MODELLING AND SIMULATION BASED TECHNIQUES TO SUPPORT TRIAL DESIGN OF ROFLUMILAST PHASE III TRIALS

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Roflumilast, an oral selective PDE4 inhibitor has been approved in EU as Daxas® (and more recently also in US and Canada under the tradename Daliresp®). Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. Model based techniques were used to describe the primary clinical endpoint (reduction in the number of exacerbations) and secondary endpoint (increase in change from baseline FEV1 (Forced Expiratory Volume in the first second) compared to placebo) in two pivotal phase III trials.

Objectives

The objectives of this analysis were to develop statistical models to predict the effect sizes in both clinical endpoints as well as to predict the probability of success to reach significance in both clinical trials.

Methods

No plasma concentrations were measured during the clinical trials used for theses analyses, so PD only models were constructed.

1. The FEV_1 Model

Data from six phase II/III trials were used to develop a nonlinear mixed effects model to describe the change from baseline FEV_1 over time.

$$\frac{fev_{1i}(t_j) - fev_{1\,base,i}}{fev_{1\,base,i}} = f(t_j, x) + \varepsilon_{ij}$$

The structural model $f(t_j, x)$ is the sum of a linear model to describe the disease progression and a negative exponential function (decreasing over time) to describe the individual drug effect:

$$fev1_i(t_j) = fev1_{\,base,i} \times (1 - slope_i \times t_j + Amp_i \times \exp(-k \times t_j)) + \varepsilon_{ij},$$
$$\varepsilon_{ij} \sim N(0,\sigma^2).$$

Patients are enumerated by *i*, observations by *j*. The parameter of interest is *Amp*, the amplitude of the drug effect, which is modelled as

$$Amp_i = \theta_1 + \theta_2 \times dose_i + \ldots + \eta_{amp,i}, \quad \eta_{amp,i} \sim LN(0,\omega_1^2)$$

with an intercept term, a dose-effect, and a log-normal distributed random effect. The parameter model for slope does not contain covariate effects but a log normal distributed random effect:

$$slope_i = \theta_0 + \eta_{slope,i}, \quad \eta_{slope,i} \sim LN(0,\omega_2^2).$$

The model was fitted in R using the nlme() function from the nlme library.

2. The Exacerbations Model

Data from two phase III trials were used to develop a generalized linear model (negative binomial model) to describe the number of exacerbations per patient per year.
The negative binomial distribution, especially in its alternative parameterization described above, can be used as an alternative to the Poisson distribution. It is especially useful for discrete data over an unbounded positive range whose sample variance exceeds the sample mean. In such cases, the observations are overdispersed with respect to a Poisson distribution, for which the mean is equal to the variance. Hence a Poisson distribution is not an appropriate model. Since the negative binomial distribution has in addition one more parameter than the Poisson, the second parameter can be used to adjust the variance independently of the mean.

Therefore, we assume that the number of exacerbations Y follow a negative binomial distribution, which can be expressed as

$$Y \sim \text{NegBin}(\theta, \lambda/(\lambda+\theta)).$$

Because of this parameterization, the expectation and variance of Y are given by

$$E(Y) = \lambda \quad \text{and} \quad Var(Y) = \lambda(1+\lambda/\theta).$$

Since we are mainly interested in the expected exacerbation rate, i.e. the number of exacerbations during the observation time, we model λ as a product of dot (days on treatment) and λ‘ (exacerbation rate). This can conveniently be done in R using the glm.nb() function from the MASS library. This function is based on glm() which fits generalized linear models but extends its functionality to use the NegBin family. The function call is

```
glm.nb( Y ~ offset(log(dot)) + dose + <covariates>,
        data=exa.data,
        link=log)
```

With this the exacerbation rate is modelled as

$$\exp(\lambda)/dot = \exp(\lambda_0 + \lambda_1 \times dose + \ldots)$$

3. Enhanced Exacerbations Model

The original exacerbation model did not fully meet our expectations. The exacerbation data contains comparatively little information (e.g. when compared to the FEV_1 data). Major reasons are (a) there is only one value per subject (total number of exacerbations during the treatment period) so no individual effect/change can be described and (b) the response variable is categorical. PK information was not available in these trials to develop a PK/PD model. Therefore it was planned to investigate potential correlations between the effect sizes on FEV_1 and exacerbations. In case there is a substantial correlation it was planned to test whether the predicted effect size (change from baseline) FEV_1 could be used as an additional source of information (covariate) to enhance the prediction of exacerbation rates.

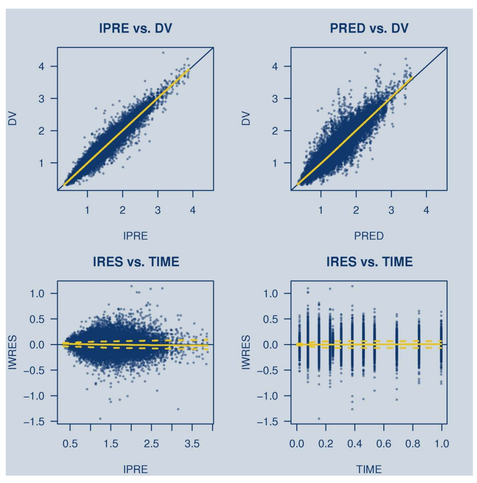
Results

1. The FEV1 Model

The FEV_1 model describes the data from all six trials very well. Significant covariates on the effect size Amp (besides dose) were FEV_1 percent predicted, reversibility, and the cough and sputum score. Estimates and standard errors of the fixed effects are listed in the table below.

Parameter	Value	Std. Error	RSE%
slope	0.000474	0.000082	17.30
log(k)	0.294326	0.064055	21.76
AMP intercept	0.055574	0.008983	16.16
dose on Amp	0.000102	0.000009	8.82
fev1p on Amp	-0.001730	0.000160	9.25
score on Amp	0.001038	0.000223	21.48
rev on Amp	0.000186	0.000016	8.60

fev1p = percent from predicted FEV1 (post), score = cough and sputum score, rev = reversibility



This model was used to simulate the effect size and power of two ongoing pivotal trials based on baseline characteristics only. The predicted effect size was 47.2 mL difference between placebo and treatment with a power of 97%.

#	Endpoint	Bronchitis	%FEV1<	Diff. Est.	2.50%	97.50%	Power
1	pre	0	50	-47.0	-72.4	-19.6	95.2%
2	pre	0	70	-43.5	-67.8	-18.2	96.0%
3	pre	1	50	-43.0	-70.6	-16.4	91.0%
4	pre	1	70	-46.1	-67.0	-21.3	97.0%
5	post	0	50	-44.2	-70.1	-20.0	95.8%
6	post	0	70	-45.8	-71.1	-23.7	98.0%
7	post	1	50	**-47.2**	-72.9	-20.6	97.0%
8	post	1	70	-45.8	-70.2	-19.3	95.8%

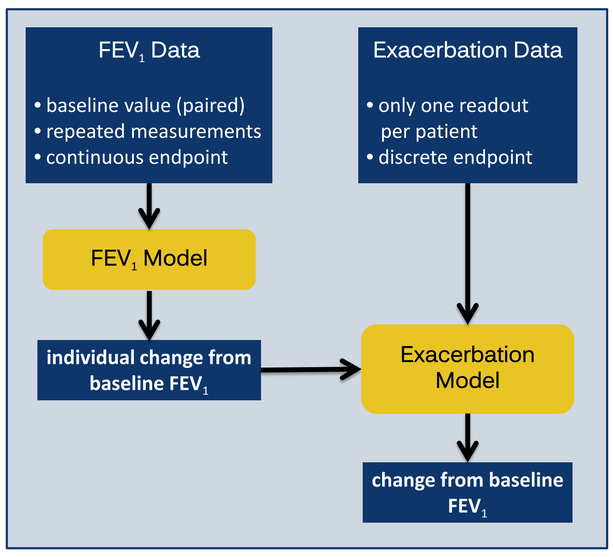
2. The Exacerbations Model

The basic exacerbation model did describe the data with relatively large variability. Covariates on the exacerbation rate λ were FEV_1 percent from predicted, sex, pre-treatment with ICS, and a complete dose×score interaction.

Parameter	Value	Std. Error	RSE%
Intercept	-1.65562	0.33327	20.13
log(dot)	-0.64177	0.04838	13.50
fev1p	-0.02653	0.00345	12.99
ICS pre-medication	0.33718	0.07198	21.35
sex (F=1, M=2)	-0.17816	0.07717	43.32
dose	0.00032	0.00026	80.26
score	0.01597	0.00478	29.91
score×dose	-0.00004	0.00001	33.53

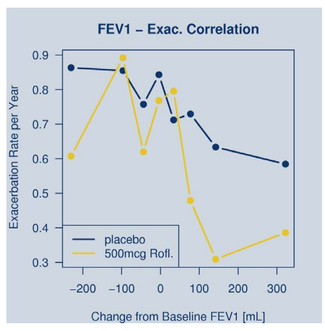
ICS = inhaled corticosteroid, dot = days on treatment

The dose-response relationship depends on scores; the effect size is higher for patients with higher cough and sputum scores.



3. Enhanced Exacerbations Model

A substantial correlation between the number of exacerbations and the predicted effect size (change from baseline) of FEV1 was found. This was used as an additional source of information (covariate on λ) to enhance the prediction of exacerbation rates. There was a substantial enhancement in model quality by including the predicted FEV1 change from baseline into the exacerbation model as an additional source of information.

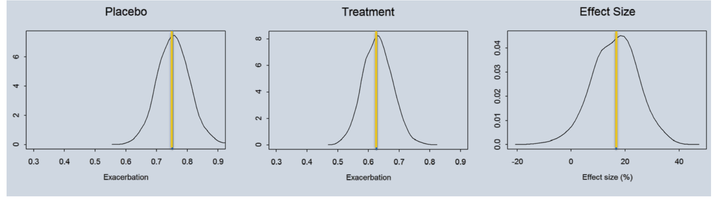


Parameter	Value	Std. Error	RSE%
Intercept	-1.362	0.3716	27%
log(dot)	-0.6428	0.05579	16%
fev1p	-0.03342	0.003665	11%
ICS pre-medication	0.31	0.07368	24%
sex (F=1, M=2)	-0.2034	0.0785	39%
dose	0.0004928	0.0002628	53%
score	0.01757	0.004813	27%
score×dose	-0.00004467	0.00001441	32%
cfbl.pred	-1.738	0.2699	16%

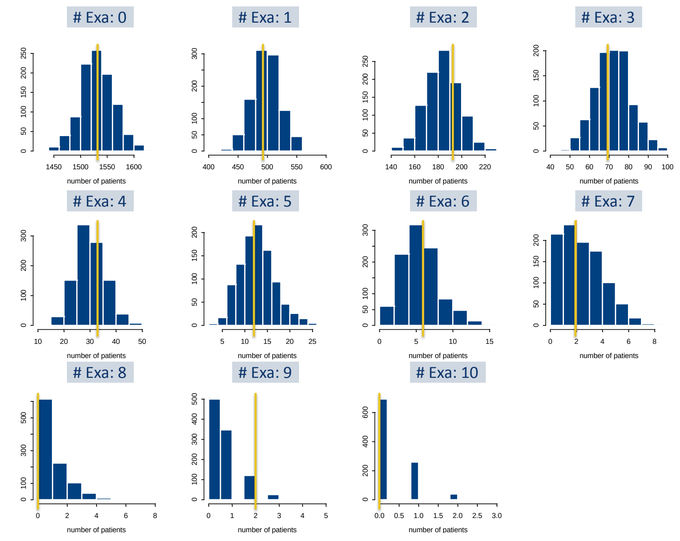
cfbl.pred = predicted change from baseline FEV_1

The model predictions changed from a predicted effect size of 25.8% to 16.7% using the enhanced exacerbation model.

	Pred.	2.50%	97.50%
R500	0.63	0.54	0.72
Placebo	0.75	0.65	0.86
Effect [%]	**16.71**	-1.27	32.24

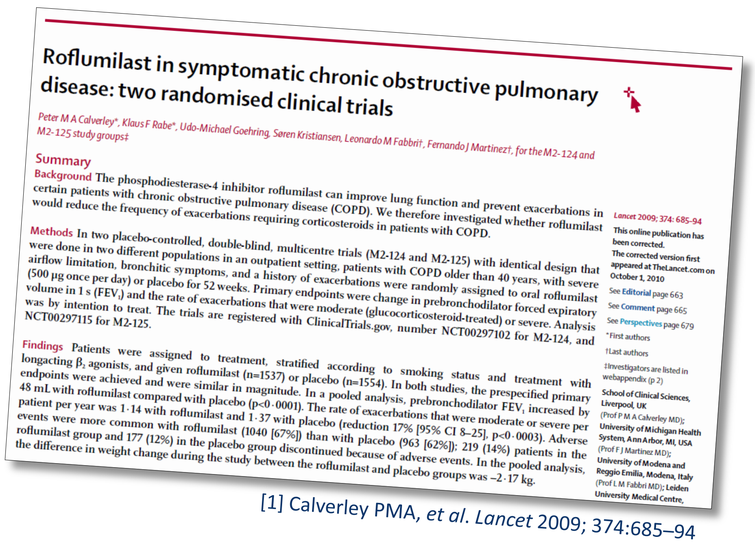


Posterior predictive checks were performed to illustrate the goodness of fit.



Conclusions

Correlated endpoints might substantially increase model quality and precision of predictions when used as additional sources of information about individual effect sizes.
The model predictions were very accurate. The actually observed effect sizes were **48 mL (predicted: 47.2 mL)** change from baseline in FEV_1 compared to placebo and a difference in the average number of exacerbations of **17% (predicted: 16.7%)** [1] between patients who were treated with Daxas and patients on placebo.



Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

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Summary

Background The phosphodiesterase-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with chronic obstructive pulmonary disease (COPD). We therefore investigated whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD.

Methods In two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design that were done in two different populations in an outpatient setting, patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to oral roflumilast (500 μg once per day) or placebo for 52 weeks. Primary endpoints were change in prebronchodilator forced expiratory volume in 1 s (FEV_1) and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Analysis was by intention to treat. The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Findings Patients were assigned to treatment, stratified according to smoking status and treatment with longacting β_2 agonists, and given roflumilast (n=1537) or placebo (n=1554). In both studies, the prespecified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, prebronchodilator FEV_1 increased by 48 mL with roflumilast compared with placebo (p<0·0001). The rate of exacerbations that were moderate or severe per patient per year was 1·14 with roflumilast and 1·37 with placebo (reduction 17% [95% CI 8–25], p<0·0003). Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was –2·17 kg.

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[1] Calverley PMA, *et al. Lancet* 2009; 374:685–94

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