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Correlations between FEV1 and Patient-Reported Outcomes: a Pooled Analysis of 23 Clinical Trials in Patients with Chronic Obstructive Pulmonary Disease

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Figures/Tables: 3 figures/2 tables; plus 2 supplementary figures/4 supplementary tables
ABSTRACT

BACKGROUND: In clinical trials of inhaled bronchodilators, chronic obstructive pulmonary disease (COPD) guidelines recommend that patient-reported outcomes (PROs) are assessed alongside lung function. How these endpoints are related is unclear.

METHODS: Pooled longitudinal data from 23 randomised controlled COPD studies were analyzed (N=23,213). Treatments included long-acting β₂ agonists, long-acting muscarinic antagonists (LABAs or LAMAs) and the LABA/LAMA combination QVA149. Outcome measures were Transition Dyspnoea Index (TDI) and St. George’s Respiratory Questionnaire (SGRQ) scores, COPD exacerbation frequency and rescue medication use. Relationships between changes in trough forced expiratory volume in one second (ΔFEV₁) and outcomes following treatment were assessed using correlations of data summaries and model-based analysis: generalized linear mixed-effect regression modeling to determine if ΔFEV₁ could predict patient outcomes with different treatments.

RESULTS: Mean age was 64 years, 73% were male, and most had moderate (45%) or severe (52%) disease. Statistically significant correlations were observed between ΔFEV₁ and each outcome measure (exacerbations Rs = 0.05; rescue medication, SGRQ, TDI, r = 0.11-0.16; all p < 0.001). Patients with greater improvements in trough FEV₁ had on average better SGRQ and TDI scores, fewer exacerbations, and used less rescue medication. For SGRQ and TDI scores, minimal clinically important differences were observed over the range of pooled ΔFEV₁ values. Model-based predictions confirmed the treatment effect was partly explained by changes in FEV₁ from baseline with improvements in PROs observed across all treatments when trough FEV₁ improved. Across all endpoints active treatments were better than placebo (p < 0.0001), and LABA/LAMA treatment resulted in numerically better treatment outcomes than either monocomponent.
CONCLUSIONS: These data suggest that FEV₁ improvements post-bronchodilation correlate with PRO improvements. Further improvements in patient outcomes may be expected by maximizing lung function improvements.

TRIAL REGISTRATION: Registration details for the 23 randomised controlled studies used in this pooled analysis are supplied in Additional File 4.

KEY WORDS: COPD; PROs; FEV₁; TDI; SGRQ; regression modelling.

1. INTRODUCTION
Inhaled long-acting bronchodilators are the mainstay in managing chronic obstructive pulmonary disease (COPD), improving lung function, health status, symptoms, and reducing exacerbations.[1, 2] For the majority of symptomatic COPD patients, dual bronchodilation using a long-acting β₂ agonist (LABA) combined with a long-acting muscarinic antagonist (LAMAs) is recommended.[3] Inhaled corticosteroids (ICS) are also commonly used in the management of symptomatic COPD patients.[2] However, the literature is evolving about the exact role of ICS in the treatment of COPD.[4, 5]

Measurement of lung function by spirometry, particularly the forced expiratory volume in one second (FEV₁), is routinely used as an indicator of efficacy in the evaluation of bronchodilators.[4] However, COPD is a complex disease with multiple symptoms, not all of which can be reflected by spirometry.[5] As such, the exclusive use of FEV₁ as the primary efficacy endpoint has increasingly become questioned, as it may underestimate the true clinical benefit of the intervention under test.[6, 7] To healthcare professionals, evaluation of patient-reported outcomes (PROs) is of more relevance than isolated lung function data, as these represent the impact of treatment from the patient’s perspective.[8] Indeed, the use of PROs such as health status measurement as co-primary endpoints in COPD trials is now recommended in COPD guidelines.[9] Such data are increasingly being requested by payers and other decision-makers to understand how changes in lung function relate to quality of
life, and how they might impact COPD-related healthcare resource use.[10] The Transition Dyspnoea Index (TDI) measures change in dyspnea from baseline. The St. George’s Respiratory Questionnaire (SGRQ), a measure of health-related quality of life, captures symptoms, impact on patient well-being, and activities of daily living. The minimal clinical important difference (MCID) for TDI is an improvement of >1 unit in the TDI total score and the MCID for SGRQ is a change of 4 units in the SGRQ total score. [11] PRO instruments, along with patient-recorded rescue medication use and COPD exacerbations are now regularly measured alongside functional measurements such as FEV₁ in clinical trials to provide an overall assessment of the effect of therapies on COPD patients.

Previous COPD studies have shown FEV₁ to be a predictor of future morbidity and mortality,[12] patient outcomes,[13-17] rescue medication use,[16, 17] and exacerbation frequency.[17] Most of these studies, however, have included data from patients treated with single-agent LABA or LAMA therapies rather than LABA/LAMA combinations. Furthermore, they were unable to detect whether a “plateau” or “ceiling” effect existed in the relationship between improvement in lung function and clinical endpoints that might occur with very large improvements.

The aim of this study was to characterise, in a large cohort of patients (N=23,213) from 23 clinical trials, the relationship between changes from baseline in trough FEV₁ (ΔFEV₁) and patient outcomes in COPD patients treated with LABAs, LAMAs and the dual LABA/LAMA bronchodilator QVA149.

2. METHODS

2.1. Study design and data selection
The investigation was a pooled analysis of data from patients enrolled in 23 randomised, parallel-group, placebo- or active-controlled studies in COPD patients (Table 1; Additional file 3: Tables S1 to S3). The studies were between 3 and 18 months’ duration and were
conducted by Novartis. Each study provided data on trough FEV$_1$ and patient outcomes, and included at least one intervention treatment arm. Interventions and doses used were the LABAs indacaterol (IND; 27.5 µg twice daily [b.i.d.] or 75/150/300 or 600 µg once daily [o.d.]), salmeterol (50 µg b.i.d.) and formoterol (12 µg b.i.d.); the LAMAs glycopyrronium (GLY; 12.5 µg b.i.d. [15.6 µg if glycopyrrolate, the bromide salt, was used] or 50 µg o.d.) and tiotropium (18 µg o.d.); and the IND/GLY combination QVA149 (27.5/12.5 µg b.i.d., 110/50 µg o.d. fixed doses or 150/50 µg o.d. co-administration). Full clinical trial reports were available for each of the studies, and in the majority of cases the methods and main findings have been reported elsewhere (Table 1). Our analysis focused on moderate and severe exacerbations (i.e., exacerbations that required additional medication or hospitalization). Symptomatic events that were not treated were classified as mild, and were excluded from the analysis.

Each study was conducted in accordance with ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with local regulations applied, and the Declaration of Helsinki.

2.2. Patients
Enrolled patients were male or female, aged ≥ 40 years, and were current or former smokers with a confirmed diagnosis of COPD. All patients with available trough FEV$_1$ measurements were included in the analysis.

2.3. Endpoints
The primary objective of the analysis was to define the relationship between ΔFEV$_1$ and the following patient outcomes: health status and dyspnea (as assessed by SGRQ and TDI), disease exacerbations, and rescue medication use (number of self-reported salbutamol puffs/day).

All trough FEV$_1$ measurements recorded during treatment were pooled into the data set. In general, trough FEV$_1$ at baseline was defined as the average of FEV$_1$ values recorded 50 and 15 minutes prior to the first dose of study drug; trough FEV$_1$ during treatment was recorded as the average of the 23 h 10 min and 23 h 45 min post-dose values. Spirometry
was conducted in each study in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) standards.[18]

Symptoms were recorded in electronic diaries: exacerbations of COPD were defined as the onset or worsening of more than one respiratory symptom for >3 consecutive days, or those that required intervention (e.g. systemic steroids, antibiotics, oxygen) and/or hospitalization or emergency room visits. Severe exacerbations were defined as those requiring hospitalization. In some studies, exacerbations were captured as safety endpoints (adverse events) and in others as efficacy endpoints.

Data for ΔFEV₁, ΔSGRQ, TDI and rescue medication use were pooled as longitudinal data, with each measurement associated to the time relative to treatment start at which the measurement was recorded. Minimal clinically important differences in SGRQ and TDI scores were described using thresholds of ≥4 units and ≥1 unit, respectively.[19, 20]

Exacerbations were pooled as the number of moderate or severe exacerbations per patient together with the total treatment duration of each patient.

2.4. Analysis Methods
Relationships between PROs and ΔFEV₁ were examined using data summarization and model-based analysis. Pooled data were summarised using descriptive statistics of correlations, and presented graphically. Correlation coefficients were computed between the summarised endpoints for each patient for ΔFEV₁ and outcomes; Spearman rank correlation coefficient was used for exacerbations and Pearson correlation coefficient for TDI, ΔSGRQ and rescue medication use.

Regression modelling was performed to determine if changes in trough FEV₁ could predict improvements in patient outcomes observed with different treatments. Linear and generalised linear mixed-effect models [21-23] were used to describe the different endpoints. For SGRQ and TDI, linear longitudinal models were used, describing baseline, treatment efficacy and drift, and including between-subject variability. For rescue medication use and
exacerbations, an overdispersed Poisson model was used with the overdispersion being expressed as between-subject variability. (An extended methodology section is provided in Additional File 1.)

2.5. Covariate modelling
Differences between studies, treatment classes and treatments were included in the initial base model as fixed effects. Predictors of treatment efficacy were systematically tested for inclusion, including interactions differentiating predictors by treatment class. Categorical predictors comprised any exacerbation in the previous 12 months; severity of disease (based on Global initiative for chronic Obstructive Lung Disease [GOLD] stages[2]); smoking history; inhaled corticosteroids (yes/no); and gender. Continuous predictors comprised age; weight; SGRQ score at baseline; FEV\textsubscript{1} at baseline; rescue medication use at baseline; baseline dyspnea index (BDI); predicted FEV\textsubscript{1}; FEV\textsubscript{1} baseline as percent of predicted FEV\textsubscript{1}; and reversibility with a short-acting β\textsubscript{2} agonist (%).

Change in trough FEV\textsubscript{1} from baseline was included as a predictor for SGRQ, TDI, rescue medication and exacerbations. As described by Jones et al.[17] the effect of positive and negative changes in trough FEV\textsubscript{1} on SGRQ was estimated as a linear relationship with a breakpoint at ΔFEV\textsubscript{1} equivalent to 0, using two separate regression coefficients.

2.6. Model analysis of simulated data assuming a high association between lung function, FEV1 and patient outcomes
Regression analysis when performed with an explanatory variable that is measured with error, such as ΔFEV\textsubscript{1}, is known to lead to a downward bias in the estimated effect of the explanatory variable on the response [24]. ΔFEV\textsubscript{1} is measured with large error of a magnitude similar to treatment effects and so its explanatory power of the response may appear to be less than it actually is. To explore this phenomenon, data were simulated assuming a high association between mean improvement of lung function (ΔFEV\textsubscript{1}) and patient outcomes. Two analyses were performed, in which the simulated ΔFEV\textsubscript{1} data was either the true ΔFEV\textsubscript{1} values, or in the second analysis ΔFEV\textsubscript{1} included measurement error.
Both sets of simulated data were analyzed using the same regression model as for the observed clinical data in order to assess the impact of ΔFEV1 measurement error on the estimated strength of association between ΔFEV1 and the response variable.

3. RESULTS

3.1 Patient characteristics
Data from 23,213 patients were included in the analyses. The mean age of the patients was 64 years, 73% were male and the majority had either moderate (45%) or severe (52%) disease (Table 2). Two studies included in the overall cohort comprised patients with more severe disease (>98% patients with prior exacerbation; mean FEV1 at baseline ~35% of predicted).

3.2 Data summaries and related inferences
The pooled trough FEV1 data shown in Figure S1 illustrates the degree of variability of the FEV1 within treatment groups; The 80 percentile of the placebo response extends beyond the median response of the active treatments. The 2nd and 3rd order polynomials showed a significant improvement of fit to the model above a linear regression, but since this was small (0.18% of variance at most; Additional File 2; Figure S2), linear regressions have been reported here. Correlation coefficients between trough FEV1 change from baseline and other endpoints were statistically significantly different from zero as follows: exacerbations Rs = -0.05; rescue medication, SGRQ, TDI, r = 0.11-0.16 (all p < 0.001) (Figure 1; Additional file 3: Table S4). The magnitude of the relationship between trough FEV1 change from baseline and other endpoints can be assessed from Figure 1, which shows mean values of the endpoints for patients grouped according to their response in FEV1 change from baseline. A clear relationship is seen, and the magnitude of the relationship is clinically non-negligible. Minimal clinically important differences in SGRQ and TDI scores were observed over the range of ΔFEV1 values observed in the pooled data; for example, for SGRQ the score between the decile of patients with the lowest and highest response in FEV1 differed by 7.1
(Figure 1). A sensitivity analysis that included only studies with 12-month duration or longer was performed and the results did not change the findings (data not shown).

There was no obvious evidence of a plateau effect: greater improvements in trough FEV\textsubscript{1} were associated with better SGRQ and TDI scores, less rescue medication and fewer exacerbations. Nevertheless, very few measurements were recorded at the extreme values of FEV\textsubscript{1} change so the existence of a plateau cannot be excluded.

Regression modelling was performed to determine if changes in FEV\textsubscript{1} predicted improvements in patient outcomes observed with different treatment options. Models were fitted using FEV\textsubscript{1} change from baseline as a predictor for changes in patient outcomes from baseline. Model-based predictions compared the efficacy observed in different patients receiving active treatment, and confirmed that part of the treatment effect can be explained by changes in FEV\textsubscript{1} from baseline (Figure 2). Improvements in PROs were observed across all treatment arms whenever an improvement in trough FEV\textsubscript{1} was observed. In general, treatments with higher improvements in trough FEV\textsubscript{1} resulted in larger improvements in patient outcomes; hence, LABA/LAMA treatment tended to be superior to either monotherapy, which each had roughly equivalent effects, and all treatments were superior to placebo. However, for TDI and rescue medication use, improvements in outcomes with LABA treatment were similar to those observed with LABA/LAMA treatment yet trough FEV\textsubscript{1} improvement was comparatively reduced. By calculating and comparing the efficacy of patients who exhibited no FEV\textsubscript{1} response with those exhibiting FEV\textsubscript{1} responses typical for the treatment class (Figure 2), it was estimated that between 5 and 35\% of the overall treatment effect could be explained by changes in FEV\textsubscript{1}, with SGRQ and TDI scores most associated, and rescue medication least associated. Thus, while the treatment effect can be partly explained by changes in FEV\textsubscript{1} from baseline, there remains a sizeable proportion of the benefit that is not predicted by FEV\textsubscript{1} changes.
All treatment options were better than placebo across all endpoints ($p < 0.0001$). LABA and LAMA treatments had comparable efficacy for the SGRQ endpoint, while for the other endpoints, differences between LAMA and LABA treatments were observed. LABA treatment provided greater reduction in rescue medication use than LAMA treatment ($p < 0.0001$), and a trend towards improvements in TDI scores ($p = 0.2$). Conversely, for exacerbation reduction, a greater effect with LAMA versus LABA treatments ($p = 0.6$) was detectable. Across all endpoints, the LABA/LAMA combination resulted in numerically better treatment outcomes than either LABA or LAMA monotherapies. At a $p$-value of 0.05, differences between LABA/LAMA combination and monotherapies were significant for SGRQ versus both LABA and LAMA, for TDI versus LAMA, for exacerbations versus LABA, and for rescue medication versus LAMA. This shows that the mechanisms of action of the LAMA and LABA drug classes complement each other.

In a sub-analysis of patients who completed 12 weeks of treatment, a substantial proportion of patients receiving LABA/LAMA treatment (56 patients; 23.7%) experienced large improvements in both lung function ($\Delta FEV_1 > 300$ ml) and quality of life ($\geq 5$ unit decrease in SGRQ). The equivalent data for patients in other treatment arms were GLY (36 patients; 15.3%); IND (26 patients; 11.2%); and placebo (3 patients; 1.4%).

The regression analysis results of data simulated using the assumption of a known strong association between endpoints were similar to the results obtained from the models of the clinical data: A sizeable proportion of the benefit was not predicted by changes in $FEV_1$ (Figure 3a). This compares to Figure 3b where the regression analysis was performed on simulated $\Delta FEV_1$ data that assumed in addition that there was no measurement error in $\Delta FEV_1$. This produced a model in which the efficacy in SGRQ scores can be attributed entirely to changes in $FEV_1$ (Figure 3b). This is seen as the change in SGRQ is described by changes in $\Delta FEV_1$ only and not by differences between treatments.
4 DISCUSSION

Our data suggest that, at a population level, improvements in FEV$_1$ post-bronchodilation correlate with improvements in SGRQ, TDI and exacerbation rate endpoints, which are each of relevance to patients, physicians and payers. FEV$_1$ as an endpoint is also a regulatory requirement in the approval of bronchodilators, and an integral part of major treatment guidelines.

In the current analysis, pooled FEV$_1$ and patient outcome data from 23,213 patients in 23 studies confirmed that, at least at a population level, statistically significant and clinically important relationships exist between improvements in trough FEV$_1$ and COPD outcomes over 12 to 78 weeks of treatment.

Our results are consistent with earlier correlative analyses of changes in FEV$_1$ with changes in outcomes in patients with COPD.[17, 25] A systematic review of 22 COPD studies also recently confirmed that FEV$_1$ increases were associated with statistically significant reductions in SGRQ.[13]

In our analysis, correlations were established using a variety of methodologies. Graphical representation of raw data was used to illustrate correlations between endpoints. Here, improvement of FEV$_1$ upon treatment with bronchodilators correlated with improvements in SGRQ and TDI as well as exacerbation rate and rescue medication use. We also modelled treatment efficacy as a function of treatment and observed improvements in FEV$_1$. Using this approach, the average change in FEV$_1$ from baseline was predictive for efficacy of other endpoints, with part of the treatment efficacy explained by improvements in FEV$_1$.

Treatments inducing greater improvements in FEV$_1$ also tended to be associated with better responses in patient outcomes, and similarly, patients with greater FEV$_1$ response also tended to have better patient outcomes. In addition to the aggregate response of the population, which is quite robust, it was intriguing to note that a substantial number of individual patients (particularly those treated with the combination LAMA/LABA treatment regimen) experienced large improvements in both lung function and outcomes.
In the regression models, a sizeable proportion of the benefit occurred without a change in FEV$_1$, in particular for rescue medication use and exacerbations. Different factors could contribute to the observed benefits that are not predicted by changes in FEV$_1$, potentially including aspects of treatment unrelated to bronchodilation, differences in placebo responses, and limitations of the regression models. Limitations of the correlation analysis include the large residual variability in the chosen endpoints and confounding of different effects (e.g., patient outcomes are dependent on treatment, disease severity, baseline values, study, FEV$_1$ change, etc). The implication of these limitations is that correlations may be underestimated making it difficult to assess whether aspects of treatment unrelated to bronchodilation are important for patient outcomes. To quantify possible contributions, SGRQ and FEV$_1$ data were simulated assuming a strong association between the two endpoints. The generated data were analyzed and found to be similar to the analysis results of the observed data in that a significant intercept shift was present, ie, an improvement without change in FEV$_1$.

With regard to COPD exacerbation rate, our data show that part of the efficacy on exacerbation reduction was due to bronchodilation following treatment. Nevertheless, ΔFEV$_1$ predicted a smaller fraction (approximately one-third) of the efficacy for exacerbations than for SGRQ and TDI suggesting that aspects of the treatment other than lung function improvement could be important in reducing exacerbations.

The differential efficacy we observed with LABAs and LAMAs is comparable to data reported previously, which suggest that LABAs tend to be better than LAMAs at improving symptoms (thus reducing rescue medication use) while LAMAs are better than LABAs at controlling exacerbations.[26-32] Combining both drug classes may be expected to maximise overall benefits, with perhaps synergistic rather than additive effects under certain conditions.[33]

One limitation of our analyses is that we are unable to examine whether FEV$_1$ is the strongest lung function predictor of improvement in patient reported outcomes. It is certainly
plausible that measures more highly correlated with dynamic hyperinflation such as inspiratory capacity might be even better predictors of bronchodilator effects on these outcomes.

5 CONCLUSIONS
In summary, a limitation of spirometry (specifically FEV$_1$ measurement) as a clinical endpoint is that it insufficienlty captures the impact of COPD on a patient’s health.[2] This reiterates the position of the ATS/ERS Task Force, which stresses the need to measure each variable separately in clinical trials. Our database of over 23,000 patients provided us with a means to examine the interplay of these variables, and demonstrated that statistically significant and clinically important relationships exist at a population level between improvements in trough FEV$_1$ and COPD PROs. Therapies that significantly increase FEV$_1$ improve clinical and patient-reported outcomes. These beneficial relationships can be further enhanced when bronchodilators from different pharmacological classes are combined.

LIST OF ABBREVIATIONS
ATS/ERS: American Thoracic Society/European Respiratory Society; BDI: baseline dyspnea index; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV$_1$: forced expiratory volume in one second; GLY: glycopyrronium; GOLD: Global initiative for chronic Obstructive Lung Disease; HR: hazard ratio; IND: indacaterol; LABA: long-acting $\beta_2$ agonists; LAMA: long-acting muscarinic antagonist; PRO: patient-reported outcome; SABA: Short-Acting $\beta_2$ Agonist; SD: standard deviation; SGRQ: St. George’s Respiratory Questionnaire; TDI: Transition Dyspnoea Index; TIO: tiotropium.

Supplementary material (Additional Files)

Additional File 1 is a supplementary figure (Figure S1: Improvements in trough FEV$_1$ upon treatment: pooled data from 23 studies, by treatment group). Additional File 2 is a supplementary figure (Figure S2: Change in SGRQ, TDI, rescue medication use, and...
exacerbation rate following treatment and observed change of trough FEV1 from baseline: linear and polynomial relationships). Additional File 3 contains four supplementary tables, which detail demographic and baseline characteristics by treatment and dose for all LABA-treated patients (Table S1), LAMA-treated patients (Table S2), all LABA/LAMA- and placebo-treated patients (Table S3), and correlation coefficients between trough FEV1 change from baseline and other endpoints (Table S4). Additional File 4 lists IRB approvals and registration details for each of the 23 studies. Additional File 5 contains an extended methodology section.

DECLARATIONS

Ethics approval and consent to participate

Supplied as Additional file 4.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors have reported the following conflicts of interest: JFD has been a consultant to AstraZeneca, GlaxoSmithKlein, Novartis, Mylan and Boehringer-Ingelheim. He has received research grants and has served on DSMBs for Novartis and AstraZeneca. PWJ is currently employed by GlaxoSmithKlein plc as a Global Medical Expert and in the past has received consulting/speakers fees from Almirall/AstraZeneca and Novartis. CB, DGM and FP are employees of Novartis Pharma AG, Switzerland and own stock/shares. JM, PD’A, DB, and RF are employees of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA and own stock/shares.
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**Author contributions**

JFD takes final responsibility for the content of this manuscript, including the data and analysis. JFD, PWJ, PD’A, DB, DGM, FP and RF, contributed to the conception/design of the study, the data analysis and interpretation, and the writing, critical review and revision of the manuscript; JM contributed to the strategic direction and writing of the manuscript; and CB contributed to the data analysis and interpretation, writing and revision of the manuscript. JFD, PWJ, CB, JM, PD’A, DB, DGM, FP and RF approved the final version of the manuscript. The sponsor, Novartis Pharma AG (Basel, Switzerland), was involved in the study design, the collection, analysis and interpretation of data, writing of the study report, and the decision to submit the manuscript for publication.

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**REFERENCES**


**FIGURE LEGENDS**

**Figure 1:** Change in SGRQ, TDI, rescue medication use, and exacerbation rate following treatment and observed change of trough FEV1 from baseline. Blue line with band, loess regression line; points with vertical line: mean with 95% CI of second endpoint for patients grouped into deciles of FEV1 response.
Figure 2: Model-based analysis by treatment

Thin lines: model predictions; thick lines and point: representative patient population for given treatment (median and 50% PI of FEV$_1$ change for treatment class). Improvements in FEV$_1$ explain part of the efficacy of bronchodilator treatment on PROs.

Figure 3: Expected change in SGRQ following treatment and observed change in FEV$_1$ from baseline: (a) data simulated assuming residual error of FEV$_1$ measurements 0.15 L and (b) data simulated assuming no error in FEV$_1$ measurement

Simulation details: Treatments (Placebo, Trt A, Trt B and Trt C) give a mean improvement of lung function ($\Delta$FEV$_1$), $\mu_{trt}$, of 0, 0.05, 0.1 and 0.15 L, respectively. Efficacy differs between patients, $i$, with standard deviation of 0.1L, $\mu_{i}\sim\text{Norm}(\mu_{trt},0.1)$. $\Delta$FEV$_1$ has measurement error of 0.15 L, $\Delta$FEVi~$\text{Norm}(\mu_{i},0.15)$. $\Delta$SGRQ is equal to -40 times lung function, and has a measurement error of 6, $\Delta$SGRQi~$\text{Norm}(-40\times\mu_{i},6)$. Alternative (b) assumes that $\Delta$FEV$_1$ measures lung function without measurement error, $\Delta$FEVi~$\text{Norm}(\mu_{i},0.0)$.

Figure S1 (additional file 1): Improvements in trough FEV$_1$ upon treatment: pooled data from 23 studies, by treatment group. Point, thick line and thin lines depict the median and the 50 and 80 percentiles, respectively.

Figure S2 (Additional file 2): Change in SGRQ, TDI, rescue medication use, and exacerbation rate following treatment and observed change of trough FEV$_1$ from baseline.

In addition to the loess regression line and mean values by decile shown in Figure 2 of the main text, linear and polynomial relationships were fitted through the data.
The resulting fits are shown and illustrate the similarity of the fitted linear and polynomial relationships.

Blue line with band, loess regression line; points with vertical line: mean with 95% CI of second endpoint for patients grouped into deciles of FEV₁ response; red, linear fit; green, yellow and orange fits of polynomials of degree 2 to 4. Fits were directly applied to the data except for exacerbation rates for which fits were applied to the mean of the rates (dots).
Table 2: Demographic and baseline characteristics: all patients and by drug class

<table>
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<th>Characteristic</th>
<th>ALL patients (N=23213)</th>
<th>LABA/LAMA (N=1944)</th>
<th>LABA (N=8852)</th>
<th>LAMA (N=8590)</th>
<th>Placebo (N=3287)</th>
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<tr>
<td>Mean (SD) age, yrs</td>
<td>63.70 (8.61)</td>
<td>63.48 (8.47)</td>
<td>63.78 (8.75)</td>
<td>63.66 (8.44)</td>
<td>63.72 (8.73)</td>
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<td>Sex (Male), n (%)</td>
<td>16843 (72.6)</td>
<td>1425 (73.3)</td>
<td>6530 (73.8)</td>
<td>6234 (72.6)</td>
<td>2654 (69.3)</td>
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<td>Mean BMI (SD), kg/m²</td>
<td>26.17 (5.46)</td>
<td>26.09 (5.21)</td>
<td>26.13 (5.32)</td>
<td>26.18 (5.62)</td>
<td>26.28 (5.54)</td>
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<td>Severity of disease</td>
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<td>Mild, n (%)</td>
<td>169 (0.7)</td>
<td>0</td>
<td>100 (1.1)</td>
<td>24 (0.3)</td>
<td>45 (1.2)</td>
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<td>Moderate, n (%)</td>
<td>10325 (44.5)</td>
<td>766 (39.4)</td>
<td>4086 (46.2)</td>
<td>3271 (38.1)</td>
<td>2202 (57.5)</td>
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<td>Severe, n (%)</td>
<td>12044 (51.9)</td>
<td>1024 (52.7)</td>
<td>4564 (51.6)</td>
<td>4922 (57.3)</td>
<td>1534 (40.1)</td>
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<td>Very severe, n (%)</td>
<td>582 (2.5)</td>
<td>151 (7.8)</td>
<td>62 (0.7)</td>
<td>352 (4.1)</td>
<td>17 (0.4)</td>
</tr>
<tr>
<td>Undefined, n (%)</td>
<td>93 (0.4)</td>
<td>3 (0.2)</td>
<td>40 (0.5)</td>
<td>21 (0.2)</td>
<td>29 (0.8)</td>
</tr>
<tr>
<td>Using inhaled corticosteroids, n (%)</td>
<td>12441 (53.6)</td>
<td>1192 (61.3)</td>
<td>4514 (51.0)</td>
<td>5077 (59.1)</td>
<td>1658 (43.3)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>9633 (41.5)</td>
<td>821 (42.2)</td>
<td>3649 (41.2)</td>
<td>3471 (40.4)</td>
<td>1692 (44.2)</td>
</tr>
<tr>
<td>Mean (SD) FEV₁ at baseline (% of predicted)</td>
<td>43.68 (13.77)</td>
<td>40.96 (13.81)</td>
<td>44.40 (13.50)</td>
<td>42.24 (13.59)</td>
<td>46.62 (14.13)</td>
</tr>
<tr>
<td>Mean (SD) Trough FEV₁, at baseline, L</td>
<td>1.21 (0.46)</td>
<td>1.14 (0.45)</td>
<td>1.23 (0.45)</td>
<td>1.17 (0.45)</td>
<td>1.27 (0.48)</td>
</tr>
<tr>
<td>Percent reversibility SABA (SD)</td>
<td>16.16 (15.87)</td>
<td>19.66 (17.91)</td>
<td>14.60 (14.63)</td>
<td>16.62 (16.26)</td>
<td>16.99 (16.26)</td>
</tr>
<tr>
<td>Mean rescue medication, puffs per day (SD)</td>
<td>3.94 (3.93)</td>
<td>4.82 (4.26)</td>
<td>3.43 (3.56)</td>
<td>4.32 (4.16)</td>
<td>3.81 (3.86)</td>
</tr>
<tr>
<td>Exacerbation in previous 12 months, n (%)</td>
<td>8204 (35.3)</td>
<td>1010 (52.0)</td>
<td>2360 (26.7)</td>
<td>4242 (49.4)</td>
<td>592 (15.5)</td>
</tr>
</tbody>
</table>

GOLD 2005

LABA, long acting β₂ agonist; LAMA, long acting muscarinic antagonist; SD, standard deviation; BMI, body mass index; FEV₁, forced expiratory volume in one second; SABA, Short-Acting β₂ Agonist.
Table 1  Phase III/IV trials providing data on FEV$_1$, TDI, SGRQ, rescue medication use and COPD exacerbations in relation to bronchodilator use

<table>
<thead>
<tr>
<th>Study (Trial name)</th>
<th>Treatments(µg)</th>
<th>Total pts (planned)</th>
<th>Duration</th>
<th>Patient population</th>
<th>Trough FEV$_1$ times</th>
<th>TDI times</th>
<th>SGRQ times</th>
</tr>
</thead>
<tbody>
<tr>
<td>QAB149 B2334[34]</td>
<td>IND(300, 600) Formoterol(12) Placebo</td>
<td>1716</td>
<td>52 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12, 16, 20, 24, 28, 36, 44, 52</td>
<td>Wks 4, 8, 12, 2, 24, 44, 52</td>
<td>Wks 4, 8, 12, 24, 44, 52</td>
</tr>
<tr>
<td>QAB149 B2346[35]</td>
<td>IND(150)</td>
<td>290</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12</td>
<td>Wks 1, 2, 4, 8, 12, 16, 20, 26</td>
<td>Wks 12, 26</td>
</tr>
<tr>
<td>D’Urzo et al 2010</td>
<td>GLY(50) Placebo</td>
<td>680</td>
<td>26 wks</td>
<td>mod-sev COPD</td>
<td>Wks 4, 8, 12</td>
<td>NA</td>
<td>Wks 4, 8, 12</td>
</tr>
<tr>
<td>GLOW 1[36]</td>
<td>IND(75, 150, 300, 600) Formoterol(12) TIO(18) Placebo</td>
<td>1945</td>
<td>26 wks extension mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12, 16, 21, 26, 36, 44, 52</td>
<td>Wks 4, 8, 12, 26</td>
<td>Wks 4, 8, 12, 26, 36, 44, 52</td>
<td></td>
</tr>
<tr>
<td>INSIST[39]</td>
<td>IND(150) Salmeterol(50bid) Placebo</td>
<td>1084</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 12</td>
<td>Wk 12</td>
<td>NA</td>
</tr>
<tr>
<td>Korn et al 2011</td>
<td>IND(150) Placebo</td>
<td>1568</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 12</td>
<td>Wk 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>INTENSITY[40]</td>
<td>IND(75) Placebo</td>
<td>326</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 8, 12</td>
<td>Wks 4, 12</td>
<td>Wks 4, 12</td>
</tr>
<tr>
<td>Kerwin et al 2011</td>
<td>IND(75) Placebo</td>
<td>326</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 8, 12</td>
<td>Wks 4, 12</td>
<td>Wks 4, 12</td>
</tr>
<tr>
<td>Kerwin et al 2011</td>
<td>IND(150) Salmeterol(50bid) Placebo</td>
<td>972</td>
<td>26 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 8, 12, 16, 21, 26</td>
<td>Wks 4, 8, 12, 26</td>
<td>Wks 4, 8, 12, 26</td>
</tr>
<tr>
<td>Korno et al 2011</td>
<td>IND(150) Placebo</td>
<td>336</td>
<td>12 wks</td>
<td>mod-sev COPD (Japanese)</td>
<td>Wks 2, 4, 8, 12</td>
<td>Wks 4, 8, 12</td>
<td>Wks 4, 8, 12</td>
</tr>
<tr>
<td>Kerwin et al 2012</td>
<td>IND/GLY(110/50) Placebo</td>
<td>745</td>
<td>52 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12, 16, 20, 26, 34, 42, 50, 52</td>
<td>Wks 12, 26, 52</td>
<td>Wks 12, 26, 52</td>
</tr>
<tr>
<td>Bateman et al. 2012</td>
<td>IND/GLY(110/50) Placebo</td>
<td>2138</td>
<td>26 wks</td>
<td>mod-sev COPD</td>
<td>Wks</td>
<td>Wks</td>
<td>Wks</td>
</tr>
<tr>
<td>Study (Trial name)</td>
<td>Treatments(µg)</td>
<td>Total pts (planned)</td>
<td>Duration</td>
<td>Patient population</td>
<td>Trough FEV(_1) times</td>
<td>TDI times</td>
<td>SGRQ times</td>
</tr>
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<td>-------------------</td>
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</tr>
<tr>
<td>2013</td>
<td>IND(150) GLY(50) TIO(18) Placebo</td>
<td>2200</td>
<td>64 wks</td>
<td>sev-very sev COPD</td>
<td>Wks 4, 12, 26, 38, 52, 64</td>
<td>NA</td>
<td>Wks 12, 26, 38, 52</td>
</tr>
<tr>
<td>SPARK[46] Wedzicha et al. 2013</td>
<td>IND/GLY(110/50) TIO(18)</td>
<td>3500</td>
<td>52 wks</td>
<td>sev COPD</td>
<td>Wks 1, 2, 12, 26, 38, 52</td>
<td>Wks 12, 26, 38, 52</td>
<td></td>
</tr>
<tr>
<td>INVIGORATE[31] Decramer et al. 2013</td>
<td>IND(150) TIO(18) GLY(50)</td>
<td>660</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 12</td>
<td>Wks 4, 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>GLOW 5[47] Chapman et al. 2014</td>
<td>IND(150)+NVA(50) IND(150) GLY(50) TIO(18)</td>
<td>450</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 8, 12</td>
<td>Wk 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>GLOW 6[48] Vincken et al. 2014</td>
<td>IND(150) GLY(50) TIO(18)</td>
<td>450</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 4, 12</td>
<td>Wks 4, 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>QAB149 B2333[49] Yao et al. 2014</td>
<td>IND(150, 300) Placebo GLY(50) TIO(18)</td>
<td>444</td>
<td>26 wks</td>
<td>mod-sev COPD (Chinese)</td>
<td>Wks 1, 2, 4, 8, 12, 16, 21, 26</td>
<td>Wks 8, 12, 26</td>
<td>Wks 8, 12, 26</td>
</tr>
<tr>
<td>GLOW 7[50] Wang et al. 2015</td>
<td>Placebo IND/GLY(27.5/15.6bid) IND(27.5bid) GLY(15.6bid)</td>
<td>450</td>
<td>26 wks</td>
<td>mod-sev COPD (Chinese)</td>
<td>Wks 1, 4, 12, 26</td>
<td>Wks 12, 26</td>
<td>Wks 12, 26</td>
</tr>
<tr>
<td>FLIGHT 1[51] Mahler et al. 2015</td>
<td>Placebo IND/GLY(27.5/15.6bid) IND(27.5bid) GLY(15.6bid)</td>
<td>1000</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12</td>
<td>Wk 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>FLIGHT 2[51] Mahler et al. 2015</td>
<td>Placebo GLY(12.5bid)</td>
<td>1000</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12</td>
<td>Wk 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>NVA237 A2317 NCT01709864</td>
<td>Placebo GLY(12.5bid)</td>
<td>426</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12</td>
<td>Wk 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>NVA A2318 NCT01715298</td>
<td>Placebo</td>
<td>426</td>
<td>12 wks</td>
<td>mod-sev COPD</td>
<td>Wks 1, 2, 4, 8, 12</td>
<td>Wk 12</td>
<td>Wk 12</td>
</tr>
<tr>
<td>QAB149 B1303 NCT00876694</td>
<td>IND(300) Salmeterol(50bid)</td>
<td>180</td>
<td>52 wks</td>
<td>mod-sev COPD (Japanese)</td>
<td>Wks 4, 8, 12, 24, 36, 44, 52</td>
<td>Wks 4, 8, 12, 24, 36, 44, 52</td>
<td>Wks 4, 8, 12, 24, 36, 44, 52</td>
</tr>
<tr>
<td>Study (Trial name)</td>
<td>Treatments(µg)</td>
<td>Total pts (planned)</td>
<td>Duration</td>
<td>Patient population</td>
<td>Trough FEV₁ times</td>
<td>TDI times</td>
<td>SGRQ times</td>
</tr>
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</tr>
</tbody>
</table>

*TDI was not assessed in this study; *Glycopyrrolate 15.8µg (equivalent to 12.5µg glycopyrronium); *SGRQ was not assessed in this study

IND, indacaterol; GLY, glycopyrronium; TIO, tiotropium; b.i.d., twice daily; pts, patients; mod-sev, moderate-to-severe; sev-very severe, severe-to-very severe; Wks, weeks; FEV₁, forced expiratory volume in one second; TDI, Transition Dyspnoea index; SGRQ, St Georges Respiratory Questionnaire.