Using Xenon MRI to Evaluate the Efficacy of Therapies for Idiopathic Pulmonary Fibrosis

Robert M Tighe, MD – Principal Investigator
Duke University, School of Medicine
Department of Medicine
Division of Pulmonary, Allergy and Critical Care
[redacted]

Bryan Kraft, MD – Co Investigator
Duke University, School of Medicine
Department of Medicine
Division of Pulmonary, Allergy and Critical Care
[redacted]

Lake Morrison, MD – Co Investigator
Duke University, School of Medicine
Department of Medicine
Division of Pulmonary, Allergy and Critical Care
[redacted]

Joseph Mammarappallil, MD PhD – Co Investigator
Duke University, School of Medicine
Department of Radiology
[redacted]

Bastiaan Driehuys, Ph.D. – Co- Investigator
Duke University, School of Medicine
Department of Radiology
[redacted]

Sponsor: Genentech

NCT04071769

RESEARCH SUMMARY

1. Protocol Title: Using Xenon MRI to Evaluate the Efficacy of Therapies for Idiopathic Pulmonary Fibrosis

2. Purpose of the Study: The purpose of this PI initiated, industry sponsored study is to perform a carefully controlled study to assess if Xenon MR imaging can be used to determine treatment efficacy of Idiopathic Pulmonary Fibrosis (IPF) therapies. IPF is a devastating disease affecting more than 100,000 US residents. Patients with IPF have poor prognosis, with a mean survival time of only 35.2 months. The hallmark of the disease is a progressive process of scaring in the lung that results in thickening of the pulmonary blood-gas barrier and impaired gas exchange. In 2014, two medications became available for treatment of IPF. Over the 52 week studies, pirfenidone and nintedanib were demonstrated to slow, but not halt, the decline in lung function (as defined by reduction in forced vital capacity (FVC)) associated with progressive pulmonary fibrosis. Since delayed decline in FVC is the treatment response, it remains difficult to determine if therapies are helping an individual patient as physicians are not able to compare the individuals rate of decline off therapy. Additionally, testing new therapies for IPF require long term studies to assess changes in physiologic parameters. This makes developing potential new therapies both time and resource limited.

We intend to address this problem by using a MRI-based 3D imaging approach to predict and observe regional therapeutic response. The objective of this study is to use these MRI approaches to identify regional diffusion limitation, and then use them to predict and observe therapeutic response earlier than standard methods (such as decline in FVC). *Our central hypothesis* is that Xenon MRI by identifying the leading edge of disease, where recovery of lung function remains possible, will allow us to define treatment responses to IPF therapies. The *rationale* for the proposed research is that therapeutic response is difficult if not impossible to detect using global metrics and thus, 3D non-invasive imaging is needed to visualize recoverable areas. If this is the case, it would allow providers to develop targeted treatments for individuals with IPF and would enable more rapid assessment of potential therapeutic efficacy with potential novel IPF therapies.

The protocol will leverage advances in MR imaging that facilitate the assessment gas exchange, as well as pulmonary structure, ventilation, and perfusion within a single integrated MRI exam. Pulmonary ventilation and gas exchange are assessed 3-dimensionally by using inhaled hyperpolarized ^{129}Xe MRI, which has been developed at Duke over the past 6 years under IRB protocol Pro00025110 (among others) and IND #109,490. As demonstrated in a recent publication by our group, we can execute a fully 3D MRI protocol, capable of assessing all relevant aspects of pulmonary structure and function in a single exam. Since this approach does not use ionizing radiation, it can more safely be utilized to follow patients over time to facilitate following treatment responses.

The study has the following *Specific Aims*: 1) Clearly establish baseline Xenon MRI characteristics in newly diagnosed IPF patients and compare them to standard measures (HRCT, Pulmonary Function testing and 6 minute walk distance), 2) Use ^{129}Xe exchange MRI to monitor progression and response to IPF therapies by comparing baseline MRI characteristics to alterations following initiation of treatment at specific time points. Our ultimate scientific objective is to develop a diagnostic paradigm that can predict patient therapeutic responses.

3. Background and Significance: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease that in a majority of cases leads to morbidity and mortality. The

median survival time from diagnosis is less than 3 years, and the disease affects an estimated 134,000 Americans, though this prevalence is likely an underrepresentation of the true disease burden. IPF is characterized by gas exchange impairment from thickening of the pulmonary blood-gas barrier. Although high-resolution CT is integral to the initial diagnosis of IPF, it has not proven useful as a means to monitor disease progression or therapy response. As noted by the American Thoracic Society, "*…the diagnosis and management of patients with IPF continues to pose a significant challenge.*" Despite the two recently approved therapies (Nintedanib and Pirfenidone), no IPF therapies have yet been developed that meaningfully reverse this progressive lung fibrosis. Furthermore, genetic and clinical studies clearly demonstrate significant disease heterogeneity. This suggests that IPF patients will required personalization of their therapies. This requires sensitive and accurate measure to assess disease progression and response to treatment. Presently the field is hampered by poor techniques for assessing lung function and development of fibrosis. Therefore, *there is a pressing need for improved methods to monitor disease progression and detect response to therapy.* It is becoming increasingly clear that the primary roadblock facing the treatment of IPF is not necessarily a lack of viable therapies, but rather a lack of adequate means to test them.

IPF manifests in a spatially heterogeneous manner pathologically defined as areas of normal lung in close approximation to areas of fibrosis. Therefore, we expect that therapeutic responses would be regional. Thus, to detect progression and therapy requires localizing effects on structure and function, and monitoring these regions over time. Advances in 3D pulmonary magnetic resonance imaging (MRI) now make this possible. Although high resolution computed tomography (HRCT) is required for IPF diagnosis, it is poorly suited to monitor therapeutic response. CT detects structural abnormalities, but the earliest harbinger of changing disease status is *function*. Additionally, CT scans and particularly HRCTs require use of ionizing radiation. The ability to image both function and structure is now ideally served by recent advancements in MRI. Because ^{129}Xe, like oxygen, must traverse the interstitial barrier to reach capillary blood, ^{129}Xe signal in RBCs is exquisitely sensitive to barrier thickness. ^{129}Xe in RBCs has a unique frequency shift, allowing it to reveal interstitial thickening of only a few microns. The exquisite sensitivity to increased blood-gas-barrier thickness makes ^{129}Xe MRI uniquely suited to study pulmonary fibrosis without ionizing radiation. This has the potential to accelerate clinical trials for IPF by literally visualizing the therapeutic response on the timescale of months versus years.

Hyperpolarized ^{129}Xe MRI has been shown to be safe and well tolerated in a phase I clinical trial for HP ^{129}Xe MRI that was completed at Duke and published in the journal Radiology in 2012. Additionally, we have now published on the use of this technology in patients with IPF, asthma, COPD, and pulmonary vascular disese. These studies have enrolled in excess of 250 patients and healthy volunteers and demonstrated that inhalation of up to four 1 liter doses of HP ^{129}Xe was well-tolerated, generated no notable changes in measured physiologic parameters and resulted in no SAEs or withdrawals. Thus, Duke has the technical experience and infrastructure to conduct this study.

4. Design and Procedures: This will be an unblinded, open-label study enrolling newly diagnosed patients with IPF. We plan to consent 50 subjects including screen fails with a goal of obtaining 30 newly diagnosed individuals with IPF prior to initiation of IPF therapies. 20 subjects will be monitored after the initiation of therapy, 10 subjects will be enrolled that do not start antifibrotic therapy. No subject will be excluded from the study on the basis of gender or ethnicity. IPF is an aging disease with highest incidence in subjects >50 years of age, and therefore subjects will be expected to be >50 years of age. Subjects will be obtained from providers in the Duke Pulmonary Clinics. Informed consent will be

obtained before a subject begins any study intervention. Subjects will undergo an approximately hour long comprehensive MRI protocol, including administration of multiple doses of HP ^{129}Xe. The subjects will have this initial study prior to initiation of IPF therapies. Then the subjects will have repeat studies at 3, 6 and 12 months following the initation of therapy. Additional studies including pulmonary function studies, serum for biomarkers, 6 minute walk distance (only at screening visit, 3 month and 6 month visit) and a HRCT (only at the screening visit and 6 month visit) will be performed to determine how 129Xe MRI performs relative to standard of care evaluations for IPF. Finally, following the study visits the research team will prospectively follow the patients' clinical course through periodic reviews of the medical record.

Prior to consideration for the study, all patients will have their IPF diagnosis formally confirmed at the Duke multidisciplinary ILD conference. Either through discussions at the multidisciplinary conference or through referral from the patient's pulmonolgist, the study coordinator will identify potential patients. With their primary doctors approval, the coordinator will have an initial screening phone call with the patient to assess their interest in the study (V0). If the patient is interested, a screening visit will occur (V1). The screening visit will start with a history and physical exam and a review of the protocol to obtain informed consent. Following informed consent, the patient will undergo spirometry including lung volume and a DLCO measurement, assessment of a 6 minute walk distance (6MWD) and a HRCT scan if not done at the initial visit with the pulmonary provider. Venous blood will be obtained to get cells for DNA and RNA and plasma for biomarkers, a nasal swab will be performed, and a urine sample will be obtained from the subject.
Following these initial screening studies, the patient will undergo a ^{129}Xe – MRI exam. The details of the ^{129}Xe MRI are as follows. The subject will be escorted to the MRI suite where they will be fitted with a ^{129}Xe transmit-receive vest coil. They will then be positioned supine on the scanner bed. They will be coached about how to inhale HP ^{129}Xe from the dose delivery bags. Then the subject and bed will be moved into the scanner and they will undergo basic ^{1}H localizer and anatomical scans. Once localization is complete, subjects will undergo several MRI scans after inhalation of HP ^{129}Xe. Each dose will be limited to a volume less than 25% of subject lung capacity (TLC) as is the case for all protocols currently carried out under IND 109,490. After each ^{129}Xe dose, the table will be moved out of the magnet bore and the subject queried for any symptoms. The next ^{129}Xe dose and scan will be administered when the subject and study personnel are ready. Subjects will undergo a ^{129}Xe dynamic spectroscopy and calibration, and ^{129}Xe gas exchange MRI. Any given ^{129}Xe MRI scan may be repeated, if necessary. After completing this sequence, the subject will get off the MRI table, rest for 5 minutes and then undergo the same scans to assess repeatability. There is no limit to the number of ^{129}Xe scans allowed during the session, although current ^{129}Xe production capabilities generally limit this to 5 ^{129}Xe doses. After completing the ^{129}Xe portion of the scan, the ^{129}Xe coil will be removed and patients fitted with a torso array ^{1}H coil. They will then undergo a free-breathing ultra-short-echo time ^{1}H MRI to delineate lung structure.

Following visit V1, the coordinator will ask the patient and/or contact the patient to confirm the start date of an FDA approved IPF therapies (pirfenidone and nintedanib). The decision of which type of therapy will be completely at the discretion of the patient and their primary pulmonologist but will be recorded by the coordinator. Following initiation of therapy, the subject will return for visits at 3 (V3), 6 (V4) and 12 (V5) months following initiation of therapy. At that time, the subjects will undergo a physical exam, spirometry and a 6MWD (only at screening visit, 3 month and 6 month visit)if not performed as a part of their usual care. At 6 months, the subjects will also undergo a HRCT scan. This will not

be performed at the other pre-specified visits. At these 3, 6 and 12 month visits, as a part of the study, subjects will undergo repeat ^{129}Xe MRI studies and a venous blood draw to obtain cells for RNA and serum for biomarkers, a nasal swab, and urine sample collection. Following the 12 month visit, a chart review will be performed at 6 month intervals and clinical IPF characteristics will be recorded to determine clinical outcomes, for a period of 5 years (V6). No additional direct study contact with the patients will occur after the 12 month visit (V5). For subjects lost to follow-up prior to completing all 4 in person visits, we will request written permission in the informed consent to use their standard of care (SOC) assessments to obtain clinical data such as physical exam, vitals, PFTS and 6MWD that pertain to the timepoints noted above (3 months, 6 months and 12 months post initiation of therapy).

5. Selection of Subjects: The population to be studied will consist of patients with a physician diagnosis of idiopathic pulmonary fibrosis.

Inclusion/Exclusion Criteria

Inclusion Criteria
Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial

1. Outpatients of either gender, age > 18.
2. Willing and able to give informed consent and adhere to visit/protocol schedules. (Consent must be given before any study procedures are performed)
3. Clinical diagnosis of IPF by confirmed by multidisciplinary diagnosis and naïve to treatment with an approved IPF therapy (either nintedanib or pirfenidone)

Exclusion Criteria
Subjects presenting with any of the following will not be included in the trial:

1. Subject is less than 18 years old
2. Subjects who have been previously on either pirfenidone or nintedanib
3. MRI is contraindicated based on responses to MRI screening questionnaire
4. Subject is pregnant or lactating
5. Resting oxygen saturation on room air <90% on supplemental oxygen
6. Respiratory illness of a bacterial or viral etiology within 30 days of MRI
7. Subject with ventricular cardiac arrhythmia in the past 30 days.
8. Subject has history of cardiac arrest within the last year
9. Subject does not fit into ^{129}Xe vest coil used for MRI
10. Subject deemed unlikely to be able to comply with instructions during imaging
11. Recent exacerbation (within 30 days) defined by the need for antibiotics and/or systemic steroids
12. Medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements

Subject Identification: Subjects will be enrolled in the study by a unique identifier, which will be used for all subsequent analyses. Image acquisition is done by entering the subject's year of birth along with height and weight into the scan set-up page. ^{129}Xe and ^{1}H MR images will be analyzed with respect to age, gender, heart rate, relevant medical history, and prior image findings. Any such personal health information (PHI) will be obtained

from the records only by trained clinical research personnel and will then be associated with this unique patient identifier. CT scans will be paid for by grant funds, if not performed for clinical reasons by the provider, and will transferred to PACs.

6. Subject Recruitment and Compensation: Subjects with IPF will be recruited from providers in the Duke pulmonary clinics via flyers, and website postings and from identification at multidisciplinary diagnosis conference. Patients with IPF will be informed about study participation by their physician or a nurse during their clinic visit. If they are interested in participating and appear to meet all inclusion criteria they will be referred to the study coordinator for formal consenting. Recruitment will be open to all demographic groups. Subjects will be compensated $100.00 after each MRI visit for their travel/parking and time. A total for 4 MRI studies will be performed to complete the study for a total compensation of $400.00. If a procedure has to be cancelled for technical reasons after a subject has arrived on site, the subject will be compensated as though he/she had completed that visit. The subject will be encouraged, but not required, to return at a later date to complete the procedure. If the subject returns, he/she will be compensated again. Patients may withdraw from the study at any time for any reason.

7. Consent Process: The study coordinator will consent prospective participants. If necessary, the participants will have no less than 24 hrs to consider their participation. The consenting will take place in the private room or laboratory setting with closed doors. Only the coordinator and prospective participant will be in the room during the consent process. We will encourage potential subjects to ask questions and to take as much time as needed to consider participation. If the subject wishes to consider the study overnight or longer, an additional appointment will be made for the subject to continue the consent process. From the time of initial contact until the participant completes the study they will have a coordinator's contact information.

8. Subject's Capacity to Give Legally Effective Consent: Subjects without capacity to give consent will not be recruited into this study.

9. Study Interventions: Hyperpolarized xenon will be administered in multiple doses in volumes up to 25% of subject TLC followed by a breath hold of up to 15 seconds. Subsequent ^{129}Xe doses will only be administered once the subject is ready to proceed. Hyperpolarized ^{129}Xe MRI will be used to acquire one or all of the following data:

Pre- treatment (Study V1)

1. 3-Plane Localizer
2. ^{129}Xe dynamic spectroscopy and calibration to test coil tuning and loading in each subject to permit optimal setting of imaging parameters.
3. ^{129}Xe distribution dissolved in the pulmonary interstitial spaces and capillary blood as an indicator of pulmonary gas exchange.
4. Breath-hold 3D radial MRI to delineate the thoracic cavity
5. Subjects will dismount the MRI table, rest for 5 minutes
6. 3-Plane Localizer
7. ^{129}Xe dynamic spectroscopy and calibration to test coil tuning and loading in each subject to permit optimal setting of imaging parameters.
8. ^{129}Xe distribution dissolved in the pulmonary interstitial spaces and capillary blood as an indicator of pulmonary gas exchange.
9. Breath-hold 3D radial MRI to delineate the thoracic cavity

Post Treatment (V3, V4, and V5)

1. 3-Plane Localizer
2. ^{129}Xe dynamic spectroscopy and calibration to test coil tuning and loading in each subject to permit optimal setting of imaging parameters.
3. ^{129}Xe distribution dissolved in the pulmonary interstitial spaces and capillary blood as an indicator of pulmonary gas exchange.
4. Breath-hold 3D radial MRI to delineate the thoracic cavity

If any of these scans are deemed by the study team to require repeating, this may be done as needed

HRCT scans will be done in the prone position at both inspiration and expiration using the protocol commonly used in IPF clinical trials.

10. Risk/Benefit Assessment: As this is the first rigororous prospective study of its kind for using MRI to monitor patients with IPF, it is not known if the data generated will be of direct benefit to the patients participating. However, the knowledge gained from these studies is expected to benefit future patients with IPF.

Risks of Hyperpolarized ^{129}Xe Inhalation of hyperpolarized ^{129}Xe may carry some minor risks. Xenon is a general anesthetic when breathed continuously at concentrations greater than 70% for extended periods of time. In the proposed study, xenon will be delivered in a single breath, with alveolar concentrations below 25%. At these concentrations, subjects may experience transient effects including dizziness, slight tingling or numbness of the extremities, nausea, smelling of flowers, or a feeling of well-being and euphoria. These effects will wane within 1-2 minutes of exhaling the xenon and are documented in the consent forms.

Risk of HRCT: Ionizing radiation exposure for the low dose CT is estimated at 2mSievert for each scan. For both inspiratory/and expiratory scans, the total dose is estimated at 4mSievert, roughly the equivalent of 1 year of natural radiation exposure.

A second risk comes from administering HP ^{129}Xe without oxygen. This is necessary to preserve good image quality, because O_2 is paramagnetic and depolarizes the HP ^{129}Xe. Therefore, ^{129}Xe is not mixed with O_2 within the dose delivery bag, but only once it is inhaled. Administration of a single anoxic 1-liter breath has been well tolerated by subjects undergoing both ^{3}He MRI and ^{129}Xe MRI. After a single breath, the residual oxygen in the subject's lungs is sufficient to maintain blood O_2 saturation during the breath-hold. For each subject, their blood-oxygenation will be monitored throughout the time they are in the MRI scanner. To reduce risk, a baseline resting oxygen saturation of 90% on supplemental oxygen will be required. Furthermore, supplemental oxygen will be provided during the MRI exam as indicated.

Incidental Findings – Incidental findings will be handled according to the policies of the Duke IRB. That is, anatomic ^{1}H MR images will not be routinely reviewed by a radiologist. However, if the technologist or study personnel note suspicious findings in the anatomic (^{1}H) images at the time of MRI, images from those subjects will be reviewed by a radiologist within 10 business days for incidental findings (tumors, hernias, aneurisms, etc). Such incidental findings will be communicated to the subject's physician. Copies of images will be made available to the subject's physician upon their request. If subjects undergo low-

dose CT as part of this protocol, those scans will be reviewed for incidental findings by a radiologist on the study team.

11. Costs to the Subject and Compensation: There are no additional costs to the subject for the MRI examination and possible CT scan. Subjects will be compensated $100.00 for travel/parking and time for each study visit. This does not include the initial screening phone call and the phone call to document initiation of IPF therapy.

12. Data Analysis & Statistical Considerations: All images will be reviewed by the study team. Given that this is an early phase study with no clinical experience this will be a research interpretation and not a clinical read. Images and spectra will be analyzed by a varieity of quantitative metrics using established methods. Imaging metrics include the ventilation defect percentage (VDP), percentage of lung with high barrier uptake ($Barrier_{high}$), and percentage of lung with defects in red blood cell transfer (RBC_{low}). Spectroscopic markers will include the ratio of ^{129}Xe transfer to RBCs vs barrier (RBC:barrier) as well as RBC oscillation and frequency oscillation amplitudes. CT scans will be evaluated by a chest radiologist using established criteria to produce a mean fibrosis score based on the extent of reticulation and honeycombing and and will range from 0-100%.

Although sensitivity to therapy response is expected to be highest for the imaging metrics, the study has been conservatively powered on the basis of the spectroscopic RBC:barrier ratio, which thus far, is most well-documented of the ^{129}Xe metrics in the literature. Early studies, which did not control carefully for lung inflation reported a variability of 6.6% in this metric. Moreover, a recent study of natural progression in a group of IPF patients (n=18, on a mix of treatments or untreated) revealed a decline in RBC:barrier of 20% in this metric over the course of 6 months. We assume that we will observe a smaller decline in RBC:barrier in our cohort, which will all receive treatment, and estimate that only a 10% decline will be observed at 12 months. Given this estimate of variability and effect size, and requiring 90% power, would be achived with a sample of only 5 patients. Based on established patterns in our clinics, we expect roughly half the patients to receive pirfenidone with the other half receiving nintedanib. Assuming that one of the drugs reduces RBC:barrier decline to only 5% over 12 months, whereas the other yields a decline of 10%, would require a sample of 19 patients, which is just achievable with the sample of 20 patients expected to be enrolled.

<u>Baseline Repeatability and Prespecified Futility Analysis</u> – As this is a new clinical study with unknown efficacy in detection a preliminary analysis of the data will be performed. Following completion of the first 10 patients in the study the study team will perform an analysis for futility based on test – retest variability. Baseline repeatability of each of the ^{129}Xe metrics will be assessed using Bland- Altman plots, and a pairwise, two-tailed *t*-test will be used to check for significant differences. For each derived parameter, the coefficient of variation will be calculated. Our threshold to stop the study is if the RBC:Barrier ratio is outside of 95% CI on test-retest of ±20% of the dynamic range. We estimate the 95% confidence interval to be better than ±10% with this sample size.

Correlation between ^{129}Xe metrics, CT scores, and clinical tests will be evaluated using the Pearson correlation coefficient.

To measure changes from baseline, we will calculate the mean, standard deviation, median and range of each metric, and at each time point, the 95% confidence interval for means and averaged changes relative to baseline will be provided. Changes compared to

baseline will be tested using the Wilcoxon Singed-Rank test. In all analyses, $P < 0.05$ (two-sided) will be considered the criterion for statistical significance. There will be no adjustment for multiple testing, because of the small number of hypothesis tests considered. The trajectory changes of these endpoints over time will be evaluated using linear models for repeated measures. Point estimates and confidence intervals for relevant parameters will be provided for descriptive purposes.

Baseline images will be analyzed for functional or structural indicators that may predict therapeutic response using mixed linear models. We will conduct this modeling, while considering differences in treatment group, clinical/demographic covariates (fixed effects), and subject (random effect). Diagnostic plots will be obtained to assess possible violations in model assumptions. All statistical analyses and graphics will be generated in R, or similar statistical package.

13. Data and Safety Monitoring: Subjects will be monitored before, during and after each dose of xenon to assess for adverse events and changes in vital signs. The parameters monitored include the following: subject assessment of anesthetic/analgesic effects, heart rate, and SPO_2. The subjective sense of analgesia is assessed by in inquiring about how the subject feels after administration of the xenon dose. The subject will be asked to describe how they feel as well as about specific symptoms including: dizziness, light-headedness, numbness, euphoria, sleepiness, and tingling in extremities. Heart rate will be measured before and after each xenon dose. Changes in heart rate of greater than +/- 20% are considered significant. If the subject is to receive another dose, the next dose will not be administered until the heart rate is within 20 % of its baseline value. If the subject has received their last dose, they will be observed until their heart rate is within +/- 20% of its base line value or until the end of the observation period, whichever is longer. SPO_2 is measured at baseline and after each xenon dose. A decrease of SPO_2 by greater than 5% is considered significant. If the subject is to receive another dose, the next dose will not be administered until the SPO_2 is within 5 % of its baseline value. If the subject has received their last dose, they will be observed until the SPO_2 is within 5% of its baseline value or until the end of the observation period, whichever is longer. The subject will be monitored for the duration of the xenon dose and post procedural period as well as the MRI with contrast by a qualified medical professional.

Research Specimens: Research material, which will be collected from human subjects and includes; serum, and DNA. These data will be collected for research purposes, but remain available, if need and agreed to, by the subject for future research use. DNA will be stored indefinitely. Samples will be de-identified by assigning a code only accessible to PIs and study team, DNA will primarily be used for this study but could also be used for future studies (outlined in the consent using standardized language). If sample is provided to outside investigators, the DNA and clinical information will only be identified by the assigned code.

Discontinuation - Participation in this study is voluntary and subjects are free to withdraw at any time and for any reason. Furthermore, the individual subject will be withdrawn from the trial should they develop any worsening of health or new medical illness that is deemed to be a result of this study. Parameters to be evaluated include but are not limited to: shortness of breath, heart rate or decreased blood oxygenation related to xenon administration. If a subject experiences a decrease in oxygenation that is greater than or equal to 5% that persists for more than 5 minutes post xenon administration, they will be withdrawn from the trial. Similarly, if patients experience a change in heart rate of more than

20% on more than one occasion after xenon administration they will be withdrawn. Other reasons for discontinuation include subject becomes uncomfortable in the magnet, subject becomes unresponsive or is unable to protect their airway, subject requests study discontinuation, or other concerns. If any subject experiences a serious adverse drug experience (as defined in 21 CFR Part 312.32(a)), the trial will be discontinued immediately.

14. Privacy, Data Storage & Confidentiality: All consent and case report forms will be stored in a locked filing cabinet in the office of the study coordinator or principal investigator. Any other digital data (images, image analysis) will be associated only with the subject identification number and the date and time of the MRI. Image data will be retrieved and analyzed only by study personnel. The data is stored in a password protected, controlled access account with authentication and mandatory password change features. After all manuscripts have been published the key to the code will be destroyed.

Schedule of Events

Protocol Activities	Screening Phone Call (V0)[1]	Study Visit (V1)	Study Visit (V2)	Study Visit (V3)	Study Visit (V4)	Study Visit (V5)	Prospective Clinical F/U (V6)
Patient phone call	X		X				
Informed Consent[1]		X					
Medical History[2]		X		(X)	(X)	(X)	
MRI Screening Form		X		(X)	(X)	(X)	
Pulmonary Function Testing[3]		X		X	X	X	
6 minute walk distance[4]		X		X	X		
Pregnancy Test[5]		(X)		(X)	(X)	(X)	
HRCT[6]		(X)			(X)		
MRI Session[7]		X		X	X	X	
Subject monitoring[8]		X		X	X	X	
Vital signs		X		X	X	X	
Adverse events followup[9]		X		X	X	X	
Prospective/Retrospecitve clinical monitoring in chart[10]							X

1. For most subjects, screening and study visit 1 will occur on the same day. However, these visits can be conducted separately if needed.
2. Full medical history will be obtained at intial visit. On subsequent visits, changes in history will be assessed if not performed as a part of the patients routine care.
3. Pulmonary function testing will include one or more of spirometry, lung volumes, DL_{CO}. If some or all PFT information is already available from the patient record (performed in the context of usual care) and deemed sufficient by study personnel, PFTs may not be collected.

4. If 6MWD (only at screening visit, 3 month and 6 month visit) is already available from the patient record performed in the contest of usual care) and deemed sufficient by the study personnel, 6MWD may not be collected.
5. Any female patients of child-bearing potential will receive a urine pregnancy test at screening. The test must be negative before MRI. The pregnancy test will be conducted and interpreted by study personnel who have completed appropriate competency training per their institution's guidelines.
6. HRCT will be performed by the study at these intervals if not a part of the patient's usual clinical care.
7. The MRI session will be conducted by the imaging study team, who will provide the necessary volumes of hyperpolarized ^{129}Xe per their standard SOPS.
8. During the 1-hr MRI session, a qualified medical professional (MD, DO, PA, LNP, RN, RT or MT) will be on hand to monitor subjects during MRI and note any symptoms related to xenon MRI or contrast administration.
9. Based on the known pharmacokinetics of xenon, no additional effects are expected after subject is released from the imaging study. However, subjects will be provided contact information for the study coordinator so they can report any concerns over the 24 hours after undergoing MRI and HRCT scan.
10. This will be to monitor the ongoing clinical care of individuals following completion of the MRI portions of the study, for a period of 5 years. This will not involve patient contact but just review of the available clinical information as a part of the individuals IPF care. In particular will focus on changes in lung function, death, lung transplant and changes in IPF therapy.