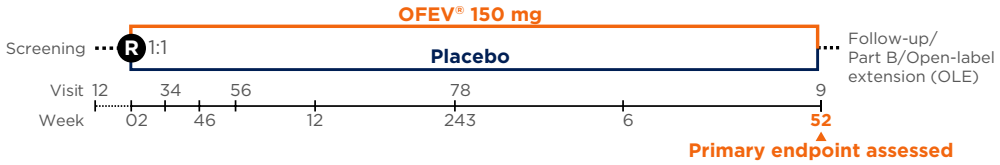
A comparison of the INBUILD® and INPULSIS® clinical trials

OFEV® nintedanib

1 Study design

INBUILD® and INPULSIS®-1 and -2 were Phase III, randomised, double-blind, placebo-controlled, parallel-group, global trials studying the safety and efficacy of OFEV® (150 mg bid) in different patient populations over an initial study period of 52 weeks[1-3]



	INBUILD®[4]	INPULSIS® pooled[3,5]
Patient population	Patients were eligible to participate in the trial if they were ≥18 years of age and diagnosed with a progressive fibrosing ILD	Patients were eligible to participate in the two trials if they were ≥ 40 years of age and diagnosed with IPF
Study locations	153 sites, 15 countries	205 sites, 24 countries
Patients randomised	n=663 (1:1)	n=1066 (3:2)
Treatment beyond 52 weeks	Patients remained on double-blinded treatment (Part B) until the OLE	Patients could enter the OLE after 4 weeks of follow-up
Primary endpoint	annual rate of decline in FVC (mL/year) assessed over 52 weeks	annual rate of decline in FVC (mL/year) assessed over 52 weeks
Main/key secondary endpoints	– Change from baseline in K-BILD total score – Time to first acute exacerbation or death – Time to death	– Time to first acute exacerbation – Change from baseline in SGRQ total score

2 Baseline characteristics

	INBUILD®[2,4]		INPULSIS® pooled[3]	
	OFEV® (n=332)	Placebo (n=331)	OFEV® (n=638)	Placebo (n=423)
Age, years, mean (SD)	65.239.7	66.339.8	66.638.1	67.037.9
Male, n (%)	179 (53.9)	177 (53.5)	507 (79.5)	334 (79.0)
BMI, kg/m2, mean (SD)	28.1 (5.1)	28.4 (5.5)	28.134.6	27.634.6
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)	464 (72.7)	301 (71.1)
FVC, mL, mean (SD)	23403740	2321372.8	27143757	27283810
FVC, % predicted, mean (SD)	68.7316.0	69.3315.2	79.7317.6	79.3318.2
DLco, % predicted, mean (SD)	44.4311.9	47.9315.0	47.4313.5	47.0313.4

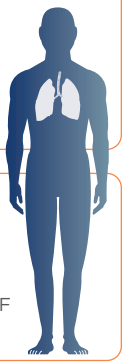
Prescribing information is available here

Adverse events should be reported to the Health Products Regulatory Authority at www.hpra.ie or by email to medsafety@hpra.ie.
Adverse events should also be reported to Boehringer Ingelheim Pharmacovigilance on 01 291 3960 or by email to PV_local_uk_ireland@boehringeringelheim.com

3 Inclusion criteria

INBUILD®[1,4]: Patients with progressive fibrosing ILDs

- Age ≥18 years
- Physician-diagnosed ILD other than IPF, including patients with HP, autoimmune ILDs such as SSc-ILD, idiopathic NSIP, unclassifiable IIPs and other fibrosing ILDs
- Extent of fibrosis >10% on HRCT with FVC ≥45% and DL_{CO} 30–79% of predicted
- Patients were required to meet ≥1 of the following criteria for ILD progression in the 24 months before screening, despite standard treatment:
  - Relative decline in FVC ≥10% predicted
  - Relative decline in FVC ≥5<10% predicted and worsened respiratory symptoms
  - Relative decline in FVC ≥5<10% predicted and increased extent of fibrosis on HRCT
  - Worsened respiratory symptoms and increased extent of fibrosis on HRCT



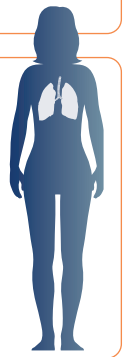
INPULSIS®[3]: Patients with IPF

- Age ≥40 years
- Diagnosis of IPF within 5 years of randomisation
- Chest HRCT performed within 12 months of screening
- HRCT pattern and, if available, surgical lung biopsy pattern consistent with diagnosis of IPF
- FVC ≥50% of predicted value

4 Exclusion criteria

INBUILD®[4]: Patients with progressive fibrosing ILDs

- FEV_1/FVC <0.7 (prebronchodilator)
- Elevated liver enzymes (ALT, AST, or bilirubin >1.5x ULN)
- Bleeding risk e.g. full-dose therapeutic anticoagulation or high-dose antiplatelet therapy
- Significant pulmonary hypertension
- Pregnancy
- Life expectancy <2.5 years for a disease other than ILD
- History of severe uncontrolled hypertension (≥160/100 mmHg) within 6 months
- History of myocardial infarction within 6 months
- History of unstable angina within 6 months
- History of thrombotic event within 12 months
- Treatment with azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or >20mg/day oral glucocorticoids. These medicines were later permitted at the discretion of the investigator, following 6 months of study treatment.



INPULSIS®[3,5]: Patients with IPF

- AST and ALT >1.5x ULN
- Cardiac disease (myocardial infarction within 6 months or unstable angina within 1 month of randomisation)
- Treatment with N-acetylcysteine or prednisone >15 mg/day or equivalent within 2 weeks of screening
- Treatment with pirfenidone, azathioprine, cyclophosphamide, cyclosporine A or any investigational drug within 8 weeks of screening
- Treatment with full-dose therapeutic anticoagulation or high-dose antiplatelet therapy at screening
- Likely to receive a lung transplant during the study (based on investigator opinion)

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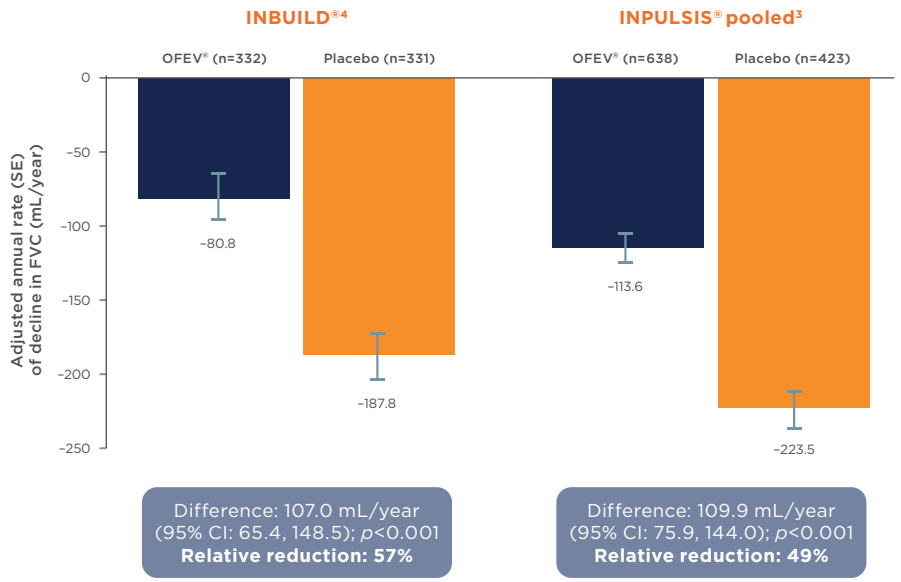
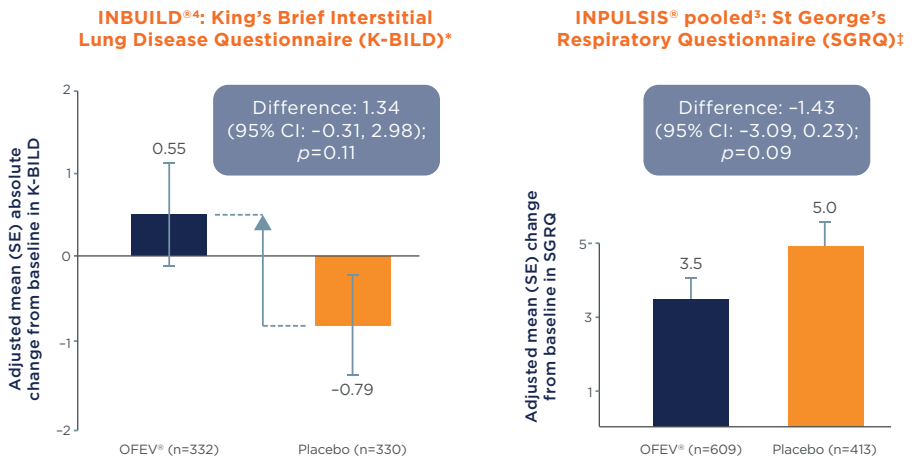
5 Efficacy

Primary endpoint: Annual rate of decline in FVC (mL) at 52 weeks



Key secondary endpoint: Quality of life measures over 52 weeks†

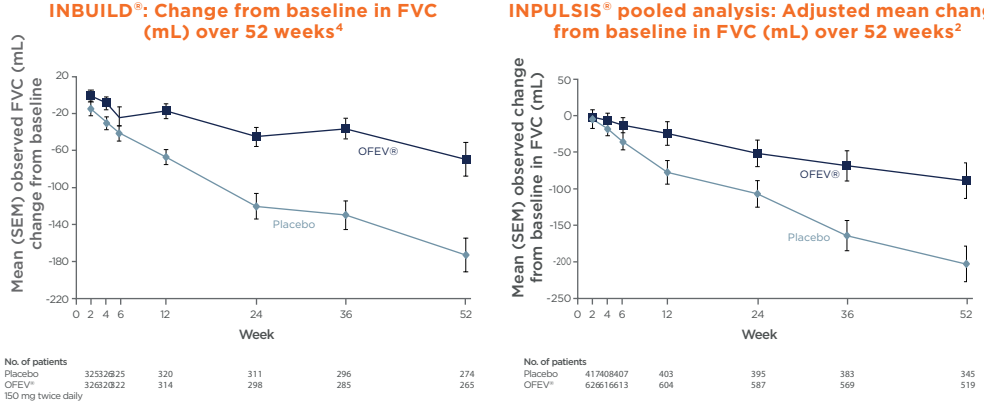


*Scores range from 0 to 100, higher scores represent better health status; †K-BILD and SGRQ are two different questionnaires and as such, a direct comparison cannot be made between these two quality of life measures. K-BILD is a self-administered, validated, 15-item, ILD-specific, health-related quality of life questionnaire scored across 3 domains (breathlessness and activities, psychological and chest symptoms) range from 0 to 100. Higher scores represent better health status.[5] SGRQ is a self-administered health-related quality of life questionnaire scored across 3 domains (symptoms, activity, and impact) range from 0 to 100. Higher scores indicate worse health-related quality of life[3]; ‡Scores range from 0 to 100, higher scores represent poorer health status

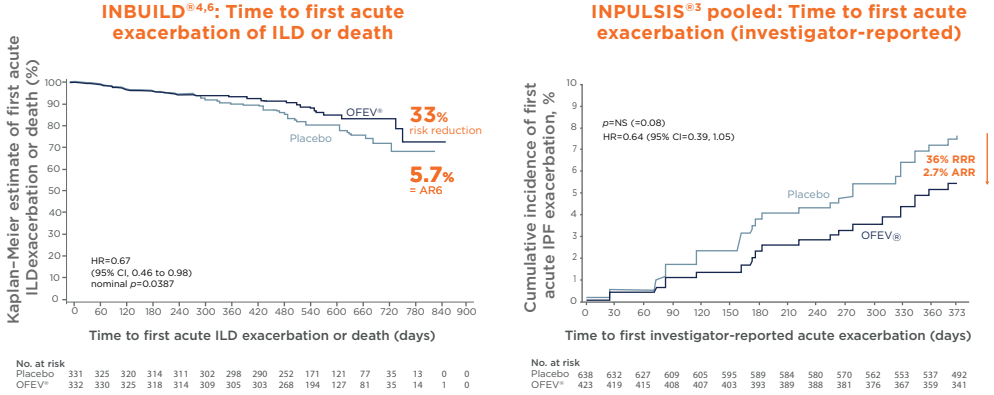
Similar relative reductions in the rate of FVC decline for OFEV®-treated patients vs placebo were observed across the INBUILD® and INPULSIS® trials. In patients who received placebo, the rate of decline in FVC was similar among the populations in the INBUILD® and INPULSIS® trials, reinforcing that some patients with ILDs other than IPF also have a progressive fibrosing phenotype.

There were no significant improvements for OFEV® compared with placebo in the total scoresof the quality of life measurements (K-BILD for INBUILD®; SGRQ for INPULSIS®)

Secondary endpoint: Observed change from baseline in FVC (mL) over 52 weeks



Key secondary endpoint: Acute exacerbations or death in progressive fibrosing ILD and acute exacerbations in IPF patients



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6 Safety

Rates of adverse events across the trials by severity

	INBUILD®[4]		INPULSIS® pooled[3]	
	OFEV® n=332 (%)	Placebo n=331 (%)	OFEV® n=638 (%)	Placebo n=423 (%)
Any adverse event(s)	317 (95.5)	296 (89.4)	609 (95.5)	379 (89.6)
Adverse event(s) leading to permanent discontinuation of study drug	65 (19.6)	34 (10.3)	123 (19.3)	55 (13.0)
Severe adverse event(s)*	60 (18.1)	73 (22.1)	174 (27.3)	99 (23.4)
Serious adverse event(s)†	107 (32.2)	110 (33.2)	194 (30.4)	127 (30.0)
Fatal adverse event(s)	11 (3.3)	17 (5.1)	37 (5.8)	31 (7.3)

*Adverse event that was incapacitating or caused an inability to work or perform usual activities.

†Adverse event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

Five most commonly observed adverse events across the trials

	INBUILD®[4]		INPULSIS® pooled[3]	
	OFEV® (n=332) n (%)	Placebo (n=331) n (%)	OFEV® (n=638) n (%)	Placebo (n=423) n (%)
1	Diarrhoea: 222 (66.9)	Diarrhoea: 79 (23.9)	Diarrhoea: 398 (62.4)	Diarrhoea: 78 (18.4)
2	Nausea: 96 (28.9)	Bronchitis: 47 (14.2)	Nausea: 156 (24.5)	Nasopharyngtis: 68 (16.1)
3	Vomiting: 61 (18.4)	Dyspnoea: 44 (13.3)	Nasopharyngitis: 87 (13.6)	IPF progression: 61 (14.4)
4	Decreased appetite: 48 (14.5)	Cough: 44 (13.3)	Cough: 85 (13.3)	Cough: 57 (13.5)
5	Nasopharyngitis: 44 (13.3)	Nasopharyngitis: 40 (12.1)	Vomiting: 74 (11.6)	Dyspnoea: 48 (11.3)

Diarrhoea incidence

Patients experiencing diarrhoea who were treated with OFEV® and placebo, respectively

INBUILD®[4,6]
- Incidence: **66.9%** vs **23.9%**
- Leading to dose reduction: **16.0%** vs **0.9%**
- Leading to discontinuation: **5.7%** vs **0.3%**

INPULSIS®[3,6]
- Incidence: **62.4%** vs **18.4%**
- Leading to dose reduction: **10.7%** vs **0%**
- Leading to discontinuation: **4.4%** vs **0.2%**

Elevations in hepatic enzymes

Patients with elevations in ALT and/or AST ≥3 the upper limit or normal, who were treated with OFEV® and placebo, respectively

INBUILD®[2]
13% vs **1.8%**

INPULSIS® pooled[3]
5.1% vs **0.7%**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice a day; BMI, body mass index; CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HR, hazard ratio; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; NS, non significant; NSIP, non-specific interstitial pneumonia; OLE, open-label extension; R, randomisation; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire; SpO2, peripheral oxygen saturation; ULN, upper limit of normal

References:
1. Flaherty KR, *et al. BMJ Open Respir Res* 2017;4:e000212.
2. INBUILD® Results. Boehringer Ingelheim International GmbH. 2019; Data on file.
3. Richeldi L, *et al. N Engl J Med* 2014;370:2071–82 (and supplementary appendix).
4. Flaherty KR, *et al. N Engl J Med* 2019;381(18):1718-171727.doi:10.1056/NEJMoa1908681 (and supplementary appendix).
5. Richeldi L, *et al. Respir Med* 2014;108(7):1023–1030.
6. OFEV® 100 mg and 150 mg soft capsules Summary of Product Characteristics. Boehringer Ingelheim.

OFEV® is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF). OFEV® is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.[6]

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