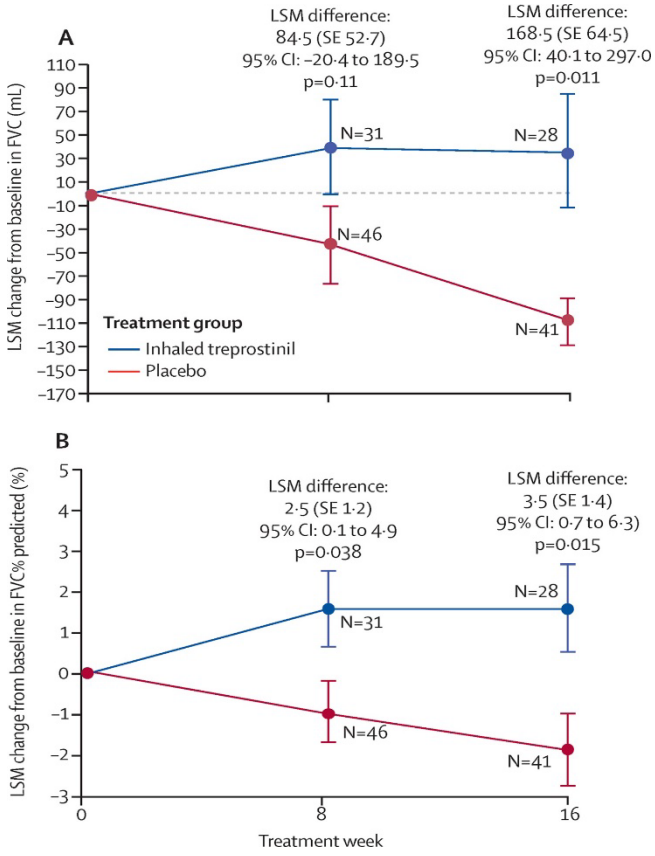
A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Efficacy and Safety of Inhaled Treprostinil in Subjects with Idiopathic Pulmonary Fibrosis

PHASE: III
SPONSOR: United Therapeutics

This study hypothesizes that inhaled Treprostinil will have a positive effect on absolute FVC after 52 weeks of therapy, as compared with placebo when administered to subjects with IPF.

The results of RIN-PH-201 (INCREASE) in patients with pulmonary hypertension (PH) associated with ILD (PH-ILD) provide strong evidence that inhaled Treprostinil may offer a treatment option for patients with IPF.



The pharmacology of Treprostinil is well-characterized, and Treprostinil is also approved for the treatment of pulmonary arterial hypertension (PAH).

Inclusion Criteria:

- ≥40 years of age
- HRCT imaging consistent with UIP or “probable UIP” based on criteria, the absence of atypical features (eg, predominant ground-glass opacity, nodules,

consolidation, etc)

- FVC ≥45% predicted at screening.
- Subjects on pirfenidone or nintedanib must be on a stable and optimized dose for ≥30 days prior to Baseline

Exclusion Criteria:

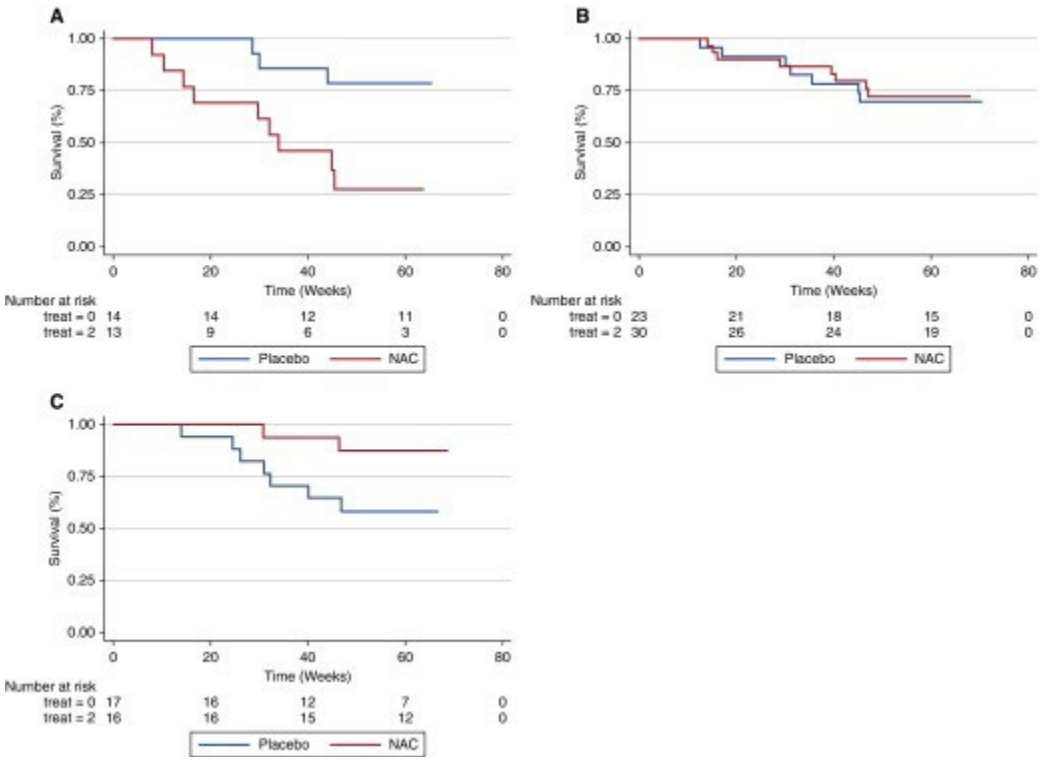
- Concomitant use of both pirfenidone and nintedanib in combination
- Use of any of the following medications: Azathioprine (AZA), cyclosporine, mycophenolate mofetil, tacroliumus, oral corticosteroids (OCS) >20 mg/day or the combination of OCS+AZA+N-acetylcysteine within 30 days prior to Baseline.
- Cyclophosphamide within 60 days prior to Baseline
- Rituximab within 6 months prior to Baseline
- The subject is receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
- Exacerbation of IPF or active pulmonary or upper respiratory infection within 30 days prior to Baseline.
- Uncontrolled cardiac disease, defined by study criteria

Prospective treatment Efficacy in IPF using genotype for Nac Selection (PRECISIONS) trial

PHASE: III
SPONSOR: National Heart, Lung, and Blood Institute (NHLBI)

This study hypothesizes that patients with idiopathic pulmonary fibrosis (IPF) who have the *TOLLIP* rs3750920 TT genotype will exhibit improved clinical outcomes when treated with N-acetyl cysteine (NAC) compared to placebo, while receiving standard care. Standard of care is defined as allowing background therapy with FDA-approved medications for IPF, such as pirfenidone or nintedanib, if taking a stable dose for at least 6 weeks prior to enrollment. NAC is a readily available supplement that is FDA approved for use in conditions such as pneumonia, bronchitis, cystic fibrosis, and post-traumatic chest conditions, and is reported to be well-tolerated.

The figure below summarizes results from the PANTHER-IPF trial, using NAC in patients with IPF:



Oldham et al, Am J Respir Crit Care Med, 2015 Dec 15; 192 (12) 1475-1482

The PRECISIONS study is a multi-center, randomized, double-blind, placebo-controlled trial of 200 participants with *TOLLIP* rs3750920 TT genotype to receive NAC or placebo for a 24-month duration. This Phase III clinical trial's primary objective is to compare the effect of NAC plus standard care vs. placebo plus standard care on the time to a composite endpoint of relative decline in lung function (10% relative decline in forced vital capacity (FVC)), first respiratory hospitalization, lung transplantation, or all-cause mortality in patients diagnosed with IPF who have the TOLLIP rs3750920 TT genotype. Secondary objectives will be to examine the effect of NAC on the components of the primary composite endpoint, the rates of clinical events, change in physiology, change in health status, and change in respiratory symptoms.

Approximately 25 ILD centers will constitute the consortium of sites, selected by the Pulmonary Fibrosis Foundation Clinical Care Network. Subjects will receive 600 mg oral N-acetylcysteine (NAC) or matched placebo three times daily for 24 months.

Inclusion Criteria:

- >40 years of age
- Meets study diagnostic criteria for IPF
- Stable dose of pirfenidone or nintedanib for at least 6 weeks prior to enrollment
- Ascertained rs3570920 TT *TOLLIP* genotype (testing provided by study protocol).

Exclusion criteria:

- Pregnancy or planning for pregnancy
- Significant medical, surgical, or psychiatric illness (including liver and renal failure)
- Use of an investigational drug or biologic agent within the previous 4 weeks
- Supplemental or prescribed NAC therapy
- Listed for lung transplantation at time of screening.

A Randomized, Double-Blind, Placebo-Controlled Phase II Clinical Trial of GKT137831 in Patients with Idiopathic Pulmonary Fibrosis

PHASE: II
SPONSOR: University of Alabama at Birmingham

This study's central hypothesis is that treatment with the NOX1/4 inhibitor GKT137831 will reduce oxidative injury in IPF patients. NOX4 inhibition block fibroblast from transforming into profibrotic myofibroblasts. The primary goal of this multi-center, randomized, double-blind clinical trial is to determine effects of GKT137831 on plasma levels of *o,o'-dityrosine,* a mechanistic biomarker of oxidative stress, in comparison to effects of placebo alone.

A total of 60 subjects will be enrolled from among IPF patients at 5 participating medical centers. Participants will be followed for up to a maximum of 32 weeks, including screening, drug administration (for 24 weeks), and then a final surveillance phone contact 4 weeks later.

Inclusion Criteria:

- 40-85 years of age
- Diagnosis of IPF by study criteria
- Duration of IPF <10 years
- FEV1/FVC >70% of predicted values.

Exclusion Criteria:

- Comorbidities that would interfere with study participation
- History of malignancy within the past 5 years
- Acute infection requiring systemic antibiotic therapy within 2 weeks prior to screening
- Recent treatment with prednisone or immunosuppressant therapy
- History of bone marrow disorder or marked anemia
- Severe cardiovascular disease, end-stage renal disease, listed for lung transplantation at time of enrollment, and/or elevated liver enzymes.