Bococizumab HIV Evaluation (B-HIVE) Study:

A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of Bococizumab, a PCSK9 Inhibitor, in HIV-Infected Subjects

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PROTOCOL SUMMARY

Indication

PF-04950615 is a humanized monoclonal antibody against the proprotein convertase subtilisin kexin type 9 (PCSK9) enzyme responsible for the degradation of the low-density lipoprotein receptor (LDLR), being developed by Pfizer, Inc. for the treatment of primary hyperlipidemia and mixed dyslipidemia.

Background and Rationale

Cardiovascular disease (CVD) due to atherosclerosis continues to be the leading single cause of death in industrialized countries. High serum lipid levels, and especially high low-density lipoprotein cholesterol (LDL-C) levels, have been demonstrated to strongly and directly correlate with CVD risks by numerous epidemiological studies. Moreover, large prospective clinical outcome trials have demonstrated that lowering LDL-C decreases cardiovascular morbidity and mortality.[1] A meta-analysis of 26 randomized clinical trials comprising 170,000 participants showed that more intensive statin therapy compared to less intensive regimens will reduce coronary deaths or myocardial infarction by an additional 13%.[2]

HIV-infected individuals represent a unique and increasing subset of atherosclerosis. With the advent of antiretroviral therapy, HIV-infected individuals now have much improved survival and are faced with health issues related to aging, including cardiovascular disease. Individuals with HIV have higher rates of coronary events compared to controls even in the setting of treated and suppressed disease and a growing body of literature suggests that they are at increased risk for myocardial infarction, atherosclerosis, and sudden cardiac death.[3-5] Many facets of atherosclerosis differ in HIV-infected individuals compared to uninfected individuals with atherosclerosis. HIV-infected patients with acute coronary syndromes are younger and more likely to be males and smokers, with low high density lipoprotein-cholesterol (HDL-C), compared to other acute coronary syndrome patients.[6] With respect to pathophysiology, viral replication, antiretroviral drugs and inflammation all contribute to atherosclerosis.[7,8]

HIV-associated inflammation induces pro-atherogenic lipid abnormalities and anti-retroviral therapy leads to the development of metabolic abnormalities such as dyslipidemia, lipodystrophy and insulin resistance.[9,10] In a large cross-sectional study, 27% of subjects receiving combination therapy including a protease inhibitor had a total cholesterol level exceeding 240 mg/dl, compared to 8% of untreated HIV subjects, and 40% had triglyceride levels above 200 mg/dl, compared to 15% in untreated subjects.[11] The prevalence and severity of dyslipidemia varies among different antiretroviral drugs;[9] however, hypertriglyceridemia and low HDL-cholesterol were associated with HIV infection even before the advent of antiretroviral therapy.[12] Total, HDL-C, and LDL-C decrease at the time of HIV infection, and with antiretroviral treatment total and LDL-C levels increase to pre-infection levels while HDL-C remains low.[13]

Abnormalities in body composition have been reported in 40-50% of HIV-infected patients, with higher rates in those receiving combination antiretroviral therapy.[9] Subcutaneous lipoatrophy commonly affects the face, limbs, and buttocks, and is

accompanied by central fat accumulation. Hyperinsulinemia is often also present. In a representative study,[14] diabetes was present in 7% of HIV-infected adults with fat accumulation or lipoatrophy, as compared to 0.5% of control subjects matched for age and BMI. The corresponding rates of glucose intolerance were 35% and 5% respectively.[14] Compared to healthy control subjects, HIV-infected men treated with combination antiretroviral therapy were 4 times as likely to develop diabetes over a 3-year observation period.[15]

The increased cardiovascular risk and dyslipidemia in HIV-infected individuals is difficult to treat for several reasons. Statins reduce LDL-C levels less in HIV-infected individuals compared to uninfected controls.[16] Fibrates reduce triglyceride levels less in HIV-infected individuals compared to uninfected controls as well.[16] Drug-drug interactions between statins and protease inhibitors increase the risk of adverse events.[17,18] Due to these interactions, simvastatin and lovastatin are contraindicated among individuals receiving protease inhibitors and the dose of atorvastatin should not exceed 40 mg.[17] Even interactions with rosuvastatin, which is not metabolized by the cytochrome P450 system, have been described.[19,20]

As a consequence, physicians may avoid treating HIV-infected individuals who would benefit from statins, or use lower doses or less potent statins, reducing the potential for cardiovascular event reduction. High triglyceride levels in HIV-infected subjects are common, and the combination of a fibrate plus antiretroviral therapy increases the risk of drug-drug adverse events, even before consideration of a statin.

Statin treatment reduces lipid levels modestly in HIV subjects. Among 72 HIV-infected subjects in the SATURN-HIV trial randomized to rosuvastatin 10 mg/day, LDL-C was reduced by 25.3% by week 24.[21] In another study, of 83 HIV-infected subjects, rosuvastatin 10 mg and pravastatin 40 mg/day reduced LDL-C by 37% and 19% respectively at 45 days.[22] Among 151 HIV-infected subjects randomized to rosuvastatin 10 mg, atorvastatin 10 mg, or pravastatin 40 mg/day, LDL-C reductions were greater with rosuvastatin at this dose, but all 3 statins significantly and similarly reduced serum levels of hs-CRP and TNF-α.[23]

That statins might favorably influence the evolution of atherosclerosis in HIV-infected subjects is suggested by a recent trial where 40 HIV subjects with mild coronary atherosclerosis by CT angiography and aortic inflammation by FDG-PET imaging were randomized to atorvastatin 20-40 mg/day or placebo and were followed for 12 months.[24] Atorvastatin significantly reduced non-calcified coronary plaque volume relative to placebo, as well as the number of high-risk plaques.

Approximately 1/3 of individuals with HIV-infection are co-infected with hepatitis C.[25] Elevated hepatic enzymes due to hepatitis C represent a relative contraindication to statin therapy, and some evidence suggests that a statin might increase hepatitis C activity.[26] Finally, HIV-infected patients often need many medications and have a large daily pill burden. Compliance suffers, but has been shown to improve when single tablet regimens reduce daily pill load.[27] Long-acting injectable antiretroviral drugs are under development as a strategy to reduce pill burden and improve compliance.[28] PCSK9 inhibitor injections would dovetail well with this approach. For these reasons, PCSK9 inhibitor therapy offers advantages over statin therapy in this unique population.

Bococizumab (RN316/PF-04950615) is a novel humanized PCSK9 monoclonal antibody. In a 24-week, multicenter, randomized, double-blind, placebo-controlled phase II trial, the LDL-C lowering effects of bococizumab, administered every 2 or 4 weeks in statin-treated adults with LDL-C ≥80 mg/dL was assessed.[29] Subjects were randomized to placebo, bococizumab 50 mg, 100 mg, or 150 mg every 2 weeks, or placebo, bococizumab 200 mg or 300 mg monthly. The dose was reduced if LDL-C was ≤25 mg/dL. The primary analysis was the placebo-adjusted treatment difference for the change from baseline in LDL-C at week 12.

Overall, 354 patients were randomized, 351 received study treatment, and 299 completed the study. Bococizumab significantly reduced LDL-C across all doses. The placebo-adjusted LDL-C reduction at 12 weeks for the 2-weekly dosing regimen was 34.3% with 50 mg, 45.1% for 100 mg and 53.4% for 150 mg, and for the monthly dosing regimen was 27.6% for 200 mg and 44.9% for 300 mg. The incidence and profile of adverse events were similar across placebo and bococizumab groups.

Based on these findings, 150 mg every 2 weeks was selected as the dose for phase III trials, including this trial. Because multiple doses of bococizumab as high as 150 mg every 2 weeks and 300 mg every 4 weeks up to 12 weeks were safe and well tolerated, the primary rationale for dose selection was the pharmacokinetic/pharmacodynamic model that predicted LDL-C change from baseline. Based on population PK/PD modeling, a dose of 150 mg every 2 weeks in patients on a background of statins is estimated to be equivalent to approximately 80% of the maximal response for LDL-C lowering (-67%). Assuming an average LDL-C at baseline of 100 mg/dL for HIV-infected individuals, the mean absolute LDL-C reduction is predicted to be approximately 60 mg/dL.

Objectives and Endpoints

Objectives

The primary objective of the study is to demonstrate the efficacy of LDL-C lowering with bococizumab 150 mg administered subcutaneously every 2 weeks compared to placebo, in HIV-infected subjects whose LDL-C is ≥70 mg/dL (1.81 mmol/L). The secondary objectives will be to assess the effect of bococizumab compared to placebo on total cholesterol (TC), HDL-C, triglycerides, non-HDL-C, apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I), and lipoprotein (a) [Lp(a)], and to assess the safety and tolerability of bococizumab.

The study has 3 important tertiary objectives. The first is to determine whether bococizumab compared to placebo improves vascular inflammation in HIV-infected individuals, as assessed by FDG-PET/CT [(18)Fluorodeoxyglucose positron emission tomography/computed tomography]. The second is to determine whether changes in arterial FDG uptake are associated with changes in coronary plaques as measured by CT angiography. The third tertiary objective is to determine whether bococizumab improves endothelial dysfunction among HIV-infected individuals as assessed by flow-mediated dilation of the brachial artery (FMD). We will correlate these findings with changes in LDL-C, inflammatory markers, and Lp(a).

Endpoints

The primary endpoint for the study is the percent change from baseline in fasting LDL-C at week 12. Key secondary endpoints are the percent change from baseline in fasting TC, ApoB, non HDL-C, HDL-C, and Lp(a) at week 12. Secondary lipid efficacy endpoints are the percent change from baseline in fasting LDL-C, TC, ApoB, non HDL-C, HDL-C, and Lp(a) at week 24; the percent change from baseline in fasting TG, and ApoA-I, at week 12 and 24; the absolute change from baseline in fasting TC / HDL-C ratio and ApoB / ApoA-I ratio at week 12 and 24, along with absolute change from baseline at week 12 in LDL-C, TC, ApoB, non-HDL-C, HDL-C and Lp(a); the proportion of subjects achieving fasting LDL-C ≤70 mg/dL (1.81 mmol/L) at week 12 and 24. Secondary safety endpoints are adverse events, and serious adverse events, including Type 1 and 3 hypersensitivity reactions and injection site reactions.

Study Design

This study is a Phase 3, double blind, placebo-controlled, randomized, parallel group study, designed to compare the efficacy and safety of bococizumab 150 mg subcutaneously every 2 weeks to bococizumab placebo subcutaneously every 2 weeks for LDL-C lowering in HIV-infected subjects. The study will enroll approximately 200 subjects in 2 treatment arms, randomized 1:1 to either bococizumab or placebo injections. Randomized subjects will receive study drug for 52 weeks. The primary comparison of interest is bococizumab 150 mg compared to placebo. Rates of discontinuation due to AEs and SAEs will be described for both treatment groups.

After providing informed consent at the screening visit, subjects will be assessed to determine eligibility for the trial. Eligible subjects will be considered enrolled and progress to the Baseline visit. Results from screening evaluations will be reviewed and only subjects who continue to meet all eligibility criteria will be randomized. Randomized subjects will enter the 52-week treatment period, followed by a 6-week follow-up, for a total of 58 weeks study participation. Subjects will attend clinic visits as shown in the Schedule of Activities. Lipid levels will be blinded to the investigator and staff, subject and sponsor.

Statistical Methods

Statistical methods are described in detail in the Statistical Analysis Plan and are summarized in Section 9. For the primary endpoint of LDL-C change with bococizumab compared to placebo at 12 weeks, 54 subjects per treatment group will provide ≥99% power to detect an expected treatment difference. This calculation is based upon a previous bococizumab study[29] and uses an α=0.05 (two-sided), a common standard deviation of 25% (based upon a previous study[29]), and the normal approximation of the test statistic for the comparison between 2 means. We assume a dropout rate of 10% per group, and thus 60 subjects per group would need to be randomized for the primary lipid endpoint. We assume a similar LDL-C response in HIV subjects as that seen in other subjects.[22]

For the FDG-PET/CT endpoint of difference of change in aortic TBR between the treatment groups, we calculate a sample size requirement of 120 subjects based upon the

following considerations: (1) 10% of subjects without inflammation at baseline will be excluded, (2) 8% of subjects will discontinue treatment or not return for repeat imaging, (3) 8% of subjects will be excluded due to insufficient image quality, leaving a total of 90-92 subjects, (4) the anticipated average TBR will be 2.5, (5) the assumed standard deviation for change in TBR will be 0.29, and (6) the minimum expected change in TBR on treatment will be 7%. These assumptions are based upon previous studies, as described in section 9. Despite the calculated sample size of 90-92 subjects, FDG-PET imaging will be done in all study participants because of the uncertainties of the estimates used in the sample size calculation. No differences in FDG-PET images were seen in the aforementioned atorvastatin study;[24] however, adequate images were available for only 21 of the 40 study subjects.

For the coronary CT angiography endpoints, little data is available for an accurate sample size calculation. In the atorvastatin HIV study of Lo et al,[24] significant differences were seen for non-calcified plaque and high-risk plaque in a group of only 40 HIV-infected subjects, but all had mild coronary lesions by CT angiography at baseline. As with FDG-PET, we plan to perform CT angiography on all of the study participants due to uncertainties in the sample size calculation.

For the FMD endpoint of the difference between the bococizumab and placebo groups for the change in mean FMD between baseline and follow-up, approximately 25 subjects per group would provide an adequate sample size based on extrapolations from previous studies. We plan to measure FMD in all subjects because it is a simple, noninvasive and inexpensive test. We plan to correlated changes in FMD and changes in lipid parameters, as outlined in section 9.

Safety will be assessed through adverse and serious adverse events, vital signs, and physical examination, 12-lead electrocardiograms (ECGs), and safety laboratory tests including hematology, ADAs and blood chemistry studies.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule unplanned visits in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject

Study Phase	**Screen**	**Rand**	**Treatment**							**Follow- Up**
Protocol Activity (Week)	**-8**	**0**	**4**	**8**	**12**	**24**	**30**	**40**	**52/EOS[a]**	**58**
Visit Day	**-57**	**1**	**29**	**57**	**85**	**169**	**211**	**281**	**365**	**407**
Informed consent	X									
CV risk factors, demographics, medical history	X									
Vital Signs (HR, BP, temperature)	X	X	X	X	X	X	X	X	X	X
Height and weight		X				X		X	X	
Physical examination	X					X		X	X	
Prior Medications	X									
Concomitant medication		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
ECG	X					X			X	
Review inclusion/exclusion criteria	X	X								
Laboratory										
Fasting Lipid Profile	X	X	X	X	X	X	X	X	X	X
Diet and contraception advice	X	X	X	X	X	X	X	X	X	X
Instruction on self-injection	X	X								
Randomization		X								
Dispense study treatment		X	X	X	X	X	X	X		
Brachial artery FMD		X,X				X				
FDG-PET/CT		X[b]				X[b]				
Coronary CT angiography		X[b]							X[b]	

a. EOS = End of Study, procedures to be completed for subjects who have early study discontinuation. Visit day 365/EOS will usually require 2 days to complete because of the requirement to perform coronary CT angiography study

b. FDG-PET/CT or coronary CT angiography reimage within 7 days if deemed necessary

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1. INTRODUCTION

1.1. Indication

Bococizumab is a humanized monoclonal antibody against the proprotein convertase subtilisin kexin type 9 (PCSK9) enzyme responsible for the degradation of the low-density lipoprotein receptor (LDLR). Bococizumab is being developed for the treatment of primary hyperlipidemia and mixed dyslipidemia.

1.2. Background and Rationale

Cardiovascular disease (CVD) due to atherosclerosis continues to be the leading single cause of death in industrialized countries. High serum lipid levels, and especially high low-density lipoprotein cholesterol (LDL-C) levels, have been demonstrated to strongly and directly correlate with CVD risks by numerous epidemiological studies. Moreover, large prospective clinical outcome trials have demonstrated that lowering LDL-C decreases cardiovascular morbidity and mortality.[1] A meta-analysis of 26 randomized clinical trials comprising 170,000 participants showed that more intensive statin therapy compared to less intensive regimens will reduce coronary deaths or myocardial infarction by an additional 13%.[2]

1.2.1. Atherosclerosis in HIV-Infected Individuals

HIV-infected individuals represent a unique and increasing subset of patients with atherosclerosis. With the advent of antiretroviral therapy, HIV-infected individuals now have much improved survival and are faced with health issues related to aging, including cardiovascular disease. Individuals with HIV have higher rates of coronary events compared to controls and a growing body of literature suggests that they are at increased risk for myocardial infarction, atherosclerosis, and sudden cardiac death.[3-5] Many facets of atherosclerosis differ in HIV-infected individuals compared to uninfected individuals with atherosclerosis. HIV-infected patients with acute coronary syndromes are younger and more likely to be males and smokers, with low high density lipoprotein-cholesterol (HDL-C), compared to other acute coronary syndrome patients.[6] With respect to pathophysiology, viral replication, antiretroviral drugs and inflammation all contribute to atherosclerosis.[7,8]

HIV-associated inflammation induces pro-atherogenic lipid abnormalities and anti-retroviral therapy leads to the development of metabolic abnormalities such as dyslipidemia, lipodystrophy and insulin resistance.[9,10] In a large cross-sectional study, 27% of subjects receiving combination therapy including a protease inhibitor had a total cholesterol level exceeding 240 mg/dl, compared to 8% of untreated HIV subjects, and 40% had triglyceride levels above 200 mg/dl, compared to 15% in untreated subjects.[11] The prevalence and severity of dyslipidemia varies among different antiretroviral drugs;[9] however, hypertriglyceridemia and low HDL-cholesterol were associated with HIV infection even before the advent of antiretroviral therapy.[12] Total, HDL-C, and LDL-C decrease at the time of HIV infection, and with antiretroviral treatment total and LDL-C levels increase to pre-infection levels while HDL-C remains low.[13]

The increased cardiovascular risk and dyslipidemia in HIV-infected individuals is difficult to treat for several reasons. Statins reduce LDL-C levels less in HIV-infected

individuals compared to uninfected controls.[16] Fibrates reduce triglyceride levels less in HIV-infected individuals compared to uninfected controls as well.[16] Drug-drug interactions between statins and protease inhibitors increase the risk of adverse events.[17,18] Due to these interactions, simvastatin and lovastatin are contraindicated among individuals receiving protease inhibitors and the dose of atorvastatin should not exceed 40 mg.[17] Even interactions with rosuvastatin, which is not metabolized by the cytochrome P450 system, have been described.[19,20]

As a consequence, physicians may avoid treating HIV-infected individuals who would benefit from statins, or use lower doses or less potent statins, reducing the potential for cardiovascular event reduction. High triglyceride levels in HIV-infected subjects are common, and the combination of a fibrate plus antiretroviral therapy increases the risk of drug-drug adverse events, even before consideration of a statin.

Statin treatment reduces lipid levels modestly in HIV subjects. Among 72 HIV-infected subjects in the SATURN-HIV trial randomized to rosuvastatin 10 mg/day, LDL-C was reduced by 25.3% by week 24.[21] In another study, of 83 HIV-infected subjects, rosuvastatin 10 mg and pravastatin 40 mg/day reduced LDL-C by 37% and 19% respectively at 45 days.[22] Among 151 HIV-infected subjects randomized to rosuvastatin 10 mg, atorvastatin 10 mg, or pravastatin 40 mg/day, LDL-C reductions were greater with rosuvastatin at this dose, but all 3 statins significantly and similarly reduced serum levels of hs-CRP and TNF-α.[23]

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1.2.2. Bococizumab

Bococizumab (RN316/PF-04950615) is a novel humanized PCSK9 monoclonal antibody targeting the evolutionarily conserved LDL receptor-binding domain of PCSK9 with high affinity. The constant region of bococizumab is based on the human IgG2 isotype bearing two amino acid mutations, called IgG2Δa, which have greatly reduced ability to bind to Fcγ receptors or fix complement.[30,31] In nonclinical models, PF-04950615 binds to secreted PCSK9, effectively prevents PCSK9 from degrading LDLR, leading to improved LDL-C clearance in plasma and reduction of circulating LDL-C.

In a 24-week, multicenter, randomized, double-blind, placebo-controlled phase II trial, the LDL-C lowering effects of bococizumab, administered every 2 or 4 weeks in statin-treated adults with LDL-C ≥80 mg/dL was assessed.[29] Subjects were randomized to placebo, bococizumab 50 mg, 100 mg, or 150 mg every 2 weeks, or placebo, bococizumab 200 mg or 300 mg monthly. The dose was reduced if LDL-C was ≤25 mg/dL. The primary analysis was the placebo-adjusted treatment difference for the change from baseline in LDL-C at week 12.

Overall, 354 patients were randomized, 351 received study treatment, and 299 completed the study. Bococizumab significantly reduced LDL-C across all doses. The placebo-adjusted LDL-C reduction at 12 weeks for the 2-weekly dosing regimen was 34.3% with 50 mg, 45.1% for 100 mg and 53.4% for 150 mg, and for the monthly dosing regimen was 27.6% for 200 mg and 44.9% for 300 mg. The incidence and profile of adverse events were similar across placebo and bococizumab groups. The incidence of moderate and severe injection site reactions and of serious adverse events was low in all treatment groups.

As of 1 December 2013, a total of 517 subjects had received at least one dose of bococizumab in completed studies, administered either as single or multiple dose both alone and in combination with current lipid lowering agents; bococizumab was generally well tolerated. No subjects in completed studies had drug-induced liver injury according to the Hy's law definition. Thirty-seven subjects (7%) exposed to bococizumab across all completed studies developed anti-drug antibodies but none were associated with any clinical signs or symptoms of hypersensitivity.

Based on the findings of the study described above,[29] 150 mg every 2 weeks was selected as the dose for phase III trials, including this trial. Because multiple doses of bococizumab as high as 150 mg every 2 weeks and 300 mg every 4 weeks up to 12 weeks were safe and well tolerated, the primary rationale for dose selection was the pharmacokinetic/pharmacodynamic model that predicted LDL-C changes from baseline. Based on population PK/PD modeling, a dose of 150 mg every 2 weeks in patients on a background of statins is estimated to be equivalent to approximately 80% of the maximal response for LDL-C lowering (-67%). Assuming an average LDL-C at baseline of 100 mg/dL for HIV-infected individuals, the mean absolute LDL-C reduction is predicted to be approximately -60 mg/dL.

1.2.3. FDG-PET/CT Imaging

FDG-PET/CT imaging is the best-validated imaging modality to detect and monitor arterial inflammation in humans.[32-35] Arterial inflammation as assessed by FDG-PET/CT correlates with atherosclerotic plaque inflammatory cell content, CV risk factors, Framingham risk score, and inflammatory biomarkers.[36-38] FDG-PET/CT predicts CV risk independently of traditional risk factors.[39-41] FDG-PET/CT has been used successfully to detect reductions in arterial inflammation by drugs that reduce CV risk.[42-45]

Arterial uptake of FDG has been shown to be higher in HIV-infected adults than in HIV-uninfected controls matched for age, gender, and Framingham risk score.[46] Other investigators have confirmed that FDG-PET/CT imaging detects inflammation in HIV-infected individuals.[47]

Several groups have demonstrated reductions in arterial FDG uptake in response to lipid lowering therapy.[42,43] Tawakol et al demonstrated in a multicenter trial that both high and low-dose atorvastatin rapidly lower arterial inflammation, and that high-dose atorvastatin reduces arterial inflammation by twice as much as low-dose atorvastatin. FDG-PET/CT has been employed to demonstrate rapid reductions in arterial inflammation in response to non-pharmacologic lipid lowering as well.[48] Specifically, in a recent study of 24 patients with familial hypercholesterolemia (FH) and 12 controls, TBR by FDG-PET/CT was significantly higher in the FH group, and significantly correlated with LDL-C levels.[48] Lipoprotein apheresis significantly lowered LDL-C in FH patients and significantly lowered TBR. Thus, FDG-PET/CT imaging is a well-established tool to evaluate and monitor arterial inflammation, and these results show that profound lipid lowering reduces arterial inflammation.

1.2.4. Coronary CT Angiography

Coronary CT angiography (CCTA) allows visualization of the coronary arteries while avoiding coronary arteriography, a much more invasive procedure. CCTA provides prognostic as well as diagnostic information: greater volumes of non-calcified plaque and vulnerable plaque morphology on CCTA have been associated with future major cardiac events.[49] Studies in HIV-infected individuals have shown an increased prevalence of subclinical atherosclerosis, including a predominant increase in non-calcified plaque compared with patients without HIV, controlling for traditional coronary risk factors.[50-52] Noncalcified plaque is lipid-laden, has higher macrophage content, and is more vulnerable to rupture.

In a recent randomized, double-blind, placebo-controlled trial using FDG-PET/CT and CCTA,[24] we showed that one year of treatment with atorvastatin 20-40 mg/day significantly reduced non-calcified plaque volume and high-risk coronary plaque features in HIV-infected patients. Changes in non-calcified plaque volume were large, with 19.4% regression in the atorvastatin group and 20.4% progression in the placebo group.

The 52-week treatment period in this trial may be too short to detect changes in coronary plaques. However, in our previous study with one year of treatment, 3 of 20 placebo-treated patients had progression of clinically significant coronary stenoses. Coronary lesions appear to progress more rapidly in HIV-infected individuals compared to other patients with coronary disease. But statin treatment limits this rapid progression. Thus, CCTA endpoints in this study should be viewed as exploratory.

1.2.5. Brachial Artery Flow-Mediated Dilation (FMD)

Endothelial dysfunction is a key step in atherogenesis. FMD, a noninvasive marker of endothelial function, predicts CV risk in the general population; specifically, a 1% absolute difference in FMD is associated with an adjusted 14% reduction in CV risk.[55,56] Interventions such as statins[57,58] and anti-hypertensive drugs[53] that reduce CV events also improve FMD.

FMD is markedly impaired in patients with HIV.[59,60] Changes in FMD with antiretroviral therapy have been used as surrogate markers for change in CV risk.[61-63] An improvement in FMD with bococizumab would parallel the improvement in FMD seen with statins, and would be expected to presage an improvement in CV events.

1.2.6. Benefits and Risks of Participation

The benefit of participation in this study for all subjects is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment group may benefit from lowering their LDL-C. Those randomized to the placebo group are not expected to obtain any additional benefit, beyond close monitoring of their medical condition and safety of their treatment, which may itself be associated with improving lipid levels. A potential risk of participation, for all subjects, is the occurrence of injection site reactions. For those receiving active treatment, there may be an additional risk of achieving a very low LDL-C. It is not known if there are any risks associated with very low LDL-C.

Complete information for this compound may be found in the bococizumab Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

The primary objective of the study is to demonstrate the efficacy of LDL-C lowering with bococizumab 150 mg administered subcutaneously every 2 weeks compared to placebo, in HIV-infected subjects whose LDL-C is ≥70 mg/dL (1.81 mmol/L).

2.1.2. Secondary Objectives

The secondary objectives will be to assess the effect of bococizumab compared to placebo on:

- Total cholesterol (TC), HDL-C, TG, and non HDL-C;
- Other lipid parameters, including ApoB, ApoA-I, and Lp(a).

To compare the safety and tolerability of bococizumab 150 mg administered subcutaneously every 2 weeks compared to placebo, in HIV subjects whose LDL-C is ≥70 mg/dL (1.81 mmol/L).

2.1.3. Tertiary Objectives

The study has 3 important tertiary objectives. The first is to determine whether bococizumab compared to placebo improves vascular inflammation in HIV-infected individuals, as assessed by FDG-PET/CT [(18)Fluorodeoxyglucose positron emission tomography/computed tomography]. The second is to correlate changes in coronary plaque characteristics as measured by CT angiography to changes in arterial FDG uptake as seen by PET, and to other parameters. The third tertiary objective is to determine whether bococizumab improves endothelial dysfunction among HIV-infected individuals as assessed by flow-mediated dilation of the brachial artery (FMD). We will correlate these findings with changes in LDL-C, inflammatory markers, and Lp(a).

2.1.4. FDG-PET Objectives

1. To compare changes in arterial inflammation (baseline to follow-up imaging) in individuals treated with bococizumab versus placebo.

2. To compare changes in arterial inflammation:

    a. To change in LDL-C with treatment across all study subjects with serial FDG-PET/CT imaging.

    b. To change in FMD with treatment across all study subjects with serial FDG-PET/CT imaging and serial FMD measurements.

    c. To changes in inflammatory markers: Lp(a), hs-CRP, IL-6, fibrinogen, sCD14, sCD163, and D-dimers.

2.1.5. Coronary CT Angiography Objectives

To correlate the changes in coronary plaque characteristics to:

1. Changes in arterial FDG uptake seen by PET.

2. Changes in LDL-C.

The coronary plaque characteristics that will be evaluated include:

1. Change from baseline to follow-up in volume of non-calcified coronary plaque.

2. Change from baseline to follow-up in volume of high-risk coronary plaque.

3. Incidence of new coronary plaque.

2.1.6. FMD Objectives

1. To compare change in FMD with treatment to change in LDL-C with treatment across all study subjects with serial FMD measurements.

2. To compare change in FMD with treatment to changes in inflammatory markers: Lp(a), hs-CRP, IL-6, fibrinogen, sCD14, sCD163 and D-dimers.

2.2. Endpoints

2.2.1. Primary Endpoint

- Percent change from baseline in fasting LDL-C at week 12.

2.2.2. Key Secondary Endpoints

- Percent change from baseline in fasting TC, ApoB, and non HDL-C at week 12;

- Percent change from baseline in fasting Lp(a) at week 12;

- Percent change from baseline in fasting HDL-C at week 12.

2.2.3. Other Secondary Endpoints

- Percent change from baseline in fasting LDL-C, TC, Apo B, non HDL-C, Lp(a) and HDL-C at week 24;
- Percent change from baseline in fasting TG, and ApoA-I at week 12 and 24;
- Absolute change from baseline in fasting LDL-C, TC, HDL-C, non HDL-C, TG, ApoB and Lp(a) at week 12;
- Absolute change from baseline in fasting TC/HDL-C ratio and ApoB/ApoA-I ratio at week 12 and 24;
- Proportion of subjects achieving fasting LDL-C ≤70 mg/dL (1.81 mmol/L) at week 12 and 24.

2.2.4. Safety Evaluations:

- Adverse events (including Type 1 and 3 hypersensitivity reactions, injection site reactions, and immunogenicity)

2.2.5. Exploratory Endpoints

- Proportion of subjects achieving fasting LDL-C ≤50 mg/dL (1.29 mmol/L) at week 12 and 24;
- Absolute and percent change from baseline in PCSK9 concentrations at week 12 and 24;
- Plasma bococizumab concentration at week 12 and 24.

2.2.6. FDG-PET/CT Endpoint

- Change in TBR from baseline to follow-up study at 24 weeks. This will be performed for several arterial endpoints, as previously described. The main arterial endpoint for this exploratory substudy is the most diseased segment of the index vessel, as described in 7.1.2.

2.2.7. Coronary CT Angiography Endpoints

- Change in non-calcified plaque from baseline to follow-up study at 52 weeks.
- Change in high-risk plaque from baseline to follow-up study at 52 weeks.
- Incidence of new lesions from baseline to follow-up study at 52 weeks.
- Correlations between change in LDL-C and

(a) change in volume of non-calcified coronary plaque

(b) change in high-risk coronary plaque

2.2.8. FMD Endpoint

- Change in FMD from baseline to follow-up study among subjects with FMD studies.

3. STUDY DESIGN

This study is a Phase 3, double blind, placebo-controlled, randomized, parallel group study, designed to compare the efficacy and safety of bococizumab 150 mg subcutaneously every 2 weeks to bococizumab placebo subcutaneously every 2 weeks for LDL-C lowering in HIV-infected subjects. The study will enroll approximately 200 subjects in 2 treatment arms, randomized 1:1 to either bococizumab or placebo injections. Randomized subjects will receive study drug for 52 weeks. Rates of discontinuation due to AEs and SAEs will be described for both treatment groups.

After providing informed consent at the screening visit, subjects will be assessed to determine eligibility for the trial. Eligible subjects will be considered enrolled and progress to the Baseline visit. Results from screening evaluations will be reviewed and only subjects who continue to meet all eligibility criteria will be randomized. Randomized subjects will enter the 52-week treatment period, followed by a 6-week follow-up, for a total of 58 weeks study participation. Subjects will attend clinic visits as shown in the Schedule of Activities. Lipid levels will be blinded to the investigator and staff, and subjects.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility will be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
    (a) Subjects who lack the capacity to consent for themselves, e.g. consent provided by a legally authorized representative (LAR) will be excluded
2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Males and females ≥ 40 years of age.
4. With documented HIV infection.
5. HIV-1 RNA level below 200 copies/mL for at least 12 weeks prior to study entry and confirmed at study entry. The assay used for eligibility can be performed by any US laboratory that has a CLIA certification or its equivalent.
6. Continuous ART for at least 12 weeks with no change in regimen prior to study entry. This is defined as continuous active therapy self-reported by subject with no treatment interruption longer than 7 consecutive days and adherence greater than 90%.

NOTE: Some modifications of ART doses during the 12 weeks prior to study entry are permitted. In addition, the change in formulation (e.g., from standard formulation to fixed-dose combination) is allowed within 12 weeks prior to study entry. A within class single drug substitution (e.g., switch from nevirapine to efavirenz or from atazanavir to darunavir) is allowed within 12 weeks prior to study entry, with the exception of a switch from any other NRTI to abacavir. No other changes in ART in the 12 weeks prior to study entry are permitted.

OR if a subject is not on ART, they may be included if:

HIV-1 RNA is < 2000 copies/mL for at least 52 weeks prior to study entry and confirmed within 12 weeks prior to study entry. The assay used for eligibility can be performed by an US Laboratory that has a CLIA certification or its equivalent.

7. Moderate or high CVD risk defined as:

   documented CVD as assessed by meeting at least 1 of 3 criteria below:

   (a) Coronary artery disease (CAD): prior MI due to atherosclerosis, coronary artery bypass graft surgery, percutaneous coronary intervention, or angiographic CAD with luminal diameter stenosis of at least one coronary artery at least 50%.

   (b) Cerebrovascular disease: prior ischemic stroke of carotid origin, carotid endarterectomy or stenting, or angiographic carotid stenosis of at least 50%.

   (c) Peripheral arterial disease: prior lower extremity arterial surgical or percutaneous revascularization procedure, or angiographic lower extremity arterial stenosis of at least 50%.

   OR any one of the following CVD risk factors:

   (a) Controlled type II diabetes mellitus (HbA1C ≤ 8.0% within the past 90 days prior to study entry, regardless of use of medications)

   (b) Family history: a first degree relative who had a heart attack, stroke, or documented CVD as defined in the previous section that occurred:

      a. When they were age 55 years or younger for males (father, uncle, or brother)

      b. When they were age 60 years or younger for females (mother, aunt, or sister)

   (c) Current smoking: participant report of smoking at least a half a pack of cigarettes a day, on average, in the past month.

   (d) Hypertension: two consecutive BP readings with either systolic >140 mmHg or diastolic > 90 mmHg; or currently on antihypertensive medications.

   (e) Dyslipidemia: defined as or HDL-C ≤ 40 mg/dL for men or ≤ 50 mg/dL for women, regardless of medication use; or currently on lipid lowering medications.

   (f) A hsCRP ≥ 2mg/L at screening.

8. Lipids at screening visit:

   - Fasting LDL-C ≥ 70 mg/dL (1.81 mmol/L);
   - Fasting TG ≤ 600 mg/dL (6.78 mmol/L).

9. If subjects meet ACC/AHA criteria for statin therapy and are not currently on a statin, subjects must be taking a stable dose of statin for at least 4 weeks, unless they are statin intolerant, refuse to take a statin, or have a medical condition (e.g. chronic hepatitis) where a statin is contraindicated.

10. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 63 days after

the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

Female subjects who are not of childbearing potential (i.e., meet at least one of the following criteria):

- Have undergone a documented hysterectomy or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved post menopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees.
2. Participation in other studies involving small molecule investigational drug(s) (Phases 1-4) within 1 month 5 half lives, whichever is longer except for cholesteryl ester transfer protein (CETP) inhibitors (indefinitely), or biological agents within 6 months or 5 half lives, whichever is longer before the current study begins and/or during study participation (the investigator should refer to documents provided by the subject on the other study to determine the investigational product half life). If the blind has been broken and the Investigator knows (with documentation) that the subject received placebo, he/she can be included.
3. Subjects with prior exposure to bococizumab or another PCSK9 inhibitor.
4. Subjects who are unable to receive injections, as either a self-injection, or administered by another person.
5. History of a cardiovascular or cerebrovascular event or procedure (e.g., myocardial infarction, stroke, transient ischemic attack, angioplasty) during the past 90 days.
6. Congestive heart failure, New York Heart Association functional class IV, or left ventricular ejection fraction measured by imaging known to be <25%. (Imaging not required for study inclusion).
7. Poorly controlled hypertension (on or off treatment) at screening visit or at randomization (defined as the average of two systolic blood pressure (BP) measurements greater than 160 mm Hg or the average of two diastolic BP measurements greater than 100 mm Hg).
8. Any history of hemorrhagic stroke or lacunar infarct.
9. For individuals with undetectable HIV RNA and on stable anti-retroviral therapy, they will be excluded if CD4 is ≤ 50 cells/mm3 at screening visit.

10. Current untreated hypothyroidism or thyroid stimulating hormone (TSH) >1 X upper limit of normal (ULN) at screening. Subjects who are treated and well controlled should be on a stable dose of thyroid hormone for at least 6 months.
11. Current history of alcoholism or drug addiction according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria within 12 months prior to screening. Use of any illicit drug confirmed by urine toxicology test at screening that would in the opinion of the investigator interfere with study procedures or results.
12. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer resolved by excision, or cervical carcinoma in situ).
13. Any disease or condition that might compromise the hematological, renal, hepatic, pulmonary, endocrine, central nervous, immune, or gastrointestinal systems (unless deemed not clinically significant by the Investigator and/or the Sponsor) or confound the interpretation of the study results. Examples of such conditions include but are not limited to nephrotic syndrome, uncontrolled diabetes, excessive alcohol consumption, cholestatic liver disease, unstable mental illness.
14. Undergoing apheresis or have a planned start of apheresis.
15. Initiation of or change in non-lipid lowering prescription drugs, herbal medicine or supplements (including foods with added plant sterols and stanols) within 6 weeks of screening with the exception of initiation or change in multivitamins used for general health purposes. Short-term use of medications to treat acute conditions, and vaccines are allowed (e.g., antibiotics or allergy medication).
16. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibodies (e.g., Enbrel® which contains the Fc portion of an antibody or Lucentis® which is a Fab).
17. Any abnormal hematology values, clinical chemistries, or ECGs at screening judged by the Investigator as clinically significant, which could impact on subject safety, were the potential subject to be included in the study, or interfere with the interpretation of study results.
18. Active phase hepatitis. Stable patients with hepatitis B or C infection >2 years before randomization are eligible.
19. Aspartate transaminase (AST) or alanine transaminase (ALT) > 5 X ULN at screening.
20. Direct bilirubin > 4 X ULN at screening.
21. Calculated fibrosis-4 score > 3.25 (see section 7.2.1.1 for instructions on how to calculate).
22. GFR[1] < 30 mL/min/1.73m^2 at screening or undergoing dialysis.
23. Plans to donate blood during the study.

1 Calculated by Modification of Diet in Renal Disease (MDRD) formula

24. Pregnant females; breastfeeding females.
25. Additional exclusion criteria for the FDG-PET/CT imaging (patients with these exclusions may participate in the rest of the trial):

    a. Significant radiation exposure during the year prior to randomization. Significant exposure is defined as i) more than 2 PCI procedures, ii) more than 2 myocardial perfusion studies, or iii) more than 2 CT angiograms.

    b. Any history of radiation therapy.

    c. Current insulin use.
26. Additional exclusion criteria for CTA imaging (patients with these exclusions may participate in the rest of the trial):

    a. Significant radiation exposure during the year prior to randomization. Significant exposure is defined as i) more than 2 PCI procedures, ii) more than 2 myocardial perfusion studies, or iii) more than 2 CT angiograms (as with FDG-PET/CT).

    b. Any history of radiation therapy (as with FDG-PET/CT).

    c. Any contraindication to β-blocker (atenolol and metoprolol) or nitroglycerin use, because these drugs are given as part of the standard cardiac CT protocol.

    d. Significant renal dysfunction (defined as an eGFR < 60 mL/min/1.73m^2).

    e. Body weight > 300 pounds (136 Kg), because of the CT scanner table limitations.

    f. Allergy to iodine-containing contrast media.

    g. Any history of CABG.

4.3. Randomization Criteria

Subjects will be randomized into the trial based on a randomization scheme prepared for each site provided they have satisfied all subject selection criteria. Subjects will be assigned to either bococizumab 150 mg subcutaneous injection every 2 weeks, or corresponding placebo injection. Subjects who do not complete the trial will not be replaced.

4.4. Lifestyle Guidelines

4.4.1. Contraception

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 63 days after the last dose of investigational product. The subject, will select the most appropriate method of contraception from the permitted list of contraception methods. The investigator will instruct the subject in its consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

5. STUDY TREATMENTS

Subjects will be randomized into one of 2 parallel groups:

- Bococizumab 150 mg subcutaneously every 2 weeks (n=100);
- Bococizumab placebo subcutaneously every 2 weeks (n=100);

5.1. Allocation to Treatment

Each subject will receive a 4 digit identification number at the screening visit. A randomization scheme will be prepared for each study site. The pharmacist at each site will assign blinded study drug according to the randomization scheme. Subjects will self-inject (or if unable to self-inject, receive an injection by a home care giver) 150 mg of bococizumab or bococizumab placebo subcutaneously every 2 weeks. Subjects eligible to be randomized will be assigned a randomization number at week 0 (visit day 1). The randomization will be stratified by statin use. Each subject will receive 26 subcutaneous injections over the period of 52 weeks.

Subjects should adhere to their treatment schedule even if their scheduled clinic visit is rescheduled or missed due to unforeseen circumstances.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Bococizumab is presented as a sterile solution for subcutaneous administration, packaged in a glass pre-filled syringe (PFS) with a fixed needle. Each PFS contains a sufficient amount of bococizumab to provide the intended dose of drug at a concentration of 100 mg/mL. Each syringe contains bococizumab in an aqueous buffered solution.

Placebo is presented as a sterile solution for subcutaneous administration, packaged in a glass PFS with a fixed needle for subcutaneous administration. Each syringe contains an aqueous buffered solution.

Each PFS is for single use only.

5.2.2. Preparation and Dispensing

Bococizumab and placebo will be provided in PFS packaged in cartons with tamper evident seals. The cartons should not be opened until the drug is to be administered. Drug will be dispensed to subjects in the sealed cartons.

5.2.3. Administration

The drug may be injected into either an upper or lower quadrant of the abdominal wall, anterior aspect of the thigh or to the lateral aspect of the upper arm. Study staff, caregivers and subjects should refer to the Subject Study Medication Dosing Booklet and Instruction for specific instructions on the handling and administration of study drug and placebo.

5.2.4. Compliance

Subjects will record their injections in a diary and all injections and dates will be collected in a data collection instrument (case-report form).

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5.3. Drug Storage

All bococizumab should be stored at 2 to 8º centigrade and protected from excessive shaking. Syringes should remain in the protective carton until the time of dosing. Storage conditions stated in the single reference safety document (Investigator Brochure) will be superseded by the label storage.

The investigational products must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

5.4. Concomitant Medication(s)

All subjects will be questioned about HIV and CV concomitant medications (from now on designated as medications) at each visit.

Subjects should take prescribed permitted concomitant medication, as needed, prior to the clinic visit, if it can be administered with water only. Subjects taking a statin should remain on the same dose of the same statin throughout the study. In general, subjects should remain on stable dosages of concomitant medications throughout the study. Changes in doses are allowed if clinically indicated.

6. STUDY PROCEDURES

Subjects will be required to fast prior to all study visits. Subjects who do not fast will be required to return for fasting laboratory tests, at the earliest possible time, before the next scheduled study visit.

6.1. Screening Visit

6.1.1. Visit Day

The following procedures and activities will be performed during this visit:

Obtain written informed consent, obtain and record cardiovascular risk factors and cardiovascular medical history, Obtain and record demographics and general medical history, Measure and record vital signs: heart rate (HR), temperature and BP (Section 7.2.5), Conduct physical examination (Section 7.2.7), Obtain and record prior medications and instruct subjects on the use of concomitant medications (Section 5.5), Conduct 12-lead ECG test (Section 7.2.4), Verify trial eligibility by checking and documenting inclusion and exclusion criteria (Section 4.1, Section 4.2).

Collect specimens for laboratory exams:

- Blood for hematology and chemistry
- Urinalysis for toxicology screen (if necessary);

Provide lifestyle and contraception recommendations (Section 4.4.1);

Do practice injection with placebo to ensure patient is comfortable self-injecting;

Determine if subject meets ACC/AHA criteria for statin therapy.

- If subject meets criteria and is not currently on statin therapy, the subject will be referred back to their PCP.

6.2. Treatment Period

6.2.1. Visit Day 1

Visit day 1 will usually require up to 7 days to complete because of the requirement to perform the brachial artery reactivity flow-mediated dilation, coronary CT angiography, and FDG-PET/CT studies after randomization and before the first treatment.

A qualified FDG-PET/CT and coronary CT angiography interpreter will measure the images. Study drug dispensing will be delayed until after the repeat scan is completed.

Randomization:

Perform brachial artery reactivity flow-mediated dilation study;

Perform FDG-PET/CT imaging;

Perform coronary CT angiography;

Drug dispensation and dosing:

Instruct subject to self-inject;

Assessment during and after subject self-injection or injection by trained study nurse:

Provide lifestyle and contraception recommendations (Section 4.4.1);

6.2.2. Visit Days 29, 57, 85, 169, 211, and 281

The following procedures and assessments should be made before subject self-injection:

Review results from laboratory values;

Measure and record vital signs: heart rate (HR), temperature and BP (Section 7.2.5);

Obtain and record on-going medications and instruct subjects on the use of concomitant medications (Section 5.5);

Inquire for and record adverse events;

Collect specimens for laboratory exams:

Provide diet and therapeutic lifestyle and contraception recommendations (Section 4.4.1);

Administer optional depression questionnaire;

Drug dispensation and dosing

6.2.3. Visit Day 365/End of Study Visit (EOS) (± 3 days)

The following procedures apply to subjects attending for Visit Day 365 or an early discontinuation visit if subjects choose to discontinue participation before Day 365. As detailed in Subject Withdrawal (Section 6.4) every effort should be made to ensure that all subjects complete study participation. Subjects who discontinue study treatment will be encouraged to continue participation in the study and complete all protocol assessments/evaluations. If, however, subjects choose not to continue attending study visits subjects should be encouraged to attend an EOS Visit and the follow up visits if indicated.

Review results from laboratory values;

Measure and record vital signs: heart rate (HR), temperature and BP (Section 7.2.5);

Conduct 12-lead ECG test (Section 7.2.4);

Obtain and record on-going medications and instruct subjects on the use of concomitant medications (Section 5.5);

Inquire for and record adverse events;

Collect specimens for laboratory exams:

Provide lifestyle and contraception recommendations (Section 4.4.1);

Administer optional depression questionnaire;

Collect all used and unused pre-filled syringe cartons.

6.3. Follow-up Visit

A follow up visit will be arranged for all randomized subjects, including those who discontinued early in which case the follow up visit will occur 42 days after EOS Visit.

6.3.1. Visit Day 407 (±3 days)

Review results from laboratory values;

Measure and record vital signs: heart rate (HR), temperature and BP (Section 7.2.5);

Obtain and record on-going medications and instruct subjects on the use of concomitant medications (Section 5.5);

Inquire for and record adverse events;

Collect specimens for laboratory exams:

Provide lifestyle and contraception recommendations (Section 4.4.1,);

Administer optional depression questionnaire.

7. ASSESSMENTS

Every effort will be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject.

7.1. Efficacy

7.1.1. Lipids

Efficacy will be based on the percent change from baseline in fasting lipids, primarily LDL-C. Other lipid efficacy measures will include TC, HDL-C, non-HDL-C, TG, ApoB, ApoA-I, and Lp(a).

The investigators and clinical staff and the subject will remain blinded to lipid results for the duration of the study.

A DMC review will be implemented on all patients with LDL-C levels ≤ 25 mg/dL.

7.1.2. FDG-PET/CT and CCTA Imaging

FDG-PET/CT and CCTA imaging will be performed in randomized subjects at the day 1 visit and again at the day 184.

Participants will have PET imaging after an overnight fast to reduce myocardial FDG uptake. PET imaging will be done 3 hours after administration of 10 mCi of fluorine-18-labelled FDG.[65]

7.1.3. Brachial Artery FMD

The imaging will be done at the primary location of our study team. Analysis of digitized images is performed using dedicated software.

7.1.4. Inflammatory Markers

We will measure inflammatory markers including IL-6, hsCRP, fibrinogen and sCD14, a receptor for endotoxin, using well validated assays. Samples will be collected at the randomization visit and at the week 24/end of study visit.

7.2. Safety

7.2.1. Laboratory

Laboratory tests for safety will be performed at times defined in the Schedule of Activities of this protocol.

7.2.2. Cardiovascular Risk Factors and Medical History

Cardiovascular risk factors and CV medical history will be collected through a dedicated case report form (CRF).

7.2.3. 12-Lead ECG

A 12-lead ECG will be obtained at time points indicated in the Schedule of Activities. ECGs will be kept at the study site as part of subject's records. Clinically significant abnormalities present at baseline will be recorded on the medical history CRF. Additional ECGs may be performed for the evaluation of adverse events at the discretion of the investigator. Clinically significant abnormal findings occurring after baseline should be captured in the adverse event (AE) CRF.

7.2.4. Vital Signs

Temperature, heart rate (HR) and BP will be measured at times specified in the Schedule of Activities.

7.2.5. Adverse Events

All AEs will be recorded in the AE CRF from the time the subject receives the first dose of study drug to the end of study visit.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.2. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.3. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

8.4. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.4.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event

8.4.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determinations

Approximately 200 subjects will be enrolled into the trial to provide comprehensive safety data for bococizumab in HIV-infected subjects. Sample size calculations indicate that smaller numbers are required to demonstrate efficacy for the main study endpoints.

The primary endpoint is percent change from baseline to week 12 in fasting LDL-C and the primary comparison of interest is bococizumab 150 mg compared to placebo. Assuming a dropout rate of 10% for the first 3 months, 54 subjects per treatment group provide more than sufficient power (≥99%) to detect expected treatment differences based on the results of a previous study.[29] These calculations are based on α=0.05 (two-sided), a common standard deviation of 25% (based on previous study results[29]), and on

using the normal approximation of the test statistic for the comparison between two means.

9.2. Efficacy Analysis

The full analysis set (FAS) will be the primary analysis set for the analysis of efficacy data in this study. The FAS includes all subjects who were randomized. Subjects will be analyzed according to their randomized treatment group. The comparison of bococizumab to placebo at week 12 is the primary lipid comparison of interest.

The experiment-wise Type I error of α=0.05 (two-sided) for the primary lipid comparison of interest for the primary endpoint and the key secondary lipid endpoints will be controlled by using gatekeeping and Hochberg procedures. Key secondary lipid endpoints will be formally tested only if the null hypothesis for the primary analysis is rejected. The Hochberg procedure will be applied to the key lipid secondary endpoints. All other statistical tests for secondary lipid endpoints will be performed at the two-sided α=0.05 level; no further corrections will be made for multiple endpoints.

9.2.1. Analysis of Primary Endpoint

Percent change from baseline to week 12 in fasting LDL-C by direct method will be analyzed with a mixed model repeated measures (MMRM) approach.

The MMRM analysis is unbiased under data missing at random, a common and plausible scenario in large confirmatory clinical trials. To support the robustness of the conclusions drawn from this analysis, several sensitivity analyses will be performed to explore the dropout pattern and its possible impact on treatment comparisons.

9.2.2. Analysis of Key Secondary Endpoints

Key secondary lipid endpoints include the following:

- Percent change from baseline in fasting TC, non HDL-C, and ApoB at week 12;
- Percent change from baseline in fasting Lp(a) at week 12;
- Percent change from baseline in fasting HDL-C at week 12.

The above key secondary endpoints will be analyzed in a similar manner as the primary endpoint, where an MMRM model will be used.

9.2.3. Analysis of Secondary Lipid Endpoints

Secondary lipid endpoints include the following:

- Percent change from baseline in fasting LDL-C, TC, Apo B, non HDL-C, Lp(a), and HDL-C at week 24;
- Percent change from baseline in fasting TG and ApoA-I at week 12 and week 24;

- Absolute change from baseline in fasting LDL-C, TC, HDL-C, non HDL-C, TG, ApoB, ApoA-I, and Lp(a) at week 12;
- Absolute change from baseline in fasting TC / HDL-C ratio and ApoB / ApoA-I ratio at week 12 and week 24;
- Proportion of subjects achieving fasting LDL-C ≤70 mg/dL (1.81 mmol/L) at week 12 and week 24;

Endpoints of change and percent change from baseline will be analyzed in a similar manner as the primary lipid endpoint, where an MMRM model will be used.

9.2.4. Analysis of Exploratory Lipid Endpoints

Exploratory endpoints include the following:

- Proportion of subjects achieving fasting LDL-C ≤50 mg/dL (1.29 mmol/L) at week 12 and week 24;
- Absolute and percent change from baseline in PCSK9 at week 12 and week 24;
- Plasma bococizumab exposure at week 12 and week 24.

Endpoints of change and percent change from baseline will be analyzed in a similar manner as the primary lipid endpoint, where an MMRM model will be used.

9.2.5. Analysis of the FDG-PET/CT Endpoints

The main FDG-PET/CT endpoint will be the relative mean change from baseline to 24 weeks in the arterial FDG-PET signal, assessed as a TBR within the most diseased MDS TBR to 24 weeks/end of study will be compared between treatments using an analysis of covariance model including terms for treatment and baseline covariates. The week 24 geometric mean fold change from baseline in the mean of the maximum TBR of segment (MDS) of the index vessel. The week 24 geometric mean fold change from baseline in the mean of the maximum TBR of the MDS will be estimated for each of the two treatment groups and assessed for statistical significance between groups. Data will be log transformed as pre-specified in the Statistical Analysis Plan. Differences between treatments will be assessed based on the observed data values, without adjusting for missing data. Additional sensitivity analyses may be performed using multiple imputation to attempt to correct for any missing data.

The secondary FDG-PET/CT endpoint will be the relative change in the whole vessel TBR within the index vessel.

9.2.6. Analysis of Brachial Artery FMD Endpoints

The main FMD endpoint is the difference between treatment groups in change in FMD between baseline and 24 weeks. Multivariate models will be constructed to assess the

effect of other variables on change in FMD, including traditional coronary risk factors, statin use, and HIV characteristics including current CD4 count, nadir CD4 count, current use of abacavir, didanosine, tenofovir or protease inhibitors, and duration of antiviral therapy and protease inhibitor therapy.

9.3. Analysis of Other Endpoints

9.3.1. Pharmacokinetics and Pharmacodynamic Data

If data permit, the following analyses will be performed for plasma bococizumab concentration data and PCSK9 concentration:

- A listing of all plasma PF-04950615 concentrations by patient at nominal time post dose. This listing will also include actual times post dose.
- A descriptive summary of plasma bococizumab concentrations.
- A listing of all plasma PCSK9 concentrations by patient at nominal time post dose. This listing will also include actual times post dose.
- Descriptive summaries for observed PCSK9 concentrations, absolute and percentage change from baseline in PCSK9 concentrations. Summary statistics of arithmetic mean, % coefficient of variation, standard deviation, median, minimum and maximum will be tabulated by study day.

If data permit, plasma bococizumb, PCSK9 and LDL-C concentrations will also be analyzed by ADA status and neutralizing antibody (nAb) status.

9.4. Safety Analysis

Safety will be assessed through adverse and serious adverse events, vital signs, and physical examination, 12-lead ECG recordings, and safety laboratory tests including anti-drug antibodies, hematology, and blood chemistry studies. Unless otherwise specified, safety analyses will be done in the Safety Analysis Set, which is comprised of all subjects who have received at least one dose of randomized study medication. All summaries of safety data will be descriptive only, unless indicated otherwise.

UCSF CHR/HRPP guidelines will be utilized when reporting adverse events. Adverse events, adverse events leading to discontinuation from treatment, and serious adverse events will be tabulated by treatment group. Summaries will also be provided by severity and relationship to study therapy.

Mean observed and mean change from baseline in systolic blood pressure, diastolic blood pressure, heart rate, and weight will be tabulated by visit according to sponsor standards. Observations of potential clinical concern for these parameters will be tabulated according to sponsor standards. Height and temperature will be listed.

Mean observed and mean change from baseline in hematology and blood chemistry parameters will be tabulated by visit according to sponsor standards. Observations of potential clinical concern for hematology and blood chemistry parameters will be

tabulated by treatment group according to sponsor standards. In addition, the proportion of subjects with anti-drug antibodies will be tabulated by treatment group.

12-lead ECGs will be locally read and the interpretations will be kept at the investigation sites as source documents. Any clinically significant ECG abnormalities will be reported as adverse events. Physical examination findings will be listed.

9.5. Subgroup Analyses

Subgroups of interest include:

- Age (<65 versus ≥65 years)
- Gender
- Any post-baseline LDL-C <25 mg/dL
- HIV status, CD4+ T-cell count above and below the median, specific antiretroviral therapy
- HCV status
- Triglyceride, Lp(a), PCSK9, hs-CRP, IL-6, fibrinogen, sCD14, sCD163 and D-dimer levels above versus below the median.

9.6. Data Monitoring Committee

A Data Monitoring Committee will be composed of an expert in HIV medicine, a lipid expert and a statistician will be responsible for ongoing monitoring of the safety of subjects in the study and will meet periodically to review the safety data according to the DMC Charter. The recommendations made by the DMC (i.e., to alter the conduct of the study, continue as planned, etc.) will be shared between the principal investigator and the sponsor. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

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