Predicting Reductions in Chronic Obstructive Pulmonary Disease (COPD) Exacerbations from FEV$_1$ – A Model-Based Meta-Analysis of Literature Data from Controlled Randomized Clinical Trials

Jakob Ribbing$^{1,2,*}$, Julia Korell$^2$, Frank Cerasoli$^2$, Peter A Milligan$^1$, Steven W Martin$^1$, Mats O Karlsson$^2$

$^1$ Pfizer LTD; $^2$ Uppsala University

**Objectives:** To describe the relationship between forced expiratory volume in one second (FEV$_1$) and annual rate of moderate-severe exacerbations (ER) utilizing summary-level, literature data.

Shorter duration Phase 2 studies assess FEV$_1$ whereas Phase 3 chronic maintenance studies assess the registerable endpoint (prevention of COPD exacerbations).

**Methods:** Data was extracted from 29 randomized trials (80 treatment arms), of 43,472 patients. As predictors of ER, model-predicted trough FEV$_1$[1] at baseline and week 12, as well as covariates, were investigated using NONMEM. Placebo ER was a function of covariates and interstudy variability. The ER ratio (treatment vs. placebo) was described by separate functions for FEV$_1$ efficacy ($\Delta\Delta$FEV$_1$) from direct bronchodilators (long-acting; LABD) and anti-inflammatory (AI) agents. Outcomes were derived as point estimate [95%-Confidence interval] vs placebo/reference arm.

**Results:** The final model predicted that placebo ER increased with a) disease severity (FEV$_1$%Predicted), b) fraction of (ICS experienced) patients required to wash out from ICS (ICS$_{washout}$), and c) inclusion criteria requiring a history of exacerbations.

The log(ER-ratio) (treated vs untreated), was described by separate linear-slopes for LABD and AI $\Delta\Delta$FEV$_1$, and in addition for %ICS$_{washout}$, by a $\Delta\Delta$FEV$_1$$_{AI-E_{max}}$ model. The model predicted that for log(ER-ratio) < -0.2 (>18% ER reduction), LABDs must achieve at least a $\Delta\Delta$FEV$_1$ 122 mL [114mL−132mL] improvement (over placebo/reference). For a scenario with 62% ICS$_{washout}$, an AI treatment (ICS/PDE4i) must achieve at least a $\Delta\Delta$FEV$_1$ 45 mL [17mL−79mL] improvement, for log(ER-ratio) < -0.2.

**Conclusions:** The investigated AIs have modest efficacy on FEV$_1$, but if patients are washed out from ICS, these treatments achieve reductions in ER comparable to the new-generation LABD. The outcomes from this analysis may be applied while designing Phase 3 efficacy studies, pharmaco-economic outcomes studies, and quantifying comparative effectiveness of available treatments.

**Reference:**