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

(GKT137831-IPF)

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Version 8.0, April 5, 2021

SPONSOR SIGNATURE PAGE

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

PROTOCOL NUMBER: IRB-300003198

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Date: April 5, 2021

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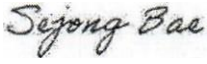

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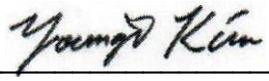

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INVESTIGATOR STATEMENT:
I agree to conduct the above-entitled study in accordance with the terms and conditions of this protocol, ICH GCP guidelines, the provisions of the Declaration of Helsinki and with all applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

I agree to conduct the study in person or to supervise the trial.

I agree to ensure that all who assist me in the conduct of the study are aware of their obligations.

Site Investigator:

Signed: _____ Date: _____

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Title:

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PROTOCOL SYNOPSIS

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Phase II Clinical Trial of GKT137831 in Patients with Idiopathic Pulmonary Fibrosis
Protocol Number:	IRB-300003198
NCT#:	NCT03865927
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Version # and Date:	Version 8.0, April 5, 2021
Clinical Phase:	Phase II clinical trial
Trial Site:	Multi-Center Trial
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Sponsors:	UAB
Study Rationale:	On the basis of substantial preliminary data, we hypothesize that reactive oxygen species (ROS) generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzymes play an important role in the development of idiopathic pulmonary fibrosis (IPF). In particular, GKT137831 has shown marked efficacy in preclinical models of IPF, including the prevention of myofibroblast activation, regression of fibrosis, and improved survival. GKT137831 is an orally available small molecule inhibitor of NOX 1 and 4, which has shown therapeutic efficacy and good safety and tolerability in patients with fibrotic liver disease. We hope that treatment with GKT137831 could result in significant benefit for a lung disease that has, until now, been almost invariably inexorable. This clinical trial has the potential to profoundly affect current paradigms and treatment approaches to patients with IPF.
Study Objectives:	The primary goal of this multicenter, randomized, double-blind, Phase II clinical trial is to determine effects of GKT137831 on plasma levels of *o,o'-dityrosine*, a mechanistic biomarker of oxidative stress, in comparison to effects of placebo alone. Drug effects on validated clinical endpoints will be also assessed, including forced vital capacity (FVC) and six-minute walk distance (6MWD). We anticipate the findings of this study will lead to larger incremental trial(s) to definitively establish the clinical efficacy and favorable safety profile of this treatment.
Study Hypothesis:	Our central hypothesis is that treatment with the NOX1/4 inhibitor GKT137831 will reduce oxidative injury in IPF patients
Study Aims:	1. To conduct a proof-of-concept, mechanistically-driven, double-blinded, placebo-controlled trial, to examine effects of GKT137831 administration on a surrogate measure of oxidative stress and pulmonary injury in IPF patients. 2. To determine effects of GKT137831 administration in IPF patients, compared to placebo, on four secondary efficacy endpoints: (a) levels of collagen degradation product, C1M, measured in sera by ELISA; (b) and forced vital capacity (FVC) at baseline and 24 weeks. Also (c) six-minute walk distances (6MWD) will be measured at baseline and 24 weeks; and (d) adverse events (AE) will be recorded throughout the subject's participation in this study.

Study Design:	Following screening assessments, IPF patients who meet all inclusion/exclusion criteria will be randomly assigned to receive one of the following treatments in a ratio of 1:1: • **Arm A** (n=30) **– GKT137831 Treatment**: GKT137831 will be administered orally, at a dose of 400 mg bid, for a total of 24 weeks. • **Arm B** (n=30) **- Placebo Treatment**: Arm B subjects will receive matching placebo for the same duration. Participants will be followed in face-to-face visits with trial personnel every 6 weeks for 24 weeks to assess drug effects and monitor safety during their treatments, and by phone surveillances one month thereafter.
Planned Sample Size:	A total of 60 subjects will be enrolled in this multi-center trial from among IPF patients at 5 participating medical centers.
Duration of Study:	Up to a maximum of 32 weeks, including screening (4 weeks maximum), drug administration for 24 weeks, and then a final surveillance phone contact 4 weeks later.
Inclusion Criteria:	1) Age between 40-85 years old. 2) A diagnosis of IPF that fulfills current ATS/ERS Consensus Criteria (1). 3) IPF duration <10 years, based on the date of definitive diagnosis. 4) Ability and willingness to give informed consent and adhere to study requirements. 5) Ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) >70% of predicted values
Major Exclusion Criteria:	1) Diagnosis of major comorbidities expected to interfere with study participation 2) History of malignancy within the last 5 years, excluding basal or squamous cell skin cancer and low-risk prostate cancer, the latter defined as stage T1 or T2a, with prostate specific antigen <10 ng/dl. NOX inhibition is not known to promote cancer, and these criteria are within current guidelines. 3) The occurrence of any acute infection requiring systemic antibiotic therapy within 2 weeks prior to Screening (Visit 1).

	4) Treatment for >14 days within the preceding month with >20 mg. prednisone (or equivalent) or any treatment during the last month with a cellular immunosuppressant (e.g., cyclophosphamide, methotrexate, calcineurin inhibitors, etc.), given increased risks of opportunistic infections. 5) Treatment with any investigational agent within 4 weeks of Screening (Visit 1) or 5 half-lives of the investigational medicinal product (whichever is longer). 6) Fertile women who do not agree to abstinence or an effective form of contraception (as approved by the investigator), or who are breast feeding, for 4 weeks before randomization until 90 days after the last administration of study medication (or placebo). 7) Men who are not surgically sterile and do not agree to remain abstinent from heterosexual intercourse or use effective contraception (as approved by the investigator), and refrain from donating sperm, from the time of giving informed consent until 90 days after the last administration of study medication (or placebo). 8) Subjects with known hypersensitivity to GKT137831 or its excipients (e.g. capsule "bulking" agents). 9) A history of bone marrow disorder including aplastic anemia, or marked anemia defined as hemoglobin < 10.0 g/dL (or 6.2 mmol/L). 10) Severe cardiovascular disease, defined as any of the following within the preceding 12 weeks: acute myocardial infarction or unstable angina, a coronary revascularization procedure, congestive heart failure (NYHA Class III or IV), or stroke, including a transient ischemic attack. 11) Evidence of cardiac conducting abnormalities, defined as second or third degree AV block not successfully treated with a pacemaker, or a personal or family history of long QT syndrome (QTc interval >450 msec for males or 470 msec for females). 12) End-stage renal disease requiring dialysis. 13) Undergoing transplantation evaluation, or listed with the United Network for Organ Sharing (UNOS) as a lung transplantation candidate at the time of enrollment in this trial. 14) Liver function tests (transaminases, alkaline phosphatase, direct and total bilirubin) >3x upper limit of normal values.

	15) Systemically administered potent CYP3A4 **inhibitors or inducers** are prohibited during the 24-week treatment period. **Inhibitors** include: boceprevir, cobicistat, conivaptan, ritonavir, itraconazole, ketoconazole, telaprevir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir. **Inducers** incude carbamazepine, enzalutamide, mitotane, phenytoin, rifampin. See also: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2
Study Endpoints:	• **Primary efficacy endpoint:** The primary efficacy endpoint is change in plasma *o,o'-dityrosine,* as determined by mass spectroscopy, from baseline to Week 24. • **Secondary efficacy endpoints:** Secondary efficacy endpoints are: (a) collagen degradation products, (e.g., C1M), measured in sera by ELISA; (b) forced vital capacity (FVC); and (c) six-minute walk distance (6MWD) comparing baseline to values at 24 weeks.
	• **Safety:** Adverse events (AEs) that occur anytime during the duration of the trial. Clinical laboratory evaluations will occur at Screening, baseline/Day 1 and Weeks 6, 12, 18, and 24. Urinalysis will be performed at Screening, baseline/Day 1 and Weeks 6, 12, 18, and 24. Pulse rate, SBP and DBP are recorded at Screening, baseline/Day 1 and Weeks 6, 12, 18, and 24. Body weight at Screening, baseline/Day 1 and Weeks 6, 12, 18, and 24. 12-lead ECG at Screening, baseline/Day 1 and Weeks 6, 12, 18, and 24.
	• **Pharmacokinetics (PK):** Plasma concentrations of GKT137831 and its main phase 1 metabolite, GKT138184. The plasma concentrations will be subjected to population PK analysis to estimate population PK parameters such as clearance and volume of distribution and associated inter-individual variability (IIV), and to determine predictors of IIV. PK-PD analysis will be carried out using the primary endpoint and selected secondary endpoints in order to explore any potential PK-PD relationships.

1. OBJECTIVE, SPECIFIC AIMS, BACKGROUND, AND SIGNIFICANCE

1.1 OBJECTIVE

The primary goal of this randomized, multi-center, double-blind, placebo-controlled Phase II clinical trial is to determine the effects of the NOX1/4 inhibitor GKT137831 on plasma levels of *o,o'-dityrosine*, a mechanistic biomarker of pulmonary oxidative stress and injury, among IPF patients. Drug effects on validated clinical endpoints including FVC and 6MWD will be also assessed. We anticipate the findings here will lead to larger incremental trial(s) to determine actual clinical efficacy of this treatment.

1.2 SPECIFIC AIMS

Central Hypothesis: Our primary hypothesis is that treatment of IPF patients with the NOX1/4 inhibitor GKT137831 will reduce pulmonary oxidative injury, as ascertained by reductions in plasma levels of a mechanistic surrogate biomarker (*o,o'-dityrosine)*. A corollary of this hypothesis is that treatments that reduce oxidative injury in these patients will have a favorable effect on the natural history of IPF.

The studies proposed here are primarily designed to determine the magnitude of the ROS metabolite reduction and further assess safety of GKT137831 in IPF patients. Nonetheless, we hope that experimental treatments may result in clinically-relevant beneficial effects, as determined by secondary endpoints that include preservation of forced vital capacities and ability to ambulate.

The Specific Aims of this Trial are:

1. To conduct a double-blinded, placebo-controlled Phase II clinical trial in 60 ambulatory IPF subjects at five major medical centers. Subjects will be randomized 1:1 to GKT137831 or matching placebo, and treated for six months. The primary endpoint of this trial will be treatment effects of the experimental drug on plasma levels of *o,o'*-dityrosine, measured by mass spectroscopy pretreatment and at six-week intervals.

   We hypothesize the experimental therapy will reduce plasma levels of o,o'-dityrosine, reflecting target engagement of the drug, and reductions of oxidative stress and injury.

2. To determine the efficacy of GKT137831 therapy in IPF patients, compared to placebo, on four secondary endpoints, measured at baseline and at six-week intervals of: (a) collagen degradation product, C1M, measured in sera by ELISA; and (b) FVC; (c) and 6MWD at baseline and 24 weeks week intervals.

   We hypothesize the experimental therapy will decrease circulating levels of C1M. Although the short-duration treatment in this Phase II clinical trial may not result in significant effects on the secondary clinical endpoints, the results of these studies will be critical for the design and power analyses of future GKT137831 Phase III trials. Moreover, this as-of-yet untested drug treatment for IPF may prove to be very effective, and these measures will enable us to detect an unprecedented benefit of this novel approach.

3. To assess the safety and tolerability of GKT137831 in patients with IPF. The incidence and severity of AEs, laboratory tests and ECG abnormalities will be assessed over the course of the trial.

   We hypothesize that GKT137831 will have a favorable safety and tolerability profile in IPF patients. There is considerable clinical experience with this compound. To date, over 240 human subjects have been exposed to GKT137831. Completed clinical studies include 4 Phase I studies in healthy subjects, and a Phase II trial in patients with diabetic kidney disease. In addition, GKT137831 is currently being assessed in 2 additional Phase II trials in patients with diabetic kidney disease (DKD) and primary biliary cholangitis (PBC), respectively. To date, no dose limiting toxicity and no safety signals have been identified. There is a major need for effective and well-tolerated therapies for IPF.

This seminal clinical trial could provide evidence that NOX1/4 inhibition is safe and beneficial in IPF patients. Results of this study will help to confirm and establish methods, validate endpoints, and provide the rationale that will facilitate and justify subsequent larger, longer trials to more definitively evaluate the clinical benefits of NOX inhibitors in IPF. *This research has the potential to be paradigm-shifting, will fill several existing gaps, and could ultimately prolong the lives of many patients with this morbid lung disorder.*

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

1.3 BACKGROUND INFORMATION

1.3.1 Idiopathic Pulmonary Fibrosis (IPF):

IPF is an enigmatic fibrotic lung disease that has an estimated annual incidence of 100,000 patients in the U.S. (1). Many other cases likely go undiagnosed, and the frequency of this disorder appears to be increasing (2,3). This morbid syndrome occurs almost exclusively in older adults. IPF is characterized by pathological accumulations of cross-linked lung extracellular matrix proteins (ECM) produced by fibroblasts, and their activated, differentiated progeny (e.g., myofibroblasts [myo-Fb]). The disease manifests with progressive, unremitting dyspnea and hypoxemia. Although two drugs were recently approved for treatment of IPF, the benefit of these agents appears to be mostly limited to slowing the progression of pulmonary restriction (4,5). IPF continues to have a median survival of 3-4 years after diagnosis, which is a worse prognosis than many common malignancies.

Given the impact and lethality of IPF, and only partial effectiveness of currently available therapeutics, there is an obvious and compelling need to develop new, more efficacious, mechanistically-based medical treatments for this disorder.

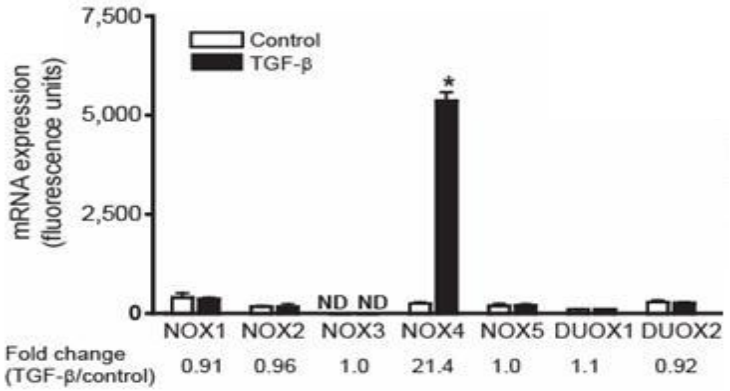
1.3.2 Oxidative Stress in IPF:

Although the etiology of IPF is unknown, several lines of evidence indicate oxidative stress plays an important role in the pathogenesis of this disease (6-8). Studies of lung tissue from IPF patients demonstrate “signatures” of chronic oxidative damage to the alveolar epithelium (9,10). The cellular/enzymatic sources of ROS in fibrotic lungs have traditionally been attributed to alveolar inflammatory cells (11-14). However, recent studies indicate that myofibroblasts (myo-

Fbs), key effector cells of fibrogenesis, also contribute to oxidative stress in fibrotic disorders (15-18). Recent studies have shown the pro-fibrotic cytokine transforming growth factor-β1 (TGF-β1) is a potent inducer of extracellular hydrogen peroxide (H_2O_2) production by human lung myo-Fbs (19-22). The enzymatic source of ROS production in myo-Fbs is a member of the NOX family of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidases, specifically NOX4 (15,23,24).

1.3.3 NOX4 Mediates myo-Fb Activation:

The biochemical and functional characteristics of NOX4 are distinct in comparison to other NOX homologs in that extracellular generation of H_2O_2 (vs $O_2^{\cdot-}$) is a consistent and unique feature of the former (25-29). NOX4 has been identified as one of the most highly induced genes in a whole-genome Affymetrix analysis of human lung fibroblasts stimulated with TGF-β1; other members of the NOX gene family were not affected at the mRNA level (**Fig. 1**). These data implicate NOX4 as the primary enzymatic source of TGF-β1-induced extracellular H_2O_2 generation by differentiated myofibroblasts. Importantly, NOX1 was not identified in these cells or in human IPF myo-Fbs.



TGF-β1-induced activation cellular H_2O_2 is specific to

Pharmacologic or RNAi-mediated inhibition of NOX4 expression/activity has been shown to significantly inhibit TGF-β1-induced myo-Fb H_2O_2 production, ECM synthesis, and contractility (15). Together, these studies indicate a critical role for NOX4-dependent H_2O_2 in conferring synthetic and contractile properties to myo-Fbs that differentiate under the influence of TGF-β1.

1.3.4 NOX4 is Expressed in Bleomycin-Induced Lung Injury:

The role of NOX4 in injury-induced fibrosis has been studied in a murine model of lung injury. Intra-tracheal instillation of bleomycin induces epithelium injury in mice that leads to fibrosis, which peaks 2-3 weeks post-injury (15,30). NOX4 expression was induced in a time-dependent manner after the induction of lung injury, increasing from day 7 up to day 28 (**Fig. 2**), supporting a temporal relationship between NOX4, myo-Fbs activation, and fibrosis. In contrast, expression of the NOX2 isoform, which is predominantly expressed in phagocytic cells, was increased on day 7 and returned to baseline levels at later time-points when inflammatory responses have subsided (**Fig. 2**).

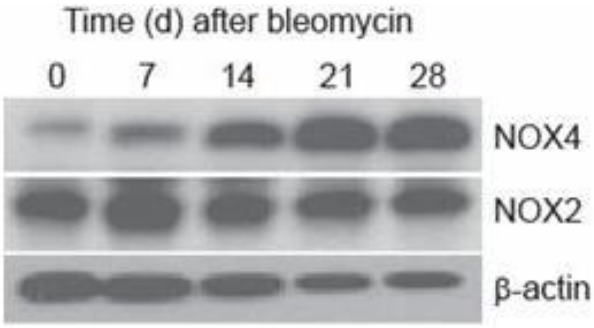


Figure 2: Expression of NOX4 and NOX2 in the lung following bleomycin-induced lung fibrosis.

1.3.5 Myo-Fb-Generated H_2O_2 Mediates *o,o'*-dityrosine-Dependent ECM Crosslinking:

The ECM overlying TGF-β1-stimulated Fbs has been previously shown to be susceptible to crosslinking reactions on L-tyrosine residues (21). A Genbank database search of the number and % tyrosine residues in 11 different ECM proteins was performed to identify endogenous targets for these residues. Of these candidate proteins, fibronectin demonstrated the highest number and % tyrosines (90 total residues; 3.84% of all amino acids). We tested to see if fibronectin co-localizes with the crosslinking reactions of tyramide FITC with endogenous tyrosine residues on the ECM proteins (**Fig. 3**); this demonstrated that fibronectin immunoreactivity is closely associated with the tyramide-FITC signal, which suggests that tyrosine residues on fibronectin may be susceptible to phenol:phenol (tyrosine:tyramide-FITC) crosslinking. This tyramide-FITC labeling reaction is present only in TGF-β1-treated cells in the presence of heme peroxidase, horseradish peroxidase (HRP), is abolished by diphenyleneiodonium (DPI) co-treatment and is markedly reduced by catalase. These findings support the requirement for heme peroxidase-catalyzed, oxidative crosslinking of ECM-associated fibronectin. However, the turnover of oxidatively modified ECM proteins in the lung and their potential release into the circulation has not been well characterized.

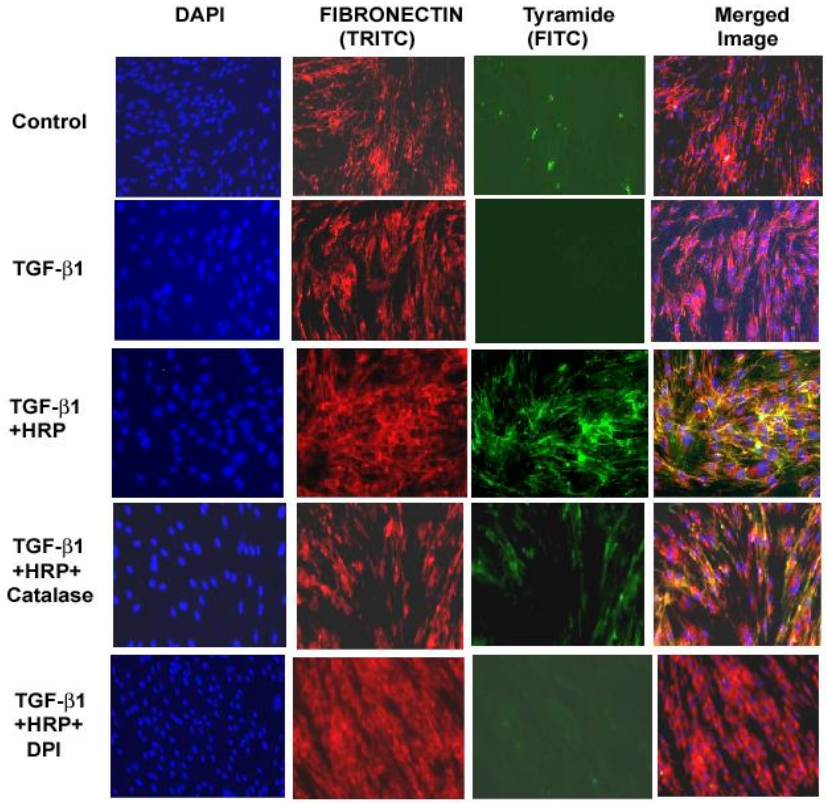


Figure 3: Fibronectin co-localizes with H_2O_2-dependent, peroxidase-catalyzed crosslinking reactions. Fbs were stimulated with TGF-β (2 ng/ml) for 16 h to generate myo-Fbs that generate extracellular H_2O_2; they were then incubated with horseradish peroxidase (HRP), and the tyrosine analog, tyramide-FITC, for a period of 1h at 37°C. Cells were then fixed and stained with a monoclonal antibody to fibronectin and a TRITC-conjugated secondary antibody (left panel). The FITC-generated signal co-localizes with the fibronectin-TRITC label only under conditions of H_2O_2 generation and peroxidative activity.

1.3.6 Evidence of *o,o'-dityrosine* Formation in IPF Fibroblast Foci:

In-vitro data in TGF-β1-stimulated myo-Fbs suggests that heme peroxidase may catalyze dityrosine-dependent protein crosslinking (**Fig 3**). Immunohistochemical (IHC) staining of IPF lung tissue using a monoclonal antibody to o,o'-dityrosine shows this moiety is specifically expressed in fibroblastic foci, a hallmark lesion of IPF (**Fig. 4**).

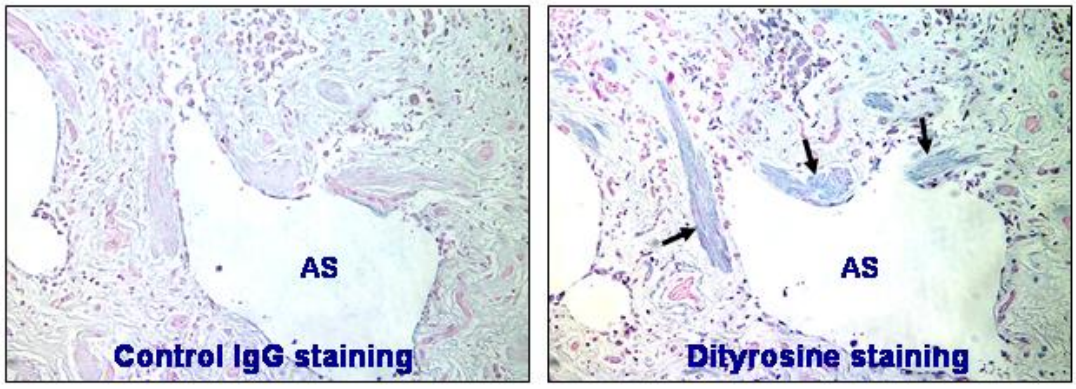


Figure 4: Fibroblastic foci in UIP/IPF demonstrate expression of dityrosine, a marker of oxidative protein cross-linking reactions. IPF tissue sections were stained with a mouse monoclonal antibody (1:50 dilution) against dityrosine by immunohistochemistry (TruBlue). Control staining was with biotinylated secondary IgG antibody. Intense staining of dityrosine was identified primarily in fibroblastic foci around alveolar spaces (AS). Arrows point to dityrosine-expressing (blue staining) fibroblastic foci in UIP/IPF.

These findings have been interpreted as evidence the myo-Fbs within these foci actively secrete H_2O_2, which then induces the formation of oxidatively- modified proteins by a o,o'-dityrosine-dependent mechanism.

1.3.7 Plasma levels of *o,o'*-dityrosine Are Increased in IPF Patients:

Tyrosine residues in proteins are susceptible to covalent oxidative modifications, including the formation of *o,o'*-dityrosine (31) (**Fig. 5**). Since these covalent modifications are stable, protein tyrosine (P-Tyr) modifications in circulating plasma may serve as a potential biomarker of oxidative injury.

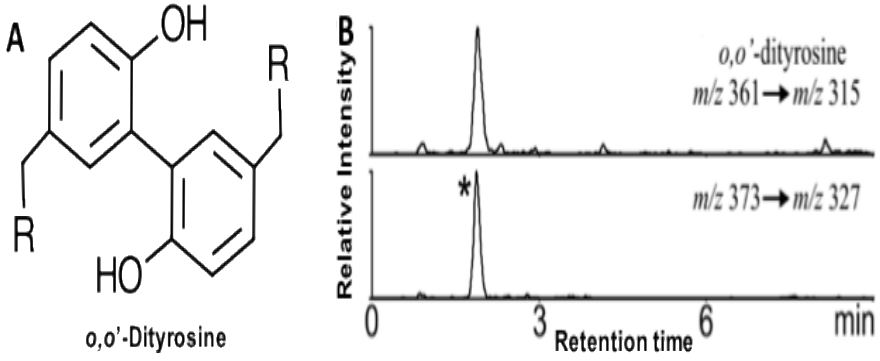


Figure 5: Chemical structure and extracted ion chromatograms measures of soluble *o,o'*-dityrosine. (A) Chemical structure of *o,o'*-dityrosine. 'R' represents the α-carbon linking the peptide bonds within a protein molecule. (B) Chromatogram from plasma of a subject with IPF. The protein hydrolysate from plasma samples were separated by reverse phase HPLC and subjected to ESI/MS. Extracted ion chromatograms were derived from the MRM transitions for *o,o'*-dityrosine. The ratio of ion currents for each amino acid compared with the internal standard (depicted by *) was utilized to quantify the levels of *o,o'*-dityrosine; note co-elution of authentic oxidized amino acid to the corresponding isotopically labeled internal standard.

We found plasma concentrations of *o,o'*-dityrosine were much greater among IPF patients (8.51 ± 0.94 μmol/mole tyrosine) compared to healthy controls (0.47 ± 0.07 μmol/mole tyrosine) (**Fig. 6**). The respective values for individuals within these two groups were almost completely separated and, overall, there was an 18-fold intergroup difference.

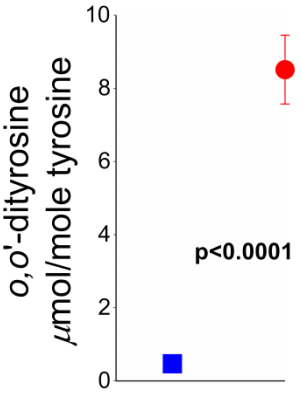


Figure 6: ***o,o'*-dityrosine is increased in plasma of IPF patients**. Plasma from IPF and healthy control subjects were analyzed by mass spectrometry for *o,o'*-Dityrosine, n=42 healthy control subjects, n=32 IPF subjects; values represent mean ± SEM.

1.3.8. The NOX1/4 Inhibitor GKT137831 Reverses Established Fibrosis:

Aged mice (18 months old) have impaired capacity for fibrosis resolution after bleomycin injury compared to young mice (2 months) (32). This model was used to test whether delayed administration of GKT137831 in aged mice results in reversal of the persistent fibrosis. The GKT137831-treated mice exhibited decreased myo-Fb accumulation (**Fig. 7A**). Recovery to baseline weights was also observed in these animals, whereas vehicle-treated (control) mice remained below baseline levels throughout the 6-week observation period (**Fig. 7B**). Most importantly, GKT137831 treatment led to a reversal of age-associated persistent fibrosis (**Figs. 7A** and **7C**), and a reduction in mortality (**Fig. 7D**). These data suggest that GKT137831 treatment in a model of persistent fibrosis leads to modulation of myo-Fb phenotype/fate that bespeaks for the potential reversibility of established lung fibrosis.

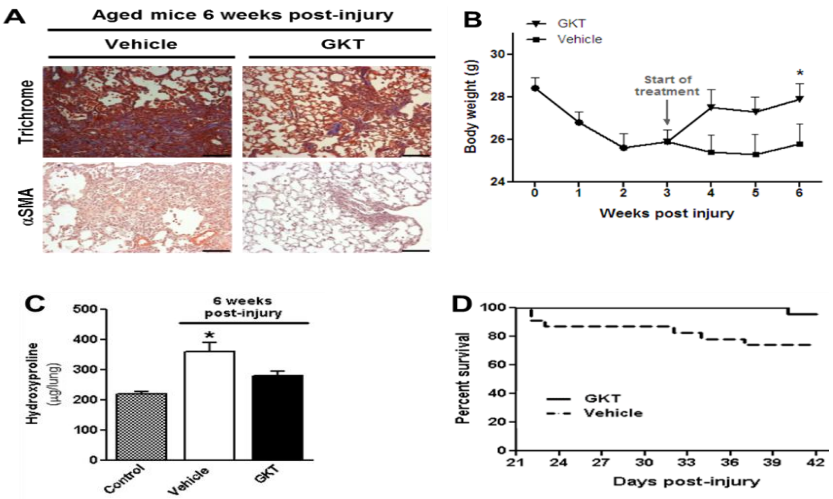


Figure 7: ***In vivo* pharmacological targeting of NOX4 with GKT137831 leads to reversal of age-associated persistent fibrosis.** (**A to D**) Aged mice (18 months old) were subjected to bleomycin-induced lung fibrosis. Mice were treated daily with GKT137831 (40 mg/kg) or vehicle by oral gavage starting at 3 weeks after injury, through week 6 (21 treatments total). Body weight of the mice was recorded weekly (**B**). Values represent means ± SEM; n = 17 to 21 per group; *$p < 0.05$ (**A and C**) Lung tissues were harvested from

control (uninjured) mice or mice at 6 weeks after injury. Tissues were evaluated by Masson's trichrome blue staining for collagen and by IHC analyses to evaluate expression of α-SMA. Whole-lung homogenates were analyzed by quantitative hydroxyproline assay (**C**). Data are expressed as total micrograms of hydroxyproline per whole lung. Values represent means ± SEM; n = 9 to 10 per group; *p < 0.05. Kaplan-Meier survival curve for GKT137831-treated (n = 22) and vehicle-treated (n = 23) mice (**D**). P < 0.05, log-rank test. Scale bars, 100 mm.

1.3.9. GKT137831 Reduces Plasma Levels of *o,o'*-dityrosine Mice with Lung Injury:

The effects of GKT137831 on plasma levels of ROS-associated biomarkers was tested in mice with and without bleomycin-induced lung injury. Bleomycin treatment again resulted in a striking increase in plasma levels of *o,o'*-dityrosine (Figure 8), analogous to findings in humans with IPF (see Section 1.3.7). Most importantly, GKT137831 therapy resulted in >5-fold reductions of plasma *o,o'*-dityrosine among the bleomycin-treated animals with pulmonary fibrosis. This GKT137831 treatment effect on *o,o'*-dityrosine was of a greater magnitude and more significant than reductions of other ROS biomarkers (3'-nitrotyrosine and 3'-chlorotyrosine) (data not shown).

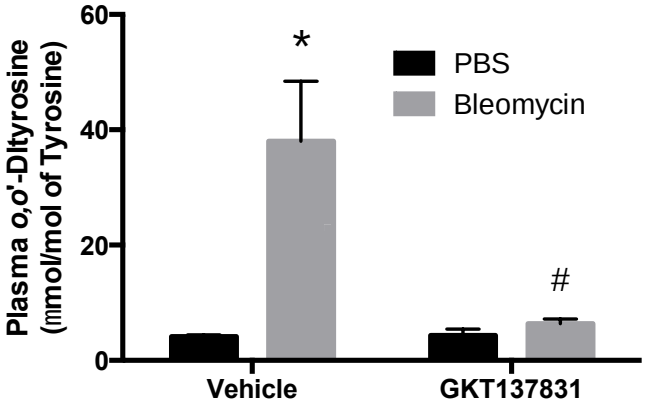


Figure 8. GKT831 administration causes *in vivo* reductions of mechanistic ROS biomarker *o,o'*-dityrosine. Aged female B6 mice were treated with intra-tracheal bleomycin or saline, and then GKT831 (40 mg/kg) was administered daily by gavage. While bleomycin treatment resulted in large increases in circulating *o,o'*-dityrosine, levels of this metabolite were normalized by GKT831 therapy. N=6 in GKT831-treated groups, # denotes p = 0.012).

1.3.10. Plasma levels of C1M are increased in human IPF subjects

Collagen degradation products are generated by proteolytic cleavage of ECM by matrix metalloproteinases (MMPs). Circulating concentrations of collagen digest fragments are reflective of ECM turnover, and several are prognostic of disease activity in IPF (16). C1M, which is a product of collagen 1 degradation by MMP-2/9/13, had the most favorable operating characteristics for prediction of IPF patient outcomes (16). Baseline C1M serum concentrations discriminated IPF vs. normal subjects (p = 0.001), (**Fig. 9A**), and these were also significantly higher in patients with progressive IPF compared to patients with stable disease (p=0.012). Longitudinal rates of later increases in C1M levels from baseline values were also predictive of mortality (**Fig. 9B**).

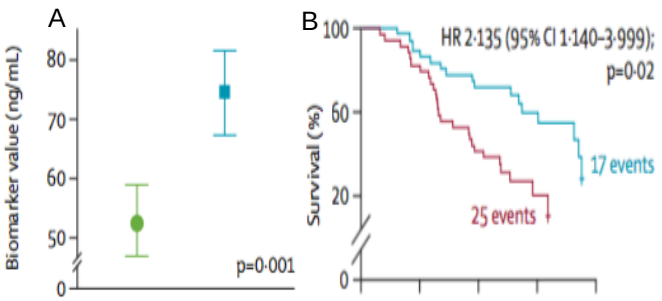


Figure 9: **C1M is increased in IPF patient plasma**. Plasma from IPF and healthy control subjects were analyzed by ELISA. A) Concentrations of C1M were significantly higher at baseline in IPF subjects (closed squares) than in healthy control subjects (closed circles). B) Mortality risk is greater in IPF subjects with increasing C1M concentrations relative to those with stable or falling concentrations. Values represent mean ± SEM. Figures from (16).

1.3.11. Summary of Non-Clinical Studies with GKT137831

A broad range of *in vitro* and *in vivo* pharmacology studies have been conducted to support the use of GKT137831 in several indications. Detailed summaries for all studies are given in Section 4.1. GKT137831 selectively inhibits human isolated NOX4 (Ki .09 µM) and NOX1 (Ki 0.15 µM) but is considerably less active at inhibiting isolated human NOX2 (Ki 2.13 µM), NOX3 (Ki 0.36 µM) and NOX5 (Ki 0.33 µM). This selectivity against NOX2 means that GKT137831 does not compromise phagocyte function. Moreover, GKT137831 was inactive against the non-NADPH oxidase flavoprotein xanthine oxidase, and inhibited glucose oxidase with an IC_{50} of 5.7µM, indicating selective inhibition of ROS generation via the NADPH oxidase pathway. Meanwhile, GKT137831 reduced DPPH with an IC_{50} of 20µM, suggesting that GKT137831 is a weak electron donor, and therefore has weak antioxidant activity. Investigation of potential effects against a broad range of receptors and enzymes confirmed that GKT137831 demonstrated no significant off-target binding, except for human recombinant 15-lipoxygenase-2 (IC_{50} 0.26). However, review of the literature suggests this inhibitory activity does not represent a safety concern.

Similarly, a literature review on the effect of gene deletion of NOX isoforms indicated that no basal phenotype has been associated with NOX1 or NOX4 gene deletion in mice. Specifically, there are no reported defects in fertility, embryonic development, life span, animal behavior or breeding. These observations did not identify potential safety concerns related to chronic inhibition of NOX1 and/or NOX4.

GKT137831 and GKT138184 (the major active metabolite) have limited selectivity (about two-fold) against the human NOX5 isoform. NOX5 is not present in rodent genomes and as a consequence there is scarce information about the function of this isoform (33). The NOX5 gene is found in other mammals such as dog or human and has been reported to be expressed in spleen, testis, fetal tissues, pancreas, atherosclerotic coronary arteries, prostate and prostate adenocarcinoma (34). The understanding of NOX5 function is still limited but there is some evidence for functional NOX5 in spermatocytes and for a role of ROS in sperm maturation and function and therefore these parameters were investigated in the chronic dog toxicology studies conducted with GKT137831. There were no treatment related effects following GKT137831 administration on sperm motility, mortality or morphology at any dose tested confirming a lack of adverse effects related to NOX5 inhibition.

Overall, there are no observations from the available literature to indicate safety concerns associated with chronic pharmacological inhibition of NOX1, NOX4 and NOX5.

In *in vitro* studies in isolated cells including primary human hepatic stellate cells, GKT137831 was shown to attenuate the induction of multiple fibrogenic pathways including TGF-β1, PDGF, TLR4, Hedgehog, and angiotensin 2. Specifically, GKT137831 markedly reduced the induction of markers of myofibroblast activation including αSMA, fibronectin, and pro-collagen 1 (35).

In addition, GKT137831 has shown potent anti-inflammatory effects including included reduced expression of adhesion molecules, cytokines, and chemokines. These effects were observed in human podocytes (36-38), primary human hepatic stellate cells (35, 39), macrophages, human endothelial cells (40, 41), and in rat retinal microglial and Müller cells (42).

These direct anti-inflammatory and anti-fibrogenic effects translated in anti-inflammatory and anti-fibrotic activity in multiple *in vivo* models of liver fibrosis. Specifically, GKT137831 attenuated the development of liver fibrosis induced by experimental cholestasis (bile duct ligation and MDR2$^{-/-}$ mouse models, GKT internal study GSN000262). GKT137831 also prevented liver inflammation and fibrosis in models of NASH (STAM, GKT internal study GSN000172 and fast food diet models) and in toxic hepatitis (CCL4 induced liver injury) (43). Reduced *in vivo* fibrogenesis was associated with a marked reduction in markers of myofibroblast activation. In addition, GKT137831 prevented the induction of adhesion molecules, cytokines, and chemokines. These effects on innate immunity resulted in a profound reduction of macrophage infiltration.

These *in vitro* and *in vivo* effects achieved by GKT137831 were consistent with NOX1 and/or NOX4 gene deletion and/or gene silencing. Importantly, recent studies have shown that the expression of NOX1 and/or NOX4 is consistently induced in the target organ of patients with IPF, NASH, SSc, and cirrhosis. Accordingly, NOX1/4 inhibition with GKT137831 has the potential to achieve anti-inflammatory and anti-fibrotic activity in these patients.

In addition, GKT137831 was shown to prevent lung fibrosis in the bleomycin model of IPF. In contrast to the spontaneously reversible fibrosis induced in young mice, bleomycin causes irreversible fibrosis in aged mice. GKT137831 was able to reverse lung fibrosis in young and aged mice (32). Importantly, GKT137831 also improved survival in aged mice. In these aged mice, GKT137831 again prevented the activation and persistence of lung myofibroblasts, and facilitated their clearance through apoptosis. This data is consistent with results obtained in mice lacking NOX4, who show protection in the bleomycin model. NOX4 over-expression in lung tissue of IPF patients has been reported by several groups, suggesting that NOX1/4 inhibition with GKT137831 may delay or reverse fibrotic lung remodeling in these patients.

Altogether, the available pre-clinical evidence in multiple models indicates that GKT137831 exerts its direct anti-fibrogenic effects through the downregulation of multiple fibrogenic and inflammatory pathways.

A separate set of animal pharmacology studies indicated that GKT137831 reduces the severity of several diabetic complications. In diabetes, a number of factors induce the expression and activity of NOX1 and/or NOX4. These factors include hyperglycemia itself, as well as insulin, angiotensin 2, aldosterone, advanced glycation end products, and multiple pro-inflammatory and growth factors. Studies in murine models of diabetic kidney disease demonstrated that GKT137831 reduces podocyte loss, glomerular and interstitial fibrosis, as well as inflammation and macrophage infiltration. These results were obtained in the Akita (37), OVE26 (36), and STZ/ApoE$^{-/-}$ mice (40,44,45). Reduced inflammation and fibrosis were associated with reduced albuminuria, a highly validated marker of disease progression in man.

These effects were also associated with a commensurate reduction in renal NADPH oxidase activity and ROS production and with improvements in glomerular structure. In the OVE26 model GKT137831 showed benefit at 10 and 40 mg/kg/day. In addition, GKT137831 (60 mg/kg/day by gavage for 10 weeks) significantly reduced atherosclerotic plaque formation in diabetic (streptozotocin-induced) ApoE$^{-/-}$ mice compared to controls. This finding was associated with reduced nitrotyrosine and 4-HNE staining and reduced expression of VCAM-1, MCP-1, TGF-β and macrophage infiltration whilst, upregulation of CTGF, collagen IV and fibronectin was also reduced. In these models of nephropathy and atherosclerosis in diabetic ApoE$^{-/-}$ mice, GKT137831 was as effective as NOX1 and NOX4 gene deletion, respectively. These preclinical

studies, sponsored by the Juvenile Diabetes Research Foundation, supported the initial clinical investigation of GKT137831 in patients with diabetic kidney disease.

Safety pharmacology studies demonstrated that there were no effects on general activity, behavior or respiratory parameters at doses up to 1000 mg/kg of GKT137831 when administered orally. Minimal dose-related effects on hERG currents were recorded with a reduction of ~20% at 300 µM with GKT137831 or major active metabolite GKT138184. In addition GKT137831 was found to be a weak inhibitor (IC_{50} = 78.8 µM) of the cardiac I_{Ks} channel while the metabolite, GKT 138184 has no activity on this channel at 100 µM. GKT137831 and GKT138184 have no significant inhibitory activity on the I_{Kr} cardiac ion channel at 300 µM and no activity on I_{Na} and I_{Ca} channels at 100 µM. Overall, review of the ECG data from the safety pharmacology and toxicology studies did not provide sufficient information that GKT137831 could prolong QTc or QT_{CF} in a way that indicated a definite risk to humans.

The non-clinical pharmacokinetics (PK) and absorption, distribution, metabolism and excretion (ADME) of GKT137831 have been investigated *in vivo* in mouse, hamster, rat and dog, and in animal and human *in vitro* preparations. GKT137831 is a rapidly and extensively orally absorbed compound. In rats and dogs, it has moderately low clearance and a volume of distribution approximately similar to that of extracellular fluid and elimination predominates in feces rather than urine.

Significant amounts of the major phase 1 active metabolite GKT138184 have been quantified in animal plasma after oral dosing. The phase 1 metabolism of GKT137831 is likely to be mediated mainly by CYP3A4, and GKT137831 showed the potential to inhibit and induce CYP3A4 *in vitro*. A human drug interaction study indicated that GKT137831 is a weak inhibitor of CYP3A4 although the modest increase in the exposure of midazolam and its metabolites upon repeat dosing of GKT137831 may be due to a combination of mechanisms.

Initial *in vitro* studies indicating that GKT137831 may also be an inhibitor of BSEP were not confirmed in later repeated studies. In addition, in a specific Phase 1 study the effects of GKT137831 on bile acids were studied and there were no signs of cholestasis (i.e. no change in plasma levels of alkaline phosphatase, bilirubin, and bile acids). It is therefore considered unlikely that treatment with GKT137831 will cause cholestatic liver injury.

GKT137831 has undergone a comprehensive toxicology testing program which has demonstrated that there is no genotoxicity with either the parent or the active metabolites. In chronic studies in rats and dogs the potential toxicity of GKT137831 following up to 6 and 9 months of daily oral dosing, respectively, was explored. The NOAEL in rats was established at 1000 mg/kg/day, the highest dose tested and findings included minimal or slight decreases in red blood cells and slight increases in platelets, modest increases in total plasma bilirubin and a small increase above control in the incidence of foamy macrophages in the lung which was of minimal severity grading. No such difference between treated and control animals was observed in animals subjected to a 5-week treatment free period after 6 months of dosing and these effects were thus not considered of toxicological significance.

The dog was the most sensitive species and the NOAEL was established at 150 mg/kg/day in the 26-Week study. Treatment related effects in the dog studies were confined to ECG changes, hypothyroidism, and hematology parameters/bone marrow abnormalities. Changes in liver function tests were generally considered to be of minimal severity, reversible led to no liver pathologies and are consequently not considered to be of toxicological relevance. In the 28-Day study, QTc(F) prolongation was observed in high dose dogs (1000 mg/kg) and there was a single animal with an AV-block. The QTc prolongation was observed at both measurement times (Day 1 and Day 23) but the increase at the Day 23 reading was limited and seemed to affect only 2/6 treated high dose animals. Although there were no such ECG alterations observed in the 13-

Week study, measurements in high dose dogs taken at Week 1 and 4 of the 26-Week study (animals still on 500 mg/kg/day) showed QTc (VdeW) increases of up to 20 msec. There were no QTc prolongation observed after the dose reduction to 300 mg/kg/day at week 13 and 26. The absence of any clear treatment-related ECG alterations at both the NOAEL of 150 mg/kg/day and the HTD (Highest Tolerated Dose) of 300 mg/kg/day in the 26-Week dog study and in already conducted clinical trials suggest that any such liability will not compromise patient safety in early stage clinical studies. Effects on bone marrow were seen at 500 mg/kg/day, the highest dose tested in the 26-Week study and in one animal resulted in a severe non-regenerative anemia which leads to euthanasia. Effects were restricted to the erythroid lineage and were preceded by a marked reduction in reticulocytes indicating the potential to monitor any potential effect in the clinic.

Exposure (AUC) in the 39-week dog studies was generally rather lower than the same dose/occasion in the 26-week dog study, however the C_{max} values were generally comparable, suggesting a possible reduced impact on AUC of secondary plasma peaks in the 39-week study.

Mild increases in plasma and urinary bilirubin were observed in this study but in the absence of related histological changes these effects were not considered significant. There was no evidence of any changes in hematology parameters and no effects on cardiovascular function.

Segment 2 embryo-fetal toxicology studies have been conducted in rat and rabbit. The NOAEL for embryo toxicity in both species is generally higher than the NOAEL defined from the general chronic toxicity studies.

Overall, this body of non-clinical data suggests that NOX1/4 inhibition with GKT137831 may represent an attractive therapeutic strategy for a broad range of fibrotic disorders.

1.3.12. Summary of Clinical Studies with GKT137831

Healthy Subjects Program

Four Phase 1 studies were conducted with GKT137831 in order, in part, to characterize the safety and tolerability profile of GKT137831 in healthy male subjects. The studies were designed to examine the safety and pharmacokinetics of single and multiple ascending doses of GKT137831, the potential for drug interactions through the inhibition of CYP3A4 substrate midazolam, as well as the relative bioavailability of micronized and unmicronized GKT137831 and the potential interactions with food.

A total of one hundred and five (105) healthy male subjects received GKT137831 in four Phase 1 studies. All the Phase 1 studies were conducted at a single clinical pharmacology unit located in Paris, France and were all conducted in accordance with the principles of Good Clinical Practice (GCP). Doses administered ranged between 10 mg and 1800 mg. In the multiple dose study, GKT137831 was administered over 10 successive days. The mean age of subjects in all four studies was between 30.0 and 33.6 years (mean) with a range of 18 to 49 years.

In the phase I program, GKT137831 was well tolerated with low incidence of adverse events. There were no deaths, no serious adverse events, and no adverse event of severe intensity. Most were treatment emergent adverse events (TEAEs) and were mild and self-limiting, and were considered not related to treatment by the Investigator. Of the 105 subjects dosed with GKT137831 or matching placebo in the 4 Phase 1 studies, 41 subjects reported adverse events (39%), of which 39 were TEAEs. The most frequently reported TEAEs in subjects receiving GKT137831 were events related to headaches (10 TEAEs i.e. 25.6%). Other TEAEs were non-specific infections unrelated to GKT137831.

There were no vital sign, ECG, hematology, clinical chemistry or urinalysis findings of any clinical significance, as defined by the principal investigator. Thyroid hormones were investigated in the multiple ascending dose study and all mean values were within the normal range and changes compared to baseline showed no trend over time.

The pharmacokinetics of GKT137831 were generally consistent between all four studies. Administration of micronized rather than unmicronized drug substance did not appear to have any notable impact on plasma exposure. Administration with food did have an impact on extent of exposure and/or inter-subject variability.

Exposure to GKT137831, measured by mean AUC and C_{max}, whether after single or repeat administration, increased with increasing dose up to 900 mg in a broadly dose proportional manner (single dose; GSN000108) or less than dose proportional manner (single and repeat dose; GSN000109). No increased exposure was seen upon single administration of doses higher than 900 mg. No reduction in mean exposure was seen upon repeat dosing either at daily doses of 100-900 mg (GSN000109) or twice-daily doses of 300-400 mg (GSN000109, GSN000198). A slight accumulation in AUC_{0-t} was seen between the first and last doses upon twice daily dosing, and this is consistent with the increased dosing frequency compared with once-daily. The mean exposure was comparable between studies. After a single dose of 300 mg (a dose level common to all four studies, and including both micronized and unmicronized drug) in either the fasted state or with a non-high-fat meal, the mean AUC_{0-t} ranged from 24,100 to 38,000 ng.h/mL.

Phase 2 Program

A multi-centre double blind randomized phase 2 study has been conducted to evaluate the efficacy and safety of GKT137831 in the treatment of diabetic kidney disease. A total 136 patients were randomized in the study. In the GKT137831 arm, 68 subjects received 100 mg bid for 6 weeks followed by 200mg bid for a further 6 weeks, representing over 15.22 subject years in GKT137831 exposure.

The trial did not meet its primary efficacy endpoint. At the end of the treatment period, no difference could be detected between GKT137831 and placebo in changes in albuminuria from baseline. GKT137831 did not appear to affect other measures of renal function and injury, including serum creatinine, eGFR, and urine MCP-1. Reasons for the lack of efficacy on the primary endpoint may include the short treatment period and/or underdosing during the first half of the trial.

However, GKT137831 achieved statistically significant reductions in gamma glutamyl transpeptidase (GGT) and high sensitivity C-reactive protein (hs-CRP), two markers which predict mortality in patients with diabetic kidney disease. Furthermore, subjects receiving GKT137831 also showed a robust trend for lower levels of serum amyloid protein A, interleukin-6, and triglyceride levels, compared to subjects receiving placebo. These changes are potentially related to a systemic anti-inflammatory effect, and/or to reduced severity of non-alcoholic fatty liver disease (NAFLD) in these subjects with type 2 diabetes and excess body weight. Trends towards reduced neuropathic pain and erectile dysfunction were also observed but did not reach statistical significance.

In this Phase 2 study, GKT137831 was well tolerated. The reporting rate of AEs was low with less than 50% of subjects reporting at least 1 AE over the course of the study. In GKT137831 treated subjects, the incidence of AEs was significantly lower than in patients receiving placebo. Most treatment-emergent adverse events were self-limiting, mild in severity, not treatment-related and resolved rapidly. The most commonly reported adverse events were events related to respiratory tract infections. Other reported events were single occurrences experienced by 1 or 2 GKT137831

subjects. There was no evidence of dose-related increase in the occurrence of treatment emergent adverse events. The only notable safety finding was a statistically significant, albeit slight and non-clinically significant (~2.5 mm Hg) increase in DBP. A trend for a marginal (~3 mm Hg) increase in SBP was also observed, but did not reach statistical significance. Finally, safety signals related to findings made in toxicology studies were not detected. In particular, there were no safety signals related to thyroid function, liver function, bone marrow function, or cardiac conduction. No bone marrow toxicity, cardiac toxicity, liver toxicity, or renal toxicity was observed.

Upon review of all available safety data, GKT137831 at doses up to 200 mg BID in 68 subjects with diabetic kidney disease indicated a good tolerability and safety profile compared to placebo.

The safety and efficacy of GKT137831 was subsequently evaluated in patients with primary biliary cholangitis (PBC). Several components of the disease were assessed, including liver inflammation and injury, liver fibrosis, cholestasis, autoimmune activation, and important symptoms such as fatigue and itching. The trial was a placebo controlled, double blind, randomized, parallel group trial that included a total of 111 subjects with inadequate response to ursodeoxycholic acid (UDCA). Eligible subjects received GKT137831 400mg OD, 400mg BID, or matching placebo for 24 weeks in addition to continued treatment with a stable dose of UDCA. The primary efficacy endpoint was changes in gamma glutamyl transpeptidase (GGT) at week 24.

The trial was conducted at 62 investigational centers located in North America, Europe, and Israel. Patient enrolment was completed in September 2018 and interim efficacy results were obtained in November 2018. The trial met its primary and secondary interim efficacy endpoints, which included markers of bile duct and liver injury measured after only 6 week of treatment. Importantly, the 400mg bid dose achieved superior efficacy compared to the 400mg od dose. The Safety Monitoring Board overseeing the safety of participating subjects conducted its third data review in October 2018, and recommended that the trial continue as planned. Top line efficacy results after 24 weeks of treatment were communicated on May 2, 2019. GKT137831 continued to induce reductions in the primary efficacy variable GGT over time, although the reduction observed at week 24 did not reach statistical significance. However, a statistically significant reduction in a secondary marker of bile duct injury (alkaline phosphatase) was significantly reduced in patients receiving GKT137831 BID. In addition, GKT137831 achieved a 22% reduction in liver stiffness (a non-invasive measure of liver fibrosis), compared to a 4% increase in liver stiffness for placebo ($p<0.05$). Furthermore, GKT137831 achieved robust reductions in pruritus, a major symptom affecting the quality of life of PBC patients. These results indicate GKT137831 has anti-inflammatory and anti-fibrotic properties in PBC patients. Importantly, GKT137831 continued to be very well tolerated over the full 24-week treatment period. Only 2 serious adverse events (SAEs) were reported. These included a case of multiple bone fractures related to a traffic accident, and a case of grade 1 urinary tract infection (the event was deemed serious because the patient was hospitalized to initiate IV antibiotic therapy). These 2 SAEs were believed to be unrelated to the study drug. Both patients completed the full treatment period without interruption of study drug administration. Over 93% of patients completed the full treatment period.

The good safety profile of the two doses tested, and the superior efficacy of the 400mg bid dose support the selection of the 400mg bid for this trial in IPF patients.

GKT137831 is currently being evaluated in an investigator-initiated trial assessing the effect of this drug on markers of kidney injury and function. The trial is a placebo controlled, double blind, randomized, parallel group trial that includes a total of 142 subjects with type 1 diabetes and micro-albuminuria despite receiving standard of care therapy. Eligible subjects receive GKT137831 200mg BID or matching placebo for 48 weeks. The primary efficacy endpoint is change in urinary albumin to creatinine ration (UACR) at week 48. The trial is being conducted at approximately 15 investigational centers located in Australia. The trial was initiated in January

2018. The study is blinded and patient enrollment is at an early stage. Following the interim and final efficacy results obtained in the PBC trial, it is planned to increase the GKT137831 dose to 400mg bid. This efficacy data also indicates GKT137831 was underdosed in the first clinical trial in patients with diabetic kidney disease.

1.4 SIGNIFICANCE

If our hypothesis is correct, treatments that reduce ROS generation and consequent injury will have beneficial effects in IPF patients. The proposed clinical trial here will generate important preliminary data regarding the magnitude and duration of GKT137831 effects in IPF patients. These data will be essential for design of a subsequent clinical efficacy (Phase III) study.

2 RESEARCH DESIGN AND METHODS

2.1 CLASSIFICATION AND METHODOLOGICAL DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled Phase II clinical trial to examine selected effects and safety of GKT137831 in IPF patients.

2.2 STUDY DESIGN

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

Following completion of screening and eligibility assessments, 60 IPF patients will be randomly assigned to one of two cohorts intended to receive either GKT137831 or matching placebo, in a ratio of 1:1 (i.e., n = 30 in each arm). Both GKT137831 and placebo will be administered by mouth (p.o.), twice daily (b.i.d.). Each GKT137831capsule will contain 100 mg of the active drug. Drug (and placebo) will be administered for 24 weeks. Each participant will also be surveyed by phone interview at week 28 (one month after completion of drug administration).

All participants will have physiological assessments that are standard of care for IPF patients, including high resolution chest CT scans (HRCT scans), and pulmonary function tests (spirometry, diffusion capacity, 6-minute walk distance) prior to and after the conclusion of therapy. These procedures and routine laboratory tests will not be repeated specifically for this study if they are deemed to be clinically indicated. The results of any standard-of-care procedures will be extracted from the participant's medical record and used as research data.

Patients will be monitored carefully for occurrences of adverse events. Adverse experiences will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Patients removed from treatment due to unacceptable adverse events will be followed for a total of 24 weeks under the principle of intent to treat.

2.3 INCLUSION AND EXCLUSION CRITERIA

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

Inclusion Criteria

1) Age between 40-85 years old.

2) A diagnosis of IPF that fulfills current ATS/ERS Consensus Criteria (1).

3) IPF duration <5 years, based on the date of definitive diagnosis.

4) Ability and willingness to give informed consent and adhere to study requirements.

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

Exclusion Criteria

1) Diagnosis of major comorbidities expected to interfere with study participation
2) History of malignancy, excluding basal or squamous cell skin cancer and low-risk prostate cancer, the latter defined as stage T1 or T2a, with prostate specific antigen <10 ng/dl. NOX inhibition is not known to promote cancer, and these criteria are within current guidelines.
3) The occurrence of any acute infection requiring systemic antibiotic therapy within 2 weeks prior to Screening (Visit 1).
4) Treatment for >14 days within the preceding month with >20 mg. prednisone (or equivalent) or any treatment during the last month with a cellular immunosuppressant (e.g., cyclophosphamide, methotrexate, calcineurin inhibitors, etc.), given increased risks of opportunistic infections.
5) Treatment with any investigational agent within 4 weeks of Screening (Visit 1) or 5 half-lives of the investigational medicinal product (whichever is longer).
6) Fertile women who do not agree to abstinence or an effective form of contraception (as approved by the investigator), or who are breast feeding, for 4 weeks before randomization until 90 days after the last administration of study medication (or placebo).
7) Men who are not surgically sterile and do not agree to remain abstinent from heterosexual intercourse or use effective contraception (as approved by the investigator), and refrain from donating sperm, from the time of giving informed consent until 90 days after the last administration of study medication (or placebo).
8) Subjects with known hypersensitivity to GKT137831 or its excipients (e.g. capsule "bulking" agents).
9) A history of bone marrow disorder including aplastic anemia, or marked anemia defined as hemoglobin < 10.0 g/dL (or 6.2 mmol/L).
10) Severe cardiovascular disease, defined as any of the following within the preceding 12 weeks: acute myocardial infarction or unstable angina, a coronary revascularization

procedure, congestive heart failure (NYHA Class III or IV), or stroke, including a transient ischemic attack.

11) Evidence of cardiac conducting abnormalities, defined as second or third degree AV block not successfully treated with a pacemaker, or a personal or family history of long QT syndrome (QTc interval >450 msec for males or 470 msec for females).
12) End-stage renal disease requiring dialysis.
13) Undergoing transplantation evaluation, or listed with the United Network for Organ Sharing (UNOS) as a lung transplantation candidate at the time of enrollment in this trial.
14) Liver function tests (transaminases, alkaline phosphatase, direct and total bilirubin) >3x upper limit of normal values.
15) Systemically administered potent CYP3A4 **inhibitors or induces** are prohibited during the 24-week treatment period.

    Inhibitors include: boceprevir, cobicistat, conivaptan, ritonavir, itraconazole, ketoconazole, telaprevir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir.

    Inducers incude carbamazepine, enzalutamide, mitotane, phenytoin, rifampin.

    See also: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

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

2.4 RANDOMIZATION

A randomization list (1:1 experimental arm to controls), stratified by gender (IPF progression is gender-dependent), and use vs. non-use of antifibrotics (i.e., either pirfenidone or nintedanib) at enrollment, will be generated by the Data Coordinating Center (DCC) in advance. Given our "n", additional stratifications could result in imbalances with no subjects in certain cells.

The subject selection and randomizations, and specimen acquisitions for primary and secondary endpoint determinations (to follow), will also enable provision of blood specimens for the translational studies in other associated translational studies. Subject selections here will also identify a population from whom potential participants in additional studies (e.g., experimental bronchoscopies) can be approached and recruited. However, experimental bronchoscopies are optional and distinct from this clinical trial and will require an additional, separate IRB approval and signed consent. The subjects randomized to this GKT137831 clinical trial may elect to not participate with experimental bronchoscopy or other experimental procedures, and they will not be pressured to do so.

2.5 STUDY TREATMENT

The two arms of the study are:

- **Arm A** (n=30) **– GKT137831 Treatment**:

GKT137831 will be administered orally (p.o.), at doses of 400 mg, twice daily (bid), for a total of 24 weeks.

- **Arm B** (n=30) **- Placebo Treatment**:

  Arm B subjects will be treated with otherwise identically-appearing placebo medication for the same duration.

Investigational pharmacies at each of the sites will be responsible for dispensing trial medications (either Arm A or Arm B), based on the randomization of that patient and transmission of that information by the DCC.

2.5.1 Description and formulation

Drug code	GKT137831	Placebo
Formulation	Micronized API formulated with excipients in capsules	Matching capsules containing only the excipients
Strength	100 mg	-
Route	Oral	Oral

GKT137831 capsules will contain 100 mg GKT137831 powder formulated with the following excipients per capsule: microcrystalline cellulose, Aerosil® (silicon dioxide), magnesium stearate and hard gelatin.

2.5.2 Packaging and labeling

The Investigational Medicinal Product (IMP) will be packed and labeled in accordance with applicable local regulatory requirements and applicable International Conference for Harmonization (ICH) Good Manufacturing Practice (GMP) and ICH Good Clinical Practice (GCP) guidelines, and to protect the blinded nature of this clinical study.

Child resistant 150 mL high-density polyethylene (HDPE) bottles with a tamper evident seal containing 70 capsules of either 100 mg GKT137831 capsules or matching placebo.

2.5.3 Storage and Stability

The IMP must be stored in a cool, dry, area at room temperature (between 15°C and 25°C). At the site IMP must be securely locked and stored with restricted access. Temperature should be controlled during shipment and during storage at study centers. The IMP must not be frozen or stored above 27°C.

2.5.4 Administration

The IMP will be orally self-administered BID, once in the morning and once in the evening (aiming for a period of at least 10 hours between doses) with meals or up to 30 minutes after a meal.

2.6 STUDY PROCEDURES AND MEASURES

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

The study will log the results of specific screening-baseline measures, and other selected tests that may be obtained during the routine provision of clinical care and/or safety monitoring of trial participants. These may include: electrocardiograms (EKG), complete blood count (CBC), comprehensive metabolic panel (CMP) that includes electrolytes, glucose, BUN, and serum creatinine, pregnancy tests, thyroid function tests (TFT) consisting of thyroid stimulating hormone (TSH), thyroxine (T4), and liver function tests (LFT) consisting of albumin, total bilirubin, aspartate alanine transaminase (ALT), and aspartate glutamine transaminase (AST).

A maximum of thirty-four (34) ml of blood for experimental research studies and endpoint measures will be obtained pretreatment and at 6 week intervals throughout 24 weeks of drug therapy.

The following information will be collected and entered into the study case report forms (CRFs) and/or web-based data collection system. Clinical and laboratory data may include results of studies otherwise obtained for routine clinical care, which can be collected from medical records.

1. Physician names and contact information, general medical and surgical histories, co-morbidities, concurrent medications, and allergies.
2. Recording of vital signs, demographics, and medication regimen.
3. Review of medications
4. Brief assessment of symptoms.
5. Recording of laboratory and clinical testing results.

2.6.1 Variances
A variance of 5 days will be allowed for the telephone contacts to account for weekends or holidays. A variance of 10 days will be allowed for each outpatient follow-up visit for similar reasons, as well as potential logistic/transportation problems. If subjects are hospitalized at the time of scheduled assessments, an identical evaluation and procedures will be performed (as feasible):

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

2.6.2 Screening
Screening (within 30 days prior to randomization):
Eligible patients will be evaluated by review and, if eligible, the study will be explained to them in detail, prior to their being asked to provide Informed Consent. Patients will undergo screening assessments to determine that inclusion/exclusion criteria are met prior to randomization and subsequent study drug treatments. The screening assessments may take place over >1 day.

The following tests and procedures will be performed after providing informed consent, but prior to randomization (see Table 1):

- Detailed medical history and demographics.
- Physical exam and inpatient progress assessment to include vital signs and blood pressure.
- Laboratory evaluations, not performed during routine clinical assessments and thus specific for Inclusion/Exclusion Criteria to include: EKG, CBC, CMP, TFT, LFT, blood pregnancy test (if applicable), FSH (if applicable)- see Section 5.7.3.1, and chest HRCT.

2.6.3 Initial experimental procedures
Day -30 to Day 1 (After Randomization, but Prior to Initiation of Therapy):

Randomization should occur as soon as possible after meeting confirmed eligibility, but within ≤30 days of their qualifying laboratory and other protocol-specific tests. Patients that meet all inclusion/exclusion criteria will be randomized to receive one of the study treatments described above in Section 2.5. In addition, the following data and specimens will be obtained (if not already obtained during screening):

- Physical exam and interval progress assessment to include vital signs and blood pressure.
- Venous blood by phlebotomy (a maximum of 34 ml) will be obtained, locally processed and stored frozen, for later batch shipment (frozen) to the Clinical Coordinating Center (CCC).
- Pulmonary function tests (PFTs) to include spirometry and diffusing capacity (DLCO).
- Six minute walk distance (6MWD). 6MWD = 0 among subjects unable to ambulate.
- Medication review
- Adverse Event (AE) assessment.

Day 1 (Initiation of Therapy):
- Subjects will receive study medication (>6 week supply), instructions, and drug compliance diary.
- Female subjects with childbearing potential (see Section 5.7.3.1) must have a negative urine pregnancy test prior to receiving study medication.

2.6.4 Follow-up monitoring (see Table 1 and Table 2)

Day 14 (2nd week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 28 (4th week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 42 (6th week):
- Physical exam and interval history assessment to include vital signs and blood pressure.
- Safety tests to include: EKG, CBC, CMP, TFT, LFT, pregnancy test, either urine or blood (if applicable).
- Venous blood by phlebotomy (a maximum of 34 ml) will be obtained, locally processed and stored frozen, for later batch shipment (while frozen) to the CCC.

- Medication review (including review of drug compliance diary)
- AE assessment.
- PK samples (2 ml each) taken upon arrival in clinic and just prior to departure from clinic

Day 56 (8th week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 70 (10th week):

- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 84 (12th week):
- Physical exam and interval history assessment to include vital signs and blood pressure.
- Safety tests to include: EKG, CBC, CMP, TFT, LFT, pregnancy test, either urine or blood (if applicable),
- Venous blood by phlebotomy (a maximum of 34 ml) will be obtained, locally processed and stored frozen, for later batch shipment (while frozen) to the CCC.
- Medication review (including review of drug compliance diary)
- AE assessment.
- PK samples (2 ml) taken upon arrival in clinic and just prior to departure from clinic

Day 98 (14th week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 112 (16th week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 126 (18th week):
- Physical exam and interval history assessment to include vital signs and blood pressure.
- Safety tests to include: EKG, CBC, CMP, TFT, LFT, pregnancy test, either urine or blood (if applicable),
- Venous blood by phlebotomy (a maximum of 34 ml) will be obtained, locally processed and stored frozen, for later batch shipment (while frozen) to the CCC.
- Medication review (including review of drug compliance diary)
- AE assessment.

Day 140 (20th week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 154 (22nd week):
- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 168 (24th week):
- Physical exam and interval history assessment to include vital signs and blood pressure.
- Safety tests to include: EKG, CBC, CMP, TFT, LFT, pregnancy test, either urine or blood (if applicable),
- Venous blood by phlebotomy (a maximum of 34 ml) will be obtained, locally processed and stored frozen, for later batch shipment (while frozen) to the CCC.

- Pulmonary function tests (PFTs) to include spirometry and diffusing capacity (DLCO).
- Six minute walk distance (6MWD). 6MWD = 0 among subjects unable to ambulate.
- Chest HRCT
- Medication review (including review of drug compliance diary)
- AE assessment.

Day 198 (28th week):

- Telephone call (if outpatient, or personal visit if an inpatient) to assess status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Every effort will be made to ascertain status among those seemingly lost to follow up by contacting patient or next of kin, conducting internet searches for obituaries, etc.

Table 1. TREATMENT PROCEDURE SCHEMATIC

The experimental interventions are outlined below:

Weeks:	-4 to 0	0	6	12	18	24
Clinic Visit	x	x	x	x	x	x
Randomization		x				
Exam and Interval History	x	x	x	x	x	x
Dispense Drug		x	x	x	x	
Review Drug Diary			x	x	x	x
Safety Assessment*	x	x	x	x	x	x
Blood Pregnancy Test	x					
HRCT		x				x
Spiro and DLCO		x				x
6MWD		x				x
PK Sampling			x	x		
K-BILD QOL Survey	x					x
Urine Pregnancy**		x	x	x	x	x

*Safety assessments include electrocardiogram (EKG), complete blood count (CBC) with platelets (plts), basic metabolic panel (BMP) with glucose, BUN, creatinine, blood pregnancy test, if applicable (Section 5.7.3.1), liver function tests (LFT) with albumin, bilirubin (total), transaminases, and thyroid function tests (TFT) with thyroid stimulating hormone (TSH) and thyroxine (T4). These assessments can be combined during screening and baseline visits as long as they are completed within 30 days of randomization and start of drug treatment. ** if applicable (see Section 5.7.3.1). In addition to the blood pregnancy test during screening, a urine (or blood) pregnancy test must be performed on the day that therapy starts. Blood tests can also substitute for urine tests at weeks, 6,12,18,24.

Table 2. PHONE CONTACTS

Weeks:	2	4	8	10	14	16	20	22	28
Phone contact	x	x	x	x	x	x	x	x	x

Subjects will be contacted by the study coordinators at these times to assess for symptoms potentially related to adverse effects of medications, review of medication changes, and interval medical or surgical histories including emergency or physician office visits.

2.6.5 Specimen Collection and Management

Specimen Collection / Documentation: A maximum of 34 ml of blood for experimental research studies and endpoint assays will be obtained pretreatment, and at weeks 6, 12, 18, and 24 after the start of therapy. The peripheral blood will be processed at the site of collection by centrifugation to separate mononuclear cells, plasma, and sera, which will be aliquoted and frozen (at -20^{o} or below) until shipment to the CCC in batches. Subsequent assays will be conducted in the laboratory of CCC investigators or their colleagues, in compliance with IRB approvals.

Each research sample will be labeled with the subject's unique identifier, sample date, and sample collection time. The code number and date on which the specimen is frozen, all other information about the specimen, and subsequent processing will be entered on a specimen processing worksheet.

Covariate information, e.g., concomitant medications, laboratory values, etc., will be obtained at each time point.

Specimen Handling and Labeling (De-Identification)
All research specimens and all records associated with the samples will be labeled only with a unique code that links to the trial data, but contains no personal identifiers. The information linking these code numbers to the corresponding subject's identity will be kept in a secure location in the PI's office at each participating center, and will not be available to staff managing samples at the research laboratories.

Specimen Management and Storage: Specimens in excess of immediate assay requirements may be stored indefinitely in a secured freezer under the control of the responsible PI. The coding information linking patient identifiers to the stored samples will be maintained in a locked, secure area that will be accessible only to the study investigator. Subjects may request to have their samples destroyed at any time. These samples will be destroyed immediately upon receipt of the subjects' written request to do so.

Restrictions to Direct Access of Specimens: Specimens will be kept in the responsible study investigators' laboratories indefinitely and will be under the control of the PI. Other personnel not involved with the management or operations of the study are not permitted direct access to the specimens.

2.7 STUDY ENDPOINTS

2.7.1 Primary Efficacy Endpoint:

The primary endpoint of this trial will be treatment effects of GKT137831 on plasma levels of *o,o'*-dityrosine, measured by mass spectroscopy pretreatment and at six-week intervals, in comparisons to effects of placebo alone.

O,o'-dityrosine is a mechanistic surrogate biomarker of oxidative stress. This metabolite is synthesized by myo-fibroblasts in fibroblastic foci, and is associated with cellular injury and ECM cross-linking (Secs. 1.3.5., and 1.3.6.). Levels of *o,o'-dityrosine* are increased in IPF patients (Sec. 1.3.7.) and were significantly decreased by GKT137831 administration in a murine model of fibrotic lung injury (Sec. 1.3.9.).

We hypothesize plasma levels of *o,o'-dityrosine* in IPF participants will be reduced by NOX inhibition with GKT137831, reflecting beneficial effects of the experimental drug on fibrosis (Sec. 1.3.8).

2.7.2. Secondary Efficacy End-Points:

Secondary endpoints are: (a) collagen degradation products (e.g.C1M), measured in sera by ELISA; (b) forced vital capacity (FVC); and (c) six-minute walk distance (6MWD) comparing baseline and values at 24 weeks; and (e) adverse events (AE) that occur anytime during the duration of the trial.

a) C1M: Circulating concentrations of collagen digest fragments (e.g., C1M) are reflective of ECM turnover, and increased levels discriminate IPF patients vs. controls, and are prognostic of disease activity and outcome (Sec. 1.3.10.). C1M will be measured by competitive ELISA in serum specimens collected by phlebotomy at visits that occur every 6 weeks in all patients. The assays will be performed at Nordic Biosciences (Herlev, Denmark), as previously described (16). We hypothesize GKT137831 treatment will result in decreased ECM turnover and reductions of sera C1M levels, in comparison to placebo effects.

b) and c) FVC and 6MWD: This is a Phase IIb study and is likely underpowered for rigorous evaluation of drug effects on clinical endpoints, such as FVC changes and/or 6MWD over time. Nonetheless, measures and comparisons of these parameters will enable us to detect striking drug efficacy, and will likely be informative with respect to power calculations for later, more definitive efficacy trials. FVC is a measure of pulmonary restriction (in turn, a function of the underlying lung fibrosis). 6MWD are simple, inexpensive, reproducible measures of global cardiopulmonary function. Values for 6MWD can be obtained in all patients, even those who are immobile (e.g., value = 0). Measures of FVC and 6MWD will be performed per ATS/ERS guidelines. These tests are standard of practice (SOP) in our IPF clinics.

2.7.3. Safety Endpoints:

Adverse events: Adverse events (AE) that occur anytime during participation in this study will be recorded and compared. The NCI Common Toxicity Criteria Scale will be used to define grades (severity) of adverse events and toxicities. An AE is defined as any untoward medical occurrence in a subject, regardless of its relationship to these treatments. Toxicity is an adverse event with a direct relationship to the study drug. All toxicities are AE, but not all AE are toxicities. Computer data entry (and case report forms- [CRF]) will require responses to all adverse events, with a particular focus on infections (including location and organism), and metabolic perturbations (e.g., cardiac, liver, bone marrow, or thyroid abnormalities) hyperglycemia, hypotension, etc.). Recording all AEs in pre-specified checklists (and free text entries), will guard against unintended bias in this unblinded trial. We hypothesize GKT137831 will be safe in this population, and will not be associated with an increased number or severity of AE in comparison to placebo.

2.7.4. Pharmacokinetic endpoints:

Plasma concentrations of GKT137831 and its main phase 1 metabolite, GKT138184. The plasma concentrations will be subjected to population PK analysis to estimate population PK parameters such as clearance and volume of distribution and associated inter-individual variability (IIV), and to determine predictors of IIV. PK-PD analysis will be carried out using the primary endpoint and selected secondary endpoints in order to explore any potential PK- PD relationships.

2.7.5 Additional Studies That are Not Formal Endpoints

Quality of Life (QoL) Measures: Patients will complete a King's Brief Interstitial Lung Disease health status questionnaire (K-BILD) at baseline and study conclusion (24 weeks). This instrument was developed for and validated in patients with interstitial lung disease, is brief, simple to administer, measures health status in three domains, and is reproducible.[46]

2.8 DATA ANALYSES AND POWER ANALYSES

2.8.1. Data analyses: Baseline demographic and clinical data of participants will be summarized using means (with standard deviations) and medians (with inter-quartile ranges) for continuous variables, and counts and percentages for discrete variables, stratified by treatment group. Differences between groups (to examine the randomization effectiveness), will be assessed by t-tests, or by Fisher's exact test for discrete data. Analyses will follow intention to treat principles, with the last observed outcome over all time points being used as the primary measure for a given variable. Multiple imputation will be used based on subject characteristics to assess the obvious issues, with last observations carried forward in these analyses. Trajectories over time, for a given patient and outcome measure, will be displayed via line graphs, and assessments conducted using generalized linear models on the repeated time points. Comparisons between the treatment arms of circulating *o,o*'-dityrosine levels at various time points will be made using these repeated measures techniques. Transformations of these tests may be needed, such as velocities, if many individuals are unable to complete the entire protocol.

2.8.2. Power analyses: The sample size of 60 for this clinical trial (equally divided between experimental and placebo arms) is based on exposing a minimum number of patients to risks of experimental therapy, while still obtaining useful information. We previously found that o,o'-dityrosine levels (μmol/mol tyrosine) in IPF patients (n = 32) were 8.51, with a standard deviation (SD) of 5.30, compared to mean and SD of 0.47 ± 0.45 in normal controls (15). Assuming o,o'-dityrosine levels are reduced in the experimental arm subjects by 50% of the difference between untreated IPF and normals (e.g., to 4.02 μmol/mol tyrosine), with a SD of 5.3 we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.82, using an unpaired, two-way t-test. The Type I error probability associated with this test of this null hypothesis is 0.05. The 50% reduction is well within ranges in which ROS and fibrosis markers are decreased by GKT137831 in other models (Sec. 1.3.9., and 8-11).

Moreover, we have 0.8 power to detect a treatment effect **within the 30 experimental arm subjects**, using paired intragroup testing, if o,o'-dityrosine levels decrease from baseline levels by merely 1.4 μM/mol tyrosine or more during GKT137831 therapy.

The characteristics of this trial, which is double-blinded, involves overlapping roles of many personnel at many centers, employs an independent and expert DCC (that routinely does QC checks and validations) for data collection and analyses, and uses an endpoint that is determined independently by blinded experimental lab investigators working with deidentified specimens, **ensure a high degree of transparency and rigor**.

2.8.3. Interim Analysis:
Interim efficacy analysis is not warranted, since the primary study endpoint is a laboratory measure of the plasma level of *o,o'*-dityrosine, a surrogate biomarker of oxidative stress, to

determine GKT137831 treatment effects. The DCC will tabulate AE and the DSMB will monitor AE in the respective trial arms.

2.8.4 Pharmacokinetics Analyses

Plasma concentrations of GKT137831 and its main phase 1 metabolite, GKT138184 will be analyzed in plasma specimens obtained at weeks 6 and 12 of the drug therapy. The plasma concentrations will be subjected to population PK analysis to estimate population PK parameters such as clearance and volume of distribution and associated inter-individual variability (IIV), and to determine predictors of IIV. The sparse PK data from this study will be integrated into a population PK model using nonlinear mixed-effects modeling. In addition, PK-PD analysis will be carried out using the primary endpoint and selected secondary endpoints in order to explore any potential PK- PD relationships.

2.9 DATA COORDINATING CENTER (DCC)

The DCC will develop a comprehensive database and, administer and maintain a data management system for this phase II clinical trial. The DCC is responsible for providing methods for data collection, entry, quality control (QC), management and analyses. By developing a data collection protocol, the DCC will train all clinical personnel in the protocol and in the use of the system. Also, the DCC will maintain documentation and usage instructions for the data collection system in addition to providing data dictionaries and code books for documentation of the data collected for this trial. The DCC will be located within the UAB Department of Medicine.

Inasmuch as possible:

- Data will not be collected on paper, but will be entered electronically into the database system via internet connected devices.
- Paper data collection forms will be developed for every measure, both to provide documentation, and to allow data collection in the unlikely event of Internet inaccessibility.
- Data collected on paper forms will be entered into the database using a double-data-entry verification system, to ensure valid data.

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

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

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

2.10 STUDY TIMELINES AND MILESTONES

We anticipate the necessary logistical and regulatory requirements (e.g., establishing data acquisition procedures, IRB approvals, convening of a DSMB, FDA approval etc.) will have been completed by 12-14 months after the beginning of the funding period. The personnel and facilities

of this consortium have considerable clinical trial experience, and the foundation for the DCC is already in place. The sizes of our potential subject populations are such that we realistically anticipate being able to meet our target goal enrollment well before the completion of the funding duration. A projected timeline, with milestones, is depicted in Table 3.

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5
Regulatory Approvals, Logistics					
Subject Enrollment (n)		20	20	20	
Data Analyses					

Figure 3. Projected timeline and milestones.

3. HUMAN SUBJECTS

3.1 SUBJECT POPULATION

Sixty (60) ambulatory IPF patients of both genders and all ethnic backgrounds, who are evaluated at any of the 5 participating medical centers, will be eligible for enrollment. Subjects must provide written informed consent prior to participation. Based on the referral populations of these medical centers, we expect ~40% of eligible subjects will be women and ~10% will be non-Caucasian.

The 5 participating centers (and the PI at each of these sites) are:

1. University of Alabama at Birmingham (Duncan)
2. Temple University (Criner)
3. University of Michigan (Flaherty)
4. University of Minnesota (Kim)
5. Tulane University (Lasky)

3.1.1 Inclusion of Women and Minorities

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

3.1.2 Inclusion of Children

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

3.2 INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria have been selected to isolate a patient population with IPF. The exclusion criteria are selected to not enroll patients with an alternative cause for their respiratory disease and to exclude patients with increased risk for the associated intervention (GKT137831). The inclusion and exclusion criteria have been previously detailed in Section 2.3

3.3. RATIONALE AND SAFETY OF EXPERIMENTAL GKT137831 TREATMENT:

Much of the preliminary data that provides the rationale for this GKT137831 trial has been previously detailed in Sec.1.3

GKT137831:

GKT137831 is a small organic molecule of low molecular weight, a member of the pyrazolopyridine dione chemical class. It is a selective inhibitor of NOX 1 and 4 isoforms of the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase family of enzymes, and is the first drug in this class of NOX inhibitors to enter the clinic.

The NADPH oxidase family (NOX) is a set of transmembrane proteins [20]. NOX enzymes require the stable assembly of transmembrane and cytosolic subunits. Upon assembly of a full enzymatic complex and activation by its substrates NADPH and molecular oxygen, NOX enzymes transport electrons through the cell membrane to produce reactive oxygen species (ROS). In turn, ROS modulate multiple signaling pathways by oxidizing regulatory cysteine residues in target proteins. ROS can also cause other types of post-translational modification of proteins, and can target lipids and nucleic acids.

When exaggerated in duration and/or magnitude, NOX activation participates in the pathogenesis of a broad range of human diseases. In particular, the NOX1 and NOX4 isoforms have been shown to play a key role in a broad range of inflammatory and fibrotic disorders. Importantly, recent studies have revealed that liver tissue expression of NOX1 and/or NOX4 is consistently elevated in patients with fibrotic liver diseases.

GKT137831 is thus being investigated in several inflammatory and fibrotic disorders, including PBC, Nonalcoholic Steatohepatitis (NASH), Idiopathic Pulmonary Fibrosis (IPF), Diabetic Kidney Disease (DKD), Systemic Sclerosis (SSc). It is also under investigation in the development of the fibrotic tumor stroma.

In *in vitro* studies in isolated cells, GKT137831 was shown to attenuate signaling evoked by a number of ligands known to induce and/or drive the fibrogenic process in multiple fibrogenic pathways, including TGF-β1, PDGF, TLR4, hedgehog and angiotensin II. As a result, GKT137831 markedly reduced the induction of markers of myofibroblast activation, including αSMA, fibronectin, and pro-collagen I.

These direct anti-fibrogenic effects translate into anti-fibrotic activity in multiple in vivo models of inflammatory and fibrotic disorders of the lungs and other target organs such as liver and kidneys. Specifically in models of interstitial lung fibrosis, GKT137831 showed marked anti-fibrotic activity and improved survival.

In addition, GKT137831 attenuated the development of liver fibrosis induced by experimental cholestasis (in the bile duct ligation and MDR2$^{-/-}$, mouse models). GKT137831 also prevented liver fibrosis in models of NASH (in the STAM and fast food diet models). GKT137831 also prevented liver fibrosis in models of NASH (in the STAM and fast food diet models and in toxic hepatitis (in CCL4-induced liver injury). Reduced *in vivo* fibrogenesis was associated with a marked reduction in markers of myofibroblast activation.

In addition, GKT137831 has shown potent anti-inflammatory effects in a number of biological settings, including metabolic and cholestatic liver injury. Specifically, GKT137831 prevented the induction of adhesion molecules, cytokines, and chemokines in CCL4-induced liver injury and fast food diet-induced NASH. These effects on innate immunity resulted in a profound reduction of macrophage infiltration. Available data suggests that these anti-inflammatory effects are mediated

through reduced activation of multiple pathways, including TLR4 and NF-kB. In these studies, reduced liver inflammation was associated with a reduction in plasma levels of liver transaminases.

GKT137831 was evaluated in patients with type 2 diabetes and kidney disease. Because this patient population has a high prevalence of the metabolic syndrome and non-alcoholic fatty liver disease, the trial assessed markers of liver injury and inflammation. GKT137831 achieved statistically significant reductions in GGT and hsCRP.

Recently, a trial of GKT137831 in patients with PBC, a chronic inflammatory and fibrotic liver disorder, met its primary and secondary efficacy endpoints. GKT137831 was well tolerated as indicated by three SMB reviews.

These extensive pre-clinical studies and initial clinical results suggest that GKT137831 has the potential to alleviate pulmonary oxidative stress and prevent or reverse progressive lung fibrosis.

Additional information on GKT137831 are provided in the GKT137831 Investigator's Brochure.

4. RECRUITMENT AND INFORMED CONSENT PROCEDURES

4.1 RECRUITMENT METHODS

Participants will be recruited from the ambulatory IPF populations among the collaborating institutions. Potential subjects may also be recruited by direct public advertising including, but not limited to newspapers, radio, television, worldwide web, internet ads, bulletin boards, posters, and flyers. Recruitments may also be obtained through referrals from other clinical practices or other databases. Since the primary endpoint of this trial is a surrogate biomarker, there is no need to limit enrollment of IPF patients who have a narrow range of pulmonary function, unlike many other clinical efficacy studies, and this will be a boon for this GKT137831 trial recruitments.

4.1.1. Recruitment Feasibility.

All of the collaborating centers have large patient populations that include an excess of potential study participants, and all of the collaborating investigators are skilled with clinical trial recruitment. As one example, UAB had the second highest enrollment in the first clinical trial sponsored by the NIH-Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet). Furthermore, during the last year of the ART-IPF study, ten (10) UAB subjects were randomized, despite more stringent exclusion criteria than that proposed here (no patient with an abnormal autoantibody test, no matter how slight, could be enrolled in ART-IPF). Based on our past history, we estimate at least 20 patients could be enrolled at UAB alone during the three-year recruitment period. By way of another example: nine (9) subjects at Temple (Dr. Criner) were randomized into ART-IPF during the same year, thus illustrating their ability to recruit too. And, the University of Minnesota IPF program (Dr. Kim) has enrolled 130 subjects in clinical trials during the last 10 years. The investigators at the other clinical sites also have proven track records for subject recruitments in numerous IPF clinical trials.

4.1.2. Strategies for Retention and to Improve Adherence to Protocol.

In large measure, the considerable experience and insights of investigators will be a first step in recruitment of participants who are more likely to remain in the study and adhere to protocol. The inclusion and exclusion criteria have been designed to eliminate, inasmuch as possible, those subjects who may be less likely to remain in the study due to comorbidities or other factors.

As an example of other factors, IPF patients who are already listed for lung transplantation will be excluded from participation. Participants will **not be prohibited from transplantation** at any time

during or after participation in this trial, since we cannot ethically preclude lung transplants (considered a definitive treatment) to a subject in this trial who, for whatever reasons, might become transplant eligible. Exclusions of subjects already listed with UNOS or those whose listing may be eminent will minimize very early drop-outs due to transplantations, and preclude any potential concerns about performing these procedures in patients currently treated with a NOX inhibitor. Notwithstanding, most ambulatory IPF in our centers are transplant ineligible due to age or co-morbidities.

Frequent outpatient visits are already routine standard of care for IPF patient care, and study compliance of these patients is typically very good (and probably better than in most other, less lethal, disease populations). As examples, study procedures were completed in 39/44 (88%) of the UAB patients entered into ACE-IPF, STEP-IPF, or PANTHER-IPF (durations of 48, 12, and 60 weeks, respectively). None of the 30 subjects enrolled in ART-IPF (including the 19 at UAB and Temple) have been lost to follow-up due to noncompliance during their 9 month trial observations. As in ART-IPF, participants will be compensated for routine travel expenses, as needed. Adherence to the treatment regime will be assessed at each outpatient visit using a combination of pill counts, reviews of patient diary data, and verbal reviews of medications taken. Assessments of adherence, and encouragement (reinforcement) for same, will also occur during phone contacts that occur at 2 week intervals in between face-to-face outpatient visits.

4.2 INFORMED CONSENT PROCEDURES

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

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

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

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

Prospective subjects who do not remember the important facts about participation in the research study after repeated testing will not be included in the study. The investigators will also assess whether a participant understands experimental procedures over time, including assessment throughout the full duration of participation in the study.

5 POTENTIAL RISKS AND BENEFITS

5.1 POTENTIAL RISKS

5.1.1 General Risks of Study Protocol and Procedures:

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

The risks of venipuncture**:**

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

The risks of chest HRCT scans**:**

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

The risks of pulmonary function tests:

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

The risks of six minute walk test:

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

5.1.2 Potential Risks of Experimental Interventions

The risks related to the administration of GKT137831:

Pre-clinical studies in dogs (the most sensitive animal species) found indications of bone marrow, cardiac conduction, hepatic and thyroid function abnormalities (generally mild and reversible) during treatment with comparatively large GKT137831 doses.

In contrast, GKT137831 has shown a very favorable safety and tolerability profile in humans at the dose range used in this trial. Overall, no clinical significant deleterious effects related to GKT137831 have been identified among subjects in other clinical trials for different indications (e.g., diabetic kidney disease, primary biliary cirrhosis).

As an example, among diabetics with renal disease, GKT137831 did not cause any detectable dose-related toxicity during the 12-week exposure. Rates of SAE were low and similar between GKT137831 (3/68 subjects, 4.4%) and placebo (5/68 subjects, 7.4%). One GKT137831 subject and 2 placebo subjects discontinued the study due to safety related events.

Furthermore, there were no clinically significant changes from baseline in routine safety laboratory assessments, physical examinations, and vital signs during the course of the study. In particular, there were no safety signals or toxicities of thyroid function, liver function, bone marrow function, or cardiac conduction.

The only notable safety finding was a statistically significant, albeit slight and non-clinically significant (~2.5 mm Hg) increase in diastolic blood pressure. There was also a trend for a marginal (~3 mm Hg) increase in systolic blood pressure, but this did not reach statistical [or clinical] significance.

Given the paucity of AE among subjects in other clinical trials, the specific risks of GKT137831 to study participants that may attributable to their participation here cannot be accurately quantified.

The risks related to the administration of placebo:

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

5.2 ALTERNATIVE TREATMENTS

Placebo and GKT137831 will be administered in addition to standard of care therapies. Accordingly, subjects receiving placebo will continue to receive optimal medical management throughout the treatment period. Accordingly, alternative treatments for the subjects participating in this investigation are to continue their medical care under the direction of their attending physician.

5.3 POTENTIAL BENEFITS

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

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

Importance of the Knowledge to be Gained

The preliminary data in this application outline a hypothesis for the progressive clinical deterioration in patients with IPF. The protocol specifically seeks to address that hypothesis. If the study intervention is found to be both safe and effective in the study population, the treatment of IPF would be altered significantly, and this could result in a change in the disease natural history. Completion of this protocol will address important questions related to this disease.

5.4. DATA SAFETY MONITORING PLAN

5.4.1 Data Safety Monitoring Board:
An independent DSMB will monitor this clinical trial. The DSMB will be constituted per the instructions of and with the approval of the NHLBI.

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

In addition, a DSMB Report addressing the following information will be provided for submission to the appropriate IRB(s) at the time of continuing review annually, or more often as required:

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

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

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

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

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

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

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

Each study site will be subject to on-going monitoring, primarily by the DCC. Study sites will be evaluated for meeting enrollment criteria and for the accurate and timely submission of data forms, and timely response to data queries from the study monitors or DCC. To assist the Protocol Chair in meeting his responsibilities as required by the DSMB, the University of Alabama at Birmingham's study team will assume the following general responsibilities:

Assist in protocol review

Maintain copies of FDA and IRB approval relevant to all participating Institutions.

Maintain an updated roster of participants.

Verify eligibility.

Verify responses.

Collect data on protocol specific CRFs.

Prepare all submitted data for review by the Protocol Chair.

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

Distribute SAE safety reports.

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

5.4.3. Data Coordination Center (DCC) – see Section 2.9:

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

- Commit to accrual to the multi-center protocol.
- Submit protocol and/or amendments to their local IRB as required.
- Maintain a regulatory binder.
- Update CCC with research staff changes on a timely basis.
- Submit source documents, research records, and CRFs to the DCC.
- Submit Serious Adverse Event reports to the CCC, and other entities, as specified.
- Submit deviations and violations to their IRB and the CCC.

5.4.5 Central IRB:
A central IRB will provide approval for all collaborating sites, in accordance with specifications, policies, and requirements of each of the local IRBs.

5.5. ADVERSE EVENTS (AE):

The safety of study drug will be assessed through the recording, reporting and analyzing of baseline medical conditions, signs, symptoms, general physical examination, laboratory tests, 12-lead ECGs, and vital sign data.

5.5.1. AE Definition and Classifications

An adverse event (AE) is defined as any untoward medical occurrence [in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline in a participant], associated with the use of a drug in the study participants, whether or not considered drug related. 21CFR312.32

Unchanged/stable pre-existing, chronic medical conditions present at baseline are NOT considered AEs and should not be recorded in the AE pages of the eCRF unless a worsening has occurred.

Adverse events after signing the informed consent form (ICF) and up to completion of the 28-day follow-up period after the last administration of study drug will be recorded. Adverse events occurring after the 28-day follow-up period may be reported by the investigator if the event is considered by the investigator of interest or importance.

The National Cancer Institute Common Toxicity Criteria Scale will be used to define grades (severity) of adverse events. The severity of adverse changes in physical signs or symptoms will be classified as follows:

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

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

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

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

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

Serious Adverse Events (SAE) Definition:
For this study, a **SAE** is any untoward adverse event that is:

1. Fatal or immediately life threatening
2. Permanently disabling, or severely incapacitating, or is a substantial disruption of the ability to conduct normal life functions.
3. Requires, or prolongs, inpatient hospitalization.
4. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.
5. Is a congenital anomaly/birth defect

Non-Serious Adverse Event Definition:
An adverse event that does not fulfil the criteria of a Serious Adverse Event.

Drug Reactions:
A drug reaction is a noxious and unintended response to a medicinal product at any dose. “Response” means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility (causality grade “possible”, “probable” or “definite”). All

drug reactions are adverse events, but not all adverse events are drug reactions. A dichotomy of causality ratings will be used for reporting purposes:

- "Related" means that a causal relationship between the drug and the event is at least a reasonable possibility, i.e. rating "possible", "probable" or "definitely".

- "Unrelated" means rating "unlikely/remote/not related".

The study investigator (local PI, in conjunction with the CCC Contact PI) will make these determinations.

Expectedness Assessment:
An unexpected AE is **any AE** (see definition above) in a study participant that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the general investigational plan (21 CFR 312.32).

Unanticipated Problem (UP):
Any incident, experience or outcome that meets ALL of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (possibly related to participation in the research means there is a reasonable possibility that the AE, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

5.5.2. AE Recording and Reporting

Assuring patient safety is an essential component of this protocol. The contact PI has primary responsibility for the oversight of the data and safety monitoring. The study investigators will evaluate all AE. All subjects who have AE, whether considered related to the use of the study medication or not, must be monitored to determine the outcome.

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

The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the PI considers it medically justifiable to terminate follow-up.

5.5.3 Regulatory Agency AE Reporting Timeline:

The investigators will report life-threatening or fatal unexpected AE related to the use of the study drug or procedures to the contact PI, DCC, NHLBI, DSMB, central IRB, FDA and local IRB (if specified) within seven (7) calendar days of discovery of the event.

Serious (but not fatal or life-threatening) and unexpected AE related to the use of the study drug or procedures must be reported to the DCC, NHLBI, DSMB, the local IRB, central IRB, and FDA (if specified), within 15 calendar days.

An unanticipated problem (UP) that that is not an SAE will be reported to the DCC, NHLBI, central IRB and local IRB (if specified) within 14 days of the investigator becoming aware of the problem.

5.5.4 Reports to Genkyotex
It will be the responsibility of the contact PI and DCC at UAB to further reports of AE to Genkyotex as specified in the Safety Data Exchange Agreement:

Serious Adverse Event reports will be forwarded by email to the attention of the clinical safety contact of the other Party. The clinical safety contact (or delegate) will acknowledge receipt of each report within 48 hours of reception.

UAB will supply to GENKYOTEX:

All reports of fatal or life-threatening Suspected Unexpected SAE (SUSAR) in subjects exposed to study drug within three (3) calendar days after first knowledge that the event is reportable, in the format of an international CIOMS I Form or similar format (e.g. MedWatch or SAE forms). Unless unblinding is medically necessary, the final specification of the actual drug (GKT137831 or placebo) on the form(s) will be completed by the UAB Investigational Pharmacy (to avoid inadvertent unblinding of study staff).

All other reports of SUSAR in subjects exposed to study drug within ten (10) calendar days after first knowledge that the event is reportable, in the format of a CIOMS I Form or similar format (e.g. MedWatch or SAE forms). Unless unblinding is medically necessary, the final specification of the actual drug (GKT137831 or placebo) on the form(s) will be completed by the UAB Investigational Pharmacy (to avoid inadvertent unblinding of study staff).

All other SAEs in subjects exposed to the study drug within 30 calendar days after first knowledge that the event is reportable, in the format of a CIOMS I Form or similar format (e.g. MedWatch or SAE forms), following the same procedures described above to prevent inadvertent stuff unblinding.

All follow-up information received regarding any SAE in the same manner and within the same period as for initial information.

5.5.5 Pregnancy:
If a female study subject who has been exposed to the study drug becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. The study drug must be discontinued. If a female partner of a male study subject who has been exposed to the study drug becomes pregnant, and the subject provides this information, then the pregnancy will be documented, based on information provided by the subject. Any pregnancy (either female study participants or female partners of male study participants) must be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Consent to report information regarding pregnancy outcome should be obtained from the female partners of male study participants. The study treatment must be discontinued for pregnant participants.

Although pregnancy itself is not considered as an AE, all pregnancies occurring inadvertently during the study pre-treatment, treatment and post-treatment period must be reported in the same timelines as a SAE. Spontaneous abortions and congenital birth defects should always be reported as SAEs.

5.6 STOPPING RULE:

5.6.1.Individual Subject-Specific Stopping Rules:

A study participant will be discontinued from further study drug treatment/Intervention(s) administration if any of the following occur:

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

- Development of any exclusion criteria may be cause for discontinuation (e.g.: cardiac conduction defect).

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

- Request by the subject to withdraw from the study.

- Investigator discretion

5.6.2. Study-wide Stopping Rule:

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

5.6.3. Parameters to be Monitored:

The following progress will be monitored by the contact PI, the DCC and DSMB throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

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

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

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

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

5.6.4. Frequency of Monitoring:
The contact PI will review subject safety data as it generated. The PI, Co-investigators, and the research staff will meet or converse at least at monthly intervals, or more frequently if necessary, to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints, and confidentiality of subjects. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The investigators will also review the outcome and AE data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or be re-evaluated and changed.

The DSMB will meet as needed, but not less than every 6 months, to review the progression of the study including patient enrollment, protocol compliance, and adverse event reports. An emergency meeting of the DSMB may be called at any time by the Chair should participant safety questions or other unanticipated problems arise.

5.7 RISK MANAGEMENT PROCEDURES

5.7.1 Protection against Loss of Confidentiality
Given our multiple safeguards, and considerable prior experiences with conducting clinical trials, the risks of loss of confidentiality are very small.

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that unnecessary sensitive information is not collected.

To avoid any violation of subject confidentiality, all data will be stored in a password-protected database, identified only by study ID number at the DCC. A confidential database linking patient identifying information with study ID number will be maintained at each clinical site; the CCC or DCC will not be in possession of patient identifying information.

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

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

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

All staff involved in this study will be properly credentialed and instructed in the areas of testing, confidentiality, and safety. All principal and co-investigators, coordinators, and other Key Personnel are required to participate in courses and be certified as mandated by local IRBs regarding Education and Certification Programs in Research & Practice Fundamentals (RPF).

5.7.2. General Measures to Reduce Risks of Experimental Intervention:
Despite the documented safety profile of GKT137831 in other human trials (see Section 5.1.2.), the study design emphasizes protecting patients against risk. General measures adopted to mitigate potential risks include:

1) Involvement by trained staff / investigators with experience in the administration of experimental agents

2) Prior human experience with the study medication in other conditions

3) Exclusion of patients with serious comorbidities or other potentially life-threatening problems.

4) Continuous monitoring by an independent DSMB

5.7.3 Specific Experimental Risk Mitigations:

5.7.3.1. Procedures to Reduce Risks of Study Drug Administration:

Although apparently safe in humans, several conservative safety measures have been implemented in this trial, singularly focusing on toxicity signals seen in preclinical dog studies. Thus, potential participants with preexistent hematological, cardiac, liver, thyroid, or renal abnormalities that could conceivably increase risks with GKT137831 will be excluded from this trial. The initial screening assessment will accordingly include the following procedures:

- Detailed medical histories.

- Physical exams to include vital signs and blood pressure.

- Laboratory evaluations, to detect safety-related exclusion criteria, include: electrocardiograms (EKG), complete blood counts (CBC), comprehensive metabolic panels (CMP), thyroid function tests (TFT), liver function tests (LFT), blood pregnancy (if applicable- see following section), and FSH (if applicable).

- Findings of laboratory abnormalities, at screening or at any subsequent assessment, irrespective of study participation or causality, that are clinically significant in the judgement of the local principle investigator will be communicated to the participant and, at their request, to

that participant's physician.

Conservative **exclusion criteria** that will further minimize potential for toxicities **include**:

A history of malignancy, excluding basal or squamous cell skin cancer and low-risk prostate cancer, the latter defined as stage T1 or T2a, with prostate specific antigen <10 ng/dl. NOX inhibition is not known to promote cancer, and these criteria are within current guidelines.

Treatment for >14 days within the preceding month with >20 mg. prednisone (or equivalent) or any treatment during the last month with a cellular immunosuppressant (e.g., cyclophosphamide, methotrexate, calcineurin inhibitors, etc.), given increased risks of opportunistic infections in these subjects, although GKT137831 is not known to be immunosuppressive.

Treatment with any investigational agent within 4 weeks of Screening (Visit 1) or 5 half-lives of the investigational medicinal product (whichever is longer) to exclude potential cross-reactions or confounding.

Subjects with known hypersensitivity to GKT137831 or its excipients (e.g. capsule "bulking" agents).

A history of bone marrow disorder including aplastic anemia, or marked anemia defined as hemoglobin < 10.0 g/dL (or 6.2 mmol/L).

Severe cardiovascular disease, defined as any of the following within the preceding 12 weeks: acute myocardial infarction or unstable angina, a coronary revascularization procedure, congestive heart failure (NYHA Class III or IV), or stroke, including a transient ischemic attack.

Evidence of cardiac conducting abnormalities, defined as second or third degree AV block not successfully treated with a pacemaker, or a personal or family history of long QT syndrome (QTc interval >450 msec for males or 470 msec for females).

End-stage renal disease requiring dialysis.

Liver function tests (transaminases, alkaline phosphatase, direct and total bilirubin) >3x upper limit of normal values.

Since the study drug is largely metabolized via the CYP3A4 pathway, systemically administered potent CYP3A4 inhibitors or induces are prohibited during the 24-week treatment period:

Inhibitors include: boceprevir, cobicistat, conivaptan, ritonavir, itraconazole, ketoconazole, telaprevir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir.

Inducers incude carbamazepine, enzalutamide, mitotane, phenytoin, rifampin.

See also: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

Although not seen in human subjects in other trials, we will be especially alert to potential hematological, thyroid, liver, and cardiac conduction abnormalities (given indications of these toxicities in dogs treated with high drug doses). The monitoring plan includes history, physical exam, and repeat laboratory assessments routinely every 6 weeks during the treatment period (a

total of 24 weeks). In addition, telephone interviews will be conducted at two-week intervals in-between the face-to-face assessments.

Other risk mitigation processes include oversights by the FDA and an independent DSMB, as well as procedures to reduce reproductive risks (to follow).

5.7.3.2 Mitigation of Specific Risks Related to Female Participants:
GKT137831 is not known to be teratogenic. Moreover, since IPF is primarily a disease of the elderly, and male predominant, very few (if any) of the trial participants are likely to be Women of Child Bearing Potential (WCBP).

Nonetheless, given the investigational nature of GKT137831, WCBP who do not agree to abstinence or an effective form of contraception (as approved by the investigator), or who are breast feeding, for 4 weeks before randomization until 90 days after the last administration of study medication (or placebo), will be excluded from participation.

WCBP participants must use a highly effective method of contraception to prevent pregnancy for 4 weeks before randomization and must agree to continue strict contraception for 90 days after the last administration of study medication.

Highly effective contraception for WCBP is defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include: combined (estrogen + progestogen) hormonal contraception (oral/intravaginal/transdermal); progestogen-only hormonal contraception (oral/injectable/implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner (provided that partner is the sole sexual partner of the WCBP study subject and that the vasectomized partner has received medical assessment of the surgical success); or sexual abstinence (defined as refraining from heterosexual intercourse from 4 weeks before randomization until 90 days after the last administration of study drug, and only if this is the preferred and usual lifestyle of the subject).

WCBP must also have a negative serum pregnancy blood test during screening, a urine pregnancy test immediately prior to their first experimental treatment.

WCBP are defined as “All female subjects after puberty unless they are post-menopausal (defined as amenorrhea for 12 months with documented date of last monthly period) or are surgically sterile (i.e., bilateral tubal occlusion).”

For female subjects aged <55 who are considered post-menopausal and who are not on concomitant estrogen replacement therapy, confirmation of postmenopausal status will be required with follicle stimulating hormone (FSH) test results in the postmenopausal range for age at Screening.

The development of pregnancy in a participant undergoing treatment will be considered and reported as a SAE, and further experimental treatment in that subject will be terminated.

5.7.3.3. Mitigation of Specific Risks Related to Male Participants:

Men who are not surgically sterile and do not agree to remain abstinent from heterosexual intercourse or use effective contraception (as approved by the investigator), and refrain from

donating sperm, from the time of giving informed consent until 90 days after the last administration of study medication (or placebo) will be excluded from participation.

Male participants with WCBP partners must be willing to use a condom and require their female partner to use an additional form of adequate contraception, as approved by the Investigator, such as an established form of hormonal contraceptive, a diaphragm or cervical/vault cap, IUD, or sponge with spermicide. This requirement begins at the time of informed consent and ends 90 days after last administration of study drug. Male study participants must also not donate sperm from baseline until 90 days after last administration of drug.

5.7.4. Physical Injury from Study Participation:

Medical treatment for conditions that arise as a result of study participation will not be treated by study personnel. The volunteer will be informed of the problems identified, and this information will be transmitted to the responsible attending physician or physician designated for the subject. In the event of physical injury resulting from the research procedures, medical treatment will be available but not offered free of charge. In addition, financial compensation is not available for wages lost because of injury related to the research protocol. This will be emphasized at the time of consent.

6 STUDY ADMINSTRATION

6.1 REGULATORY AND ETHICAL CONSIDERATIONS

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

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

6.2 PROTOCOL DEVELOPMENT

6.2.1 Activation of a protocol

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

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

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

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

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

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

6.2.2 Clinical Coordinating Center Support Function

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

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

Maintain regulatory documents for all participating institutions.

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

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

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

Assistance in preparation and maintenance of case report forms.

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

Maintain documentation of all communications.

6.3 PROTOCOL MANAGEMENT

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

6.3.1 Protocol distribution

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

6.3.2 Protocol revisions and closures

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

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

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

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

6.4 INFORMED CONSENT REQUIREMENTS

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

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

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

6.5 IRB DOCUMENTATION

All activities of this trial will be under auspices of approval by a central IRB, administered thru UAB. Sites must obtain individual clearance and approval for the Central IRB thru their local IRB. The following must be on file with the Coordinating Center or designee and must be submitted and approved by the Coordinating Center prior to initiation of the study:

- Approval of the Central IRB
- Letters, if necessary, of Approval of the institution's IRB
- Copy of the Central IRB-approved Informed Consent Form

- IRB approval for all amendments

6.5.1 IRB Renewal Approval

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

6.6 QUALITY CONTROL AND QUALITY ASSURANCE

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

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

6.7 DATA HANDLING AND RECORD-KEEPING

6.7.1 Subject Identification / Study IDs

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

The clinical coordinator will write the date and the consenting person's name on the site-specific ID Generation Log. These designations are not sufficient to identify the participant.

6.7.2 Data Recording/Case Report Forms

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

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

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

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

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

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

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

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

6.7.3. Record maintenance and retention

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

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

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

6.8. LEADERSHIP PLAN

This proposal has an overall project and contact PI (Dr. Duncan) and physician-investigators (Co-Investigators) at each clinical site. This consortium will provide the necessary experience in patient clinical care, as well as management of complex multicenter clinical trials. This structure will thus ensure adequacy of clinical trial enrollment, appropriate protocol compliance, data acquisition and transmission, and acquire, catalogue, store and ultimately utilize the data and invaluable clinical specimens that will be generated here. The PI, Co-Investigators, and DCC head have complimentary and overlapping skill sets, and each has special expertise and proven track records with clinical and/or translational investigations. The numbers of subjects that this consortium can enroll is a major strength of this proposal, and will be more than adequate to accomplish the research objectives here.

The contact PI for this trial will have primary responsibility for fiscal administration, protocol and consent refinement, development and implementation of the clinical coordinating center, fulfil the myriad administrative, regulatory and legal requirements of a multicenter clinical trial, and develop data acquisition methods in conjunction with Dr. Sejong Bae. Dr. Duncan will also be the common interface for inter-actions with physician-investigators at the collaborating centers, the DSMB, NHLBI, FDA, Genkyotex, and IRB, etc.

An Executive Committee, consisting of the PI, Co-Investigators, including the DCC director, will be constructed, prior to enrollment of subjects. The Executive Committee will utilize at least monthly conference calls (and others as needed) during the initiation and implementation phase, in order to review the status of the clinical protocol and mechanisms. This Committee will function as the proximate governing body for this project. Each of the respective physician-investigators will share responsibility for the establishment of the network and trial execution at their center, in collaboration with the DCC and Project PI. Annual face-to-face meetings will occur at a central location or in the context of other conferences (e.g., annual ATS Conventions, fibrosis meetings, etc.). If problems arise that cannot be resolved with informal mutual agreement, the pertinent issues will be discussed and voted upon by the Executive Committee for adjudication. We believe this structure will also be useful for reviews of IRB submission preparations and dealing with any unforeseen problems.

Publication authorship will be based on the relative contributions of the investigators.

7 COSTS AND PAYMENTS

7.1 COSTS

Experimental research testing consists of trial-specific studies that are not SOC will be supported by the research grant. All experimental medications will also be paid for by the research grant. Routine lab tests and procedures will be considered routine medical care and will be billed to the subjects' health insurance company. Subjects will be responsible for paying any deductibles, co-payments or co-insurance that are a normal part of their health insurance plan. Subjects who do not have health insurance will be responsible for these costs.

7.2 PAYMENTS

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

8 QUALIFICATIONS AND SOURCES OF SUPPORT

8.1 QUALIFICATIONS OF THE INVESTIGATORS

University of Alabama at Birmingham:

Steven Duncan, M.D.: Principle Investigator. Dr. Duncan is Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham. Dr. Duncan has been the PI of several clinical trials in IPF and other lung diseases. His translational research interests center on understanding the role of adaptive immunity in the pathogenesis of IPF and COPD. Dr. Duncan is also the head of the Clinical Coordinating Center for this study and will provide daily leadership and supervision to all aspects of the clinical trial execution.

Temple University Medical Center:

Gerald J. Criner, MD, Co-Investigator Dr. Criner is Professor of Medicine at Temple University. Dr. Criner is also Chief, Section of Pulmonary and Critical Care Medicine, and Director, Medical Intensive Care Unit and Ventilator Rehabilitation Unit at the Temple University Medical Center. Dr. Criner's internationally recognized clinical work focuses on advanced lung disease (COPD, emphysema, pulmonary fibrosis, pulmonary hypertension, respiratory failure), and critical care medicine. Dr. Criner, will provide daily leadership and supervision to all aspects of the clinical trial execution at the Temple University Medical Center.

University of Michigan Medical Center:

Kevin Flaherty, M.D., Co-Investigator Dr. Flaherty is a Professor of Medicine at the University of Michigan and Director of the Interstitial Lung Disease Program. Dr. Flaherty has served in leadership roles for industry and NIH-sponsored trials of novel treatments for IPF. He also serves as vice-chair for the University of Michigan Human Subjects IRB and is Chair of the Pulmonary Fibrosis Foundations Clinical Care Network/Patient Registry Steering Committee.

University of Minnesota

Hyun Joo Kim, M.D., Co-Investigator. Dr. Kim is an Associate Professor and attending physician in the hospital and clinics of University of Minnesota. She is also the Director of the U of MN Interstitial Lung Disease (ILD) Program and the Director of the Pulmonary Fibrosis Foundation Care Center Network site at the University of Minnesota. As Director of the U of MN ILD program, she has conducted eight major clinical trials exploring novel therapies for idiopathic pulmonary fibrosis (IPF). She has recognized expertise in the conduct of clinical trials in IPF.

Tulane University Medical Center:

Joseph Lasky, M.D., Co-Investigator. Dr. Lasky is a Professor of Medicine and Chief of the Section of Pulmonary Diseases, Critical Care, and Environmental Medicine at Tulane University in New Orleans, LA. His primary research interests focus on furthering our understanding of the mechanisms involved in fibrogenesis. Additionally, Dr. Lasky has recognized expertise in the design and conduction of clinical trials. He served as the PI for the NHLBI IPFnet Gulf South Consortium, which was a collaboration between Tulane University and UAB. He also served as the PI for an investigator-initiated lung fibrosis trial and serves on data safety monitoring boards for several ongoing international pulmonary fibrosis trials.

8.2 SOURCE OF SUPPORT: National Heart, Lung, and Blood Institute (HL119960). Genkyotex will also provide the experimental agent GKT137831 and placebo, and pay for selected biomarker and drug assays.

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10. AMENDMENTS

Amendments and Modifications to Earlier Versions of GKT-IPF

Protocol Modifications made on August 15, 2019 (to v.3.0, May 5, 2019)

1) The date and version number were updated on header and Synopsis (from v.3.0, May 5, 2019, to current iteration v.4.0 August 15, 2019).

2) An exclusion criterion (#15) that prohibits use of strong CYP3A4 inducers or inhbitors during the 24 week treatment period was added to Synopsis (page 9-10) and Inclusion/Exclusions (page 26), as recommended by the FDA.

3) Appropriate page number corrections were made to the Table of Contents (pages 4-5)

4) A protocol Amendments section was added (page 62)

5) Typographical errors (mislabeled Figure 7 panel) were corrected (page 16)

Protocol Modifications made on Jan. 26, 2020 to now become Protocol v5.0 1/26/2020. Changes to the former Protocol are delineated with yellow highlighting.

1) The date and version number were updated on header and Synopsis to current iteration v.5.0, Jan. 26, 2020).

2) The IRB number has been corrected (to: IRB- 300003198) throughout the document.

3) Correction of typos: page 9: "induces" is now "inducers"; page 23: "standard if care" is now "standard of care"; page 31: "uring" is now "urine"

4) Clarification and reconciliation throughout text (pages 7,9-11) that 6MWD tests will be performed at baseline and 12 week intervals. In some places it was erroneously stated or implied these tests would be performed every 6 weeks while in the trial.

5) A "free-standing", additional Data Safety Monitoring Plan (for use by the DSMB) was written at the request of the NHLBI and has been approved by them. To streamline study paperwork this DSMP has been incorporated nearly verbatim into the Protocol (Sections 5.4-5.7). Since the DSMP was, in turn, derived from the original protocol, very little has changed, and the only new procedures or additions that were requested by NHLBI are: A) Unexpected problems (UP) associated with this research have been defined (Section 5.5.1) and reporting timeline for these UP detailed (Section 5.5.3). B) The DSMB will now have sole responsibility (instead of **either** the DSMB or NIH) for evoking a study wide stopping rule (Section 5.6.2). C) A formalized specification that incidental clinically-significant lab abnormalities will be reported to the subject has been added here (Section

5.7.3.1) and the ICF. Details of most recent human safety data have been revised and updated (Section 5.1.2).

Informed Consent Modifications made on Jan. 26, 2020 to now become ICF v2.0 1/26/2020. Changes to the former ICF are delineated with yellow highlighting.

1) It is now explicitly stated herein that subjects will be notified regarding incidental or other clinically-significant lab abnormalities.

2) Clarification and correction that 6MWD tests will be made at 12 weeks, rather than 6 week intervals.

Protocol Modifications made on March 6, 2020 to now become Protocol v6.0 3/6/2020. Changes to the former Protocol are delineated with tracked changes. These changes were requested by the DSMB and are largely changes to phrases, corrections of typos or grammar. None of these changes represent a significant change of procedures or practices.

1) The date and version number were updated on header and Synopsis to current iteration v.6.0, March 6, 2020).

2) The wording of Interim Analysis (section 2.8.3) has been changed in accordance with DSMB suggestions. The context/meaning remains the same.

3) A phrase describing how the study population is at high risk in Section 5.7.2 has been deleted.

Informed Consent Modifications made on March. 6, 2020 to now become ICF v3.0 3/6/2020. These changes, delineated with tracked changes, were requested by the DSMB and are largely changes to phrases, corrections of typos or grammar. None of these changes represent a significant change of procedures or practices.

1) The words of the bulleted summary on page 1, "What should I know about this research", have been changed to be identical to another, near identical bulleted summary later in the ICF, to maintain consistency.

2) In various and multiple places (page 2 and several others) the definition of "placebo" and "randomization" have been reiterated.

3) The potential organizations that could potentially share private information has been streamlined to omit Genkotex (page 13).

PROTOCOL MODIFICATIONS: Made on August 1.0 to Version 6.0 (to now become V7.0)

1) Dates and protocol version numbers were changed throughout (to now become V7.0 August 1, 2020)

2) The interval PFTs (spirometry and DLCO) and 6MWD at 6, 12, and 18 weeks have been deleted. These tests instead will be performed at baseline and compared to values obtained at the conclusion of the study at week 24. This change was made in considerations of difficulting involved in obtaining these particular tests during the covid pandemic.

PROTOCOL MODIFICATIONS made to Version 7.0 on April 5, 201 (to become Version 8.0)

1) The interval since original diagnosis of IPF has been changed from 5 years to 10 years

2). The exclusion for history of cancer has been modified to “within the last 5 years”.

INFORMED CONSENT MODIFICATIONS made on August 1, 2020 to now become ICF v4 08/01/2020.

1) The serial PFTs and 6MWD measures at 6, 12, and 18 weeks (see #2 above) have been deleted.