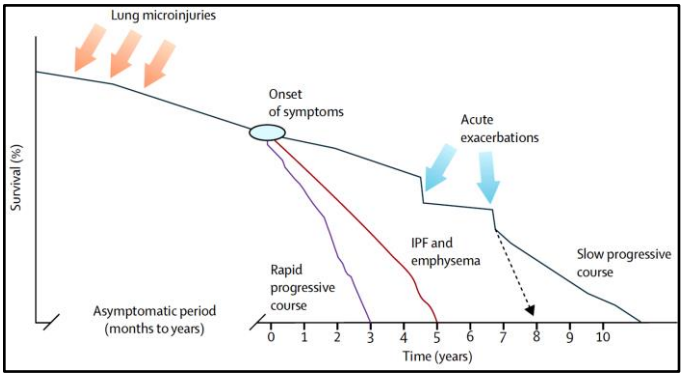
IDIOPATHIC PULMONARY FIBROSIS – UPCOMING DATA COULD CLARIFY POSITIONING

Idiopathic pulmonary fibrosis (IPF) occurs predominantly in middle-aged and older adults and accounts for 20% to 30% of interstitial lung diseases. In the U.S. the incidence of IPF is estimated to be between seven to 17 per 100,000 person-years, while the prevalence appears to be between 20 to 60 per 100,000 persons. The age at diagnosis of IPF is usually between 50 and 85 years. Hence, by our estimates there are about 140K to 170K patients in the U.S. with IPF. IPF is progressive, resulting in respiratory failure and death, however, the clinical course of IPF can be unpredictable and may be punctuated by acute deteriorations (acute exacerbation). A decline in forced vital capacity (FVC) is consistent with disease progression and is predictive of reduced survival time. Median survival for patients with IPF is estimated to be approximately 3 years.

Exhibit 40: Varying rates of clinical progression in IPF patients making appropriate patient selection crucial for outcomes



Source: Lancet Vol 378 December 3, 2011

In October 2014, FDA approved two novel agents pirfenidone (Roche/InterImmune) and nintedanib (Boehringer Ingleheim) for the treatment of IPF.

Pirfenidone, a small molecule inhibitor of multiple pathways implicated in fibrosis, including:

- Transforming growth factor beta (TGFβ),
- Fibroblast growth factor (FGF) and
- Platelet-derived growth factor (PDGF)

Three phase 3 studies were needed to get pirfenidone over the regulatory hurdle as the first two studies (SP3 trial in Japan and the multinational CAPACITY) had equivocal data. The final phase 3, The ASCEND study was designed to determine definitely whether pirfenidone, compared to placebo, slowed progression of disease in patients with mild to moderate IPF:

- Pirfenidone treatment resulted in significant benefit in forced vital capacity (FVC, the primary endpoint) over one year
- A reduction in the rate of decline in six-minute walk test distance
- Improved progression-free survival
- However, there was clinical impact on respiratory symptoms or mortality

Exhibit 41: Key clinical measures from the pirfenidone clinical programs

Study	Year	Number of patients	Study design	Inclusion criteria	Primary outcome	Secondary outcomes
Taniguchi et al. [2]	2010	275	Phase III double-blind, placebo-controlled	IPF per ATS/ERS guideline Age 20–75 years O_2 desaturation ≥5 % on 6MET SpO_2 ≥ 85 % during 6MET	**Vital capacity decline at week 52:** Placebo (−0.16 L) High dose (−0.09 L) p = 0.042	**Progression free survival** (p = 0.028)
CAPACITY 004 [3]	2011	435	Phase III double-blind, placebo-controlled	Definite IPF by CT or biopsy proven Age 40–80 years FVC ≥50 % D_{LCO} ≥35 % Either FVC or D_{LCO} ≤90 % 6MWT ≥150 m	**Change in % predicted FVC at week 72:** Placebo (−12.4 %) High dose (−8.0 %) p = 0.001	**Progression free survival** (p = 0.023)
CAPACITY study 006 [3]	2011	344	Phase III double-blind, placebo-controlled	Definite IPF by CT or biopsy proven Age 40–80 years FVC ≥50 % DLco ≥35 % Either FVC or DLco ≤90 % 6MWT ≥150 m	**Change in % predicted FVC at week 72:** Placebo (−9.6 %) Pirfenidone (−9.0 %) p = 0.501	**Mean change in 6MWT distance:** Placebo (−76.9 m) Pirfenidone (−45.1 m) p = 0.0009
ASCEND [4]	2014	555	Phase III double-blind, placebo-controlled	Definite IPF by CT or biopsy proven Age 40–80 years FVC 50–90 % D_{LCO} 30–90 % FEV1/FVC ratio ≥0.8 6MWT distance ≥150 m	**Change in % predicted FVC at week 52:** p < 0.001	**6MWT change at week 52:** p = 0.04 **Progression free survival:** p < 0.001

6MET 6 min steady-state exercise test, *6MWT* 6 min walking test, *ATS* American Thoracic Society, *CT* computed tomography, D_{LCO} diffusing capacity of the lungs for carbon monoxide, *ERS* European Respiratory Society, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *L* liters

Source: Adapted from *Guide to Clinical Management of Idiopathic Pulmonary Fibrosis*, DOI 10.1007/978-3-319-32794-5_7, by Janney Montgomery Scott LLC

Nintedanib is a tyrosine kinase inhibitor that blocks the profibrotic pathways mediated by PDGF, FGF and vascular endothelial growth factor (VEGF).
Following the encouraging results of the Phase II TOMORROW trial the INPULSIS program was designed as two concurrent phase III studies. The primary endpoint was similar to pirfenidone with a focus on FVC decline in patients with mild to moderate IPF.

- In both studies, nintedanib significantly reduced decline in FVC compared to placebo
- In only one of the two trials, nintedanib significantly increased time to first exacerbation
- And similar to pirfenidone there was no detectable difference in mortality

Exhibit 42: Key clinical measures from the nintedanib clinical programs

Study	Year	Number of patients	Study design	Inclusion criteria	Primary outcomes	Secondary outcomes
TOMORROW [8]	2011	432	Phase II double-blind, placebo-controlled	IPF by ATS/ERS criteria FVC ≥ 50 % predicted D_{LCO} 30–79 % predicted PaO_2 ≥ 55 mmHg up to 1500 m altitude PaO_2 > 50 mmHg >1500 m altitude	**Annual rate of decline in FVC:** Placebo (0.19 L/year) 150 mg twice daily (0.06 L/year) p = 0.06	**Acute exacerbations:** Placebo (15.7 per 100 patient years) 150 mg twice daily (2.4 per 100 patient years) p = 0.02
INPULSIS-1 [7]	2014	513	Phase III double-blind, placebo-controlled	IPF adjudicated prior to enrollment FVC ≥ 50 % predicted D_{LCO} 30–79 % predicted	**Annual rate of decline in FVC:** Placebo (−239.9 mL/year) Nintedanib (−114.7 mL/year) p < 0.001	**Time to acute exacerbation:** No difference (p = 0.67)
INPULSIS-2 [7]	2014	548	Phase III double-blind, placebo-controlled	IPF adjudicated prior to enrollment FVC ≥ 50 % predicted D_{LCO} 30–79 % predicted	**Annual rate of decline in FVC:** Placebo (−207.3 mL/year) Nintedanib (−113.6 mL/year) p < 0.001	**Time to acute exacerbation:** HR = 0.38 (p = 0.005)

ATS American Thoracic Society, D_{LCO} diffusing capacity of the lungs for carbon monoxide, *ERS* European Respiratory Society, *FVC* forced vital capacity, *HR* hazard ratio, *IPF* idiopathic pulmonary fibrosis, *L* liters, PaO_2 partial pressure arterial oxygen

Source: Adapted from *Guide to Clinical Management of Idiopathic Pulmonary Fibrosis*, DOI 10.1007/978-3-319-32794-5_7, by Janney Montgomery Scott LLC

Unfortunately, neither nintedanib nor pirfenidone has translated into a survival benefit for patients with mild to moderate IPF. Hence, there remains an unmet clinical need for IPF patients and IPF has recently become the focus of significant research dollars with at least seven mid-to-late-stage programs. Multiple avenues still remain to be explored including:

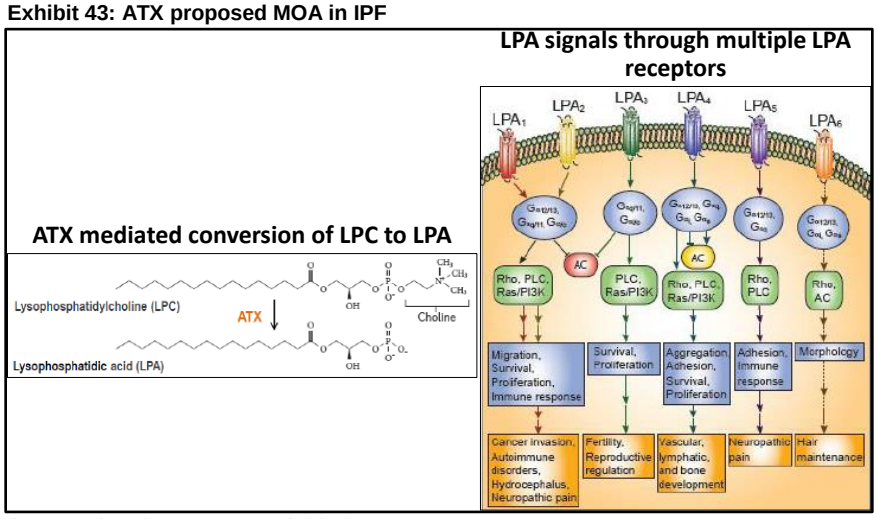
- Lack of clinical options for patients with severe disease, i.e. FVC <50% predicted or lung diffusion capacity testing (DLCO) <30% predicted
- Both nintedanib and pirfenidone clinical programs were limited to one-year hence, the ongoing extension studies are likely are important to determine the long-term safety and efficacy
- Can these drugs be used in combination or with other agents
    - Note, a small study in Japan hints at potentially tolerable combination
- Do these drugs work in other fibrotic interstitial lung diseases (ILDs)?

GLPG-1690, EXPLORATORY STUDY IN IPF PATIENTS UNDERWAY WITH DATA IN 2017

GLPG1690 is a potent and selective inhibitor of ATX:

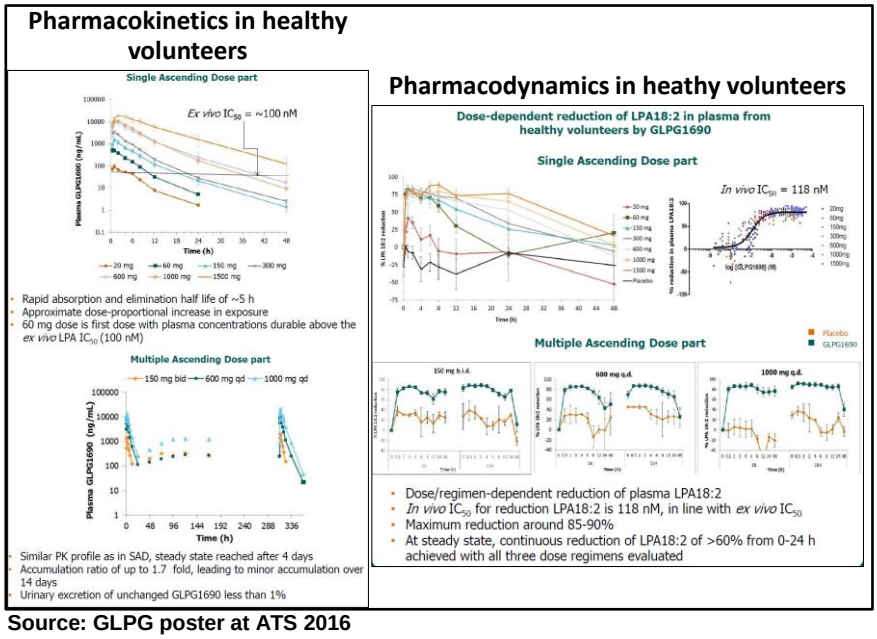
- Targets Autotaxin (ATX) and reduces plasma LPA ex vivo and in vivo
  - Secreted lysophospholipase which has a central role in the production of bioactive lysophosphatidic acid (LPA)
  - LPA signals through multiple LPA receptors, controlling a range of cell activities like migration, proliferation and survival
- Effective in mouse models: - tobacco smoke model (predictive for COPD) - bleomycin model (predictive for IPF)
- First ATX inhibitor evaluated in man

Exhibit 43: ATX proposed MOA in IPF



Source: GLPG poster at ATS 2016

Exhibit 44: First-in-human healthy volunteer study of GLPG1690



Source: GLPG poster at ATS 2016