Appendix 1

Data sources: covariate adjustments for LSM estimates

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Analysis models</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cross-over, 14-day</td>
<td>96</td>
<td>patient + treatment + period + period baseline + daytime + treatment × daytime, with patient included as random effect</td>
</tr>
<tr>
<td>2</td>
<td>Parallel-group, 52-week</td>
<td>1732</td>
<td>treatment + baseline + FEV₁ reversibility components + smoking status + country + center (country), with center (country) as a random effect</td>
</tr>
<tr>
<td>3</td>
<td>Parallel-group, 26-week</td>
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<td>treatment + baseline + FEV₁ reversibility components + smoking status + country + center (country), with center (country) as a random effect</td>
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<tr>
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<td>treatment + period + patient + period baseline with patient included as random effect</td>
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<tr>
<td>5</td>
<td>Parallel-group, 12-week</td>
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<td>treatment + baseline + FEV₁ reversibility components + smoking status + center, with center as a random effect</td>
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<tr>
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<td>treatment + baseline FEV₁ + FEV₁ reversibility components + smoking status + country + center (country), with center (country) as a random effect</td>
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<tr>
<td>7</td>
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</tr>
<tr>
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<td>treatment + baseline FEV₁ + FEV₁ reversibility components + smoking status + country + center (country), with center (country) as a random effect</td>
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<td>treatment + baseline FEV₁ + FEV₁ reversibility components + smoking status + ICS use + center, with center as a random effect</td>
</tr>
<tr>
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<td>treatment + baseline FEV₁ + FEV₁ reversibility components + smoking status + ICS use + center, with center as a random effect</td>
</tr>
<tr>
<td>11</td>
<td>Parallel-group, 2-week</td>
<td>552</td>
<td>treatment + baseline FEV₁ + FEV₁ reversibility components + ICS use + smoking history + center, with center as a random effect</td>
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</tbody>
</table>
Study-level analysis

We use an E_{max} model,

\[ E = \frac{E_{\text{max}} \times \text{dose}}{ED_{50} + \text{dose}}, \]

to characterize the dose-response relationship for indacaterol. The E_{max} parameter describes the maximum possible response, whereas ED_{50} characterizes drug potency and corresponds to the indacaterol dose producing 50% of the maximum effect. \( E \) is the effect (mean trough response in this case). Since the summary data used in the analysis are contrasts to placebo, the model is constrained to have a null response with placebo (dose=0).

To benchmark indacaterol to other compounds, summary information collected on three comparators (formoterol, salmeterol, tiotropium) was added to the analysis. The complete model equation is:

\[ y_{ijk} = \text{FOR}_{ij} \times \mu_F + \text{SAL}_{ij} \times (\mu_S + \gamma_{Sij}) + \text{TIO}_{ij} \times \mu_T + \text{IND}_{ij} \times \left( \frac{E_{\text{max}} + \delta_i + \gamma_{ij}}{ED_{50} + \text{dose}_{ij}} \right) + \varepsilon_{ijk}, \]

where:

- \( y_{ijk} \) is the trough FEV\(_1\) least-squares mean contrast to placebo at visit \( k \) for arm \( j \) within study \( i \).
- \( \text{FOR}, \text{SAL}, \text{TIO}, \text{IND} \) are indicators of whether a record is from formoterol, salmeterol, tiotropium or indacaterol respectively.
- \( \mu_F, \mu_S, \) and \( \mu_T \) represent the mean effects of formoterol, salmeterol and tiotropium respectively.
- \( \gamma_{Si} \) represents the (random) deviation of salmeterol results for study \( i \) to the mean effect (\( \mu_S \)). It is assumed to be randomly distributed with mean 0 and standard deviation \( \sigma_{S,A} \). There was only a single and couple of studies available for tiotropium and formoterol, respectively, and the between-arm component was not estimated for those treatments.
- \( \delta_i \) represents the (random) deviation for study \( i \), and \( \gamma_{ij} \) the (random) deviation for arm \( j \) within study \( i \), relative to the typical maximal effect (\( E_{\text{max}} \)) of indacaterol. Those are assumed to be normally distributed with mean 0 and standard deviation \( \sigma_{m,T} \) and \( \sigma_{m,A} \), respectively.
- The terms \( \varepsilon_{ijk} \) are assumed to be normally distributed with mean 0 and standard deviation \( \text{SE}_{ijk} \), with \( \text{SE}_{ijk} \) the estimated standard error originating from the statistical analysis that yielded \( y_{ijk} \). Note the SE_{ijk}’s are considered known (fixed) at this stage of the hierarchy.

To complete the model specification, prior distributions were specified for all model parameters:

- \( E_{\text{max}} \sim N(0, 100^2) \) i.e. normal distribution with mean 0 and standard deviation 100.
• $ED_{50} \sim \text{unif}(0, 600)$ i.e. a uniform distribution over the dose range 0 to 600 µg.
• $\sigma_{m,T}, \sigma_{m,A} \sim \text{unif}(0, 0.25)$
• $\sigma_{S,A} \sim \exp(45)$ i.e. exponential distributions with rate parameter equal to 45
• $\mu_F, \mu_S, \mu_T \sim \mathcal{N}(0, 100^2)$

The Bayesian analyses were implemented by using Markov chain Monte Carlo methods with the software WinBUGS v 1.4.3 called from R v 2.10.1, via the library R2WinBUGS tailored to run under the Novartis computing environment.

The iterative algorithm involved monitoring of three Markov chains starting from randomly generated initial values. Each chain was run for a total of 32000 iterations with a thinning rate of 10 and a burn-in of 2000 iterations. This effectively left $3 \times 3000 = 9000$ simulation draws for each parameter in the model. Convergence was assessed by means of the Gelman-Rubin (Rhat) statistic, i.e. the square root of the ratio of the between- to within-chain variances of simulation draws.

The posterior distributions of the structural model parameters were summarized by the mean, SD, and 2.5th, 50th (median), and 97.5th quantiles.

Posterior information was presented graphically with the least-squares summary data overlaid on a plot of the mean dose-response curve on which the 95% confidence and 95% prediction limits were superimposed. The prediction limits were derived by accounting for the between-study variability and uncertainty in least-squares estimates (the median SE value in the dataset being used for the latter).

**Patient-level analysis**

Efforts were made in the consideration of the base model to incorporate patient level characteristics (covariates) to account for some of the inter-patient differences in dose response. This process was guided by physiological principles such as:

- Baseline FEV1 is a surrogate measure of disease severity before treatment and is a known, important predictor. It might also be expected that a patient with greater forced expiratory lung volumes at baseline has the potential to show a greater bronchodilatory response when absolute changes in FEV1 are analysed. That is, baseline FEV1 should also be an important covariate on Emax.
- Likewise, reversibility of bronchial obstruction following inhalation of short acting beta2 agonists (SABA) should also be an important covariate affecting Emax rather E0, since reversibility is a measure of responsiveness to treatment with beta2 agonists.

The base model equation can be written as follows:

$$y_{ij} = \left[ \frac{E_0 + E_{ui} + \beta_i \times \text{base}_i}{[E_{\text{max}} \times (\text{base}_i / \text{mean}_{\text{FEV1}})^{\beta_2} \times \exp(E_{mi}) + \beta_3 \times (\text{revers}_i - \text{mean}_{\text{REY}})] \times \text{dose}_i} \right] \times e_{ij},$$

where:

- $y_{ij}$ represents trough FEV1 measured on patient $i$ at day $j$.  

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• $E_0$ is the intercept fixed effect, and the $E_{\text{max}}$ and $ED_{50}$ fixed effects are defined as in the Bayesian mixed-effects model for the meta-analysis.

• $base$ represents baseline FEV$_1$ taken as the average of four FEV$_1$ measurements available before treatment with indacaterol, that is, two measurements obtained prior to treatment in the reversibility testing sessions and two measurements taken pre-dose on Day 1. Baseline FEV$_1$ acts on $E_0$ (additive effect) and $E_{\text{max}}$ (multiplicative effect) in the base model.

• $mean_{FEV1}$ denotes the mean value of baseline FEV$_1$ over the dataset.

• $revers$ represents SABA reversibility, that is, the ratio of the difference between post and pre-test FEV$_1$ values to the pre-test value. SABA reversibility acts on $E_{\text{max}}$ (additive effect) in the base model.

• $mean_{REV}$ denotes the mean value of SABA reversibility over the dataset.

• $E_{0i}$ and $E_{mi}$ are random effects to account for inter-patient variation in response, assumed to be independently normally distributed with mean 0 and standard deviation $\sigma_0$ and $\sigma_m$, respectively. Inter-patient variability is additive on $E_0$ and multiplicative (through a log normal distribution) on $E_{\text{max}}$. Note that correlation between $E_{0i}$ and $E_{mi}$ could not be estimated.

• $\epsilon_{ij}$ denotes the within-patient multiplicative errors, assumed to be independently distributed as log-normal $(0, \sigma)$ variables.

A transform-both-sides approach was used to deal with the log-normal errors, with the logarithm transformation applied to both the response and the model. In addition to providing some improvement with respect to distributional assumptions of the model (especially in residuals), this has the immediate benefit of ensuring positive values for trough FEV$_1$, which would not be guaranteed otherwise.

Additional covariates considered in the analysis were: day (trough measurements at Day 14 were uncontrolled, i.e. dosing on the previous day did not take place at the clinic), study, COPD severity (moderate or lower versus severe or worse, based on the classification of severity of COPD defined in GOLD (2007)), use of inhaled corticosteroids, smoking status (ex versus current smoker), gender, age (< versus $\geq$ 65). Race was not considered as more than 88% of the patients were Caucasian in the dataset. A sigmoidal Emax shape was also tested in the model building step. This entails adding a further coefficient ($\gamma$) in the $E_{\text{max}}$ equation in order to make the model more flexible:

$$E_{\text{max}} \times \text{dose}^\gamma / (ED_{50}^\gamma + \text{dose}^\gamma).$$

Starting from the base model, the likelihood ratio test was used to guide model building, the addition of a single parameter being significant at the 5% level when the difference in objective function value (- 2 times log likelihood) between the restricted and full models is greater than 3.84.