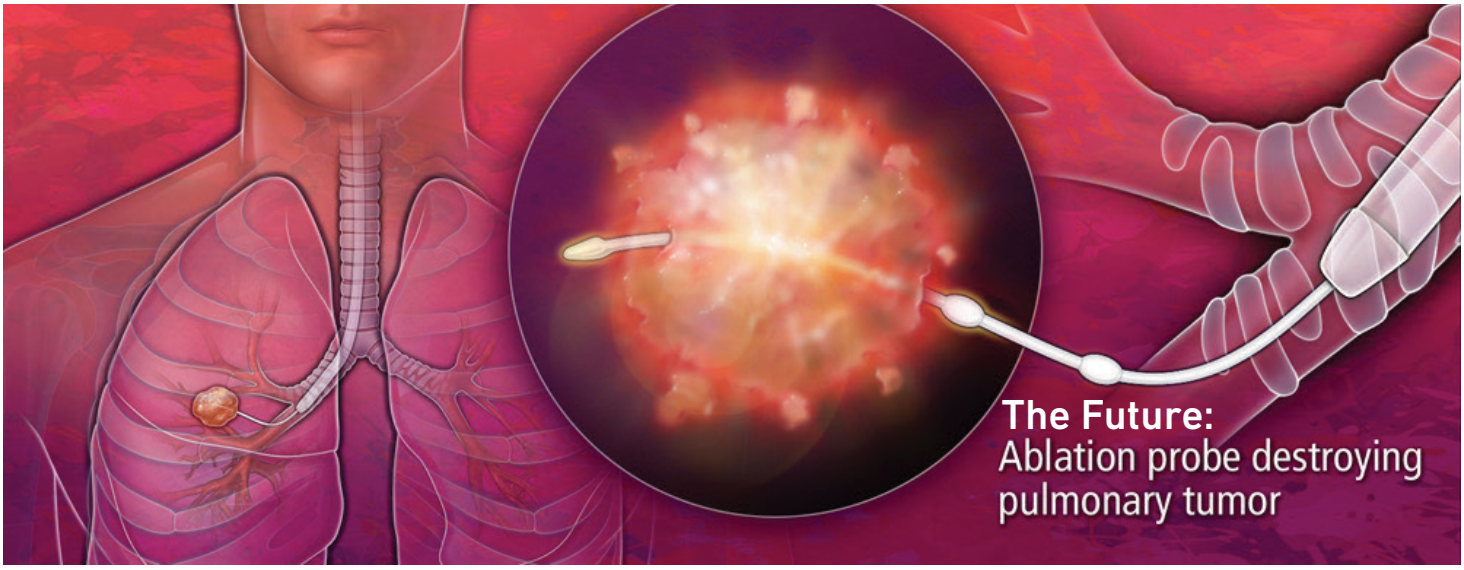
TEMPLE HEALTH

Temple Lung Center | *Updates in research & practice*

# Bronchoscopic Techniques May Be the Future of Lung Cancer Diagnosis, Treatment

By Mark Weir, MBChB, MRCP




**The future of lung cancer treatment may lie in bronchoscopic techniques such as radiofrequency ablation.**

Lung cancer is the leading cause of cancer death worldwide. Stage 1 non-small-cell lung cancer can be effectively cured by surgery or radiotherapy, but Stage 4 lung cancer carries a very poor prognosis. Improved survival depends on diagnosing lung cancer in the early asymptomatic stages; the only effective way of doing this currently is CT-based lung cancer screening to identify nodules for evaluation and risk-stratification (usually those 8 mm or larger). The ability to efficiently biopsy and accurately diagnose CT-identified high-risk lung nodules will be key to improving overall survival of this devastating disease, and bronchoscopic techniques stand to play an increasingly important role.

Bronchoscopic biopsy techniques carry a lower risk of pneumothorax and bleeding compared with CT-guided needle biopsies, a difference that is especially important in patients with other advanced lung disease. However, while bronchoscopic techniques can be combined with simultaneous mediastinal staging, the diagnostic yield is less than transthoracic needle biopsy under CT guidance. However, transthoracic needle biopsy has an increased rate of pneumothorax, and can't be performed in many patients with advanced lung disease or anatomic concerns. Of the three most common bronchoscopic techniques, radial endobronchial ultrasound (R-EBUS), when combined with electromagnetic navigational bronchoscopy (ENB), increases the diagnostic yield—but that varies widely based on operator, nodule location, size and presence of a 'bronchus sign.' Nodules distal to the bronchial tree also pose a diagnostic difficulty for bronchoscopic techniques.

Novel bronchoscopic methods are being developed that will allow improved diagnostic accuracy with minimal complications and may even facilitate treatment of early-stage lung cancer. New image-guided bronchoscopic methods, such as the Archimedes system, are allowing Temple Health to reach previously unattainable nodules using a tunneling technique. Trials are currently underway to determine the efficacy and refinement of this technology, including the recent EAST 2 trial at Temple.

*{continued on page 5}*

# GOLD COPD 2019 INTERNATIONAL CONFERENCE

## Tuesday, November 5, 2019

### Hilton Philadelphia City Avenue — Philadelphia, PA

**HOSTED BY THE TEMPLE LUNG CENTER IN COLLABORATION WITH THE GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)**

# All Together to End COPD

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**Gerard J. Criner, MD, FACP, FACCP**

*Chair and Professor, Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University*

**WHO SHOULD ATTEND**

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**This activity was planned in collaboration with the Global Initiative for Chronic Obstructive Lung Disease and the Temple Lung Center.**

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VOL 3 • ISSUE 2 • FALL 2019

Temple Lung Center
*Updates in research & practice*

The Temple Lung Center is the nation's first entirely multidisciplinary hub for thoracic medicine and surgery. Bringing together basic science and clinical faculty, collaboration among specialties reinforces Temple's leadership in lung transplantation, thoracic surgery, acute and chronic care of pulmonary diseases, clinical and scientific research, and medical education.

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**EMERGENCY PATIENT TRANSFER LINE: 215-707-TRAN (8726)**

A Temple team provided targeted lung denervation to the first three U.S. patients in the AIRFLOW-3 international clinical trial.

# First U.S. Patients Receive Targeted Lung Denervation Therapy at Temple

## *AIRFLOW-3 international clinical trial*

By Gerard J. Criner, MD, FACP, FACCP

Temple introduced a new experimental COPD treatment to the United States in June, completing targeted lung denervation (TLD) procedures on three patients. Gerard J. Criner, MD, FACP, FACCP, Lung Center Director, Chair and Professor of Thoracic Medicine and Surgery at the Lewis Katz School of Medicine, headed the team that treated the first three U.S. patients as part of the AIRFLOW-3 international clinical trial. AIRFLOW-3 is the first interventional COPD trial with a primary end goal to reduce COPD exacerbations. This Phase III trial is currently enrolling at the Temple Lung Center.

The third-leading cause of death worldwide, COPD is characterized by chronic and progressive airflow limitation, and affects approximately 29 million people in the United States. Current COPD treatment focuses largely on anticholinergic medications, which prevent the binding of acetylcholine to airway receptors and thereby reduce the lungs' inflammatory response to viral and bacterial infections, environmental irritants, toxins and allergens that would otherwise result in symptom exacerbation.

Patients with airway hyper-responsiveness, however, may continue to experience frequent exacerbations despite anticholinergic drugs, as neurons release excessive levels of acetylcholine in response to even minor stimuli. The goal of TLD—developed by Nuvaira™—is to interrupt this cycle of nerve signaling by ablating the pulmonary nerves at the level of the bronchus, leading to reduced release of acetylcholine and reduced hyper-reactivity. In addition to its potentially greater efficacy for patients with airway hyper-responsiveness, TLD is a one-time bronchoscopic procedure, which patients may prefer over anticholinergic drugs that must be taken every day.

To discuss enrolling a patient in the AIRFLOW-3 trial, contact 215-707-1359 or breathe@temple.edu. ■

# Case Study: Rapidly Progressive Interstitial Lung Disease with Right Ventricular Failure

*Young father with a devastating diagnosis gets a second chance after receiving a heart and double-lung transplant*

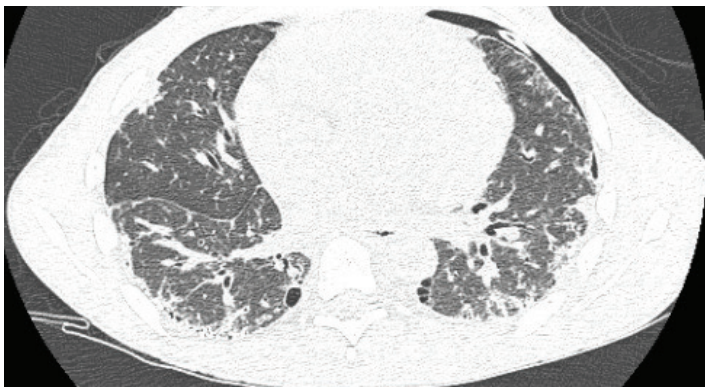


**Image 1: Non-enhanced high-resolution CT scan of thorax demonstrating interstitial lung disease from suspected NSIP, paraseptal emphysema, and left pneumothorax with 8Fr tube.**

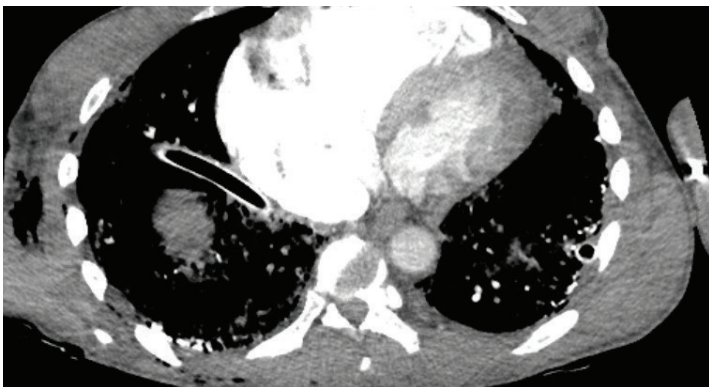


**Image 2: CTA thorax demonstrating a linear defect in the right atrium consistent with clot in transit. Also visualized are dilated right atrium and ventricle with right heart strain, underlying pulmonary fibrosis, and thoracostomy tube.**

A 40-year-old male never-smoker with a past medical history of non-ischemic heart failure, beta thalassemia, sickle-cell trait, and interstitial lung disease presented to the TUH emergency room with chest pain. He was found to have a large left pneumothorax that was treated with tube (8Fr) thoracostomy. A right pneumothorax, a week prior to this presentation, was treated at another hospital. His first abnormal chest X-ray result was found about two years ago at a different emergency room. Since that time, his shortness of breath progressed rapidly.

## Diagnostic Findings

CT scan of the thorax demonstrated interstitial lung disease with paraseptal emphysema. Evaluation for connective tissue diseases revealed a positive ANA as well as positive SS-A and SS-B antibodies, which can be found in lung diseases secondary to connective tissue disorders.

Echocardiogram showed right ventricular dilation with reduced function. Prior records also revealed normal coronaries and normal pulmonary pressures via right heart catheterization one month ago. The non-ischemic cardiomyopathy was believed to be an isolated yet advanced right ventricular cardiomyopathy.

## Clinical Course

- The patient developed an acute left-lower-extremity deep vein thrombosis and pulmonary embolism with clot visualized in his right atrium via echo and CT chest.
- He underwent surgical embolectomy requiring insertion of a centrally placed right ventricular assist device.
- Despite a number of interventions to stabilize his cardiopulmonary status and liberate him from mechanical support, his condition did not improve.

Further evaluation with CT scans and cardiac imaging confirmed that recent insults had resulted in irrecoverable cardiopulmonary failure.

## Treatment

While fully supported by a centrally cannulated mechanical assist device, the patient actively participated in physical therapy. After multidisciplinary evaluation, he was listed for heart and double-lung transplantation. Within the week, he underwent an uneventful transplant.

## Outcomes

He was discharged to home, breathing room air, 44 days after his initial presentation. He reports feeling well and has been enjoying getting back to being an active father for his three children.

## Discussion

The patient's pulmonary embolism unmasked the severity and lethal nature of his rapidly progressive interstitial lung disease and chronic cardiomyopathy. Yet, with a dedicated multidisciplinary team, as well as hard work by the patient and family, even such seriously ill patients may have a second chance at survival.

James C Brown MD, MBA
Assistant Professor of Pulmonary and Critical Care Medicine
Lewis Katz School of Medicine at Temple University

# New Online Tool to Improve AATD Diagnosis

By Frederich Kueppers, MD

Frederich Kueppers, MD

Alpha-1 antitrypsin deficiency (AATD) is associated with lung and liver disease, and less commonly with necrotizing panniculitis (a skin disorder) and a type of vasculitis. Early diagnosis of AATD is crucial to help slow disease progression—yet, because alpha-1 antitrypsin (AAT) levels fluctuate, accurate diagnosis by conventional quantitative blood tests can be challenging. A new algorithm developed at Temple is now available online to help physicians make a more definitive determination of baseline AAT levels and improve diagnostic speed and accuracy.

AAT is normally present in human blood in the concentration of 83–220 mg/dL. The levels are under genetic control so that most people are homozygous for the common normal gene. Patients who carry variant genes, however, may have low levels of AAT: 40–100 mg/dL, depending on the specific variant and combination with normal alleles.

AAT levels are also influenced by other factors: inflammation, infection or injury may cause an "acute phase reaction" that raises concentrations of AAT temporarily to values 100% or more above the baseline levels, which can obscure an underlying deficiency. Levels of AAT and C-reactive protein (CRP) are closely correlated, because they rise together during an acute phase reaction. At the Temple Lung Center, we have developed an online algorithm that factors in CRP levels to adjust for acute phase responses, thereby allowing us to calculate the baseline AAT level. The tool also takes into consideration the most common deficient genotypes. The algorithm is now available as an easy-to-use online calculator: **visit https://predictaat.us**

*{continued from cover}*

## Bronchoscopic Techniques May Be the Future of Lung Cancer Diagnosis, Treatment

Endobronchial ablation treatments are also under investigation.

Interest in robotic bronchoscopic techniques is increasing. Robotic bronchoscopes have a greater degree of maneuverability combined with reduced diameter, and therefore can theoretically make use of much smaller airways to reach a nodule. Two new robotic systems—the Ion system and the Monarch Platform, both FDA approved in 2018–2019—await further use and data collection to confirm their reliability and accuracy in a clinical setting.

An additional image-guided technique under preliminary investigation is cone beam CT biopsy, which could be particularly promising for peripheral lung nodules. Cone beam CT allows for real-time 3D CT guidance and location confirmation (as well as renavigation, if necessary) and appears to have a relatively low-risk profile in preliminary trials. If such techniques prove reliable, researchers speculate that they could then provide a platform for treatment of confirmed cancerous nodules bronchoscopically (with, for example, a radiofrequency ablation catheter), sparing vulnerable patients from invasive surgical procedures. That's all in the future, but the future is looking closer than ever.

To learn more about bronchoscopic nodule biopsy trials at Temple, call 215-707-1359. ■

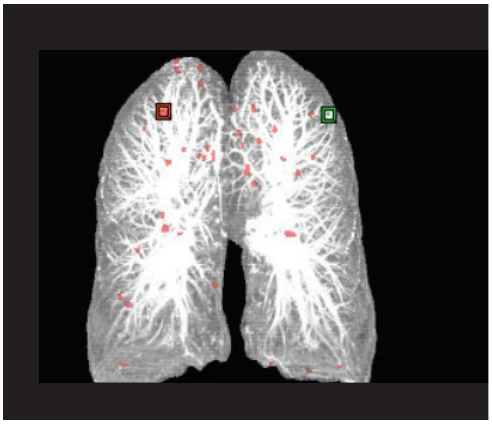
Dale, C.R., et al. 2012. Navigational Bronchoscopy With Biopsy Versus Computed Tomography—guided Biopsy for the Diagnosis of a Solitary Pulmonary Nodule: A Cost-Consequences Analysis. *J Bronchology Interv Pulmonol.* 19(4): 294–303. DOI: 10.1097/LBR.0b013e318272157d

Steinfort, D.P. et al. 2011. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. *Eur Respir J.* 37(4): 902–910. DOI: 10.1183/09031936.00075310

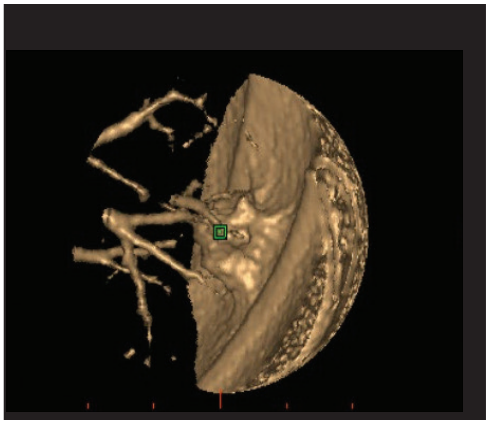
Eberhardt, R., et al. 2007. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. *Am J Respir Crit Care Med.* 176(1): 36–41

# CT and the Fight Against Lung Cancer

By Maruti Kumaran, MD, MBBS, FRCR



CT with computer-aided detection (CAD) of lung nodules.



Volumetric assessment of lung nodule.

Automated lung segmentation helps localize pathologies to assist the surgeon.

Computed tomography (CT) lung-imaging technology has evolved tremendously over the decades since its advent in 1967. Development of faster helical scanners with high resolution has made sub-second scanning possible. This enables us to obtain high-quality images and re-create movement throughout the lungs in dynamic imaging, while sometimes reducing the radiation dose received by the patient. Fast scanning also allows us to obtain imaging scans without patients having to hold their breath for long durations. Modern scanners allow us to view thin slices across lung tissue to pinpoint and examine any issues with greater accuracy.

These advances are now helping us make strides in the early diagnosis of lung cancer. At present, there is no cure and little effective treatment for lung cancer once it reaches a symptomatic stage; catching cancerous lung nodules with imaging screens while they are still small and asymptomatic is our only method for improving survival of the disease. Screening with low-dose CT is currently the most effective tool available for detecting very small, early-stage lung nodules in high-risk patients. These can then be biopsied using needle, bronchoscopic, surgical, or other techniques. Computer-aided CT helps automate nodule detection as well as allowing for volumetric quantification of nodules, thus helping the care team determine diagnostic and treatment course.

CT scans are also useful in the biopsy process; CT-guided needle biopsy remains the most diagnostically efficient biopsy method for lung nodules, with a diagnostic accuracy of more than 90%[1] for lung nodules smaller than 2 cm. Automated lung segmentation based on CT scans (see image above) can also help surgeons localize nodules that are to be removed.

CT is on the front lines of lung cancer diagnosis and treatment; an experienced radiology team with cutting-edge equipment can be a valuable asset for improving detection and survival. ■

1 Ribeiro de Andrade, J., et al. 2018. CT-guided percutaneous core needle biopsy of pulmonary nodules smaller than 2 cm: technical aspects and factors influencing accuracy. *J Bras Pneumol.* 44(4): 307–314. DOI 10.1590/S1806-37562017000000259

# Clinical Spotlight: Collaborative Treatment for ILD Patients with Connective Tissue Disease

By Erin R. Narewski, DO

Connective tissue diseases (scleroderma, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, polymyositis, dermatomyositis and mixed connective tissue disease) in about 11% of patients can be associated with interstitial lung disease (i.e., CT-ILD). Patients may first present with rheumatologic or lung complaints; however, patients usually initially present with manifestations of the connective tissue disease. The CT-ILD may cause inflammation of the lungs or fibrosis, or in some cases, both. Additionally, patients require assessment and treatment of their underlying rheumatologic disorder. Recently, antifibrotic agents have been reported to help attenuate the rate of lung function decline in patients with rheumatologic disease (scleroderma)[1] and in other forms of non-UIP fibrotic lung disease.[2]

The Temple Lung Center, in collaboration with the Temple Department of Rheumatology, has formed a joint clinic specifically for the care of ILD patients with possible connective tissue disease. This clinical partnership allows us to bring collaborative data to multidisciplinary committee discussions and to improve diagnostic accuracy and evidence-based treatment for patients, a particularly important feature as

Erin Narewski, DO

steroid-sparing therapies become more available for use in this population. In addition, this partnership allows for close collaboration on research to fill the medical evidence gap that has long hampered treatment efforts for CT-ILD patients.

All ILD patients should receive careful screening and examination for serologic, symptomatic and physical examination findings suggestive of CTD. If screening suggests CTD as a potential cause of ILD, please consider early referral of your patient to a CT-ILD center of excellence where these patients may receive a thorough evaluation and evidence-based care.

To make a referral to Temple, please call 215-707-5555. ■


1 Distler, O., et al. 2019. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med.* 380:2518–2528. DOI: 10.1056/NEJMoa1903076

2 Flaherty, K., et al. 2019. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med.*, September 29 (online ahead of print). DOI: 10.1056/NEJMoa1908681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**As a national leader in pulmonology and thoracic surgery, we aim to provide updates in research and practice for medical professionals.**

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Philadelphia, PA 19140



# Enrolling Clinical Trials

**For more information, email breathe@temple.edu or call 215-707-1359.**

**Alpha1-antitrypsin Deficiency**

A Phase 3/4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha1-Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects
**NCT02525861**

**Asthma**

Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations; PeRson EmPowered Asthma REIief (PREPARE)
**NCT02995733**

**Bronchiolitis Obliterans Syndrome (BOS)**

Extracorporeal Photopheresis for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts (ECP Registry).
**NCT02181257**

**Chronic Bronchitis**

Gala Early Feasibility Study for the Treatment of Chronic Bronchitis in the United States (Gala_EFS)
**NCT03631472**

**COPD**

Evaluation of the Safety and Efficacy of TLD in Patients With COPD (AIRFLOW-3)
**NCT03639051**

Predicting Sleep, Smoking, and Lung Health Disparities in African American Adults
**NCT03534076**

Losartan Effects on Emphysema Progression
**NCT02696564**

RETHINC: REdefining THerapy In Early COPD for the Pulmonary Trials Cooperative
**NCT02867761**

**Idiopathic Pulmonary Fibrosis (IPF)**

Continuation of Nintedanib After Single Lung Transplantation in IPF Subjects
**NCT03562416**

Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Efficacy and Safety Study with Inhaled RVT-1601 for the Treatment of Persistent Cough in Patients with Idiopathic Pulmonary Fibrosis (IPF): SCENIC Trial
**NCT03864328**

Study of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis (IPF)
**NCT03717012**

A Clinical Study to Test How Effective and Safe GLPG1690 is for Subjects With Idiopathic Pulmonary Fibrosis (IPF) When Used Together With Standard Medical Treatment (ISABELA1)
**NCT03711162**

**Inpatient**

A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning from Mechanical Ventilation in ICU Patients (RESCUE 3)
**NCT03783884**

Autoantibody Reduction for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF)
**NCT03286556**

Extracorporeal CO2 Removal With the Hemolung RAS for Mechanical Ventilation Avoidance During Acute Exacerbation of COPD (VENT-AVOID)
**NCT03255057**

Study to Assess Efficacy and Safety of Baloxavir Marboxil In Combination With Standard-of-Care Neuraminidase Inhibitor In Hospitalized Participants With Severe Influenza
**NCT03684044**

The Frequency of Screening and SBT Technique Trial: The FAST Trial
**NCT02969226**

**Mycobacterium Avium Complex Disease**

Comparison of Two- Versus Three-antibiotic Therapy for Pulmonary Mycobacterium Avium Complex Disease (MAC2v3)
**NCT03672630**

**Pulmonary Arterial Hypertension**

A Study Evaluating the Efficacy and Safety of Ralinepag to Improve Treatment Outcomes in PAH Patients
**NCT03626688**

OPsumit USers Registry (OPUS)
**NCT02126943**

A Registry for Patients Taking Uptravi (SPHERE)
**NCT03278002**

**Pulmonary Hypertension**

A Phase 3 Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients With PH Due to COPD
**NCT03496623**

Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE (INCREASE)
**NCT02630316**

A Randomized, Double-Blind, Placebo-Controlled Clinical Study To Assess The Safety And Efficacy of Pulsed, Inhaled Nitric Oxide (iNO) in Subjects With Pulmonary Hypertension Associated With Pulmonary Fibrosis on Long Term Oxygen Therapy (Part 1 and Part 2)
**NCT03267108**

**Pulmonary Embolism**

First - In - Man Study to Assess the Safety and Feasibility of The Bashir™ Endovascular Catheter for the Treatment of Acute Pulmonary Embolism
**NCT03927508**

An International Pulmonary Embolism Registry Using EKOS (KNOCOUT PE)
**NCT03426124**

Randomized Study to Assess the Safety, Pharmacokinetics/Dynamics of DS-1040b in Subjects With Acute Submassive Pulmonary Embolism
**NCT02923115**

**Pulmonary Fibrosis**

A Dose Escalation Study to Assess the Safety and Efficacy of Pulsed iNO in Subjects With Pulmonary Fibrosis
**NCT03267108**

**Sarcoidosis**

Riociguat for Sarcoidosis Associated Pulmonary Hypertension (RioSAPH)
**NCT02625558**