New trials on IPF

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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

Roche


Roche
gsk
GlaxoSmithKline
IMMUNE
WORKS
GeNO
Healthcare Corp
MOERAE
MATRIX
biogen idec
SANOFI
AstraZeneca
Galecto Biotech
Promedior
Boehringer
Ingelheim
GILEAD
FIBROGEN
Takeda
Janssen
ucb
Pharma
Bristol-Myers Squibb

Tralokinumab

Cotrimoxazole

Nintedanib

GSK2634673F

FG-3019

BMS-986020

SAR156597

STX-100

TD139

PRM-151

Simtuzumab

IW001

Pirfenidone

Sirolimus

Carlumab

Lebrikizumab

EDITORIAL
INTERSTITIAL LUNG DISEASE

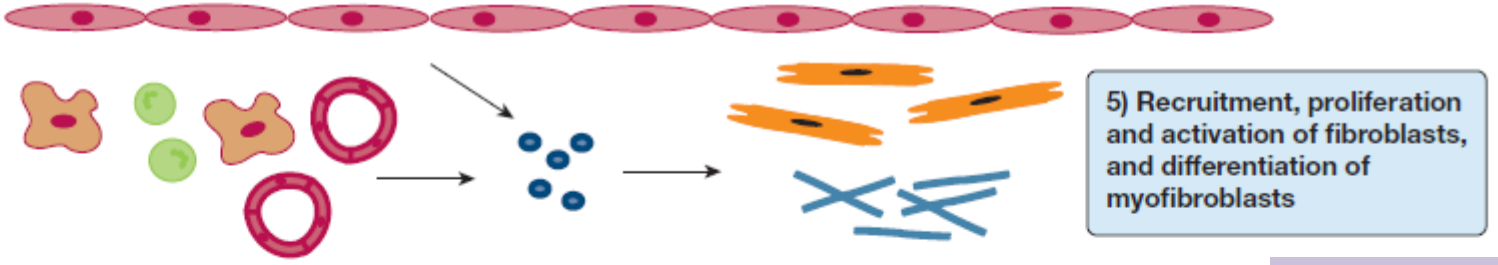
Where do we go from here? Clinical drug development in idiopathic pulmonary fibrosis

Harold R. Collard

- Issue 1: *which **mechanism** to target*
- Issue 2: *which **patients** to enrol*
- Issue 3: *which **end-points** to measure*

ERJ 2015; 45: 1218-1220

Linking IPF Pathogenesis to Potential Therapies



1) Susceptible host

- Genetics
- Aging

2) Injury to alveolar epithelium

- Cigarette smoke
- Industrial dusts
- Gastroesophageal reflux
- Viral infection

3) Aberrant wound healing response

- Recruitment and activation of immune cells
- Increased vascular permeability
- Activation of epithelium
- Increased apoptosis and premature senescence of alveolar epithelium

Lebrikizumab
Tralokinumab
NAC

4) Release of profibrotic cytokines

Lebrikizumab
Simtuzumab
Tralokinumab
SAR156597

5) Recruitment, proliferation and activation of fibroblasts, and differentiation of myofibroblasts

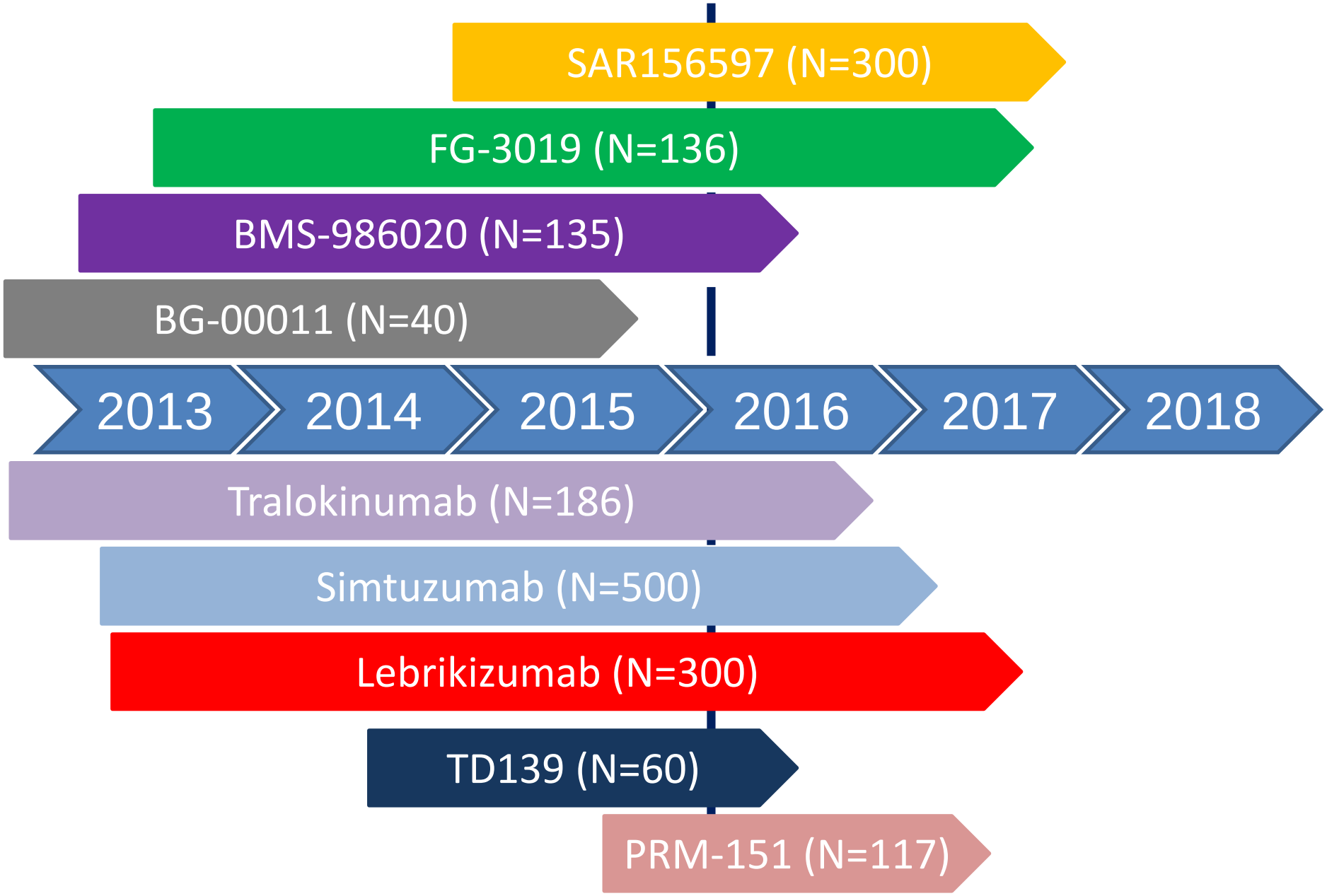
6) Increased extracellular matrix deposition

Nintedanib
Pirfenidone
STX-100
BMS-966020
TD139
Simtuzumab
PRM-151/pentraxin-2

7) Impaired gas exchange, leading to respiratory failure

Goodwin et al. Chest 2016; 149: 228

Recent and ongoing phase 2 pharmacological trials



SAR156597 (ESTAIR phase 2 study, Sanofi)

SAR156597 is a monoclonal antibody that specifically blocks IL-4 and IL-13

Both IL-4 and IL-13 are cytokines that may induce inflammation

Inflammation may contribute to the damage that is seen in the lungs of IPF patients.

A randomized, double blind, placebo-controlled, 52-week, dose ranging study

Phase 2b study in patients with IPF has started in May 2015 (ClinicalTrials.gov Identifier: NCT02345070) ended October 2017

Lebrikizumab (RIFF phase 2 study, Roche)

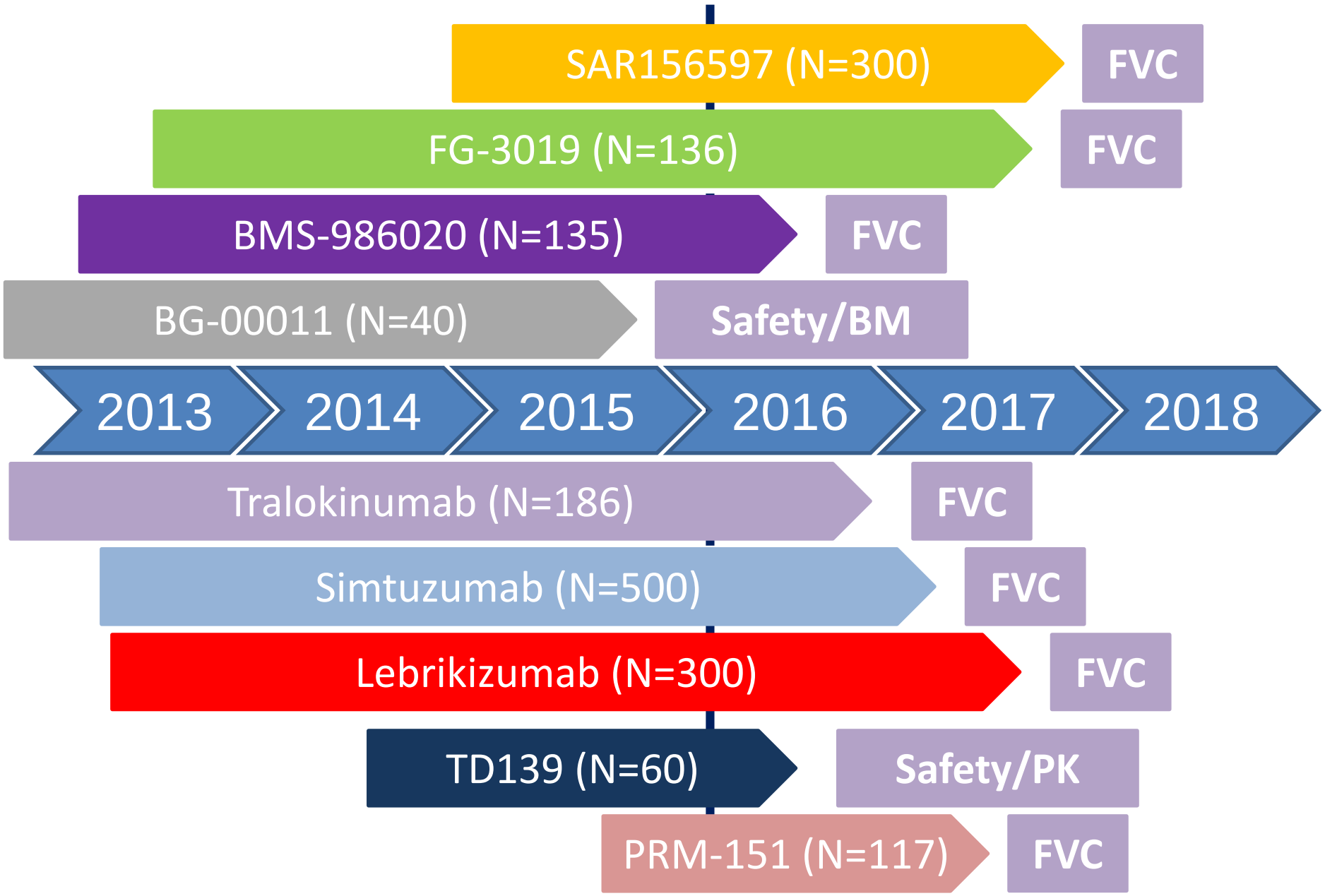
Lebrikizumab is a monoclonal antibody against IL-13

To evaluate the efficacy and safety of lebrikizumab as monotherapy in the absence of background IPF therapy (Cohort A) or as combination therapy with pirfenidone background therapy (Cohort B) in patients with IPF.

A randomized, double blind, placebo controlled, study to assess the efficacy and safety of lebrikizumab

Phase 2 study in patients with IPF has started in June 2013 (ClinicalTrials.gov Identifier: NCT01872689)

Ongoing phase 2 pharmacological trials



Why FVC as the Primary Endpoint?

Pros

Standard measurement of pulmonary function

Simple, easy to perform

Reproducible

Placebo group change is well understood (predictable)

Changes may be observed in a short time frame

Precedent –Clinical trials

Correlates with survival

Cons/controversies

FVC is a biomarker

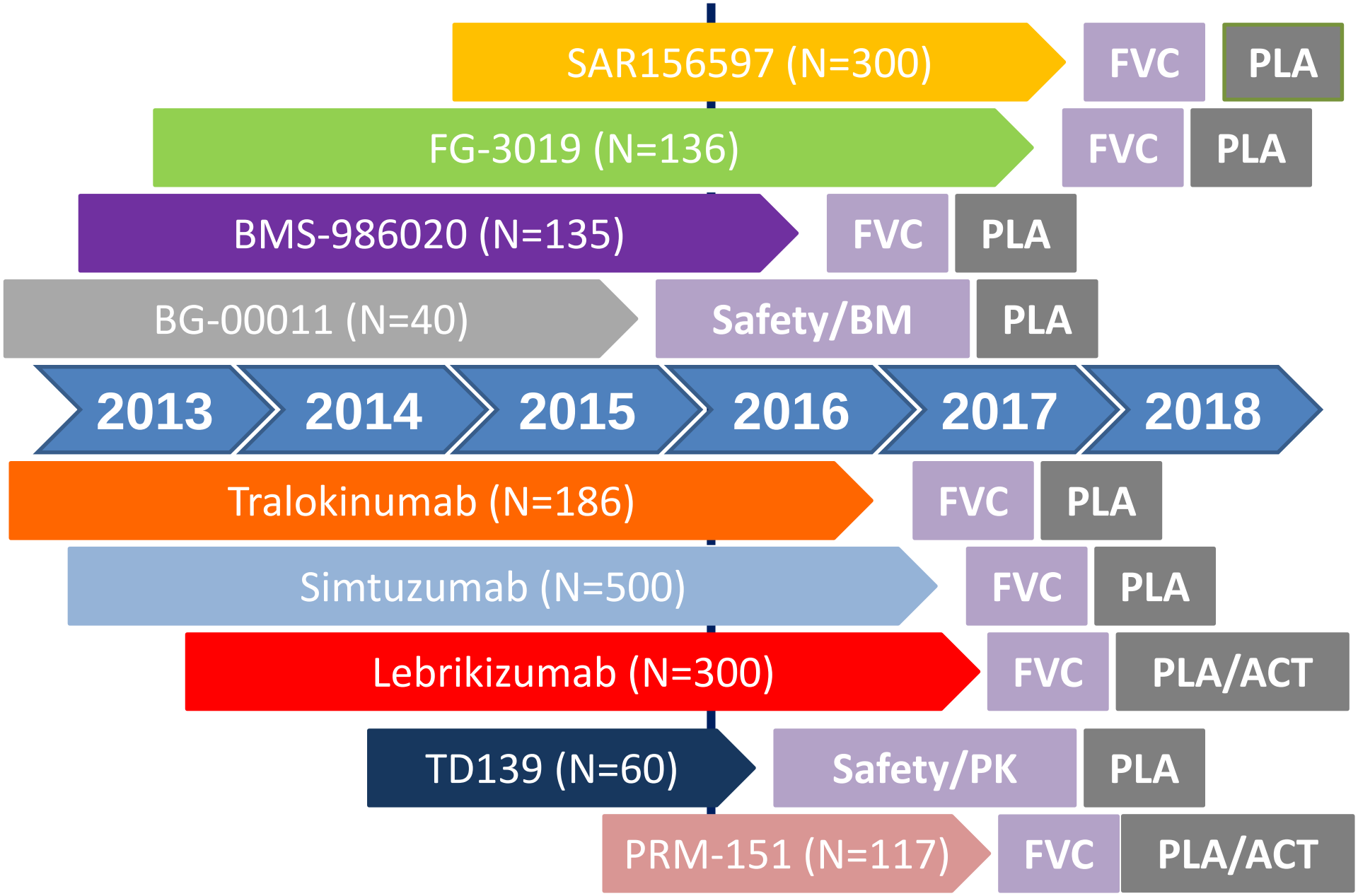
FVC is not a validated surrogate for clinical events that are meaningful to patients (e.g. acute exacerbations, mortality)

Minimal ΔFVC: ? (e.g. 10% decline over 52 weeks)

How to deal with death and missing data?

Is the true placebo arm ethical today?

Ongoing phase 2 pharmacological trials



PRM-151 (phase 2 study, Promedior)

PRM-151 is a recombinant human pentraxin-2 protein

Pentraxin-2 is an endogenous human protein that plays an important role in regulating the response to fibrosis.

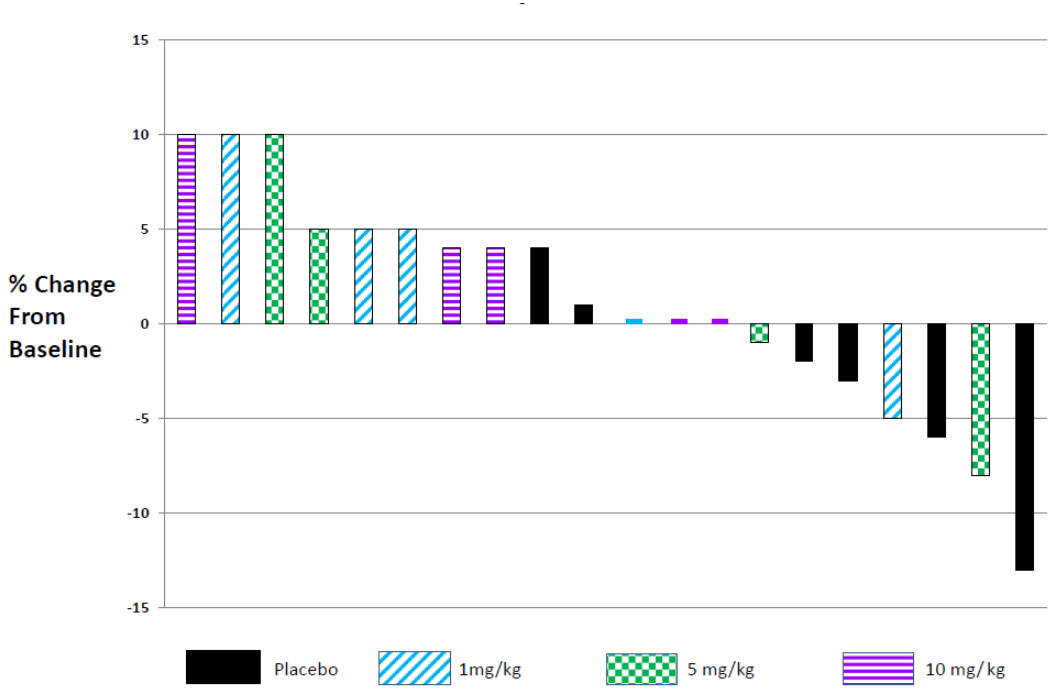
PRM-151/Pentraxin-2 binds to damaged tissue and monocytes and directs monocyte differentiation towards resolution of fibrosis

If on pirfenidone or nintedanib, subject must have been on a stable dose for at least 3 months

Phase 2 study in patients with IPF has started in August 2015 (ClinicalTrials.gov Identifier: NCT02550873)

PRM-151 (phase 1b study, Promedior)

PRM-151 in Patients with IPF:
Relative change from Baseline on Day 57 in FVC % Predicted



A randomized, placebo-controlled Phase 1b multiple ascending dose study in IPF patients demonstrated that PRM-151 was generally safe and well-tolerated and resulted in a mean improvement in FVC at 8 weeks

GLPG1690 (phase 2b study, Galapagos)

FLORA was an exploratory, randomized, double-blind, placebo-controlled trial investigating a once-daily oral dose of GLPG1690 (an autotaxin inhibitor).

Autotaxin is a secreted enzyme important for generating the lipid signaling molecule lysophosphatidic acid (LPA). Autotaxin has lysophospholipase D activity that converts lysophosphatidylcholine into LPA.

The drug candidate was administered for 12 weeks in 23 IPF patients, 17 of whom received GLPG1690 and 6 placebo.

Primary objectives of the trial were to assess safety, tolerability, pharmacokinetics and pharmacodynamics of GLPG1690 in an IPF patient population.

Secondary objectives included the evaluation of lung function, changes in disease biomarkers, FRI, and quality of life.

Over the 12-week period, patients receiving GLPG1690 showed an FVC increase of 8 mL, while patients on placebo showed an FVC reduction of 87 mL (mean from baseline).

GLPG1690 (phase 2b study, Galapagos)

FVC stabilized over the 12-week treatment period, placebo arm show the expected decline

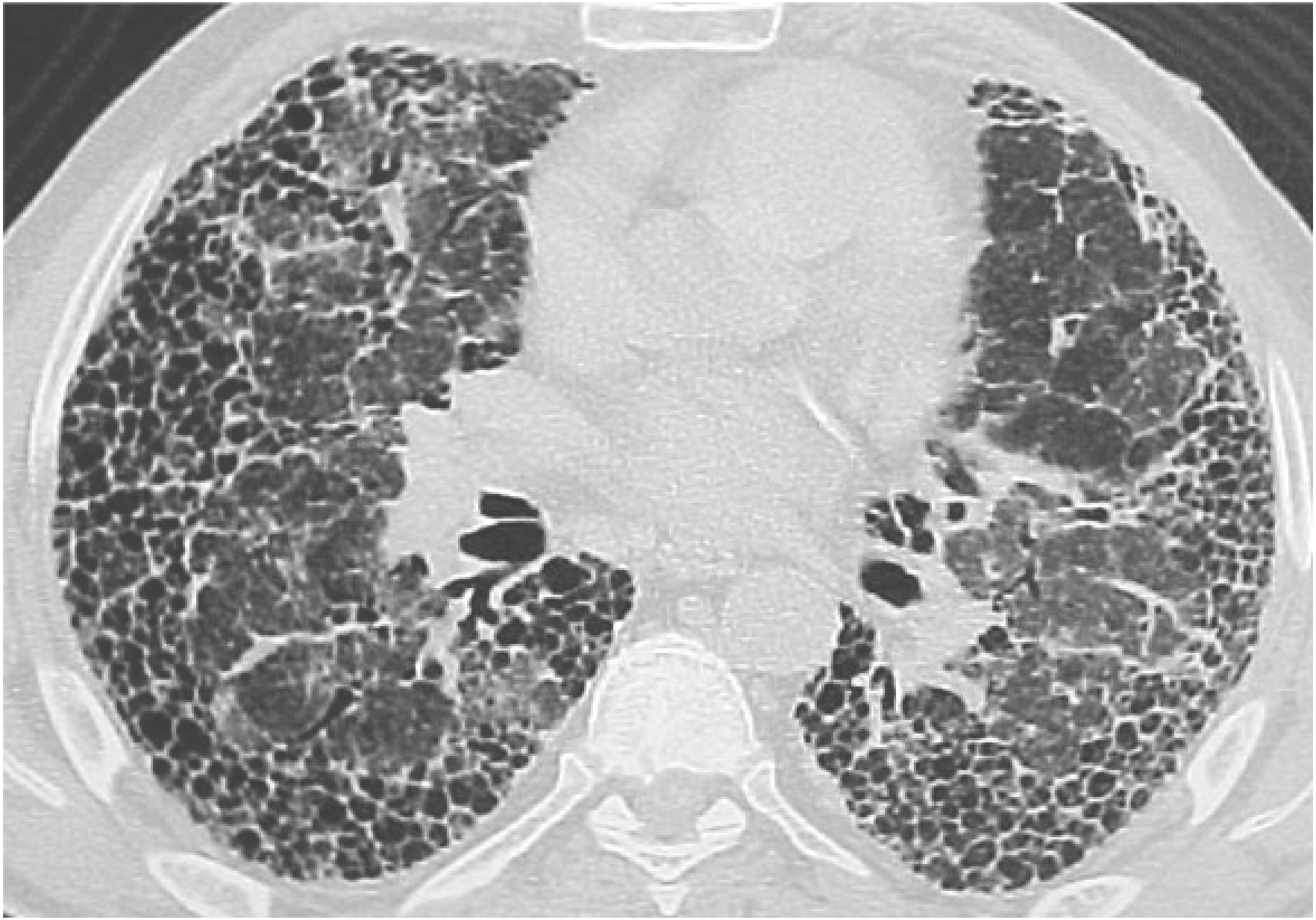
GLPG1690 was generally well tolerated

First autotaxin inhibitor to show effect in IPF patient trial

GLPG1690 expected to progress to late stage trial

Severe IPF

A phase IIb, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and intermediate or high probability of group 3 pulmonary hypertension



Rationale

- PH is common in patients with IPF, and its prevalence increases with disease severity
- PH is a major contributor to morbidity and mortality in patients with advanced IPF, and it has an adverse impact on survival
- There are currently no approved therapies for PH secondary to lung disease (Group 3 PH), including PH secondary to IPF
- Phase II and III clinical trials in IPF, including pirfenidone trials, have generally excluded patients with advanced disease and/or PH
- Patients with PH secondary to advanced IPF therefore represent a group with a high unmet medical need

Rationale

STEP-IPF: RCT, sildenafil studied in 180 patients with advanced IPF (DLCO< 35%), failed to meet its primary endpoint of ≥20% improvement in 6MWD; secondary endpoints such as DLCO, dyspnoea, SaO2 and QoL achieved statistical significance

- Pre determined analysis of a subgroup of patients with RV systolic dysfunction treated with sildenafil experienced a 99 m lower decline in 6MWD and improved QoL compared with those who received placebo7

Pirfenidone and sildenafil

- A phase IIb multicenter, randomized, double-blind placebo controlled study to evaluate the **efficacy**, **safety and tolerability** of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and intermediate or high probability of group 3 pulmonary hypertension
- Clinical phase: II b

Study design

- Patients with advanced IPF and intermediate or high probability of Group 3 PH who are on pirfenidone in a range dose of 1602-2403 mg/day with demonstrated tolerability
- 176 patients to be enrolled
- Randomization 1:1

Primary endpoint

- The primary efficacy endpoint is will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:
  - Relevant decline in 6MWD of at least 15% from baseline (as defined per protocol), respiratory – related non-elective hospitalization, or all cause mortality

Key inclusion criteria

For the purpose of this study, patients have to present with:

Advanced IPF

(defined as a measurable %DLCO≤40% at screening)

AND

Intermediate or high probability of Group 3 PH

(defined as a mPAP≥ 20 mmHg with PAWP≤15 mmHg) on a previous RHC of acceptable quality

OR

In the absence of a previous RHC, patients with ECHO intermediate or high probability of PH, as defined by the 2015 ESC/ERS giudelines (peak TRV ≥ 2.9 m/S), will be considered eligible for the study

Efficacy and Safety of Nintedanib When Co-administered With Sildenafil in Idiopathic Pulmonary Fibrosis Patients With Advanced Lung Function Impairment

Nintedanib and sildenafil

- A 24-week, double-blind randomized parallel group study evaluating the **efficacy and safety** of oral nintedanib co-administered with oral sildenafil
- Clinical phase: III b
- **Objective:** To assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung **function impairment**

Nintedanib and sildenafil

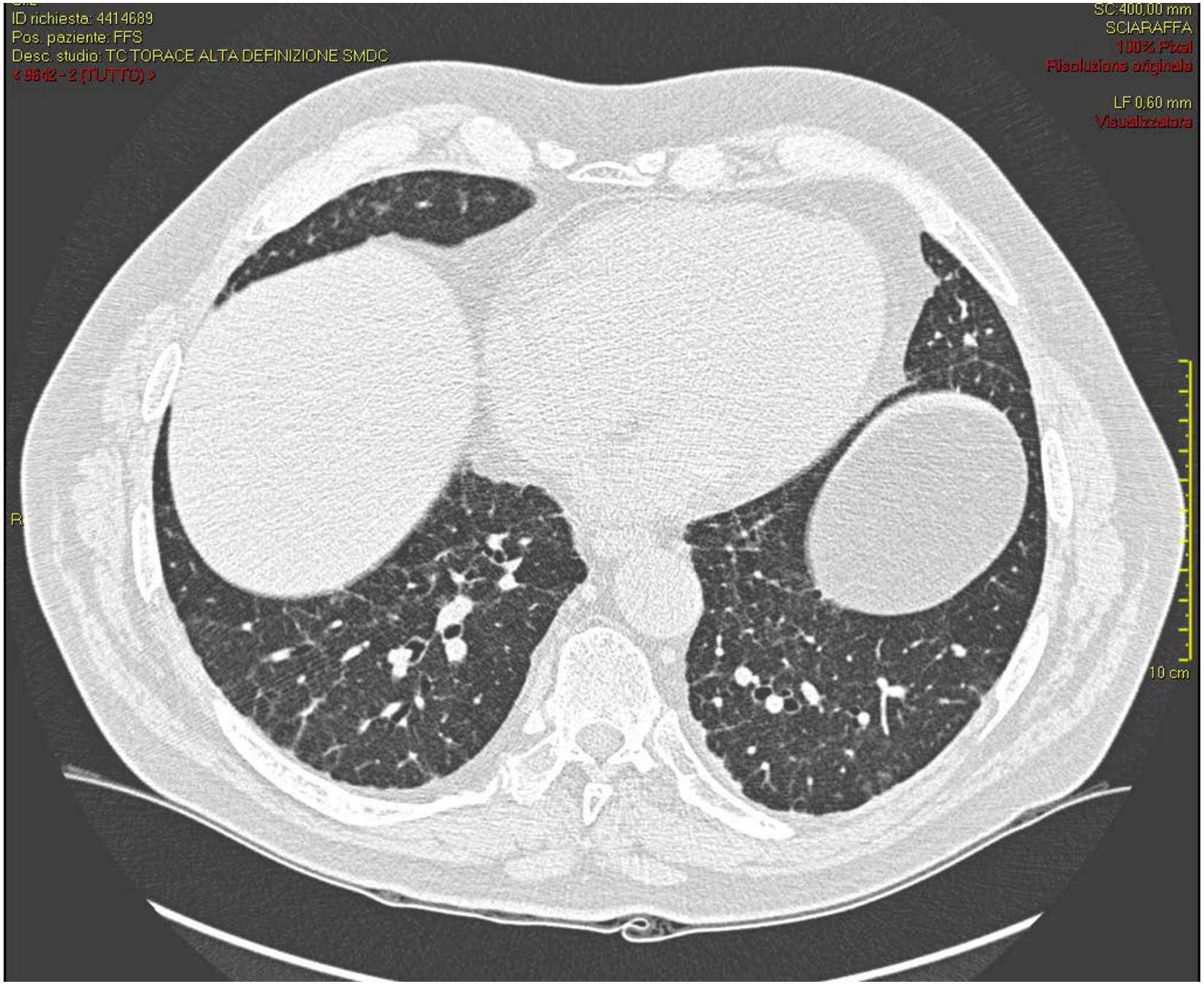
- 300 patients to be included, ≥ 40 years and with DLCO ≤ 35%
- Randomization 1:1
- Nintedanib 150 mg bid with the possibility to reduce to 100 mg bid to manage adverse events or placebo and sildenafil 20 mg tid
- 24 weeks of randomized treatment
- **Primary Endpoint**: Change from baseline in SGRQ total score at week 12

Other key inclusion criteria

- Age 40-80 years
- Diagnosis of IPF for at least 3 months prior the screening
- Confirmation of IPF diagnosis by the Investigator, in accordance with the 2011 international consensus giudelines
- WHO Functional class II/III
- 6MWD of 100-450 m

Unclassificable “ILD”

Multicenter, international, double-blind, two arm, randomized, placebo-controlled, phase II trial of pirfenidone in patients with unclassifiable progressive fibrosing ILD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Background

- Unclassifiable ILD represents a heterogeneous collection of undiagnosed fibrosing ILDs, which have a prognosis between IPF and other non-IPF fibrosing
- Owing to the heterogeneous nature of the disease, the choice of pharmacotherapy for unclassifiable ILD is unquestionably complex
- Treatment usage is complicated by both a lack of direct evidence in this patient population and by clinical data that indicate that different therapeutic strategies need to be employed in patients with IPF compared with patients with other fibrotic ILDs

This trial will evaluate the efficacy and safety of pirfenidone in patients with fibrosing interstitial lung disease (ILD) who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by multidisciplinary team (MDT) review (**“unclassifiable” ILD**).

Clinical phase: II

- **Efficacy objective:** rate of decline in FVC measured in mL by daily handheld spirometer over the 24-week double-blind treatment period

- Patients will be randomized in a 1:1 ratio, on a double-blind basis using a stratified algorithm, to receive either pirfenidone (801 mg TID) or placebo. The randomized patients will be stratified by concomitant MMF treatment (yes/no), the presence/absence of interstitial pneumonia with autoimmune features (IPAF) as defined by the MDT

- In total, approximately 90 clinical centers (sites) in Australia, Europe, the Middle East, and North America are expected to enroll approximately 250 patients.
- Patients who are withdrawn from the trial will not be replaced.

Inclusion criteria

- Age 18–85 years
- Progressive disease as considered by the investigator using the following definition: Patient deterioration within the last 6 months, which is defined as:
  - A rate of decline in FVC >5% OR
  - Significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes
- Extent of fibrosis >10% on high-resolution computed tomography (HRCT; visual scoring) within the last 12 months
- FVC ≥45% of predicted value
- Diffusing capacity of the lung for carbon monoxide (DLco) ≥30% of predicted value 9.
- 6-minute walk distance (6MWD) ≥150 meters

Progressive fibrosing ILD (PF-ILD)

Several patients with ILD develop a progressive fibrosing phenotype, characterised by self-sustaining fibrosis, deterioration in lung function, and worsening of symptoms and quality of life

Is there a distinct phenotype of patients with PF-ILD who might benefit from antifibrotic treatment similar to IPF?

Randomised placebo-controlled trials in progressive fibrosing ILDs other than IPF

Drug/patient population	Clinicaltrials.gov	Sample size	Primary endpoint
Nintedanib			
SSc-ILD (SENSCIS™)	NCT02597933	**n=520**	Rate of decline in FVC over 52 weeks
PF-ILD	NCT02999178	**n=600**	Rate of decline in FVC over 52 weeks
Pirfenidone			
Chronic HP	NCT02496182	n=60	Change in FVC at week 52
PF-ILD associated with clinically amyopathic dermatomyositis	NCT02821689	n=57	Survival 12 months from onset of ILD
LTx recipients with BOS grade 1-2	NCT02262299	n=80	Change in FEV_1 at month 6
Fibrotic HP	NCT02958917	n=40	Change in FVC at week 52
Unclassifiable PF-ILD	NCT03099187	n=250	Rate of decline in FVC over 24 weeks
RA-ILD	NCT02808871	n=270	PFS at week 52 (progression defined as FVC decline ≥10% predicted)
SSc-ILD (SLS III) - on top of MMF	NCT03221257	n=150	Change in FVC % predicted at 18 months

BOS, bronchiolitis obliterans syndrome; HP, hypersensitivity pneumonitis; LTx, lung transplant; MMF, mycophenolate mofetil; PFS, progression-free survival; RA-ILD, rheumatoid arthritis-associated ILD; SSc-ILD, systemic sclerosis-associated ILD.

A Double Blind, Randomized, Placebo-controlled Trial Evaluating the Efficacy and Safety of Nintedanib Over 52 Weeks in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

- The aim of the study is to investigate the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT) and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD.

- There is currently no efficacious treatment available for PF-ILD.

- This study is recruiting partecipants (start Jan 2017)

Target patient population

Enroll a group of patients with ILD that are getting worse, despite treatment

- progressive symptoms
- progressive decline in physiology
- progressive fibrosis on imaging

Primary Outcome Measures:

- Annual rate of decline in Forced Vital Capacity

Secondary Outcome Measures:

- Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score
- Time to first acute ILD exacerbation or death over 52 weeks
- Time to death over 52 weeks
- Time to death due to respiratory cause over 52 weeks
- Time to progression (defined as a equal or more than 10% absolute decline in FVC % pred) or death over 52 weeks
- Proportion of patients with a relative decline from baseline in FVC % pred of more than 10% at week 52
- Proportion of patients with a relative decline from baseline in FVC % pred of more than 5% at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnea domain score at week 52 [Time Frame: 52 weeks]
  Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52

Inclusion criteria:

Patients with physician diagnosed ILD with:

- Clinically significant decline in FVC % pred based on a relative decline of >=10%
- Marginal decline in FVC % pred based on a relative decline of .>=5-<10% combined with worsening of respiratory symptoms
- Marginal decline in FVC % pred based on a relative decline of >=5-<10% combined with increasing extent of fibrotic changes on chest imaging
- Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging
- Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 12 months of Visit 1 as confirmed by central readers.
- For patients with underlying Connective Tissue Disease (CTD): stable CTD as defined by no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1.
- DLCO ≥ 30% and <80% predicted of normal
- FVC >= 45% predicted at Visit 2

Acute Exacerbation of IPF

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a major event of IPF with an annual incidence between 5 and 10% and is responsible for the death of one third of IPF patients. When AE-IPF occurs, it is associated with poor survival with an overall mortality at 3 months upper of 50%. To date, no treatment has been proved to be effective in AE-IPF

Phase III Clinical Study of ART-123 for the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis: a Multicenter Randomized Placebo-controlled Double-blind Study to Assess the Efficacy and Safety of ART-12

- The purpose of this study is to assess the efficacy and safety of the intravenous drip infusion of ART-123 (a Recombinant human soluble thrombomodulin) in patients with acute exacerbation of IPF in a multicenter, double-blind, randomized, placebo-controlled, parallel group comparison study, and to confirm its superiority over placebo

- This study is currently recruiting participants

- Study Start Date: May 2016
- Estimated Study Completion Date: March 2018

Primary Outcome Measures:

Survival rate on Day 90

Secondary Outcome Measures:

- Overall survival [Time Frame: 180 days after the start of investigational product administration in the last subject]
- Survival time up to Day 90 [Time Frame: 90days]
- P/F ratio [Time Frame: 4 days, 7 days, 15 days, 28 days, 60 days, 90 days]
- Coagulation tests [Time Frame: 4 days, 7 days, 15days, 28 days, 60 days, 90 days]

Main Inclusion Criteria:

- Patients diagnosed with IPF who meet all criteria from (1) through (4) during the course of IPF

  (1) Unexplained development or worsening of dyspnea within 1 month during the course of IPF

  (2) Finding of new, bilateral ground glass opacities and/or consolidation on HRCT

  (3) No apparent pulmonary infections, pneumothorax, malignant tumors, pulmonary embolism, or left heart failure

  (4) A decrease* in PaO_2 of ≥10 mmHg or SpO_2 of ≥4% under the same conditions compared with the level at the previous measurements

  (*) In cases where no PaO_2 or SpO_2 test values under the same conditions are available, a patient with a P/F ratio ≤300 in the current episode of acute exacerbation is considered to have met criterion (4)

- Aged 40 years or older and no older than 85 years at the time of informed consent with either sex

Main Exclusion Criteria:

- Have intracranial hemorrhage, pulmonary hemorrhage, gastrointestinal bleeding (continued hematemesis, bloody discharge, gastrointestinal ulcer-induced hemorrhage)
- Have a history of cerebrovascular disorder (e.g., cerebral hemorrhage or cerebral infarction) within 52 weeks (364 days) before informed consent
- Patients for whom the completion of hemostatic treatment has not been confirmed after undergoing surgery of the central nervous system or after trauma
- Have a high risk for fatal or life-threatening hemorrhage
- Patients with malignant tumors
- Have acute exacerbation attributable to drug induced pulmonary disorder, after surgery for malignant tumors, chemotherapy, or radiation therapy
- Have acute exacerbation due to a thoracic surgical procedure (including thoracoscopic lung biopsy)
- Have a history of acute exacerbation of IPF

Cyclophosphamide Added to Corticosteroid in the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis: a Placebo-controlled Randomized Trial

The efficacy of cyclophosphamide (CYC) on survival has been suggested, mainly by retrospective series and needs to be confirmed.

Patients will be randomly assigned to receive Intravenous Cyclophosphamide (CYC), 600 mg/m² (adapted to age and renal function, maximal dose of 1.2 g) at Day 0, Day 15, M1, M2 or placebo in association to corticosteroids

This study is recruiting partecipants

Actual Study Start Date: December 2015; Estimated Study Completion Date: December 2018, Estimated Primary Completion Date: December 2018

(Final data collection date for primary outcome measure)

Primary Outcome Measures:

"Early" survival [Time Frame: 3 months]All cause of mortality at 3 months.

Secondary Outcome Measures:

- Overall Survival
- Respiratory disease-specific mortality
- Worsening dyspnea or Increase need of supplemental oxygen of more than 3l/min to obtained a SaO2 > 90% or decrease of PaO2 of more than 10 mmHg with the same rate of flow supplemental oxygen or Decrease FVC of more than 10% of predicted value or Decrease diffuse capacity for carbon monoxide (DLCO) of more than 15%
- Prognosis factors of AE-IPF [Time Frame: 3 months]PFTs results before AE-IPF
- Hemorrhagic cystitis (occurence of hematuria on urine dipstick and pelvic pain and/or dysuria should lead to cystoscopy)
- Number of Infectious disease

Inclusion Criteria:

- ≥18 years of age
- Definite or probable IPF diagnosis defined on 2011 international recommendations
- Definite or suspicion of AE defined by IPFnet criteria after exclusion of alternative diagnosis of acute worsening.
- Efficient contraceptive method within 1 month for women and 3 months for men after the last dose of treatment
- Affiliation to the social security
- Able to understand and sign a written informed consent form

Exclusion Criteria:

- Identified etiology for acute worsening (i.e. infectious disease)
- Known hypersensitivity or contra-indication to CYC or to any component of the study treatment
- Patient on mechanical ventilation
- Active bacterial, viral, fungal or parasitic infection
- Active cancer
- Patient on a lung transplantation waiting list
- Treatment with CYC in the last 12 months
- Patient participating to another clinical trial
- Pregnancy or lactation