OBJECTIVES

- Construct a meta-analysis database using summary-level clinical data extracted from the literature, specifically from pirfenidone and nintedanib and from other approved therapies.
- Utilize MBMA to evaluate the full time course of the response (speed of onset, maintenance, and magnitude) of drug effects.
- Compare treatment effects of different drugs across different patient populations and treatments that have not been directly evaluated in the same trial, to make during drug development decisions.
- For IPF prompts the need for indirect comparisons by leveraging data currently available.

METHODS

- Database Construction:
  - A systematic review of publicly available data from the PubMed database was conducted in September 2015 according to a pre-specified database building protocol and based on the relevant identification screening and assessment steps described in the Cochrane Handbook for Systematic Reviews of Interventions and reporting items in the PRISMA statement.
  - The search used the following keywords: "idiopathic pulmonary fibrosis," "IPF," "nintedanib," "pirfenidone," "laboratory," "clinical trial," "randomized controlled trial," "publication type," and "search term/words.
  - The database was augmented for trials with missing study-specific statistical values, and transformation was performed to generate the normalized (%predicted) FVC from reported FVC in the three nintedanib trial and two placebo trials using a standard equation.
  - Missing covariate values were imputed using multi-variate linear regression, based on non-missing clinically relevant trial variables.

- Model Development:
  - The longitudinal profile of %predicted FVC (%predicted FVC) was characterized by a regression model using maximum likelihood estimation, and a non-parametric placebo model was implemented to analyze the data from the placebo trial arms.
  - A systematic review of publicly available data from the PubMed database was conducted in September 2015 according to a pre-specified database building protocol and based on the relevant identification screening and assessment steps described in the Cochrane Handbook for Systematic Reviews of Interventions and reporting items in the PRISMA statement.
  - The search used the following keywords: "idiopathic pulmonary fibrosis," "IPF," "nintedanib," "pirfenidone," "laboratory," "clinical trial," "randomized controlled trial," "publication type," and "search term/words.
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  - Missing covariate values were imputed using multi-variate linear regression, based on non-missing clinically relevant trial variables.

- Model Evaluation:
  - Model diagnostic plots in the form of longitudinal plots, as well as a forest plot.
  - The model diagnostic plots in the form of longitudinal plots, as well as a forest plot.
  - The results showed that the parameter estimates were not greatly different between the two drugs with respect to pulmonary function decline or survival benefit.
  - The model evaluation plots for each trial showed that the final MBMA model predicts the observed longitudinal data well; and overall the model was able to capture the observed variability of primary timepoint, despite the large differences in treatment duration time.
  - The present MBMA framework can be applied to inform future trials designs by utilizing the developed model to perform clinical trial simulations.

REFERENCES

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DISCLOSURE

P Chan, Os Chan, P H Huang, H Snares, G Rosen, M Alzer and were all current employees of Bristol-Myers Squibb during the analysis conduct and hold the company. R Burns had been paid consulting fees for work related to the database construction and analysis.

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