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Rationale and design of a Phase II clinical trial of aspirin and simvastatin for the treatment of pulmonary arterial hypertension: ASA-STAT

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Abstract

Background—Pulmonary arterial hypertension (PAH) is a progressive disease which causes exercise limitation, heart failure, and death. Aspirin and simvastatin are highly effective and safe therapies for other cardiovascular diseases characterized by platelet activation and endothelial dysfunction, but have not been formally studied in PAH.

Methods—ASA-STAT is a Phase II, randomized, double-blind, placebo-controlled 2 × 2 factorial clinical trial of aspirin and simvastatin in patients with PAH. A total of 92 subjects were to be randomized to aspirin or aspirin placebo and simvastatin or simvastatin placebo. The primary outcome is the distance walked in six minutes at six months after randomization. Secondary measures include brachial artery flow-mediated dilation, circulating biomarkers of platelet and

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endothelial function, functional class, quality-of-life, and time to clinical end points. The incidence of adverse events will be compared between treatment groups.

Screening and Enrollment—We screened a total of 712 individuals with PAH. Sixty-five subjects were enrolled when the trial was terminated for futility in reaching the primary end point for simvastatin.

Conclusions—This study aims to determine whether aspirin or simvastatin have beneficial biologic or clinical effects in patients with PAH. The safety and side effects of these commonly prescribed cardiovascular drugs will also be assessed.

Keywords

Pulmonary hypertension; Endothelial dysfunction; platelets; Clinical trial

Background

Pulmonary arterial hypertension (PAH) includes idiopathic (IPAH) and heritable forms, as well as PAH associated with connective tissue disease, portal hypertension, anorexigen use, HIV infection, congenital systemic-to-pulmonary shunts, and other comorbidities. In PAH, the small muscular pulmonary arteries show endothelial proliferation and smooth muscle hypertrophy, *in situ* thrombosis, and plexiform lesions. Right ventricular failure ensues, leading to exercise limitation and death.

Reduced prostacyclin (PGI_2) production, elevated endothelin-1 (ET-1) levels, and deficits in nitric oxide (NO) have invited interventions which have proven effective in PAH. Platelet activation, endothelial nitric oxide synthase (eNOS) dysfunction, oxidative stress, and inflammation have not been specifically targeted however. Activated platelets metabolize arachidonic acid via cyclooxygenase (COX), producing thromboxane (Tx) A_2 which causes platelet aggregation, vasoconstriction, and vascular smooth muscle hypertrophy. Patients with PAH have increased TxA_2 production and decreased PGI_2 production, even with treatment. [1, 2] Thrombocytopenia due to platelet trapping in the lungs occurs during PAH "crises"[3, 4] and is associated with worse hemodynamics.[5] Aspirin permanently inactivates platelet COX, lowers the TxA_2/PGI_2 ratio, and has clear benefit in systemic cardiovascular disease. We have shown that aspirin potently inhibits platelet aggregation and synthesis of Tx in PAH as well,[2] offering a potential therapeutic approach through inhibition of this maladaptive eicosanoid pathway.

NO production and eNOS activity are reduced, whereas oxidative stress is increased in patients with PAH.[6, 7] Pulmonary and systemic vascular endothelial dysfunction may impact on symptoms and exercise performance in PAH, therefore therapies which normalize vascular dysfunction could be effective. Statins affect vascular smooth muscle cells (inhibition of proliferation, induction of apoptosis, vasorelaxation) and endothelial cells (enhanced expression and activity of eNOS) and reduce oxidative stress and inflammation. Several studies in animal models of pulmonary hypertension have demonstrated efficacy.[8, 9] One randomized clinical trial in patients with PAH showed that simvastatin decreased right ventricular mass and plasma N-terminus pro-brain natriuretic peptide (NT-proBNP), but had no effect on six minute walk distance (6MWD) at six months.[10] By targeting platelets and endothelial dysfunction, aspirin and simvastatin have potential for the treatment of PAH. The goals of this randomized clinical trial are to show the feasibility of studying these "traditional" cardiovascular therapies in PAH in a National Institutes of Health-funded study and to get estimates of efficacy and safety to guide future studies of these interventions, if beneficial.

Study overview

ASA-STAT is a Phase II randomized, double-blind, placebo-controlled 2 × 2 factorial study to determine the efficacy and safety of aspirin and simvastatin in patients with PAH. The primary hypothesis is that the 6MWD at six months will be greater in subjects assigned to active aspirin or simvastatin than to the respective placebo after adjustment for baseline 6MWD. Secondary outcomes include measures of platelet activation (serum TxB_2, plasma β-thromboglobulin (β-TG), soluble P-selectin) and endothelial function (brachial artery flow-mediated dilation (FMD), plasma von Willebrand factor (vWF)), WHO functional class, Borg dyspnea score, Short Form-36 (SF-36) scores, and time to clinical worsening. Other end points include plasma NT-proBNP, plasma C-reactive protein (CRP), and the incidence of adverse events.

The trial was designed by the PI and the co-investigators and was conducted at four Field Centers (Appendix). The study was funded by the National Heart, Lung and Blood Institute (NHLBI). Study drugs and placebos were provided free of charge by Bayer HealthCare LLC and Merck & Co., Inc. who had no role in the study design, conduct, monitoring, or data analysis or interpretation.

Method

Study subjects

We initially planned to recruit 128 subjects with PAH (anticipating 100 completers) over approximately three years. Due to slower than anticipated recruitment, the target sample size was revised to 92 (anticipating 80 completers) in May 2009 by request of the Data and Safety Monitoring Board (DSMB) (See below). The first patient was randomized in January 2007 and a total of 65 were randomized by September 2009, when the study was terminated for futility of the simvastatin arm (See below).

We included patients with PAH without an indication for aspirin or statin therapy and without risk factors for adverse events from these medications (Table 1). Study participation included a six-month treatment period and a one-month follow-up period (Table 2).

Recruitment and randomization

The Institutional Review Board at each Field Center and an independent DSMB approved the protocol prior to initiation of screening and recruitment.

Patients were identified by medical staff at each Field Center. At baseline, subjects were randomly assigned in a 1:1:1:1 ratio by a Web-based computerized system to daily aspirin 81 mg/simvastatin 40 mg, aspirin 81 mg/simvastatin placebo, aspirin placebo/simvastatin 40 mg, or aspirin placebo/simvastatin placebo. The four combinations of medications were prepackaged in numbered kits and dispensed based on the randomization number provided by the Web-based system. The randomization scheme was permuted block randomization, stratified by type of PAH (idiopathic/heritable vs. other) and center. All study personnel (other than the Data Coordinating Center (DCC) Chair) were masked to treatment assignment, and masking was not broken until all study assessments were completed.

Trial organization

The ASA-STAT Executive Committee was responsible for all aspects of the study (See Appendix). The DCC is based at Columbia University. There are four Field Centers (Columbia University, Johns Hopkins University, University of Pennsylvania, and Tufts Medical Center). The Ultrasound Core Laboratory and the Exercise Core are based at

Columbia University. Blood biomarker assays are being performed at the Laboratory Core at the University of Vermont. An Endpoint Adjudication Committee will review all bleeding events, hospitalizations, and deaths. The trial is registered at clinicaltrials.gov (NCT00384865)

Study drugs

Enteric-coated aspirin 81 mg (Tiny Tablets) and matching placebo were supplied by Bayer HealthCare LLC. Simvastatin 40 mg (Zocor) and matching placebo were supplied by Merck & Co., Inc.

Major bleeding assessed by the investigators warranted permanent discontinuation of the aspirin/placebo study medication, but the simvastatin/placebo medication was continued as were study assessments. Severe or acute anemia and INR > 5.0 warranted interruption of aspirin study drug. A new absolute indication for anti-platelet therapy or statin therapy required discontinuation of both study medications. Persistent elevations in CPK or with symptoms mandated cessation of the simvastatin study drug. Management for increased transaminases depended on whether the subject was also receiving an endothelin receptor antagonist.

If surgical or other invasive procedures warranted temporary discontinuation of aspirin/aspirin placebo, the medication was reinstituted after the procedure according to usual clinical practice. Study drugs were not interrupted for serious adverse events which were not drug-related. Even with permanent discontinuation of one or both study medications, participants were strongly urged to complete all scheduled study visits and assessments. Upon termination of the trial, the DSMB recommended and the NHLBI mandated stopping all study medications of active subjects.

Outcome measures and data collection

The schedule of assessments is presented in Table 2. Each subject had study visits at baseline, six weeks, three months, and six months. There were telephone calls at 1 month, 4.5 months, and 7 months from baseline. At screening, a Research Coordinator provided the subject with a Medication Diary, which included a section for notation of new “as needed” medications or medication changes and a list of generic and trade names of non-steroidal anti-inflammatory drugs (NSAID)/aspirin-containing drugs. The Research Coordinator provided instructions regarding the avoidance of aspirin and NSAIDs and smoking for 14 days prior to the Baseline Visit and throughout the trial.

The Research Coordinator called the study subject 1-2 days before each study visit remind him or her: 1) to not eat or drink (except water) for twelve hours before the study visit, 2) to not exercise heavily in the twelve hours before the study visit, 3) to bring all medications with him or her to the study visit, 4) to bring the Medication Diary, 5) to wear loosely fitting clothing and comfortable walking shoes, and 6) to remind her/him where to go for the study visit.

All subjects underwent evaluation at each study day in the following order, beginning in the early morning: phlebotomy, brachial artery ultrasound, light snack (if desired by the patient), detailed history and physical examination, completion of the SF-36 questionnaire, and six minute walk test (performed > one hour after a light snack).

Biological samples

Phlebotomy was performed using a standardized methodology and minimal tourniquet technique. Study staff presented to Field Center personnel information relating to the

standardized collection of blood samples and proper processing procedures for the array of draw tubes and certified them for quality assurance (QA). Blood was centrifuged and plasma, serum, and cells were stored at −70°C. One phlebotomy and sample processing procedure was observed by central study staff every six months for quality controls (QC).

Flow-mediated dilation (FMD)

Brachial artery ultrasound measures peripheral vascular NO-dependent FMD after transient ischemia. Lower FMD predicts an increased risk of cardiovascular events and death in disease-free participants and congestive heart failure,[11, 12] and interventions which increase FMD improve outcomes.[13, 14] In brief, a blood pressure cuff is placed on the forearm, and a baseline rest image of the brachial artery is acquired. Then, inflation of the cuff above systolic pressure causes artery occlusion; forearm ischemia results in downstream vessel dilation. Cuff deflation produces a brief high-flow state (reactive hyperemia) to accommodate the dilated vessels. The resulting increase in shear stress on the brachial artery endothelium produces FMD, expressed as % increase in artery diameter.

Image acquisition was performed according to a standard protocol at three Field Centers (Columbia University, Johns Hopkins University, and Tufts Medical Center). Two trained readers at the Ultrasound Core will interpret the studies using Vascular Tools (Version 5.05) (Medical Imaging Applications). We will compare FMD at one minute after cuff deflation, maximal FMD, and baseline vessel diameter between treatment groups. All ultrasonographers underwent a one day training session at Columbia University and submitted five mock studies for review for QA. QC measures included having the supervising physician observe a study performed for ASA-STAT every six months at each Field Center. For assessment of reliability, the ultrasonographers performed mock studies on a volunteer on two sequential days every six months.

WHO functional class

The WHO functional classification for PAH has been modified from the well-known New York Heart Association functional classification, with Class I being defined by no symptoms, Class II as symptoms with more than usual activity, Class III as symptoms with less than usual activity, and Class IV with symptoms at rest.

Addition of PAH medication or increased doses of current PAH therapies

The addition of new therapy for PAH or dose increase indicates disease worsening. Often, clinicians will increase medication dose with clinical worsening (specifically, PGI_2 analog therapy). PAH medication additions and dose changes will therefore be analyzed as a secondary end point.

SF-36

The SF-36 is a widely used measure of subjective health status and includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical and emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality; and 8) general health perceptions.

Six-minute walk distance (6MWD)

The primary outcome of the study is the 6MWD at six months after adjustment for the baseline 6MWD. The 6MWD is considered an intermediate end point in PAH and has served as the primary end point for virtually every Phase III clinical trial in PAH. Study staff

trained the technicians at the Field Centers responsible for conducting the unencouraged six minute walk test. QA consisted of a lecture and demonstration of the methodology and certification of each technician after he or she performed an acceptable test on a mock subject. For QC, ASA-STAT clinical coordinating staff observed one ASA-STAT patient performing the six minute walk as a part of a study visit at each Field Center every six months.

Laboratory analyses

Platelets and endothelial cells release several substances upon activation and dysfunction/injury, respectively; inflammation and cardiac dysfunction result in the release of other circulating biomarkers. P-selectin (CD-62P) is a glycoprotein expressed on the platelet surface during activation and shed into the plasma. Patients with PAH have increased soluble P-selectin levels, which correlate with pulmonary vascular resistance and decrease after aspirin administration or chronic epoprostenol therapy.[2, 15] Soluble P-selectin will be measured using an ELISA (R & D Systems).

In platelets, eicosanoid metabolism mostly produces TxA_2, which is rapidly metabolized to the more stable TxB_2, which will be measured in serum using ELISA (Cayman Chemical) . β-TG is released upon platelet activation and will be measured using an ELISA (Asserachrom B-TG, Diagnostica Stago, Inc.)

Plasma vWF is a large multimeric glycoprotein which is released by endothelial injury. vWF will be measured using an immunoturbidimetric assay (Diagnostica Stago, Inc.). Plasma CRP levels will be measured using a nephelometric assay (Siemens BNII). Plasma NT-proBNP will be measured using a chemiluminescent immunometric assay (Roche Elecsys 2010).

Hospitalization for right-sided heart failure

We recorded all hospitalizations during the study. Records from each hospitalization are reviewed by the Endpoint Adjudication Committee. A hospitalization because of lower extremity edema or dyspnea refractory to outpatient increases in dose or frequency of diuretics or specific PAH medications will be considered a right-sided heart failure hospitalization. Hospital admissions that do not meet this definition will be considered non-right-sided heart failure hospitalizations.

Other clinical endpoints

Clinically significant events, such as atrial septostomy, lung transplantation, or death, will be recorded. Cardiovascular death will be defined as: 1) sudden death or 2) death preceded by: a) cardiogenic shock (hypotension resulting in a failure to maintain normal renal or cerebral function for >15 minutes prior to death) or b) heart failure symptoms or signs requiring intravenous therapy or oxygen in the hospital or confinement to bed, in the absence of secondary causes (such as systemic infection or dysfunction of intravenous or subcutaneous medication delivery devices) or alternative causes of death. Other deaths will be considered non-cardiovascular deaths.

Major and minor bleeding will be assessed. A major bleeding episode is defined as: 1) symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), 2) overt bleeding causing a fall in hemoglobin level of ≥ 2 g/dl or requiring surgery or transfusion, or 3) bleeding resulting in permanent functional disability or death. A minor bleeding episode is bleeding which does not meet any of the preceding criteria. All potential endpoints

(bleeding, hospitalization, death) will be evaluated by the Endpoint Adjudication Committee which is blinded to study medication and other information regarding study subjects.

Adherence

Study staff instructed each subject to check a box in the Medication Diary when he or she took each of his study medications for each day. If medications were held or not taken for any reason, the subject left the box empty and made a brief notation for why one, the other, or both medications were not taken.

Statistical considerations

As a Phase II study, the main goals are to assess safety and side effect profiles of aspirin and simvastatin in PAH and to provide initial effect estimates of efficacy for use in designing larger Phase III trials.

The primary end point of the trial is the 6MWD at six months after randomization after adjustment for the baseline 6MWD. Preliminary data suggested that a difference of > 50 m in 6MWD was associated with an improvement in symptoms and survival. A total of 100 subjects (25 in each of the four randomized groups, 50 in each active drug and placebo group) was necessary to detect a difference of 57 m with 80% power assuming no significant interaction between study drugs and without adjustment for the baseline 6MWD. Anticipating 20% attrition, we initially planned for the enrollment of 128 subjects. With a significant interaction between study medications, we had 80% power to detect a difference of 80 m.

In May 2009, the DSMB requested revised sample size calculations using the correlations of baseline and six month 6MWD thus far in the trial and from other sources and using an attrition rate closer to that seen in the trial to that point. With a correlation coefficient between baseline and six-month 6MWD ≥ 0.60, we had 80% power to detect a 57 m difference in 6MWD after adjustment for baseline 6MWD with 80 completers in the absence of a significant interaction between study medications. Using the approximate completion rate in the study, 92 subjects were deemed necessary. With an interaction, there was 80% power to detect an 82 meter difference using the same assumptions. The revised sample size of 92 was approved by the DSMB and NHLBI on June 4, 2009.

Data analysis

Eligible patients were randomized in equal proportion to one of four possible treatment assignments (Figure 1). Patients were stratified at randomization by Field Center and type of PAH. The primary analysis will proceed according to the intent-to-treat principle, including all randomized participants regardless of their compliance with the study treatment or follow-up schedule. Hypothesis testing for the primary and secondary endpoints will be conducted using two-sided $\alpha = 0.05$.

The treatment groups will be compared at baseline with respect to demographics. We will characterize subjects with regard to baseline and follow-up 6MWD, FMD, biomarker levels, and other outcome measures as well as absolute and percentage change between the baseline and six-month assessments.

A very important aspect of a factorial trial is the assessment for an interaction between the two study treatments. As this Phase II trial was not powered for formal statistical testing for an interaction, we will construct 95% confidence intervals for the interaction term for study drugs for each analysis.[16] If the upper bound of this confidence interval for this interaction

term exceeds a clinically relevant effect size, we will consider a significant interaction to be present for those analyses.

The primary analysis will compare the absolute measurement of each primary and secondary endpoint at six month follow-up between active therapy and placebo groups while adjusting for the baseline value. We will use linear regression models for the analysis of the outcome measures with treatment assignment as the independent variable of interest and the endpoint as the dependent variable. If there is no interaction between the study medications, bivariate analyses will proceed "at the margins" by comparing patients assigned to simvastatin compared to those who were not (AS + S0 vs. A0 + 00) and patients assigned to aspirin to those who were not (AS + A0 vs. 0S + 00) for each end point (Figure 1). If a significant interaction exists, we will include an aspirin × simvastatin interaction term in the models. Multiple imputation will be used for missing data for the primary end point. Exploratory analyses will be performed incorporating all of the endpoint assessments (baseline, six weeks, three, and six months) in linear mixed-effects models.

We will assess time to failure (as defined by the addition of new therapies or previously stable PAH therapy dose increases, hospitalization for right-sided heart failure, lung transplantation, atrial septostomy, and cardiovascular and all-cause death) using Kaplan-Meier curves and Cox proportional hazards models. Patients will be censored if they have not experienced any of the events of interest at the end of the study period. There were no interim analyses or stopping rules planned *a priori* for the trial.

Time-line and trial enrollment

The enrollment period lasted from January 2007 to September 2009. In July 2009, the DSMB requested a conditional power calculation by the DCC using the subjects enrolled and it was determined that the trial had a 4.9% chance of detecting a statistically significant difference in 6MWD for simvastatin vs. simvastatin placebo.[17, 18] The DSMB determined that continuing the study with only the aspirin vs. aspirin placebo comparison would lead to a study with low scientific credibility and could not be justified, and the DSMB recommended termination for futility. The DSMB recommended that subjects currently in the trial (N = 16) should discontinue receiving all study drugs and should not be followed or exposed to any additional study procedures after the date of termination (September 25, 2009). Therefore, active subjects stopped study medications and did not return to the Field Centers or have telephone follow-up as of that date. The DSMB reported that there were no significant safety concerns related to the recommendation for termination. The NHLBI accepted these recommendations.

There were 712 PAH patients screened during the enrollment period (Figure 2). Treatment with statins was the reason for exclusion in 155 of patients. Other reasons for non-eligibility included aspirin use in 41 and pulmonary function tests not meeting inclusion criteria (or unavailable) in 241. Those enrolled were somewhat younger, but similar in terms of gender and race, to those screened and not enrolled (Table 3).

Summary

ASA-STAT is a multi-center, Phase-II, randomized, placebo-controlled 2 × 2 factorial trial of aspirin and simvastatin in PAH. This study is designed to 1) explore the feasibility of performing an NIH-funded clinical trial in PAH, 2) find treatment-related effect sizes of aspirin and simvastatin on clinical endpoints in order to plan a Phase III trial, and 3) study the effects of these therapies on platelet and endothelial function.

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Appendix

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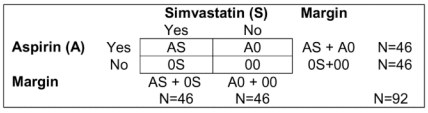

Figure 1.
Randomization scheme

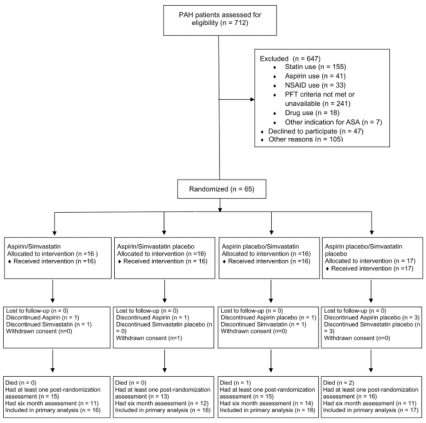

Figure 2.
Flow diagram

Table 1

Inclusion and exclusion criteria

Inclusion criteria

- Previous documentation of mean pulmonary artery pressure of > 25 mm Hg at rest with a pulmonary capillary wedge pressure < 16 mm Hg (or left ventricular end-diastolic pressure < 16 mm Hg) at any time before study entry.
- Diagnosis of PAH which is a) idiopathic, b) heritable, or c) associated with: connective tissue disease, HIV infection, congenital systemic-to-pulmonary shunt, or former anorexigen use.
- Most recent pulmonary function tests showing FEV_1/FVC >50% AND either a) total lung capacity > 70% predicted or b) total lung capacity between 60% and 70% predicted with no more than mild patchy interstitial lung disease on high resolution computerized tomography.
- Ability to perform six minute walk testing without limitations in musculoskeletal function or coordination.
- Negative pregnancy test (women of childbearing potential) at screening.
- Use of medically acceptable contraceptive precautions (women).
- Informed consent.

Exclusion criteria

- Diagnosis of sickle cell disease.
- Clinically significant untreated sleep apnea.
- Left-sided valvular disease (more than moderate), pulmonary artery or valve stenosis, or ejection fraction < 45% on echocardiography.
- Hospitalized or acutely ill.
- Renal failure (creatinine ≥ 2.0).
- Initiation of PAH therapy within three months of enrollment.
- Allergy or hypersensitivity to aspirin or simvastatin administration.
- Absolute indication for aspirin or other anti-platelet therapy.
- Current treatment with statin therapy.
- Inability to avoid non-steroidal anti-inflammatory medications for six months.
- Current or recent use or planned treatment with: amiodarone, cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, cimetidine, danazol, large quantities of grapefruit juice, verapamil, fibrates or niacin.
- Peptic or duodenal ulcer diagnosed within one year.
- Gastrointestinal bleeding within six months.
- Bleeding diathesis.
- History of intracranial hemorrhage.
- Anemia (Hematocrit < 30%) at screening.
- International normalized ratio > 3.0 at screening.
- Severe thrombocytopenia (< 75,000) at screening.
- Hepatic transaminases > 2x the upper limit of normal at the center at screening.
- Chronic liver disease (cirrhosis, chronic hepatitis, etc.) with portal hypertension
- Current or recent (< 6 months) chronic heavy alcohol consumption.
- History of myositis.
- Creatine phosphokinase > 1.5x the upper limit of normal at screening.
- Abnormalities of the arm or hand or radical mastectomy (preventing assessment of flow-mediated dilation).
- Pregnant or lactating women.
- Current use of another investigational (non-FDA approved) drug for PAH.
- Lung transplant recipients.

- Age < 18 years.

Table 2

Schedule of assessments

	Screening	Baseline	Month 1	Week 6	Month 3	Month 4.5	Month 6	Month 7
Visit #	**0**	**1**		**2**	**3**		**4**	
Day#	**−120 − 15**	**0**	**28 ± 7**	**42 ± 7**	**84 ± 7**	**126 ± 7**	**168 ± 7**	**196 ± 7**
Telephone follow-up			X			X		X
Informed consent	X							
Medical history	X	X						
Symptoms/WHO class		X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
Vitals/Physical exam		X		X	X		X	
Blood work (Safety)	X*			X	X		X	
Six minute walk test		X		X	X		X	
Brachial artery ultrasound		X		X	X		X	
Blood biomarkers**		X		X	X		X	
Lipid levels		X		X	X		X	
SF-36		X		X	X		X	
Dispense study drug		X		X	X			
Adverse events			X	X	X	X	X	
Medication compliance			X	X	X	X	X	
Assessment of masking							X	

*Within 28 days of baseline visit.

**Include vWF, TxB_2, B-TG, P-selectin, nt-proBNP, CRP.

Table 3

Screened and enrolled subjects

	Screened, not enrolled* (N = 647)	Eligible, enrolled (N = 65)
Age, years	55 ± 16	50 ± 14
Female gender, %	78	85
Race/ethnicity, %		
Non-Hispanic Caucasian	68	65
Hispanic	7	14
African-American	20	17
Asian	4	5
Multiracial	1	--

*N = 16 missing age, 19 missing gender, 110 missing race/ethnicity