

# Model-based meta-analysis of publicly available aggregate data in idiopathic pulmonary fibrosis (IPF)

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## Introduction

- Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease of unknown cause [1].
- Several pharmacologic therapies including corticosteroids, immunosuppressive/cytotoxic agents and antifibrotic agents have been considered.
- Most of the drugs investigated for the treatment of IPF have failed to show clinical efficacy in stand-alone randomized, placebo-controlled trials.
- Following the release of a consensus statement by the American Thoracic society (ATS) and European Respiratory Society (ERS) [2], diagnosis of IPF is now more standardized and specific.
- To date, only pirfenidone has been approved for the treatment of IPF in Japan [3], and in Europe [4]. New treatments such as tyrosine kinase inhibitor BIBF1120 have shown promising results [5].
- A comprehensive extract of published (summary level) trial data, and a subsequent analysis of such data increases the understanding of the treatments, the various clinical outcomes, and may support more efficient designs for future IPF studies.

## Objectives

To capture summary level data for the clinical efficacy and safety outcomes from publicly available data sources in IPF and to analyze this database using model-based meta-analysis techniques to evaluate treatments effects of various drugs, as well as effects of other explanatory variables on lung function parameters.

## Methodology

- A database was developed from publicly available data sources reporting summary level trial information involving various investigational drugs evaluated for clinical efficacy and safety outcomes in IPF. PubMed was the key source, complemented with published abstracts or presentations of clinical trial data from conferences and corporate websites.
- Forced vital capacity % predicted (FVC), one of the most frequently reported outcomes was the endpoint of interest. FVC is a measure of lung volume, and is widely used and accepted as a clinically meaningful measure of IPF disease status.
- A nonlinear regression model including a non-parametric placebo-response and an asymptotic time-dependent treatment effect was defined as follows:

$$y_{ijk} = P_{ij} + E_{MAX}^D \cdot (1 + \beta_q X_{qi}) \cdot (1 - \exp(-\exp(\alpha) \cdot t_{ij})) \cdot \text{TRT} + \varepsilon_{ijk}, \text{ where}$$

- $y_{ijk}$  denotes the mean FVC change from baseline for trial  $i$  ( $i=1, \dots, T$ ) at time point  $t_{ij}$  ( $j=1, \dots, n_i$ ) in arm  $k$
- $P_{ij}$  is the placebo response for trial  $i$  at time point  $j$
- $E_{MAX}^D$  is the maximum drug effect for drug (or drug class)  $D$ ,  $\alpha$  is the logarithm of the rate constant of onset of drug effect, TRT is a treatment indicator (1=drug treatment, 0=placebo), and the (correlated) residual errors  $\varepsilon_{ijk} \sim N(0, \sigma^2/n_{ijk})$ .
- $\beta_q$  is a parameter that captures the effect of a covariate  $X_q$  on the maximal drug effect.
- The drug treatments were stratified into three classes; pirfenidone (2 trials), BIBF1120 (1 trial), and other drugs (8 trials) which included a single trial each for azathioprine, bosentan, and etanercept, 3 trials for interferon, and 2 trials for sildenafil.
- Pirfenidone is approved and the investigational BIBF1120 has shown promising results and therefore responses are expected to be higher from these drugs.
- The other drugs have not been shown to be dissimilar in effect from placebo.

- The models were fitted using the maximum likelihood estimation technique in the nlme package in R2.12.1.
- Testing for effects of covariates on drug effect was based on the likelihood ratio testing procedure, and non-nested models were compared based on the AIC criteria.
- Trial simulations to address issues of power and sample size for designing future trials were performed based on a simplified model which assumed a common  $E_{MAX}$  for all drugs.

## Summary of the data and exploratory analysis

- Twenty three clinical trials involving 4378 patients with 15 drugs were included in the final database. Eleven of these were placebo-controlled and reported FVC % pred as an outcome and formed the analysis data set (Table 1).

Table 1: Summary of drugs investigated in trials that reported FVC as an outcome.

| Reference                            | Drug                | Number of trials | Number of patients |
|--------------------------------------|---------------------|------------------|--------------------|
| Raghu 1991                           | Azathioprine        | 1                | 14                 |
| Richeldi 2011                        | BIBF 1120           | 1                | 340                |
| King 2008                            | Bosentan            | 1                | 71                 |
| Raghu 2008                           | Etanercept          | 1                | 45                 |
| Strieter 2004, King 2009, Raghu 2004 | Interferon gamma-1b | 3                | 730                |
| PIPF-004 2010, PIPF-006 2010         | Pirfenidone         | 2                | 432                |
| Jackson 2010, Zisman 2010            | Sildenafil          | 2                | 103                |
|                                      | Placebo             | 11               | 1099               |
|                                      | Total               | 11               | 2834               |

Figure 1: Mean FVC changes from baseline for the placebo and treatment arms for the 11 trials that reported FVC. Size of the symbols is proportional to sample size.

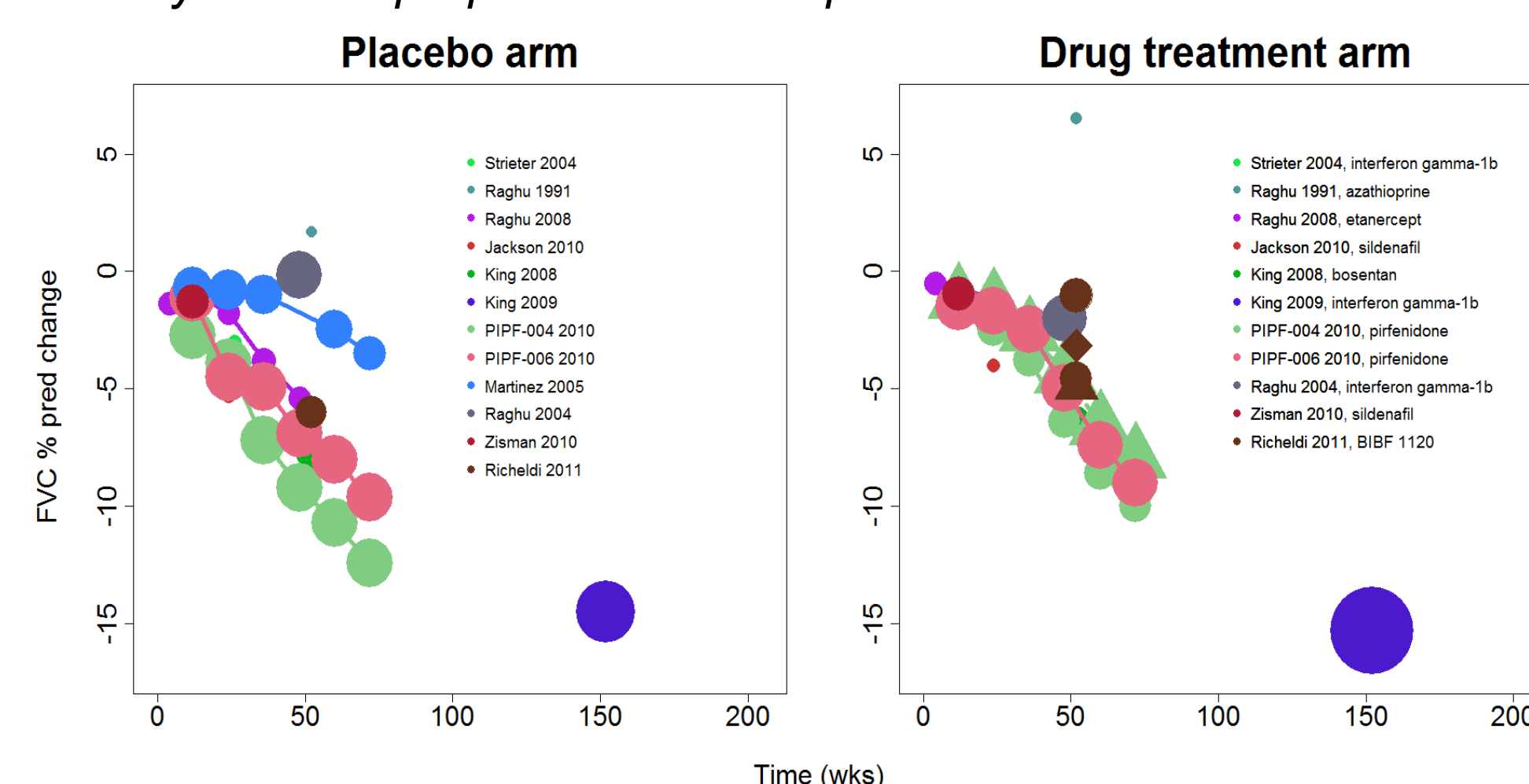
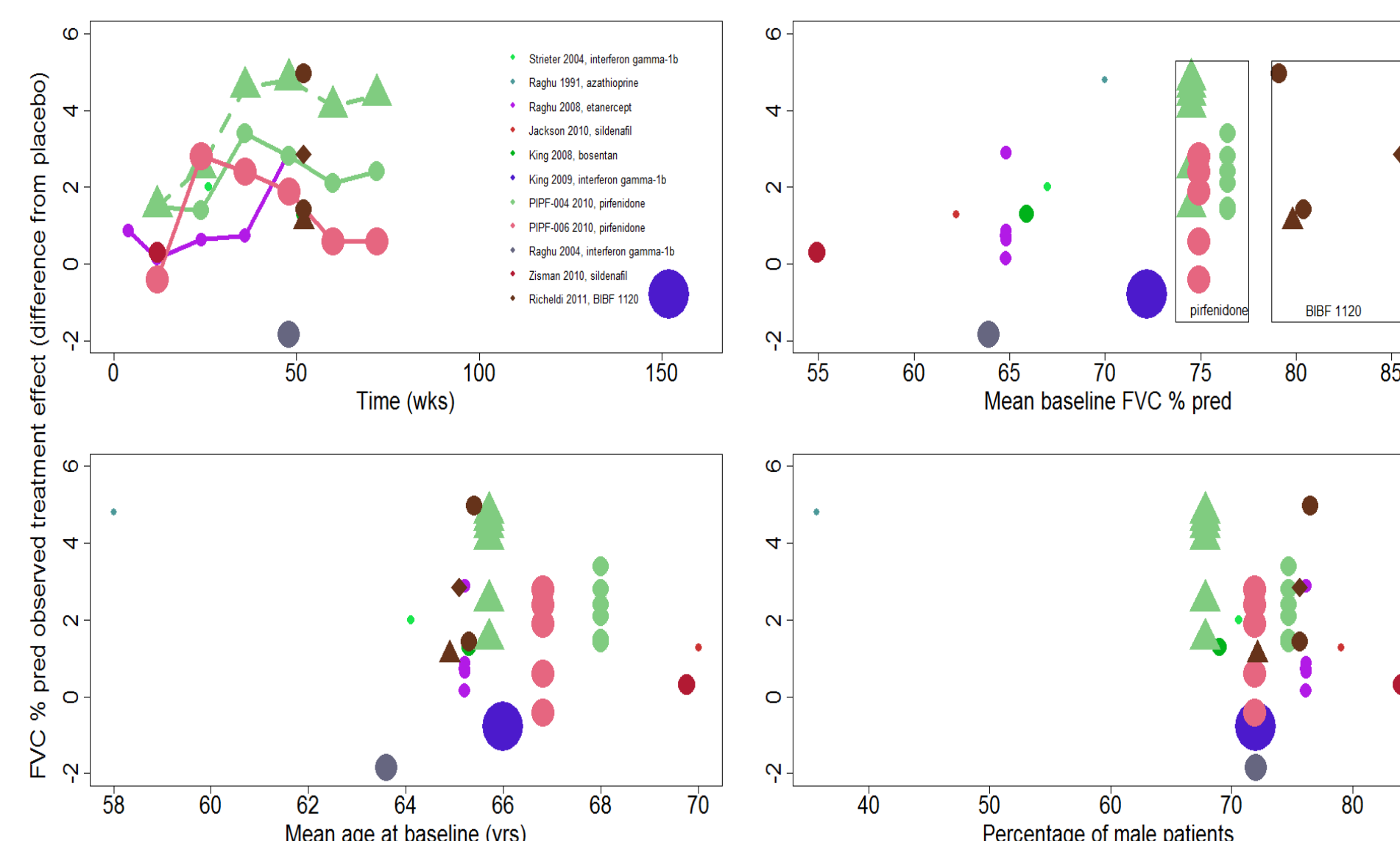


Figure 2: Relationship between observed treatment effect (difference from placebo) and some covariates.



- Figure 2 suggests a general increasing trend in FVC treatment effect over time and trials with higher baseline values tend to have larger drug effects. There appears to be no relationship between treatment effect and age, and treatment effect and gender.

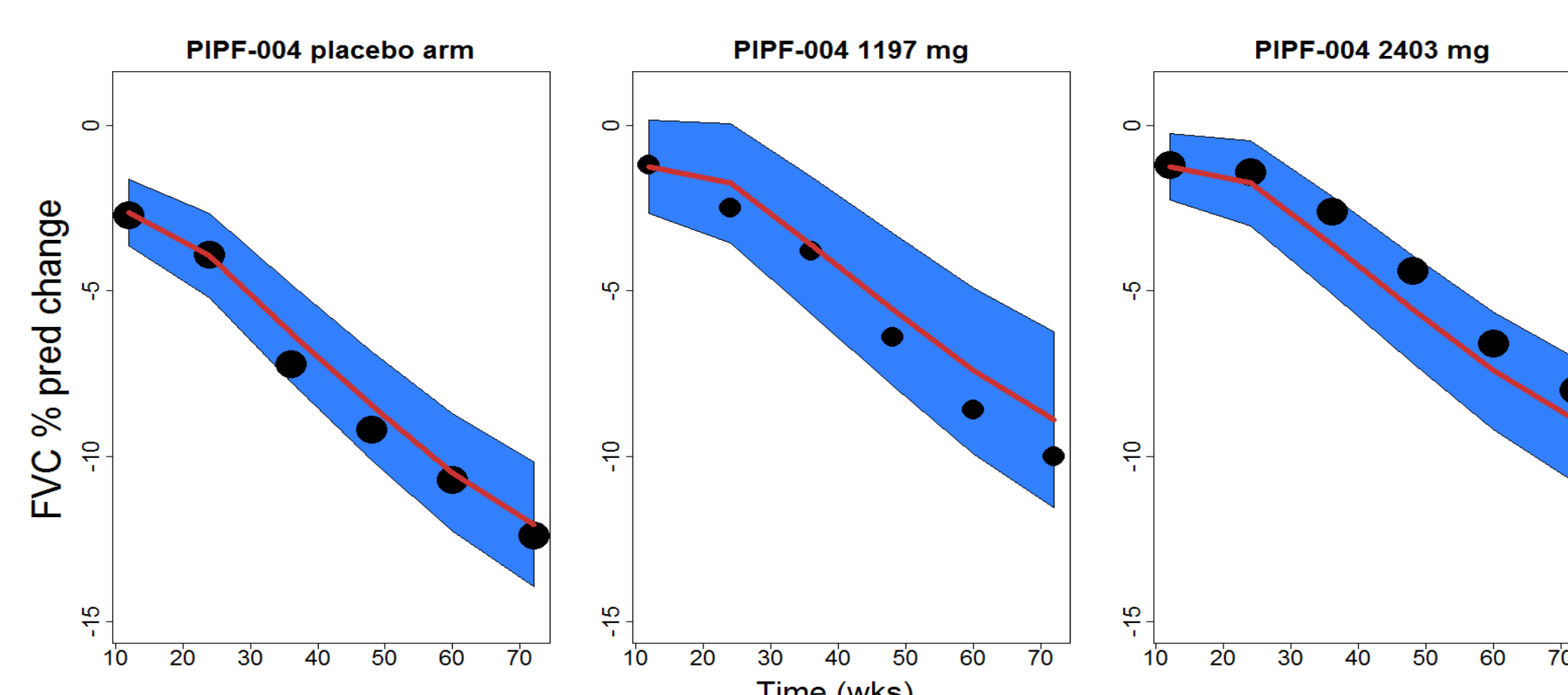
## Comparative effectiveness of three drug classes

- A statistically significant linear dose effect on FVC was obtained for BIBF1120 ( $p=0.01$ ); no dose treatment effect relation was observed for pirfenidone or for the other drugs.

Table 2: Maximum expected FVC treatment effect for pirfenidone and expected treatment effect for BIBF1120 doses.

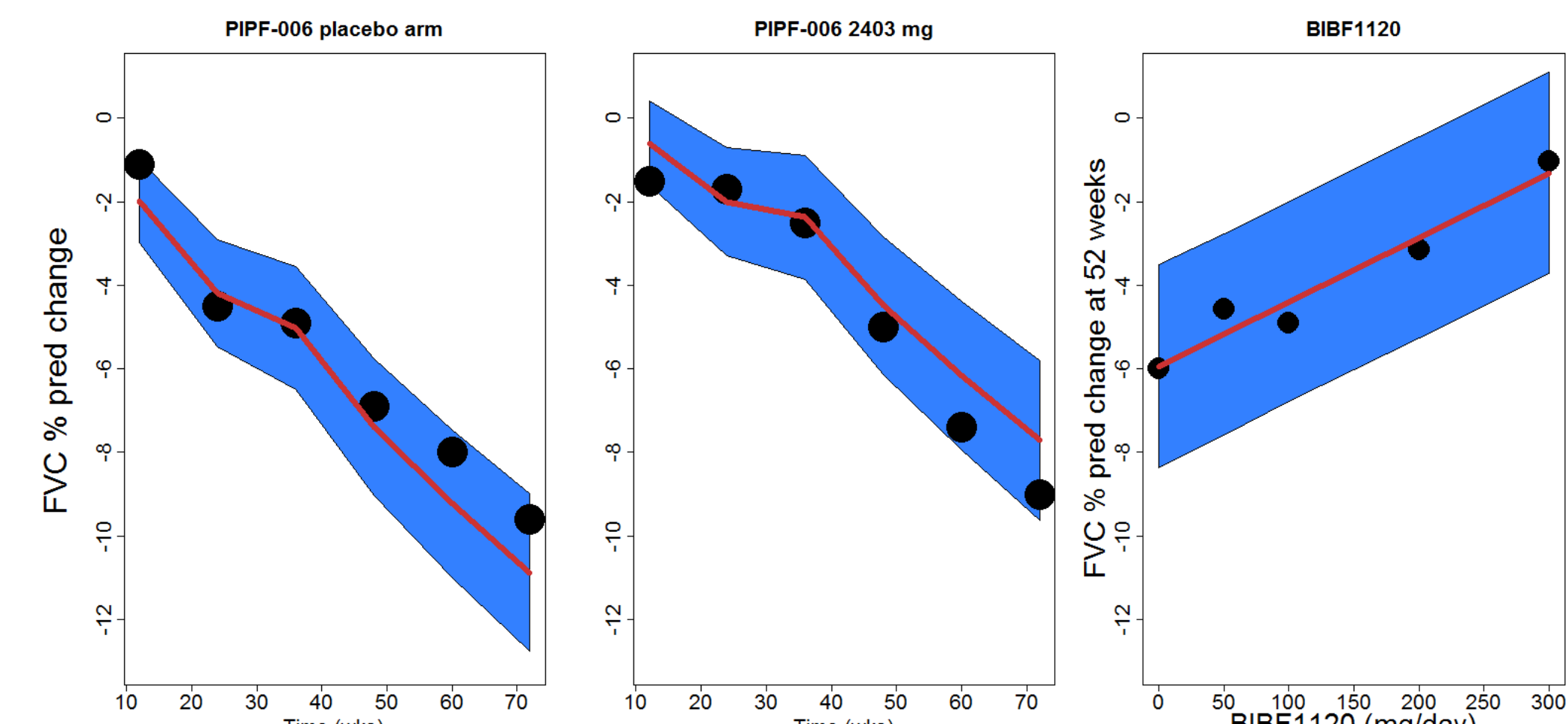
|                    | Difference from placebo [95% CI] | Difference from pirfenidone [95% CI] |
|--------------------|----------------------------------|--------------------------------------|
| Pirfenidone        | 3.28 [1.67; 4.70]                | 0.00 [0.00; 0.00]                    |
| BIBF1120 50mg/day  | 0.77 [0.28; 1.26]                | -2.09 [-3.37; -0.71]                 |
| BIBF1120 100mg/day | 1.54 [0.57; 2.52]                | -1.33 [-2.85; 0.19]                  |
| BIBF1120 150mg/day | 2.32 [0.85; 3.78]                | -0.54 [-2.38; 1.15]                  |
| BIBF1120 200mg/day | 3.09 [1.13; 5.04]                | 0.24 [-1.98; 2.32]                   |
| BIBF1120 250mg/day | 3.86 [1.41; 6.30]                | 1.02 [-1.67; 3.50]                   |
| BIBF1120 300mg/day | 4.63 [1.70; 7.56]                | 1.79 [-1.39; 4.73]                   |
| Other drugs        | -0.26 [-1.68; 1.14]              | -3.03 [-4.73; -1.30]                 |

Figure 3: Fit of the model in the pirfenidone trial PIPF-004. Points are observed FVC changes from baseline, lines are model fit and shaded area is 95% CI for model fit.



## Results

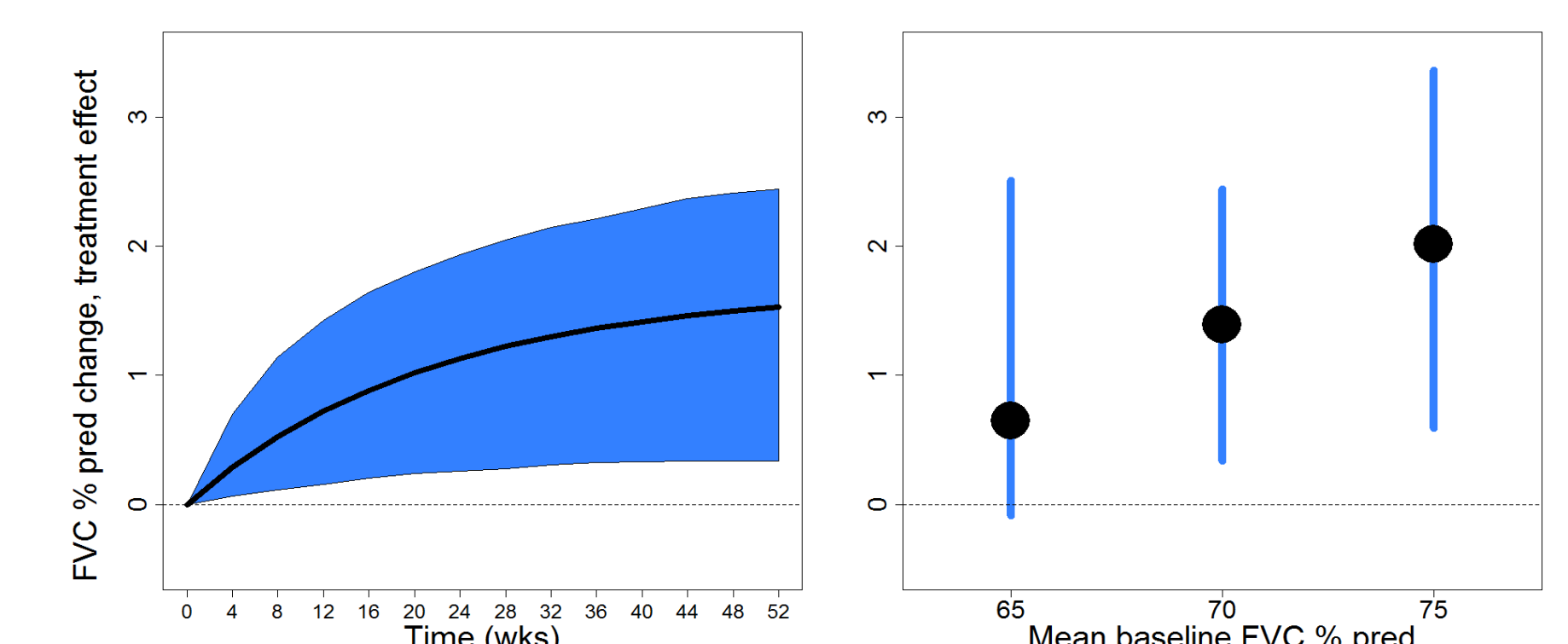
Figure 4: Fit of the model in the pirfenidone PIPF-006 trial and the BIBF1120 trial (Richeldi 2011). Points are observed FVC changes from baseline, lines are model fit and shaded area is 95% CI for model fit.



## Effect of all drugs combined together

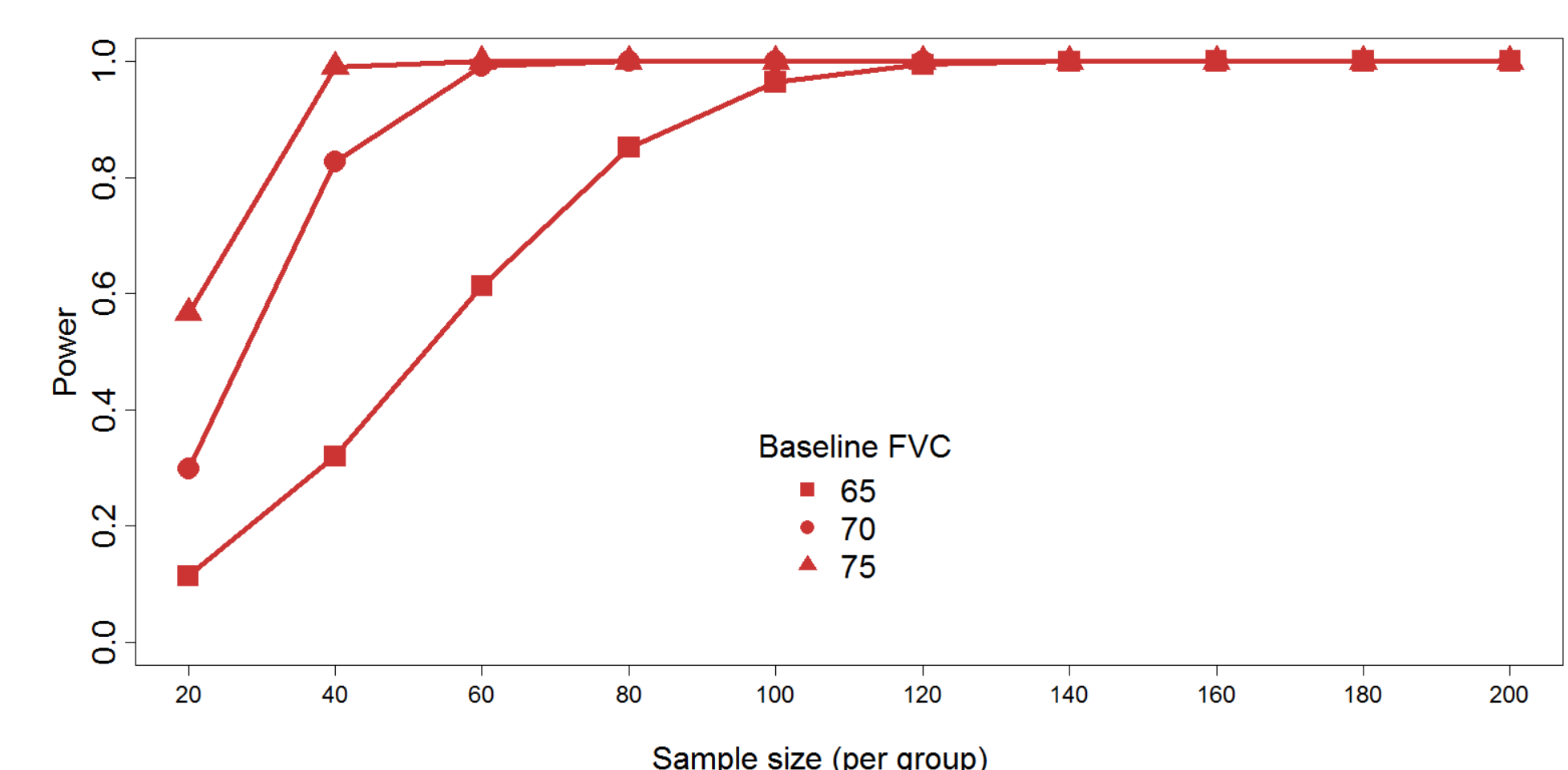
- Maximal drug effect on FVC estimated to be 1.67% [0.25, 3.09 %]
- Significant effect of mean baseline values on maximal drug effect ( $p=0.01$ ): higher baseline values tend to be associated with larger treatment effect (see Figure 2 and Figure 4).
- Based on model estimates, it will take approximately 15 weeks to observe a treatment effect of about 0.8% for a mean baseline FVC of 70%.

Figure 4: Expected treatment effect for a 52 week trial (typical) and baseline FVC of 70% (left) and expected treatment at 52 weeks for varying baseline FVC values (right).



- Figure 5 shows the power to detect the specified treatment effect corresponding to different baseline FVC values based on initial trial simulations. Further investigations are under way.
- Since baseline has a significant impact on treatment effect, based on the model, the treatment effect to be detected is a function of baseline values and not a particular predefined value; baseline values of FVC 65%, 70%, and 75% lead to treatment effect levels of 0.78%, 1.53% and 2.27% respectively.
- From Figure 5, it can be observed that, for example, a trial with mean baseline FVC of 70%, duration of 52 weeks, and enrolling 40 patients per group will have a power of ~80% to detect a treatment effect of 1.53% (CV%=36.4%).

Figure 5: Power for trials with different baseline FVC values for a 52 week trial with different sample sizes.



## Conclusions

- Model-based meta-analysis of aggregate clinical outcome data with this IPF database provided insights about treatment effects of various drugs (magnitude, rate of onset) on forced vital capacity percent predicted (FVC).
- Significant treatment effects in reducing the decline in FVC were identified for BIBF1120 and pirfenidone, and for BIBF1120 a dosing regimen of 200 mg/day is expected to give a similar effect as pirfenidone.
- Treatment effect in patients with higher baseline values may be more pronounced than in (more severely diseased) patients with lower baseline FVC values.
- Trial simulations provided suggestions for designing trials in IPF in terms of trial inclusion criteria.

## References

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