Autoantibody Reduction Therapy in Patients with Idiopathic Pulmonary Fibrosis (ART-IPF)

Study Protocol & Statistical Analysis Plan

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Autoantibody Reduction Therapy in Patients with Idiopathic Pulmonary Fibrosis

(ART-IPF)

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PROTOCOL SYNOPSIS

Protocol Title:	Autoantibody Reduction Therapy in Patients with Idiopathic Pulmonary Fibrosis
Protocol Number:	PRO13110227
NCT Number:	NCT0196409
Version # and Date:	Version 3.1 / December 11, 2014
Clinical Phase:	Phase II clinical investigation
Trial Site:	Multi-Center Trial
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Participating Medical Centers:	1. University of Pittsburgh Medical Center 2. Geisinger Medical Center 3. Temple University Medical Center 4. University of Chicago Medical Center 5. University of Alabama at Birmingham
Data Coordinating Center:	Epidemiology Data Center University of Pittsburgh Graduate School of Public Health

Sponsor:	National Heart, Lung, and Blood Institute (HL119960)
Study Rationale:	On the basis of substantial preliminary data, we hypothesize that autoantibodies play a pathogenic role in the progression of idiopathic pulmonary fibrosis (IPF). Autoantibody-mediated lung diseases are often refractory to treatments with nonspecific agents, including glucocorticoids. Rituximab, the experimental therapy here, is mechanistically targeted to decrease autoantibody concentrations. We hope that autoantibody-targeted treatments could result in significant benefit for a lung disease that has, until now, been almost invariably inexorable. This clinical trial has the potential to profoundly affect current paradigms and treatment approaches to patients with IPF.
Study Objectives:	The primary goal of this multicenter, randomized, double-blind, Phase II clinical trial is to determine effects of rituximab on selected relevant immunological parameters of IPF patients, in comparison to effects of placebo alone. We anticipate the findings of this will lead to larger incremental trial(s) to definitively establish the clinical efficacy of this treatment.
Study Hypothesis:	Our central hypothesis is that antibody-mediated autoimmunity can play an important role in IPF. We propose to begin to test our central hypothesis by establishing the efficacy and duration of autoantibody reductions by rituximab in IPF patients.
Study Aims:	1. To conduct a proof-of-concept, mechanistically-driven trial to reduce autoantibodies against HEp-2 cells. 2. To determine the effects of the experimental treatment (rituximab), compared to placebo therapy, on secondary endpoints of: 1.) anti-heat shock protein 70 (HSP70) concentrations; 2.) changes in forced vital capacities; 3.) acute IPF exacerbation incidences; 4.) survival; 5.) hospitalization rates; and 6.) adverse event-rates.
Study Design:	Following screening assessments, IPF patients who meet all inclusion/exclusion criteria will be randomly assigned to receive one of the following treatments in a ratio of 1:1: • **Arm A** (n=29) **- Rituximab Treatment**: Premedications, consisting of 100 mg methylprednisolone I.V., and P.O. acetaminophen and diphenhydramine, will be followed by rituximab 1 g. I.V. • **Arm B** (n=29) **- Placebo Treatment**: To maintain double-blinding, Arm B subjects will also

	receive the premedication regimen (above), and placebo infusions of dextrose 5% in water (D5W), in lieu of rituximab, that are indistinguishable from the rituximab unit doses. <u>Both treatments (premedications + either rituximab or D5W will be repeated 14 days after the first treatments.</u> Patients will be monitored carefully for occurrence of adverse events, and changes in vital signs. Patients will be followed for a total of 9 months after their first study treatments.
Planned Sample Size:	A total of 58 subjects will be enrolled in this multi-center trial from 5 participating medical centers
Duration of Study:	Nine months
Inclusion Criteria:	1) Diagnosis of IPF, not established >5 years from the enrollment date, that fulfills ATS/ERS Consensus Criteria (1). 2) Ability and willingness to give informed consent. 3) Age 50-85 years old. 4) Ambulatory. 5) Presence of autoantibodies against HEp-2 cells at plasma titrations of $\geq$1:20, the assay for the primary endpoint.
Major Exclusion Criteria:	1) Diagnosis of current infection, proven or suspected by participating physicians based upon their clinical assessments. 2) Presence of active hepatitis B or C, or HIV infection. 3) History of conventional autoimmune syndromes (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis, myositis, Sjogren's syndrome, anti-neutrophil cytoplasmic autoantibody vasculitis, Goodpasture's syndrome) by clinical evaluation or positive conventional autoimmune serologic tests (i.e., ANA, RF, Anti-Ro, ANCA, Anti-LA, Anti-RNP, Anti-Jo-1). 4) History of reaction to murine-derived products or any of the trial medications, or prior exposures to human-murine chimeric antibodies.

	5) Malignancy, excluding basal or squamous cell skin cancer or low-risk prostate cancer. The latter is defined as stage T1 or T2a with PSA less than 10 ng/dl. Rituximab is not known to promote cancer progression, and these criteria are within current guidelines. 6) Unwillingness to complete post-treatment surveillance for 9 months. 7) Diagnosis of major morbidities (aside from IPF) expected to interfere with subjects' study participation for 9 months. 8) Treatment for >5 days within the preceding month with >10 mg. prednisone (or equivalent corticosteroid) or any treatment during the preceding month with a potent cellular immunosuppressant (e.g., cyclophosphamide, methotrexate, mycophenolate, azathioprine, calcineurin inhibitors, etc.). 9) Uncontrolled diabetes or hypertension that precludes safe treatment with methylprednisolone. 10) Concurrent participation in other experimental trials. 11) Pregnancy or unwillingness to use contraception during the duration of the study among female participants with child-bearing potential. The safety of rituximab during pregnancy has not been established. 12) Ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) <70% of predicted values.
Study Endpoints:	• <u>Primary endpoints</u>: The primary endpoint is reduction of autoantibody titers to HEp-2 epithelial cells, comparing baseline measures of each individual to results of their interval measures during the next 9 months. • <u>Secondary endpoints</u>: Secondary endpoints are: 1.) treatment-related effects on anti-HSP70 autoantibody concentrations, 2.) forced vital capacities, 3.) incidences of acute IPF exacerbations, 4.) survival durations; 5.) hospitalization rates; and 6.) adverse event-rates

1. OBJECTIVE, SPECIFIC AIMS, BACKGROUND, AND SIGNIFICANCE

1.1 OBJECTIVE

The primary goal of this randomized, multi-center, double-blind Phase II clinical trial is to determine the effects of rituximab treatment in terms of autoantibody reductions (magnitude and duration) in IPF patients. We anticipate the findings here will lead to larger incremental trial(s) to determine actual clinical efficacy of this treatment.

1.2 SPECIFIC AIMS

Hypothesis: Our central hypothesis is that antibody-mediated autoimmunity plays an important role in IPF progression. A corollary of this hypothesis is that treatments that reduce autoantibodies in these patients will have a favorable effect on the natural history of this disease. The studies proposed here are primarily designed to determine the magnitude and duration of autoantibody reductions affected by rituximab, as a prelude to design of a definitive Phase III efficacy study. Nonetheless, we hope that experimental treatments may result in clinically-relevant beneficial effects as determined by secondary endpoints: preservation of forced vital capacities or reductions of acute exacerbation incidences.

Specific Aims:

1. To conduct a proof-of-concept, mechanistically-driven trial to reduce autoantibodies against epithelial HEp-2 cells among IPF patients.

   We hypothesize the experimental treatment with rituximab will more effectively reduce anti-HEp-2 autoantibodies, the primary endpoint of this clinical trial, compared to placebo treatment.

2. To determine the effects of the experimental rituximab treatment on secondary endpoints of anti-HSP70 autoantibodies, preservation of forced vital capacities, survival, need for hospitalizations, incidences of acute IPF exacerbations, and adverse event-rates.

   We hypothesize the experimental treatment will also have a demonstrable effect on these secondary endpoints, in comparison to placebo therapy, and will have acceptable adverse event profile.

Findings of this study will also further develop the potential of focused immunologic assays as prognostic and disease phenotyping tools of individual IPF patients. We anticipate this proposal will establish the feasibility of autoantibody-targeted interventions, and results here will be a nidus for subsequent incremental clinical trials in this population.

The preliminary data that support our central hypothesis are novel findings from a series of innovative investigations.

1.3 BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a morbid interstitial lung disease that is characterized by lung parenchymal fibroproliferation (1-4). IPF manifests with progressive shortness of breath and hypoxemia. The absence of a valid pathological paradigm has precluded the rational selection of mechanistically-targeted therapy. Only two medications, whose mechanisms of action remain largely speculative (pirfenidone and nintedanib), have been recently shown to have partial efficacy for IPF. IPF continues to have a worse prognosis than many common malignancies, with a median survival of approximately 3 years from the time of diagnosis.

Our recent studies and others (5-21), support an autoimmune pathogenesis, leading us to posit the central hypothesis of this proposal: Antibody-mediated autoimmunity plays an important role in IPF progression. Among these findings, B-cell follicular-like aggregates are evident in IPF lungs (5,6,20), along with over-expressions of immunoglobulin (Ig) genes (8). Antigen-antibody (immune) complexes with considerable pathogenic potential are present in sera, bronchoalveolar lavage (BAL) and lung parenchyma of IPF subjects (7,9,14,20). Injurious complement deposits are also common in IPF lungs (20). Enhanced B-cell differentiation induced by antigen exposure and increased circulating levels of B-lymphocyte stimulating factor (BLyS) are characteristics of autoantibody-mediated diseases, and are similarly increased and proportionate to disease activity among IPF patients (20). Various circulating antibodies with self-avidities are detectible in ~80% of IPF cohorts (10,14). Several of these IPF autoantibodies exert direct cytopathic or other function-altering effects, and/or are associated with clinical manifestations and prognoses of the afflicted individuals (9-17). We have also recently found that CXCL13, an important mediator for B-cell trafficking to inflammatory foci, is similarly increased in lungs and plasma of IPF patients, proportionate to their disease activity, and inversely proportionate to their survival (21).

Other autoantibody-mediated lung diseases are refractory to nonspecific therapies, notably including steroids. In contrast, however, specific treatments to remove or reduce autoantibodies are now a mainstay of therapy for anti-donor HLA antibody-mediated lung transplant rejection and other patients with autoantibody-mediated lung diseases (22-28).

Pilot Study of Autoantibody-Targeted Therapy in IPF. Based on these and other interrelated findings, we initiated an experimental trial to reduce autoantibodies in critically-ill patients with rapidly progressive IPF (28). The first seven (7) subjects were treated at Presbyterian University Hospital of the University of Pittsburgh Medical Center (PUH-UPMC). The most recent subject (#8) was treated by Dr. Vincent Valentine at the University of Texas Medical Branch (UTMB) in Galveston, Texas.

All subjects fulfilled ATS/ERS diagnostic criteria (1) and were having very severe acute IPF exacerbations (4). None had other causes of lung dysfunction per extensive clinical evaluations, nor abnormal conventional autoantibody tests (14). None of the subjects were transplantation candidates at their presentations due to contraindications of advanced age, irreparable coronary artery disease or not having already undergone the necessary transplantation evaluations. This was a pilot, "compassionate-use" trial to explore feasibility and gain insights for incremental studies.

Rituximab onset of clinical benefit can take weeks (29-39). Since these subjects were expected to die within days, we used plasma exchange (PEX) to rapidly remove autoantibodies and "buy time" for rituximab effects. PEX consisted of 1.5x plasma volume exchanges with 95-100% replacement using albumin:saline (3:1), on days 1-3, and 5-6. The number of PEX treatments (five) was chosen empirically *a priori*, as a balance of risk and expense in this novel application *vs.* the potential to see

some benefit. PEX has rapid onset, but effects have limited duration in the absence of other treatments (40,41). Rituximab (1 g I.V.) was given after the last PEX and 1 week later, without apparent complications.

All but the first subject, in whom treatment was initiated while he was in severe respiratory failure (ventilated with FIO2 0.7, PEEP 10) had a striking improvement of gas exchange. And even though other studies (autoantibody titers) suggest that >5 PEX will be necessary to treat some severely ill IPF with acute exacerbations, our results implied the experimental treatment prolonged survival. Accordingly, we performed a *post hoc* comparison to a historical control cohort of IPF subjects with acute exacerbations admitted to PUH-UPMC in the two years prior to commencement of this experimental trial. Data were extracted from the Medical Archival Record System using a search query for hospital discharges with diagnoses of idiopathic pulmonary fibrosis (CPT 516.3) or post-inflammatory pulmonary fibrosis (CPT 515). The medical records of these potential subjects were deidentified and reviewed. Twenty-three (23) of the IPF patients admitted to PUH during May 2008-April 2010 fulfilled the same criteria as the trial participants, i.e., worsening hypoxemia and/or dyspnea during the preceding 30 days, new characteristic radiographic abnormalities, and no other etiology of pulmonary dysfunction found on thorough clinical evaluations. Several of these historical controls did not require an interval increase of their baseline supplemental oxygen requirements during their hospitalizations, unlike the experimental trial subjects.

Even though the control cohort included subjects who were less severely-ill than the trial participants, there was at least a trend for better survival among the latter (Figure 1). Overall median survival, with lung transplantations censored (end of observations), was 76 days among the experimental subjects, and 24 days among the historical controls. One-year survival was 44±19% in trial subjects vs. 13±7% in the controls (p=0.11).

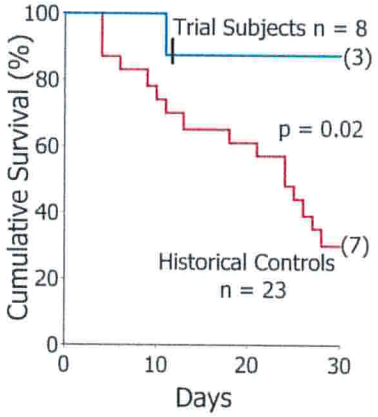

Figure 1. Survival Comparisons. There is at least a trend for greater survival in experimental patients compared to outcomes of 23 historical controls, many of whom were less severely ill than the trial subjects. Cross hatches and numbers in parentheses denote censored observations.

Among the inferences drawn from our experiences so far: **1.)** Specific autoantibody-targeted treatments in IPF patients may be associated with improved lung function and survival. **2.)** Autoantibody changes with treatments may correlate with clinical responses and relapses.

1.4 SIGNIFICANCE

If our hypothesis is correct, treatments that reduce autoantibody production (e.g., rituximab) will have beneficial effects in IPF patients. The proposed clinical trial here will generate important preliminary data regarding the magnitude and duration of rituximab effects on autoantibody production in IPF patients. These data will be essential for design of a subsequent clinical efficacy (Phase III) study.

2 RESEARCH DESIGN AND METHODS

2.1 CLASSIFICATION AND METHODOLOGICAL DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled Phase II clinical trial to determine the effects of rituximab on autoantibody production in IPF patients.

2.2 STUDY DESIGN

Participants will be recruited from the ambulatory IPF patient populations among the collaborating institutions.

Following completion of screening and eligibility assessments, N=58 subjects will be randomly assigned to one of two cohorts intended to receive either rituximab or placebo, in a ratio of 1:1. The rituximab (or placebo) will be administered over two doses (1 g each), following premedications, with a 14 day interval in between these replicate treatments.

All patients will have physiological assessments that are standard of care for IPF patients, including initial chest radiographs (CT scans) and serial pulmonary function tests (spirometry, diffusion capacity, 6 minute walk distance). These procedures and routine laboratory tests will not be repeated specifically for this study if they are deemed to be clinically indicated. The results of these standard of care procedures will be extracted from the participant's medical record and used as research data. All enrolled subjects will also have serial measures of circulating autoantibodies.

Patients will be monitored carefully for occurrences of adverse events. Adverse experiences will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Patients will be followed for nine (9) months after random assignment. Patients removed from treatment due to unacceptable adverse events will be followed throughout the 9 months under the principle of intent to treat.

2.3 INCLUSION AND EXCLUSION CRITERIA

Potential subjects will be identified by attending physicians (i.e., collaborating center Co-Investigators or their designees). Subjects who sign informed consent will be assigned a deidentified study ID and will be screened for inclusion and exclusion criteria.

Inclusion Criteria

1) Diagnosis of IPF, not established >5 years from the date of enrollment, that fulfills ATS/ERS Consensus Criteria (1).

2) Ability and willingness to give informed consent.

3) Age 50-85 years old.

4) Ambulatory.

5) Presence of autoantibodies against HEp-2 cells.*

*HEp-2 autoantibody determinations will be performed in peripheral blood specimens from potential subjects who otherwise fulfill all inclusion and exclusion criteria, AFTER they have given written informed consent. Specimens from potential subjects will be shipped to the central laboratory of the PI (Dr. Duncan) at the University of Alabama at Birmingham for these assays.

Exclusion Criteria

1) Diagnosis of current infection, proven or suspected by participating physicians based upon their clinical assessments.

2) Presence of active hepatitis B or C, or HIV infection.

3) History or presence of conventional autoimmune syndromes (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis, myositis, anti-neutrophil cytoplasmic antibody vasculitis, Sjogren's syndrome, Goodpasture's syndrome) by clinical evaluation or positive conventional autoimmune serologic tests, i.e., ANA, RF, ANCA, Anti-Ro, Anti-LA, Anti-RNP, ANCA, Jo-1).

4) History of reaction to murine-derived products or any of the trial medications, or prior exposures to human-murine chimeric antibodies.

5) Malignancy, excluding basal or squamous cell skin cancer and low-risk prostate cancer, defined as stage T1 or T2a with PSA less than 10 ng/dl. Rituximab is not known to promote cancer progression, and these criteria are within current guidelines.

6) Unwillingness to complete post-treatment surveillance for 9 months.

7) Diagnosis of major morbidities (aside from IPF) expected to interfere with subjects' study participation for 9 months.

8) Treatment for >5 days within the preceding month with >10 mg. prednisone (or equivalent corticosteroid) or any treatment during the preceding month with a potent cellular immunosuppressant (e.g., cyclophosphamide, methotrexate, mycophenolate, azathioprine, calcineurin inhibitors, etc).

9) Uncontrolled diabetes or hypertension that precludes safe treatment with methylprednisolone.

10) Concurrent participation in other experimental trials.

11) Pregnancy or unwillingness to use contraception during the duration of the study among female participants with child-bearing potential. The safety of rituximab during pregnancy has not been established.

12.) Ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) <70% of predicted values.

Subjects who fulfill all inclusion criteria and meet no exclusion criteria will be eligible for randomization.

2.4 RANDOMIZATION

Following a determination of eligibility, subjects will be randomly assigned to one of two treatment arms (1:1 ratio), after stratification on the basis of gender, disease severity (DLCO <35%≥ of predicted values), and current use of either/both pirfenidone and/or nintedanib. These stratifications will ensure ~equal proportions of severely ill patients, and ~equal proportions of males, in each arm. Male IPF patients have worse prognoses than females (1-4). Randomization assignments will be made in random block sizes of 2 and 4.

Randomizations will occur on the day of initial treatment, to reduce the possibility of "wasting" a randomization on a patient who fails to return for treatment.

2.5 STUDY TREATMENT

Study treatments will be administered twice, with the first being administered on Day 1.

- **Arm A** (n=29) **- Rituximab Treatment**:

  Premedications, consisting of 100 mg methylprednisolone I.V., and P.O. acetaminophen and diphenhydramine, will be followed by rituximab 1 g I.V. by slow infusion. The drug is initially administered at a rate of 50 mg/hr for 30 min, with rate increases by 50 mg/hr at 30 min intervals (as tolerated) to a maximum rate of 400 mg/hr.

- **Arm B** (n=29) **- Placebo Treatment**:

  To maintain double-blinding, Arm B subjects will also receive the premedication regimen (above) and infusions of dextrose 5% in water (D5W) that are indistinguishable from the rituximab unit doses.

  Both treatments will be repeated 14 days later. These treatments will be administered in dedicated, experienced infusion centers at each collaborating site with close monitoring of subject vital signs and symptoms.

Pharmacies at each of the sites will be responsible for preparing rituximab (Arm A) and placebo (D5W) infusion sets (Arm B) that are in all respects indistinguishable. Rituximab will be

reconstituted on the same days of treatment for each individual subject, based on the randomization of that patient and transmission of that information by the DCC.

2.6 STUDY PROCEDURES AND MEASURES

Scheduling. The initial pre-treatment laboratory evaluations (conventional autoantibodies, viral studies, CBC with differential and platelets, pulmonary function tests-see Table 1 and Appendix A), if not otherwise clinically indicated, will be performed after informed consent is obtained, but within the subsequent two-week interval (maximum) prior to randomization and first treatment. Chest CTs must be obtained within 30 days prior to randomization and first study treatment. The conventional autoantibodies (ANA, RF, etc.), viral studies, and initial C3, C4, will be performed in the clinical lab of UAB. The CBC (with differential counts and platelets), and pulmonary function tests will be performed locally at each collaborating center and repeated at 1, 3, 6, and 9 months after treatment. These are standard of care tests for IPF patients. Screening and baseline studies can be performed concurrently or over the course of several days, if medically necessary or in best interests of subjects, **as long as these studies are performed within the 14 day interval prior to first study treatment (or 30 days for CT scans)**.

Other routine clinical care for IPF patients will be followed as ordered by the primary physician.

Experimental immunologic studies for research purposes (experimental autoantibodies, lymphocyte phenotypes and mediators, longitudinal C3 and C4) will also be drawn after randomization, but within the 14 day period prior to the first treatment, and at 1, 3, 6, and 9 months after first treatments. These experimental tests will be performed using specimens shipped to UAB.

Following completion of screening assessments and determination of eligibility, the initial experimental treatment will be scheduled for a date within the next 14 days (allowing time for anti-HEp-2 autoantibody specimen processing, shipping to the central laboratory, and performing these assays). Computer-based randomization will occur on the day of initial treatment.

Subsequent study events will be scheduled relative to the date of randomization.

The second treatment will be scheduled for 14 days post-randomization, +/- two days. A window of +/- five days will be allowed in scheduling the 1-month assessment post-randomization, and a +/- seven-day window is allowed for subsequent evaluations at 3, 6, and 9 months post-randomization.

For use in study management, patient contact, physician contact, and other identifiable information will be collected and stored in a password-protected database separated from the research data. The following routine clinical information will be collected and entered into the study case report forms (CRFs).

1. Demographics, general medical and surgical histories (including smoking history), co-morbidities, concurrent medications, and allergies, radiology and lung pathology reports. Demographics include age, gender, duration of IPF diagnoses and symptoms, past medications (including past clinical trials).
2. Recording of vital signs.

3. Review of medications
4. Brief assessment of symptoms to allow documentation of subsequent adverse effects of study treatment.
5. Recording of laboratory and clinical testing results.

A telephone contact will occur on the days following treatments and at non-visit months 2, 4, 5, 7, and 8 for additional surveillance. Subjects will be contacted by the study coordinators to assess for symptoms potentially related to adverse effects of medications, review of medication changes, and interval medical or surgical histories including emergency or physician office visits.

The schedule for patient assessment and data collection is outlined as follows.

2.6.1 Screening and Randomization (see Table 1 and Appendix A)

Patients will undergo the screening assessment to determine that all inclusion/exclusion criteria are met prior to receiving the study drug treatments. The following tests and procedures will be performed prior to randomization to verify eligibility:

Eligibility Screening (Days -14-to-0):
The screening assessment may take place over more than one day to rule out infections and to confirm the diagnosis of IPF.

- Informed Consent
- Medical History
- Physical exam.
- Laboratory evaluations to exclude the presence of conventional autoimmune syndromes (ANA, RF, ANCA, Anti-Ro, Anti-LA, Anti-RNP, Jo-1, and C3/C4) and CBC with differentials and platelet counts. These tests are standard of care evaluations for IPF patients.
- Tests for hepatitis B surface antigen (HBsAg) and anti-hepatitis B core (HBc) antibodies, and Hepatitis C and HIV antibodies.
- Anti-HEp-2 autoantibody titer determinations.
- Serum pregnancy test for women of childbearing potential.
- Baseline symptom assessment

Summary of Eligibility Determinations/Screening Procedures:

	SEQUENCE OF EVENTS			
	1	2	3	4
Medical Record Review to Begin Eligibility Ascertainment	x			
Sign Informed Consent		x		
Protocol Specific Tests: Anti-HEp-2 Auto-antibody, Hepatitis, HIV, Pregnancy Conventional autoantibodies (ANA, RF, etc.)			x	
Randomization				x

Table 1. Processes and sequences of eligibility determinations. Sequences denote the order of these processes. Randomization should occur within 14 days of obtaining informed consent (thereby allowing time for anti-HEp-2 specimen shipping to the central laboratory, and performing these assays).

2.6.2 Experimental procedures (see also Table 2 and Appendix A)

Pretreatment:
Patients that meet all inclusion/exclusion criteria will be randomized to receive one of the study treatments as described above. Baseline studies to be performed within 14 days prior to the first study treatment include:

- Laboratory evaluations: complete blood count (CBC) with differential and platelet count, performed at the respective collaborating centers. These are standard of care tests.
- Blood draw and specimen shipment to the Coordinating Center lab for HEp-2 autoantibody, anti-HSP70 autoantibody, initial C3, C4, viral studies, lymphocyte phenotypes, and B-cell mediator studies- see also Section 2.6.1 and Table 1) A total of 29 ml of blood will be procured at this time for various assays and experimental studies..
- Pulmonary function tests (complete spirometry, DLCO, 6 minute walk distance, O_2 requirement and saturations at rest and with exertion, Borg scale dyspnea assessment).
- Chest CT scan within 30 days prior to randomization and first study treatment.

Day 1 (first treatment):
- Review of study protocol with subject, confirmation of subject's understanding of protocol and informed consent.
- Physical exam and assessment to include vital signs and blood pressure.
- First administration of study medications.

Day 2 (one day after first treatment):
- Phone interview to assess for new symptoms and AE.

Day 14 (after first treatment):
- Physical exam and assessment to include vital signs and blood pressure.
- Second administration of study medications.

Day 15 (one day after second treatment):
- Phone interview to assess for new symptoms and AE.

Month 1 (after first treatment):
- Physical exam and assessment to include vital signs and blood pressure.
- Current medication assessment
- Laboratory evaluations: complete blood count (CBC) at the respective collaborating centers
- Blood draw and specimen shipment to the Coordinating Center lab for experimental autoantibodies, serial C3, C4, lymphocyte phenotypes, and B-cell mediator studies. A total of 29 ml of blood will be procured at this time for CBC and experimental immunology tests
- Pulmonary function tests (complete spirometry, DLCO, 6 minute walk distance, O_2 requirement and saturations at rest and with exertion, Borg scale dyspnea assessment).
- AE assessment

Month 2 (after first treatment):
- Phone interview to assess for new symptoms and AE.

Month 3 (after first treatment):
- Physical exam and assessment to include vital signs and blood pressure.
- Current medication assessment
- Laboratory evaluations: complete blood count (CBC) at the respective collaborating centers

- Blood draw and specimen shipment to the Coordinating Center lab for experimental autoantibodies, serial C3, C4, lymphocyte phenotypes, and B-cell mediator studies. A total of 29 ml of blood will be procured at this time for CBC and experimental immunology tests
- Pulmonary function tests (complete spirometry, DLCO, 6 minute walk distance, O_2 requirement and saturations at rest and with exertion, Borg scale dyspnea assessment).
- AE assessment

Month 4 (after first treatment):
- Phone interview to assess for new symptoms and AE.

Month 5 (after first treatment):
- Phone interview to assess for new symptoms and AE.

Month 6 (after first treatment):
- Physical exam and assessment to include vital signs and blood pressure.
- Current medication assessment
- Laboratory evaluations: complete blood count (CBC) at the respective collaborating centers
- Blood draw and specimen shipment to the Coordinating Center lab for experimental autoantibodies, serial C3, C4, lymphocyte phenotypes, and B-cell mediator studies. A total of 29 ml of blood will be procured at this time for CBC and experimental immunology tests
- Pulmonary function tests (complete spirometry, DLCO, 6 minute walk distance, O_2 requirement and saturations at rest and with exertion, Borg scale dyspnea assessment).
- AE assessment

Month 7 (after first treatment):
- Phone interview to assess for new symptoms and AE

Month 8 (after first treatment):
- Phone interview to assess for new symptoms and AE.

Month 9 (after first treatment):
- Physical exam and assessment to include vital signs and blood pressure.
- Current medication assessment
- Laboratory evaluations: complete blood count (CBC) at the respective collaborating centers
- Blood draw and specimen shipment to the Coordinating Center lab for experimental autoantibodies, serial C3, C4, lymphocyte phenotypes, and B-cell mediator studies. A total of 29 ml of blood will be procured at this time for CBC and experimental immunology tests
- Pulmonary function tests (complete spirometry, DLCO, 6 minute walk distance, O_2 requirement and saturations at rest and with exertion, Borg scale dyspnea assessment).
- Chest CT scan
- AE assessment

Summary of Monitoring Procedures (see also Appendix A):

	Pre-treatment	1 month	3 months	6 months	9 months
Complement (C3, C4)	x	x	x	x	x
Hemoglobin, hematocrit, platelets**	x	x	x	x	x
WBC with differential	x	x	x	x	x
Chest CT Scan	x				x
Spirometry, DLCO, Resting and Exercise SaO_2	x	x	x	x	x
6 minute walk distance and Borg Questionnaires	x	x	x	x	x
Blood for Experimental Studies*	x	x	x	x	x

Table 2. Schedule of observational and endpoint measures. All of these parameters, except experimental studies (*) will be performed at each clinical site. *Experimental studies consisting of autoantibody determinations (anti-HEp-2 titers, anti-HSP70 concentrations by ELISA), lymphocyte phenotypes, C3, C4, and circulating concentrations of BLyS and CXCL13, will be performed at the coordinating center (laboratory of the PI).

2.7 EXPERIMENTAL SPECIMEN COLLECTION AND MANAGEMENT

2.7.1 Specimen Collection / Documentation

Peripheral blood (29 ml) will be collected from subjects at specified times (pre-treatment, and 1, 3, 6, and 9 months after treatment). Studies to be performed at the coordinating center lab of the PI (Dr. Duncan) at the University of Alabama at Birmingham will be centrifuged, and shipped overnight (4°C). Following their arrival in the coordinating center laboratory, the plasma/sera will be aspirated from the tubes, aliquoted, and frozen (-80°C) until used in batched assays of autoantibody titers and other circulating mediators. PBMNC will be used immediately in flow cytometry lymphocyte phenotyping studies. RBC + neutrophils will be similarly aliquoted and stored for potential later experiments.

Each research sample will be labeled with subject's unique identifier and sample collection date.

2.7.2. Specimen Handling and Labeling (De-Identification)

Immediately upon receipt of the biological specimens, the unique de-identified code number and date on which the specimen is frozen, all other information about the specimen, and subsequent processing will be entered on the specimen processing worksheet.

2.7.3. Specimen Management and Storage

Specimens in excess of immediate assay requirements may be stored indefinitely in a locked freezer under the control of the principal investigator.

These samples will be destroyed immediately upon receipt of the subjects' written request to do so. Identification of which samples to destroy will be available from the coding information linking patient identifiers to the stored samples as described earlier in this paragraph.

2.7.4. Restrictions to Direct Access of Specimens

Specimens will be kept in the responsible study investigators' laboratory indefinitely and will be under the control of the principal investigator. Investigators or other personnel not involved with the management or operations of the study are not permitted direct access to the specimens.

2.8 STUDY ENDPOINTS

2.8.1. The Primary End-Point

The primary end-point is reduction of autoantibody titers to HEp-2 cells, using indirect immunofluorescence (IFA), from baseline to the nine-month assessment point.

HEp-2 Autoantibody Titers: IFA methods to detect and quantify autoantibodies have been detailed by us previously (10,14). In brief, commercially available HEp-2 slide wells are incubated with titered dilutions of subject plasma (i.e., at 1:20, 1:40, 1:80, etc). After washing, the bound autoantibodies are detected with the secondary mAb (FITC-conjugated anti-human IgG). IPF specimens will be scored as positive if fluorescence intensity at titers $\geq$1:20 is greater than that of concurrent normal plasma specimens (determined by imaging in a fluorescent microscope) (14).

2.8.2. Secondary End-Points

Secondary end-points are: a.) treatment-related effects on anti-HSP70 concentrations, b.) forced vital capacities, c.) incidences of acute IPF exacerbations, d.) survival durations, e.) hospitalization rates, and f.) adverse event-rates.

a.) Anti-HSP70 IgG concentrations- We have found anti-HSP70 is **ONE OF MANY** autoantibodies present in IPF patients, and it happens too to be **ONE OF SEVERAL** associated with IPF progression (14). Thus, we will be able to test for effects of rituximab on both global autoantibody production (Primary Endpoint), as well as its effects on a particular, clinically-associated specific autoantibody (anti-HSP70), pretreatment and 1,3,6 and 9 months post-treatment. Anti-HSP70 IgG will be measured by ELISA, as detailed in citation #14.

b.) Forced vital capacities (FVC) by spirometry- In addition to FVC, other pulmonary function variables that are not formal endpoints (FEV_1, DL_{CO}, and O_2 requirement at rest and with walking), 6 minute walk distance, and Borg Dyspnea Assessments will be routinely measured pretreatment and at 1,3,6, and 9 months thereafter. These tests are standard operating procedures (SOP) for care of IPF patients at our centers.

c.) Acute exacerbation frequencies- IPF patients typically experience slowly progressive, if somewhat episodic, lung function deterioration. Nonetheless, a sizeable proportion, variously estimated as 10-to-50% or more, develop acute exacerbations that can result in very rapid onset respiratory failure and death within days (4). Results of studies indicate that autoantibodies are involved in acute exacerbations of IPF. It is hoped that rituximab therapy will decrease the frequency or delay onset of acute exacerbations. Acute exacerbations will be defined by

participating physicians using current consensus criteria, i.e., worsening hypoxemia and dyspnea within the preceding 30 days, characteristic new radiographic pulmonary infiltrates, and no other evident cause of lung dysfunction after thorough clinical assessments (4).

d.) Survival- Given the high mortality of IPF patients, efficacy of the experimental therapy could result in prolonged survival among treated subjects. Survival durations from study enrollment will be tabulated as both absolute survival and transplant-free survival.

e.) Hospitalizations- Indirect evidence of treatment efficacy could also be discerned by reductions of subsequent needs for hospital admissions. The frequencies and durations of hospitalizations among trial subjects will be tabulated and analyzed.

f.) AE Monitoring- The National Cancer Institute Common Toxicity Criteria Scale will be used to define grades (severity) of AE and toxicities. An AE is defined as any untoward medical occurrence in a subject, regardless of its relationship to these treatments. Toxicity is an AE with a direct relationship to the study drug. All toxicities are AE, but not all AE are toxicities.

2.8.3 Other Experimental Studies

Although not formal endpoints of this trial, the acquisition of specimens here will enable extensions of preliminary findings that have considerable biologic relevance. Complement levels (C3, C4) will also be determined among enrolled subjects pre- and 1, 3, 6, and 9 months after treatment. The rationale for measuring complement is two-fold: 1.) certain complement abnormalities are an adjunct finding of conventional autoimmune diseases and 2.) autoantibodies interact with complement, and studies in other autoimmune populations suggest changes of complement levels are associated with disease activity and rituximab treatment effects.

Quantitative immunoglobulin (Ig) concentrations in the serial specimens will be determined at the central clinical lab. Based on analogous trials, we anticipate rituximab will cause autoantibody levels to fall disproportionately greater than total Ig levels, and this is another consideration for designs of later trials.

B-cell counts and phenotypes will be determined in specimens shipped to the Duncan lab, using familiar flow cytometry based methods (20). Effects of rituximab on B-cell phenotypes are controversial and may vary among different disease populations. The premature re-emergence of differentiated B-cells could be an indication that more frequent rituximab and/or other agents may be optimal in IPF, perhaps due to large B-cell reservoirs in diseased lungs.

BLyS and CXCL13 are highly associated with IPF manifestations (20,21). Increases in these important B-cell trophic and chemotactic factors might occur after rituximab treatment and play a role in autoantibody rebound. Indeed, it has been suggested that combination therapy with both rituximab and anti-BLyS (belimumab) may have greater efficacy for autoantibody diseases than single agent treatments, but to our knowledge this has not yet been attempted (or at least not reported) in patients with autoimmune diseases. Hence, measuring BLyS levels in the current trial seems highly relevant. Anti-CXCL13 agents are in development. Serial levels of these mediators in placebo and rituximab–treated subjects will be measured by commercially available ELISA kits (20,21)

2.9 DATA AND POWER ANALYSES

2.9.1 Power Analyses:

Given the initial nature of this trial, definitive power calculations are speculative. Nonetheless, even moderate efficacy of the experimental treatment (as we anticipate) will produce evidence of same. Assuming a type 1 error rate of 0.05, a two-sided alternative hypothesis, n = 29/arm, and **very conservative event rates** (i.e., reduction of autoantibody titers in 33% of the experimental arm subjects, and 3% reduction in placebo controls) there is 80% power to detect a statistically significant effect.

The sample size of 58 for this clinical trial is based on exposing a minimum number of patients to potential risks of the experimental treatment, while still obtaining useful information. Analyses will follow intention to treat principles. Missing data techniques (e.g., multiple imputation) will be employed for subjects lost to follow-up, had transplants, or those who died. A sensitivity analysis will also be conducted in which transplantations and deaths will be considered failures.

2.9.2 Data Analyses:

Data analyses begin by describing baseline demographic and medical characteristics of the cohorts. Descriptive statistics, including measures of central tendency and dispersion, will be computed for continuous data (e.g., age). Frequency distributions will be estimated for categorical data (e.g., gender). To ensure balanced random assignments, treatments are examined in relationship to demographic and medical characteristics using the appropriate parametric (e.g., t-test) or nonparametric test (e.g., chi-square, Wilcoxon tests). Reduction of autoantibody titers from baseline to the nine-month follow-up visit will be calculated as a binary indicator (yes/no). A Fisher's Exact test will be used to compare rates of autoantibody titer reductions between the two groups. To control for the stratification variables, an exact logistic regression model will be used, including main effect for treatment and the stratification variables. Unbalanced baseline characteristics will also be included in the regression model.

Linear regression models will be used to assess the treatment effect on continuous variable secondary endpoints. Main effects will include treatment, the stratification variables, and unbalanced baseline characteristics. Both the proportion of individuals with AEs and the count of AEs per person will be compared by treatment. A logistic regression model will be used to compare the proportion of subjects with acute exacerbations, hospitalizations, or adverse events (AEs) by treatment group, with main effects as described above. A negative binomial model will be used to evaluate the average count of AEs per subject by treatment group. For all models, the model assumptions (e.g., normality of residuals, over dispersion) will be investigated. If the assumptions are violated, transformations will be investigated. If adequate transformations cannot be identified, nonparametric approaches will be utilized. Small cell sizes may exist and exact methods may need to be employed.

Additional exploratory analyses will be conducted. This may include the use of mixed-effects regression models to examine the longitudinal course of the outcomes as well as survival analyses (e.g., Kaplan-Meier curves, log-rank test, Cox proportional hazards models) to evaluate time to event outcomes, such as time to death.

2.9.3 Data Coordination Center (DCC)

The DCC will provide methods for data collection, entry, quality control (QC), management and analyses, and will provide administration and maintenance of a comprehensive database. The DCC will be located within the U. Pittsburgh Epidemiology Data Center (EDC). A Co-Investigator of this trial is co-director of the EDC (Dr. Wisniewski). The DCC will establish a data collection protocol and a data management system, and will train all clinical personnel in the protocol and in the use of the system. The DCC will maintain current documentation and usage instructions for the data collection system, and will provide data dictionaries and code books for documentation of the data collected for this trial.

Inasmuch as possible, data will not be collected on paper, but will be directly entered into the database system via laptop, desktop, tablet, or any mobile device connected to the Internet. Paper data collection forms will be developed for every measure both to provide documentation and to allow collection in the unlikely event of Internet inaccessibility. Data collected on paper will be entered into the database using a double-data-entry verification system to ensure valid data.

The data entry system will include point of entry validation checks such as range and dependency checks, and missing data will be flagged to ensure completeness. Correct study IDs will be verified, and a data collection grid will be established for each subject to allow site coordinators to view a patient's progress through the study, as well as to identify missed visits or forms.

The database system will include utilities for the coordinators to report missed visits and forms, as well as to log protocol deviations and early study exits.

Each clinical site will be visited to assure that they are collecting data and treatment is being provided in accordance with the protocol. Audits of a random selection of data, and all protocol consents will also be reviewed. A report will be sent to the Clinical Sites, DSMB, and NHLBI after each site visit.

2.10 ANTICIPATED RESULTS AND PITFALLS

2.10.1. Primary Endpoint:

By analogy to other rituximab-treated disease populations (29-39) we hypothesize the experimental treatment will result in reductions of autoantibodies. We are less certain of the time-to onset, magnitude, and duration of these effects in IPF patients, which is a primary goal of this trial.

We do not expect technical pitfalls, being very proficient with the anti-HEp-2 assays. To clarify, however, **we are using these assays to detect nonspecific patterns that are not diagnostic for SLE, scleroderma, etc.** (see Fig. 4 and citation 14). IPF patients with classic ANA tests diagnostic for SLE or other known autoimmune disorders will not be eligible for enrollment.

Findings herein of early autoantibody reappearances (e.g., within <6 months) would indicate that sequential, repeated rituximab dosing might be necessary in later definitive trials to test for clinical efficacy in IPF patients, or perhaps even warrant considerations for addition of a second agent (e.g., belimumab).

2.10.2. Secondary Endpoints:

We are proficient with ELISA and do not anticipate technical problems with the anti-HSP70 assays. We are able to reproducibly measure anti-HSP70 in all IPF plasma specimens, even when concentrations are <<mean normal values, and anticipate having serial, quantitative assay measures in all subjects. We expect rituximab will result in anti-HSP70 reductions, compared to controls, but pharmacodynamics of the effects remain to be determined.

Admittedly, expectation of treatment effects on forced vital capacities (or frequencies of acute exacerbations) is much more speculative than the anti-HSP70 IgG measures. We nonetheless anticipate reductions of autoantibodies in the experimental arm, especially if persistent (e.g., for ≥6 months) could possibly result in better preservation of lung function, even in this small cohort. IPF tends to rapidly progress compared to many other chronic lung diseases, so even a relatively minor alteration of the natural history might be detectable (we admit to some high risk:high yield speculation here- but note too Figure 3). We will also record and collate other clinical parameters (notably patient survival), but these are not formal end-points of this more exploratory, early-phase clinical trial. Based on multiple other rituximab studies involving thousands of patients with various autoimmune diseases (29-39), we do not believe high grade AE will be significantly more frequent among experimental trial subjects compared to placebo.

2.11 STUDY TIMELINES AND MILESTONES

We anticipate the necessary logistical and regulatory requirements (e.g., establishing data acquisition procedures, IRB approvals etc.) will have been completed by ≤six months after the beginning of the funding period. The personnel and facilities of this consortium have considerable clinical trial experience, and the foundation for the DCC is already in place. The sizes of our potential subject populations are such that we realistically anticipate being able to meet our target goal enrollment well before the completion of the funding duration. The duration of funding is 8/16/2013-7/31/2018. A projected timeline, with milestones, is depicted in Table 3.

Study Year	**0-0.5**	**0.5-1**	**2**	**3**	**4**	**4-4.3**	**4.3-5**
Dates (mon./yr)	8/2013-2/2014	2/2014-8/2014	8/2014-8/2015	8/2015-8/2016	8/2016-8/2017	8/2017-11/2017	11/2017-8/2018
Cumulative months	0-6	6-12	12-24	24-36	36-48	48-51	51-60
Comments	Regulatory approval	Start enrollment	Cont'd enrollment	Cont'd enrollment	Cont'd enrollment	Finish enrollment	Data analyses
Enrollments during interval	0	5	15	15	15	8	
Cumulative enrollment		5	20	35	50	58	

Table 3. Timelines and milestones of the clinical trial.

3. HUMAN SUBJECTS

3.1 SUBJECT POPULATION

Fifty-eight (58) ambulatory IPF patients of both genders and all ethnic backgrounds, who are evaluated at any of the 5 participating medical centers, will be eligible for enrollment. Subjects must provide written informed consent prior to participation. Based on the referral populations of these medical centers, we expect ~40% of eligible subjects will be women and ~10% will be non-Caucasian.

The 5 participating centers are:

Site 01: University of Chicago Medical Center

Site 02: Geisinger Medical Center

Site 03: Temple University Medical Center

Site 04: University of Pittsburgh Medical Center – Presbyterian Hospital

Site 05: University of Alabama at Birmingham

3.1.1 Inclusion of Women and Minority

Women who meet the inclusion criteria, and have none of the exclusion criteria, will be enrolled without restriction as dictated by the study protocols. Because of the use of a study medication, women of child bearing potential must meet specialized inclusion/exclusion criteria to minimize this risk. We will make efforts to enroll participants in this research in a distribution which mirrors the populations of the respective clinical sites.

3.1.2 Inclusion of Children

Children under 18 years of age will not be enrolled because they do not develop this disease.

3.2 INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria have been selected to isolate a patient population with idiopathic pulmonary fibrosis. The exclusion criteria are selected to not enroll patients with an alternative cause for their respiratory disease and to exclude patients with increased risk for the associated intervention (rituximab). The inclusion and exclusion criteria have been previously detailed in Section 2.3

3.3 INFECTIOUS CONSIDERATIONS

Rituximab depletes or diminishes peripheral $CD20^+$ B-cells and **decreases autoantibody titers**, but total immunoglobulin levels are usually less reduced (if at all) (29-39). Infection rates after rituximab treatment are generally not significantly different than those of placebo controls (29-39).

IPF is infrequently complicated by **clinically occult** pulmonary infections from bacteria or viruses (even during acute exacerbations) and, in the absence of ongoing/recent treatment with cellular immunosuppressants, **rarely** (if ever) is complicated by occult opportunists (1-4). Invasive

diagnostic tests (e.g., bronchoalveolar lavage [BAL]) are not SOP for administration of rituximab to ambulatory autoimmune populations, many of whom have lung diseases that resemble IPF (and are also taking other immunosuppressants). Invasive diagnostic procedures to **exclude occult pulmonary infection** are not SOP for IPF evaluations at any participating centers due to the rarity of infections, poor diagnostic yields, and their potential risk. Some IPF subjects will have tenuous respiratory function, and BAL will result in premature or gratuitous intubations, while providing questionably useful data. Instead, BAL or other procedures can be performed prior to enrollment of potential subjects **when in the judgment of the attending physician the procedure can be safely performed and is otherwise clinically indicated.** We would rather simply exclude equivocal cases of possible infections given the excess numbers of potential subjects at our respective institutions.

3.4. RATIONALE AND SAFETY OF EXPERIMENTAL RITUXIMAB TREATMENT:

Rituximab is a chimeric monoclonal antibody with specificity for B-cell CD20. The murine Fab' fragment binds to CD20, while the human Fc region mediates cytotoxic effects on the bound B-cells. Innumerable studies show rituximab reduces pathogenic autoantibodies in autoimmune patients (29-39).

Rituximab is specifically indicated and efficacious for autoantibody-mediated diseases. Rituximab is FDA approved for treatment of rheumatoid arthritis and anti-neutrophil cytoplasmic antibody vasculitis, and is widely used off-label for a plethora of other autoantibody-mediated syndromes (29-39, and many others).

The mechanisms responsible for beneficial clinical effects of rituximab are complex and incompletely understood, but include elimination of autoantigen-reactive $CD20^+$ memory cells (**plasma cell precursors**), as well as alterations of B-cell antigen presentation, or B-cell costimulatory and/or chemotactic functions. **Rituximab obviates or reduces deleterious effects of pathogenic autoantibodies**. It has been used in thousands of patients over many years, and has a well-characterized and acceptable safety profile, unlike other much more experimental anti-B-cell agents (e.g., alemtuzumab, bortezomib, etc.). These other treatments are less specific, more toxic, and have only rarely been used in <u>autoimmune patients</u>. **Their safety and efficacy for therapy of autoantibody diseases are unknown.**

Reported serious adverse events (AE) following rituximab treatment include fatal transfusion reactions, although **these seem to occur <u>primarily in lymphoma patients</u> and may be indistinguishable or overlap with tumor lysis syndrome** (29-39,42) Serious transfusion reactions to rituximab have occurred in <1% of RA patients. Reactions occurring in >5% of these subjects were nausea (8%), hypertension (8%), upper respiratory tract infections (7%), and arthralgia (6%). Corresponding event rates in placebo controls were: 5%,5%,6%, and 4%, respectively. Uncommon or rare events include mucocutaneous reactions, progressive multifocal leukoencephalopathy, hepatitis B reactivations, and rare infections (29-39,42).

4. RECRUITMENT AND INFORMED CONSENT PROCEDURES

4.1 RECRUITMENT METHODS

Participants will be recruited from the ambulatory IPF populations among the collaborating institutions. Potential subjects may also be recruited by direct public advertising including, but not limited to newspapers, radio, television, worldwide web, internet ads, bulletin boards, posters, and flyers. Recruitments may also be obtained through referrals from other clinical practices or other databases. The IRB at each participating center must review and approve all recruitment procedures and materials prior to their use.

4.2 INFORMED CONSENT PROCEDURES

The consent process will begin via one of two possible pathways:

1) Referral of the prospective participant to the investigators/research coordinator by a physician who has knowledge of the proposed research, and obtains patient consent for the research team to approach the patient.

2) Individuals who have provided signed IRB-approved HIPAA compliant consent for participation in clinical trial research registries.

Prior to performing any of the study procedures the subjects must provide informed consent. The information about this study will be given to subjects in language understandable to subjects. Only physician investigators will present the study to the potential subjects. The physician investigator will verbally present a general outline of the research plan, including inclusion and exclusion criteria, to the prospective participant. The consent form, outlining the design of the study, will include the risks and benefits of participating, and will be reviewed, and the investigator will answer any questions. Prospective participants may take as much time as required to make an informed decision. Written informed consent will be obtained from each participant prior to performing any research study procedures.

In addition, older potential study participants whose competency to consent is in question will be tested for sufficient comprehension and recall of the information presented. Prospective subjects who do not remember the important facts about participation in the research study after repeated testing will not be included in the study. The investigators will also assess whether a participant understands experimental procedures over time, including assessment throughout the full duration of participation in the study.

5 POTENTIAL RISKS AND BENEFITS

5.1 POTENTIAL RISKS

5.1.1 General Risks of Study Protocol and Procedures:

The potential risks specifically related to the study protocol procedures could include:

<u>The risks of venipuncture</u>:

Common Risks: temporary minor discomfort, bruising, redness, swelling. Infrequent Risks: dizziness, fainting. Other Risks: infection, phlebitis.

The risks of HIV testing:

The experience of being tested and learning the results of the HIV test may cause the subject and any partner stress and anxiety. Being told a person tests positive for HIV antibodies has been associated with depression, suicidal thoughts, denial as well as feeling isolated from society. If others would become aware of the subject's HIV status, it could result in discrimination which may impact the subject's employability, insurability, or even prevent the subject from traveling to certain countries.

The risks of chest CT scan:

The amount of radiation exposure that the subject will receive from each CT scans is approximately 2 rems. to the chest/lungs with minimum exposure to the other body areas. For comparison, radiation workers are permitted, by federal regulation, a maximum annual radiation exposure of 20 rems to the most sensitive organs of their body. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive in this study is considered to be low and comparable to everyday risks.

The risks of pulmonary function test:

Lung function tests rarely cause side effects. The subject may feel some discomforts such as fatigue, shortness of breath, and/or lightheadedness during the performance of the testing.

The risks of six minute walk test:

Rare side effects include slight soreness in muscles and/or breathlessness due to the effort involved.

5.1.2 Potential Risks of Experimental Interventions

The risks of steroid (methylprednisolone) (used as a premedication):

Common: insomnia, nausea, vomiting, or stomach upset; fatigue or dizziness; muscle weakness or joint pain; problems with diabetes control; or increased hunger or thirst.

Rare: acne, increased hair growth, thinning of the skin, cataracts, glaucoma, osteoporosis, roundness of the face, and changes in behavior

The risks of acetaminophen (Tylenol) (used as a premedication):

Uncommon risks include liver or kidney toxicities. In the doses used here these risks are rare.

The risks of diphenhydramine (Benadryl) (used as a premedication):

Common risks are drowsiness. Other, less common risks include dry mouth, urinary retention, cardiac rhythm disturbances, confusion.

The risks of Rituximab:

Common Risks: Fever, chills, headache, pain, rash, pruritus, angioedema, nausea, abdominal pain, cytopenias, weakness, cough, rhinitis. Infusion related reactions: angioedema, bronchospasm, chills, dizziness, fever, headache, hyper-/hypotension, myalgia, nausea, pruritus, rash, rigors, urticaria, and vomiting.

Infrequent Risks: Hypotension, peripheral edema, hypertension, flushing, edema, dizziness, anxiety, agitation, depression, hypoesthesia, insomnia, malaise, nervousness, neuritis, somnolence, vertigo, migraine, urticaria, hyperglycemia, hypoglycemia, hypercholesterolemia, diarrhea, vomiting, dyspepsia, anorexia, weight loss, anemia, pain at the injection site, back pain, myalgia, arthralgia, paresthesia, arthritis, hyperkinesia, hypertonia, neuropathy, conjunctivitis, lacrimation disorder, throat irritation, bronchospasm, dyspnea, upper respiratory tract infection, sinusitis, LDH increased.

Other Risks: Rare events associated with rituximab include severe mucocutaneous reactions, progressive multifocal leukoencephalopathy due to LC virus reactivation, hepatitis B reactivations, and other infections.

The risks of placebo:

Placebo contains no active medication. It is unlikely to be associated with any side effects.

5.2 ALTERNATIVE TREATMENTS

The alternative treatments for the subjects participating in this investigation are to continue their medical care under the direction of their attending physician.

5.3 POTENTIAL BENEFITS

Participation in the proposed research may or may not provide a direct benefit to the study participants. Information obtained from the proposed research will provide information about the relationship between IPF treatment and patient outcome. Potential benefits from the participation in these protocols include enhanced survival, improved respiratory symptoms, and decreased exacerbation frequency. Identification of the mechanism(s) mediating these outcomes will facilitate risk-stratification for these adverse outcomes, and development of targeted treatment strategies for the future.

Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. The research presents a balance of risks and expected direct benefits similar to that available in the clinical setting.

Importance of the Knowledge to be Gained
The preliminary data in this application outline a hypothesis for the progressive clinical deterioration in patients with IPF. The protocol specifically seeks to address that hypothesis. If the study intervention is found to be both safe and effective in the study population, the treatment

of IPF would be altered significantly, and this could result in a change in the disease natural history. Completion of these protocols will address important questions related to this disease.

5.4. DATA SAFETY MONITORING PLAN

5.4.2 Data Safety Monitoring

A *Network* Data and Safety Monitoring Board (DSMB) independent of the study investigators will monitor this clinical trial for the duration of this proposal. The DSMB consists of experts in the field: Drs. Jesse Roman (U. Louisville) (chairman), John Connett (U. Minn), Ramsey Hachem (Wash U.) and Vincent Valentine (U. Texas Medical Branch).

The DSMB will be expected to convene as needed, but not less than every six months to review the progression of the study including patient enrollment, protocol compliance, and adverse event reports. The DSMB will conduct interim monitoring of accumulating data from research activities to assure the continued safety of human subjects, relevance and appropriateness of the study, and the integrity of research data.

The Food and Drug Administration (FDA) has exempted this clinical trial from IND regulations [21 CRF 312.2(b)] in recent correspondence (PIND 119573).

Each collaborating site will obtain local IRB approval prior to their enrollment of subjects.

5.4.3 Data Safety Monitoring Plan

5.4.3.1 Coordinating Center

The coordinating center is the University of Alabama at Birmingham's study team, led by the PI and Protocol Chair, Dr. Steven Duncan. The coordinating center, in conjunction with the Data Coordinating Center, will ensure that all participating institutions within the multi-center protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and HIPAA requirements.

Each study site will be subject to on-going monitoring. Study sites will be evaluated for meeting enrollment criteria and for the accurate and timely submission of data forms, and timely response to data queries from the study monitors or data coordinating center.

To assist the Protocol Chair in meeting his responsibilities as required by the DSMB, the University of Alabama at Birmingham's study team will assume the following general responsibilities:

Assist in protocol review

Maintain copies of FDA and IRB approvals from all participating Institutions.

Maintain updated roster of participants.

Verify eligibility.

Verify response.

Collect data on protocol specific CRFs.

Prepare all submitted data for review by the Protocol Chair.

Maintain documentation of serious adverse event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.

Distribute SAE safety reports.

Monitor at participating institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Coordinating center.

5.4.3.2 Data Coordination Center (DCC)

The DCC will provide methods for data collection, entry, quality control (QC), management and analyses, and will provide administration and maintenance of a comprehensive database. The DCC will be located within the U. Pittsburgh Epidemiology Data Center (EDC). A Co-Investigator of this trial is co-director of the EDC (Dr. Wisniewski). The DCC will establish a data collection protocol and a data management system, and will train all clinical personnel in the protocol and in the use of the system. The DCC will maintain current documentation and usage instructions for the data collection system, and will provide data dictionaries and code books for documentation of the data collected for this trial.

Inasmuch as possible, data will not be collected on paper, but will be directly entered into the database system via laptop, desktop, tablet, or any mobile device connected to the Internet. Paper data collection forms will be developed for every measure both to provide documentation and to allow collection in the unlikely event of Internet inaccessibility. Data collected on paper will be entered into the database using a double-data-entry verification system to ensure valid data.

The data entry system will include point of entry validation checks such as range and dependency checks, and missing data will be flagged to ensure completeness. Correct study IDs will be verified, and a data collection grid will be established for each subject to allow site coordinators to view a patient's progress through the study, as well as to identify missed visits or forms.

The database system will include utilities for the coordinators to report missed visits and forms, as well as to log protocol deviations and early study exits.

5.4.3.3 Participating Institutions

Each Participating Institution will provide to the Coordinating Center a list of the key personnel assigned to the role for oversight of data management at their site. The general responsibilities for each Participating Institution are as follows:

Commit to accrual to the multi-center protocol.

Submit protocol and/or amendments to their local IRB.

Maintain a regulatory binder.

Update Coordinating Center with research staff changes on a timely basis.

Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.

Submit Serious Adverse Event reports to local IRB and provide copies to the Coordinating Center

Submit deviations and violations to local IRB and the Coordinating Center.

Assuring patient safety is an essential component of this protocol. The study Principal Investigator has primary responsibility for the oversight of the data and safety monitoring. The study investigators will evaluate all adverse events. All subjects who have AEs, whether considered associated with the use of the study medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up.

All untoward medical occurrences observed in subjects receiving the study drug will be recorded on the participants' adverse event case report forms (CRF) by the study coordinator under the supervision of the principal investigator. The CRFs will then be reviewed for completeness and internal consistency. Subsequently, the CRFs will be recorded on an electronic password-guarded study database. In addition to internal safeguards built into a computerized system, external safeguards will be put in place to ensure that access to the computerized system and to the data is restricted to authorized personnel. Training conducted by qualified individuals on a continuing basis will be provided to individuals in the specific operations with regard to computerized systems that they are to perform during the course of the study.

The PI will work with the reporting investigators to prepare a detailed written summary of serious, unexpected, and treatment related adverse events, and will compare and contrast the event with prior events. The detailed written summary will be provided to the DSMB and the IRB.

In addition, the DSMB Report addressing the following information will be submitted to the IRB at the time of continuing review annually or more often as required:

A list of the research personnel who participated in the data and safety monitoring.

The frequency of monitoring that took place during the renewal intervals and/or the dates that data and safety monitoring was conducted.

A summary of cumulative data related to unanticipated problems (including adverse events) including a determination of causality and whether the risk to benefit assessment has changed.

If appropriate, a summary of pertinent scientific literature reports, therapeutic developments, or results of related studies that may have an impact on the safety of

study participants or the ethics of the research study.

A summary of the outcome of reviews conducted to ensure subject privacy and research data confidentiality.

Final conclusions regarding changes to the anticipated benefit-to-risk assessment of the study participation and final recommendations related to continuing, changing, or terminating the study.

STOPPING RULE:

Individual subject-specific stopping rules:
A study participant will be discontinued from further study drug treatment/Intervention(s) administration if any of the following occur:

Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

Intercurrent illness or an unexpected fatal or life-threatening adverse event, which requires discontinuation of study treatment

Request by the subject to withdraw from the study

Investigator discretion

A study-wide stopping rule will be based on the comparison of rate of serious adverse events between the two treatment groups. This safety endpoint will be used instead of the primary endpoint since the primary endpoint is not a clinical marker of efficacy, but a biomarker of a clinical outcome. The DSMB and sponsor (NIH) will have responsibility for invoking a study-wide stopping rule based on their evaluations of the data.

5.4.4 Parameters to be Monitored

The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.

A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.

An assessment of external factors or relevant information (eg. pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.

A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

The National Cancer Institute Common Toxicity Criteria Scale will be used to define grades (severity) of adverse events and toxicities. An adverse event is any untoward medical occurrence in a participant who received study drug, regardless of its relationship to the study drug. Toxicity is an adverse event with a direct relationship to the study drug. All toxicities are adverse events, but not all adverse events are toxicities. This is a determination made by the study investigator. The study investigators will classify adverse events as "definitely or most likely," "possibly," or "very unlikely" due to the study drug. Toxicity will be defined as an adverse event that is definitely, most likely, or possibly caused by the study drug.

The severity of adverse changes in physical signs or symptoms will be classified as follows:

Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.

Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living).

Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Grade 4 (Life-threatening): serious potential consequences; urgent intervention indicated.

Grade 5 (Death): event is a direct cause of death.

5.4.5 Frequency of Monitoring

The principal investigator will review subject safety data as it generated. The principal investigator, co-principle investigators, and the research staff will communicate by conference calls or visits at monthly interval to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints and confidentiality of subjects. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The principal investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

5.4.6 Reportable Adverse Events

For this study, a serious adverse event is any untoward clinical event that is thought by the investigator to be study-related, that is also:

1. Fatal or immediately life threatening
2. Permanently disabling, or severely incapacitating.
3. Requires or prolongs inpatient hospitalization.
4. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may

require medical, or surgical intervention to prevent one of the serious outcomes listed above.

If clinically important and unexpected adverse experiences, or clinically important study-related adverse experiences occur, they will be recorded on the adverse event case report form.

5.4.7 Adverse Events Reporting Timeline

1. Serious and unexpected, suspected adverse reactions to the study drug: The serious and unexpected, suspected adverse reaction will be reported to the DCC and overall study PI as soon as possible, but no later than 15 calendar days after the site Investigator receives the respective information.

All reviewing IRBs will also be notified of serious and unexpected, suspected adverse reactions in accordance with the respective policies and procedures of the IRBs. The DSMB and all Investigators (i.e., study site principal investigators) will also be promptly notified of serious and unexpected, suspected adverse reactions.

2. Unexpected life-threatening or fatal, suspected adverse reactions associated with the use of the study drug: The unexpected, life-threatening or fatal, suspected adverse reaction will be reported to the DCC, overall PI, and DSMB as soon as possible, but no later than 2 working days after the site Investigator receives the respective information.

All reviewing IRBs will also be notified of unexpected, life-threatening or fatal, suspected adverse reactions in accordance with the respective policies and procedures of the IRBs.

All Investigators (i.e., study site principal investigators) will also be promptly notified of these adverse events.

3. Other adverse events (eg, unexpected related adverse events of lesser severity or expected adverse events of any severity): These events will be reported in aggregate form to the DCC, overall study PI, and the DSMB at the time of regular data reports. However, sites will have the option of bringing any event to the immediate attention of the Study PI and DCC (via faxing the interim event report form) for review and discussion by the Steering Committee and for consideration of immediate reporting to the Head of the DSMB. Similarly, the DCC will have the option of bringing any event to the attention of the Steering Committee.

Sites will also follow and comply with their own local institution's adverse event reporting requirements. Depending on the local requirements, a site may report events locally that are not reported to the DCC.

5.4.8. Reporting Adverse Events (AE) and Unanticipated Problems (UP) to NHLBI

Unexpected, life-threatening or fatal suspected adverse reactions will be reported to the NHLBI within 7 calendar days. Unanticipated problems suggesting greater risk of harm to study participants than was previously known or recognized will be reported to NHLBI within 30 calendar days. Expedited SAE/UP reports to NHLBI will include the following elements:

- Study title, grant/contract number, PI name
- Description and date of the event or problem, including why it merits expedited reporting

- When available, date(s) when the event was reported to applicable governing bodies (e.g., IRB)
- Any corrective action planned or taken in response to the event or problem (e.g., study suspension, consent or protocol changes, additional training or security measures)

Communications from other applicable oversight bodies (eg: IRBs, DSMB) regarding any applicable SAE/UP will also be reported to NHLBI.

5.5 RISK MANAGEMENT PROCEDURES

5.5.1 Protection Against Risks

General Risks of Study Protocol and Procedures

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

To avoid any violation of subject confidentiality, all data will be stored in a password-protected database, identified only by study ID number at the DCC. A confidential database linking patient identifying information with study ID number will be maintained at each clinical site.

All demographic and clinical information about the subject will be stored on an electronic password-guarded study database under the supervision of the PIs for this protocol. All staff will sign confidentiality statements. Access to the database will be limited to the data manager and staff under the supervision of the PIs.

Specimens will be stripped of subject identifiers and stored according to a similar coding protocol as described above. These specimens will be stored safely in the custody of the PI responsible for the individual assays. The Investigators will limit future access to any remaining sample to only those investigators with prior IRB approval for their studies.

All staff involved in this study are properly credentialed and instructed in the areas of testing, confidentiality, and safety.

The PIs will retain the data for the entire period of this study. The investigators may continue to use and disclose subjects de-identified information for the purpose of this study for a minimum of seven years after final reporting or publication of the study. If the subject and/or legal representative decide to withdraw or be withdrawn from study participation, they may request that the study data and samples be destroyed.

5.5.2 Protection Against Potential Risks of Experimental Intervention

Despite the documented safety profile of rituximab in other human disorders of abnormal immune regulation, the study has been designed with a focus on protecting patients against risk including:

Selection of a target patient population with a very high risk of morbidity and mortality due to the absence of a defined treatment for the disorder

Involvement by trained staff / investigators with experience in the administration of Rituximab

Prior human experience with the study medication in similar conditions with an autoimmune hypothesis including rheumatoid arthritis and myositis

Exclusion of all patients with conditions which might simulate IPF such as congestive heart failure, pneumonia, and pulmonary thromboembolism

Continuous monitoring by an independent DSMB

Rituximab:

The patient population will receive pre-treatment with oral acetaminophen, oral diphenhydramine, and methylprednisolone (100mg IV) prior to drug administration. Based upon the experience of the study investigators to date, and published reports, this regimen will significantly lessen the risk of general reactions to the medication.

Required Education in the Protection of Human Research Participants

All investigators and study personnel involved in the conduct or oversight of human participant research are required to complete initial and continuing education in the protection of human research participants.

6 STUDY ADMINSTRATION

6.1 REGULATORY AND ETHICAL CONSIDERATIONS

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; International Conference of Harmonization (ICH) Guidelines on Good Clinical Practice, and relevant policies, requirements, regulations of the IRB, and applicable federal regulations, including those required under an IND exemption.

The investigators will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigators will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

6.2 PROTOCOL DEVELOPMENT

6.2.1 Activation of a protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting AEs, violations and deviations per IRB guidelines.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

Identify, qualify and initiate participating institutions and obtain accrual commitments.

Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.

Ensure that there is only one version of the protocol and that all participating institutions use the correct version.

Oversee the development of data collection forms (case report forms) that are of common format for use at all the participating institutions.

6.2.2 Coordinating Center Support Function

The University of Alabama at Birmingham's study team will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the University of Alabama at Birmingham's study team include:

Maintain regulatory documents for all participating institutions.

Review of the protocol and consent to check for logistics, spelling, and consistency.

Provide the Protocol Chair a list of queries related to any inconsistencies.
Provide necessary administrative sections, including paragraphs related to randomization, data management schedules, and multi-center guidelines.

Maintenance of contact list of all participating institutions in the multi-center protocol and the distribution of updates to the sites as needed.

Assistance in preparation and maintenance of case report forms.

Conduct regular communications with all participating institutions (conference call, emails, etc)

Maintain documentation of all communications.

6.3 PROTOCOL MANAGEMENT

The Coordinating Center is responsible for assuring that each participating institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Coordinating Center must maintain copies of all IRB approvals, for each participating institution.

6.3.1 Protocol distribution

The Coordinating Center will distribute the final approved protocol and any subsequent amended protocols to all participating institutions.

6.3.2 Protocol revisions and closures

The participating institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Coordinating Center or designee. It is the individual participating institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening causes: Participating institutions will receive telephone notification from the Coordinating Center or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

Protocol closures and temporary holds: Participating institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds from the Coordinating Center or designee. Closures and holds will be effective immediately. In addition, the Coordinating Center or designee will update the participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

6.4 INFORMED CONSENT REQUIREMENTS

The Coordinating Center approved informed consent document will serve as a template for the informed consent from participating institutions. Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for their revision prior to submission to the participating site's IRB.

The Principal Investigator at each participating institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols.

All study participants in this study will be provided a consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study. This consent form will be submitted along with the protocol for review and approval by the IRB at each participating center. The study participant MUST be consented with the IRB approved consent form before the participant is subjected to any study procedures. The approved consent form MUST be signed and dated by the study participant or legally acceptable representative and the investigator obtaining the consent.

6.5 IRB DOCUMENTATION

Sites must obtain local IRB initial approval. The following must be on file with the Coordinating Center or designee and must be submitted and approved by the Coordinating Center prior to initiation of the study:

- Approval Letter of the institution's IRB

- Copy of the Informed Consent Form approved by the participating institution's IRB
- IRB approval for all amendments

It is the participating institution's responsibility to notify its IRB of protocol amendments. Participating institutions will have 90 days from receipt to provide the Coordinating Center their IRB approval for amendments to a protocol.

6.5.1 IRB Renewal Approval

Annual IRB renewal approval from the participating institution is required in order to continue research and recruit participants onto a protocol. There is no grace period for continuing approvals.

6.6 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet GCP and, when appropriate, regulatory guidelines, the DCC may conduct a quality assurance audit (site monitoring) of the site records at any time during or after completion of the study. Each clinical site will be visited to assure that they are collecting data and treatment is being provided in accordance with the protocol. Audits of a random selection of data, and all protocol consents will also be reviewed.

Monitoring visits are scheduled periodically throughout the conduct of the study to assure compliance with the approved protocol, and to verify the completeness and accuracy of study data. Monitoring also aids in identifying any research-related problems for the investigator to correct. The DCC will conduct monitoring visits with appropriately trained clinical research professionals. A brief written report on each site visit will be prepared by the DCC and sent to the clinical center, DSMB, and NHLBI after each site visit.

The clinical center Co-Investigators will jointly review de-identified historical, laboratory, and radiographic data that are determinants of study entry, from each subject entered into this trial during the interim, in the context of semiannual teleconferences chaired by the Study PI.

6.7 DATA HANDLING AND RECORD-KEEPING

6.7.1 Subject Identification / Study IDs

When a potential participant signs informed consent to be evaluated for eligibility in this trial, s/he will be assigned a unique Study ID that will be used on all study documents and in the study database.

The coordinator will write the date and the consenting person's name on the site-specific ID Generation Log. Based on position in the log, the person will be assigned an ID number comprised of the site number (01=Chicago, 02=Geisinger, 03=Temple, 04=Pitt, 05=University of Alabama at Birmingham), the enrollment sequence in the log (i.e. fifth patient will have sequence number 05), and the patient's 3 initials. If the patient does not have a middle initial, the letter "X" will be used. These initials are not sufficient to identify the participant, and are

invaluable in catching mistakes of transposition that frequently occur with solely numeric identifiers.

6.7.2 Data Recording/Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. Fields that might be left blank because a procedure was not done or the question was not asked, or the respondent refused or did not know an answer will include response options for "Not Done" "Not Applicable" "Don't Know" and "Refused," thus ensuring a response to every question.

If data are collected on paper, all entries must be printed legibly in black ink. Any corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and entered in the database will be audited against the appropriate component of the medical record.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. Information recorded in the database must be consistent with the *Source Data* recorded on the *Source Documents* or discrepancies must be explained.

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to DCC.

Research records for each case should contain copies of the source documents for the data reported to DCC. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. All source data stored in the research charts must be identified only by the Study ID. Any names, contact information, medical record numbers, or other identifying information must be masked prior to copying. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and provide the ability to verify the document and the data reported.

Every effort will be made to collect complete data for each study visit. Causes of *missing data* will be fully documented. With respect to safety evaluation, it is not planned to impute missing data.

Research charts must be kept in a location separate from the clinical records used to contact patients and schedule appointments. No personal identifying information shall be kept within the research charts.

6.7.3. Record maintenance and retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be easily accessible when needed (e.g., for the DCC audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The minimum retention time will meet the strictest standard applicable to each participating site, as dictated by local laws/regulations, and/or institutional requirements.

7 COSTS AND PAYMENTS

7.1 COSTS

Experimental research testing consists of serial autoantibody and complement studies, lymphocyte subset monitoring, plasma IgG, BLyS, and CXCL13, will be supported by the research grant. All experimental medications (and premedications) will also be paid for by the research grant. Routine lab tests, and any procedures described will be considered routine medical care and will be billed to the subjects' health insurance company. Subjects will be responsible for paying any deductibles, co-payments or co-insurance that are a normal part of their health insurance plan. Subjects who do not have health insurance will be responsible for these costs.

7.2 PAYMENTS

Participation in this protocol is completely voluntary. Travel costs, for subjects returning for serial assessments, may be provided on an as-needed basis.

8 QUALIFICATIONS AND SOURCES OF SUPPORT

8.1 QUALIFICATIONS OF THE INVESTIGATORS

University of Alabama at Birmingham:

Principal Investigator:

Steven Duncan, M.D.: Pulmonary Physician and Immunologist; Dr. Duncan is Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine,

University of Alabama at Birmingham. He will supervise the autoantibody, B-cell phenotyping, and B-cell mediator studies in his laboratory. His research aims to understand the role of adaptive immunity in the pathogenesis of IPF and COPD. Dr. Duncan will provide daily leadership and supervision to all aspects of the clinical trial execution.

Co-Investigators:

Joao de Andrade, M.D.: Dr. de Andrade is an Associate Professor of Medicine in the Division of Pulmonary, Allergy and Critical Care Medicine at UAB. He is the Director of the UAB Interstitial Lung Disease (ILD) Program. As director of this program, he has conducted eight major clinical trials exploring novel therapies for IPF. He was the Principal Investigator of the UAB site for the NHLBI IPFnet. He serves as a member of the Steering and Adjudication Committees. He has recognized expertise in the conduction of clinical trials in IPF. Dr. de Andrade will provide daily leadership and supervision to all aspects of the clinical trial execution at UAB.

Tracy R. Luckhardt, M.D.: Dr. Luckhardt is an Assistant Professor in the Division of Pulmonary, Allergy and Critical Care Medicine, as well as Associate Program Director of the Pulmonary Fellowship Program, at UAB. She has both clinical and research experience in pulmonary fibrosis. Dr. Luckhardt has extensive experience in using the bleomycin model of pulmonary fibrosis and the role of herpesviruses in the pathogenesis of pulmonary fibrosis. She has also been an investigator in several clinical trials in IPF. Dr. Luckhardt will provide daily leadership and supervision to all aspects of the clinical trial execution at UAB.

University of Pittsburgh Medical Center:

Co – Principal Investigator:

Daniel Kass, M.D.: Pulmonologist, Dr. Kass is an Associate Professor of Medicine in the Division of PACCM, University of Pittsburgh. Dr. Kass is the medical director of the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease. He is in charge of all clinical research in the center and is the PI on several drug studies. His research interests focus on interstitial lung diseases including IPF, including mechanisms of fibrosis.

Geisinger Medical Center:

Co- Investigator:
Paul F. Simonelli, MD: Dr. Simonelli is Director, Thoracic Medicine at the Geisinger Medical Center. Dr. Simonelli is one of the nation's leading pulmonologists. Dr. Simonelli, will provide daily leadership and supervision to all aspects of the clinical trial execution at the Geisinger Medical Center.

Temple University Medical Center:

Co- Investigator:

Gerald J. Criner, MD: Dr. Criner is Professor of Medicine, Temple University. Dr. Criner is also Chief, Section of Pulmonary and Critical Care Medicine, and Director, Medical Intensive Care

Unit and Ventilator Rehabilitation Unit at the Temple University Medical Center. Dr. Criner's clinical work focuses on advanced lung disease (COPD, emphysema, pulmonary fibrosis, pulmonary hypertension, respiratory failure), and critical care medicine. Dr. Criner, will provide daily leadership and supervision to all aspects of the clinical trial execution at the Temple University Medical Center.

University of Chicago Medical Center:

Co- Investigator:

Imre Noth, MD: Dr. Noth is Professor of Medicine at the University of Chicago. Dr. Noth has longstanding research and clinical interests in interstitial lung disease and is also Co-Director of the Respiratory Clinical Research Program at the University of Chicago Medical Center. Dr. Noth will provide daily leadership and supervision to all aspects of the clinical trial execution at the University of Chicago Medical Center.

8.2 SOURCE OF SUPPORT: National Heart, Lung, and Blood Institute (HL119960)

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APPENDIX A. STUDY ASSESSMENT TABLE AND EVENTS

	Pre-Treatment		Treatment				Post Treatment Follow-Up								
Visit Number	1	2	3	4	5[β]	6	7[#]	8	9[‡]	10	11	12[‡]	13	14	15[‡]
Day (D) or Month (M) from First Treatment	Screen*	Base Line*	D 1	D2	D 14	D 15	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9
Informed Consent	x														
Inclusion Exclusion Criteria	x														
History and Medication Review	x		x		x		x		x			x			x
Physical Exam	x		x		x		x		x			x			x
Screening Lab Tests: ANA,RF, anti-Ro, Anti-La, anti-RNP, anti-Jo-1, HCV, HBsAg, HBcAb, HIV Ab, serum pregnancy test	x														
Complement (C3,C4)		x					x		x .			x			x
CBC/Diff/plat		x					x		x			x			x
Chest CT scan		x													x
Spirometry, DLCO, Exercise SaO2, 6 min walk, Borg		x					x		x			x			x
Experimental Immunology		x					x		x			x			x
Randomization (1:1)			x												
Study Treatment			x		x										
AE Assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Phone assessment				x		x		x		x	x		x	x	
Study Completion															x

*Screening and Baseline evaluations can occur concurrently, or on separate days, **as long as all tests and procedures are performed in the 14 days prior to first study treatment**. Chest CT can be performed within the 30 day interval prior to first study treatment.

[β] The second treatment (Day 14) has a +/- two day window.

[#] The Month 1 visit has a +/- five day window.

[‡] The Months 3, 6 and 9 have a +/- seven day window.