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Progressive Pulmonary Fibrosis: A Modelling Analysis of Long-Term Progression Based on INBUILD

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Introduction

- Patients with some types of fibrotic interstitial lung disease (ILD) are at risk of progressive pulmonary fibrosis (PPF).[1]
- Nintedanib has been shown in clinical trials to delay the progression of both idiopathic pulmonary fibrosis (IPF) and non-IPF PPF.[2,3]
- Subsequent disease progression has been analysed for up to two years in patients included in the phase 3 INBUILD trial,[4] but little is known about the progression of PPF beyond this time point.

Objectives

- To compare the efficacy of nintedanib and placebo by modelling disease progression over the lifetime of patients with non-IPF PPF.

Materials and methods

Clinical data

- This analysis used data from patients with non-IPF PPF in the INBUILD trial.[2,4]
  - INBUILD was a double-blind, placebo-controlled trial that enrolled patients with non-IPF PPF affecting > 10% of lung volume who had had disease progression in the past two years despite treatment.
  - In total, 663 patients received nintedanib 150 mg twice daily (n = 332) or placebo (n = 331) for at least 52 weeks.
  - Data up to the second database lock (median of 19 months of blinded treatment) were used in the analysis.

Regression modelling

- The change in the forced vital capacity (FVC) of patients was first evaluated with a regression analysis using either:
  - two separate independent models for nintedanib and placebo, or
  - a general model including all patient data and a treatment coefficient for nintedanib-allocated patients.
- The covariates were selected using a backward stepwise regression process.

Simulation to derive time-to-progression estimates

- Disease progression was simulated using an individual patient-level model incorporating 500 randomly generated patients with characteristics similar to those from the INBUILD trial.
- Disease progression was defined as a ≥ 10% relative decline in FVC within 12 months.
- Acute exacerbations and discontinuation of nintedanib were included in the calculations with estimates informed from the INBUILD trial; post-discontinuation, patients were assumed to have the same risk of progression as in the placebo group.
- Patient mortality was estimated using a Bayesian survival analysis,[5] and was additionally assumed to occur when patients' FVC declined to ≤ 40%.

Survival analysis

- As an alternative approach, a traditional survival analysis was conducted on time-to-progression data from INBUILD.
  - Exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalised gamma parametric survival models were considered.
  - The best-fitting models were selected using the Akaike information criterion and the Bayesian information criterion.

Results

Regression model and simulated progression

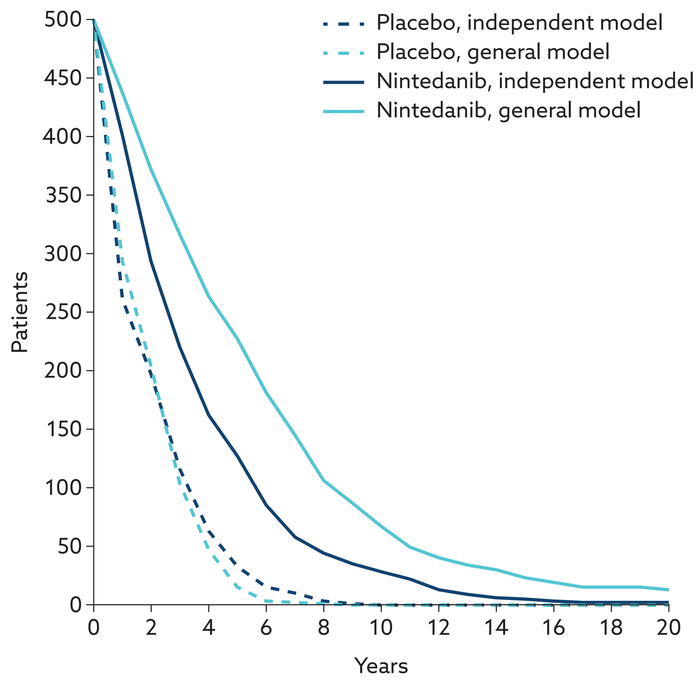
- The parameters selected for the final regression models included baseline FVC, age, criteria for progressive ILD, acute exacerbation and interaction effects between time and fixed factors.
  - All parameters other than acute exacerbation were statistically significant at the 5% level.
- In the comparison with placebo, the simulation results showed improved survival without disease progression with nintedanib.
- The incremental time to disease progression or death for nintedanib over placebo was:
  - 1.56 years using the independent models
  - 2.89 years using the general model.

Survival analysis

- The best-fitting survival models were exponential and Weibull for placebo, and log-normal for nintedanib.
  - The incremental time to disease progression or death for nintedanib over placebo ranged from 0.52 to 0.99 years.

Independent and general FVC regression models

Patients without disease progression or death

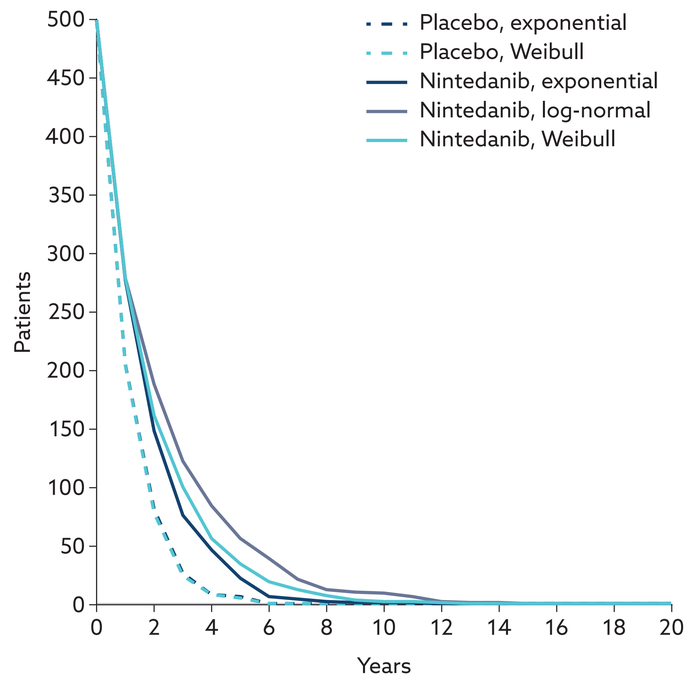


Estimated mean time to disease progression or death (years)

Regression model	Nintedanib	Placebo	Incremental
Independent	3.56	2.00	1.56
General	4.76	1.87	2.89

Survival models

Patients without disease progression or death



Estimated mean time to disease progression or death (years)

Survival curve	Nintedanib	Placebo	Incremental
Nintedanib: exponential Placebo: exponential	1.64	1.12	0.52
Nintedanib: log-normal Placebo: exponential	2.11	1.12	0.99
Nintedanib: Weibull Placebo: Weibull	1.81	1.10	0.71

Exponential and Weibull models were selected for nintedanib in addition to the log-normal model to align with the best-fitting models for placebo.

Covariates used in the FVC regression analysis

Covariate	Independent regression model: nintedanib			Independent regression model: placebo			General regression model		
	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value
(Intercept)	−0.171	1.574	0.914	1.878	1.653	0.257	0.298		
Baseline FVC	0.993	0.013	0.000	0.977	0.014	0.000	0.988		
Age	0.007	0.022	0.735	−0.015	0.021	0.496	−0.001		
PGGR1_marginal				0.316	0.507	0.534			
PGGR1_worsening				−0.089	0.595	0.881			
Acute exacerbation	−4.029	1.534	0.009	−7.020	1.413	0.000	−5.740		
Age and analysis year interaction	−0.038	0.007	0.000	−0.102	0.008	0.000	−0.100		
PGGR1_marginal and analysis year interaction				2.137	0.917	0.020			
PGGR1_worsening and analysis year interaction				2.177	1.058	0.041			
Nintedanib							0.400	0.306	0.191
Placebo and analysis year interaction							0.888	2.114	0.675
Nintedanib and analysis year interaction							4.056	2.079	0.052

PGGR1_marginal, marginal decline in FVC (≥ 5, < 10%) combined with worsening of respiratory symptoms or increasing extent of fibrotic changes on chest imaging; PGGR1_worsening, a clinically significant decline in FVC (≥ 10%).

Conclusion

- Extrapolating progression estimates beyond the randomised controlled period of INBUILD showed that nintedanib could potentially slow progression over the lifetime of patients with PPF, potentially translating to improved survival.

Discussion

- This analysis explored two different approaches to modelling disease progression, with a larger difference in progression-free life years found when using the regression models than the traditional survival analysis.
  - The lowest estimate in the simulation extrapolation was 50% higher than the highest time-to-event analysis.
- The survival analysis categorises patients only according to the ≥10% relative decline in FVC threshold, which does not account for variability in FVC decline across patients.
- By contrast, FVC is analysed as a continuous outcome in the regression models, using all of the data on FVC changes in the INBUILD trial.
- Heterogeneity analysis of the patient characteristics at baseline could address the uncertainty observed in the estimates.

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Abbreviations

FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; SE, standard error.

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