Predicting Reductions in COPD Exacerbations from FEV_1

A model-based meta-analysis of literature data from controlled randomized clinical trials

Jakob Ribbing[1,2,a], Julia Korell[2,b], Frank Cerasoli[1,c], Peter A Milligan[1], Steven W Martin[1], Mats O Karlsson[2]

Affiliation: 1 Pfizer LTD; 2 Uppsala University Current employment: a) Pharmetheus AB; b) Model Answers Pty Ltd; c) Medical Dynamics

Introduction

In Chronic Obstructive Pulmonary Disease (COPD), shorter duration Phase 2 studies assess forced expiratory volume in one second (FEV_1) whereas Phase 3 chronic maintenance studies assess the registrable endpoint: prevention of COPD exacerbations.

The main objective was to describe the relationship between FEV_1 and annual rate of moderate-severe[1] exacerbations (ER) utilizing summary-level, literature data.

Conclusions

- The investigated AIs have modest efficacy on FEV_1, but for patients washed out of ICS, these treatments achieve reductions in ER comparable to the new-generation LABD
- The outcomes from this analysis may be applied for designing Phase 3 efficacy studies, pharmaco-economic outcomes analyses[4,5], and assessing comparative effectiveness (CE).
- Using model-predicted FEV_1 allowed including studies without proper FEV_1 trough measurements, and to separate efficacy into LABD and AI components, for combination treatments.
  - This approach also allowed separating covariate effects acting indirectly, via the FEV_1 biomarker (e.g. interaction between LABA and LAAC)[2], from those acting directly on the FEV1-ER translation (interaction between ICS and PDE4i), which enabled accounting for the full uncertainty (in FEV_1 and FEV_1-ER models), e.g. for CE in different subpopulations and conmeds.

Methods

Data was extracted from 29 randomized trials (80 treatment arms), of 43 472 patients. As predictors of ER, model-predicted trough FEV_1[2] at baseline and week 12, as well as covariates, were investigated using NONMEM. Placebo ER was a function of covariates and interstudy variability (ISV). The ER ratio (treatment vs. placebo) was described by separate functions for FEV_1 efficacy ($\Delta\Delta FEV_1$) for direct bronchodilators (long-acting; LABD) and anti-inflammatory (AI) agents.

The placebo ER (mean number of exacerbations per patient, per year) was a function of a) baseline FEV_1 percent of normal (%FEV_1), b) percent of patients washed out from ICS ($ICS_{washout}$) and c) requirement of patient history of exacerbation(s) ($ER_{history}$), according to:

$$TVERplac_{ij} = \begin{cases} ERplac \cdot e^{(\%FEV1_{ij}-41)\cdot E_{\%FEV1}+(\%ICS_{washout_{ij}}-54)\cdot E_{ICSwashout}} & \text{if } ER_{hist_i}=1 \\ ERplac \cdot e^{(\%FEV1_{ij}-49)\cdot E_{\%FEV1}+(\%ICS_{washout_{ij}}-44)\cdot E_{ICSwashout}} \cdot (1+E_{ERhist}) & \text{if } ER_{hist_i}\neq 1 \end{cases}$$

The ER ratio (relative to placebo) was a function of FEV_1-efficacy contributions (difference from placebo) from LABD ($\Delta\Delta FEV1_{LABD}$) and AI ($\Delta\Delta FEV1_{AI}$), the latter in interaction with the percent ICS-experienced patients ($\%ICS_{exp}$), according to:

$$RAT_{ij} = e^{\Delta\Delta FEV1_{LABD_{ij}}\cdot Slope_{LABD}+\Delta\Delta FEV1_{AI_{ij}}\cdot Slope_{AI}} \cdot \left(1-\frac{\%ICS_{exp_{ij}}}{100}\cdot\frac{\Delta\Delta FEV1_{AI_{ij}}\cdot Emax_{AIexp}}{\Delta\Delta FEV1_{AI_{ij}}+EFEV1_{50_{AIexp}}}\right)$$

Outcomes were derived as point estimate [95% confidence interval (CI)] versus the reference arm.

Results

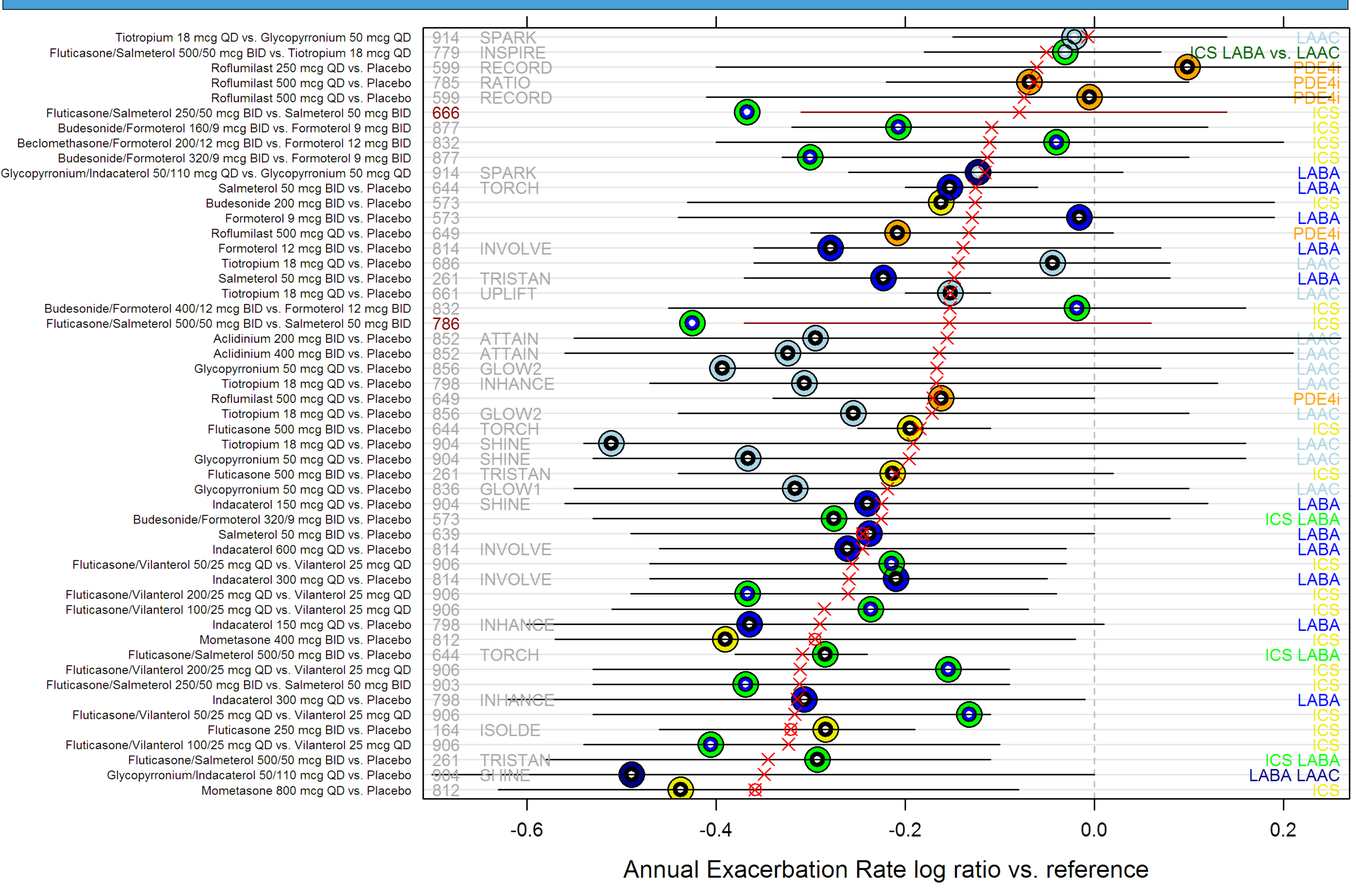

***Figure 1**. Simulated and observed log ER ratios for all main contrasts in the analysis. The prediction based on simulation is marked with **x** (surrounded by circle in case based on an unweighted mean[3]), and with a horizontal black line representing the 95% CI. The filled circle represents the observed mean, with colors based on whether the treatment class in active (outer ring) and reference (inner ring) was **Placebo**, **LABA**, **LAAC**, **ICS**, **PDE4i**, **LABA/LAAC** or **ICS/LABA**. Two out of 51 observed main contrasts were outside the simulated 95% CI (highlighted in red), indicating an appropriate coverage probability.*

Table 1. Parameter estimates relevant for appropriately weighted means[3]

Name	Description	Point Estimate	RSE (%)
ERplac	Mean annual rate for the typical trial with requirement of exacerbation history	1.38	4
E_{ERhist}	Change in ER for the typical trial without requirement of exacerbation history	-0.322	13
$E_{\%FEV1}$	Change in ER for each percentage point change in %FEV_1	-0.0264	34
$E_{ICSwashout}$	Change in ER for each percentage point change in $\%ICS_{washout}$	0.00286	21
$Slope_{LABD}$	$\Delta\Delta$FEV1 slope for LABD (L^{-1})	-1.63	3
$Slope_{AI}$	$\Delta\Delta$FEV1 slope for AI (L^{-1})	-1.17	36
$Emax_{AIexp}$	Maximal reduction for AI in ICS experienced patients	0.22	17
$E_{FEV1,50}$	$\Delta\Delta FEV1_{AI}$ that achieves half of the E_{max}-driven ER reduction (L)	0.001	-
σ	Residual error for 500-subject arm & 1-year study duration (CV)	0.0702	10
ω	ISV in exacerbation rate (CV)	0.169	23

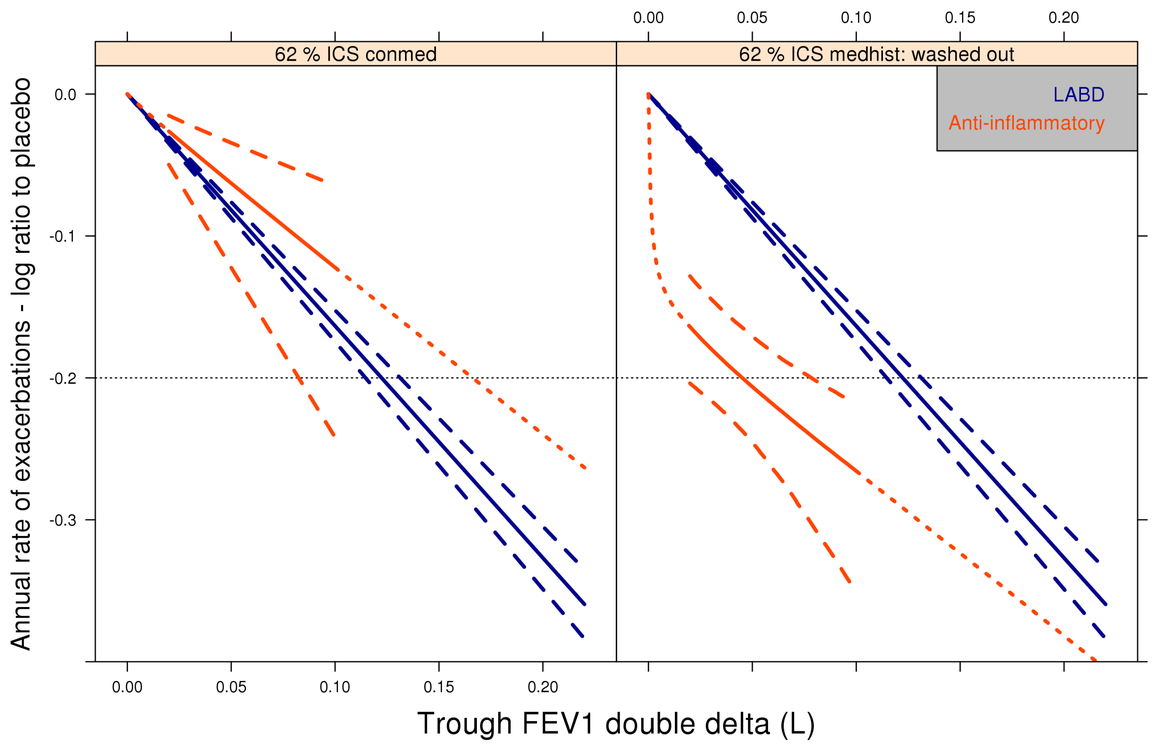

***Figure 2**. Model predicted log ER ratio versus trough $\Delta\Delta$FEV1 for the two different types of treatment, and given two different scenarios; In both scenarios a more severe population is considered, but left-hand panel represents a study design where ICS experienced patients remain on ICS background whereas in the right-hand panel they are required to wash out from ICS prior to randomization. The solid line represents the median, and the broken lines the 95% CI, based on the uncertainty in population parameters. For AI treatment, the solid line has been extended with a dotted line, to indicate extrapolation outside the available data range. For log(ER-ratio) < -0.2 (>18% reduction in ER), LABDs must achieve at least a $\Delta\Delta FEV_1$ of 122 mL [114mL−132mL]. For the scenario with 62% ICS washout, an AI treatment (ICS/PDE4i) must achieve at least a $\Delta\Delta FEV_1$ of 45 mL [17mL−79mL], to reach log(ER-ratio) < -0.2.*

References

1. M. Cazzola, et al., Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J, 2008. 31(2): 416-69.
2. J. Korell, S.W. Martin, M.O. Karlsson and J. Ribbing. A model-based longitudinal meta-analysis of FEV_1 in randomized COPD trials. Clin Pharmacol Ther. 2016 Mar;99(3):315-24. Epub 2015 Oct 22.
3. S. Suissa, Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2006. 173(8):842-6.
4. J.F. Slejko, R.J. Willke, J. Ribbing and P. Milligan. Translating Pharmacometrics to a Pharmacoeconomic Model of COPD (in manuscript).
5. R.J. Willke, J.F. Slejko, J. Ribbing and P. Milligan. Calibration of a Health Economic Microsimulation Model to Pharmacometric Model-Based Meta-Analysis Predictions: A Chronic Obstructive Pulmonary Disease Example (in manuscript).