Efficacy and Safety of Sildenafil Added to Pirfenidone in Patients With Advanced Idiopathic Pulmonary Fibrosis and Risk of Pulmonary Hypertension

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RATIONALE

- Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease associated with a 5-year survival rate worse than that for many cancers, if treatment is not initiated[1,2]
- Two antifibrotics, pirfenidone and nintedanib, have been shown to slow IPF progression; however, the pivotal trials did not include patients with advanced IPF[3,4]
  - The efficacy and safety of antifibrotics in patients with advanced IPF have not been fully characterized
- The benefit of sildenafil in patients with advanced IPF at risk of poor outcomes from pulmonary hypertension (PH), whether already present or likely to develop, is uncertain[5]
- Here, we assessed the efficacy and safety of sildenafil added to pirfenidone over 52 weeks in patients with advanced IPF and risk of Group 3 PH

METHODS[6]

- This was a Phase IIb, randomized, double-blind, placebo-controlled trial (NCT02951429)
- Eligible patients had advanced IPF (percent predicted carbon monoxide diffusing capacity ⩽ 40%) and risk of Group 3 PH
  - Risk of Group 3 PH was defined as mean pulmonary arterial pressure ⩾ 20 mmHg with pulmonary arterial wedge pressure ⩽ 15 mmHg on previous right-heart catheterization OR intermediate/high probability of Group 3 PH defined by Galiè et al. 2016,[7] with echocardiogram showing peak tricuspid valve regurgitation velocity ⩾ 2.9 m/s

DISCLOSURES

Data within the poster are directly derived from research sponsored by F. Hoffmann-La Roche, Ltd.

Jürgen Behr has received personal fees for lectures and consulting services from Actelion, Bayer, Biogen, Boehringer Ingelheim, F. Hoffmann-La Roche, Ltd., and Galapagos. He is a member of national and international guideline committees for IPF.

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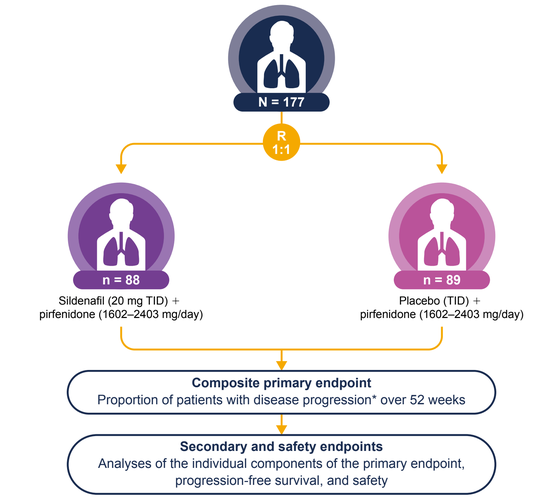
Combination therapy with sildenafil + pirfenidone did not provide a clinically meaningful treatment benefit vs. placebo + pirfenidone over 52 weeks in patients with advanced IPF and at risk of Group 3 PH

No new safety signals were identified for either treatment

	Sildenafil + pirfenidone group	Placebo + pirfenidone group
Composite primary endpoint:		
Proportion of patients with disease progression* over 52 weeks	64 (72.7%) patients	*P*=0.6527; 62 (69.7%) patients
Secondary endpoints:		
Relevant ⩾ 15% decline from baseline in 6MWD	47 (53.4%) patients	HR 0.94 (95% CI 0.62, 1.41)†; 45 (50.6%) patients
Respiratory-related non-elective hospitalization	40 (45.5%) patients [51 events]	HR 1.02 (95% CI 0.65, 1.61)†; 36 (40.4%) patients [56 events]
All-cause mortality	15 (17.0%) patients	HR 0.76 (95% CI 0.38, 1.50)†; 18 (20.2%) patients
Safety	Safety outcomes were comparable between treatment groups, and no new safety signals were identified	

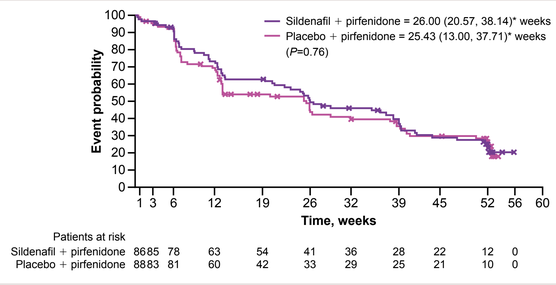
* Defined as relevant decline in 6MWD from baseline, respiratory-related non-elective hospitalization, or all-cause mortality. Relevant decline from baseline in 6MWD was specified as > 25% decline, or 15–25% decline if accompanied by at least one of the following: worsening SpO_2 desaturation during the 6MWT; worsening of the maximum Borg scale during the 6MWT; or increased O_2 requirements during the 6MWT.
† Based on time-to-event rate.

Figure 1. Primary Analysis Population (ITT Population)



6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ITT, intention-to-treat; SpO_2, oxygen saturation; TID, three times daily.
* Defined as relevant decline in 6MWD from baseline, respiratory-related non-elective hospitalization, or all-cause mortality. Relevant decline from baseline in 6MWD was specified as > 25% decline, or 15–25% decline if accompanied by at least one of the following: worsening SpO_2 desaturation during the 6MWT; worsening of the maximum Borg scale during the 6MWT; or increased O_2 requirements during the 6MWT.

Figure 2. Progression-Free Survival Presented as Time to First Occurrence of Disease Progression (ITT Population)



CI, confidence interval; ITT, intention-to-treat.
* Median (95% CI).

Table 1. Summary of TEAEs (Safety Population)

n (%)	Sildenafil + pirfenidone (n = 88)	Placebo + pirfenidone (n = 89)
Any TEAEs	87 (98.9)	83 (93.3)
Any treatment-related TEAEs	31 (35.2)	30 (33.7)
Any serious TEAEs	54 (61.4)	55 (61.8)
Any treatment-related serious TEAEs	2 (2.3)	4 (4.5)
Any severe TEAEs	65 (73.9)	66 (74.2)
Any treatment-related severe TEAEs	9 (10.2)	11 (12.4)
TEAEs leading to mortality	22 (25.0)	26 (29.2)
Treatment-related TEAEs leading to mortality	1 (1.1)	1 (1.1)
TEAEs leading to treatment discontinuation	22 (25.0)	29 (32.6)
Treatment-related TEAEs leading to treatment discontinuation	8 (9.1)	5 (5.6)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
MedDRA version 22.1 was used for coding. TEAEs were defined as AEs that started or worsened on or after first intake of randomized treatment until last positive dose + 28 days.

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