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TITLE: Safety of Simvastatin in LAM and TSC (SOS)

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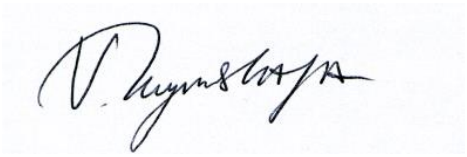

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A Pilot, Safety Study of Simvastatin in Patients with Sporadic Pulmonary Lymphangioleiomyomatosis (LAM) and LAM Associated with Tuberous Sclerosis Complex (The SOS Study)

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Participating Institutions and Investigators

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PROTOCOL SUMMARY

Protocol Number:	04
Protocol Title:	A Pilot, Safety Study of Simvastatin in Patients with Sporadic Pulmonary Lymphangioleiomyomatosis (LAM) and LAM Associated with Tuberous Sclerosis Complex (TSC) (The SOS Study)
Study Chair:	Vera P. Krymskaya
Statistician:	Kathleen J. Propert, ScD
Current Status:	Development; pre IND and Pre-IRB submission
Sample Size:	Up to 10 patients
Target Enrollment Period:	3-6 months
Participating Sites:	University of Pennsylvania
Study Design:	Phase II, open label, safety study
Study Duration:	5.5 months (approximately 164 days)

OBJECTIVES:

The primary objective of this study is to determine the safety of simvastatin in the treatment of LAM-S or LAM-TS in patients on a stable (for at least 3 months) dose of sirolimus or everolimus.

Secondary objectives include:

- To assess the effect of simvastatin on forced expiratory volume in 1 second (FEV_1).
- To assess the effect of simvastatin on forced vital capacity (FVC).
- To assess the effect of simvastatin on diffusing lung capacity (DLCO).
- To assess the effect of simvastatin on VEGF-D serum levels.
- To assess the effect of simvastatin with questionnaire- based assessments of dyspnea, fatigue, and quality of life (QOL) using the **St.** George's Respiratory Questionnaire (SGRQ) and the Functional Performance Inventory (FPI).

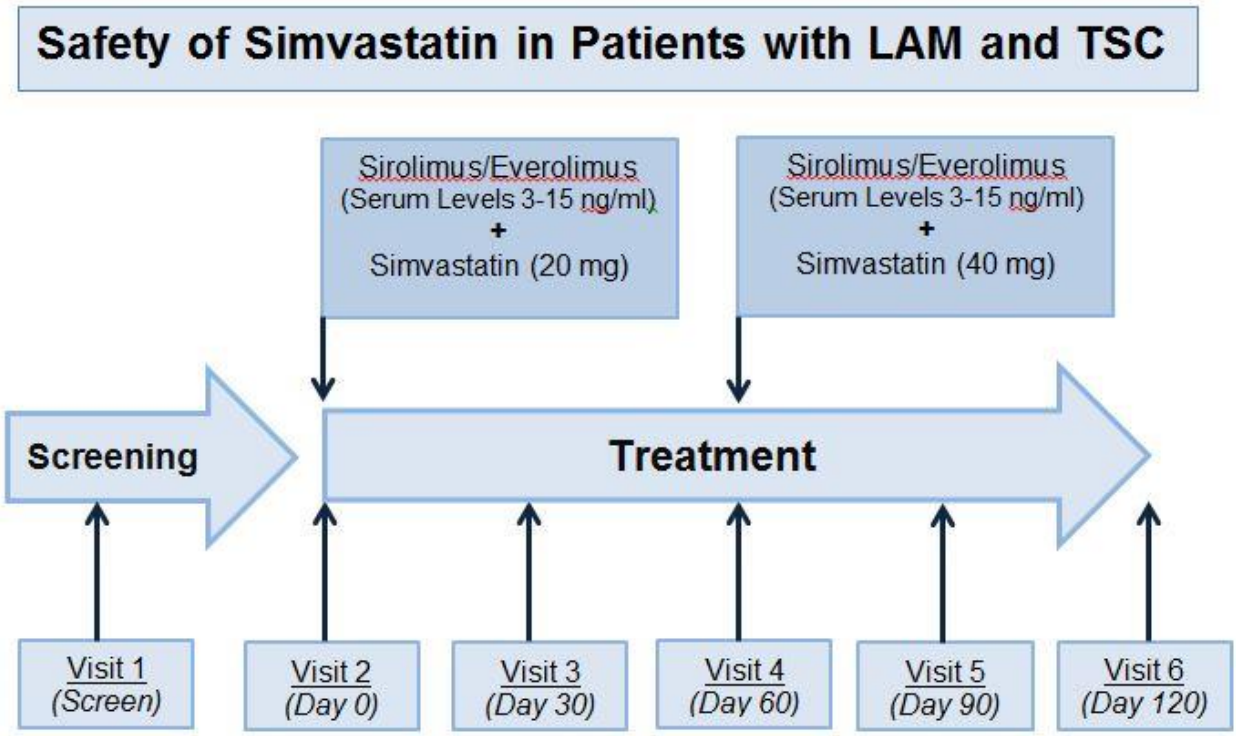
- Preliminarily assess effectiveness and clinical benefit in this patient population.

TREATMENT:

Agent:	Simvastatin
Dosage, schedule, route of administration:	Dose escalation from 20 mg once-daily (QD) for the first two months to 40 mg QD for months 3 and 4. The study drug will be given orally.
Safety Issues:	Simvastatin, a cholesterol lowering agent, is effective in preventing cardiovascular diseases. Concomitant administration of strong CYP3A4 inhibitors, gemfibrozil, cyclosporine, or danazol is contraindicated. Simvastatin is not to be used in patients with myopathy, hypersensitivity to any component of the medication, active liver disease, pregnant women, or nursing mothers. The most commonly experienced adverse events with simvastatin are: rhabdomyolysis, upper respiratory infection, headache, abdominal pain, constipation, and nausea.
Primary Outcome Measures:	Safety of simvastatin in the treatment of LAM-S and LAM-TS patients on a stable (for at least 3 months) dose of sirolimus or everolimus.
Secondary Outcome Measures:	FEV1, FVC, DLCO, VEGF-D, and QOL; signs of clinical benefit.
Statistical Considerations (sample size and analysis plan):	Up to 10 evaluable patients will be enrolled and treated with increasing doses of simvastatin for 120 days. We anticipate a 10% attrition rate. The analysis will be based on an intention to treat design. The final analysis will occur after the last enrolled patient has completed the 120 day visit.
Sponsors (federal, state, foundation and industry support):	LAM Foundation

STUDY DESIGN:

A Phase II, open label, safety study of up to 10 patients with LAM-S and LAM-TS on a stable (for at least 3 months) dose of sirolimus or everolimus. Eligible patients will be assigned to receive 20 mg of simvastatin once daily for a period of two months. The dosage of simvastatin will be advanced to 40 mg once daily in months 3 and 4.



STUDY POPULATION:

Inclusion criteria:

- Female, age 18 and older with clinically definitive diagnosis (biopsy proven or compatible chest CT/MRI scan) of sporadic LAM (LAM-S) or LAM associated with TS (LAM-TS).
- Treated with a stable (at least 3 months) dose of sirolimus or everolimus
- Negative pregnancy test (women of child bearing potential) at screening.
- Women of childbearing potential must be using barrier, medically acceptable contraceptive precautions.
- Signed and dated informed consent.

Exclusion criteria:

- Age < 18 years
- Known allergy to simvastatin or currently taking simvastatin, or therapy with a medication in the same class as simvastatin within the past 30 days.
- Allergy to sirolimus or everolimus.
- Current use of other than sirolimus or everolimus investigational drug for TSC or LAM within the past 30 days.
- Use of estrogen containing medications, including birth control pills, within the 30 days prior to enrollment.
- Treatment within 30 days of screening with drugs having known metabolic interactions with statin drugs, including: strong CYP3A4 [cytochrome P450 3A4 metabolism] inhibitors (such as itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, azithromycin, erythromycin, clarithromycin, etc), gemfibrozil, cyclosporine, danazol, verapamil, diltiazem,

dronedarone, amiodarone, amlodipine, ranolazine, lomitapide, and other lipid lowering medications (such as niacin [nicotinic acid], digoxin, warfarin, sildenafil, etc)

- Participation in another clinical study(ies) of an investigational treatment or drug within 30 days prior to the screening visit.
- amiodarone; within the past 30 days.
- Significant dysfunction of liver (ALT > 2X ULN), kidney (serum creatinine > 1.5X ULN), or blood (leucopenia (ANC<2000), anemia, Hgb < 11 gm/dl).
- History of inflammatory muscle disease or myopathy.
- Bleeding diathesis or anticoagulant therapy.
- Uncontrolled hyperlipidemia or diabetes.
- Pregnant, breast feeding, or plan to become pregnant within the next 6 months
- Inadequate contraception (must agree to barrier method)
- History of organ transplant.
- Active on transplant list.
- Severe or uncontrolled medical conditions which would cause an unacceptable safety risk or compromise compliance with the protocol.
- Unstable seizures (recent changes in pattern or anti-epileptics).
- Mental illness or cognitive deficit precluding informed consent..
- Inability to attend scheduled clinic visits or comply with study procedures.

PRIMARY ENDPOINTS:

- Safety of simvastatin in the treatment of LAM-S or LAM-TS patients on a stable (for at least 3 months) dose of sirolimus or everolimus.

SECONDARY ENDPOINTS:

- Effect of simvastatin on forced expiratory volume in 1 second (FEV1) at days 0, 60, and 120.
- Effect of simvastatin on forced vital capacity (FVC) at screening and at days 0, 60, and 120.
- Effect of simvastatin on diffusing lung capacity (DLCO) at screening and at days 0, 60, and 120.
- Effect of simvastatin on VEGF-D serum levels at days 0, 30, 60, 90, and 120.
- Signs of clinical benefit.

STUDY OBSERVATIONS:

- Patients will be evaluated in person at baseline and at each study visit day.
- Chest x-rays will be obtained at screening and day 120.
- Laboratory tests including a complete blood count, routine chemistry tests (creatinine and transaminases) and lipid panel will be performed at screening and at days 30, 60, 90, and 120.
- Blood work for VEGF-D will be performed at days 0, 30, 60, 90 and 120 and for sirolimus or everolimus blood levels at screening and days 30, 60, 90 and 120.
- Patients will have spirometry (FEV1, FVC, and DLCO) performed at days 0, 60, and day 120.

SAMPLE SIZE AND POWER:	A total of up to 10 evaluable patients will be enrolled. As this is a safety study with a small number of patients, data will be compiled in descriptive tables of results.
DATA ANALYSIS:	All study data will be collected via systems that comply with all applicable guidelines regarding patient confidentiality and data integrity. University of Pennsylvania IRB approval for the protocol must be on file before accrual can occur. Data will be collected on the study case report forms and will be stored in the research team's office, which is secured and locked daily. Patients will be evaluated for safety if they have received at least one dose of simvastatin. The frequency, severity and duration of all adverse events, regardless of cause, will be recorded on the case report forms. Adverse events will be tabulated by body system and by severity using the NCI Common Terminology Criteria for Adverse Events v4.0, which can be obtained from the CTEP Website: http://ctep.cancer.gov/reporting/ctc.html. Tables will be generated for all adverse events including those that are judged to be possibly, probably or definitely related to the simvastatin. All adverse events will be reviewed by a Data Safety Monitoring Board.

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ABSTRACT

Pulmonary LAM, which can be sporadic (LAM-S) or associated with tuberous sclerosis (LAM-TS), is a rare lung disease affecting predominantly women of childbearing age that manifests by neoplastic growth of atypical smooth muscle-like LAM cells, lung cyst formation, obstruction of lymphatics, and spontaneous pneumothoraces (*1*). Current treatment with rapamycin analogs, which are not FDA-approved for treatment of LAM-S and LAM-TS, but are commonly used based upon published reports, stabilize lung function but does not prevent further disease progression (*1, 2*). The rapalogs are cytostatic agents and cessation of treatment resumes decline in lung function. Because of this limitation new combinational therapy targeting LAM cell death is needed.

Preclinical evidence demonstrates that simvastatin acts as a pro-apoptotic agent in *in vitro* and *in vivo* studies in cells and tumor lesions deficient for *TSC2*, inactivation mutation of which cause LAM and TS (*3, 4*). HMG-CoA reductase inhibitors (statins) are very safe, highly effective therapies used by millions of people (*5, 6*). Simvastatin decreases cholesterol, reduces cancer incidence, stabilizes the endothelial cell layer and decreases inflammation. In preclinical studies the combination of rapamycin and simvastatin inhibited xenograft tumor growth and completely blocked the recurrence of xenograft tumors after treatment withdrawal (*4*). In mouse model of LAM, treatment with rapamycin and simvastatin prevented both growth of TSC2-null lesions and lung destruction (*3*). These findings have fundamental translational significance for combinatorial therapeutic strategies to induce the death of LAM cells, potentially obviating the need for continuous, life-long suppressive therapies. We have designed a Phase II, open label, safety trial to initiate the study of this potentially useful intervention.

We propose to conduct a safety study of simvastatin treatment of patients with LAM-S and LAM-TS. We aim to determine the safety of simvastatin in combination with sirolimus or everolimus over 4 months.

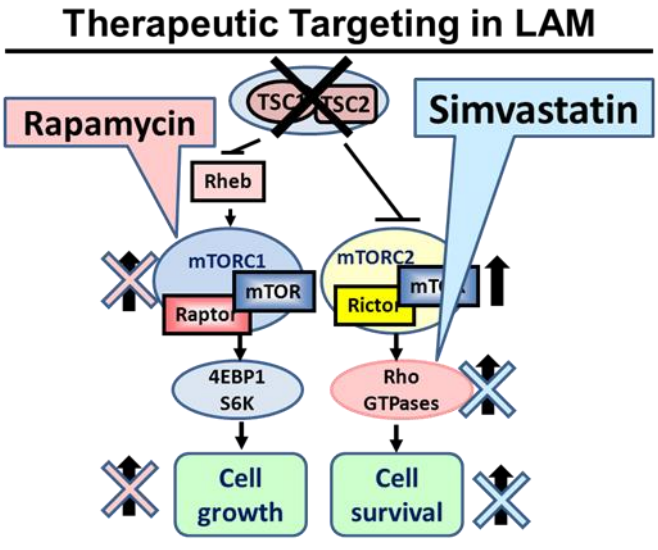


Figure 1. Deregulated cell signaling in LAM and its therapeutic targeting.

1. Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures

1.1 Background and Significance

Pulmonary lymphangioleiomyomatosis (LAM) is a slowly progressive neoplasm that targets the lung, causing cystic destruction and respiratory failure over one to two decades (*1*). LAM occurs in about 3.4–7.8 per million women (although it is likely to be substantially underdiagnosed) and in at least 30% of women with tuberous sclerosis complex. Clinically significant LAM occurs almost exclusively in women, although radiographic evidence of cystic lung disease consistent with LAM and a few biopsy-documented cases of LAM have been reported in men with and without TSC. The average age at diagnosis is about 35 years, typically delayed by 3–5 years due to confusion with more common causes of dyspnea, including asthma or chronic obstructive lung disease (*1*).

Up to 93% of patients with TSC and 32% of patients with LAM develop renal tumors called kidney angiomyolipomas (AML) (*1*). These tumors cause significant morbidity and mortality, and effective systemic treatment is not currently available. Both TSC and LAM are known to be caused by mutations in either of two tumor suppressor genes *tuberous sclerosis complex 1* (*TSC1*), encoding hamartin protein, or *TSC2*, encoding protein tuberin. When either *TSC1* or *TSC2* gene contain inactivating mutations, tuberin or hamartin produced by the gene is defective or deficient, protein function is lost, inducing the constitutive activation of mTOR signaling pathway that deregulates cell growth and survival (*1*). Figure 1 illustrates the deregulated TSC1/TSC2 signaling and its potential therapeutic targeting in LAM and TSC patients. Growth of LAM cell lesions in the lung and AML in kidney is partially suppressed by treatment with the FDA-approved drugs Everolimus or Sirolimus targeting the mTOR signaling pathway. Cessation of therapy results in tumor regrowth. While this therapy intervenes with tumor growth, none adequately addresses the tumor cell survival.

1.2 Activation of mTOR signaling and increased cell growth

A breakthrough in understanding neoplastic pathophysiology in TS and LAM has resulted from the discovery of TSC1/TSC2 tumor suppressor complex as a negative regulator of the mechanistic target of rapamycin (mTOR) (*7*), an integrator of growth factor, nutrient, energy and stress signaling (*8, 9*). TSC2 forms a tumor suppressor complex with TSC1 and regulates mTORC1 by directly controlling the activity of the small GTPase Rheb via the GTPase activating protein (GAP) domain of TSC2 (*10*). Rheb binds to raptor and controls the activity of the mTOR that phosphorylates p70 S6 kinase (S6K1) and 4E-BP1 (*9*). Importantly, TSC2-dependent S6K1 activation suppresses

phosphatidylinositol 3-kinase (PI3K) signaling, named a negative feedback loop, that may explain the benign tumorigenesis in TS and LAM (*11*) and has implications for the therapeutic targeting of mTORC1. Activity of mTORC1 is sensitive to the inhibition by bacterial microlide rapamycin (*12*), which by binding with FKBP12 (FK506-binding protein of 12 kDa) interacts with FKBP12-binding domain of mTOR and inhibits mTORC1 (*13*). The discovery of the TSC2 as a negative regulator of the mTORC1 (*14, 15*) and inhibitory effects of rapamycin in preclinical studies (*14, 16-18*) provided a rationale for use of rapamycin analogs in the clinic. Current rapamycin-based therapy stabilizes lung function in LAM (*19*) and slows down the disease progression that is resumed upon the cessation of treatment (*20-22*). The limitation of rapamycin as a cytostatic agent indicates the need for novel TS and LAM therapy targeting cell survival.

1.3 Small GTPase RhoA, statins, and TSC2-null cell survival

TSC1/TSC2 regulates mTOR, which forms two functionally distinct complexes mTORC1 and mTORC2 (*9*). mTORC1-independent regulation of the actin cytoskeleton occurs through mTORC2-dependent regulation of RhoA and Rac1 GTPases (*9, 23*), and Rac1 is required for mTOR activation (*24*). In TSC2-null and human LAM-derived cells, Rho GTPase activity is required for cell adhesion, motility, proliferation and survival (*4, 25, 26*).

TSC2-deficient cells may also evade apoptosis via activation of RhoA GTPase. We found that downregulation of RhoA in TSC2-deficient rat-derived cells increases apoptosis and upregulates the proapoptotic proteins Bim, Bok, and Puma (*4*). Importantly, the RhoA activation appears to be dependent on TORC2, rather than TORC1, and inhibition of RhoA using simvastatin induces apoptosis *in vitro* and *in vivo*. Most importantly, the combination is sirolimus and simvastatin inhibited xenograft tumor growth and completely blocked the recurrence of xenograft tumors after treatment withdrawal (*4*). In another study using mouse model of LAM, TSC2-null lesions and alveolar destruction were differentially inhibited by rapamycin, which inhibits TSC2-null lesion growth by a cytostatic mechanism, and simvastatin, which inhibits growth of TSC2-null lesions by a predominantly pro-apoptotic mechanism (*3*). Treatment with simvastatin markedly inhibited MMP-2, MMP-3 and MMP-9 levels in lung and prevented alveolar destruction. The combination of rapamycin and simvastatin prevented both growth of TSC2-null lesions and lung destruction by inhibiting MMP-2, MMP-3 and MMP-9 (*3*). The results thus support further investigation of the combination of rapamycin and simvastatin as a potential treatment for subjects with AMLs in TSC and LAM.

Statins are small molecule inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the synthesis of mevalonate, a fatty acid intermediate in *de novo* cholesterol biosynthesis. Statins including simvastatin, pravastatin, lovastatin and mevastatin are derived from fungi, or made synthetically such as atorvastatin and fluvastatin (*27*). All statins are lipophilic except pravastatin (*27*). These agents are effective in preventing cardiovascular disease largely due to lowering cholesterol levels (*5, 6*) and due to their "pleiotropic" effects (independent of their lipid-lowering properties) in non-cardiovascular diseases, including cancer (*28*), rheumatologic

(*29*), and neurological disorders. Pleiotropic effects of statins include among others, the inhibition of isoprenoid intermediates involved in oxidative stress, inhibition of L-type Ca^{2+} current (*30*), cell proliferation (*4*), invasion, metastasis, induction of apoptosis in leukemia, smooth muscle, prostate, and breast cancer (*27*). Statins (simvastatin) have protective effects against oxidative stress, matrix metalloproteinase and inflammation in preclinical studies (*3, 31*). Statins also show potential uses in COPD, osteoporosis, diabetes and depression (*32*).

HMG-CoA inhibition in cholesterol biosynthetic pathway suppresses synthesis of isoprenoids such as geranyl pyrophosphate and farnesyl pyrophosphate, which are required for posttranslational modification of membrane-bound small GTPase including Rho, Rac1, and Ras (*33*). Geranylgeranylation and farnesylation of these proteins regulate their translocation to plasma membrane and activation. Inhibition of geranylgeranylation and/or farnesylation induces statin-dependent cell apoptosis (*32*). In some cell types inhibition of geranylgeranylation stimulates apoptosis while farnesylation appears to be less important (*32*). In our studies co-treatment of geranylgeranyl pyrophosphate with simvastatin rescued rat TSC2-null ELT3 cell survival, indicating that simvastatin effects on RhoA activity in TSC2-null cells are modulated by geranylgeranylation. Simvastatin had little effect on mTOR and S6K activation suggesting little effect of simvastatin on Rheb farnesylation. In contrast, atorvastatin inhibited both farnesylation of Rheb and geranylgeranylation of RhoA in TSC2-/- mouse embryonic fibroblasts (*34*). Thus, inhibition of geranylgeranylation and/or farnesylation may have differential effect depending on type of cell and/or statin.
In vitro and *in vivo* preclinical studies using atorvastatin and simvastatin alone and in combination with rapamycin have been reported. Atorvastatin inhibited growth of *TSC2-/-p53-/-* MEFs and TSC2-null ELT3 cells from Eker rat *in vitro* (*34*) but had little effect on subcutaneous tumors formed by *TSC2-/-p53-/-* MEFs (*35*). We found that downregulation of RhoA in TSC2-deficient rat-derived cells increases apoptosis and upregulates the proapoptotic proteins Bim, Bok, and Puma (*4*). Importantly, the RhoA activation depends on mTORC2, rather than mTORC1, and inhibition of RhoA using simvastatin induces apoptosis *in vitro* and *in vivo*. Importantly, the combination of rapamycin and simvastatin inhibited xenograft tumor growth and completely blocked the recurrence of xenograft tumors after treatment withdrawal (*4*). In another study using mouse model of LAM, TSC2-null lesions and alveolar destruction were differentially inhibited by rapamycin, which inhibits TSC2-null lesion growth by a cytostatic mechanism, and simvastatin, which inhibits growth of TSC2-null lesions by a predominantly pro-apoptotic mechanism (*3*). The combination of rapamycin and simvastatin prevented both growth of TSC2-null lesions and lung destruction by inhibiting MMP-2, MMP-3 and MMP-9 (*3*).

1.3.1 Rationale for proposed study

This is a pilot, safety study with plans for a multi-center Phase II once safety has been established. These findings have fundamental translational significance for combinatorial therapeutic strategies to induce the cell death in LAM lung lesions. Pre-clinical results demonstrate the beneficial effects of combinational treatment with rapamycin and simvastatin and support further investigation of the combination of rapamycin and statins

as a potential treatment for subjects with TS and TS-LAM. While statins are very safe, highly effective therapies and used by millions of people to reduce the incidence of cancer, this study plans to better understand the mechanism and evaluate the safety of simvastatin when given to LAM-S and LAM-TS patients treated with everolimus or sirolimus.

1.4 Study Agents

1.4.1 Simvastatin Information, Interactions, Administration, Toxicities

Simvastatin, a HMG-CoA reductase inhibitor statin, is a lipid lowering drug (*36*). Statins are commonly used in the treatment of hyperlipidemia and cardiovascular diseases. Simvastatin reduces the levels of LDL cholesterol, triglycerides and total cholesterol and raises HDL cholesterol. The metabolism of this medication may affect the occurrence of side effects and cause drug interactions. Simvastatin is also metabolized in the liver by cytochrome P450 (CYPs) CYP3A4 is specifically responsible for simvastatin metabolism (*37*). Since simvastatin is metabolized by CYP3A4, it may interact with other drugs that are also metabolized by the same isoform of the enzyme such as rapamycin. Some possible side effects of simvastatin use includes myopathy, muscle weakness, rhabdomyolysis (*38*).

Rapamycin, also known as sirolimus or everolimus, is an inhibitor of mTOR and a potent immunosuppressive drug that is clinically used for organ transplants (*39*). It prevents the rejection of transplanted organs and tissues. Metabolism of rapamycin occurs in the liver and the small intestine by the CYP3A4 family of enzymes; 3A4 is most likely to be the main isoform of the 3A subfamily responsible for sirolimus or everolimus metabolism. Statistics show a significant parallel between rapamycin metabolism and P450 3A4 activity. Inactivation of P450 3A4 inhibits metabolism of rapamycin. So, concomitant administration of rapamycin with other P450 3A substrates or inducers can alter the oral bioavailability of these drugs (*40*). Rapamycin is also a substrate of P-glycoprotein, a membrane protein in the small intestine that pumps drugs out of the cell (*41*).

Since simvastatin and rapamycin are metabolized by the same enzyme, using them together can potentially increase the blood levels or add to the side effects of either medication. Because they bind to the same protein, the drugs compete for binding sites and may have antagonistic effects when used together. Competition can potentially result in elevated concentration of sirolimus, increasing the risk of myopathy or rhabdomyolysis (*42*). This may have a dangerous side effect on the muscles; so, patients should be monitored for muscle pain or weakness. There have not been many clinical reports on the interactions between simvastatin and rapamycin. However, one report explains the severe interaction between simvastatin and rapamycin which resulted in rhabdomyolysis in a liver transplant patient. A 56 year old man underwent liver transplantation and was simultaneously administered rapamycin and simvastatin. Thereafter, he experienced severe muscle pain and was unable to ambulate. He suffered from rhabdomyolysis and acute renal failure probably due to secondary drug interaction between simvastatin and rapamycin (*43*). Due to the pharmacokinetic interaction between these two agents, they

should be administered hours apart since co-administration can increase the risk of side effects. Dosage modification of sirolimus may also ameliorate the hyperlipidemic effects (*42*).

The study will use generic simvastatin 20 mg and 40 mg for daily oral administration. Simvastatin 40 mg daily is the recommended dosage for patients at high risk for cardiac events, due to existing coronary heart disease, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease. Simvastatin has been extensively studied at the recommended dose of 40 mg per day (*5*). Simvastatin is metabolized by cytochrome P450 isoform 3A4 (CYP3A4). The primary indications include secondary prevention for coronary artery disease and for treatment of hypercholesterolemia. Drug interactions include a slight potentiation of warfarin anticoagulant effect and mild increase in serum digoxin concentration, neither of which are clinically significant.

Simvastatin has been evaluated for adverse reactions in over 21,000 patients; only 1.4% discontinued therapy due to adverse experience. Rhabdomyolysis and elevations in serum transaminases are the two main side effects of simvastatin. Large clinical trials have shown no significant differences in the incidence of elevated creatine phosphokinase (CPK) 4-10X the upper limit of normal (ULN) between simvastatin (0.19%) and placebo (0.13%) or myopathy (CPK > 10X ULN) (*5*). The number of subjects with elevated transaminases (2-4X ULN) was also small and no different than placebo (1.35% for simvastatin, 1.28% for placebo, p=NS) (*5*). Treatment cessation due to this complication was comparable between the groups (0.5% for simvastatin, 0.3% for placebo).

Patients who are eligible will receive instructions for simvastatin and the initial one month supply. Patients will be instructed to take simvastatin in the evening and advised to avoid grapefruit juice due to the potential for an interaction. Patients will be reminded about the side effects of simvastatin, and will be given a drug information sheet, including all adverse drug interactions.

Patients will be carefully monitored at visits 3, 4, 5 and 6 for signs and symptoms of simvastatin side effects including upper respiratory infection, headache, abdominal pain, constipation, and nausea.

1.4.2 Drug Information for Simvastatin

Simvastatin is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to (per package insert):

- Reduce the risk of total mortality by reducing coronary heart disease (CHD) deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events.
- Reduce elevated total-C, LDL-C, Apo B, triglycerides (TG) and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

- Reduce elevated triglycerides (TG) in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.
- Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

We will monitor patient lipids to ensure adequate levels of HDL.

Limitations of Use – Simvastatin has not been studied in Fredrickson Types I and V dyslipidemias.

The use of simvastatin is contraindicated with the administration of strong CYP3A4 inhibitors and gemfibrozil, cyclosporine, or danazol. It is also not to be used in patients with hypersensitivity to any component of this medication, active liver disease, and with elevations in hepatic transaminase levels. It is also recommended that the dose of simvastatin not exceed 10 mg daily if patients are taking verapamil, diltiazem, and dronedarone. Simvastatin should not exceed 20 mg daily if patients are taking amiodarone, amlodipine, and ranolazine. Women who are pregnant or may become pregnant or are nursing mothers should not take simvastatin. All patients should avoid grapefruit juice.

Most common adverse reactions (incidence ≥5.0%) are: upper respiratory infection, headache, abdominal pain, constipation, and nausea.

Patients should be advised of the increased risk of myopathy: rhabdomyolysis has been seen in patients taking the 80 mg dose.

Simvastatin dosing ranges from 5 mg to 40 mg once daily. The typical starting dose is 10 mg or 20 mg once a day in the evening. The recommended starting dose for patients at high risk of CHD is 40 mg/day.

2. Objectives and Specific Aims

2.1 Objectives

The hypothesis to be tested is whether simvastatin can be safely added to the treatment of LAM-S or LAM-TS patients who have been on a stable (for at least three months) dose of mTOR inhibitors either sirolimus or everolimus. Specific objectives are:

Primary:

- Safety of simvastatin in the treatment of LAM-S and LAM-TS patients on a stable (for at least 3 months) dose of sirolimus or everolimus

Secondary:

- To assess the effect of simvastatin on forced expiratory volume in 1 second (FEV_1).
- To assess the effect of simvastatin on forced vital capacity (FVC).
- To assess the effect of simvastatin on diffusing lung capacity (DLCO).
- To assess the effect of simvastatin on VEGF-D serum levels.
- To assess the effect of simvastatin with questionnaire-based assessments of dyspnea, fatigue, and quality of life (QOL)) using the **St. George's Respiratory Questionnaire (SGRQ) and the Functional Performance Inventory (FPI)**.
- To preliminarily assess effectiveness and clinical benefit in this patient population.

2.2 Specific Outcomes

2.2.1 Primary Outcome

The primary outcome will be to determine if simvastatin can be used safely in the treatment of LAM-S or LAM-TS patients on sirolimus or everolimus.

2.2.2 Secondary Outcome

Secondary outcome measures will include effect of simvastatin addition to mTOR inhibitor therapy, either sirolimus or everolimus, on forced expiratory volume in one second (FEV1), forced vital capacity (FVC), diffusing lung capacity (DLCO), serum VEGF-D levels, questionnaire based assessments of dyspnea, fatigue, and quality of life (QOL), and clinical benefit. The final analysis will occur after the last actively enrolled patient has completed the four month study visit.

3. Study design

This is an open label, non-randomized, dose-escalation study conducted as a pilot safety study. Patients will continue on their existing background therapy of either sirolimus or everolimus for treatment of their LAM or LAM-TS disease. Each patient is anticipated to participate in the study for approximately 5.5 months (approximately 164 days).

3.1 Identification and screening

Patients will be identified by the medical staff that care for patients with LAM-S and LAM-TS at the LAM clinic at the University of Pennsylvania Health System. Study staff expect to screen up to 10 patients over 3-6 months. Potentially eligible patients will be approached by their physician, and then by study staff. Potential patients will be informed about the study, and following completion of the informed consent process, a

screening evaluation will be performed. The patient will provide informed consent *before* any study procedures are performed.

3.2 Patient selection criteria

3.2.1 Inclusion criteria

- Female, age 18 and older with clinically definitive diagnosis (biopsy proven or compatible chest CT/MRI scan) of sporadic LAM (LAM-S) or LAM associated with TS (LAM-TS). Treated with a stable (at least 3 months) dose of sirolimus or everolimus
- Treated with a stable (at least 3 months) dose of sirolimus or everolimus
- Negative pregnancy test (women of child bearing potential) at screening.
- Women of childbearing potential must be using barrier, medically acceptable contraceptive precautions.
- Signed and dated informed consent.

3.2.2 Exclusion criteria

- Age < 18 years
- Known allergy to simvastatin or currently taking simvastatin, or therapy with a medication in the same class as simvastatin within the past 30 days.
- Allergy to sirolimus or everolimus.
- Current use of other than sirolimus or everolimus investigational drug for TSC or LAM within the past 30 days.
- Use of estrogen containing medications, including birth control pills, within the 30 days prior to enrollment.
- Treatment within 30 days of screening with drugs having known metabolic interactions with statin drugs, including:
    - strong CYP3A4 [cytochrome P450 3A4 metabolism] inhibitors (such as itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, azithromycin, erythromycin, clarithromycin, etc), gemfibrozil, cyclosporine, danazol, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine, lomitapide, and other lipid lowering medications (such as niacin [nicotinic acid], digoxin, warfarin, sildenafil, etc)
- Participation in another clinical study(ies) of an investigational treatment or drug within 30 days prior to the screening visit.
- Significant dysfunction of liver (ALT > 2X ULN), kidney (serum creatinine > 1.5X ULN), or blood (leucopenia (ANC<2000), anemia, Hgb < 11 gm/dl).
- History of inflammatory muscle disease or myopathy.
- Bleeding diathesis or anticoagulant therapy.

- Uncontrolled hyperlipidemia or diabetes.
- Pregnant, breast feeding, or plan to become pregnant within the next 6 months
- Inadequate contraception (must agree to barrier method)
- History of organ transplant.
- Active on transplant list.
- Severe or uncontrolled medical conditions which would cause an unacceptable safety risk or compromise compliance with the protocol.
- Unstable seizures (recent changes in pattern or anti-epileptics).
- Mental illness or cognitive deficit precluding informed consent.
- Inability to attend scheduled clinic visits or comply with study procedures.

3.3 Recruitment

After IRB approval has been obtained, the LAM community will be notified about the existence of the study by postings in public places and on the internet,. Patients will also be referred by physicians and LAM support groups such as the LAM Foundation, and the Tuberous Sclerosis Alliance. The study will be posted on clinicaltrials.gov.

3.4 Enrollment

Potential study patients will be contacted by the study staff to determine interest in study participation. Contact may be made by postal mail, electronic mail or in person. Interested individuals will receive study information, including a cover letter and a consent form. Patients may be consented and preliminarily assessed prior to the actual screening visit.

All patients enrolled will be female. Up to ten evaluable patients will be enrolled. As in prior studies, an attrition rate of 10% is expected; appropriate adjustments will be made in the number of enrolled patients.

3.5 Study drug treatment

Patients who meet eligibility criteria, provide informed consent and and are enrolled in the study will receive instructions regarding simvastatin dosage, route and administration. A one month supply of simvastatin 20 mg will be provided at visit 2.. Patients will be reminded about the side effects of simvastatin, and will be given a drug information sheet. Patients will be instructed to take the study medication in the evening every day. Patients will be carefully monitored monthly at visits 3, 4, 5 and 6 for signs and symptoms of simvastatin side effects including: upper respiratory infection, headache, abdominal pain, constipation, myalgias, arthralgias and nausea. Patients will be instructed to contact the study staff should they experience any of these side effects. Simvastatin doses may be held or reduced in the event of unacceptable side effects.

3.5.1 Treatment Regimen

We have chosen an intra-patient dose escalation strategy because there is no previous data from human studies to demonstrate the safety of simvastatin in combination with sirolimus or everolimus, in patients with LAM-S and LAM-TS. Dose escalation strategy will be performed only for patients who tolerate 20 mg daily simvastatin. If patients do not tolerate the 20 mg simvastatin dose, the dose will be down-titrated to 10 mg daily. If 20 mg daily is well tolerated, at visit 4 the dose will be increased to 40 mg daily for months 3 and 4. If 40 mg daily is not well tolerated, the dose will be reduced back to 20 mg daily.
Intermediate dose reductions to 15 or 30 mg/day may be undertaken if the side effect(s) is reasonably mild and tolerable.

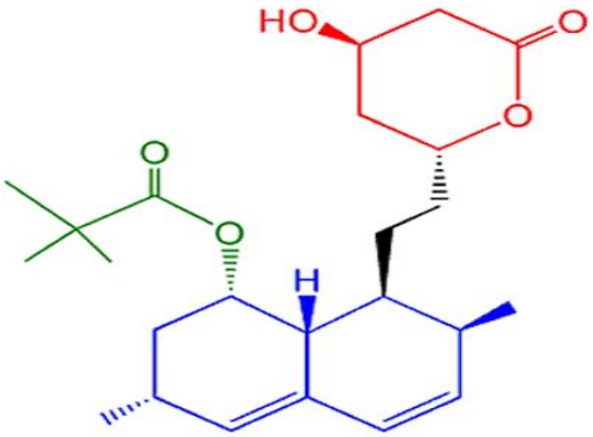
Patients will remain on their current dose of sirolimus or everolimus without interruption, as clinically indicated.

3.5.2 Drug and Drug Procurement

Simvastatin Description

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is C25H38O5 and its molecular weight is 418.57. Its structural formula is:



Simvastatin

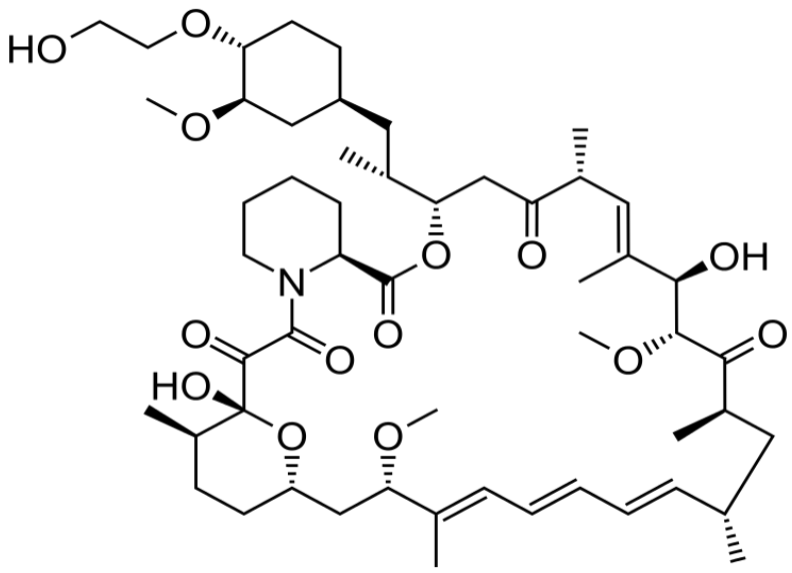
Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Simvastatin's inactive ingredients include: ascorbic acid, citric acid, hydroxypropyl cellulose,

hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.

Marketed under the trade name ZOCOR, simvastatin is available for oral administration as 5 mg, 10 mg, 20 mg, 40 mg or 80 mg tablets. Simvastatin is commercially available but will be provided to patients in this clinical study through Penn's Investigational Drug Service.

Everolimus Description

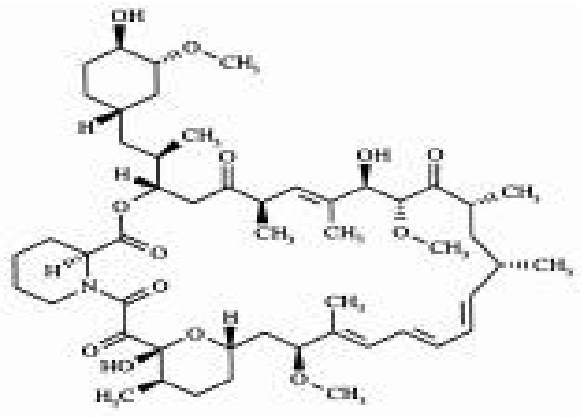
Everolimus, an inhibitor of mTOR, is an antineoplastic agent.
The chemical name of everolimus is
(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20- pentaone.
The molecular formula is C53H83NO14 and the molecular weight is 958.2. The structural formula is:



Everolimus is supplied as tablets for oral administration containing 2.5 mg, 5 mg, or 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and lactose anhydrous as inactive ingredients.

Sirolimus Description

Sirolimus is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The chemical name of sirolimus (also known as rapamycin) is (3S,6R ,7E,9R ,10R,12R ,14S,15E ,17E,19E ,21S,23S ,26R,27R ,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4H,6H ,31H)-pentone. Its molecular formula is C51H79NO13 and its molecular weight is 914.2. The structural formula of sirolimus is:



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Sirolimus is available for administration as an oral solution containing 1 mg/mL sirolimus. Sirolimus is also available as a white, triangular-shaped tablet containing 1 mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2 mg sirolimus.

The inactive ingredients in sirolimus Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol.

The inactive ingredients in sirolimus tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, and other ingredients. The 2 mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.

Patients will remain on everolimus or sirolimus and continue to obtain those agents in the manner already established.

4. Study Procedures and Timeline

4.1 Study and Timeline Overview

The study will enroll up to 10 evaluable patients over 3-6 months. All study patients will be assigned to a starting dosage of 20 mg of simvastatin daily for a period of two months. If patient tolerability to the 20 mg simvastatin dosage decreases, the dose will be down-titrated to 10 mg daily. Intra-patient dose escalation strategy will be performed only for patients who tolerate simvastatin 20 mg daily and the daily dosage of simvastatin will be escalated to 40 mg daily during months 3 and 4. . Patients who are escalated to 40 mg daily who do not tolerate that dose, will be reduced back down to the previously tolerated 20 mg daily.

The patient will be given a copy of the informed consent form. Patients will be given ample time to read and discuss the consent form with the study staff. The study staff will then answer any outstanding questions asked by the patient. The patient will be offered the option of signing the consent form. Those who agree to participate will undergo the remainder of screening at visit 1.

Prior to starting study drug, pulmonary function tests and chest X-ray will be obtained. The spirometry values obtained that contain the best values for FEV1, FVC and DLCO will constitute the baseline values. Patients will be followed with serial VEGF-D levels collected at each visit over a four month period.

4.2 Study schedule of procedures

The table below summarizes the study procedures.

Table 1: Study Procedures

Event	Screen	Day 0	Day 30	Day 60	Day 90	Day 120
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Informed consent	X		-	-	-	-
History and physical	X		X	X	X	X
Chest X-ray	X					X
Blood levels of sirolimus (target range 3-20 ng/ml) or everolimus (target range of 3-20 ng/ml)	X		X	X	X	X
CBC, CPK, CMP *	X		X	X	X	X
Lipid profile**	X		X	X	X	X
VEGF-D		X	X	X	X	X
Saved serum and plasma		X	X	X	X	X
Urine pregnancy test	X	X	X	X	X	X
Spirometry (FEV1, FVC DLCO)		X		X		X

Review concomitant medications	X	X	X	X	X	X
Review adverse events			X	X	X	X
Study drug (simvastatin) management		X	X	X	X	X
SGRQ and FPI		X	X	X	X	X

***CMP to include BUN, creatinine, ALT, AST, Alk Phos, total bilirubin**
****Lipid Panel to include total cholesterol, LDL, HDL and triglycerides.**

4.3 Study Visits

4.3.1 Visit 1 - Screening

At the screening, the consent form will be presented to the potential patient. If the patient is competent to understand the risks, agrees to participate and provides informed consent and HIPAA release, the patient will undergo screening.

During this visit, the following will be performed:

- review the inclusion/exclusion criteria
- obtain a urine pregnancy test (for women of childbearing potential)
- review current medications
- review medical history and conduct a physical examination
- obtain clinical labs including: CBC, CPK, Complete Metabolic Panel (CMP), lipid panel, and sirolimus or everolimus drug level
- obtain a chest x-ray

4.3.2 Visit 2 - Day 0 (≤ 14 days of Visit 1)

After review of screening tests and confirmation the patient continues to meets eligibility criteria, the patient will return to the clinic where the following will be performed:

- obtain a urine pregnancy test (for women of childbearing potential)
- review current medications
- obtain blood for VEGF-D measurement and, if the patient has consented obtain an additional sample to be stored on-site for potential future use
- perform spirometry with appropriate safety procedures. All spirometry tests during all visits will be performed after supervised administration of bronchodilator in the pulmonary function laboratory.
- administer the SGRQ and FPI instruments for dyspnea, fatigue and quality of life
- dispense simvastatin 20 mg with instructions regarding dosing and potential side effects
- provide a study calendar to document drug compliance. The patient should bring the completed calendar back at Visit 3.

4.3.3 Visit 3 – Day 30 (± 7 days)

The patient will return 30 days (+/- 7 days) after Visit 2. During this visit, the following will be performed:

- obtain a urine pregnancy test (for women of childbearing potential)
- review current medications
- review the interval medical history and conduct a physical examination
- assess for adverse events
- obtain clinical labs including: CBC, CPK, Complete Metabolic Panel, lipid panel, and sirolimus or everolimus drug level
- obtain blood for VEGF-D measurement and, if the patient has consented obtain an additional sample to be stored on-site for potential future use
- administer the SGRQ and FPI instruments for dyspnea, fatigue and quality of life
- assess for simvastatin drug compliance
- as necessary, perform simvastatin down-titration and manage drug dispensing
- provide a study calendar to document drug compliance. The patient should bring the completed calendar back at Visit 4.

4.3.4 Visit 4 – Day 60 (± 7 days)

The patient will return 30 days (+/- 7 days) after Visit 3. During this visit, the following will be performed:

- obtain a urine pregnancy test (for women of childbearing potential)
- review current medications
- review the interval medical history and conduct a physical examination
- assess for adverse events
- obtain clinical labs including: CBC, CPK, Complete Metabolic Panel, lipid panel, and sirolimus or everolimus drug level
- obtain blood for VEGF-D measurement and, if the patient has consented obtain an additional sample to be stored on-site for potential future use
- perform spirometry with appropriate safety procedures. All spirometry tests during all visits will be performed after supervised administration of bronchodilator in the pulmonary function laboratory.
- administer the SGRQ and FPI instruments for dyspnea, fatigue and quality of life
- assess for simvastatin drug compliance
- dispense simvastatin 40 mg (if not contraindicated) with instructions regarding dosing and a reminder regarding potential side effects
- provide a study calendar to document drug compliance. The patient should bring the completed calendar back at Visit 5.

4.3.5 Visit 5 – Day 90 (± 7 days)

The patient will return 30 days (+/- 7 days) after Visit 4. During this visit, the following will be performed:

- obtain a urine pregnancy test (for women of childbearing potential)
- review current medications
- review the interval medical history and conduct a physical examination
- assess for adverse events
- obtain clinical labs including: CBC, CPK, Complete Metabolic Panel, lipid panel, and sirolimus or everolimus drug level
- obtain blood for VEGF-D measurement and, if the patient has consented obtain an additional sample to be stored on-site for potential future use
- administer the SGRQ and FPI instruments for dyspnea, fatigue and quality of life
- assess for simvastatin drug compliance
- as necessary, perform simvastatin down-titration and manage drug dispensing
- provide a study calendar to document drug compliance. The patient should bring the completed calendar back at Visit 6.

4.3.6 Visit 6 - Day 120 (± 7 days)

The patient will return 30 days (+/- 7 days) after Visit 5. During this visit, the following will be performed:

- obtain a urine pregnancy test (for women of childbearing potential)
- review current medications
- review the interval medical history and conduct a physical examination
- assess for adverse events
- obtain clinical labs including: CBC, CPK, Complete Metabolic Panel, lipid panel, and sirolimus or everolimus drug level
- obtain blood for VEGF-D measurement and, if the patient has consented obtain an additional sample to be stored on-site for potential future use
- obtain a chest x-ray
- perform spirometry with appropriate safety procedures. All spirometry tests during all visits will be performed after supervised administration of bronchodilator in the pulmonary function laboratory.
- administer the SGRQ and FPI instruments for dyspnea, fatigue and quality of life
- assess for simvastatin drug compliance
- advise women of childbearing potential that they should continue to use their method of birth control for at least 30 days after the study ends
- remind patients they will be contacted by phone in approximately 30 days as a follow-up.
- remind the patient to follow up with her regular physician for routine care.

If at visit 6, it is determined there has been clinical benefit, the patient and her regular physician will decide how to proceed after the conclusion of the clinical study.

4.3.7 End of Study Telephone Call – Day 150 (+/- 7 days)

An end of study phone call will be conducted at 30 days (+/- 7 days) after the study visit 6. The purpose of the call is to follow up on any open or unresolved adverse events.

5. Dose Limiting Toxicity Rules, Dose Delays, and Dosing Modifications

5.1 Definition of Dose Limiting Toxicity (DLT)

DLTs will be defined by toxicity occurring during the first 5 weeks of this study. A DLT will be any non-pulmonary AE of Grade 3 or higher that is at least possibly treatment-related with the exception of nausea and vomiting which have not been treated with optimal anti-emetic therapy. Any DLT that causes a patient to miss > 28 consecutive days of simvastatin will result in the patient being taken off treatment.

A DLT is defined as a toxicity considered at least possibly related to simvastatin. In this regard, it is important to consider the possibility that co-administration of simvastatin may increase the toxicity of sirolimus or everolimus. Conversely, sirolimus or everolimus might influence the toxicity profile of simvastatin. Thus, it may be difficult to confidently attribute certain observed toxicities solely to either simvastatin and sirolimus, or simvastatin and everolimus. With this potential complication in mind, an attempt will be made to define dose-limiting toxicities (DLTs), which apply specifically to simvastatin. In this study, DLTs will include any possibly, probably, or definitely simvastatin-related Grade 3 or 4 toxicity. Known toxicities specific to sirolimus and everolimus such as mucositis will not be considered dose limiting unless the treating physician considers the toxicity to be exacerbated by simvastatin. Toxicities that will be attributable to simvastatin include but are not limited to abdominal pain, nausea, diarrhea, headache, and infectious complications.

The target DLT rate is $\leq 33\%$. The maximum tolerated dose (MTD) will be defined as a) the dose producing DLT in 2 out of 6 patients, or b) the dose level below the dose which produced DLT in ≥ 2 out of 3 patients, or in ≥ 3 out of 6 patients. Patients will be evaluable for a DLT if they have finished 5 weeks of combined therapies. Patients who are removed from study due to clinical progression prior to the 5 week period will be replaced. Patients will be evaluable for response if they have completed 90% of their expected dose of simvastatin for the 8 weeks. Patients will be evaluated for toxicity if they received at least one dose of simvastatin.

5.2 Toxicity Criteria, Dose Delays, and Modifications

5.2.1 Toxicity Criteria

This study will utilize the CTCAE version 4.0 for toxicity and Adverse Event Reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of

the CTCAE version 4.0.

5.2.2 Dose Delays

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of sirolimus or everolimus must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Section 6.4. Major Events are non-treatment-related grade 3 and 4 pulmonary and non-pulmonary toxicities. Treatment should be delayed for major events if simvastatin may further complicate the non-treatment related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ Grade 1 or ≤ Baseline). For treatment-related toxicities and major events, if toxicity is not resolved in ≤ 4 weeks, patient will be taken off the treatment that is most likely to be related to the toxicity. While this most likely will result in coming off study, at the investigator's discretion patients may continue on single agent therapy, if toxicities are ≤ grade 2 and there is some evidence of clinical benefit to the patient.

Table 2A: Approach to overlapping toxicities of simvastatin and sirolimus*

Overlapping Toxicity	Dose Reduce First	Dose Reduce Second
Mucositis	sirolimus	simvastatin
Nausea	sirolimus	simvastatin
Abdominal pain	simvastatin	sirolimus
Infections	sirolimus	simvastatin
Diarrhea	sirolimus	simvastatin
Headache	simvastatin	sirolimus

Table 2B: Approach to overlapping toxicities of simvastatin and everolimus*

Overlapping Toxicity	Dose Reduce First	Dose Reduce Second
Mucositis	everolimus	simvastatin
Nausea	everolimus	simvastatin
Abdominal pain	simvastatin	everolimus
Infections	everolimus	simvastatin
Diarrhea	everolimus	simvastatin
Headache	simvastatin	everolimus

*At the discretion of the treating physician.

5.2.3 Simvastatin Dose Reduction

Any AE of ≥ Grade 3 and attributed as possibly, probably or definitely related to simvastatin will result in the dose being held until the AE has resolved to ≤ grade 1 or baseline, while sirolimus dosing may continue uninterrupted. If the AE resolves, reinstitution of treatment can occur but at a reduced dose as described in Table 3. If the AE recurs at the reduced dose, treatment will be held until the AE has resolved to ≤ grade 1 and when resolved treatment can be reinstituted at the next lower dose level. No more than 2 dose reductions are allowed during the maintenance cycles.

Table 3: Simvastatin Dose Reduction Schema

Dose mg/day	Reduce to
20 mg daily	15 mg daily
15 mg daily	10 mg daily
40 mg daily	30 mg daily
30 mg daily	20 mg daily

Toxicities that may attributable to simvastatin include nausea, abdominal pain, diarrhea, upper respiratory infections, headache, and diarrhea. If any of these AEs occur at grade ≤ 2, simvastatin may be continued and the AE managed with supportive care. For any AE with a grade ≥ 3, the rules outlined in Sections 5.3 apply for holding of dose, dose reduction, removal from study and reporting requirements.

The main laboratory abnormalities which may result from simvastatin include increased CPK and liver transaminases. Patients who develop increased CPK levels (> 2X ULN) will be followed with weekly CPK levels until the abnormalities return to normal. Simvastatin will be continued if CPK values are decreasing on the following week's blood sample. If persistent elevations (> 2X ULN) occur over two weeks (three assessments), or symptoms such as muscle pain are present, the simvastatin study drug will be stopped. The simvastatin study drug will be stopped immediately if myositis (CPK > 10 x ULN) is documented at any time.

5.2.4 Sirolimus or Everolimus Dose Reduction

Known sirolimus and everolimus toxicities will not be attributed to simvastatin but will only be attributed to sirolimus or everolimus and will result in the following sirolimus or everolimus dose modifications. Pulmonary toxicity of unexpected severity may be attributed to simvastatin (in addition to sirolimus or everolimus) at investigator discretion. Non-pulmonary toxicities of possible, probable or definite anddefinite and having an attribution to sirolimus or everolimus will result in the following sirolimus or everolimus dose modifications. Blood counts will be evaluated weekly. Within -3 days prior to sirolimus or everolimus dosing, the patient must have an ANC > 1.0 x 10^9/L and platelet count > 75 x 10^9/L. All non-pulmonary toxicity grade 3 or 4 **(**except for mucositis, diarrhea, nausea, and acneiform rash) must have resolved to CTCAE grade ⩽ 2. If toxicity persists, treatment should be delayed by one week for up to 3 consecutive

weeks. If after 3 weeks of delay, all toxicity has still not resolved, then any further treatment with sirolimus or everolimus should be stopped. Simvastatin may be continued after sirolimus or everolimus has been stopped.

If any non-pulmonary toxicity observed Grade ≥ 3 (except for mucositis, diarrhea, nausea, acneiform rash, and swelling of extremities) and/or if platelets < 75 x 10^9/L and/or ANC < 1 x 10^9/L, causing delay of two weeks of sirolimus then the dose should be reduced by one dose level (Table 5). For patients requiring more than 2 dosage reductions, sirolimus or everolimus will be stopped. If any non-pulmonary toxicity observed was CTCAE **Grade 4 (**except for mucositis, diarrhea, nausea, acneiform rash, and swelling of extremities) then sirolimus or everolimus should be stopped**.**

Table 4: Sirolimus or Everolimus dose level modification guidelines

Dose reduction	Dose and schedule
Starting dose	10 mg daily
1	5 mg daily
2	5 mg every other day

6. Duration of Participation

6.1 Patient retention and drug compliance

Patient retention will be encouraged in several ways. Extensive contact information will be captured for each patient, at the time of study enrollment. This will include home, work, and cellular telephone numbers. Prior to each study visit, the study staff will contact the patient to remind her about the upcoming study visit. Patients will receive a stipend in the amount of $25 per study visit, for their participation in the study. A check for the reimbursement of expenses will be issued after each study visit.

The study staff and physician will explain the importance of compliance with the study protocol at each patient contact. If a patient fails to comply with a study visit, the study staff will contact her by telephone. If the study staff is unsuccessful in reaching the patient, a follow up letter will be sent by Federal Express, on two consecutive weeks, seeking follow-up.

Compliance with the protocol and drug administration will be strongly emphasized. Pill counts will be performed at visits and episodes of medication noncompliance will be recorded, including the reason for noncompliance. Patients will receive a calendar to document medication and any side effects experienced that day. If a patient wishes to withdrawal from the treatment phase of the study or has a serious adverse event (SAE) (whether related to study drugs or not), patient follow-up assessments will continue for safety monitoring and to avoid problems associated with missing data. The inclusion of such follow-up data will allow for analysis by intention-to-treat.

If a patient is withdrawn from the treatment portion of the study for any reason, the patient will be strongly encouraged to continue with and complete the remainder of the study assessments, as scheduled.

6.2 Consent for Future Contact

During the consent process, patients will have the option to provide permission for future contact. This permission allows for patient contact information, including their full name, address and telephone number, to be collected. The permission for future contact also allows for possible patient contact regarding future IRB-approved studies. If the patient denies permission, no future contact will be made.

6.3 Consent for Continuing Data Review of Medical Records

During the consent process, patients will have the option to provide permission for future data review of their medical records. This permission allows for study staff to contact the patient (or the patient's caregiver(s)) to obtain medical records and other information for a period of up to two years after the patient has withdrawn from or completed the study. The purpose of this data review is to capture information including but not limited to clinical, radiographic, pathologic, laboratory and pulmonary function data, after the patient has exited the study.

6.4 Consent for Storage of Blood Samples for Future Use

Patients will be asked to consent to the storage of leftover blood and serum samples for future use related to LAM. Patients can refuse without impacting their care or ability to participate in this study.

7. Stopping Rules

7.1 Criteria for Terminating Participation on Study

An intent-to-treat approach will be used in this study. All data acquired prior to patient termination for the following reasons will be included in the primary analysis.

- Withdrawal of patient consent
- Withdrawal by the patient
- Withdrawal by the investigator
- Intercurrent illness or event that precludes further administration of treatment or ability to evaluate lung function (e.g.-mental status change, large pleural effusion).
- Pregnancy or failure to comply with adequate contraception
- Continuing patient non-compliance

Every effort will be made to conduct a final study visit and patients will be followed clinically until all study-related adverse events resolve, the patient's condition stabilizes or the adverse events are determined to be permanently ongoing.

7.2 Criteria for Terminating the Study

Up to ten patients will be enrolled in this study. The maximum duration of patient participation is up to 164 days, including a follow-up phone contact one month after the last study visit. In the event of any death, or Grade III SAE attributable to the study agent, enrollment and treatment will be suspended, pending Data Safety Monitoring Board (DSMB) review.

8. Study Variables and Measuring Methods

8.1 Physical Exams

Exams will be performed in a routine manner, consistent with the standard of care.

8.2 Pulmonary Function Testing

Pulmonary function testing (PFT) including FEV1, FVC, and DLCO, will be performed in a standardized manner according to American Thoracic Society (ATS criteria) for acceptability and repeatability. The study site will attempt to have the same respiratory therapist administer testing to patients for consistency in the study. All PFTs during visits 2, 4 and 6 will be performed post bronchodilator only, regardless of whether bronchodilator responsiveness is demonstrated. Although, plethysmography is the preferred method, lung volumes may be obtained by plethysmography or gas dilution. All spirometry data will be assessed for quality by the attending pulmonary physicians at the Penn Lung Center

8.3 Questionnaires

8.3.1 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being. It has been developed to be used by patients with fixed or reversible airway obstruction. It has been shown to correlate well with physiologic parameters and to show changes with time, as the lung disease progresses (*44*). The administration is performed by face to face or telephone interview; completion takes approximately 10 minutes. The questionnaire consists of 76 items divided into 3 domains: symptoms (frequency and severity); activity (activities that cause or are limited by breathlessness); and impacts (social functioning, psychological disturbances resulting from airways disease). The questionnaire has been translated into many languages, including Spanish and Japanese.

8.3.2 Functional Performance Inventory (FPI)

The FPI includes many domains that are particularly relevant to women, including body care, maintaining the household, physical exercise, recreation, spiritual and social interaction. The inventory is short, containing only 16 items, and is easy to use. The instruments do not require licenses.

8.4 Biomarker Analyses

VEGF-D biomarker analysis will be conducted on blood samples collected from each study patient at scheduled times. Samples will be sent to the central laboratory in Cincinnati, where the assays will be performed. Serum VEGF-D has been shown to be elevated in LAM and TSC patients and is diagnostically specific to these diseases (*45, 46*).

9. Data Management

9.1 Registration

All study data will be collected via systems that comply with all applicable guidelines regarding patient confidentiality and data integrity. University of Pennsylvania IRB approval for the protocol must be on file before patient enrollment and accrual can occur.

The investigators will use a system of coded identifiers to protect patient confidentiality and safety. Each patient enrolled will be assigned a unique identifier. Access to the linkage between the coded identifier and the patient identity will be limited to the study team. The file containing the linkage between the coded identifiers and patient names will be stored in a location separate from the data collection forms and analysis spreadsheet and will be maintained on a secure server.

9.2 Safety Monitoring and Adverse Event Reporting

Patients will be evaluated for safety if they have received at least one dose of simvastatin. The frequency, severity and duration of all adverse events, regardless of cause, will be recorded on the case report forms. The frequency and severity of adverse events will be calculated by patient. The most severe grade of adverse event experienced by patient will be counted once. The duration of adverse events will be calculated by the number of days each event persisted. Adverse events will be tabulated by body system and by severity using the NCI Common Terminology Criteria for Adverse Events v4.0, which can be obtained from the CTEP Website: http://ctep.cancer.gov/reporting/ctc.html. Tables will be generated for all adverse events including those that are judged to be possibly, probably or definitely related to the simvastatin.

All adverse events will be reviewed by a DSMB created for this study and composed of pulmonologists Vivek Ahya, M.D., Reynold A. Panettieri, Jr., M.D., and John Hansen-Flaschen, M.D. Any serious AE (generally grade 3 or 4 toxicity or defined by lead pulmonologist) will result in patient discontinuation of simvastatin until the DSMB

reviews the case and make a recommendation made regarding re-institution of the study drug.

As this is a safety study with a small number of patients, data will be compiled in descriptive tables of results. A study participation summary will be written for each patient and for trends in the data. Special attention will be given to adverse reactions to the simvastatin and any changes in the pulmonary function testing or the laboratory values outside of normal ranges.

9.3. Adverse Events

The investigator must grade AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0) and provide an opinion regarding the causal relationship of the AE to study drug.

Patients will be carefully monitored for adverse events from the initial dose of study medication through the 30 day post telephone call.

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the adverse event page(s) of the case report form.

Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses will be recorded. Exacerbation of pre-existing illness, including the disease under study, is defined as a manifestation (sign or symptom) of the illness that indicates a significant increase in the severity of the illness, as compared to the severity noted at the start of the study.

9.3.1 Serious Adverse Events

A serious adverse event is any adverse drug experience occurring at any dose that:

- Results in death;
- Is life-threatening;
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in congenital anomaly or birth defect;
- Results in a persistent or significant disability/incapacity; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A life-threatening adverse event is any adverse drug experience that places the patient at immediate risk of death from the reaction as it occurred; ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Initial hospitalization is defined as any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (eg, from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit).

Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting. For example:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (eg, for work-up of persistent pretreatment lab abnormality)
- Social admission (eg, patient has no place to sleep)
- Administrative admission (eg, for yearly physical exam)
- Protocol-specified admission during the clinical study (eg, for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery)
- Hospitalization for what is clearly progressive disease

However, if a hospitalization for an unknown event occurs, it should be considered as a serious adverse event.

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician.

Preplanned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient.

Disability is a substantial disruption of a person's ability to conduct normal life functions.

Any serious adverse event or death must be reported to the IRB immediately, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study, through 30 days after the last administration of study drug. Any serious adverse event occurring beyond 30 days after the last administration of study drug must be promptly reported, if a causal relationship to study drug is suspected. The only exception to these reporting requirements are serious adverse events that occur during a pre-randomization/washout run-in period, during which either placebo alone is administered, or no active study drug or protocol-specified background drug is administered.

9.3.2 Abnormal Laboratory Test Results

Laboratory results will be assessed for adverse events as described in CTCAE v4.0 using normal ranges specified for the institution's laboratory.

The results of all laboratory tests required by the protocol will be recorded in the patient's case report form. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or a level deemed acceptable by the investigator or until a diagnosis that explains them is made. The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, 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 leads to any of the outcomes included in the definition of a serious adverse event, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet Condition 2 above for reporting as an adverse event.

9.3.3 Abnormal Physical Examination Findings

Clinically significant changes, in the judgment of the investigator, in physical examination findings (abnormalities) will be recorded as adverse events.

9.4 Investigator reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that patients or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

9.4.1 Adverse Events, Unanticipated Problems Death, and Other Reportable Events

Adverse Events

Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Unanticipated Problems

Unanticipated problems posing risks to patients or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Death

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

Report the event within 24 hours when the death is unforeseen (unexpected) and indicates patients or others are at increased risk of harm.

Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable Events

For clinical drug studies, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).

- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that, in the opinion of the investigator, placed one or more participants at increased risk, or affects the rights or welfare of subjects.

9.4.2 Exception

An exception is defined as a one time, intentional action or process that departs from the IRB approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMB approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMB.

9.4.3 Deviation

A deviation is defined as a one time, unintentional action or process that departs from the IRB and DSMB approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMB within 5 business days and the IRB within 10 business days.

Examples of Exceptions/Deviations that must be submitted (not meant to be inclusive):

May/can/have affects/affected subject safety. So, a subject missing a visit is not an issue unless a critical/important treatment or procedure was missed and must have been done at that specific time.

• Violate eligibility
• Dose adjustment
• Stopping criteria
• Affect sample size (adding more subjects, decreasing number of subjects, changing the number of subject in a specific arm/cohort)

Other deviations should be explained in a memo to file or on a deviation log.

10. Ethical and Administrative Aspects

10.1 Risks and Discomforts of Testing

Occasional shortness of breath or light-headedness can occur while performing pulmonary function tests.

Rarely after blood drawing, the vein in which the needle has been inserted to draw blood, may become sore and red. A temporary "black and blue mark" may develop, and rarely fainting may occur.

As part of routine care while participating in this study, patients will undergo 2 chest x-rays. There is a level of radiation exposure from these x-rays that is considered low, when compared with other everyday risks of radiation exposure.

10.2 Confidentiality

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patient in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients who have revoked authorization to collect or use PHI,

attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled study period.

Several mechanisms will be in place to maintain confidentiality. Patient names will not be abstracted and all of the data will be reported in aggregate. Each patient in all phases of the study will be assigned a unique study code number to be used on all data forms, study records, and blood samples. A list of patient names and code numbers will be maintained separately, in a locked office or on password protected computers. Only the investigators and study staff will have access to this information. No other personally identifiable information will be available.

10.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

10.4 Case Report Forms

Data will be collected on the study case report forms and will be stored in the research team's office, which is secured and locked daily. Data will be entered onto a case report form or into an Excel spreadsheet using the patient identifier described above. Any data set leaving the University of Pennsylvania site will be de-identified.

10.5 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with a sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents may be discarded.

10.6 Study Monitoring, Auditing, and Inspecting

10.6.1 Data Monitoring Plan

Data will be reviewed and recorded in a timely manner. The PI or their designee will be responsible for ensuring protocol compliance and appropriate reporting.

10.6.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) by the IRB, government regulatory bodies, and University compliance and quality assurance groups. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.7 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to the Penn IRB in agreement with local legal prescriptions for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and retained before commencement of this study.

All patients for this study will receive a consent form describing this study and providing sufficient information for them to make an informed decision about their participation in this study. See a copy of the Patient Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a patient, using the IRB-approved consent form, must be obtained before that patient undergoes any study procedure. The consent form must be signed by the patient or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

10.8 Study Finances

This study will be funded through a grant from the LAM Foundation.

10.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and

approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

10.10 Patient Stipends or Payments

Patients may receive a stipend of up to $25 per study visit for participating in this study.

10.11 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

10.12 Patient withdrawal

A patient has the right to withdraw from the study entirely, at any time, for any reason, without prejudice to future medical care by the investigator or other physicians. The investigator also has the right to withdraw patients from the study in the event of concurrent illness, AEs, or other reasons deemed to be in the patient's best interest.

A patient should be withdrawn from the study if there is:

- Withdrawal of consent
- Termination of the study by the funding agency

In order to preserve the integrity of the intention-to-treat analysis, even if the patient is withdrawn from the treatment portion of the protocol (either due to patient, physician, or investigator decision), it is imperative to continue with the scheduled follow-up assessments, both for the safety of the patient and for completeness of data collection. This will be explained to potential patients at the time of informed consent. The importance of compliance with study visits will be reinforced throughout the study. If the treatment is permanently withdrawn, the patient will return to the LAM clinic for safety assessment (history, physical examination, and clinical laboratories, if necessary).

11.0 Statistical Considerations

11.1 Sample Size Determination

A total of up to 10 evaluable patients will be enrolled. As this is a safety study with a small number of patients, data will be compiled in descriptive tables of results.

Assuming a 10% rate of attrition, this will yield 9 evaluable patients for the entire 120 days of follow-up. The table below shows the exact 95% confidence interval (CI) for the true probability of dose-limiting toxicity (DLT), given the observed rates out of 9 patients and the probability of failing to observe at least one DLT among 9 patients for various underlying dose-limiting toxicity rates.

Table 5: Dose-limiting toxicity rates

Observed DLT	**1/9 (11%)**	**2/9 (22%)**	**3/9 (33%)**	**4/9 (44%)**	**5/9 (56%)**
95% CI	(3%, 48%)	(3%, 60%)	(7%, 70%)	(13%, 9%)	(22%, 87%)
Probability fail to observe at least one DLT if true rate is equal to the above	35.0%	10.7%	2.7%	<1.0%	<1.0%

11.2 Data Analysis

All study data will be collected via systems that comply with all applicable guidelines regarding patient confidentiality and data integrity. Patients will be evaluated for safety if they have received at least one dose of simvastatin. The frequency, severity and duration of all adverse events, regardless of cause, will be recorded on the case report forms. Adverse events will be tabulated by body system and by severity using the NCI Common Terminology Criteria for Adverse Events v4.0, which can be obtained from the CTEP Website: http://ctep.cancer.gov/reporting/ctc.html. Tables will be generated for all adverse events, including those judged to be possibly, probably, or definitely related to the simvastatin.

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