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Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design

Peter J. Barnes [a,*], Stuart J. Pocock [b], Helgo Magnussen [c], Amir Iqbal [e], Benjamin Kramer [d], Mark Higgins [e], David Lawrence [e,1]

[a] Imperial College, London, UK
[b] London School of Hygiene and Tropical Medicine, London, UK
[c] Pulmonary Research Institute at Hospital Grosshansdorf, Germany
[d] Novartis Pharmaceuticals, East Hanover, NJ, USA
[e] Novartis Horsham Research Centre, West Sussex, UK

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ABSTRACT

Background: The drug development process can be streamlined by combining the traditionally separate stages of dose-finding (Phase IIb) and confirmation of efficacy and safety (Phase III) using an adaptive seamless design. This approach was used in a clinical study of indacaterol, a novel once-daily (od) inhaled long-acting β_2-adrenoreceptor agonist bronchodilator for the treatment of COPD (chronic obstructive pulmonary disease).

Methods: The study comprised a dose-finding stage with dose selection after 14 days of treatment, and a second stage evaluating efficacy and safety during 26 weeks of treatment. The dose-finding stage included seven randomized treatment arms: double-blind indacaterol 75 μg, 150 μg, 300 μg or 600 μg od, the β_2-adrenoceptor agonist formoterol 12 μg twice-daily or placebo, or the anticholinergic tiotropium 18 μg od open-label. An independent data monitoring committee selected two indacaterol doses based on unblinded results of an interim analysis performed by an independent statistician. The sponsor, investigators and patients remained blinded to the results. The indacaterol doses were selected using pre-set efficacy criteria for trough (24-h post-dose) and early (1–4 h post-dose) bronchodilator effect after 14 days, and all safety data. To qualify for selection, the doses had to exceed a threshold for clinical relevance or be superior to either tiotropium or formoterol, whichever was the highest value. Selected doses were continued into the second, 26-week stage. The two other indacaterol doses not selected, and formoterol, were discontinued following dose selection.

Results: 801 patients with moderate-to-severe COPD were evaluated. Indacaterol 150 μg was the lowest effective dose, exceeding criteria for trough FEV_1 (reference value 140 mL vs placebo) and FEV_1 AUC_{1-4h} (reference value 220 mL vs placebo). No safety signal was observed with any dose of indacaterol. Thus, indacaterol 150 and 300 μg were selected to continue into the second, 26-week stage.

Conclusion: The adaptive seamless design is a novel and efficient way to combine dose selection with efficacy evaluation and safety confirmation in a single trial.

1. Introduction

Dose-finding (phase IIb) studies are an essential step in the traditional drug development process and are usually completed before longer-term, large-scale phase III studies that are designed to confirm safety and efficacy. The adaptive seamless design is a novel approach to drug development that combines phases II and III in a single, two-stage study. The design is adaptive in that the wider choice of doses included in stage 1 is narrowed down to the dose(s) of interest to be evaluated in stage 2. The trial is a seamless experience for both investigators and patients in that there is no interruption of ongoing study treatment between the two phases. Combining the dose-finding and confirmatory phases of development into a single, uninterrupted study has the advantages of speed, efficiency and flexibility [1,2].

* Corresponding author. Airway Disease Section, National Heart & Lung Institute, Dovehouse St, London SW3 6LY, UK. Tel.: +44 (0)207 351 8174; fax: +44 (0)207 351 5675.
E-mail address: p.j.barnes@imperial.ac.uk (P.J. Barnes).
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Indacaterol is a novel inhaled long-acting β_2-adrenoceptor agonist providing 24-h bronchodilation on once-daily (od) dosing. Short-term, phase II studies demonstrating the efficacy, safety and tolerability of indacaterol monotherapy in patients with COPD [3–5] were conducted using various inhaler devices. The present report aims to show how the adaptive seamless design can be applied to respiratory clinical development, using as an example a two-stage, phase II/III study employing an adaptive seamless design. Stage 1 of this study, described here, evaluated the efficacy and safety of four indacaterol doses against placebo and active comparators (tiotropium and formoterol) using pre-set criteria, in order to identify two doses of indacaterol for further assessment of efficacy and safety in stage 2.

2. Methods

2.1. Patients

The study enrolled male and female patients aged 40 years or above, with a smoking history of at least 20 pack-years and a diagnosis of moderate-to-severe COPD (as classified by 2005 GOLD guidelines: forced expiratory volume in 1 second [FEV_1] $<80\%$ and $\geq 30\%$ predicted, and FEV_1/forced vital capacity [FVC] <0.7 [FEV_1 and FVC measured within 30 min of inhaling salbutamol 400 μg]). Patients were not enrolled if they had been hospitalised for a COPD exacerbation within 6 weeks prior to screening, had received oral corticosteroids in the month prior to screening, or had a history of asthma. Patients with co-morbid conditions could be included, but not if that condition might compromise patient safety, interfere with evaluation or preclude completion of the study.

2.2. Study objective

The primary aim of stage 1 of the study was to determine the risk-benefit of four doses of indacaterol (based on efficacy and safety results in a pre-planned interim analysis) in order to select two doses to carry forward into the second stage of the study.

2.3. Data monitoring committee (DMC)

The DMC was an autonomous group of recognized experts in the respiratory and statistical fields (PJB, HM, SP). The DMC was appointed by the study sponsor but functioned independently of all other persons involved with the study. The responsibilities of the DMC were pre-defined as follows. (1) To review and approve the DMC charter, which set out responsibilities, functions, rules of conduct and the basis for evaluating the interim analysis results; (2) to review the results of the interim analysis; (3) to recommend two indacaterol doses to be evaluated in the second stage, and (4) to make recommendations on safety if warranted by the safety results.

2.4. Study design

This was a double-blind, double-dummy, randomized, placebo and active controlled, adaptive and seamless, parallel-group study in two stages: a dose-selection stage (reported here), and a 26-week confirmatory stage evaluating efficacy, safety and tolerability (reported separately elsewhere [6]).

Patients first attended a screening visit and gave their informed consent. Their current COPD medications were reviewed and adjusted if necessary. Any previous fixed-dose combination treatment with inhaled corticosteroid (ICS) and long-acting β_2-adrenoceptor agonist was replaced with the equivalent monotherapy ICS, plus salbutamol as needed. Patients on ICS monotherapy continued with the ICS unchanged. All patients were given salbutamol as rescue medication, and other bronchodilators were not allowed.

Following confirmation of eligibility during a 14-day run-in, patients were randomized to receive one of six double-blind, double-dummy treatments (indacaterol 75 μg, 150 μg, 300 μg or 600 μg od, placebo, formoterol 12 μg twice daily [bid]) or open-label treatment with tiotropium 18 μg od using an equal allocation ratio with stratification for smoking status. The tiotropium arm was open-label because technically it was not possible to blind tiotropium. The indacaterol dose range of 75–600 μg was based on previous phase II studies [3–5].

All study drugs were taken in the morning (08.00–10.00) and (for formoterol and placebo) in the evening (20.00–22.00). Indacaterol was inhaled via a single-dose dry powder inhaler (SDDPI), and formoterol and tiotropium via their proprietary SDDPIs (Aerolizer® and HandiHaler®, respectively).

The interim analysis was pre-planned for when at least 110 patients per group (770 total) had completed at least 2 weeks of treatment. At this point, patient recruitment to the study was temporarily halted. The patients who were already randomized continued their assigned treatment until the two indacaterol doses for stage 2 had been selected.

Following dose selection, patients on the selected indacaterol doses, placebo or tiotropium continued their treatment seamlessly to 26 weeks. Additional patients were recruited to these four arms in Stage 2 of the study, with equal randomization to the four continuing treatment arms. Patients in these four arms completed 26 weeks of treatment irrespective of whether they were randomized before or after the interim analysis. Patients who were receiving formoterol and the indacaterol doses that were not continued into stage 2 were told by the investigator, after the dose selection had been made, to stop their treatment and asked to attend the clinic for an end-of-study visit. They were not re-randomized to other treatments.

2.5. Assessments

Spirometry (for FEV_1 and FVC) was performed 50 and 15 minutes before dosing of study treatment, and at 5 and 30 min and 1, 2, 4, and 23 h 10 min and 23 h 45 min post-dose on Days 1 and 14. ECG (for heart rate and QTc interval) was monitored and blood samples (to measure serum potassium and blood glucose) were taken at 25 min pre-dose and at 30 min and 1 h post-dose on Days 1 and 14. All reported adverse events were noted.

2.6. Outcomes

For the dose selection, the joint primary efficacy outcomes were the trough FEV_1 on Day 15 (mean of measurements at 23 h 10 min and 23 h 45 min after the morning dose on Day 14) and standardized (average) FEV_1 area under the curve (AUC) between 1 and 4 h after the morning dose on Day 14 (FEV_1AUC_{1-4h}), for the treatment comparisons detailed below. Safety outcomes of interest were adverse events, QTc interval (correction by Fridericia's formula), heart rate, serum potassium and blood glucose. For stage 2 of the study, the primary efficacy outcome was trough FEV_1 after 12 weeks (of the 26-week treatment period). Data on clinical outcomes (e.g. symptoms, health status) were also collected in the second stage of the study.

2.7. Dose selection guidelines

The dose selection guidelines were based on efficacy and safety. The mean effect of each indacaterol dose versus placebo was judged against pre-set efficacy reference criteria for trough FEV_1 and FEV_1AUC_{1-4h}. For trough FEV_1, the reference efficacy criterion was the highest value of: (a) the difference between tiotropium and placebo, (b) the difference between formoterol and placebo, or (c) 120 mL (regarded as the minimum clinically important difference). For standardized FEV_1AUC_{1-4h}, the reference efficacy criterion was the highest value of: (a) the difference between tiotropium and placebo or (b) the difference between formoterol and placebo. If more than one indacaterol dose exceeded both the efficacy criteria, the lowest effective dose plus the next higher dose were to be selected. Data on peak FEV_1, % change in FEV_1, and FVC were also supplied to the DMC for possible consideration, but these measures were not part of the formal dose selection process and are not presented here.

The DMC also took into consideration any safety signals observed in any treatment arm. In addition to the present study, blinded safety data from a separate 1-year study [7] were made available to the DMC. These data are not presented here.

2.8. Blinding

In accordance with general study design principles, indacaterol, formoterol and placebo were blinded from randomization to database lock (unless an emergency arose for a patient). For this study, it was particularly important to maintain blinding for the adaptive dose selection. The interim analysis was carried out by an independent statistician (from ClinResearch GmbH, Köln, Germany), who was the only person outside the DMC with access to the semi-blinded randomization codes (treatment groups identified by letters A to G). This statistician functioned independently of the investigators, the sponsor's clinical trial team members and the team that produced statistical programming for the interim analysis (DATAMAP GmbH, Freiburg, Germany). The independent statistician was responsible for all analyses of efficacy and safety data for the interim analysis. The DMC was given semi-blinded results with treatment groups identified by the letters A to G, with separate decodes sealed in an envelope to be opened for decision making. The personnel involved in the continuing clinical study were told which two doses had been selected, but study blinding remained in place and the results of the interim analysis were not communicated. No information on the effects of the indacaterol doses (including the two selected) was communicated outside the DMC.

2.9. Statistical methods

For both co-primary efficacy variables in the dose-selection stage, treatment differences were estimated by using a mixed-model analysis of covariance, with baseline trough FEV_1 (measured 50 and 15 min prior to first dose of study drug) and baseline FEV_1 reversibility to salbutamol and ipratropium as covariates. The model included treatment, smoking status (current/ex-smoker) and country as fixed effects with centre within country as a random effect. Following a request from the DMC, a supportive analysis was performed using a similar mixed model without centre as a random effect. Estimates of adjusted treatment effects are presented with associated 95% confidence intervals. In the analysis of the primary efficacy variable in the second, 26-week stage of the study where two indacaterol doses were evaluated, statistical correction using Bonferroni's methodology was applied to reflect the four doses in the design of the study. This approach is statistically somewhat conservative, but it has the merit of simplicity.

The interim intention-to-treat (efficacy) population was used for these analyses. This population included all randomized patients who were treated for at least 2 weeks or who prematurely discontinued after at least one dose of study drug in the first 2 weeks of treatment, analysed according to their randomized treatment.

Safety evaluation was based on all available data, i.e. for the actual treatment period (up to 84 days) and not just the 2-week period of efficacy evaluation. A mixed model similar to that used for the primary efficacy variables was used to analyse blood glucose, serum potassium, pulse rate and QTc interval. Results are also presented as the incidence of newly occurring or worsening clinically notable abnormalities (serum potassium <3.0 mmol/L; blood glucose >9.99 mmol/L), pulse rate >90 bpm, and QTc interval (Fridericia's) $>450/470$ ms (males/females) or an increase from baseline of >60 ms. The DMC was given all available safety data; however, for potassium, glucose, QTc interval and heart rate information, any data generated after Day 15 for any visit with less than 50 total evaluable patients was not included since estimates would have been unreliable. The interim safety population for these analyses was the same as the interim intention-to-treat (efficacy) population but analysed according to treatment received.

Demographic and baseline characteristics were summarized with standard descriptive statistics. The number of patients and the length of time (in days) exposed to the study drug up to the last visit before interim database cut-off were summarized by treatment. The safety population was used for these analyses.

All analyses were performed using SAS. Based on repeated simulation run in S-Plus, a sample size of 110 patients per treatment group was considered sufficient to provide adequate power to select the correct dose pair.

3. Results

The first patient was screened in April 2007 and the 805th patient was randomized in September 2007. Of these, 801 (who either completed up to Day 15 of treatment or withdrew early) were included in the interim analysis (Tables 1 and 2). Patients received study treatment for an average of 48–55 days across the groups.

3.1. Efficacy

The mean differences versus placebo in trough FEV_1 after 14 days are shown in Fig. 1. The higher of the mean values for the two comparator bronchodilators was the tiotropium–placebo difference of 140 mL, and this was therefore taken as the first reference efficacy criterion. This was exceeded by mean indacaterol–placebo differences for all the indacaterol doses.

The mean differences versus placebo in FEV_1 AUC_{1-4h} after 14 days are shown in Fig. 2. Here, the higher of the mean differences between the comparators was the formoterol–placebo treatment contrast, at 220 mL, which was taken as the second reference efficacy criterion. This was exceeded by the mean indacaterol–placebo differences for indacaterol doses of 150 μg and higher.

Although dose selection was not based on statistically significant differences, these may be inferred when the 95% confidence intervals associated with the treatment contrasts do not include zero. All active treatments had a significantly greater effect than placebo for both efficacy criteria.

Table 1
Patient disposition during the study, *n* (%).

	Indacaterol 75 μg $N = 115$	Indacaterol 150 μg $N = 111$	Indacaterol 300 μg $N = 114$	Indacaterol 600 μg $N = 111$	Tiotropium $N = 119$	Formoterol $N = 112$	Placebo $N = 119$
Randomized	115 (100.0)	111 (100.0)	114 (100.0)	111 (100.0)	119 (100.0)	112 (100.0)	119 (100.0)
Safety population	112 (97.4)	110 (99.1)	114 (100.0)	111 (100.0)	118 (99.2)	111 (99.1)	116 (97.5)
Intent-to-treat population	112 (97.4)	110 (99.1)	114 (100.0)	111 (100.0)	118 (99.2)	111 (99.1)	116 (97.5)
Completed 2 weeks	106 (92.2)	105 (94.6)	110 (96.5)	108 (97.3)	112 (94.1)	108 (96.4)	103 (86.6)
Discontinued within 2 weeks	9 (7.8)	6 (5.4)	4 (3.5)	3 (2.7)	7 (5.9)	4 (3.6)	16 (13.4)
Discontinued after 2 weeks	9 (7.8)	6 (5.4)	3 (2.6)	9 (8.1)	13 (10.9)	5 (4.5)	9 (7.6)
Total discontinued	18 (15.7)	12 (10.8)	7 (6.1)	12 (10.8)	20 (16.8)	9 (8.0)	25 (21.0)
Adverse event(s)	8 (7.0)	4 (3.6)	2 (1.8)	5 (4.5)	2 (1.7)	3 (2.7)	7 (5.9)
Subject withdrew consent	5 (4.3)	2 (1.8)	1 (0.9)	3 (2.7)	4 (3.4)	1 (0.9)	7 (5.9)
Protocol deviation	1 (0.9)	2 (1.8)	2 (1.8)	1 (0.9)	6 (5.0)	1 (0.9)	4 (3.4)
Unsatisfactory therapeutic effect	1 (0.9)	2 (1.8)	1 (0.9)	0	3 (2.5)	1 (0.9)	5 (4.2)
Administrative problems	2 (1.7)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	2 (1.7)
Lost to follow-up	0	0	1 (0.9)	1 (0.9)	2 (1.7)	2 (1.8)	0
Abnormal test result	0	1 (0.9)	0	2 (1.8)	2 (1.7)	0	0
Abnormal lab value	1 (0.9)	0	0	0	0	0	0

3.2. Safety

The overall incidence and the most common (>5%) adverse events occurring during study treatment are shown in Table 3. The majority of adverse events were mild or moderate in severity. The frequency and type of adverse events leading to withdrawal and of serious adverse events (Table 3) showed no particular pattern or relation to dose. There were no deaths during stage 1 of the study.

The incidence of notable values of safety variables (Table 4) did not show any particular safety signal or dose relation for indacaterol. Mean values for these variables (Table 5) showed little or no change with any treatment.

3.3. Dose selection (stage 1)

The two doses of indacaterol selected against the two reference efficacy criteria were 150 μg (as the lowest dose exceeding both criteria) and 300 μg (as the next highest dose). The safety results, together with the safety data from the other 1-year study, led the DMC to conclude that there was no safety signal associated with indacaterol at any dose. Thus, the two doses selected to continue into stage 2 of the study were indacaterol 150 and 300 μg.

3.4. Efficacy evaluation (stage 2)

The four treatment arms continuing in the second stage of the study included a total of 1683 patients. Results of the second stage are reported elsewhere [6]. The mean indacaterol–placebo differences in effect on trough FEV_1 observed after 14 days in the dose-selection stage (180 mL and 220 mL for 150 μg and 300 μg, respectively) were maintained at a statistically significant level after 12 and 26 weeks of treatment in the second stage of the study, as was the tiotropium–placebo mean difference of 140 mL.

4. Discussion

The adaptive seamless design of this study provided an opportunity to combine dose selection with confirmation of efficacy and safety in the same clinical trial. To our knowledge this is the first example of a clinical trial using an adaptive seamless phase II/III design to be reported in the respiratory field. Integrating the dose selection and confirmatory phases of drug development in this way has a number of advantages, most obviously in the lack of delay between the two phases and a faster overall drug development process. The design makes efficient use of patient resources by reducing patients' exposure to potentially less effective or unnecessarily high doses. For the selected doses, the data from both study

Table 2
Patient characteristics at baseline.

	Indacaterol 75 μg $N = 112$	Indacaterol 150 μg $N = 110$	Indacaterol 300 μg $N = 114$	Indacaterol 600 μg $N = 111$	Tiotropium $N = 118$	Formoterol $N = 111$	Placebo $N = 116$
Age (years), mean (SD)	65.7 (9.27)	64.5 (8.75)	62.8 (9.82)	64.4 (9.17)	64.7 (8.65)	65.4 (8.43)	65.1 (8.79)
Sex, *n* (%)							
Male	69 (61.6)	62 (56.4)	71 (62.3)	67 (60.4)	66 (55.9)	63 (56.8)	62 (53.4)
Female	43 (38.4)	48 (43.6)	43 (37.7)	44 (39.6)	52 (44.1)	48 (43.2)	54 (46.6)
Height (cm), mean (SD)	169 (9.7)	169 (8.7)	169 (8.3)	168 (9.8)	168 (9.1)	168 (9.7)	168 (10.1)
Weight (kg), mean (SD)	78.9 (16.57)	79.9 (16.66)	78.4 (17.91)	77.9 (22.54)	76.3 (18.51)	79.2 (20.10)	78.7 (17.18)
Body mass index (kg/m^2), mean (SD)	27.64 (4.719)	28.16 (5.847)	27.59 (6.337)	27.59 (7.229)	27.25 (6.499)	27.88 (6.034)	27.75 (5.207)
Duration of COPD (years), mean (SD)	7.1 (7.70)	7.2 (7.04)	7.1 (7.67)	6.5 (5.34)	7.3 (7.65)	5.9 (4.81)	7.1 (6.22)
FEV_1 (L), mean (SD)[a]	1.50 (0.492)	1.56 (0.487)	1.57 (0.530)	1.52 (0.528)	1.42 (0.464)	1.43 (0.471)	1.50 (0.476)
FEV_1 (% predicted), mean (SD)	52.1 (12.38)	55.1 (13.35)	53.9 (13.28)	53.7 (13.29)	51.1 (13.21)	50.5 (13.30)	54.3 (13.88)
FVC (L), mean (SD)[a]	2.86 (0.832)	2.89 (0.808)	3.00 (0.897)	2.88 (0.926)	2.66 (0.768)	2.87 (0.836)	2.82 (0.825)
FEV_1/FVC, mean (SD)[a]	0.53 (0.01)	0.54 (0.01)	0.53 (0.01)	0.54 (0.01)	0.54 (0.01)	0.51 (0.01)	0.54 (0.01)
Smoking history, *n* (%)							
Ex-smoker	68 (60.7)	65 (59.1)	66 (57.9)	67 (60.4)	70 (59.3)	65 (58.6)	67 (57.8)
Current smoker	44 (39.3)	45 (40.9)	48 (42.1)	44 (39.6)	48 (40.7)	46 (41.4)	49 (42.2)
Concomitant ICS, *n* (%)	48 (42.9)	44 (40.0)	39 (34.2)	39 (35.1)	38 (32.2)	55 (49.5)	40 (34.5)

[a] Post-salbutamol/albuterol. ICS = inhaled corticosteroids.

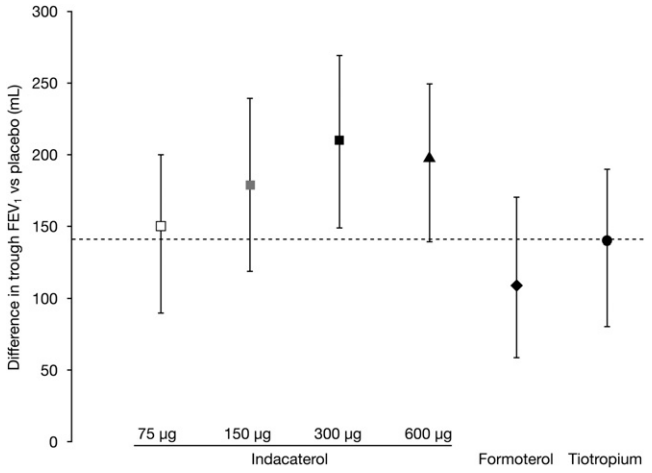

Fig. 1. Treatment differences (least squares means and 95% CI) versus placebo in trough FEV_1 at Day 15. The dotted line represents the pre-set efficacy criterion (i.e. the highest value among formoterol, tiotropium and 120 mL), which was exceeded by all indacaterol doses.

stages contribute to the confirmatory analysis of the overall study. However, the adaptive seamless design requires careful pre-planning and involves additional resources. A DMC that is independent of the sponsor is preferred in order to avoid bias and ensure scientific integrity, while an independent statistician dedicated to providing interim data analysis to the DMC was needed to avoid any risk of unintentional unblinding. We aimed to evaluate over 100 patients per treatment arm in the dose-finding stage, based both on power calculations and previous experience with similar numbers from phase II of indacaterol development [4]. This number of patients also enabled a robust safety assessment as part of the risk:benefit evaluation, and had the consequence of reducing the time spent in recruitment when randomization was re-opened after the interim analysis. Stages 1 and 2 of the study together involved 2059 patients, of whom 18% were randomized into treatment groups that did not continue beyond stage 1.

The adequacy of the interim dose selection procedure is critical to the success of any seamless phase II/III trial. Ideally, the endpoint(s) used at the interim analysis should be the same as or shown to be strongly correlated with the final study primary endpoint, and should be recognized and accepted [2]. Here, trough FEV_1 was both a pre-set efficacy criterion for dose selection, measured after 14 days of treatment, and the primary efficacy endpoint of stage 2 of the study, measured after 12 weeks of the 26-week treatment period. FEV_1 is widely used in COPD studies and is a required endpoint for drug registration studies in COPD. The way in which FEV_1 was assessed in the present study was designed to provide a fair and comprehensive efficacy comparison with the other treatments. The comparators were chosen to reflect current standards for bronchodilator therapy in COPD, tiotropium being a once-daily bronchodilator with established efficacy [8,9], while formoterol is a twice-daily agent with a fast onset of action and a 12 h bronchodilator effect [10,11]. Indacaterol also has a fast onset, with bronchodilator effects within 5 minutes of dosing [4], while tiotropium has a slower initial bronchodilator effect [4,12].

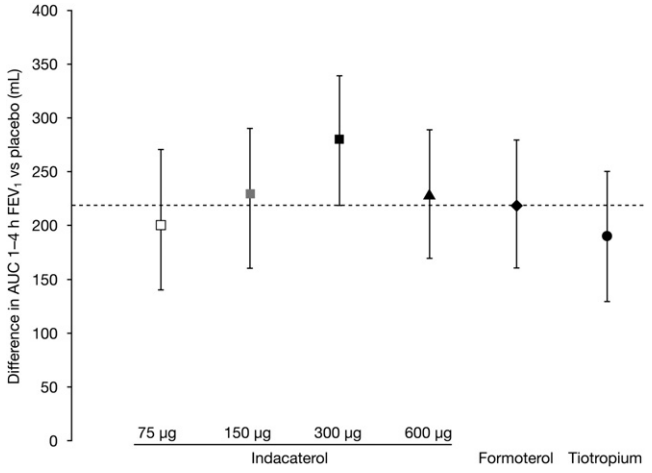

Fig. 2. Treatment differences (least squares means and 95% CI) versus placebo in FEV_1 AUC_{1-4h} at Day 14. The dotted line represents the pre-set efficacy criterion (i.e. the highest value among formoterol and tiotropium), which was exceeded by indacaterol doses of 150 µg and higher.

The criteria for dose selection after 14 days of treatment reflected the overall profile of bronchodilation over time by including indicators of peak/early (1–4 h) and trough (~24 h post-dose) effect. To remove any possible impact or bias due to fast onset, the FEV_1 AUC was measured over 1–4 h to exclude the first hour of bronchodilator effect, rather than using the more common starting point of 0 h. The pre-set efficacy criteria for trough FEV_1 started at the level of 120 mL versus placebo. This level has been routinely pre-specified in clinical studies with indacaterol as representing a clinically relevant level of bronchodilation that would ideally be demonstrated 24 h following dosing. Literature sources quote different levels of minimal important effect for FEV_1 although the time point being assessed is not specified, i.e. whether FEV_1 is measured at peak (early) effect, at the latest possible time or trough before the next dose, as an average over the dosing interval, or over a longer timeframe as an indicator of long-term decline in lung function. Recently, a joint European Respiratory Society/American Thoracic Society statement concluded that the minimal important difference for FEV_1 lies within a range of 100–140 mL [13]. At approximately the mid-point of this range, and in terms of a trough effect, 120 mL is a reasonable cut-off. For comparison, a difference of 100 mL has been reported as a level at which a COPD patient can perceive an effect [14]. Thus, the selected indacaterol doses met a high threshold in order to qualify for selection, not only in providing a clinically relevant bronchodilator effect per se but also in outperforming the two most effective bronchodilators currently available for the treatment of patients with COPD.

It may be argued that a volume measurement such as FVC should have been included in the dose selection criteria, since this variable may be more sensitive than FEV_1 to the acute effects of bronchodilators in patients with very severe and apparently 'irreversible' COPD [15–17]. However, the patients in the present study were moderately reversible at screening in terms of both FEV_1 and FVC, and the pre-set efficacy criteria proved effective in discriminating between the treatments. Results for FVC (not shown) were less clear-cut, and the addition of these results would not have contributed significantly to the decision-making process. The dose-response data for FEV_1 AUC_{1-4h} and, to a lesser extent, trough FEV_1 suggest a plateau in bronchodilator effect occurring approximately at an indacaterol dose of 300 µg. The bronchodilator effects following the first dose (not shown) showed a similar pattern of dose-response, together with some increase in efficacy to Day 14. This suggests that the pattern of dose–response results from pharmacological properties of the molecule rather than receptor desensitization, and it seems likely that the results for the 600 µg dose reflect a degree of biological variation around the dose at which the plateau potentially occurs. A separate study evaluating

Table 3
Patients with adverse events (*n*, %): overall incidence, most common (≥5% of any group), and leading to discontinuation of treatment.

	Indacaterol				Tiotropium $N = 118$	Formoterol $N = 111$	Placebo $N = 116$
	75 μg $N = 112$	150 μg $N = 110$	300 μg $N = 114$	600 μg $N = 111$			
Any adverse event	57 (50.9)	47 (42.7)	43 (37.7)	36 (32.4)	34 (28.8)	38 (34.2)	40 (34.5)
Mild or moderate (n)	52	44	40	31	30	36	37
Headache	7 (6.3)	7 (6.4)	2 (1.8)	2 (1.8)	3 (2.5)	6 (5.4)	1 (0.9)
Mild or moderate (n)	7	7	1	2	3	6	1
Cough	6 (5.4)	6 (5.5)	2 (1.8)	3 (2.7)	2 (1.7)	1 (0.9)	5 (4.3)
Mild or moderate (n)	6	6	2	3	2	1	3
Muscle spasms	1 (0.9)	2 (1.8)	4 (3.5)	6 (5.4)	0	1 (0.9)	1 (0.9)
Mild or moderate (n)	1	1	4	4		0	1
Adverse events leading to withdrawal	6 (5.4) Atrial flutter, cough, dyspnoea, throat irritation, ventricular asystoles, ventricular tachycardia	3 (2.7) Headache, nausea, ventricular tachycardia, vomiting	2 (1.8) ECG change, lung neoplasm	5 (4.5) Bronchitis, fatigue, intestinal obstruction, oedema peripheral, URTI	2 (1.7) Lung neoplasm, ventricular tachycardia	1 (0.9) Crohn's disease	6 (5.2) Chest pain, COPD, dyspnoea, nasal congestion, pulmonary hilum mass, URTI bacterial
Serious adverse events	3 (2.7) Pneumonia, COPD, transient ischaemic attack	2 (1.8) Angina pectoris, benign prostatic hyperplasia	2 (1.8) Lung neoplasm, haematuria	2 (1.8) Lung neoplasm, intestinal obstruction, drug hypersensitivity	4 (3.4) Staphylococcal infection, lung neoplasm, multiple injuries, road traffic accident, deep vein thrombosis	1 (0.9) Mental disorder	3 (2.6) URTI (2), dyspnoea, chest pain, pain in extremity

URTI = upper respiratory tract infection. COPD = COPD worsening.

the 600 μg dose for 1 year compared with formoterol showed no loss of bronchodilator effect over time with indacaterol but some loss with formoterol [18].

As well as efficacy, it was equally important to include a thorough assessment of safety as a basis for dose selection, and this included scrutiny of adverse event incidence, type and severity, and serious adverse events leading to withdrawal of treatment. In addition, since indacaterol is a new once-daily long-acting β_2-adrenoceptor agonist, the safety assessment included markers of potential effect on systemic β_2-adrenoceptors (potassium, glucose), and QTc interval as an indicator of any unwanted ECG changes.

The use of the adaptive seamless design is not without potential risk. The initial dose-finding period needs to be long enough for a thorough evaluation of effects. Two weeks was considered a fully adequate period in which to attain pharmacodynamic steady state. In the event, the differences in trough FEV_1 between active and placebo treatments were maintained at the same or very similar level at Day 14 and Week 26 for all the continuing treatment arms [6]. The addition of blinded data from a separate 1-year study helped ensure that safety was comprehensively monitored.

While there is enthusiasm for streamlining the clinical trial process both from regulatory authorities and drug developers [1,19–21], the adaptive seamless design needs to be approached carefully. Additional early planning is required compared with the traditional separation of dose-finding and confirmatory stages, with careful attention to the critical points of the decision process, the maintenance of blinding and the independent personnel involved (DMC and statisticians). Difficulties may arise with a study design that is unduly complicated or which changes radically between the two stages, or if there are too many unknown factors associated with the therapeutic area or the drug under investigation.

The unblinded interim results of an adaptive trial design need to inform the future conduct of the remainder of the trial, without compromising its validity and integrity [2]. The present study provides a successful example of how this may be achieved, by using stringent pre-set efficacy criteria to make a confident selection of the most appropriate doses of indacaterol for longer-term evaluation of efficacy. The adaptive seamless design can help streamline the development process in

Table 4
Patients (*n*, %) with newly occurring or worsening clinically notable values for key safety variables.

	Indacaterol				Tiotropium $N = 118$	Formoterol $N = 111$	Placebo $N = 116$
	75 μg $N = 112$	150 μg $N = 110$	300 μg $N = 114$	600 μg $N = 111$			
Potassium <3.0 mmol/L	0	0	0	0	0	0	0
Glucose >9.99 mmol/L	4 (3.6)	4 (3.7)	2 (1.8)	8 (7.3)	5 (4.3)	3 (2.7)	4 (3.5)
Pulse rate >90 bpm	15 (13.4)	8 (7.3)	9 (7.9)	13 (11.7)	11 (9.4)	9 (8.1)	11 (9.5)
QTc(F) interval >450/470 ms	6 (5.4)	3 (2.7)	2 (1.8)	5 (4.5)	7 (5.9)	1 (0.9)	3 (2.6)
QTc(F) interval >60 ms	0	0	0	0	0	0	0

Values are overall post-baseline maximum or minimum. QT interval calculated using Fridericia's correction (QTc(F) interval).

Table 5
Mean values (least squares means and 95% confidence intervals) for serum potassium, blood glucose, pulse rate and QTc(F) interval measured at 1 h post-dose on Day 14.

	Indacaterol				Tiotropium $N = 118$	Formoterol $N = 111$	Placebo $N = 116$
	75 μg $N = 112$	150 μg $N = 110$	300 μg $N = 114$	600 μg $N = 111$			
Potassium, mmol/L	4.40 (4.28, 4.52)	4.38 (4.26, 4.50)	4.44 (4.32, 4.56)	4.36 (4.24, 4.48)	4.44 (4.32, 4.57)	4.40 (4.28, 4.52)	4.45 (4.33, 4.56)
Glucose, mmol/L	5.44 (5.07, 5.82)	5.31 (4.94, 5.69)	5.58 (5.21, 5.96)	5.57 (5.19, 5.94)	5.18 (4.81, 5.55)	5.32 (4.94, 5.69)	5.21 (4.85, 5.57)
Pulse rate, bpm	70.0 (67.2, 72.7)	69.3 (66.6, 72.1)	71.0 (68.2, 73.7)	71.3 (68.5, 74.0)	68.9 (66.1, 71.6)	70.3 (67.6, 73.1)	68.8 (66.2, 71.5)
QTc(F) interval, ms	407 (403, 411)	406 (402, 410)	408 (404, 412)	406 (402, 410)	405 (401, 409)	404 (400, 408)	405 (401, 409)

QT interval calculated using Fridericia's correction (QTc(F) interval).

different therapeutic areas and help bring new and effective therapies to patients faster.

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