrollment criteria will be randomized at Week 2 (the end of the pravastatin 40ml daily run-in period) in a 1:1 ratio according to the study treatment that has been randomly assigned to the Patient Number on the Randomization List held by the local site pharmacist.

Randomization will be stratified by type of ART: patients taking any booster (ritonavir or cobicistat) as part of their ART regimen and patients not taking a booster.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

After a 2-week pravastatin 40mg daily run-in period, subjects will be randomly assigned to rosuvastatin 20mg daily or pravastatin 40mg daily at week 2 in a 1:1 ratio. At week 6, subjects on the Rosuvastatin arm may have their dose escalated to 40mg daily.

Run-in: Pravastatin 40mg daily for 2 weeks (Weeks 0-2)

Randomization (1:1 ratio) at Week 2:

- Moderate intensity strategy: Pravastatin 40mg once daily for 12 weeks (Weeks 2-14)

  OR

- High-intensity strategy: Rosuvastatin 20mg once daily for 4 weeks (Weeks 2 to 6)
  - Continue Rosuvastatin 20 mg once daily (Weeks 6 to 14) if:
    - AST or ALT between 1.5x and 3x ULN

      OR
    - CK between 3x and 10x ULN

      OR
    - Grade 1 or 2 toxicity attributable to rosuvastatin is present
  - Escalation of Rosuvastatin to 40 mg daily (Weeks 6 to 14) if:
    - AST, ALT, and CK $\leq$ 1.5x ULN at week 6

      AND
    - CK ≤3x ULN at week 6

      AND
    - No grade 1 or greater toxicity attributable to rosuvastatin is present

5.1.1 Regimen

Subjects should begin study treatment within 72 hours after entry and continue on study treatment for 14 weeks.

Study drugs will be supplied in bottles for this open-label study. The pharmacist will dispense 2 weeks (15 tablets) of pravastatin 40 mg at week 0 to all participants. At week 2, subjects will be randomized to receive either 12 weeks (3 bottles, 90 tablets) of rosuvastatin 20 mg tablets or 12 weeks (85 tablets) of pravastatin 40 mg tablets.

Based on LFTs, CK, and safety/toxicity assessments at Week 6, participants in the rosuvastatin arm will be notified within 5 days whether or not they are to escalate to two 20mg tablets daily or continue taking one tablet daily. If the dose is escalated, participants will need to return to the pharmacy within the next 4 weeks to receive an additional supply of 30 tablets (1 bottle) of rosuvastatin 20mg.

At the Week 14 visit, subjects should return any remaining study-provided study products.

5.1.2 Administration

Pravastatin will be administered orally as one 40 mg tablet once daily with or without food.

Rosuvastatin will be administered orally as one or two (high-dose) 20 mg tablet(s) once daily with or without food.

5.2 Study Product Formulation and Preparation

5.2.1 Pravastatin sodium 40 mg tablets. Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°-86°F). Each bottle contains 100 tablets.

Rosuvastatin 20 mg tablets. Store at 25C (77F); excursions permitted to 15 to 30C (59 to 86F). Each bottle contains 30 tablets.

The study drug will be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). Subjects will be instructed to store the medication in original packaging at room temperature according to the instructions outlined on the Drug Administration Instructions.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply/Distribution

The drug products used will be rosuvastatin 20 mg oral tablets (AstraZeneca: London, UK) and pravastatin 40 mg oral tablets (Bristol-Meyers Squibb: New York, NY, USA).

These are approved drugs in regular clinical use at the doses proposed in this study and will be purchased through the Northwestern Memorial Hospital Investigational Pharmacy.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received. All unused study products must be returned to the site (or as otherwise directed by the sponsor) after the study is completed or terminated.

5.4 Concomitant Medications

Below are lists of selected concomitant medications. These lists are only current as of the date of this protocol. Therefore, whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, and Investigator's Brochures to obtain the most current information on drug interactions, contraindications, and precautions.

5.4.1 Required Medications:

All subjects should be maintained on the same antiretroviral medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

Standard therapy for HIV and care in the setting of CHD and/or high risk for ASCVD is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

5.4.2 Prohibited Medications

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Atazanavir/ritonavir
- Lopinavir/ritonavir (Kaletra)
- Cyclosporine
- Rifampin
- Simeprevir
- Cholestyramine / aspartame
- Cholestyramine / sucrose
- Colesevelam
- Colestipol
- Prevalite
- Questran
- Questran Light
- Welchol
- Colestid
- Ezetimibe
- Zetia
- Liptruzet
- Vytorin
- Fenofibrate
- Fenofibric acid
- Gemfibrozil
- Antara
- Lipofen
- Lofibra
- Tricor
- Fenoglide
- Triglide
- Trilipix
- Fibricor
- Lopid
- Icosapent ethyl
- Lomitapide
- Mipomersen
- Vascepa
- Juxtapid
- Kynamro
- Niacin
- Niaspan
- Simcor
- Niacinamide
- Simvastatin

- Fluvastatin
- Lovastatin
- Cerivastatin
- Atorvastatin
- Pitavastatin
- Advicor
- Altocor
- Altoprev
- Atorlip
- Baycol
- Caduet
- Canef
- Inegy
- Lescol
- Lipex
- Lipitor
- Lipobay
- Lipostat
- Lipvas
- Mevacor
- Pitava
- Selektine
- Simcard
- Simcor
- Simlup
- Sortis
- Torvacard
- Torvast
- Totalip
- Tulip
- Vytorin
- Zocor

5.4.3 Precautionary Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures to obtain the most current information on drug interactions, contraindications, and precautions.

5.5 Adherence Assessment

Adherence to all study drugs will be monitored by self-report.

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

	SCREEN-ING	WEEK 0[a]	WEEK 2[a]	WEEK 6[a]	WEEK 10	Week 14/ or discontinuation
Informed Consent	**X**	**X**				
Medical and Medication History (including cardiovascular risk; HIV RNA and CD4, lipids)	**X**					
Complete Physical Exam	**X**					
Targeted Physical Exam		**X**	**X**	**X**	**X**	**X**
Height , Weight	**X**				**X**	
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**
Chemistry Panel, Liver Function Tests	**X**	**X**	**X**	**X**	**X**	**X**
Creatine Kinase	**X**	**X**	**X**	**X**	**X**	**X**
Fasting Lipid Panel	**X**	**X**	**X**	**X**	**X**	**X**
Pregnancy Test	**X**	**X**				**X**
Hematology, Hemoglobin A1c		**X**				**X**
Stored Plasma/Serum/PBMCs		**X**	**X**			**X**
Pharmacokinetics/dynamics			**X**	**X**		**X**
Randomization			**X**			
Dispensing of Study Drug		**X**	**X**	**X**	**(X)***	
Adherence Assessment			**X**	**X**	**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**	**X**	X	**X**
AE Determination		**X**	**X**	**X**	X	**X**
Phone Call					(X)*	
Statin Intolerance Survey			**X**	**X**	X	**X**

*(X) if on escalated rosuvastatin dose (40mg daily)

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the subject starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 45 days prior to study entry, unless otherwise specified.

In addition to data being collected on subjects who enroll into the study, reason(s) for screening failures will be captured on a Screening Failure form and will not be entered directly in REDCap.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluation and be completed prior to the initiation of study medications.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations
Evaluations should occur +/- 2 days of the scheduled visit.

6.2.4 Discontinuation Evaluations

Evaluations for Registered Subjects Who Do Not Start Study Treatment
Subjects who do not begin study treatment should have screening and entry forms completed and entered in the database. Beyond the entry visit, no further evaluations are required. These subjects will be replaced.

Premature Treatment Discontinuation Evaluations
Subjects who discontinue the study medications before the end of the study (Week 14) should have the Premature Treatment Discontinuation evaluations done within 7 days after stopping study drugs. They will be encouraged to continue to attend all study visits and receive study evaluations as per section 6.1 through Week 14.

Premature Study Discontinuation Evaluations
All subjects who prematurely discontinue participation in the study should have the Premature Study Discontinuation evaluations done.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol must be present in the source documents.

All stated evaluations are to be recorded on the CRF and keyed into the REDCap database unless otherwise specified.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses within 30 days. In addition, the following diagnoses should be reported regardless of when the diagnosis was made:

- AIDS-defining conditions
- Coronary heart disease
  - Previous ACS, which includes myocardial infarction and unstable angina
  - Angina
- Cerebrovascular disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes

Any allergies to any medications and their formulations must also be documented.

Cardiovascular risk: An assessment of general cardiovascular risk factors, smoking, alcohol use, substance use, family history of premature CVD, hormonal history will be assessed at screen. ASCVD risk will be calculated using the ACC/AHA ASCVD Risk Estimator (http://tools.acc.org/ASCVD-Risk-estimator/).

6.3.3 Medication History

A medication history must be present in the history and recorded in the source documents:

Medication History Table

Medication Category	Complete History or Timeframe	Record in CRFs
Antiretroviral therapy	Start date of initial ART regimen, current ART regimen	Yes
Statin and other lipid-lowering therapy (prescription and non-prescription)	Complete history	Yes
Prescription drugs	Within 30 days prior to entry	Yes
Non-prescription drugs	Within 30 days prior to entry	No
Complementary and alternative medicines	Within 30 days prior to entry	No

6.3.4 Clinical Assessments

Complete Physical Exam
A complete physical examination performed at any time between screening and the entry evaluation is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include signs

and symptoms, diagnoses, height, weight, and vital signs (temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam
A targeted physical examination is to be performed after screening and will be driven by any previously identified or new signs or symptoms including diagnoses that the subject has experienced since the last visit. This examination includes vital signs (temperature, pulse, respiration rate, and blood pressure).

Signs and Symptoms
At entry, record on the CRFs all signs/symptoms occurring within 30 days prior to entry.

After entry, record all Grade ≥1 signs/symptoms, any signs/symptoms regardless of grade that lead to a change in treatment, or that meet EAE, SAE, or ICH guidelines.

Diagnoses
At screening, record diagnoses in the medical history per section 6.3.2. At study entry and thereafter, record all new diagnoses since the last study visit identified by the ACTG criteria for clinical events and other diseases.

Concomitant Medications
Record any prescription medications taken since the last study visit, including actual or estimated start dates and stop dates in the CRF. Current non-prescription, alternative and traditional medications are recorded in the source documents and CRFs.

Study Treatment
Record all study treatment modifications, including initial doses, subject-initiated and/or protocol-mandated modifications, and inadvertent and deliberate interruptions of more than 1 day since last visit. Record any permanent discontinuation of treatment.

6.3.5 Laboratory Evaluations

Sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, which can be found at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx**.**

Record all protocol-required laboratory values, regardless of grade, obtained at screening and entry on the CRFs.

After entry, record all laboratory values Grade ≥2. Record all lipid values (Total, HDL, and LDL cholesterol, triglycerides) regardless of grade on the CRF. All laboratory values that lead to a change in study treatment, and all serum creatinine and liver function tests (AST, ALT, alkaline phosphatase, total bilirubin) regardless of grade, must be recorded.

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), with differential, absolute neutrophil count (ANC), and platelet count.

Liver Function Tests
AST (SGOT), ALT (SGPT), alkaline phosphatase, total and direct bilirubin

Blood Chemistries
sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, total protein, and albumin.

Fasting Lipids
Total, HDL, and LDL cholesterol, triglycerides.
If triglycerides are >400 at screening and/or high enough that LDL can't be calculated, then come back for direct LDL. Subsequent LDL should be direct in those patients.

Subjects should be instructed to fast for 8 hours prior to this test. Fasting is defined as no food or drink, except for sips of water with medications. If the subject has not been fasting, the visit must be rescheduled. Record the non-fasting status on the CRF.

Pregnancy Test
All women with reproductive potential must have a negative serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test result at screening and within 48 hours prior to initiating protocol-specified medications and any time thereafter when pregnancy is suspected. (The urine test must have a sensitivity ≤50 mIU/mL).

6.3.6 Laboratory Results from Clinical Care

CD4 count and HIV-1 RNA results will be obtained from routine clinical care and available in the EMR.

6.3. 7 Adherence Assessment

Adherence to all study medications will be assessed by self-report. Sites will provide adherence reinforcement, according to local standard practice throughout the study. Subjects with poor adherence will be provided counseling by the site.

6.3.8 Storage of PBMCs, Plasma and Serum for l future studies

Virologic and Immunologic Studies:

40 mL of blood will be collected in EDTA tubes. Peripheral blood mononuclear cells (viable PBMCs) and plasma will be processed or stored for possible later analyses of cell-associated HIV RNA and DNA and T cell subsets, soluble and cellular markers of immune activation.

5 mL of blood will be collected in SST tubes and 3 mL in sodium citrate tubes and stored for later analyses of inflammatory biomarkers.

Pharmacology:

5 mL of blood for determination of plasma concentrations of pravastatin and rosuvastatin will be collected approximately 12 hours after dosing at weeks 2, 6, and 14. Participants will be instructed to take their study medications in the evening, about 12 hours before their clinic visit. Time of last dose and blood draw will be collected.

The samples will be processed and cryopreserved at the study repository at the Lurie Special Infectious Diseases (SID) Laboratory

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity Management

Criteria for subject management, dose interruptions, modifications, and discontinuation of study treatment will be mandated only for toxicities attributable to study-provided drugs (pravastatin and rosuvastatin).

The grading system for drug toxicities is the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, located at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

The lone difference between the grading system for drug toxicities used in this trial and the DAIDS Table is that our protocol has a lower threshold for grading transaminase (AST and ALT) elevations; based on the current ACC/AHA and National Lipid Association Guidelines, we consider elevation of AST or ALT ≥3x ULN as grounds for holding the study drug (and a grade 3 adverse event in this protocol), and CK ≥10x ULN as a grade 3 adverse event and grounds for holding the study drug.

NOTE: The HILLCLIMBER protocol chair must be notified by e-mail regarding toxicities that result in regimen interruption or discontinuation. Email: matthewjfeinstein@northwestern.edu. General guidelines presented in sections 7.1.1 to 7.1.3 apply to toxicities that are not specifically discussed further below.

7.1 Toxicity Management

7.1.1 General Reactions

Grade 1 or 2
Subjects who develop a Grade 1 or 2 toxicity may continue study treatment.

Grade 3
Subjects who develop a Grade 3 toxicity that is judged by the site investigator to be study drug-related should have the study drug held and the study team should be consulted. The subject should be followed closely and if the toxicity does not return to Grade ≤2 within 2 weeks, the study drug must be permanently discontinued with subject evaluations as per section 6.2.4.

If the study drug is resumed and the same Grade 3 toxicity recurs within 4 weeks of reintroduction, and the site investigator considers this AE related to the study drug, the drug must be permanently discontinued.

With a Grade 3 toxicity that is judged not related to the study drug by the site investigator, the study drug may be continued at the discretion of the site investigator in consultation with the study team.

Grade 4
Subjects who develop a Grade 4 toxicity will have the study drug permanently discontinued, with clinical assessments and laboratory testing as described for Grade 3 toxicity. If the investigator feels that the toxicity is clearly related to another cause and that the toxicity is not caused by the study drug, and after consultation with the study team, dosing may continue when the toxicity has resolved to Grade 2 or less.

Subjects experiencing Grade 4 toxicities should be followed closely with additional clinical assessments and laboratory testing as clinically indicated in consultation with the study team.

NOTE: Direct and indirect bilirubin elevations that reach Grade 4 elevations according to the DAIDS toxicity schema and are related to atazanavir are excluded from reporting.

7.1.2 ALT and AST elevations

ALT and AST levels will be routinely evaluated at screening, week 0, 2, 6, 10, and 14 visits. All other evaluations of ALT and AST will be performed at the discretion of the site investigator based on subject symptoms.

Grade 3
Subjects who develop *asymptomatic* >3 x ULN ALT or AST elevations (Grade 3), study drug should be held for 2 weeks and the individual should be re-evaluated 3 week after drug discontinuation. If at that time the ALT or AST elevation is ≤3 x ULN and subjects remain asymptomatic, the subjects are eligible to continue on study treatment at the discretion of the site investigator. If the ALT and AST are not ≤3 x ULN within the 2 week period, the study drug must be permanently discontinued unless the ALT and AST elevations are deemed not related to study drug upon further assessment as per the discretion of the care provider (ie, acute hepatitis A or other clear causation).

For any *symptomatic* (eg, fatigue, nausea and vomiting, right upper quadrant pain, rash or eosinophilia) ALT or AST >3 x ULN (Grade 3), study drug should be held. Subjects should be asked to return to the research site for repeat testing 2 weeks later. If repeat ALT and AST is ≤3 x ULN and the subject is no longer symptomatic, study drug can be resumed.

Grade 4
For any ALT or AST >6 x ULN (Grade 4), the study drug should be discontinued. The subject should be brought back for repeat testing every 1 week until the ALT and AST ≤3 x ULN. Even if ALT and AST are ≤3 x ULN upon repeat testing for these patients, the study drug will not be restarted at that time.

NOTE: If the Grade 3 or 4 elevation is clearly related to another cause and not related to study drug (eg, acute hepatitis A infection), the subject should be brought back for repeat testing every 2 weeks for Grade 3 or every 1 week for Grade 4 until the ALT or AST ≤3 x ULN. The local site investigators should contact the study team for approval before resuming study drug. Subjects who permanently discontinue study drug will be followed on study, off treatment through the study termination visit with subject evaluations as per section 6.2.4.

NOTE: For those subjects with ALT or AST >3 x ULN upon repeat testing, whether symptomatic or not, INR should also be performed (in addition to bilirubin and alkaline phosphatase, which will be evaluated with ALT and AST routinely) as part of the study to help determine etiology of increased LFTs. Other labs including hepatitis serologies may also be indicated and performed in the context of clinical care by PCP.

NOTE: If the subject has recurrent elevations of ALT or AST >3 x ULN but the site investigator deems the elevation not related to study drug, the site investigator must contact the study team to discuss continuation of study drug.

Abnormal ALT or AST determinations occurring in the course of clinical care should be repeated by the treating clinician. Persistently abnormal values which would trigger the toxicity guidelines above should be reported to the protocol team. If the ALT or AST abnormality is not due to another cause, eg, acute hepatitis, follow the toxicity algorithm above.

7.1.3 Myalgias and Myopathy

Persons who present with significant myalgias (Grade ≥3, ie, muscle pain causing inability to perform usual social and functional activities) should be evaluated with a clinical assessment that includes an evaluation of CK, serum creatinine, potassium, and urinalysis. Myopathy is defined as muscle aches, soreness, tenderness, or weakness with creatinine kinase (CK) >10 x ULN not related to exercise or other causes, including trauma. If the symptoms are associated with Grade ≥3 elevation in CK (10 x ULN) (see table below) that is not related to exercise or other cause, study medications should be permanently discontinued. Subjects will be followed on study, off treatment through the study termination visit with subject evaluations as per section 6.2.4.

NOTE: Mitochondrial toxicity related to nucleoside therapy and not related to study medication is a possibility, and evaluations for lactic acidosis should be considered by the subject's primary care provider.

Serum CK Toxicity Grading*

Toxicity Grade	Value
Grade 1	3 – <6 x ULN
Grade 2	6 – <10 x ULN
Grade 3	10 – <20 x ULN
Grade 4	≥20 x ULN

* Not related to exercise or other cause

7.1.4 Rhabdomyolysis

Rhabdomyolysis is defined as the presence of myopathy as per section 7.1.3 plus one or more of the following:

- Hematuria on urine dipstick in the absence of microscopic hematuria (myoglobinuria)
- Grade ≥2 hyperkalemia
- Grade ≥2 creatinine elevation

If rhabdomyolysis occurs, study medications should be permanently discontinued. The team should be consulted. Subjects will be followed on study, off treatment through the study termination visit with subject evaluations as per section 6.2.4. In addition, CK will be added to the laboratory evaluations performed until it has declined to ≤1 x ULN.

7.2 Requirement for Precautionary or Prohibited Medications (see PSWP)

Subjects who need to initiate therapy with erythromycin, colchicine, cyclosporine, or rifampin should be asked to hold study drug. If use of one of these precautionary medications is anticipated to be short-term, the site investigator may consider restarting study drug after use of prohibited medication is discontinued.

Subjects who begin a statin medication provided through clinical care should discontinue study drug. Taking two statins can increase the risk of toxicity.

Subjects who temporarily or permanently discontinue study treatment will be followed on study, off treatment through the study termination visit with subject evaluations as per section 6.2.4.

7.3 Pregnancy

If the pregnancy test is positive at entry, then the subject should not start study treatment. No further evaluations are necessary, provided that the subject did not initiate study drug.

Subjects who become pregnant after study entry must discontinue study treatment immediately. These subjects should be seen for a premature treatment discontinuation evaluation within 7 days. The core team must be notified of any pregnancies that occur in subjects on study.

All pregnancies should be followed until the final outcome can be determined. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052 (Non-US sites: Fax: 44-1628-789-666 or 910-246-0637; phone: 910-679-1598.)

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Study Treatment Discontinuation

- Drug-related toxicity requiring permanent study treatment discontinuation (see section 7.0)
- Requirement for prohibited concomitant medications (see section 5.4)
- Pregnancy
- Breast-feeding
- Completion of treatment as defined in the protocol
- Request by subject to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol
- Failure by the subject to attend 2 consecutive clinic visits

8.2 Premature Study Discontinuation

- Request by the subject to withdraw
- Request of the primary care provider or investigator if s/he thinks the study is no longer in the best interest of the subject
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the IRB, FDA, IND sponsor, or pharmaceutical supporters

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

HILLCLIMBER is a randomized, controlled, open-label phase II trial. 40 subjects not already on high dose statin therapy who have CHD and/or calculated 10-year ASCVD risk >15% will be included and started on moderate dose statin therapy (pravastatin 40mg daily) for an initial two-week run-in period. Subjects not demonstrating significant toxicity at week 2 will then be randomized to high intensity statin therapy (rosuvastatin 20mg) versus continuing moderate intensity statin therapy (pravastatin 40mg daily). At week 6, subjects in the rosuvastatin arm who do not demonstrate significant toxicity and whose LDL-c is >60mg/dl and decreased by less than 25% compared with week 2 will then have doses increased to rosuvastatin 40mg (high dose group). Efficacy and safety will be evaluated at Week 14.

9.2 Endpoints

9.2.1 Primary Endpoints:

Efficacy: The primary efficacy endpoint is mean percent change in fasting LDL-c (mg/dl) from week 2 (end of run-in period) to week 14

- The mean percent change in fasting LDL-c from week 2 to week 14 will be compared for the high dose group (rosuvastatin 20mg daily uptitrated to 40mg daily) and the moderate dose group (pravastatin 40mg daily).

Safety:

- All treatment-emergent adverse events, including but not limited to:
  - Incidence of adverse event-related study drug discontinuation (following initial 2 week wash-in) or hospitalizations
  - Grade 3 or greater adverse events;
  - Study drug-related symptoms
  - CK elevation > 3x upper limit of normal;
  - AST or ALT elevation >3x upper limit of normal;

9.2.2 Secondary Endpoints

Secondary endpoints include mean percent changes in the following from week 2 to week 14:

- Lipid parameters (HDL-c, triglycerides, and total cholesterol),
- Inflammatory biomarkers (soluble CD163, ST2, high sensitivity troponin I, high-sensitivity CRP, PAI-1, Lp-PLA2)
- Viral and immunologic markers derived from PBMCs (such as T cell reactivity and viral reservoir persistence).
- Statin drug levels >400% expected steady-state dose level
- Hemoglobin A1c level

An additional secondary endpoint will evaluate safety, as measured by treatment-

emergent clinical and laboratory adverse events, of high versus moderate intensity statin therapy in HIV-infected persons taking ART who have coronary heart disease (CHD) and/or 15% or greater risk for ASCVD.

9.3 Randomization and Stratification

Subjects who meet enrollment criteria will be randomized at Week 2 in a 1:1 ratio according to the study treatment that has been randomly assigned to the Patient Number on the Randomization List held by the local site pharmacist. Randomization will be stratified by: (1) type of ART: patients taking any booster (ritonavir or cobicistat) as part of their ART regimen and patients not taking a booster; and (2) known CHD or not.

9.4 Sample size and Accrual

The predicted percent reduction in LDL-c by rosuvastatin dose is as follows: 20mg (55-60%), and 40mg (60-63%). The predicted percent reduction in LDL-c by pravastatin 40mg is 30%. The expected difference in LDL-c for subjects receiving high (rosuvastatin 20-40mg daily) versus moderate (pravastatin 40mg daily) intensity statin doses in this study is therefore approximately 25-30% compared with moderate. In a landmark study of patients with CHD comparing high intensity statin (atorvastatin 80mg, which is similar in intensity of expected lipid lowering to rosuvastatin 20-40mg) versus pravastatin 40mg, mean LDL cholesterol levels during treatment were 62mg/dl and 95mg/dl for high intensity and pravastatin groups (with standard deviations of approximately 20mg/dl), respectively.

Given potentially lower baseline LDL cholesterol levels in this study (we expect mean LDL of participants will be approximately 105, including patients off statin therapy and those on low intensity therapy), realistic expected mean LDL cholesterol levels are 75mg/dl for the pravastatin group and 50mg/dl for the high-intensity/rosuvastatin group. These expected LDL cholesterol levels are similar to those seen in the high intensity versus lower intensity treatment groups in a more recent trial of lipid-lowering strategies in high-risk patients, in which there was no excess of adverse events in the higher-intensity group which achieved a mean LDL of 53.7mg. In order to have a power of 0.80 with a two-sided alpha of 0.05 to detect a 25mg/dl difference in LDL-c lowering with a standard deviation of LDL-c of 20, the desired sample size would be at least 11 cases and 11 controls. Given the potential for study drug discontinuation in an expected 8 or fewer patients (based on on-treatment symptoms being present in 5-20% of patients on statins), the goal subject enrollment for this study is 30 with a possible enrollment of up to 50 participants in order to ensure adequate power.

9.5 Monitoring

When approximately 50% of patients have completed the study through week 6, an interim analysis for safety will be conducted by an independent data monitoring committee. Patients with levels of CK, AST, ALT at weeks 2, 6, or 10 that are 3 times the upper limit of normal or greater will have the study drug discontinued at that time. If >25% of study enrollees are required to have the study drug discontinued at the interim analysis, the trial will be stopped. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study. If a study patient has CK, AST, or ALT levels of 3 times the upper limit of normal or greater any time prior to the interim safety analysis, the study coordinator will alert the medical safety officer (Kunal N. Karmali, MD), who will contact the patient and instruct the patient to immediately discontinue the study drug. Such patients who discontinue the study drug at the

medical safety officer's request will continue to be followed in the study and included in intention-to-treat analyses.

9.6 Analyses

9.6.1 Primary Anaysis

Lipid measurements from week 2 and week 14 will be used for analyses of the primary endpoints. We will use intention-to-treat analyses for evaluation of the primary endpoint and logistic regressions to compare percent change in LDL-c from week 2 to week 14 for the high-intensity statin group versus the lower intensity statin group.

The primary analysis will evaluate percent changes in LDL-c at week 14 compared with week 2 (following wash-in with pravastatin 40mg daily) for patients randomized to a high intensity versus lower intensity strategy. Two-sample t-tests will be performed using STATA version 14 (Stata Statistical Software: Release 14; College Station, TX: StataCorp LP).

9.6.2 Secondary Analyses

Safety and tolerability data will be summarized by treatment group.

Adverse events (signs, symptoms, and diagnoses) will be analyzed and reported using the AIDS Clinical Trials Group (ACTG) medical dictionary and standardized coding for Signs, Symptoms, and Diagnoses for Clinical and Adverse Events. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

Incidence of clinical and/or laboratory toxicities. The safety and tolerability measures will include:

- Time to discontinuation of any study medication due to adverse events (AEs), -- Proportion of Grade 3 or Grade 4 clinical AEs,
- Proportion of Grade 3 or Grade 4 laboratory abnormalities,
  Summaries of all treatment-related AEs

Possible future analyses

- Measures of the HIV reservoir size
- Soluble and cellular markers of immune activation and inflammation

10.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

10.1 Records to Be Kept

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by the Patient Number and Screening Number provided upon registration.

10.2 Role of Data Management

10.2.1 Instructions concerning the recording of study data on CRFs will be provided by the central data management team at Northwestern University. The Research Electronic Data Capture (REDCap) data management system will be used.

10.2.2 It is the responsibility of the data management team to assure the quality of computerized data for the study. This role extends from protocol development to generation of the final study databases. The REDCap data management system will be used for data entry, data queries, and data reports.

10.3 Clinical Site Monitoring and Record Availability

10.3.1 Site monitors will review the individual subject records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies, and to review product storage and management.

10.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the OHRP, and the pharmaceutical supporter(s) or designee for confirmation of the study data.

10.4 Expedited Adverse Event Reporting

The adverse events (AEs) that must be reported in an expedited fashion to the IND Sponsor (Dr. Donald Lloyd-Jones at Northwestern University) are all serious adverse events (SAEs) as defined by International Conference on Harmonization (ICH) guidelines regardless of relationship to the study agent(s). The protocol for reporting AEs will be as follows:

- We will report any unexpected fatal or life-threatening suspected adverse reactions to the Division of Metabolism and Endocrinology Products no later than 7 calendar days after initial receipt of the information [21 CFR 312.31(c)(2)].
- We will submit 7-day reports by rapid means of communication (facsimile or email) and will address each submission to the Regulatory Product Manager and/or to the Chief, Project Management Staff;
- We will report any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the Division of Metabolism and Endocrinology Products and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting.

SAEs as defined by ICH guidelines are: deaths, life-threatening events, events that require hospitalization or prolongation of hospitalization, events that result in persistent or significant disability or incapacity, and congenital anomalies or birth defects. Important medical events as assessed by medical and scientific judgment may also be considered SAEs by the investigator and should be reported in an expedited fashion. Possible drug-induced liver injury is also considered an SAE in this study and requires expedited reporting.

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to the IND Sponsor are pravastatin and rosuvastatin.

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, must be used and is available at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Any SAE occurring during the study and up to 28 days post the last dose of study drug must

be documented on the Serious Adverse Events Form and faxed to the IND Sponsor, Dr. Donald Lloyd-Jones at 1-312-980-9588 within 24 hours of awareness. The IND Sponsor and the HILLCLIMBER Principle Investigator and Research Manager should be alerted about the faxed form by sending an email to matthewjfeinstein@northwestern.edu and baiba@northwestern.edu with the title: HILLCLIMBER SAE REPORT.

The FDA also requires sponsors to submit a written Safety Report of all serious and unexpected AEs. The study investigators in this study have the responsibility of promptly reporting all SAEs so that IND Sponsor can comply with these regulations. A non-blinded safety officer (Kunal N. Karmali, MD) will be available to review SAEs and determine the potential relation of the study drug to SAEs.

The protocol-defined expedited event reporting period for this protocol is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

After the end of the protocol-defined reporting period stated above, sites must report serious, unexpected, suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

11.0 HUMAN SUBJECTS

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix II) and any subsequent modifications will be reviewed and approved by each local IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject (or legal guardian or person with power of attorney for subjects who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject or legal guardian, and this fact will be documented in the subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All records will be kept locked. All REDCap entry will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the FDA, or the IND sponsor.

11.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the IND Sponsor, pharmaceutical supporters, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by Northwestern University policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical supporters prior to submission.

13.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the NIH.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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