Forced vital capacity (FVC) decline in idiopathic pulmonary fibrosis (IPF) – modelling the myth

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Background and objective

FVC is the only registrational endpoint in IPF clinical trials.
As most new treatments will be administered **on top of standard of care (SOC; pirfenidone** or **nintedanib)**, estimating treatment response will become more challenging.
The objective of this study was to use data simulations to **quantify the variability associated with FVC decline over time** to model effects of an investigational drug for IPF, when given on top of SOC in a clinical trial setting.

Methods

Publicly available **summary data** from FDA review of **nintedanib***

Source data

Daily **home spirometry** data†

*Pirfenidone data were excluded because the primary endpoint in key studies was ppFVC rather than FVC; †Obtained from a study of 50 patients with IPF who provided daily FVC readings over a median of 279 days

10,000 simulations

FVC data simulation

based on assumptions for the mean, variance and correlation structure (CAR[1][1])*

*Mean at baseline: 2,700 mL; SD at baseline: 800 mL; constant SD over time; SD on change from baseline at Week 52: 275 mL

50% assumed to be taking SOC at study start and **50%** not

400 IPF patients

Base simulation setting

(illustrative example of a clinical trial)

1:1 — **Investigational drug** / **Placebo**

Measurements at: Weeks 0, 2, 4, 8, 12, 18, 26, 34, 42 and 52

Week 52

Assumed treatment difference in FVC change from baseline: 90 mL

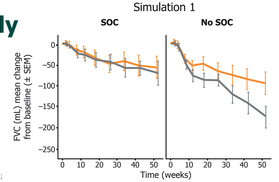
10,000 analyses

Data analysis

ANCOVA **LMM** **MMRM**

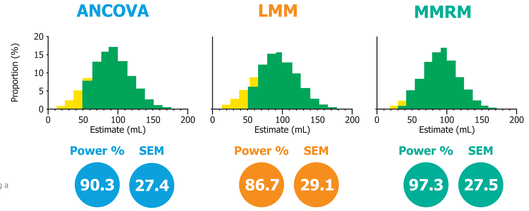
Results

Summary graph of two **randomly** selected simulations



n=100 per treatment group–strata combination
The two simulations result from the same setting; they differ due to variability

Estimated **treatment difference** at Week 52



Non-significant trial
Significant trial*

This figure shows the range and probability of observing a certain treatment effect for the same underlying setting
*Significance level: 5%

Simulated trial scenarios

	Decrease in trial power (%)			Increase/decrease in estimated treatment effect (mL)		
	ANCOVA	LMM	MMRM	ANCOVA	LMM	MMRM
15% annual random dropout	5.2	3.4	0.6	0.2	0.3	0.2
15% annual dropout due to observed FVC decline*	9.3	1.5	0.8	11.9	4.4	3.3
15% annual dropout due to unobserved FVC decline†	12.2	4.9	2.7	15.0	8.5	12.0
50% of placebo group initiate SOC during trial	7.9	8.9	3.7	11.2	11.3	11.2
25% of subjects on SOC lower investigational drug dose	1.0	1.2	0.3	2.6	2.7	2.7
25% of subjects on SOC discontinue investigational drug	3.5	4.5	1.4	5.6	5.9	5.6
Combined effect of 5% dropout‡ and 15% initiating SOC	6.2	4.4	1.7	7.1	5.8	6.7
Shortening of trial length to 26 weeks	28.3	27.5	15.6	0.5	0.8	0.5

*Dropout resulted from an observed, confirmed FVC decline of >10% relative to baseline; †Dropout preceded an unobserved, confirmed FVC decline of >10% relative to baseline; ‡Dropout due to unobserved FVC decline

Conclusions

New IPF treatments will likely be given on top of SOC (pirfenidone or nintedanib)[2,3] and will need to show efficacy in this scenario, in terms of FVC, in clinical trials

GLPG1690, a first-in-class autotaxin inhibitor, is under evaluation on top of SOC in the phase 3 **ISABELA** studies[4]

Demonstrating efficacy on top of SOC is challenging
Due to FVC variability and the complex nature of such trials[5]

Several clinical trial complexities may lead to reduced power to detect a significant treatment effect in trials of novel IPF treatments
Treatment effect and underlying changes in FVC need to be distinguished

Our model allowed us to quantify variability associated with FVC decline in a number of clinical trial scenarios
It can be adapted/extended to other trial settings

This permits robust power calculations to optimize clinical trial design
Ultimately benefitting **patients** and helping healthcare professionals **better understand the pattern of FVC decline** that might be seen in clinical practice

Disclosures

MW reports no personal fees; the Erasmus MC received an advisory board fee from Galapagos, and speaker and advisory board fees from Boehringer Ingelheim and Hoffmann-La Roche. **ES** is an employee of Galapagos. **PF**, **NV** and **PM** are employees of, and have received warrants from, Galapagos. **MK** reports grants and personal fees from Boehringer Ingelheim, Galapagos, and Roche. **WW** reports no personal fees; the University Hospitals Leuven has received consultancy fees from Galapagos and grants from Boehringer Ingelheim and Roche. **KKB** reports grants from the National Institutes of Health, and advisory board participation for Biogen, Blade, Boehringer Ingelheim, Galapagos, Galecto, Genoa Pharmaceuticals, Hultai Biomedicine, Lifemax, MedImmune, monARC Bionetworks, Open Source Imaging Consortium (OSIC), Pliant, ProMetic, Theravance, Third Pole, Three Lakes Partners, and Veracyte. **DJL** is a full-time employee of Regeneron Pharmaceuticals, Inc. He also reports personal fees from Boehringer Ingelheim, Galapagos, Philips Respironics, Roche, Sanofi Genzyme and Veracyte; grants and personal fees from Boehringer Ingelheim, Fibrogen, and Global Blood Therapeutics; unpaid Steering Committee membership for Galecto; unpaid advisory board membership and consultancy for Pliant; unpaid consultancy for Bristol-Myers Squibb; and institutional fees for consultancy work from the Pulmonary Fibrosis Foundation. **TMM** via his institution, has received industry-academic funding from GlaxoSmithKline R&D and UCB, and has received consultancy or speakers fees from Apellis, AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Galapagos, GlaxoSmithKline R&D, Indalo, Novartis, Pliant, ProMetic, Respivnat, Roche, Samumed, and UCB.

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ANCOVA, analysis of covariance model; CAR(1), continuous-time autoregressive model of order 1; FDA, US Food and Drug Administration; IPF, idiopathic pulmonary fibrosis; LMM, linear mixed model; MMRM, mixed model repeated measures; (pp)FVC, (percent predicted) forced vital capacity; SD, standard deviation; SEM, standard error of the mean; SOC, standard of care