A double blinded, phase II, randomized controlled trial to study the effects of simvastatin in patients with uterine leiomyoma.

Protocol Version: 1

IND Exempt
Principal Investigator:

Mostafa Borahay M.D., PhD, Gynecology and Obstetrics, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine.

Sub Investigators:

James Segars, M.D. FACOG, Gynecology and Obstetrics, Div. Reproductive Sciences and Women's Health, Johns Hopkins University School of Medicine.

Gayane Yenokyan, PhD, Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health.

Paul Driggers, PhD, Gynecology and Obstetrics, Div. Reproductive Sciences and Women's Health, Johns Hopkins University School of Medicine.

Bhuchitra Singh, M.B.B.S., MPH, MS, Gynecology and Obstetrics, Div. Reproductive Sciences and Women's Health, Johns Hopkins University School of Medicine.

Sponsor of IND:
Mostafa Borahay M.D., PhD
Assistant Professor, Minimally invasive gynecologic surgeon
Department of Gynecology and Obstetrics
Johns Hopkins School of Medicine
Johns Hopkins Bayview Medical Center
4940 Eastern Ave, Building A, Room A121C
Baltimore, MD 21224-2780
Phone: (410) 550-0337
Fax: (410) 550-0196

REVISED
December 8, 2017

TABLE OF CONTENTS

SYNOPSIS

Title	A double blinded, phase II, randomized controlled trial to study the effects of simvastatin in subjects with uterine leiomyoma.
Short Title	Treatment of fibroids with simvastatin.
Project Phase	2
Sponsor	None.
Principal Investigator	Mostafa Borahay M.D., PhD, Department of Gynecology & Obstetrics, Johns Hopkins School of Medicine, Johns Hopkins Bayview Medical Center.
Clinical Site	Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center.
Indication	Uterine leiomyoma/ Fibroids.
Hypothesis	The hypothesis is that treatment of clinically relevant leiomyomas (fibroids) with simvastatin leads to tumor size reduction and symptom improvement through inhibition of cellular proliferation, apoptosis induction and modulation of extracellular matrix and mechanical signaling.
Objectives	Preliminary Efficacy Objectives: • Tumor size measured by ultrasound imaging comparing tumor volume pre- and post-study using ultrasound imaging. Feasibility Objectives: • Clinical symptom improvement using validated questionnaires. • Subject retention and satisfaction. • Adherence to the recommended treatment dosing. • Completeness of the outcome measures. Safety Objectives: • Adverse events reporting by organ systems. • Pre and post study blood tests. Exploratory Objectives:

	• Characterize the cellular effects of simvastatin on fibroid cells using TUNEL assay. • Evaluate effects of simvastatin on ECM production and synthesis using immunoblotting techniques.
Sample size	60 females.
Study design	This is a phase 2 double blinded clinical trial to determine the feasibilty, safety, and preliminary efficacy of simvastatin in improving symptoms and reducing size of uterine fibroids. The study will enroll 60 eligible participants; the participants will be randomized into two groups with 30 subjects each. The Study Group receives 40 mg/ day oral simvastatin and the Placebo group receives daily oral placebo for a duration of 12 weeks. The study medication will be dispensed once the participant's eligibilty has been established after the screening visit. The participants will have study visits at intervals of 0, 6 and 12 weeks after initiation of the study drug intake. The study nurse will follow up with the subject at regular intervals of 1 week throughout the duration of the study to monitor adverse events and ensure compliance with the study drug. After the 12 week study duration, the subject will undergo hysterectomy or myomectomy and the fibroid sample will be collected for analysis. This will help establish molecular, cellular and histologic effects of the study drug on fibroid tissue. The subject will be followed by the study team at their post operative visits at 2 and 6 weeks during their regular visits with their gynecologist.
Inclusion criteria	To be eligible, subjects must meet all of these criteria: • Signed informed written consent. • Gender: female.

	• Age: 18-55 years at time of signing consent.
	• BMI of subjects: < 45 kg/m^2.
	• Uterine fibroids:
	  • Diagnosed by ultrasound (MRI will be used only if ultrasound is inconclusive).
	  • Number: any number of fibroids.
	  • Location: submucosal or intramural.
	  • At least one fibroid of diameter > 3cm.
	• Symptoms: one or more of the following symptoms of heavy menstrual bleeding (HMB), defined as: Experienced cyclic (22 to 35 days) abnormal uterine bleeding (heavy or prolonged) in at least 3 of the last 6 menstrual periods, including menstrual bleeding lasting 5 or more days or heavy bleeding per participant recall. Examples of heavy bleeding may include, but are not limited to the following:
	  • Requires the use of double protection to manage menstrual bleeding.
	  • Menstrual bleeding accompanied by the sensation of "gushing" or "flooding".
	  • Saturates more than 1 tampon or sanitary pad per hour for 3 or more consecutive hours.
	  • Regularly needs to change the tampon or sanitary pad at night or regularly soils bedclothes.
	  • Heavy bleeding that affects work, school, or social activities.
	  • Pelvic pain/ pressure likely caused by fibroids.
	• Plan for surgery (hysterectomy or myomectomy).
	• Normal Pap smear within the last year.
	• Use of contraception during study such as non-hormonal oral contraceptives, intrauterine devices (IUD)/ intrauterine systems (IUS), barrier contraceptives, abstinence or sterilization.

Exclusion criteria	To be eligible, subjects must not meet any of these criteria:

	• Pregnancy or lactation. • Previous or current uterine, cervical or ovarian cancer. • Current endometrial hyperplasia or history of atypical endometrial hyperplasia. Endometrial biopsy will be done during screening (if not done within last 12 months). • Suspicion of leiomyosarcoma. • Recent rapid growth of fibroids (i.e. doubling in size within 1-6 months period). • Unevaluated gynecologic abnormalities (unexplained vaginal bleeding, cervical dysplasia, or abnormal adnexal/ovarian mass). • Menopausal status. • Surgery is urgently indicated (< 3 months) for medical or social reasons. • Hemoglobin ≤ 6 g/dL. • Currently enrolled in another investigational study. • Mental condition or other barrier preventing informed written consent. • Allergy or hypersensitivity to simvastatin. • Current use of simvastatin or other drugs of the same class. • Concomitant administration of strong CYP3A4 inhibitors including itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, elithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, and cobicistat-containing products. • Concomitant administration of gemfibrozil, cyclosporine, or danazol, verapamil, diltiazem, amiodarone, diltiazem, dronedarone, amlodipine, ranozoline, lopitamide, and grapefruit juice. • Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.(elevation of AST and/or ALT > 2 s.d. above the normal range at screening visit) • Known increased risk or diagnosis of a myopathy. •
Intervention	Drug: Placebo or Simvastatin 40 mg/day tablets taken orally with water.

	Simvastatin Tablets, USP. Both the placebo and the study drug will look similar after being encapsulated by the Investigational Drug Pharmacy at Johns Hopkins.
Dosage	One oral encapsulated tablet daily, 40 mg, Simvastatin Tablets, USP or placebo Starch1500.
Study drug administration	One oral tablet, taken in the evening, at the same time every day with water during the study duration.
Subject follow-up visits	Data will be collected on 0 (initiation), 6 and 12 week follow up visits. Our research coordinator will also call the subjects weekly for compliance (feasibility) and side effects/ adverse events monitoring (safety).
Hysterectomy/ myomectomy	The surgery will be performed as per standard of care. A fibroid sample will be collected after the surgery.
Study duration	12 week treatment period, 18-20 weeks total.
Efficacy parameters	Tumor size: We will compare tumor volume pre and post-study using imaging techniques.
Feasibility parameters	• Subject retention: percentage of subjects who complete the study (as opposed to drop-outs). • Completeness of the outcome measures: percentage of subjects for whom treatment efficacy endpoints will be available by the end of the follow-up. • Adherence to the recommended treatment dosing: percentage of subjects who take at least 80% of the doses. • Clinical symptom improvement: We will use the validated uterine fibroid symptom and quality-of-life (UFS—QoL) (2) questionnaires to compare symptoms from pre and post-study assessment.
Safety parameters	• Percentage of adverse events (AE) and serious adverse events (SAE) by organ systems, including signs/symptoms, laboratory values, and clinical events. • Lab: We will compare hemoglobin, hematocrit, ferritin, liver enzymes and lipid panel pre and post-study.

A double blinded, phase II, randomized controlled trial to study the effects of simvastatin in patients with uterine leiomyoma.

1. INTRODUCTION

1.1 Background on Condition

Uterine leiomyomas (fibroids) represent a formidable clinical problem. With an incidence of 50-80% of women by age 50 (3), they are the most common tumors of the female reproductive tract (4). They are characterized by smooth muscle cellular proliferation and excessive disordered extracellular matrix. The medical and economic burden of fibroids is significant with estimated annual fibroid-related costs in the US of $5.9-34.4 billion (5). Although hormonal treatments including oral contraceptives are used, efficacy remains limited. Treatment with Gonadotropin-releasing hormone (GnRH) agonists results in tumor shrinkage (6). However, the effect is usually transient and has significant side effects which prohibits long term use (7). Thus, uterine artery embolization and surgery are required in many cases. In fact, symptomatic fibroids are the most common indication for hysterectomy in the US (8). Myomectomy is a fertility-preserving alternative to hysterectomy but it is an invasive procedure including complications in subsequent pregnancies. Thus, there is an urgent need for a novel long term non-hormonal treatment for uterine leiomyomas.

1.2 Study Hypothesis

We hypothesize that simvastatin has therapeutic effects on leiomyoma through modulating cellular proliferation and extracellular matrix deposition and structure. Clinically, this will be associated with shrinkage of the size of leiomyoma tumors, and possibly with improvement of symptoms.

1.3 Supporting Studies

The compelling data from administrative database (9), animal (10) and in vitro (10) studies strongly suggests a therapeutic role for simvastatin in uterine leiomyomas. Simvastatin has ben FDA-approved since 1991, and so, its long term safety profile is well known. (See Appendix 1)

Statin use is associated with a lower risk of uterine fibroids and fibroid-related symptoms

In a nested case-control study using one of the nation's largest administrative insurance databases including a cohort of >190,000 women aged 18-65 years with a diagnosis of hyperlipidemia, we found that statin use is associated with decreased odds of uterine fibroids (adjusted odds ratio: 0.87, 95% confidence interval: 0.85-0.89). Furthermore, in a subanalysis restricted to fibroid cases, statin users were

less likely to have menorrhagia, anemia, pelvic pain, or undergoing myomectomy, compared to nonusers (9).

Simvastatin inhibits tumor growth in a subject-derived xenograft animal model

To examine the effect of simvastatin treatment on uterine leiomyoma in animal model, we used a subject-derived xenograft mouse model. After subcutaneous implantation of estrogen/progesterone pellets, leiomyoma tissues were implanted subcutaneously. Animals were treated for 28 days with simvastatin (20 μg/gm body weight/day) vs vehicle control. Treatment was associated with >40% tumor size reduction compared to controls. Furthermore, simvastatin was associated with lower (>50% reduction) expression of the proliferation marker Ki67 (10).

1.4 Relevance and Priority

The completion of this project will be significant as a successful non-hormonal treatment of uterine leiomyomas which will have an enormous impact on women's health through:

1) better quality of life through symptom improvement;

2) avoiding hysterectomy or myomectomy in women interested in fertility preservation;

3) reduction of surgery-related morbidity and mortality; and

4) significant savings of healthcare cost through reduced operative procedures and hospital admissions.

2. STUDY OBJECTIVES

We will compare the two arms for:

2.1 Preliminary Efficacy Objectives

2.1.1 Tumor size: We will compare tumor volume pre- and post-study using ultrasound imaging.

2.2 Feasibility Objectives

2.2.1 Clinical symptom improvement: We will use the validated uterine fibroid symptom and quality-of-life (UFS—QoL) (2) questionnaires to compare symptoms from pre and post-study assessment.

2.2.2 Subject retention: percentage of subjects who complete the study (as opposed to drop-outs).

2.2.3 Adherence to the recommended treatment dosing: percentage of subjects who take at least 80% of the doses.

2.2.4 Completeness of the outcome measures: percentage of subjects for whom treatment efficacy endpoints will be available by the end of the follow-up.

2.3 Safety Objectives

2.3.1 Percentage of adverse events (AE) and serious adverse events (SAE) by organ systems, including signs/symptoms, laboratory values, and clinical events.

2.3.2 Lab: We will compare hemoglobin, hematocrit, ferritin, liver enzymes and lipid panel pre and post study.

2.4 Exploratory Objectives

2.4.1 Characterize the cellular effects of simvastatin on fibroid cells using TUNEL assay.

2.4.2 Evaluate effects of simvastatin on ECM production and synthesis using immunoblots.

3. STUDY DESIGN

3.1 Study Structure

This is a double blinded, phase 2 clinical study to determine the feasibility, safety and preliminary clinical efficacy of simvastatin in women with symptomatic fibroids that are candidates for, and are seeking surgical management (hysterectomy/ myomectomy) for the treatment of fibroid related symptoms.

3.2 Sample Size Determination

We plan to enroll 60 study participants (30 in each arm). With a 20% anticipated withdrawal rate (from prior experience in similar studies), we plan to recruit 72 subjects. Sample size was estimated based on pre-clinical results of tissue effect where we expect a difference of 0.2 (20% effect size). This is a pilot study, and based on a 20% effect size and ability to measure within 0.5 centimeter (sigma) with an alpha of 0.5 and power of 0.8, the sample size is 50 subjects using a two sided t-test. We will enroll 60 subjects, to be conservative, which provides confidence that we will observe a difference, if one exists.

3.3 Study Groups

This is a double blinded study. Neither the participants nor the study team will know which group the participant has been assigned to. Records of the assignment will be kept with the pharmacist and can be accessed by the study team immediately in case of adverse events.

All study participants will undergo the same study procedures for screening and on the follow up visits. Women with symptomatic uterine fibroids planning to undergo surgery will be screened for participation.

Those found to be eligible will undergo pre-study evaluation during the screening period including:
1) Complete clinical evaluation.
2) Inclusion and exclusion criteria.
3) Uterine fibroid symptom and quality-of-life (UFS—QoL) questionnaires.
4) Fibroid number, location and size using ultrasound, and MRI if ultrasound is inconclusive.
5) Endometrial biopsy (if not done in the last 12 months).
6) Cervical smear (if not done in the last 12 months).
7) Lab: complete blood count, ferritin, liver enzymes, lipid panel.

We will use stratified block randomization with randomly permuted blocks of sizes 4 and 6 into one of the two arms. The randomization scheme will be stratified by race/ethnicity in three categories: African American, Caucasian, and Hispanic. All other races will be excluded (small numbers precludes proper stratification and analysis). The stratification will ensure similar distribution of race/ethnicity categories across the arms.

This is an “add-on” study, i.e. subjects in both arms will continue their current treatments for fibroids except hormonal birth control and medications contraindicated as per simvastatin prescribing information.

After 12 weeks of treatment, study participants will be re-evaluated, both clinically and by imaging. The results of the ultrasound will be discussed with the study subjects and they will be counselled about the need for the surgery if there are significant changes in fibroid size.

The fibroid tissue samples will be obtained for examination after the surgery (either myomectomy or hysterectomy). The fibroid tissue samples will be obtained for examination after the surgery (either myomectomy or hysterectomy). The study team will collect a 2.5 X 2.0 X 1.0 cm (or up to half of the tumor size) tissue sample from one fibroid for this study after the surgical pathology team has completed a preliminary evaluation of the delivered uterus.

3.3.1 **Study Group**

The 30 participants randomized in this group will intake 40mg / day of simvastatin orally at the same time in the evening, every day for the study duration of 12 weeks prior to undergoing hysterectomy/ myomectomy. The fibroid sample will be collected after the surgery to evaluate the effects of the study medication on the fibroid tissue.

3.3.2 **Placebo Group**

The 30 participants randomized in this group will intake 40mg / day of placebo orally at the same time in the evening every day for the study duration of 12 weeks prior to undergoing hysterectomy/ myomectomy. The fibroid sample will be collected after the surgery to evaluate the effects of the study medication on the fibroid tissue.

3.4 Study Duration

The participants will be enrolled in the study for a duration of 18-20 weeks. They will be visiting the study site 4 times for the study related visits and will be seen by the study team for follow up after their hysterectomy or myomectomy during their scheduled post-operative visits with their gynecologist. The first visit is the screening visit to obtain the informed consent and assess if the subject is eligible to participate in the study.

The study visits include:

1. Visit 1: Screening visit
2. Visit 2: Drug intake initiation visit at 0 weeks
3. Visit 3: 6 weeks after visit 2 during treatment period

4. Visit 4: 6 weeks after visit 3 during the treatment period

Follow up visits: Scheduled at subject's post-operative visits with their gynecologist for follow up.

The participant will receive the study medication at the treatment visits (Visit 2 and 3) for the next 6 weeks and study related assessments will be done at each of these visits. The study nurse will also remain in contact with the participant for the 12 week duration weekly to enhance compliance to study medication intake and to record adverse events if any.

The study nurse will also perform a drug reconciliation at each of the study visits to ensure that the patient is adherent to the study drug medication. The subjects will be instructed to bring all the medications that they forgot to intake or were left at the time of the research visit, these will be counted by the study nurse and a log of this information will be kept by the study research team. The regular weekly reminder calls from the study team will also complement the delivery of information about restricted food items such as grape fruit, cranberry juice for the intervals when the subject is not visiting the research team at Johns Hopkins Outpatient Clinic.

The subject undergoes hysterectomy or myomectomy at the end of treatment period (Visit 4) at week 12 and samples are obtained to study the fibroid tissue for molecular, cellular and histologic effects of simvastatin on human leiomyoma tissues. The study team will collect a 2.5 X 2.0 X 1.0 cm (or up to half of the tumor size) tissue sample from one fibroid for this study after the surgical pathology team has completed a preliminary evaluation of the delivered uterus. This tissue sample will undergo histopathological evaluation to study the effects of the study drug on fibroids.

We do not anticipate having a participant in this study who will have an unexpected diagnosis of leiomyosarcoma. We will keep all tissue sections and samples until the final pathology report is made and are capable or returning tissue to the pathologist for evaluation, if necessary. Even when the patient has had a hysterectomy or myomectomy, the collected fibroid itself is not manipulated at the time of surgery, minimizing any untoward cell spillage into the peritoneal cavity. In the highly unlikely event that we do enroll a subject with the final pathological diagnosis of leiomyosarcoma we will treat this as a serious adverse event and report it immediately.

The subjects will be scheduled to undergo surgery within 1 week following the 12 weeks treatment period of the study.

Standard clinical care will be provided pre and post hysterectomy/ myomectomy to the participants independent of the study assessments. The study nurse will follow up with the study participants during their 2 and 6 weeks post-operative visits with the subject's gynecologist.

More detailed information about the study visits and study related procedures is shown in Figure 1 and Table 1 below.

Study Design: Flowchart of the study design can be seen in Figure 1 below.

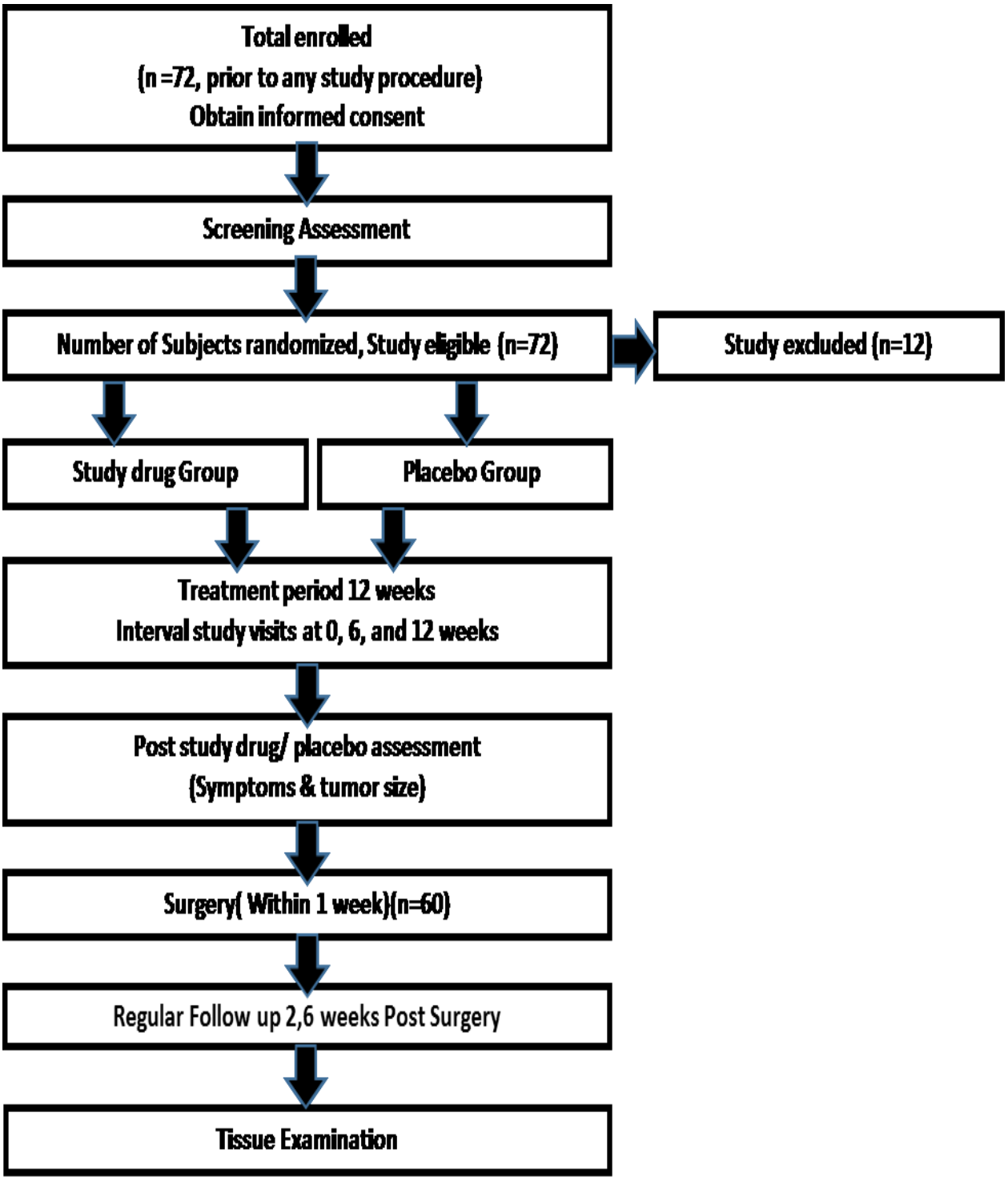

Figure 1: Study design flowchart.

Table 1: Detailed Flowchart of Study Assessments

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Follow up Visit
Activity	Screening	Beginning of the treatment period	6 weeks after start of treatment period	12 weeks after start of treatment period	Scheduled at 2 and 6 weeks post surgery
Informed Consent	X				
I/E criteria	X				
Demographics	X				
Smoking/Alcohol History	X				
Medical History	X				
Reproductive, menstrual, fibroid history	X				
Medication reconciliation & restricted food discussion	X	X	X	X	
Vital signs	X	X	X	X	
Physical examination	X			X	
Gynecological exam	X			X	
Cervical smear	X				
Ultrasound examination	X			X	
Endometrial biopsy	X				
Labs	X			X	
Inform about contraception	X	X	X	X	

Dispense/ collect / review subject diary for fibroid related symptoms	X	X	X	X	X
Home urine pregnancy test	X	X	X	X	
Randomization	X				
Drug accountability		X	X	X	
Drug dispensation		X	X		
Adverse event monitoring		X	X	X	X
Assess subject compliance		X	X	X	
Questionnaires	X	X	X	X	X

3.5 Rationale for Dosage Regimen and Study Drug Dosage

To propose dosage for this study, we extensively reviewed the pharmacokinetics of simvastatin including bioavailability, hepatic metabolism, serum levels and tissue distribution (1, 11-13). We also used published epidemiologic, animal and in vitro fibroid studies (9, 10, 14). About 60-80% of orally administered simvastatin is absorbed, 5% is bioavailable, and 78-87% is metabolized by liver, including several active metabolites. With rodents metabolizing statins about 25 fold compared to humans (1), 20 µg/g body weight/day subcutaneously was effective in the animal study (10). In addition, in vitro data shows effective concentrations as low as 0.1 µM. Importantly, dosage range for simvastatin in hyperlipidemia at 10-80 mg/day orally is associated with a peak plasma level of approximately 0.1-0.3 µM, with many active metabolites extending efficacy beyond simvastatin plasma level. Thus, 40 mg/day orally in humans appears appropriate.

3.6 Known and Potential Risks

Potential risks are primarily those of simvastatin. We will counsel all study candidates about potential side effects of simvastatin as per NIH prescribing information (1). The most important ones are muscle side effects such as muscle pain, tenderness, weakness or the more serious rhabdomyolysis. Other side effects include gastrointestinal (GI) side effects, liver function abnormalities, allergic reactions, headache, confusion, memory problems, fever, joint pain, cold symptoms, skin rash and sleep problems. The full list of side effects will be discussed at length with potential study candidates and a printed handout will be given as well.

The study nurse will remain in contact with the study subject throughout the study duration and will monitor the subject for any side effects and adverse events that may occur.

4. SELECTION AND ENROLLMENT OF STUDY SUBJECTS

4.1 Inclusion Criteria

To be eligible, subjects must meet all of these criteria:

4.1.1 Signed informed written consent

4.1.2 Gender: female

4.1.3 Age: 18-55 years at time of signing consent

4.1.4 BMI of subjects: < 45 kg/m^2

4.1.5 Uterine fibroids:

4.1.5.1 Diagnosed by ultrasound (MRI will be used only if ultrasound is inconclusive)

4.1.5.2 Number: any number of fibroids

4.1.5.3 Location: submucosal or intramural

4.1.5.4 At least one fibroid of diameter > 3cm

4.1.6 Symptoms: one or more of the following symptoms of Heavy menstrual bleeding (HMB), defined as:

Experienced cyclic (22 to 35 days) abnormal uterine bleeding (heavy or prolonged) in at least 3 of the last 6 menstrual periods, including menstrual bleeding lasting 5 or more days or heavy bleeding per participant recall. Examples of heavy bleeding may include, but are not limited to the following:

4.1.6.1 Requires the use of double protection to manage menstrual bleeding

4.1.6.2 Menstrual bleeding accompanied by the sensation of "gushing" or "flooding"

4.1.6.3 Saturates more than 1 tampon or sanitary pad per hour for 3 or more consecutive hours

4.1.6.4 Regularly needs to change the tampon or sanitary pad at night or regularly soils bedclothes

4.1.6.5 Heavy bleeding that affects work, school, or social activities

4.1.6.6 Pelvic pain/ pressure likely caused by fibroids

4.1.7 Plan for surgery (hysterectomy or myomectomy)

4.1.8 Normal Pap smear within the last year

4.1.9 Use of contraception during study such as non-hormonal contraceptives, intrauterine devices (IUD)/ intrauterine systems (IUS), barrier contraceptives, abstinence or sterilization

4.2 Exclusion Criteria

To be eligible, subjects must not meet any of these criteria:

4.2.1 Pregnancy or lactation.

4.2.2 History or current uterine, cervical or ovarian cancer.

4.2.3 Current endometrial hyperplasia or history of atypical endometrial hyperplasia. Endometrial biopsy will be done during screening if not done within last 12 months.

4.2.4 Suspicion of leiomyosarcoma.

4.2.5 Recent rapid growth of fibroids (i.e. doubling in size within 1-6 months period).

4.2.6 Unevaluated gynecologic abnormalities (unexplained vaginal bleeding, cervical dysplasia, or abnormal adnexal/ovarian mass).

4.2.7 Menopausal status.

4.2.8 Surgery is urgently indicated (<3 months) for medical or social reasons.

4.2.9 Hemoglobin ≤ 6 g/dL.

4.2.10 Currently enrolled in another investigational study.

4.2.11 Mental condition or other barrier preventing informed written consent.Allergy or hypersensitivity to simvastatin.

4.2.12 Current use of simvastatin or other drugs of the same class.

4.2.13 Concomitant administration of strong CYP3A4 inhibitors including itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, elithromycin,

HIV protease inhibitors, boceprevir, telaprevir, nefazodone, and cobicistat-containing products.

4.2.14 Concomitant administration of gemfibrozil, cyclosporine, or danazol, verapamil, diltiazem, amiodarone, diltiazem, dronedarone, amlodipine, ranozoline, lopitamide, and grapefruit juice.

4.2.15 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.(elevation of AST and/or ALT > 2 s.d. above the normal range at screening visit)

4.2.16 Known increased risk or diagnosis of a myopathy.

4.3 Study Enrollment Procedures

Recruitment will occur through referrals from gynecologists and primary care physicians for diagnosis and treatment of leiomyoma. All recruitment materials such as flyers will be sent to the IRB for review prior to dissemination. The discussion for enrollment in this study will be deferred until the women, in consultation with their physician, have made the decision to undergo hysterectomy or myomectomy. The main goal of screening is to ascertain if a fibroid can be obtained for evaluation post-surgery.
NOTE: Women undergoing other operative approaches to hysterectomy or myomectomy will be considered to be a subject in the study if a fibroid can be obtained intact.

A screening / enrollment log will be kept for documenting the reasons for ineligibilty and non-participation of the candidates in the study.

Prior to obtaining informed consent from the participants, the study investigator will provide subjects with adequate information about the study, including risks and benefits, and answer any questions. This will provide the opportunity for the participants to consider all available options and understand their rights as a subject. The investigator will ensure that the subject comprehends this information in order to agree to participate in the clinical trial.

The subject must sign a statement (complying with the requirements of the U.S. Code of Federal Regulations, Title 21 CFR Part 50) which indicates that they have given their consent to participate in the study.

A flow chart of the study design and study related procedures is depicted in Figure 1 and Table 1. All the study related visits and procedures will occur in an outpatient area at Johns Hopkins.

At the screening visit the following procedures will be performed:

1. Complete history including medical conditions, headaches, depression, and chest pain. Reproductive health history regarding sexually transmitted infections, gynecologic conditions, menstrual history, contraceptive use, pregnancy history and smoking/ alcohol consumption history.
2. Physical examination with pelvic exam.
3. Review of concomitant medications.
4. Pregnancy test (Urine beta-hCG).
5. Laboratory testing including: CBC with differential, hemoglobin, hematocrit, ferritin, liver enzymes and lipid panel. Total amount of blood <20 ml. Blood will be drawn and held for research purposes.
6. Evaluation of fibroid size (volume) and location by ultrasound and/or MRI (only if ultrasound is inconclusive) by study physicians.

After enrollment the following procedures will be performed:

1. Standardized questionnaires (all attached in the appendix) will be administered to assess:
    - Quality of life and sexual activity questionnaires. These instruments have been used to assess subject's response in treatment of fibroids and are accepted surveys. (Uterine Fibroid Symptom and Health-related Quality of Life Questionnaire (UFS-QOL) and Female Sexual Function Index (FSFI)).
    - Pain (McGill Pain Questionnaire (MPQ) and Visual Analog Scale (VAS).

2 A baseline ultrasound scan of the uterus with careful measurement of fibroid size in three dimensions (width, height and depth, example 4 cm x 4 cm by 5 cm).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, Duration

5.1.1 **Intervention:** Simvastatin tablets and placebo tablets will be encapsulated prior to being dispensed to the subject from the investigational drug pharmacy and will look similar. The participant will receive the study medication for a duration of 6 weeks at a time. The dose of the simvastatin tablets is 40 mg/ day. More information of dosage is in the section for "Rationale for Dosage Regimen". The subject will be advised to take the medicine in the evening at a fixed time every day. The placebo will consist of Starch 1500 packed into matching capsules.

A safety report will be generated and will include updated information such as adverse event monitoring, compliance rates, etc. about all the participants in the study.

5.1.2 **Administration:** The study drug will be taken orally by the participant for a total period of 12 weeks divided into intervals of 6 weeks each followed by study visits with the team. The participants will be advised to take the tablet orally at the same time every day, in the evening, with water.

5.1.3 **Duration:** The participants will take the study drug/ placebo for a duration of 6 weeks at a time (12 weeks in total). The prescriptions for the study drug/ placebo will be refilled at an interval of 6 weeks. The subject will be seen at the drug intake initiation week (Visit 2), after 6 weeks (Visit 3) and 12 weeks (Visit 4). After the last visit, the subject will undergo their scheduled hysterectomy/ myomectomy to collect fibroid samples.

After the hysterectomy / myomectomy, fibroid samples collected will be examined and stored for further evaluations.

Thus, the participant will effectively be a part of the study for a duration of 12 weeks prior to their hysterectomy/ myomectomy. The study team will follow up the subjects after their surgery at their 2 and 6 weeks post-surgery visits to monitor for any adverse events.

5.2 Handling of the Study Interventions

Study medication is Simvastatin Tablets, USP.. The 40 mg tablets will be dispensed to the participants for this study. Both simvastatin and placebo will be encapsulated, prepared and dispensed by the Johns Hopkins Investigational Drug Service (IDS). A manual of operations describing procedures for storage and dispensation of the study drug/ placebo and accountability records will be kept at the IDS.

5.3 Concomitant Medications

No medication will be given outside of the study drug simvastatin or the placebo except for treatment of conditions that are clinically indicated. Prophylactic antibiotics may be given prior to hysterectomy or myomectomy based on standard pre-operative procedures at the research site.

Prescription or over-the-counter systemic medications will be allowed at the discretion of the investigators. Medicines will be allowed for depression, headache migraines, allergies, hypertension, and other medical conditions that are not part of the exclusion criteria.

All women will be protected from pregnancy by intrauterine devices (IUD)/ intrauterine systems (IUS), barrier contraceptives, abstinence or sterilization for the duration of the study.

All concomitant medication must be recorded in the subject's medical records. Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period will be recorded including the date, indication, and description of the procedure(s) and any clinical findings.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Study Assessments. See Table 1. Besides the study related procedures, standard clinical care will be provided pre and post hysterectomy or myomectomy to the study participants.

6.2 Visit Description

6.2.1 Scheduled Visits

For the timing of each visit, see Table 1. Site personnel will determine the start of each treatment period and the participants will be informed about the visit dates.

Visit 1: Screening visit

The following procedures will be performed during this visit:

- Informative discussion about the study and obtaining of the informed consent.
- Obtain signed and dated informed consent.
- Subject identification number assigned.
- Assess inclusion/ exclusion criteria.
- Demographic data, smoking history, and alcohol consumption.
- Medical, reproductive, menstrual, and fibroids histories.
- Prior and concomitant medications the subject is taking.
- Information about adverse events assessment.
- Physical examination, gynecological examination.
- Vital signs.
- Urine pregnancy test.
- Pap smear (may be waived if a normal result has been documented in the subject's medical record within the previous 12 months).
- Endometrial biopsy if not done in the last 12 months.
- Ultrasound for fibroid location, size, and MRI only if the ultrasound is inconclusive.
- Laboratory evaluations: CBC with differential, hemoglobin, hematocrit, ferritin, liver enzymes and lipid panel. Urine pregnancy test.
- Instruct the subject to complete the questionnaires.

Visit 2: Drug intake initiation visit

If the subject is eligible for the study based on the screening visit information, the subject will be invited to come for the second visit.

The study subjects will be randomized into 12 weeks of simvastatin (40 mg/day orally) or placebo arms (1:1). We will use stratified block randomization with randomly permuted blocks of sizes 4 and 6 into one of the two arms.

The randomization scheme will be stratified by race/ethnicity in three categories: African American, Caucasian, and Hispanic. All other races will be excluded (small numbers precludes proper stratification and analysis). The stratification will ensure similar distribution of

race/ethnicity categories across the arms. This is a double-blinded study, neither subjects nor interacting personnel will know arm designation.

This is an “add-on” study, i.e. subjects in both arms will continue their current treatments excluding homronal contraceptives and medications contraindicated as per precribing information for simvastatin.

The study medication will be dispensed through the Investigational Drug Pharmacy at Johns Hopkins. The subject will be infomed about the medication intake. The study medication is an oral tablet to be taken once a day in the evening at the same time. The dose of the simvastatin group is 40 mg/ day.

The restricted foods such as grapefruit, cranberry juice, and dietary supplements willl be disucssed with the subject.

At one time the participant will be provided medication for 6 weeks. The study nurse will contact the partcipant every week at the participant’s preferred time to ensure compliance and monitor any adverse events that may occur after starting the intake of the medication.

Visit 3 and 4: At 6 and 12 weeks from Drug Initiation Visit

Visits 3, and 4 will be at 6 and 12 weeks after the initiation of the study drug. These will occur at Johns Hopkins outpatient clinic to follow up with the study participant at intervals throughout the study duration of 12 weeks.
There will be review of concomitant medications that the subject is taking and an adverse events assesment at each visit. The restricted foods such as grapefruit, cranberry juice, and dietary supplements willl be disucssed with the subject.

The study questionnaires will be filled at visit 4. The subject will be informed about the ultrasound result at 12 weeks, and counselled about the need for surgery if there are significant changes in fibroid size.

Follow up Visit

The participant will have their scheduled hysterectomy or myomectomy and the fibroid sample will be collected and evaluated for histologic effects of simvastatin on fibroids.
The standard clinical care follow up will be provided to the subject by their gynecologists.
The study team will follow up with the subjects after their surgery at their 2 and 6 weeks post-surgery visits to monitor for any adverse events. The subjects will fill the final questionnaires for the study at the 6 week post surgery visit.

6.3 Study Outcomes

The primary outcome will be to assess the preliminary clinical efficacy of simvastatin in reducing size of fibroids. The study will also evaluate the effects of simvastatin on fibroid related symptoms. This will be done by collection of data on symptoms and health related quality of life as obtained through questionnaires and by maintaining a daily log of symptoms on a subject diary during the treatment period of the study.

For the safety outcomes, the study will evaluate the percentage of adverse events (AE) and serious adverse events (SAE) by organ systems, including signs/symptoms, laboratory values, and clinical events.

We will also compare hemoglobin, hematocrit, ferritin, liver enzymes and lipid panel pre and post-study.
For the secondary objectives to characterize the molecular, cellular and histologic effects of simvastatin on human fibroids, the tissue will be characterized using TUNEL and immunoblotting techniques.

6.4 Blood sampling

15-20 mL blood will be obtained for CBC with differential, hemoglobin, hematocrit, ferritin, liver enzymes and lipid panel pre and post study duration to compare the results at baseline and end of study.

6.5 Special Instructions and Definitions of Evaluations

Fibroid tissues will be collected after hysterectomy or myomectomy and fixed in formalin or snap-frozen. Tissue sections will be analyzed for apoptosis (i.e. by TUNEL) and for effects of simvastatin on ECM production and synthesis using immunoblotting techniques.

7. MANAGEMENT OF ADVERSE EXPERIENCES

Although there are no anticipated serious adverse events associated with this protocol, the subjects will be monitored weekly for any side effects of simvastatin. They will be educated about risks and warning signs, and instructed to call immediately if they believe they are having a reaction or adverse event.

If any adverse event does occur, regardless of who is responsible for the costs, immediate necessary care for adverse events will be provided at Johns Hopkins. As in all clinical trials at Johns Hopkins, adverse events are monitored, addressed and handled most expeditiously.

For this study, serious adverse events are defined as any adverse event not relating to surgery complications, or the presence of fibroids, such as bleeding. All serious adverse events, either observed by the physicians, nurses or reported by the subject, will be recorded on the Johns Hopkins Serious Adverse Event Case Report Form.

The FDA, via form 3500A, and the institutional IRB will be notified in a written IND safety report of any adverse experience that is both serious and unexpected if there is evidence to suggest a causal relationship between the drug and the adverse event. In each written IND safety report, the sponsor will identify all safety reports previously filed with the IND concerning a similar adverse experience, and will analyze the significance of the adverse experience in light of previous, similar reports. Telephone report: FDA will be notified by telephone of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information. Each telephone call to the FDA shall be transmitted to the Center for Drug Evaluation and Research, which has responsibility for review of the IND. For purposes of this section, life-threatening means that the subject was, in view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

All other anticipated or unanticipated adverse events not considered as serious adverse events will be reported to the FDA and IRB at the time of annual reports. The inevstigator will review accumulated adverse events after 30 subjects have completed the study, or earlier if the investigators notice any trend in complaints or abnormal laboratory results.

We plan to conduct first interim analysis after 30 subjects complete the study and if the results are sufficient to establish the primary hypothesis, safety and efficacy of the study drug, the study may be discontinued.

For all serious and/or unexpected adverse events, the PI will forward a copy of the adverse event report to the IRB and the FDA for the protocol.

Expected adverse events, (i.e., those events included as potential risks in the consent form) which are not serious, will be reported yearly on the Annual Progress Report (APR) for each protocol. A summary of all serious or unexpected side effects also will be included in the APR. If there were no adverse events, this will be stated in the APR. All serious adverse reactions occurring during the study, either observed by the physicians, nurses or reported by the subject, will be recorded on the Johns Hopkins Serious Adverse Event Case Report Form.

Potential risks are primarily those of simvastatin. We will counsel all study candidates about potential side effects of simvastatin as per prescribing information (1). The most important ones are muscle side effects such as muscle pain, tenderness, weakness or the more serious rhabdomyolysis. Other side effects include gastrointestinal (GI) side effects, liver function abnormalities, allergic reactions, headache, confusion, memory problems, fever, joint pain, cold symptoms, skin rash and sleep problems. The full list of side effects will be discussed at length with potential study candidates before signing of the consent form.

8. CRITERIA FOR INTERVENTION DISCONTINUATION

Subjects will only receive the study drug simvastatin or placebo as a participant of the research study. Subjects may voluntarily withdraw from the study at any time and for any reason. The investigator may discontinue the subject's participation in the study if he believes it necessary for any reason including:

8.1 Intercurrent pregnancy

8.2 Symptom improvement where surgery is not necessary

8.3 Occurrence of an adverse event that precludes further participation in the study at the discretion of the investigator

8.4 Clinically significant adverse results in laboratory testing

8.5 Failure to comply with the protocol

8.6 Evidence of significant, persistent side effects

9. STATISTICAL CONSIDERATIONS

Exploratory data analysis will be used to evaluate variable distributions at study entry. Any unusual, outlying and out-of-range observations will be checked. Missing data patterns, especially due to drop-out, will be evaluated and reported. We will explore the distributions of potentially confounding variables, i.e. any demographic, family and medical history characteristics that are strongly predictive of the study efficacy outcomes. Differences in distributions of these potential confounders will be checked across the study arms as these might occur due to chance despite the randomization, especially for relatively small clinical trials (25). Results of these analyses will be used to refine the analyses and guide model building. The final model will include adjustments for the confounders that are differentially distributed by arm.

For feasibility endpoint, we will report the following proportions: subject retention, outcomes, and adherence to the study regimen, with their 95% exact binomial confidence intervals. Subject satisfaction score will be summarized (using mean and standard deviation) for the overall study sample and by treatment arm. Two-sided t-test will be used to compare subject satisfaction scores between the treatment arms.

Safety endpoint, including adverse events will be tabulated overall and by the study arm. Proportions of events by type across the treatment arms will be compared using Fisher's exact test. To account for multiple comparisons, false discovery rate (FDR) procedure will be used. FDR controls the expected proportion of incorrectly rejected null hypotheses ("false discoveries") at 5%.

Preliminary efficacy endpoint will be reported by treatment arm. Primary analysis will focus on 12-week outcomes. The efficacy outcomes will be compared across the treatment arms using generalized

linear models (GLM) with treatment arm as the primary explanatory variable, with an indicator variable representing comparison simvastatin vs. placebo. We will use Gaussian distribution for continuous outcomes (such as tumor size, lab values or quality of life) and Poisson distribution for binary outcomes (such as fibroid symptoms). The estimates of slopes for the treatment indicator variable represents either the difference in means for continuous outcomes or the log relative risk ratio of binary outcomes for the treatment arm vs. placebo. The model will additionally include adjustment for potential confounders identified through exploratory analyses. Standard regression diagnostics will be performed for the model for each outcome. The unadjusted and adjusted effect sizes will be reported for each outcome in form of either the standardized mean difference (for continuous outcomes) or risk ratios (for binary symptoms). Statistically significant Wald test will indicate a significant difference in outcomes between the treatment arms.

In addition to this primary analysis of 12-week outcomes, we will use generalized linear mixed models to look at the change in outcomes over three follow-up time points: study entry, week 6 and week 12 visits. The model will include an indicator variable for the study arm, 23 indicator variables for time (6 and 12 weeks vs. study entry) and their interactions. These interaction variables will test whether the change over time is different by treatment arm. The model will include a random intercept for the subject to account for within-person correlation of study outcomes over time. In this analysis, missing outcome data will be assumed to be missing at random conditional on past outcomes and adjusted variables.

Missing Data

We hope to minimize the amount of missing data on both explanatory variables and study outcomes. Rates of missing data will be reported. No imputation of the primary outcome measures will be undertaken. If the overall missing data rate is less than 5%, no formal approach will be used to impute the missing data. For more than 5% missing data, multiple imputation methods will be used to impute missing covariates incorporated in the final model for the primary outcome estimating the adjusted treatment effect. In addition, the effects of incompleteness due to drop-out will be quantified through sensitivity analyses.

Anticipated Results

From the subject volume and similar trials at our institution, we expect to be able to complete the trial. We also expect safety of simvastatin in symptomatic leiomyoma subjects to be similar to the general population. We also expect the preliminary efficacy to show symptom improvement and smaller tumors in the simvastatin arm.

10. DATA AND SAFETY MONITORING PLAN

The data will be monitored by verification that informed consent was obtained appropriately prior to any study-specific procedures and documented properly. The following will also be monitored: adherence to protocol eligibility criteria; compliance with protocol procedures; documentation of procedures and assessments related to protocol-required safety assessments; evaluation and documentation of adverse events, especially any serious adverse events or withdrawals related to adverse events; conduct and documentation of study endpoints; procedures for documenting accountability and; appropriate administration of the investigational drugs.

The collection and reporting of adverse events identified in the execution of this clinical study will be described as follows: definitions of adverse events and study period; description of the identification and reporting of on-going adverse events; description and reporting procedure for serious adverse events; procedure for IND Safety Reports and; Procedure for IRB notification and study stopping rules.
The PI will have the sole responsibilty for monitoring and oversight of problems / events.

10.1 Data Collection

Data will be collected on week 0 (initiation), week 6, and week 12 visits. Our research nurse will also call the subjects weekly for compliance and side effects (feasibility and safety). Case Report Forms (CRFs), source documents, other data collection forms will be completed for each subject.
Confidentiality of all subjects will be maintained.

10.2 Role of Data Management

Interval analysis may be conducted by a statistician. We expect that it may take 5 years to accrue 60 evaluable subjects for analysis and to complete the study procedures. The following types of data and processes will be the main focus for each subject:

10.2.1 Verification that informed consent was obtained appropriately prior to any study specific procedures and documented properly.

10.2.2 Adherence to protocol eligibility criteria.

10.2.3 Compliance with protocol procedures.

10.2.4 Documentation of procedures and assessments related to protocol-required safety assessments, evaluation and documentation of adverse events, especially any serious adverse events or withdrawals related to adverse events.

10.2.5 Conduct and documentation of study endpoints.

10.2.6 Procedures for documenting accountability and appropriate administration of the investigational product.

11. HUMAN SUBJECTS

11.1 IRB

This protocol and any accompanying material provided to the subject will be submitted by the investigator to the Johns Hopkins Institutional Review Board (IRB 00149869). Approval from the committee must be obtained before starting the study and prior to shipment of study medication. Approval should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after initial IRB approval must be likewise submitted and approved. Notification will be given to the IRB in the event any serious adverse events occur.

11.2 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each subject prior to performing any study-related procedure. The subject must sign a statement (complying with the requirements of the U.S. Code of Federal Regulations, Title 21 CFR Part 50) which indicates that they have given their consent to participate in the study.

11.3 Confidentiality

The investigator will assure that the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. CRFs or other documents submitted to the sponsor should not be

identified by their names but by an identification code. Documents not submitted to the sponsor shall be maintained by the investigator in strict confidence.

11.4 Study Modification/Discontinuation

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

11.5 Investigator Study File (Regulatory Binder)

A file of documents critical to study conduct (clinical SOP, "Documents required for the Conduct of a Clinical Trial") will be established for the investigator to complete and maintain. These files will be kept in a study binder and will be reviewed for completeness. The binder will include sections for the following:

11.5.1 FDA Form 1572

11.5.2 Financial Disclosure Form

11.5.3 Investigator Brochure: Simvastatin Prescribing Information (See Appendix)

11.5.4 Protocol and Protocol Amendments: Includes a signed investigator agreement

11.5.5 CVs (and licenses) of Personnel

11.5.6 Laboratory Normal Ranges

11.5.7 Laboratory Certification

11.5.8 Study Signature List

11.5.9 Delegation of Responsibility

11.5.10 IRB Approvals including print ad and review of subject histories

11.5.11 Informed consent

11.5.12 Correspondence with IRB

11.5.13 Monitoring Log

11.5.14 Subject Roster

11.5.15 Subject Screening/Enrollment Log

11.5.16 Study Drug Records

11.5.17 SAEs / IND Safety Reports

12 REFERENCES

1. NIH National Library of Medicine. Simvastatin prescribing information: National Library of Medicine; 2017 [cited 2017 3/18/2017]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=34b56f73-bea4-4265-8b2a-c57520cf8e70.

2. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002;99(2):290-300. PubMed PMID: 11814511.

3. Hoekstra AV, Sefton EC, Berry E, Lu Z, Hardt J, Marsh E, Yin P, Clardy J, Chakravarti D, Bulun S, Kim JJ. Progestins activate the AKT pathway in leiomyoma cells and promote survival. J Clin Endocrinol Metab. 2009;94(5):1768-74. PubMed PMID: 19240153.

4. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22(4):571-88. PubMed PMID: 18534913.

5. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012;206(3):211 e1-9. Epub 2011 Dec 11. PubMed PMID: 22244472.

6. Olive DL, Lindheim SR, Pritts EA. Non-surgical management of leiomyoma: impact on fertility. Curr Opin Obstet Gynecol. 2004;16(3):239-43. PubMed PMID: 15129053.

7. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol. 2008;112(2 Pt 1):387-400. PubMed PMID: 18669742.

8. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. Obstet Gynecol. 2002;99(2):229-34. PubMed PMID: 11814502.

9. Borahay MA, Fang X, Baillargeon JG, Kilic GS, Boehning DF, Kuo YF. Statin use and uterine fibroid risk in hyperlipidemia subjects: a nested case-control study. Am J Obstet Gynecol. 2016. doi: 10.1016/j.ajog.2016.06.036. PubMed PMID: 27371355.

10. Borahay MA, Vincent K, Motamedi M, Sbrana E, Kilic GS, Al-Hendy A, Boehning D. Novel Effects of Simvastatin on Uterine Fibroids: In vitro and Subject-Derived Xenograft Mouse Model Study. Am J Obstet Gynecol. 2015. doi: 10.1016/j.ajog.2015.03.055. PubMed PMID: 25840272.

11. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther. 1999;84(3):413-28. PubMed PMID: 10665838.

12. Schmidmaier R, Baumann P, Bumeder I, Meinhardt G, Straka C, Emmerich B. First clinical experience with simvastatin to overcome drug resistance in refractory multiple myeloma. Eur J Haematol. 2007;79(3):240-3. PubMed PMID: 17655704.

13. Thibault A, Samid D, Tompkins AC, Figg WD, Cooper MR, Hohl RJ, Trepel J, Liang B, Patronas N, Venzon DJ, Reed E, Myers CE. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in subjects with cancer. Clin Cancer Res. 1996;2(3):483-91. PubMed PMID: 9816194.

14. Borahay MA, Kilic GS, Yallampalli C, Snyder RR, Hankins GD, Al-Hendy A, Boehning D. Simvastatin Potently Induces Calcium-Dependent Apoptosis of Human Leiomyoma Cells. J Biol Chem. 2014. doi: 10.1074/jbc.M114.583575. PubMed PMID: 25359773.

13. INVESTIGATOR'S SIGNATURE PAGE

I have thoroughly read and reviewed the study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the international Good Clinical Practice principles and regulatory authority requirements for source document verification and auditing / inspection of the study.

I agree to use the study medication only as specified in the protocol.

I understand that changes to the protocol must be made in the form of an amendment, which has prior written approval of the Sponsor.

I understand that any violation of the protocol may lead to early termination of the study.

I agree to follow the study time schedule as outlined in the protocol.

I agree to report to the Sponsor, within one working day, of any clinical adverse event that is serious, whether considered treatment-related or not.

_____ _____

Signature Date

APPENDIX

1. Precribing Information Simvastatin Tablets, USP
2. HDMA Sheet (Standard Pharmaceutical Product Information)
3. Safety Data Sheet, SIMVASTATIN TABLETS, USP