Protocol Synopsis

Title
Targeted Therapy of Bronchiolitis Obliterans Syndrome (BOS)

Protocol Number
RDCRN-6503

Short Title
FAM for BOS

Clinical Phase
Phase II

IND Exemption
106040

Study Objectives
Primary Objective:
To determine if the combination treatment of inhaled fluticasone, azithromycin, and montelukast (FAM) administered in post Hematopoietic Cell Transplantation (HCT) recipients after the diagnosis of new onset bronchiolitis obliterans syndrome (BOS) can decrease the rate of treatment failure relative to an estimated historical rate of 40% using current therapies.

Secondary Objectives:
1. To confirm the safety profile of FAM.
2. To describe the effect on other standard pulmonary function test parameters: FEF_{25-75}, RV, DLCO, FEV_{1}/FVC ratio and FEV_{1}/SVC ratio with FAM treatment.
3. To determine the change in molecular markers of inflammation and fibrosis in the blood with FAM treatment.
4. To assess the impact of FAM on other chronic graft-versus-host (GVHD) manifestations.
5. To assess the impact of FAM on functional status, and health-related quality of life (HRQOL).
6. To describe changes in steroid dosing.

Study Design
This is a prospective, Phase II, multi-center clinical trial in subjects who develop bronchiolitis obliterans syndrome after hematopoietic cell transplantation.

Primary Endpoint
The primary endpoint of the study is treatment failure, defined as:

- A sustained, absolute decrease (worsening) of the FEV_{1} by $\geq 10\%$ predicted in comparison to the baseline FEV_{1} within 3 months after initiation of study medications and confirmed by a second PFT 2 weeks after the first measurement.
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<th>Secondary Endpoints</th>
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| 1. Incidence and types of NCI-CTCAE (v4.0 or current version) Grade 3-5 SAEs attributable to FAM; and the proportion of subjects who stop each drug during the study period.  
2. Changes in FEF 25-75, RV, DLCO, FEV₁/FVC ratio and FEV₁/SVC ratio at months 3 and 6 (including FEV₁ at month 6).  
3. Changes in blood molecular markers at month 3 and month 6: IL8 (azithromycin), cysteinyl and LTB4 (montelukast), and IL1B, TNFα, and IL6, as well as neutrophil count (fluticasone).  
4. Using the NIH consensus criteria, the proportion of subjects with improvements in other chronic GVHD characteristics at month 3 and month 6.  
5. Changes in HRQOL, exercise capacity, and symptoms at month 3 and month 6 compared to baseline, using the following measurements:  
   a. SF36, FACT, HAP, chronic GVHD symptom scale for participants ≥ 18 years of age  
   b. ASK for participants < 18 years of age  
   c. Six minute walk test  

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| 40 evaluable participants  
| Study Duration |  
| 2.5 years (2 year accrual period, 6 month active follow up period)  
| Treatment Description |  
| All participants meeting eligibility criteria will receive the following medications:  
   • Fluticasone: Inhaled fluticasone propionate, 440 mcg twice a day (ages 12-99 years) or 220 mcg twice a day (ages 6-11 years).  
   • Azithromycin: 250 mg orally for adults (19-99 years) and 5mg/kg orally (max 250mg) for children (6-18 years) taken three days per week.  
   • Montelukast: 10mg oral tablet nightly (14-99 years old) or 5 mg oral nightly (6-13 years old)  
Corticosteroids: If participants are receiving prednisone < 1 mg/kg/day (or equivalent), they will take prednisone 1 mg/kg/day (or equivalent) orally for 2 weeks. After 2 weeks, prednisone is tapered by 0.25 mg/kg/day (or equivalent) weekly until on 0.25 mg/kg/day unless higher doses are required for management of non-pulmonary chronic GVHD manifestations or other non-GVHD related diagnoses.  

**FAM for BOS**  
**Version 2.0 – August 20, 2012**
## Inclusion Criteria

Participants must meet ALL of the following criteria.

1. Diagnosis of BOS after HCT within the 6 months before study enrollment. For this study, BOS is defined as: (a) FEV\(_1\) < 75\% of the predicted normal and FEV\(_1\) to slow or inspiratory vital capacity ratio (FEV\(_1\)/SVC or FEV\(_1\)/IVC) ≤ 0.7, both measured before and after administration of bronchodilator OR (b) pathologic diagnosis of BOS demonstrated by lung biopsy.

2. The baseline absolute FEV\(_1\) must be ≥ 10\% lower than the pre-transplant absolute FEV\(_1\) as defined by the pre-transplant FEV\(_1\) minus the baseline FEV\(_1\), both measured before administration of bronchodilator.

3. Prior or current diagnosis of chronic GVHD per NIH criteria.

4. Participant (or parent/guardian) has the ability to understand and willingness to sign a written consent document.

## Exclusion Criteria

Participants must not have ANY of the following conditions.

1. Recurrent or progressive malignancy requiring anticancer treatment.

2. Known history of allergy to or intolerance of montelukast, zafirlukast, azithromycin, erythromycin, or clarithromycin.

3. Pregnancy or nursing. All females of childbearing potential must have a negative serum or urine pregnancy test < 7 days before study drug administration.

4. Hepatic dysfunction: transaminases > 5X ULN or total bilirubin > 3X ULN.

5. Chronic treatment with any inhaled steroid for > 1 month during the past three months.

6. Treatment with montelukast or zafirlukast for > 1 month during the past three months.

7. Treatment with prednisone at > 1.2 mg/kg/day (or equivalent steroid).

8. Treatment with rifampin or phenobarbital, aspirin at doses > 325 mg/day, or ibuprofen at doses > 1200 mg/day.

9. Treatment with any FDA non-approved study medication within the past 4 weeks. Off-label treatment with an FDA-approved medication is allowed.

10. Chronic oxygen therapy.

11. Evidence of any viral, bacterial or fungal infection involving the lung and not responding to appropriate treatment.

12. Clinical asthma (variable and recurring symptoms of airflow obstruction and bronchial hyper-responsiveness).

13. Patient age < 6 years.

14. Any condition that, in the opinion of the enrolling investigator, would interfere with the subject’s ability to comply with the study.
requirements.

15. Uncontrolled substance abuse or psychiatric disorder.
16. Inability to perform pulmonary function tests reliably, as determined by the enrolling investigator or the PFT lab.
17. Life expectancy <6 months at the time of enrollment as judged by the enrolling investigator.’
18. Baseline post-bronchodilator FEV1 < 20% of predicted normal