Evolocumab treatment in patients with HIV and hypercholesterolemia/mixed dyslipidemia: BEIJERINCK study design and baseline characteristics

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Background People living with human immunodeficiency virus (PLHIV) are at higher risk of atherosclerotic cardiovascular disease (ASCVD) due to traditional and HIV- or antiretroviral treatment (ART)-related risk factors. The use of high-intensity statin therapy is often limited by comorbidities and drug–drug interactions with ART. Herein, we present the design and baseline characteristics of the BEIJERINCK study, which will assess the safety and efficacy of evolocumab in PLHIV and hypercholesterolemia/mixed dyslipidemia.

Methods Randomized, double-blind, placebo-controlled, multinational trial that investigates monthly subcutaneous evolocumab 420 mg versus placebo in PLHIV with hypercholesterolemia/mixed dyslipidemia who are treated with maximally-tolerated statin therapy. The primary outcome is the baseline to week 24 percent change in low density lipoprotein cholesterol (LDL-C). Secondary outcomes include achievement of LDL-C < 70 mg/dL and percent change in other plasma lipid and lipoprotein levels. Safety will also be examined.

Results This study enrolled and dosed 464 patients who had a mean age of 56.4 years and were mostly male (82.5%). Mean duration with HIV was 17.4 years, and, by design, HIV viral load at screening was ≤50 copies/mL. ASCVD was documented in 35.6% of patients. Mean LDL-C of enrolled patients at baseline was 133.3 mg/dL. Statin use was prevalent (79.3% overall) with 74.6% receiving moderate or high-intensity statins. In total, 20.7% of patients did not receive statins due to intolerance/contraindications.

Conclusions The BEIJERINCK study is the first clinical trial to examine the lipid-lowering efficacy and safety of a fully human PCSK9 monoclonal antibody inhibitor in a moderate/high cardiovascular risk population of PLHIV. (Am Heart J 2020;220:203-12.)

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Since the advent of potent antiretrovirals, human immunodeficiency virus (HIV) infection has become a chronic disease. People living with HIV (PLHIV), even those with an undetectable viral load, are at a higher risk for atherosclerotic cardiovascular disease (ASCVD) and its manifestations, including myocardial infarction, stroke, and lower extremity peripheral arterial disease, than uninfected individuals.[1-5] This excess risk is multifactorial including higher rates of traditional risk factors (smoking, hypertension, and dyslipidemia) and HIV-related risk factors (chronic inflammation, immune dysregulation, and metabolic abnormalities caused by antiretroviral drugs).[5-7] The higher risk of ASCVD events in PLHIV has led US cholesterol and European dyslipidemia guidelines to classify HIV as a risk-enhancing factor.[1-3] Thus, PLHIV are likely candidates for more intensive cholesterol lowering.

Statins are first-line therapy for lowering LDL-C; however, the use of high-intensity statins in PHLIV may be limited by comorbidities (impaired renal function, impaired liver function, or myopathy related to the use of first generation nucleoside reverse transcriptase inhibitors associated with mitochondrial toxicity), and drug–drug interactions (DDIs) with certain classes of antiretroviral therapy (ART).[8-10] Concomitant therapy with protease-inhibitors or cobicistat-containing ART increase blood concentrations of nearly all statins, thereby limiting dose escalation to limit statin-related toxicities.[10-12] In contrast, non-nucleoside reverse transcriptase inhibitors (NNRTIs) reduce blood concentrations of most statins, thereby reducing LDL-C efficacy.[10,13] As such, guideline-directed LDL-C lowering goals are often more challenging to achieve with statin monotherapy in PLHIV.[1,12] Thus, the combined use of a maximally-tolerated statin and non-statin cholesterol lowering therapy represents an opportunity for ASCVD risk reduction in PLHIV.

Evolocumab, a fully human monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9), diminishes LDL-receptor degradation, resulting in lower LDL-C levels among patients with primary hypercholesterolemia and mixed dyslipidemia.[14] Anti-PCSK9 therapy may be particularly effective in PLHIV due to elevated PCSK9 levels associated with chronic inflammation.[15]

Given the elevated ASCVD risk of PLHIV, the complex management of HIV-related dyslipidemia, and the associations of high PCSK9 levels with ASCVD, it is important to evaluate the effects of PCSK9 inhibition in this high-risk patient population. BEIJERINCK (NCT02833844, Evolocumab Effect on LDL-C Lowering in Subjects with Human Immunodeficiency Virus and Increased Cardiovascular Risk) is the first randomized, double blind, placebo-controlled trial to examine the use of a PCSK9 inhibitor (evolocumab) in patients with HIV who have elevated LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C). This study will explore the lipid-lowering efficacy and safety of 24 weeks of evolocumab, as compared with placebo, in PLHIV with hypercholesterolemia or mixed dyslipidemia who receive maximally tolerated statin therapy. In this report, we present the baseline characteristics of enrolled participants and study design of the BEIJERINCK trial.

Methods

BEIJERINCK is an ongoing multinational, randomized, placebo-controlled phase 3 trial designed to assess the lipid-lowering efficacy and safety of evolocumab in patients with HIV and hypercholesterolemia/mixed dyslipidemia.

Patients were enrolled from approximately 75 sites globally (Figure 1) in 15 countries from May 22, 2017 to January 23, 2019. In this two-phase study, patients were randomized (2:1) to receive 24 weeks of double-blind treatment with monthly subcutaneous injections of evolocumab 420 mg or matching placebo. In the open-label period that follows, all patients will receive evolocumab 420 mg monthly for 24 weeks (Figure 2). Randomization was stratified by statin treatment (yes/no) at entry and hepatitis C status. We anticipated that 10% to 20% of the overall group would have complete statin intolerance as indicated by prior studies.[16]

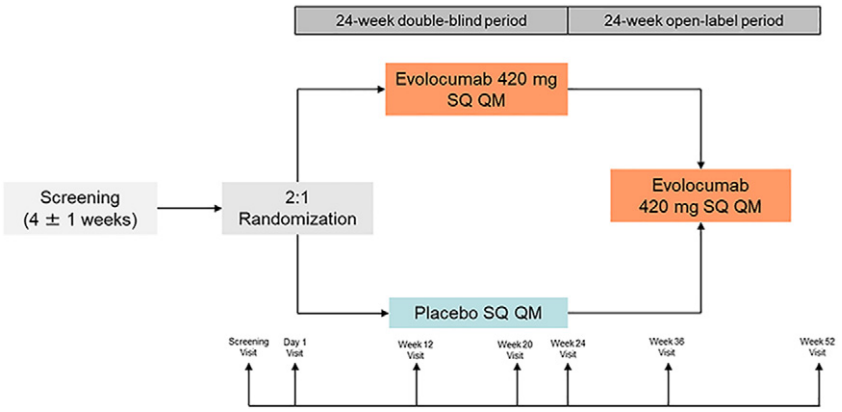
Patients ≥18 years of age were eligible for participation in this study if they received stable HIV therapy for ≥6 months before randomization and stable, maximally-tolerated lipid-lowering therapy for ≥4 weeks before randomization. (Table I) Statin intolerance was defined as a trial of at least 2 statins with the failure of at least 2 statins due to intolerable myopathy or myositis, or at least 1 statin due to rhabdomyolysis, which improved or resolved upon down-titration or discontinuation of statin therapy (Table I). Details of baseline medication use including name, dose, unit, frequency, route, start date, and stop date were collected by investigators. During the study, if a therapy was started, discontinued, or changed, the reason for adjusting the medication, including for an adverse event, worsening of an underlying condition, or noncompliance, was recorded.

Patients without ASCVD needed to have fasting low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-C) ≥130 mg/dL; patients with documented clinical ASCVD needed to have fasting LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL. Exclusion criteria included fasting triglycerides >600 mg/dL and CD4 count <250 cells/mm^3 or HIV viral load >200 copies/mL (or>50 copies/mL at screening) in the 6 months prior to randomization.

The primary objective is to evaluate the effect of evolocumab versus placebo on percent change in LDL-C from baseline to 24 weeks. Secondary objectives include the percent of patients attaining LDL-C <70 mg/dL, the percent of patients achieving a 50% or greater reduction in LDL-C, and percent change in non-HDL-C, apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein(a), triglycerides, HDL-C, and very-low density lipoprotein cholesterol (VLDL-C). The safety of evolocumab will be examined during both phases of the trial. Exploratory objectives include the evaluation of evolocumab compared with placebo on biomarkers of inflammation, immune regulation, and thrombosis.

With a planned sample size of 450 patients, randomized 2:1 to evolocumab and placebo, it was anticipated that 300 patients would be exposed to evolocumab 420 mg monthly, which would provide approximately 95% probability of detecting adverse events that occur at a rate of 1% or greater. The study was not powered to assess cardiovascular event rates.

Figure 1



BEIJERINCK Study Schema.The BEIJERINCK study randomized (2:1) patients to receive 24 weeks of double-blind treatment with monthly subcutaneous evolocumab 420 mg or matching placebo, after which all patients received 24 weeks of open-label monthly subcutaneous evolocumab 420 mg. QM indicates once monthly; SQ, subcutaneously.

Descriptive statistics of baseline data are provided. Clinical ASCVD was defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or lower extremity peripheral arterial disease presumed to be of atherosclerotic origin.

Efficacy and safety analyses will be performed on all randomized patients who receive at least 1 dose of investigational product in the double-blind period. Repeated-measures linear mixed-effects models will assess both primary and secondary efficacy endpoints. Models will include terms for the treatment group, statin use stratification factor (hepatitis C stratification factor will not be included in the analysis since there were an insufficient number of patients [less than 5 patients] in each stratum), scheduled visit, and the interaction of treatment with the scheduled visit. Multiplicity adjustment for the primary and secondary efficacy endpoints will be performed using sequential gatekeeping and Hochberg procedures to preserve the family-wise error rate at 0.05. Safety endpoints will be summarized descriptively by treatment group.

Safety summaries will include the incidence of patient-reported adverse events, abnormalities in laboratory parameters, and anti-evolocumab antibodies (binding and neutralizing).

All procedures in this study are conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. The Ethics Committees and Institutional Review Boards at each site reviewed and approved the final protocol and informed consent forms. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing. Funding from Amgen Inc. was used to support this work, which included the provision of editorial support.

Results

Enrollment by country (Figure 2)

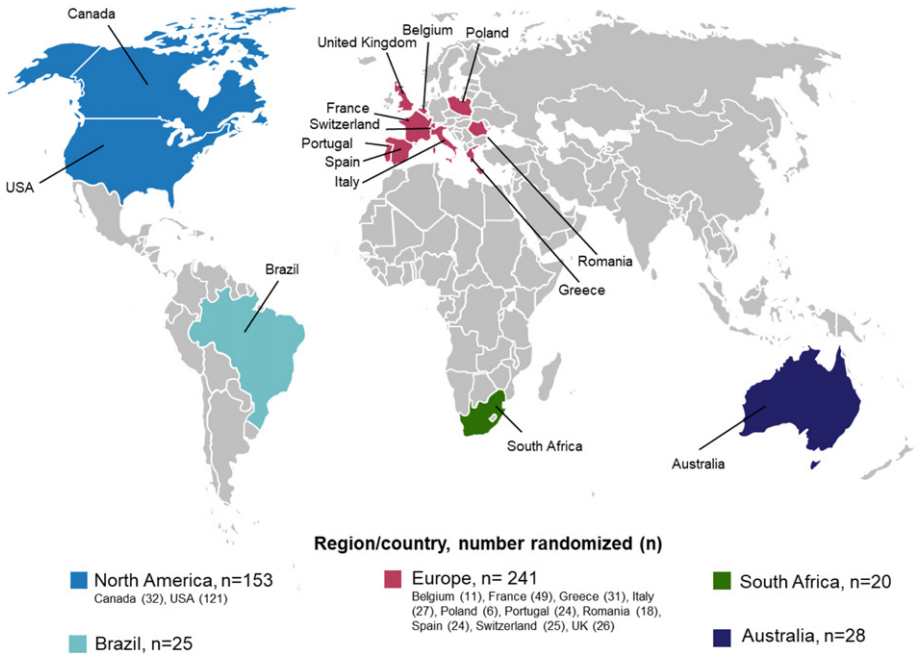
A total of 467 patients were randomized into the BEIJERINCK study from May 22, 2017 to January 23, 2019. Enrolled patients were from sites in the United States (121), France (49), Canada (32), Greece (31), Australia (28), Italy (27), United Kingdom (26), Brazil (25), Switzerland (25), Portugal (24), Spain (24), South Africa (20), Romania (18), Belgium (11), and Poland (6).

Baseline characteristics (Table II)

Of the 467 randomized patients, 464 received at least one dose of the blinded investigational product (either evolocumab or placebo) and were included in the full analysis set. Patients were predominantly middle-aged white males with a long mean duration of HIV infection (17.4 years). The viral load at screening was ≤50 copies/mL as required by the protocol. Hepatitis C antibodies were present in 5% of patients.

Clinical ASCVD was present in 35.6% of patients including a total of 28.2% of patients with coronary heart disease (15.5% who had a prior myocardial infarction), 5.2% with a prior stroke, and 5.8% with peripheral artery disease. The majority of patients without ASCVD had intermediate or moderate-to-high 10-year ASCVD risk scores (53% to 86%, depending on risk score used), that were calculated using standard algorithms that have been validated in non-HIV infected

Figure 2



BEIJERINCK Regional Enrollment. The BEIJERINCK study randomized a total of 467 patients from multinational sites in Europe (n = 241), North America (n = 153), Australia (n = 28), Brazil (n = 25), and South Africa (n = 20).

adults.[2,17,18] There were 22 patients (4.7%) who met Simon Broome criteria for definite or possible familial hypercholesterolemia (FH) and 177 patients (38.1%) without sufficient data to assess FH status.[19]

Cardiovascular risk factors, in addition to HIV, were prevalent in this patient population, including hypertension (47.8%), low high-density lipoprotein cholesterol (<40 mg/dL in men and< 50 mg/dL in women, 31.9%), current cigarette smoking (27.6%), and obesity (BMI ≥30 kg/m^2, 21.6%). Chronic kidney disease (stage 1 through 3) was present in a small number of patients (3.4%).

Lipid-lowering therapy and lipid parameters (Table II)

At baseline, 79.3% of patients received statin therapy including high-intensity statins in 31.7%, moderate-intensity statins in 42.9%, and low-intensity statins in 4.7%.[2] The 20.7% of patients not receiving statins were considered completely statin intolerant by the study investigator or had a documented contraindication to statin use. The most commonly prescribed statins were atorvastatin (33.0%) and rosuvastatin (24.8%). Ezetimibe was used by 90 (19.4%) patients, of which 64 patients received ezetimibe and a high- or moderate-intensity statin. Few patients received fenofibrate or gemfibrozil, 7.3% and 0.6%, respectively.

Mean (standard deviation, SD) LDL-C at baseline was 133.3 (40.1) mg/dL. At baseline, mean (SD) total cholesterol, HDL-cholesterol, and triglycerides were 219.9 (45.9) mg/dL, 48.3 (13.9) mg/dL, and 193.5 (108.4) mg/dL, respectively. Median (Q1, Q3) Lp(a) protein concentration was 54.5 (interquartile range of 18.0, 186.0) nmol/L.

HIV treatment (Table II)

Antiretroviral regimens varied, with 81.3% of enrolled patients receiving nucleoside reverse transcriptase inhibitor (NRTI)-containing regimens, 52.6% receiving integrase inhibitor (INSTI)-based regimens, 40.7% receiving protease inhibitor (PI)-based regimens, and 39.4% receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. Cobicistat and ritonavir were taken by 20.3% and 31.0% of patients, respectively.

Discussion

The BEIJERINCK study is the first randomized, placebo-controlled trial to examine the use of the fully human PCSK9 monoclonal antibody inhibitor evolocumab in PLHIV who have elevated LDL-C and/or non-HDL-C on maximally tolerated statin therapy. Strengths of the study include enrollment of a large, representative group of PLHIV from 75 sites in 15 countries. The enrolled population comprises both primary and secondary prevention patients. We suggest that this population is representative of the moderate-to-high ASCVD risk levels

Table I. Eligibility criteria.

Criteria	Description
Inclusion	• Signed informed consent • Male or female patients ≥18 years of age • Known HIV infection and receiving stable HIV therapy (no new agents/dose changes) for ≥6 months prior to randomization • CD4 ≥ 250 cells/mm^3 for ≥6 months prior to randomization • HIV viral load ≤50 copies/mL at screening and ≤ 200 copies/mL for ≥6 months prior to randomization • On stable lipid-lowering therapy with maximally-tolerated statin dose for ≥4 weeks before screening - Statin intolerance must be evidenced by a trial of at least 2 statins with failure of at least one statin (due to rhabdomyolysis) or two statins (due to intolerable myopathy or myositis) at an average daily dose at or below the following doses AND symptoms resolved or improved when statin dose was decreased or discontinued atorvastatin 10 mg simvastatin 10 mg pravastatin 40 mg rosuvastatin 5 mg lovastatin 20 mg fluvastatin 40 mg pitavastatin 2 mg • Fasting triglycerides at screening ≤600 mg/dL
Exclusion	• Background lipid-lowering therapy and HIV therapy known to have significant drug–drug interactions • Known opportunistic infection/AIDS defining illness within 1 year prior to randomization • Known illness: - Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to randomization - Type 1 diabetes or new-onset or poorly-controlled type 2 diabetes - Uncontrolled hypertension (SBP> 180 mmHg or DBP> 110 mmHg at screening) - NYHA Class III or IV heart failure or last known LVEF<30% - Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ or stage 1 prostate cancer) within the last 5 years - Moderate to severe renal dysfunction (eGFR <30 mL/min/1.73 m^2 at screening) - Persistent active liver disease or hepatic dysfunction (Child-Pugh Score C). Stable chronic hepatitis C of at least 1-year duration before randomization was allowed - History or evidence of any other clinically significant condition or planned or expected procedure that, in the opinion of the Investigator or Amgen physician, would pose a risk to patient safety or interfere with the study • Medications: - CETP inhibitor (last 12 months prior to screening) - Evolocumab or any other investigational therapy to inhibit PCSK9 (any time) • Other: - Unavailability for protocol-required study visits or procedures - Unreliability as a study participant - Pregnancy, breastfeeding, or inadequate birth control in premenopausal female patients - Known sensitivity to any of the active substances or their excipients administered during dosing

AIDS indicates acquired immunodeficiency syndrome; ASCVD, atherosclerotic cardiovascular disease; CD4, cluster of differentiation 4; CETP, cholesteryl ester transfer protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein-cholesterol; LVEF; left ventricular ejection fraction; NYHA; New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; SBP, systolic blood pressure.

of PLHIV encountered in countries represented in this study. As these patients were receiving maximally-tolerated statin therapy and because HIV is a known ASCVD risk-enhancing factor, they may be considered candidates for a PCSK9 monoclonal antibody inhibitor.

Recently, there has been a decline in the higher relative risk for ASCVD events in PLHIV versus those without HIV.[20-22] Several factors possibly accounting for the lower incidence of ASCVD include improved access to care, earlier detection, and treatment with more effective and less atherogenic ART, and an emphasis on the treatment of cardiovascular risk factors. Nevertheless, PLHIV continue to have a higher ASCVD event rate that requires better tolerated and more effective LDL-C lowering therapies.

Therapeutic strategies for lowering ASCVD risk in PLHIV are often more challenging due to comorbidities and DDIs that limit the use of high-dose, high-potency statins. Certain statins are either contraindicated (simvastatin and lovastatin) or limited to low or moderate doses (atorvastatin, rosuvastatin) in patients treated with either a protease inhibitor or cobicistat. Other DDIs in patients treated with NNRTIs reduce blood statin concentrations resulting in less than anticipated LDL-C lowering. A retrospective US-based analysis found that only one-third of PLHIV achieved LDL-C reductions ≥30% after statin initiation of predominately moderate intensity versus an anticipated 30% to <50% LDL-C reduction.[12] Underutilization of high-intensity statins for the secondary prevention of ASVD represents a challenge for PLHIV versus

Table II. Baseline data.

	Full analysis set (n = 464)
Demographics	
Age in years, mean (SD)	56.4 (8.7)
Sex, male, n (%)	383 (82.5)
Race, n (%)	
White	370 (79.7)
Black or African American	77 (16.6)
Other	17 (3.7)
Ethnicity, n (%)	
Hispanic/Latino	62 (13.4)
Region, n (%)	
Europe	239 (51.5)
North America	152 (32.8)
Asia Pacific	48 (10.3)
Latin America	25 (5.4)
Clinical Characteristics	
HIV	
Years since diagnosis at randomization, mean (SD)	17.4 (8.9)
CD4 count (cells/mm^3), median (Q1, Q3)	656 (506, 853)
Viral load ≤50 copies/mL at baseline, n (%)*	452 (97.4)
Hepatitis C antibody positive	24 (5.2)
ASCVD, n (%)	165 (35.6)
Coronary artery disease, n (%)	131 (28.2)
Myocardial infarction	72 (15.5)
Coronary artery stenosis >50%	54 (11.6)
Percutaneous coronary artery intervention	53 (11.4)
Coronary artery bypass graft surgery	26 (5.6)
Cerebrovascular or peripheral arterial disease, n (%)	58 (12.5)
Stroke	24 (5.2)
Cerebrovascular disease	27 (5.8)
Lower extremity arterial disease (LEAD)	27 (5.8)
Definite or possible familial hypercholesterolemia†	22 (4.7)
Chronic kidney disease	16 (3.4)
Cardiovascular risk factors, n (%)	
Hypertension	222 (47.8)
Low HDL-C‡	148 (31.9)
Current cigarette smoking	128 (27.6)
Type 2 diabetes mellitus	75 (16.2)
Family history of premature CHD	65 (14.0)
BMI (kg/m^2), mean (SD)	26.8 (4.7)
Overweight (BMI ≥ 25 kg/m^2, <30 kg/m^2)	183 (39.4)
Obese (BMI ≥ 30 kg/m^2)	100 (21.6)
Waist circumference (cm), mean (SD)	97.5 (13.0)
European male	95.9 (11.7)
European female	98.4 (12.4)
American male	99.0 (15.8)
American female	103.6 (14.5)
10-year ASCVD risk scores in the non-ASCVD cohort (primary prevention, n = 299)	
Framingham heart CHD	
High risk (>20%)	58 (19.4)
Moderately high risk (10%-20%)	82 (27.4)
Moderate risk (6 to <10%)	72 (21.4)
Low risk (<6%)	86 (28.8)
Systematic coronary risk evaluation (SCORE)	
Very-high risk (≥10%)	1 (0.3)
High risk (5% to <10%)	38 (12.7)
Moderate risk (1% to <5%)	220 (73.6)
Low risk (<1%)	39 (13.0)
ASCVD pooled cohort risk equation	
High risk (>20%)	37 (12.4)
Intermediate risk (7.5% to <20%)	120 (40.1)
Borderline risk (5 to <7.5%)	0 (0.0)
Low risk (<5%)	142 (47.5)

Table II (*continued*)

	Full analysis set (n = 464)
Medication use	
Lipid-lowering therapy	
Statins, n (%)	368 (79.3)
Atorvastatin	153 (33.0)
Rosuvastatin	115 (24.8)
Pravastatin	45 (9.7)
Pitavastatin	25 (5.4)
Fluvastatin	19 (4.1)
Simvastatin	10 (2.2)
Lovastatin	1 (0.2)
Statin intensity, n (%)	
High-intensity	147 (31.7)
Moderate-intensity	199 (42.9)
Low-intensity	22 (4.7)
Ezetimibe, n (%)	90 (19.4)
Fibrates, n (%)	46 (9.9)
Fenofibrate	34 (7.3)
Gemfibrozil	3 (0.6)
Bile acid sequestrants, n (%)	2 (0.4)
Nicotinic acid, n (%)	7 (1.5)
High-dose prescription fish oil, n (%)	3 (0.6)
Aspirin, n (%)	65 (14.0)
Antiretroviral therapy, n (%)	
NRTI	377 (81.3)
Integrase inhibitor	243 (52.4)
Elvitegravir boosted with cobicistat	66 (14.2)
Boosted protease inhibitor	182 (39.2)
NNRTI	183 (39.4)
Maraviroc	11 (2.4)
Lipid levels at baseline	
LDL-C (mg/dL)[§], mean (SD)	133.3 (40.1)
TC (mg/dL), mean (SD)	219.9 (45.9)
ApoB (mg/dL), mean (SD)	113.2 (26.4)
Non-HDL-C (mg/dL), mean (SD)	171.6 (46.0)
HDL-C (mg/dL), mean (SD)	48.3 (13.9)
TG (mg/dL), mean (SD)	193.5 (108.4)
Lp(a) (nmol/L), median (Q1, Q3))	54.5 (18.0, 186.0)
PCSK9 (ng/mL)	542.6 (188.0)

Baseline data shown include patients who were randomized and received at least one dose of unblinded investigational product.
[\^]At screening, all patients met the criterion of viral load ≤50 copies/mL per protocol
[†]Diagnosed using Simon Broome criteria.
[‡]Defined as HDL-C < 40 mg/dL in men and< 50 mg/dL in women
[§]Calculated LDL-C was replaced by ultracentrifugation LDL-C when calculated LDL-C was <40 mg/dL or triglycerides were> 400 mg/dL
ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CD4, cluster of differentiation 4; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TC, total cholesterol; TG, triglycerides.

those without HIV.[23] Adherence to a dosing regimen that is monthly versus daily may be favorable in PLHIV, who are susceptible to polypharmacy.[24]

Most patients (75%) in the full analysis set were taking moderate- or high-intensity statins. The use of ezetimibe (19%) was higher than other studies with PCSK9 inhibitors. The use of antiretroviral drugs that either increase or decrease blood statin levels were common in this population, including NNRTIs in 39.4%, cobicistat in 20.3%, and/or protease inhibitors in 40.7%.

The primary objective of our trial is to measure changes in LDL-C. In addition, we will evaluate for the first time the effects of evolocumab on Lp(a) protein concentration in PLHIV. Lp(a) is a genetically-determined risk marker for ASCVD that may also be elevated in PLHIV due to chronic inflammation. Among PLHIV, allele-specific apo(a) levels are also correlated with elevated CD4 counts and low plasma HIV RNA viral load, suggesting that HIV affects levels of Lp(a).[25] ART increases Lp(a) mass and allele-specific apo(a) levels, which have been associated with increased carotid artery intima-media thickness in young women with HIV.[26,27] Thus, evaluation of Lp(a) represents another novel aspect of this trial.

Further assessment of anti-PCSK9 therapy in patients with chronic inflammation is warranted based on its broad repertoire of molecular effects in both experimental and

human mechanistic studies.[28] In addition to modulation of hepatic LDL-receptor expression, in-vitro and in-vivo studies suggest that PCSK9 is involved in various other physiologic processes mediated by other members of the PCSK9 superfamily of receptors.[28] Higher levels of PCSK9 are associated with endothelial dysfunction[29] but not with coronary plaque parameters[15] in PLHIV. However, the clinical implications beyond lipid metabolism appear to be limited.[30] Transcriptional regulation of PCSK9 suggests a potential role for PCSK9 in vascular and systemic inflammation with levels of PCSK9 increased in acute and chronic inflammatory states. However, examination of the potential benefit of evolocumab on biocellular inflammatory pathways is ongoing, as is another study of vascular inflammation with alirocumab.[28,31]

We will also evaluate the effects of evolocumab on biomarkers of the immune system in PLHIV. Overexpression of PCSK9 in experimental models of hypercholesterolemia is associated with disruption of T-cell homeostasis in the lung and the liver, with an increase in CD4 and CD8 memory T-cells and a reduction in circulating regulatory T-cells.[32] In PLHIV, there is an association of higher levels of PCSK9 with low CD4 count[33], cannabis use[34], monocyte activation[15], and HIV infection severity[33] in HIV-naïve individuals; whereas, in PLHIV who receive ART, PCSK9 is associated with lipid parameters.[33]

The role of HCV co-infection (nearly 25% of PLHIV in most of PLHIV cohorts from western countries) on PCSK9 levels is also of interest. Co-infection with HIV and HCV is associated with higher PCSK9 levels than observed in either HIV mono-infected or non-infected individuals.[35] Elevated PCSK9 levels and PCSK9-mediated downregulation of CD81 expression promotes entry of HCV into hepatocytes, thus potentially increasing HCV infectivity.[36,37] Therefore, data on the use of evolocumab in HIV-HCV co-infected individuals are warranted.

As the first randomized, placebo-controlled, multicenter trial to assess the use of a PCSK9 inhibitor in an HIV patient population, the BEIJERINCK trial will report lipid-lowering efficacy and safety data in this moderate/high ASCVD risk population. Final results will be available in the first half of 2020.

Contribution Statement

Dr. Boccara wrote the first draft of the manuscript. All authors had full access to the data, participated in the interpretation of the results, contributed to writing the manuscript, and take responsibility for the integrity of the data and the accuracy of the analysis. Amgen Inc. provided funding for the study, was responsible for the design and conduct of the study, and participated in the review of the manuscript in partnership with the independent authors. All authors approved the manuscript for submission.

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