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TITLE: Targeting Autophagy for the Treatment of TSC and LAM

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CONTRACTING ORGANIZATION:

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13. SUPPLEMENTARY NOTES

14. ABSTRACT : Lymphangioleiomyomatosis (LAM), a disease that primarily affects women, is characterized by cystic lung destruction. LAM results from the proliferation of LAM cells that harbor mutations in the *TSC*1 or *TSC*2 genes, leading to activation of the mammalian target of rapamycin complex 1 (mTORC1). Recently, sirolimus (rapamycin) has been shown to stabilize lung function decline and decrease angiomyolipoma tumor size. Discontinuation of therapy results in progression of lung function decline and tumor growth, suggesting that continuous use is required to maintain its beneficial effects. Autophagy (self eating) is a mechanism by which tumor cells recycle proteins and organelles. Blocking TORC1, a known autophagy inhibitor, with rapamycin increases autophagy and promotes survival of TSC2-deficient cells. The Sirolimus and Autophagy Inhibition in LAM (SAIL) trial is a phase I clinical trial to test the safety and tolerability of a combination of hydroxychloroquine and sirolimus in women with LAM.

We will measure the effect of therapy using the following secondary endpoints:

1. Forced expiratory volume in 1 sec (FEV1), 2. Forced vital capacity (FVC), 3. 6-minute walk test (6MWT), 4. Angiomyolipoma size, 5. Quality of life and 6. VEGF-D serum levels

15. SUBJECT TERMS
sirolimus, hydroxychloroquine, lymphangiomyoleiomatosis

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INTRODUCTION:

This is a phase I, open label, dose escalating, two-center trial of the combination of sirolimus and hydroxychloroquine in women with LAM. The combination of sirolimus (2mg adjusted to keep trough levels between 5-15ng/ml) and hyrdroxychloroquine (200mg or 400mg) will be taken orally daily for 6 months. Up to 18 female subjects ages 18 and older with LAM will be enrolled at Brigham and Women's Hospital in Boston, MA and the National Heart, Lung, and Blood Institute in Bethesda, MD. The primary endpoint of this study is safety and tolerability of the combination of sirolimus and hydroxychloroquine in LAM patients. This trial will also investigate whether, in LAM patients, 6 month of combination therapy results in improvement of indicators of disease, and whether the gains are sustained after stopping therapy. The role of LAM-specific peripheral blood signature to predict rates of disease progression and determine responsiveness to combination therapy will also be investigated. The projected duration of the trial is 4 years.

KEY WORDS:

sirolimus, hydroxychloroquine, lymphangiomyoleiomatosis

OVERALL PROJECT SUMMARY:

This study is planning to enroll up to a total of 18 subjects at Brigham and Women's Hospital (BWH) and the National Heart, Lung, and Blood Institute (NHLBI). BWH obtained IRB approval on 6/21/2013 and is activated and enrolling subjects. The NHLBI received IRB approval on 9/20/2013 and has completed the site initiation visit. Four subjects were screened at BWH. Three women have been enrolled. One subject is still in screening. All three subjects have completed at least an 8 week course of hydroxychloroquine and sirolimus. Two subjects have completed a 24 week course of study drug. No serious adverse events have been reported.

There have been 4 amendments to the protocol.

Summary of Amendment 01

- The Department of Defense was added to the consent form. A prescreening script and prescreening questionnaire was added to the protocol to help identify eligible subjects for screening.

Summary of Amendment 02

- A study drug information sheet was created to distribute to enrolled subjects as requested by the DSMB during the meeting on 11/5/2012.
- The DSMB Charter was amended to include an additional DSMB meeting to review analysis data if data is collected before the 6 month timepoint.

Summary of Amendment 03

- Instructions for use of contraceptives were clarified in the protocol and consent form.
- **Summary of Amendment 04**
- A spirometry measurement was added to visit 6
- Urinalysis was included in visit 6
- Urine pregnancy was moved from visit 7 to visit 6
- Dose limiting toxicity for visual disturbances was further defined to include "Any visual disturbance as outlined in the risk section of this protocol or in the hydroxychloroquine package insert."
- Risk of stopping study drugs was added to the risk section of the protocol

Two DSMB meetings have been held on 11/5/2012 and 6/13/2013. Per protocol, the DSMB convened for an interim analysis of safety data on 8/6/2013. Safety data was reviewed and the DSMB approved the dose escalation. A second interim analysis will occur once 3 more patients have completed an 8 week course of therapy with sirolimus and hydroxychloroquine at 400mg/day.

The plan from the originally approved SOW will remain the same in the upcoming year.

Subject Status

Subject ID	Screening Date	Start of Study Drug	Last visit Completed	Status
01-001	11/19/2012	12/09/2012	Visit on 08/19/2013	Completed Study drug
01-002	03/22/2013	04/05/2013	Visit 5 on 09/25/2013	Completed Study drug
01-003	05/17/2013	05/28/2013	Visit 4 on 09/12/2013	On study drug
01-004	10/01/2013			

KEY RESEARCH ACCOMPLISHMENTS: Nothing to report

CONCLUSION: Nothing to report

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS: Nothing to report

INVENTIONS, PATENTS, AND LICENSES: Nothing to report

REPORTABLE OUTCOMES: Nothing to report

OTHER ACHIEVEMENTS: Nothing to report