

June 15, 2009

SUBJECT: MILES Trial

Dear colleagues:

You may be aware that the Canadian site for the MILES trial is up and running in Toronto. We have been referred patients from across Canada but I wanted to ensure that all Canadian respirologists have an opportunity to refer eligible patients for this important study, as enrolment is expected to close later this summer. Please note that subjects' travel expenses are reimbursable.

A summary of study eligibility criteria and design appear below. If you have any questions or would like to refer a patient, please contact:

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Protocol Title:

Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus Trial (The MILES Trial)

Sample Size:

120 subjects randomized to placebo or sirolimus groups
Target Enrollment Period: 2 years

Study Design:

Phase III treatment, randomized, double-blind, placebo controlled, safety/efficacy study

Primary Study Objective:

Determine the safety and efficacy of sirolimus (rapamycin) in patients with LAM

Inclusion Criteria

- a. Female, age 18 or over
- b. Signed and dated informed consent
- c. Diagnosis of LAM as determined by 1) biopsy (lung, abdominal mass, lymph node or kidney or cytology from thoracic or abdominal sources revealing HMB45+ staining of spindled/epithelioid cells), and chest CT scan findings compatible with LAM; or 2) compatible chest CT scan findings in the setting of tuberous sclerosis, angiomyolipomata (diagnosed by CT, MRI by the site radiologist or biopsy) or chylous pleural effusion (verified by tap) or 3) chest CT scan findings compatible with LAM (confirmed by the two MILES core radiologists) and a VEGF-D level ≥ 800 pg/ml.
- d. Post-bronchodilator forced expiratory volume in one second of $\leq 70\%$ of predicted during baseline visit.

Exclusion Criteria

- a. History of myocardial infarction, angina or stroke related to atherosclerosis
- b. Pregnant, breast feeding, or plan to become pregnant within the next 2 years
- c. Inadequate contraception
- d. Significant hematologic or hepatic abnormality (i.e. transaminase levels > three times the upper limit of normal range, HCT < 30%, platelets < 80,000/cumm, adjusted absolute neutrophil count < 1,000/cumm, total WBC < 3,000/cumm)
- e. Intercurrent infection at initiation of study drug
- f. Recent surgery (involving entry into a body cavity or requiring 3 or more sutures) within eight weeks of initiation of study drug
- g. Use of an investigational drug within 30 days prior to randomization
- h. Uncontrolled hyperlipidemia
- i. Previous lung transplantation or active on transplant list
- j. Inability to attend scheduled clinic visits
- k. Inability to give informed consent
- l. Inability to perform pulmonary function testing
- m. Creatinine > 2.5 mg/dl.
- n. Chylous ascites sufficient to affect diaphragmatic function based on the opinion of the site investigator
- o. Pleural effusion sufficient to affect pulmonary function based on the opinion of the site investigator (generally > 500cc)
- p. Acute pneumothorax within the past 8 weeks
- q. History of malignancy in the past two years, other than squamous or basal cell skin cancer.
- r. Use of estrogen containing medications within the 30 days prior to randomization.
- s. Known allergy to sirolimus

This trial will test the safety and efficacy of sirolimus (Rapamycin) in patients with lymphangioleiomyomatosis. One hundred and twenty patients will be randomized to placebo or sirolimus groups, treated for one year and followed off of drug or placebo for one additional year. The primary outcome will be change in forced expiratory volume in one second slope (FEV1 slope) over twelve months. The analysis will be based on an 'intention to treat' design. Interim analyses will occur when 50 participants reach the one year point. The final analysis, which will assess the durability of response, will occur at 24 months. Secondary outcome measures will include forced vital capacity, residual volume, diffusing capacity, six minute walk, all cause mortality and questionnaire based assessments of dyspnea, fatigue, quality of life, and depression.