The HPCGG laboratory facility has an information management system to handle information from genetics studies. Once genetics blood samples are logged into the information management system, the system will print labels with unique bar codes assigned to each subject. When the samples are analyzed, they will be identified and analyzed only by that code number. The staff and scientists of the HPCGG laboratory will not be able to link the samples back to the subject. The HPCGG research laboratory staff will store information from studying your DNA in a secure file and release the coded results to other researchers working on this study.

-PEF: AM and PM PEF will be recorded on diaries and will be electronically recorded on AM1 peak flow meters (Cardinal Health, Yorba Linda, CA). Data will be compared for accuracy and adherence.

7.5 Clinical Laboratory Tests

7.5.1 Laboratory Parameters

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at visits with safety labs (see Appendix 1: Study Visit Table).

Clinical chemistry

Blood urea, creatinine, glomerular filtration rate, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, and uric acid will be measured at visits with safety labs (see Appendix 1: Study Visit Table). PT, PTT and platelet counts will be measured before each bronchoscopy procedure.

PK Monitoring

Blood will be taken at visits 11 and 15 for pharmacokinetic monitoring of imatinib. Subjects will be asked to withhold their dose of imatinib until the study visit. Blood will be taken prior to administration of imatinib (to determine trough levels) and then 2 hours post dose (for peak levels).

In addition, pregnancy tests will be performed at visits 2, 3 and 4 during the run in period and each month during the treatment period of the study (**Please see Appendix 1: Study Visit Table**)

7.6 Adverse Events Assessments

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical

conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events if they are considered clinically significant or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events Form with the following information:

1. The severity grade (mild, moderate, severe)
2. Its relationship to the study drug/procedures (s) (unrelated, unlikely, possibly, probably or definitely related)
3. Its duration (start and end dates or if continuing at final exam)
4. Whether it constitutes a serious adverse event (SAE)
5. Nature of the adverse event (expected or unexpected)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- syncope

During the course of the study, subjects may experience an increase in asthma symptoms. While an increase in asthma symptoms may be brief and self-limited, any increase in symptoms or changes in PEF will be carefully monitored by the subject, the clinic coordinator, and the physician. Symptoms may be of sufficient severity so as to warrant

documentation as an asthma exacerbation, defined for this protocol as events of worsening asthma requiring oral or parenteral corticosteroids, or in patients regularly taking OCS, a doubling or increase of >10 mg/d of OCS (whichever is less) (eg: unscheduled physician visits, ER visits, hospitalizations, or physician judgment of clinical asthma status.

Asthma exacerbations will be treated with a doubling dose or more of OCS as deemed necessary by the treating physician. During medical management of the exacerbation, other trial medication will be continued, unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial medications will occur when the exacerbation has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during exacerbations. Subjects will be terminated if they have a 50% increase in the number of asthma exacerbations compared to the rate of the prior year or more than 2 exacerbations during treatment (whichever is greater). In addition subjects will be terminated if they have a 50% increase in the number of asthma hospitalizations compared to the rate of the prior year or more than 1 hospitalization during treatment (whichever is greater).

Throughout the study, subjects are closely monitored for early recognition of worsening asthma by monitoring diary cards and peak flow measurements at every visit. In addition to this, the subject is instructed to call his/her individual physician or the asthma research center if he/she experiences an asthma exacerbation

Physicians at each asthma research center will review and sign-off on adverse event documents for accuracy and completeness. Immediate action is taken on all adverse events (AE's); these events are logged in asthma research center AE logs, and these are reviewed with medical personnel as soon as an AE occurs and weekly thereafter for follow up. All new adverse events and all unresolved adverse events are regularly reviewed. AE's are also recorded in individual subjects' charts and case report forms. All AE's will be reported to the DCC and the IRB in accordance with the policy of Institutional Human Research Committees and the DSMB.

7.6.1 Serious Adverse Events

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject 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.

Serious adverse events occurring after signing the informed consent and during the follow-up period, including laboratory test abnormalities fulfilling the definition of SAE, whether or not considered related to the study medications or procedures, will be recorded on the Serious Adverse Event form and faxed to the DCC or designee as soon as site personnel are aware of the event but no later than 72 hours. The DCC or designee will forward the reports to appropriate authorities (DSMB, FDA, NHLBI, Pharmaceutical supplier) according to their institutional guidelines. Each study site will report all adverse events to their IRBs according to their institutional AE reporting guidelines. Every attempt will be made to collect discharge summaries for each hospitalization to provide further details.

A Data Safety Monitoring Board (DSMB) has been formed which is comprised of experts in severe asthma, biostatistics and clinical trial design and is charged with reviewing data and safety throughout the study. The DSMB will meet at least twice a year though phone conferences or in person. The DSMB will be provided access to blinded safety data including AEs by frequency and by body system, study withdrawals, and SAEs. The DSMB may also review data on study progress including subject enrollment and disposition, especially as related to discontinuation across study sites.

A Data and Safety Monitoring Plan (DSMP) has been developed to assure subject safety. The DSMP delineates monitoring the safety of study subjects, monitoring compliance with the study protocol, especially as it relates to subject safety and the integrity of the study; and study stopping criteria as they relate to study drug/study procedure-related AEs.

Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person.

7.7 Removal of Subjects From the Trial or Study Drug

All patients who discontinue study drug should be considered withdrawn from the study and should complete the Study Completion visit assessments. If patients fail to return for these visits or are unable to do so, every effort should be made by the Investigator to contact them or a knowledgeable informant by telephone or by sending appropriate correspondence (i.e., certified letter) that will become part of the Investigators' file to record that efforts were made to reach the patients. The study is also terminated without asking for reasons, if the patient wants to discontinue. In general, treatment is stopped, if a physician thinks that continuation of the treatment has negative effects on the patients. The reason for termination of the study is noted on the individual study protocol. Patients that discontinue the study are followed in the same way as other participants.

Premature patient withdrawal

Patients may voluntarily withdraw from or be withdrawn from the study at the discretion of the Investigator or the sponsor at any time. Patients must be withdrawn from the study if any of the following occur:

- eGFR<60ml/min/1.73 sq m;
- serious arrhythmia requiring therapy;.
- thrombocytopenia < 50,000/µl ; neutropenia < 500/µl;
- elevation of liver enzymes persisting at > 3 times of normal for > 2 weeks;
- intractable nausea or vomiting;
- pregnancy;
- asthma deterioration requiring intubation;
- > 50% increase in the number of asthma exacerbations compared to the rate of the prior year or more than 2 exacerbations during treatment (whichever is greater).
- > 50% increase in the number of asthma hospitalizations compared to the rate of the prior year or more than 1 hospitalization during treatment (whichever is greater).

If such withdrawal occurs, patients should complete the Study Completion visit assessments. If patients fail to return for these visits or are unable to do so, every effort should be made by the Investigator to contact them or a knowledgeable informant by telephone or by sending appropriate correspondence (i.e., certified letter) that will become part of the Investigators' file to record that efforts were made to reach the patients. If the patients fail to return for visits, the Investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF page.

Study interruption

All interruptions, reductions, or any changes in study drug administration must be captured on the Case Report Form. The study may be terminated prematurely when the principal Investigators consider that the number and/or severity of adverse events justify discontinuation of the study or at the request of the DSMB.