Poster

Safety and Efficacy of BI 1015550, a Preferential Inhibitor of Phosphodiesterase 4B, in Patients With Idiopathic Pulmonary Fibrosis: a Phase 2 Trial

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Safety and efficacy of BI 1015550, a preferential inhibitor of phosphodiesterase 4B, in patients with idiopathic pulmonary fibrosis: a phase 2 trial

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INTRODUCTION

- PDE4 inhibitors have both anti-inflammatory and antifibrotic properties.[1–3]
- BI 1015550 is an oral preferential inhibitor of PDE4B and candidate drug for the treatment of IPF.[2]

AIM

- To investigate the efficacy and safety of BI 1015550 in patients with IPF.

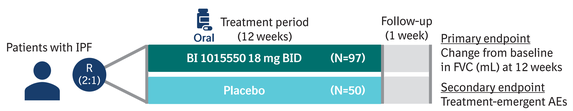
METHODS

Design

- A Phase 2 trial with a randomized, double-blind, placebo-controlled design (NCT04419506).

Intervention and endpoints

- Eligible patients were ≥40 years old and had a confirmed diagnosis of IPF, FVC ≥45% predicted, DL_{CO} corrected for hemoglobin ≥25 to <80% predicted, and UIP or a probable UIP pattern on HRCT consistent with IPF. Patients were permitted to continue antifibrotic therapy (nintedanib or pirfenidone) if they had been receiving a stable dose for at least 8 weeks prior to screening.
- Patients with airways obstruction (FEV_1 /FVC <0.7), a recent respiratory tract infection, a history of suicidal behavior in the past 2 years, an acute IPF exacerbation within 4 months, or who had been taking >15 mg/day prednisone were excluded.



- Randomization was stratified based on use of background antifibrotics (without or with) at baseline.

Primary endpoint analysis

- Change from baseline in FVC (mL) at 12 weeks was evaluated in patients without and with background antifibrotics using: (1) a mixed model with repeated measures (MMRM) and (2) a Bayesian approach using historical data.
- The primary analysis used a Bayesian approach to incorporate historical data for the placebo arms via a meta-analytic predictive prior derived from previous nintedanib clinical development program in IPF (TOMORROW,[a] INPULSIS-1[b] and -2,[c] INMARK,[d] INSTAGE,[e] INJOURNEY[f] and NCT01979952). This reduced the number of patients randomized to placebo in the trial.

[a]NCT00514683; [b]NCT01335464; [c]NCT01335477; [d]NCT02788474; [e]NCT02802345; [f]NCT02579603.

CONCLUSIONS

- Compared with placebo, treatment with BI 1015550, either alone or with background antifibrotics, prevented a decline in lung function in patients with IPF.
- The observed safety and tolerability of BI 1015550 were acceptable and, in combination with the beneficial effects on FVC, warrant further clinical development as a treatment for IPF and other forms of progressive pulmonary fibrosis.

RESULTS

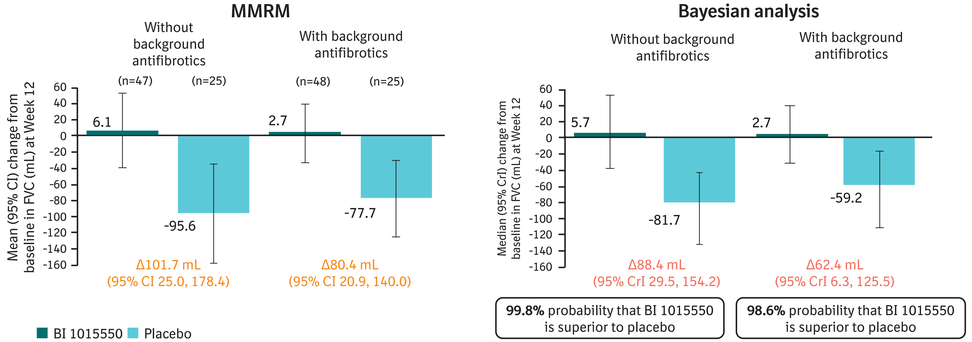
Baseline characteristics

- Overall, 147 patients were randomized 2:1 to receive BI 1015550 18 mg BID or placebo.

Without background antifibrotics			With background antifibrotics	
BI 1015550 (n=48)	Placebo (n=25)		BI 1015550 (n=49)	Placebo (n=25)
70.8	68.0	Male, %	89.8	72.0
69.9±8.3	71.8±9.3	Age, years	69.3±6.6	67.5±10.7
75.0	84.0	White, %	75.5	84.0
75.9±15.2	78.2±16.3	Weight, kg	77.4±12.8	81.0±16.8
2.7±2.4	2.2±2.6	Time since first IPF diagnosis, years	4.6±3.7	3.9±3.3
0	0	Nintedanib treatment, %	53.1	68.0
0	0	Pirfenidone treatment, %	46.9	32.0
80.4±16.0	82.1±17.7	FVC % predicted	75.8±17.9	71.7±12.3
52.0±16.7	48.3±12.1	DL_{CO} % predicted	49.0±18.3	47.2±14.8

Changes from baseline in FVC at Week 12 estimated using MMRM or Bayesian analysis

- Treatment with BI 1015550 prevented a decline in FVC, in contrast with the placebo arm where there was a marked decline in FVC.

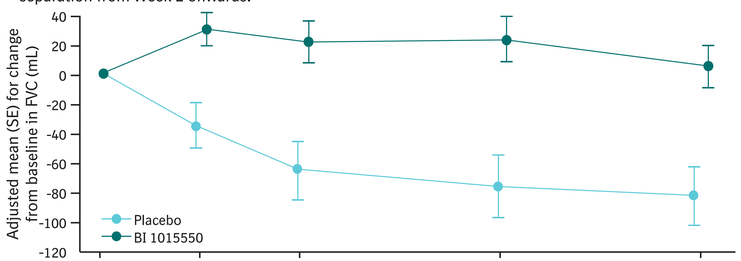


99.8% probability that BI 1015550 is superior to placebo

98.6% probability that BI 1015550 is superior to placebo

Change in FVC over time in all patients

- The treatment effect of BI 1015550 on FVC over time in the pre-specified MMRM analysis showed early separation from Week 2 onwards.



Number of patients	0	2	4	8	12
Placebo		49	50	50	49
BI 1015550		90	89	87	81

Treatment-emergent AEs

- The tolerability of BI 1015550 seemed acceptable, and the most common AEs were gastrointestinal.

AEs, n (%)	Without background antifibrotics		With background antifibrotics	
	BI 1015550 (n=48)	Placebo (n=25)	BI 1015550 (n=49)	Placebo (n=25)
Any AEs	31 (64.6)	13 (52.0)	36 (73.5)	17 (68.0)
Severe AEs	2 (4.2)	1 (4.0)	2 (4.1)	1 (4.0)
AEs leading to discontinuation	3 (6.3)	0	10 (20.4)	0
Most frequent AE (>10% in at least one arm)				
Diarrhea	8 (16.7)	2 (8.0)	15 (30.6)	4 (16.0)
Fatigue	2 (4.2)	1 (4.0)	1 (2.0)	3 (12.0)
Serious AE				
All	3 (6.3)	5 (20.0)	3 (6.1)	0
Resulted in death	1 (2.1)	0	1 (2.0)	0
Most frequent AE leading to discontinuation (>5% of patients)				
Diarrhea	0	0	3 (6.1)	0

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ABBREVIATIONS

AE, adverse event; BID, twice daily; CI, confidence interval; CrI, credible interval; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; MMRM, mixed model with repeated measures; PDE4, phosphodiesterase 4; SE, standard error; UIP, usual interstitial pneumonia.

DISCLOSURES

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