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Efficacy of BIBF 1120 in patients with IPF is dose-dependent: Results from the TOMORROW trial

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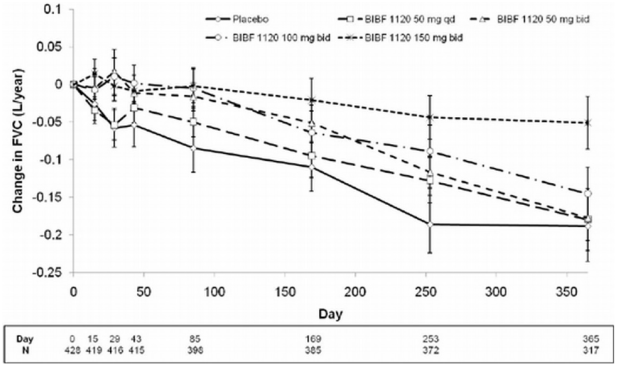
Background: BIBF 1120 is an inhibitor of tyrosine kinase receptors involved in lung fibrosis progression.

Methods: The TOMORROW trial was a 12-month, placebo (PBO)-controlled study to investigate efficacy and safety of BIBF 1120 (50 mg, 100 mg, 200 mg, 300 mg per day) in IPF (~85 pts per group). Annual rate of decline in forced vital capacity (FVC) was measured.

Results: FVC decline decreased from 0.17 L/year (50 mg) to -0.06 L/year (300 mg) vs 0.19 L/year in PBO (300 mg vs PBO: p=0.014; closed-testing multiplicity-corrected: p=0.064). Absolute changes from baseline in% pred FVC were -6.00, -4.58, -4.90, -3.15 and -1.04% in PBO and rising dose groups (200 mg: p=0.031; 300 mg: p=0.0002).



Absolute difference of% change in SpO2 was superior vs PBO by 0.44, 0.33, 1.36 and 1.12% for rising doses (200 mg: p=0.005; 300 mg: p=0.021). Incidence of acute exacerbations fell with dose (15.67, 13.03, 12.46, 7.46 and 2.44 per 100 patient years for PBO and rising doses). Gastrointestinal adverse events (AEs) increased with dose (31.8%, 38.4%, 36.0%, 57.0% and 74.1% in PBO and rising doses). AEs leading to discontinuation occurred in 25.9%, 23.3%, 16.3%, 14.0% and 30.6% of pts in PBO and rising dose groups. Fatal AEs (on-treatment) fell with dose (12, 10, 4, 5 and 1 pts for PBO and rising doses).

Conclusion: Treatment of IPF with BIBF 1120 reduced decline in lung function and incidence of acute exacerbations in a dose-dependent way.

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Effect of baseline FVC on preservation of lung function with BIBF 1120: Results from the TOMORROW trial

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Background: BIBF 1120 is an inhibitor of tyrosine kinase receptors involved in the progression of lung fibrosis.
Methods: The efficacy and safety of 50 mg, 100 mg, 200 mg and 300 mg daily doses of BIBF 1120 were evaluated in 428 patients diagnosed with IPF in a Phase 2 randomized, double-blind placebo (PBO)-controlled trial. Subgroup analyses of the annual rate of decline in forced vital capacity (FVC) by baseline lung function were carried out to evaluate the impact of stage of disease on the effect of BIBF 1120.
Results: Baseline FVC was similar in all groups (mean: 2.8 L; 81.3% predicted). The annual rate of decline in FVC was -0.060 L/year with BIBF 1120 300 mg vs -0.190 L/year with PBO (p=0.014; closed-testing multiplicity-corrected: p=0.064). Patients with baseline FVC ≥70% of predicted value showed almost no FVC decline with BIBF 1120 300 mg (-0.010 L/year [n=57] compared with -0.186 L/year in the PBO group [n=61]; p=0.004). However, there were no significant differences in FVC decline in patients with baseline FVC <70% of predicted value (-0.176 L/year with 300 mg [n=27] vs -0.203 L/year with PBO [n=22]; p=0.794). Similarly, lower rates of FVC decline were observed with 300 mg vs PBO in patients with baseline FVC ≥85% (-0.027 L/year [n=30] vs -0.160 [n=31]; p=0.112) and ≥90% (-0.019 L/year [n=23] vs -0.186 [n=25]; p=0.088) of predicted value; however, these findings were based on small sample sizes and the differences did not reach significance.
Conclusion: The effects of IPF treatment may be more easily demonstrable in patients with FVC values closer to predicted values.

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The long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF): Interim data from the RECAP extension study

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Introduction: The CAPACITY (CAP) trials were randomized controlled studies evaluating pirfenidone (PFD) in patients with IPF. Pooled data from these studies support a treatment effect on forced vital capacity, progression-free survival, and 6-minute walk distance. To examine the long-term safety of PFD, an open-label extension study for eligible CAP patients was initiated (RECAP). An interim analysis of safety data from RECAP is presented.
Aims and objectives: Examine the long-term safety of PFD in patients with IPF.
Methods: Safety data from the RECAP study through Wk 72 were analyzed and compared to pooled safety data from the CAP trials.
Results: In the CAP studies, 779 patients were randomized to treatment with PFD or placebo for ≥72 weeks. Of these, 603 enrolled in RECAP. At Wk 72 in RECAP, mean exposure to PFD 2403 mg/d across both studies was 2.9 yrs (range, 1–4); 114 patients had received PFD 2403 mg/d for ≥3 yrs. In RECAP, 98.2% of patients reported ≥1 treatment-emergent adverse event (TEAE) compared to 98.6% in CAP, and 32.8% of patients had a serious TEAE compared to 32.8% during CAP. Common AEs in RECAP were similar to those observed in CAP and were generally mild to moderate in severity. The overall incidence of photosensitivity or rash was lower in RECAP than CAP (19.7% vs. 44.4%); however, patients who received placebo during CAP had a higher incidence than those who received PFD (28.1% vs. 12.3%).
Conclusions: Long-term safety data demonstrate that PFD is safe and generally well tolerated in patients with IPF. Given the unmet medical need and efficacy results from 3 Phase III studies, PFD has a clear role in the treatment of IPF.

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Antifibrosic effects of sulforaphane in human lung fibroblasts from idiopathic pulmonary fibrosis

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Rationale: Nrf2 pathway has been implicated in myofibroblastic differentiation, a key step in idiopathic pulmonary fibrosis (IPF) pathophysiology. Sulforaphane (SFN), an isothiocyanate compound found in cruciferous vegetables, is known to activate Nrf2. The aim of this study was to assess the effects of SFN on oxidative stress and fibroblast phenotype in IPF.
Methods: The effects of SFN were assessed on human pulmonary fibroblasts from IPF and control patients in vitro. Oxidant/antioxidant balance, nuclear Nrf2 expression, fibroblast phenotype, in basal and profibrosing conditions (TGF-β or PDGF-BB stimulation) were experienced.
Results: SFN increased antioxidant enzymes and Nrf2 nuclear expression, and decreased oxidative stress in IPF fibroblasts, in basal conditions and after TGF-β stimulation. SFN stimulation induced a myofibroblastic dedifferentiation of IPF fibroblasts with morphologic aspect of control-like fibroblasts and concomitant reduction of α-SMA and collagen I expression, proliferation, migration and contraction. Moreover, addition of SFN after TGF-β and PDGF-BB stimulation, inhibited their deleterious effects on IPF and control fibroblasts, and restored antioxidant defenses. Nrf2 siRNA transfection abolished antifibrosing effects of SFN.
Discussion: The effects of SFN on cell differentiation have been reported in renal tubular epithelial cells in a rat model of renal fibrosis, but its effects on human pulmonary fibroblasts from IPF and control patients were unknown.
Conclusion: These results suggest the potential therapeutic effect of SFN on pulmonary fibroblasts in IPF in vitro.

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Presence of right ventricular dysfunction predicts dyspnea and quality of life improvements with sildenafil in IPF

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Background: IPF is a progressive lung disease with impaired gas exchange. The STEP-IPF trial was conducted to determine if sildenafil would increase 6-minute walk distance by ≥ 20%. The primary endpoint was not reached, but a substudy tested whether baseline evidence of pulmonary hypertension would predict treatment response.
Methods: Echocardiograms were available for review in 119/180 subjects and read by two cardiologists. Right ventricular hypertrophy (RVH), RV systolic dysfunction (RVSD) and RV systolic pressure (RVSP) were assessed. A general linear model determined the relationship between cardiac abnormality, sildenafil treatment and improvement in quality of life (QOL) as measured by EuroQol EQ-5D, EuroQol thermometer and SGRQ at 12 weeks.
Results: Mean FVC% predicted was 57%; DLCO% predicted 26%. Prevalence of RVH was 13%; RV systolic dysfunction 19%. Mean RVSP was 42.5, measurable in 71/119 subjects. Mean EuroQoL thermometer score was 69.1, EuroQol EQ-5D 0.73, and SGRQ 53.1. Significant interactions between RV systolic dysfunction and sildenafil treatement were seen for SGRQ (p=0.048), SGRQ symptom score (p=0.002) and EuroQol Thermometer (p=0.05). Sildenafil treated subjects with RVSD improved by 13.4 SGRQ points, 28.0 SGRQ symptom score points, and 17.9 EuroQol Thermometer points vs placebo. Those with RVSD treated with placebo increased their SGRQ by 2.9 points, SGRQ symptom score by 3.8 points, and dropped their EuroQoL Thermometer score by 1.4 points vs placebo.
Conclusions: In IPF patients with RV systolic dysfunction, sildenafil treatment is associated with improvements in QOL as measured by SGRQ total and symptom scores and EuroQol Thermometer score.

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A prospective, non randomized, clinical trial to study the safety and efficacy of the endobronchial autologous infusion of adipose-derived mesenchymal stem cells (ADMSCs) in patients with idiopathic pulmonary fibrosis (IPF)

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Background: IPF is a chronic, progressive, lethal fibrotic lung disease of unknown etiology and treatment yet ineffective. The aim of the study was to investigate the safety and efficacy of endobronchial autologous infusion of adipose-derived mesenchymal stem cells (ADMSCs) in patients with IPF.
Methods: We performed a prospective, non-randomized trial of endobronchial autologous ADMSCs in IPF patients who met ATS/ERS 2000 criteria with mild to moderate lung disease as assessed by Forced vital capacity (FVC) >50% and diffusion capacity of the lung for carbon monoxide (DLCO) >35%. All eligible

patients (n=14) underwent lipoaspiration and ADMSCs were isolated using a standard protocol provided by Adistem Ltd. ADMSCs were labelled with Technetium (Tc)-99m and endobronchially infused to both lower lobes.Tc-99m lung scanning was performed to visualize infused cells. The primary end point was incidence of treatment-emergent adverse events within 6 months after first infusion. FVC, DLCO and 6-minute walking distance (6MWD), were exploratory efficacy end points.
Results: No cases of clinically significant allergic reactions, disease acute exacerbation or infection were recorded in all patients. There were no significant alterations in FVC and DLCO 6 months post-treatment, though an almost marginal trend towards improvement in 6MWD (p=0.07) was reported.
Conclusions: This ongoing clinical trial provides pivotal safety and provisional efficacy data for endobronchial autologous infusion of ADMSCs in patients with IPF. Larger studies are sorely needed.

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Effect and safety of mycophenolate mofetil in idiopathic pulmonary fibrosis. A retrospective study

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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic interstitial lung disease with poor prognosis and treatment yet ineffective. Mycophenolate Mofetil (MMF) represents an immunomodulatory agent, acts by inhibiting lymphocyte proliferation and is commonly used to prevent rejection following organ transplantation.
Objective: We sought to determine the safety and efficacy profile of MMF in IPF patients.
Methods: We retrospectively identified ten patients, all males, who met the ATS/ERS 2000 criteria for IPF and received MMF 1,44gr/day for 12 months. All of them had routine laboratory, pulmonary function and radiological (high resolution computed tomography-HRCT) data available and therefore were enrolled in the study. Forced vital capacity (FVC), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DLCO), 6-minute walking distance (6MWD), alveolar-arterial gradient of oxygen tension (PA-aO2), HRCT scans and routine laboratory data at treatment onset were compared with respective values 12 months after treatment onset.
Results: There were no significant alterations in FVC, TLC, DLCO, 6MWD and PA-aO2 pre- and 6 and 12 months post-treatment. HRCT evaluation showed a moderate deterioration of the total extent of disease (p=0.002). No cases of clinically significant infection, leucopenia, or elevated liver enzymes were recorded.
Conclusions: The above data suggest that MMF is a safe therapeutic modality which resulted in overall stable disease regarding functional status while it demonstrated a moderate progression as assessed by radiological parameters in a small cohort of IPF patients. Larger, prospective studies are sorely needed.