WEIGHING RISKS AND BENEFITS OF LAPAROSCOPIC ANTI-REFLUX SURGERY IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (WRAP-IPF): **A PHASE II CLINICAL TRIAL**

Version 6.0 (amendment #4.1)

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Protocol Summary

TREATMENT	Laparoscopic anti-reflux surgery
CLINICALTRIALS.GOV IDENTIFIER	NCT01982698
PROTOCOL TITLE	Weighing Risks and benefits of Laparoscopic Anti-Reflux Surgery in Patients with Idiopathic Pulmonary Fibrosis (WRAP-IPF)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Confirmed idiopathic pulmonary fibrosis (IPF) and evidence of abnormal acid gastro-esophageal reflux (GER) by 24-hour pH testing (DeMeester score of >14.7)
STUDY OBJECTIVES	To demonstrate slowed decline of forced vital capacity (FVC) through anti-reflux surgery compared with standard care.
STUDY DESIGN	Multi-center, randomized, un-blinded
TREATMENT REGIMEN	Laparoscopic anti-reflux surgery or standard care.
DURATION OF STUDY PARTICIPATION	52 weeks
NUMBER OF SUBJECTS	Approximately 58 (randomized in a 1:1 ratio)
NUMBER OF SITES	6 sites (U.S. only)
PRIMARY ENDPOINTS	Change in FVC from baseline to 48 weeks
SECONDARY ENDPOINTS	Mortality Non-elective hospitalization Acute exacerbation Disease Progression Change in UCSD SOBQ score Change in SGRQ score Time to death, acute exacerbation, or non-elective hospitalization (composite endpoint) Time to death, acute exacerbation, non-elective hospitalization, or disease progression (composite endpoint) Categorical change in FVC Change on cough visual analog scale (VAS)

	Change in ICECAP-O score Change in EuroQOL EQ-5D score Change in 6-minute walk distance (6MWD) Reduction in acid GER assessed by serial pH testing and GER questionnaire Quantitative change in HRCT fibrosis score

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6MWD	6-minute walk distance
6MWT	6-minute walk test
ABG	arterial blood gas
AE	adverse event
AEx	acute exacerbation
BAL	bronchoalveolar lavage
CRF	case report form
DCC	Data Coordinating Center
DL_{CO}	diffusing capacity of the lung for carbon monoxide
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
FVC	forced vital capacity
GER	Gastroesophageal reflux
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high-resolution computed tomography
ICECAP-O	ICEpop CAPability measure for Older People
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
MOP	Manual of Operating Procedures
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health (U.S.)
PFT	pulmonary function test
PI	principal investigator
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
UCSD SOBQ	University of California at San Diego Shortness of Breath Questionnaire
VAS	Visual Analog Scale

1. Summary

This protocol proposes to test the following hypothesis: Treatment with laparoscopic anti-reflux surgery in subjects with idiopathic pulmonary fibrosis (IPF) and abnormal gastroesophageal (GER) reflux will slow the decline of forced vital capacity (FVC) over 48 weeks.

This study will randomize approximately 58 subjects with IPF and abnormal acid reflux on 24-hour pH monitoring to laparoscopic anti-reflux surgery or standard care (randomization ratio 1:1). Subjects will be followed for 52 weeks or until the time of lung transplantation or death.

2. Hypothesis and Specific Aims

2.1. Study Hypothesis

Our primary hypothesis is that the reduction of abnormal GER with laparoscopic anti-reflux surgery will slow the progression of IPF as measured by FVC. We further hypothesize that laparoscopic anti-reflux surgery will reduce the frequency of acid reflux, will be safe and well tolerated, will improve symptoms and quality of life, and will reduce the incidence of acute exacerbation, hospitalization, disease progression and death. Specifically, we will address the following aims:

2.2. Specific Aim 1

We aim to determine the impact of laparoscopic anti-reflux surgery on change in FVC over 48 weeks in patients with IPF and abnormal GER.

2.3. Specific Aim 2

We aim to correlate the reduction in acid reflux events with the change in FVC over 48 weeks in patients with IPF and abnormal GER.

2.4. Specific Aim 3

We aim to determine the safety of laparoscopic anti-reflux surgery in patients with IPF and abnormal GER.

2.5. Specific Aim 4

We aim to explore the impact of laparoscopic anti-reflux surgery on key secondary endpoints over 48 weeks in patients with IPF and abnormal GER.

2.6. Specific Aim 5

To identify molecular markers of IPF disease activity and gastroesophageal reflux in biological samples from patients with IPF and abnormal GER.

3. Background and Significance

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease of unknown cause and increasing prevalence in the United States.[1,2] An estimated 100,000 Americans will die from IPF this year, and aside from lung transplantation, which only 1% will receive, there is no FDA-approved therapy.

Over the last decade, a potential role for gastroesophageal reflux (GER) in the progression of IPF has been suggested.[3] This is based on several observations: First, it is clear that the overwhelming majority of patients with IPF have abnormal GER.[4-6] Second, small case series of patients with IPF treated for GER demonstrated stabilization of pulmonary physiology and oxygenation.[7,8] Third, the treatment of GER has been associated with improved survival in two large, independent retrospective cohorts of patients with IPF.[9]

Importantly, there are no prospective, randomized data addressing the treatment of GER in IPF and there is a real chance that the data collected to date are misleading. A prospective, controlled trial is essential to answer this question.

The mechanistic hypothesis for GER causing progression of IPF is as follows. Abnormal GER is a known risk factor for microaspiration of gastric contents.[10,11] In patients with IPF, microaspiration may be an important contributor to disease progression through increasing the alveolar epithelial stress and abnormal repair characteristic of the disease.[12,13] In support of this are data from patients with IPF experiencing acute exacerbation of their disease that demonstrate increased levels of pepsin in the bronchoalveolar lavagate compared to stable IPF patients.[14]

Both acid and non-acid GER may be important to disease progression in IPF based on data from animal models that show aspiration of both acid and non-acid refluxate causes pulmonary fibrosis,[15-17] and data from IPF patients suggest an increased benefit of

laparoscopic anti-reflux surgery over medical antacid therapy alone.[9] Surgical treatment for GER with laparoscopic anti-reflux surgery reduces the incidence of all GER, both acid and non-acid; medical treatment for GER does not reduce the incidence of GER substantially – instead it simply reduces the acidity of the refluxate. Laparoscopic anti-reflux surgery has been safely performed in patients with IPF and other forms of advanced lung disease awaiting lung transplantation.[8,18,19]

Together, these data provide an argument for a possible benefit to the treatment of abnormal GER in patients with IPF and associated GER, a fact recently recognized by the ATS/ERS/JRS/ALAT evidence-based guidelines committee authors and others.[1,20] The data further suggest that therapy with laparoscopic anti-reflux surgery, that reduces the incidence of both acid and non-acid reflux, is the most appropriate intervention to test.

4. Preliminary Studies

4.1. Animal models

Animal models show that both the acid and non-acid components of gastroesophageal refluxate are relevant. In one animal model of acute gastric acid aspiration, widespread collagen deposition developed in the lungs within two weeks.[15] In other animal models investigating chronic aspiration of various components of the gastric refluxate showed that development of lung fibrosis was independent of the acidity of the aspirate, and suggesting perhaps gastric contents (e.g. bile, pepsin, or food particulates) were responsible.[16,17] These data support the concept that there are multiple components of the gastroesophageal refluxate (both acid and non-acid) that could contribute to ongoing alveolar epithelial stress in patients with IPF through chronic aspiration into the lungs.

4.2. Retrospective data in patients with IPF

Abnormal GER is highly prevalent in patients with IPF, with a reported 67-88% of patients demonstrating abnormal 24-hour pH monitoring.[4-6] The most recent and largest study studied 65 consecutive patients with IPF regardless of symptoms or a pre-existing diagnosis of abnormal GER.[5] All patients underwent 24 hour pH monitoring and esophageal manometry testing. The prevalence of abnormal GER was 87%, with 63% demonstrating abnormal reflux into the proximal esophagus. Only 47% of patients had classic GER symptoms of heartburn and dyspepsia. Manometry was largely within normal limits. These and other data have led investigators to hypothesize that abnormal GER might contribute to the progression of IPF through predisposing patients to aspiration of gastroesophageal

refluxate that in turn causes chronic stress to the alveolar epithelium.[3] A small case series of four patients demonstrated relative stabilization of forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) with medical therapy for GER.[7] A second case series of fourteen patients with advanced IPF on the waiting list for lung transplantation demonstrated stabilization of oxygen requirements after laparoscopic anti-reflux surgery compared to 31 patients with IPF on the waiting list for lung transplantation that did not undergo laparoscopic anti-reflux surgery.[8]

Retrospective data from a cohort of IPF patients followed as part of a clinical trials consortium demonstrated a reduction in the rate of decline in FVC over 30 weeks for subjects taking anti-acid therapy.[21] Additional retrospective data from the University of California San Francisco and the Mayo Clinic, Rochester demonstrated that a history of laparoscopic anti-reflux surgery was associated with prolonged survival time in patients with IPF (Figure 1).[9] Medical therapy (mostly with proton pump inhibitor (PPI)) appeared less effective. These data are limited by their retrospective nature, but support the hypothesis that treatment of abnormal GER in IPF slows progression of disease, and that laparoscopic anti-reflux surgery is more effective that medical therapy.

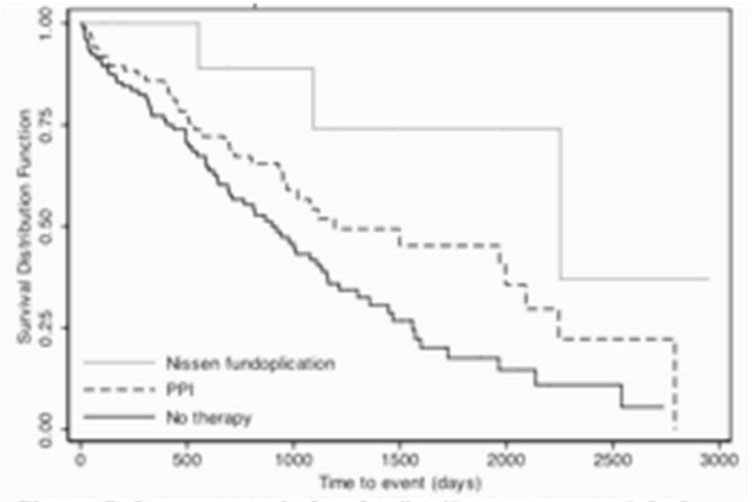

Figure 1: Laparoscopic fundoplication was associated with increased survival compared to no therapy (p = 0.001) and medical therapy (p = 0.11) in patients with IPF.

A total of 14 patients with progressive IPF (mean age 63 years, mean FVC 66 percent predicted (range 40-99%)) and abnormal GER who underwent laparoscopic anti-reflux surgery at University of Washington had pre- and post-surgical FVC measurements obtained (Figure 2). FVC was assessed prior to the surgery (mean of 105 days prior to anti-reflux surgery) and post-surgery (mean of 115 days following the anti-reflux surgery). Over

the average of 7 months between the pre- and post-anti-reflux surgery assessments, the mean FVC increased by 0.08L (3.5 percent predicted) and the majority of participants (10/14) experienced an increase in FVC. All patients were discharged after the standard one night of post-operative observation without any medical or surgical complications.

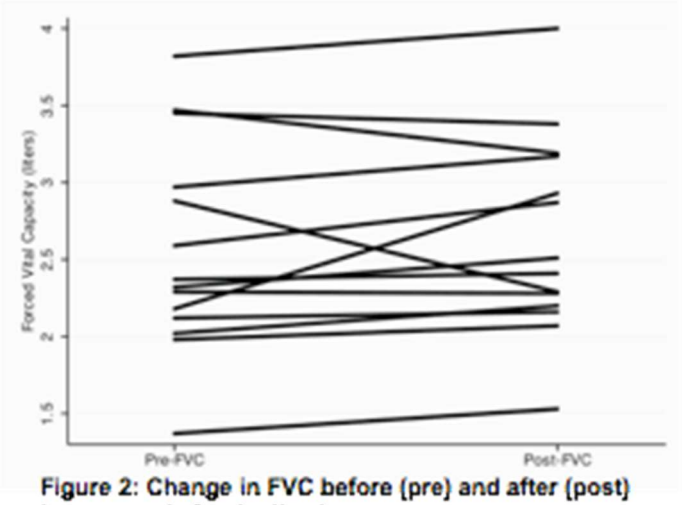

Figure 2: Change in FVC before (pre) and after (post) laparoscopic fundoplication.

5. Methods

5.1. Inclusion Criteria

Only subjects with confirmed IPF, abnormal GER on 24-hour pH monitoring (as defined by a DeMeester score of > 14.7) and esophageal manometry that is acceptable for full laparoscopic anti-reflux surgery will be eligible for this study. Subjects must be able to provide informed consent and be willing to undergo laparoscopic anti-reflux surgery.

5.2. Diagnosis of Idiopathic Pulmonary Fibrosis

Subjects will be evaluated for IPF at the enrolling center. Study investigators will follow the most current ATS/ERS/JRS/ALAT evidence-based guidelines in making this determination.

A subject with suspected interstitial lung disease (ILD) should be evaluated for secondary causes including, but not limited to, environmental exposures, drugs, and systemic diseases. Presence of any of these findings felt to be significant enough to cause an ILD should disqualify the subject from entry into the trial.

5.3. Exclusion Criteria

1. FVC < 50% predicted
2. FEV1/FVC ratio < 0.65
3. Resting room air PaO2 < 60mm Hg
4. Unable to walk 50 meters on 6 minute walk test
5. Recent acute respiratory illness in last 12 weeks
6. Participated in an interventional clinical trial for an IPF therapy in the last 28 days (subjects may be screened, but cannot be enrolled until 28 days after trial participation) **[Note: open-label extensions or expanded access programs (EAPs) for pirfenidone or nintedanib are not considered interventional clinical trials and are not exclusionary.]**
7. Listed for lung transplantation at screening
8. Unable to safely undergo full (complete) laparoscopic gastric anti-reflux surgery (i.e. not a partial fundoplication), in the judgment of the investigators
9. History of esophageal / bariatric / gastric surgery
10. History of cancer (other than non-melanoma skin cancer) in the last 3 years
11. Pregnant at the time of screening or enrollment
12. Unlikely to obtain pre-authorized approval from a third party payer for laparoscopic anti-reflux surgery and related costs in the opinion of the investigators.
13. Life expectancy < 48 weeks due to another illness
14. BMI > 35
15. Known severe pulmonary hypertension (mean pressure > 35 mm Hg on RHC; RVSP > 50 mm Hg on ECHO)

5.4 Study Design and Study Visits

Subjects who appear to meet entry criteria will review the informed consent (a written description of the purpose, procedures, and risks of the study) with the principal investigator (PI), co-investigator, or study coordinator, and all questions will be answered. The informed consent form will be signed by the subject at the beginning of the screening visit. No protocol-specific procedures will be performed until the subject has signed and dated an informed consent form. This includes the screening procedures.

The enrollment visit should occur within 90 days of the screening visit. However, it is preferred that the enrollment visit occur within 28 days of the screening visit to avoid repeating procedures.

All follow-up study visits will occur within 10 business days of their designation (e.g. week 12 will occur +/- 10 business days from the week 12 timepoint).

Table 1. Table of Study Visits

Study Procedure	Procedure details	Visit							
		Screen V1	Enroll V2	Surgery V2A	Wk 12 V3	Wk 24 V4	Wk 36 V5	Wk 48 V6	Wk 52
Medical history	➢ Complete medical history	**X**							PHONE VISIT
Physical examination	➢ Physical exam	**X**			**X**	**X**	**X**	**X**	PHONE VISIT
Documentation of GER	➢ Symptom questionnaire	**X**				**X**		**X**	PHONE VISIT
Assessment of esophageal motility and pH	➢ pH and manometry	**X**+				**X**&			PHONE VISIT
Laparoscopic anti-reflux surgery *				**X**					PHONE VISIT
Bronchoscopy *				**X**				**X**^	PHONE VISIT
Spirometry (Hand-held)			**X**	**X**	**X**	**X**	**X**	**X**	PHONE VISIT
Spirometry (Office based)		**X**	**X**#		**X**!	**X**!	**X**!	**X**!	PHONE VISIT
DLCO			**X**		**X**!	**X**!		**X**!	PHONE VISIT
Arterial blood gas		**X**			**X**	**X**		**X**	PHONE VISIT
6 minute walk test		**X**	**X**#		**X**	**X**		**X**	PHONE VISIT
HRCT			**X**@					**X**	PHONE VISIT
Patient reported outcomes	➢ UCSD SOBQ ➢ Cough VAS ➢ SGRQ ➢ ICECAP ➢ EQ-5D		**X**		**X**	**X**	**X**	**X**	PHONE VISIT
Blood collection			**X**		**X**	**X**	**X**	**X**	PHONE VISIT

***** These procedures will be performed only in those subjects randomized to surgery.

+Does not need to be completed if done within 6 months of V2 at the study site in accordance with the study protocol.

@ Does not need to be completed if done within 3 months of V2 at the study site in accordance with the study protocol.

Only performed if V2 performed > 28 days after V1.

^ This is an optional procedure and will only be performed if the subject has consented for it.

! If a subject has undergone fundoplication surgery (regardless of treatment assignment) within 8 weeks of this visit date, the subject should not undergo this procedure.

& The pH and manometry should be done a minimum of 12 weeks after surgery, and only in those subjects randomized to surgery.

At screening, all potential subjects will undergo a complete medical history, physical examination and testing (spirometry (performed pre-bronchodilator), arterial blood gas, GER symptom questionnaire, and 6 minute walk testing) with assessment of eligibility according to the inclusion and exclusion criteria. All potential subjects who meet entry criteria based on these assessments will undergo 24-hour pH testing and esophageal manometry, unless these procedures have been performed within 6 months of the enrollment visit (Visit 2) at the study site in accordance with the study protocol.

Subjects meeting eligibility criteria will return for an enrollment visit within 90 days (but preferably within 28 days), and will complete baseline evaluations as outlined in this protocol, including:

- Physical examination
- Diffusing capacity of the lung for carbon monoxide (DLCO)
- High-resolution computed tomography (HRCT) (unless performed in the past 3 months according to study protocol and available for review and databasing)
- Patient reported outcome questionnaires
    - UCSD Shortness of Breath Questionnaire (UCSD SOBQ)
    - St. George's Respiratory Questionnaire (SGRQ)
    - Cough visual analog scale (VAS)
    - ICECAP-O
    - EuroQOL EQ-5D
- Blood collection (5 tsp) for measurement of biomarkers

If the enrollment visit occurs within 28 days of screening, the screening values for spirometry and the 6 minute walk test (6MWT) will be recorded as the baseline values. If the subject is unable to return for enrollment until more than 28 days from screening, the spirometry and 6MWT procedures will need to be repeated, and those measurements recorded as the baseline values.

Enrolled subjects will be randomized to either receive anti-reflux surgery or standard medical care.

Subjects randomized to anti-reflux surgery will undergo additional evaluations as directed by the surgical team (these may include but are not limited to esophagram, endoscopy, and echocardiography) and will have pre-surgical evaluation by anesthesiology. These subjects

will undergo preapproval for billing the laparoscopic anti-reflux surgery and related activities and tests to the subject's insurance (all other study procedures will be paid for by the study). In the unlikely event that a randomized subject is denied authorization, the subject will not have surgery but will be followed on an intention to treat basis. All subjects in the surgical arm will receive a bronchoscopy at the time of surgery. Bronchoscopy is a separate procedure from the surgical intervention. Bronchoscopy will be performed according to standardized protocol and samples (BAL and endobronchial brushings) will be collected. These patients will then undergo surgery according to study protocol (see section 8). They will have a post-operative visit with the surgeon at approximately 2 weeks to ensure appropriate recovery.

Subjects randomized to no surgery will be followed clinically. If there is evidence of significant disease progression (defined by a relative decline in FVC of ≥ 10% over 24 weeks or longer), these patients will be allowed to undergo laparoscopic anti-reflux surgery as part of the clinical trial. These patients will otherwise complete the study visits as scheduled.

All subjects in the study will be provided with a home spirometer and instructed to perform spirometry daily throughout the course of the clinical trial. Subjects who are randomized to surgery will be instructed to halt daily spirometry from the date of their surgery until they return to the site for the week 12 visit.

Subjects will be blinded to the results of the home spirometry measurements. Subjects will be instructed to bring home spirometers to each study visit so that data can be downloaded and sent to the DCC for databasing. Subjects will have the option after study completion to keep the home spirometer for personal use.

Safety assessments: Subjects will be contacted by telephone for safety assessments in months where no study visit occurs (months 1, 2, 4, 5, 7, 8, 10, 11) and at week 52. The calls should visits will occur within 10 business days of their designation (e.g. month 1 will occur +/- 10 business days from the month 1 timepoint). One month is defined as 28 days. These phone calls will involve confirming the subject's vital status and asking questions about serious adverse events or adverse events related to the surgical procedure, for subjects randomized to surgery.

At weeks 12, 24, and 36, and 48, subjects will return for evaluation. Each visit will include:

- Physical examination
- Spirometry
- DLCO (except week 36)
- Arterial blood gas (ABG) measurement (except week 36)
- 6MWT (except week 36)
- Patient reported outcome questionnaires (USCD SOBQ, SGRQ, Cough VAS, ICECAP-O, EuroQOL EQ-5D)
- GER questionnaire (at weeks 24, and 48 only)
- Manometry and 24-hour pH testing (at week 24 only, and for subjects randomized to surgery only)
- Blood collection (5 tsp) for measurement of biomarkers
- HRCT (at week 48 only)
- Bronchoscopy with collection of samples (at week 48 only, and for subjects randomized to surgery who have consented to the procedure). This procedure will be performed in an outpatient setting.

At week 52, or 4 weeks after the final study visit, subjects will be contacted by the site coordinator for updates on outstanding AEs and serious adverse events (SAEs).

Study staff may make a long-term follow up at one or more times after subjects complete the study visits to request additional information or talk to subjects about clinical or research issues that are relevant to patients with IPF.

If a subject withdraws early from the study, s/he will be asked to return to complete the battery of assessments scheduled at week 48.

5.5 Travel Reimbursement

Subjects participating in this study will be eligible to receive up to $250 per study visit for covered costs associated with travel to study visits. Covered costs may include:

- Mileage (round-trip from the subject's home address to the study clinic)
- Parking fees at the study clinic
- Airfare to and from the study clinic
- Hotel costs
- Taxi fare

Sites will reimburse subjects as necessary, and submit documentation of payment to the Data Coordinating Center for reimbursement of these expenses.

Subjects who are screened and enrolled on consecutive days and stay overnight for these visits can be reimbursed for two study visits (screening and enrollment) – up to $500.

5.6. Recruitment Procedures

Subjects recruited for this study will be physician-referred or self-referred to centers participating in this study.

Clinical center subjects previously diagnosed with IPF will be notified of the trials by mail whenever possible.

Recruitment of minorities and women will be monitored by the Data Coordinating Center (DCC) and Data and Safety Monitoring Board (DSMB). If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate subject sample contains appropriate representation of women and minorities.

6. Study Endpoints

6.1. Primary Endpoint

The primary endpoint of this study will be the change in FVC (in liters) from baseline to week 48.

6.2. Secondary Endpoints

The secondary endpoints of this study will be:

- Disease progression
- Categorical change in FVC
- Acute exacerbation
- Non-elective hospitalization
- Mortality
- Time to disease progression
- Time to categorical change in FVC, acute exacerbation, or death (composite endpoint)

- Time to non-elective hospitalization or death (composite endpoint)
- Change in UCSD SOBQ score (continuous and categorical)
- Change in SGRQ score (continuous and categorical)
- Change on cough visual analog scale (VAS)
- Change in ICECAP-O score (continuous and categorical)
- Change in EuroQOL EQ-5D scores (continuous and categorical)
- Change in 6-minute walk distance (6MWD) (continuous and categorical)
- Reduction in acid GER by serial pH testing and GER questionnaire
- Quantitative change in HRCT fibrosis score and honeycombing

6.3. Definition of Disease Progression

Disease progression is defined as one or more of the following: relative decline in FVC of ≥ 10%; increase in UCSD SOBQ of ≥ 5 points; suspected or definite acute exacerbation; death. Subjects and their treating physician will be notified of disease progression documented during the course of the study.

6.4 Definition of Acute Exacerbations

Both definite and suspected acute exacerbations of IPF will be identified. The following 4 criteria will define definite AEx in subjects with acute exacerbation of IPF:

1. Unexplained worsening or development of dyspnea within 30 days
2. High-resolution computed tomography with new bilateral ground glass abnormality and/or consolidation superimposed on a background UIP pattern
3. No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage.
4. Exclusion of alternative causes including heart failure, pulmonary embolism, or an identifiable cause of acute lung injury.

Idiopathic acute respiratory worsening thought to represent acute exacerbation but failing to meet one or more criteria will be classified as suspected acute exacerbations.

6.5 Method for Identification of Acute Exacerbation

All subjects will be educated regarding the importance of identifying AEx. At the time of enrollment, subjects will be educated to the possibility of developing acute symptomatic worsening that might represent an AEx of IPF and instructed to contact their study site coordinator within 48 to 72 hours of the apparent event. All subjects will be questioned about any change in dyspnea or cough at any interim clinic visits or hospitalizations.

All respiratory worsenings will be identified and classified by site investigators utilizing the following template:

-- Community/hospital acquired pneumonia
-- Bronchitis
-- Aspiration pneumonitis
-- Pulmonary embolism
-- Pneumothorax
-- Unknown cause
-- Non-pulmonary cause (e.g. anxiety)

If “unknown cause” is selected by the site investigator, further categorization as follows will be required:

-- Definite acute exacerbation (meets protocol criteria in section 6.4)
-- Suspected acute exacerbation as defined in section 6.4.
-- Unclassifiable

An AEx will be treated at the discretion of the treating physician.

7. Policies and procedures for identifying, reviewing, and reporting adverse events

7.1 Definitions

Adverse event (AE) means any unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research.

Serious adverse event (SAE) means any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity

In addition, important medical events that may be considered an SAE if they require medical or surgical intervention to prevent one of the outcomes listed above.

An Unexpected SAE is an SAE that the nature or severity of which is not expected from the disease or interventions within the clinical trial.

An AE Associated with Research means there is a reasonable possibility that the AE may have been caused by the interventions (including tests) in the clinical trial.

7.2 Reporting

SAE Reporting - All deaths and all SAEs require reporting from the start of randomization to week 52. Any ongoing SAEs as of week 52 should be followed to resolution. The research staff at the site where the subject is seen is required to contact the coordinating center to inform them of the SAE within 1 business day of knowledge of the event. The site should also submit an SAE form via the eCRF system within 1 business day of knowledge of the event.

The clinical center investigator will provide an assessment of causality of the event to the study intervention (i.e. is it an SAE associated with research) based upon the information available at the time of the report. It is understood that complete information about the event may not be known at the time the initial report is submitted, though investigators should make every effort to obtain information. All events submitted without a causality assessment

will be considered “associated with research” until a clarification is made. The investigator must also sign each SAE form.

The clinical center investigator must enter follow-up information (e.g., diagnosis, outcome, and results of specific investigations) as it becomes available. Follow-up should be submitted according to the same process used for reporting the initial event as described above (i.e. within 1 business day of knowledge). All SAEs will be followed until resolution, stabilization, or the event returns to baseline condition or value, whichever occurs first. Investigators are responsible for reporting SAEs to their local IRB in accordance with local guidelines. The coordinating center will be responsible for tracking all SAEs, performing a clinical review of the SAE data, querying the clinical centers for additional data, and following unresolved SAEs.

AE Reporting

This study intends to capture information on all serious adverse events, acute exacerbations as described in section 6.5, as well as non-serious adverse events related to the surgical intervention. Non-serious, non-surgery related adverse events should not be reported.

The DCC will submit a detailed report of pre-specified AEs of interest and all SAEs monthly to NHLBI and DSMB chair. In addition, each SAE will be reported to NHLBI and DSMB chair by DCC within one business day after receiving the report. The DSMB Chair will review the information presented and determine if any additional information is needed, and/or a DSMB teleconference should be held. Guidelines for the DSMB procedures will be detailed in the DSMB charter.

8. Surgical Intervention

Subjects randomized to laparoscopic anti-reflux surgery will undergo preoperative evaluation by the surgical team after randomization. This will include a standard pre-operative surgical assessment, anesthesia clearance, and other testing as medically indicated. During surgery, standard American Society of Anesthesiologists protocols will be used to monitor patients under general anesthesia. All subjects will be mechanically ventilated using the minimal tidal volumes and supplemental oxygen required to maintain adequate gas exchange. All subjects who undergo laparoscopic anti-reflux surgery will have

a post-operative visit to insure appropriate recovery. There will be no scheduled study procedures during this visit.

Laparoscopic anti-reflux surgery generally involves the following steps. Individual patient issues may require modifications depending on the surgeon's intraoperative assessment. All efforts will be made to adhere exactly to the same surgical procedure, but if needed, the surgical team can deviate from the standardized protocol to ensure the safety of the patient and to achieve maximum beneficial results. Completion or modification of each stage will be documented in the clinical research form.

Step 1: Division of gastrohepatic ligament; identification of right crus of the diaphragm and posterior vagus nerve.

Step 2: Division of peritoneum and phreno-esophageal membrane above esophagus; identification of the left crus of diaphragm and anterior vagus nerve.

Step 3: Division of short gastric vessels.

Step 4: Creation of a window between gastric fundus, esophagus, and diaphragmatic crura.

Step 5: Placement of Penrose drain around the esophagus.

Step 6: Closure of crura.

Step 7: Insertion of the bougie into esophagus and through esophageal junction.

Step 8: Wrapping of gastric fundus around lower esophagus.

Step 9: Final inspection, removal of instruments and trocars from the abdomen, and closure of the port sites.

9. Data Management

9.1. Design and Development

The DCC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and

training clinical center staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

9.2. Data Collection Forms

The data collection process consists of direct data entry at the study clinical centers into the EDC system(s) provided by the DCC. A data collection worksheet will be provided to clinical centers for recording data in the event the EDC system is unavailable. Data entry of the eCRFs should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

9.3. Data Acquisition and Entry

Data entry into eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's written signature or electronic signature, as appropriate. Electronic CRFs will be monitored for completeness, accuracy, and attention to detail during the study.

9.4. Data Center Responsibilities

The DCC will 1) develop a data management plan and will conduct data management activities, 2) provide final eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data, 5) monitor any preliminary analysis data clean-up activities, and 6) rigorously monitor final study data clean up.

9.5. Data Editing

Completed data will be entered into the DCC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be

generated and distributed to clinical centers for a response. Clinical centers will resolve data inconsistencies and errors and enter all corrections and changes into the DCC automated data acquisition and management system.

9.6. Training

The training plan for clinical center staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of computerized systems.

10. Data Analysis

10.1. Sample Size Determination and Randomization

We are planning to enroll approximately 58 subjects randomized in a 1:1 ratio to laparoscopic anti-reflux surgery or standard care. Patients will be allocated using a computer generated randomization scheme. Due to the unblinded nature of the study intervention, the randomization will not be stratified. If enough subjects randomized to surgery are unable to undergo surgery due to failure of insurance authorization or medical eligibility reasons, consideration will be given to rebalancing and/or adjusting randomization to insure sufficient subjects undergo surgery to meet the aims of the study.

In powering the study, we have considered the potential impact of PPI use for symptomatic GER (part of standard medical care) on the rate of FVC change in the no surgery group. Under the assumption that the use of PPIs will be partly effective, our statistical power will be reduced. Based on historical knowledge of change in FVC over time in patients with IPF a difference of 1.0 standard deviation over a one-year period would be approximately 0.25 liters. We believe that a treatment difference of that size would be both clinically meaningful and consistent with our preliminary data. We have conservatively estimated that 40% of individuals in the no surgery group will take PPIs on a regular basis for control of typical GER symptoms (i.e. heartburn and dyspepsia), and that PPIs are 50% as effective as surgery in reducing the rate of decline in FVC over time. With these adjustments, the expected effect size is reduced to 0.8 standard deviations. For that reason, this study is powered to detect an effect size of 0.8 standard deviations (or approximately 0.20 liters) in

the change in FVC between the two groups with a two-sided alpha of 0.05 and 80% power. The estimated number of subjects required for varying effect size and power are shown in Table 3. These calculations are based on the two-sample t-test with an increase in the sample size to allow for up to 10% withdrawal of consent.

Table 3: Enrollment requirements for varying effect size and power

Total subjects	Effect size	Two-sided alpha	Power
38	1.0	0.05	80%
52	1.0	0.05	90%
58	0.8	0.05	80%
76	0.8	0.05	90%
100	0.6	0.05	80%
134	0.6	0.05	90%

*Calculations allow for 10% withdrawal of consent.

10.2. Specification of the Primary Analysis

The primary endpoint will be change in FVC (in liters) from baseline to 48 weeks. A mixed model repeated measures (MMRM) analysis, will be used to compare differences in the FVC measurements across treatment groups at 48 weeks.[22] Response variables are values of the FVC measured at baseline and every 12 weeks until study completion at 48 weeks. Covariates in the model will include treatment time terms and the baseline FVC values. Contrast estimates of differences between treatments (along with confidence intervals) will be used to estimate the treatment effect. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures. The MMRM models will be implemented using PROC MIXED in SAS. For subjects randomized to no surgery who subsequently undergo surgery as part of the study (per protocol), post-surgical FVC measurements will be obtained but will not be included in the assessment of the primary endpoint. Instead, a 48 week FVC value will be imputed based on the pre-surgical FVC values obtained in each individual patient.

10.3. Analysis of Secondary Endpoints

The MMRM models will be applied to analyze the longitudinal data secondary endpoints. Regression modeling approaches using either the logistic regression model or Cox proportional hazards regression model will be employed for binary and time-to-event endpoints, respectively. All statistical analysis will be conducted using SAS version 9 or higher software. Statistical significance will be defined at the two-sided 0.05 level.

11. Study Administration

11.1. Steering Committee

Members of the study Steering Committee will be responsible for overseeing the study conduct and will make all decisions regarding the trial.

11.2. Data and Safety Monitoring Board

An independent data safety and monitoring board (DSMB) comprised of experts in lung disease and clinical trials, GER, laparoscopic anti-reflux surgery, and biostatistics who are not involved in any other way with this study will be responsible for monitoring the clinical trial for the duration of this award. A chair of the DSMB will be identified who will be responsible as the point of contact for DSMB-related matters. Written documentation of no conflict of interest will be required. Prior to enrollment, the DSMB will review and approve the study protocol and other documents as appropriate. The DSMB will meet prior to the start of enrollment and at intervals as defined in the DSMB charter to review the safety and conduct of the study procedures, in particular laparoscopic anti-reflux surgery, as well as the following additional duties:

1. Evaluate the progress of the trial, including assessment of recruitment and retention rates, data quality and timeliness, and participant risk versus benefit (including reviewing all significant adverse events).
2. Consider factors external to the clinical trial that may have an impact on the safety of the participants or the ethics of the trial (e.g. an approved therapy for IPF becomes available).
3. Assist in the resolution of concerns or problems expressed by the principal investigators or staff.
4. Report on the safety and progress of the trial on a twice-yearly schedule.
5. Make recommendations to the NHLBI, the principal investigators, and if required other organizations concerning the continuation, termination, or other modifications to the trial based on the observed beneficial or adverse effects of the treatment under study. Specific guidance regarding stopping criteria will be provided to the DSMB.
6. Request the data-coordinating center to conduct interim analyses of the data to perform the above duties.
7. Insure the confidentiality of the trial data and the results of monitoring.

The data-coordinating center at the DCRI will provide logistical support to the DSMB by providing reports of adverse events, recruitment, and efficacy, analyses, and other items as required and requested by the DSMB.

12. Investigator and Sponsor Obligations

12.1. Site and Remote Monitoring

All site and remote monitoring activities will be performed in accordance with the DCRI standard operating procedures. Information regarding the methods and frequency of monitoring will be outlined in the study clinical monitoring plan.

12.2. Confidentiality and Health Insurance Portability and Accountability Act (HIPAA) Considerations

Subject confidentiality will be protected throughout the study. All subject data will be kept strictly confidential, and no subject-identifying information will be released to anyone outside the project. Confidentiality will be assured through several mechanisms. First, each subject will be assigned a unique study ID number, which will then be used on all study forms. Second, any study forms, blood samples, and paper records that contain subject information (eg, address lists and phone lists) will be kept at the clinical sites in secured, locked areas, coded by study ID number. Once blood or bronchoscopy samples are collected, there will be no subject identifiers placed on the samples—only the study ID number and the date of sample collection will be identified. Third, access to all subject data and information, including laboratory specimens, will be restricted to authorized personnel. In the case of computerized data, this restricted access will be assured through user logon IDs and password protection.

At the DCC only authorized personnel will have access to the study data files containing study data. Security will be assured through user logon IDs, passwords, and appropriate access privileges. Personal identifying information, such as name, address, and Social Security number, will not be entered into the DCC database. Subject-specific data reported to the Steering Committee will be identified by the study ID number only.

Finally, subjects will not be identified by name in any reports or publications, nor will the data be presented in such a way that the identity of individual subjects can be inferred. Analysis

files created for further study by the scientific community will have no subject identifiers. These data files will be created in accordance with the DCC SOPs.

Investigator Agreement

WEIGHING RISKS AND BENEFITS OF LAPAROSCOPIC ANTI-REFLUX SURGERY IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (WRAP-IPF)**: A PHASE II CLINICAL TRIAL**

I have read the foregoing protocol, and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals accountable to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the intervention and the conduct of the study.

I will fulfill all responsibilities for submitting pertinent information to the local IRB, if applicable, that is responsible for this study.

I further agree that NHLBI and/or DCRI will have access to any source documents from which case report form information may have been generated.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (printed or typed)

Protocol Version Date 11 Dec 2015

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