International Journal of COPD

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Bronchodilator efficacy and safety of indacaterol 150 µg once daily in patients with COPD: an analysis of pooled data

This article was published in the following Dove Press journal:
International Journal of COPD
17 August 2011
Number of times this article has been viewed

Eugene R Bleecker[1]
Thomas Siler[2]
Roger Owen[3]
Benjamin Kramer[4]

[1]Center for Genomics and Personalized Medicine Research and Translational Medicine Institute, Wake Forest University Health Sciences, Winston-Salem, NC, USA; [2]Midwest Chest Consultants, Saint Charles, MO, USA; [3]Novartis Horsham Research Centre, Horsham, West Sussex, UK; [4]Respiratory Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

International Journal of Chronic Obstructive Pulmonary Disease downloaded from https://www.dovepress.com/
For personal use only.

Background: Indacaterol is an inhaled, once-daily long-acting β_2-agonist bronchodilator for regular use in patients with chronic obstructive pulmonary disease (COPD). As indacaterol is the first once-daily β_2-agonist to be developed, it is relevant to evaluate its bronchodilator efficacy, safety, and tolerability.

Methods: Data were pooled from three randomized, double-blind, clinical studies in patients with moderate-to-severe COPD treated with indacaterol 150 µg qd (n = 627) or placebo (n = 1021). Bronchodilator efficacy was assessed as trough (24-hour post-dose) forced expiratory volume in 1 second (FEV_1) after 12 weeks (primary endpoint in individual studies) and FEV_1 measured serially post-dose. Rescue use of albuterol was monitored.

Results: At week 12, indacaterol increased trough FEV_1 by 160 mL compared with placebo ($P < 0.001$), exceeding the 120 mL level prespecified as clinically important. FEV_1 during the first 12-hour post-dose at week 12 averaged 210 mL higher with indacaterol than with placebo ($P < 0.001$). Patients receiving indacaterol recorded 53% of days without use of rescue albuterol, compared with 38% of days in the placebo group ($P < 0.001$). Adverse events (mostly mild or moderate) were reported for 52% and 46% of patients receiving indacaterol and placebo, respectively, and serious adverse events for 4% and 5%. Worsening of COPD was the most frequent adverse event (10% indacaterol; 15% placebo). Indacaterol had little effect on pulse or blood pressure or measures of systemic β_2-adrenoceptor activity (blood glucose, serum potassium, and corrected QT interval).

Conclusion: Indacaterol was an effective bronchodilator and was well tolerated, with a good safety profile over 12 weeks of treatment. It should prove a useful treatment for patients with moderate-to-severe COPD.

Keywords: chronic obstructive pulmonary disease, tolerability, inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive pulmonary disease characterized by progressive resting and exertional dyspnea and is associated with major comorbidities.[1] In 2005, approximately 1 in 20 deaths in the United States was caused by COPD,[2] and COPD was reported to affect an estimated 6% of US adults in 2008,[3] with higher prevalence figures in higher-risk groups such as veterans (9%) and Medicare beneficiaries (11%).[4,5] However, COPD is often underdiagnosed and is relatively undertreated compared with other, less morbid, chronic conditions such as hypertension and hypercholesterolemia.[6]

According to current guidelines for the treatment of stable COPD, the regular use of long-acting bronchodilators is recommended for initial maintenance treatment of COPD.[1]

Correspondence: Eugene R Bleecker
Wake Forest University Health Sciences, Center for Genomics and Personalized Medicine Research, Medical Center Boulevard, Winston-Salem, NC 27157, USA
Tel +1 336 713 7521
Fax +1 336 713 7566
Email ebleeck@wakehealth.edu

© 2011 Bleecker et al, publisher and licensee Dove Medical Press Ltd. This is an Open Access article which permits unrestricted noncommercial use, provided the original work is properly cited.

These agents are either β_2-agonists administered twice daily (formoterol and salmeterol) or the once-daily anticholinergic, tiotropium. In the management of stable COPD, bronchodilator treatment improves forced expiratory volume in 1 second (FEV_1) with a concomitant reduction in hyperinflation, and reduction in symptoms such as breathlessness (dyspnea).[7]

Indacaterol is a novel, inhaled, long-acting β_2-agonist providing 24-hour bronchodilation on once-daily dosing,[8–10] currently approved in many countries for the maintenance treatment of COPD. The purpose of this manuscript, using data pooled from the indacaterol clinical trial database, is to provide a comprehensive evaluation of the bronchodilator efficacy, safety, and tolerability of indacaterol 150 µg compared with placebo in a large sample of patients with COPD. The 150 µg dose was identified in the dose-ranging stage of a Phase II/III adaptive seamless design study as the lowest dose of indacaterol providing effective bronchodilation in COPD.[11] The data presented represent the results from the first 12 weeks of dosing in three registration studies with identical patient entry criteria. The 150 µg dose of indacaterol was evaluated in two of the studies; only data from the placebo group in the third study (which assessed higher indacaterol doses) are included in the pooled dataset. All three studies are the subject of separate publications.[8–10]

Methods

The study designs are described in detail in the individual publications.[8–10] All were randomized, double-blind, parallel-group comparisons of indacaterol and placebo prescribed once daily. One was a 12-week comparison of indacaterol 150 µg and placebo;[8] one was a 6-month comparison of indacaterol 150 µg and placebo (and indacaterol 300 µg and tiotropium; not reported here)[10] and the third study, which contributed placebo data only to the present analysis, was a comparison of indacaterol 300 and 600 µg qd, formoterol, and placebo.[9] Indacaterol 150 µg and placebo were administered using identical single-dose dry-powder inhalers and were used daily each morning. All study protocols were approved by the independent ethics committee or institutional review board for each participating center. All patients provided written informed consent prior to participation.

The studies recruited patients aged ≥40 years with moderate-to-severe COPD and a smoking history of ≥20 pack-years. Patients had relatively stable COPD, and were excluded if they had a recent chest infection or had recently been hospitalized for a COPD exacerbation.

Other bronchodilator treatments were discontinued before the start of study treatment, apart from albuterol, which patients could use as required. Patients were allowed to continue treatment with inhaled corticosteroids (ICS) during the study, providing they were using ICS at the time of screening; the dose and regimen were not altered for the duration of the study. Treatment with combination ICS and bronchodilators was replaced with the ICS component alone, at equivalent dose and regimen.

Spirometry was performed at screening, at baseline, and at regular clinic visits during the studies, according to recognized standards.[12] The primary efficacy outcome in each study was FEV_1 measured at 'trough' (the mean of measurements taken at 23 hours and 10 minutes and 23 hours and 45 minutes post-dose) after 12 weeks of treatment. In each study, a difference between indacaterol and placebo of 120 mL in FEV_1 was prespecified as a minimal clinically important difference. Spirometry was also performed at serial time points post-dose at clinic visits, including those at baseline and week 12. The patients' use of albuterol as rescue medication, recorded on daily diary cards, was a secondary efficacy outcome.

A secondary objective of the studies was to assess safety, including adverse events, electrocardiograms (ECGs) (measurement of corrected QT [QTc] interval), laboratory tests (measurement of blood glucose and serum potassium concentrations), and vital signs (blood pressure and pulse rate) measured at baseline and pre- and post-dose at week 12.

Statistical methods

The methodology used for pooling the data was to include all available data from studies that were designed with identical or near-identical methods and patient entry criteria. Hence, data from the placebo treatment group of a study investigating higher doses of indacaterol (300 and 600 µg qd)[9] were included in the pooled dataset. The primary endpoint, trough FEV_1, was analyzed using a mixed-model analysis of covariance (ANCOVA) with treatment as a fixed effect, and baseline FEV_1 and FEV_1 reversibility as covariates. Smoking status (current/ex-smoker), country, and study were included as fixed effects, and center nested within country as a random effect. Estimates of adjusted treatment effects and pairwise treatment differences from the ANCOVA are presented along with the associated 95% confidence intervals (CIs) and two-sided *P*-values. The percentage of days with no rescue use during the 12 weeks and the standardized area under the curve for FEV_1 at week 12 (measured from 5 minutes to 11 hours and 45 minutes post-dose) were analyzed using the same mixed model, with the appropriate baseline measurement as covariates. No adjustment was made for multiple testing for the pooled analyses.

Results

Table 1 shows the patients' demographic and clinical characteristics. Apart from a slightly higher proportion of men compared with women in the placebo group, the two treatment groups were well matched. Baseline prebronchodilator percent predicted FEV_1 was 49% in both treatment groups; post-bronchodilator (albuterol) values were also similar in the two groups (indacaterol 56%; placebo 55% predicted).

Efficacy

Spirometry

Trough FEV_1 (24 hours post-dose) was significantly higher with indacaterol compared with placebo both after the first dose and at week 12 (both $P < 0.001$) (Figure 1). The difference of 160 mL at week 12 was one-third greater than the prespecified difference of minimal clinical importance (120 mL). After the first dose, trough FEV_1 was 100 mL greater with indacaterol than with placebo.

In terms of mean changes from baseline, the effects of indacaterol on trough FEV_1 equated to 130 mL (9.7%) after the first dose, and 150 mL (11.4%) at week 12 (Figure 2). Corresponding values with placebo treatment were 20 mL (1.5%) after the first dose and 10 mL (0.8%) at week 12.

Table 1 Patient characteristics at baseline

	Indacaterol 150 µg N = 627	Placebo N = 1021
Age, years	63.2 (9.56)	63.6 (8.69)
Age ≥65 years, %	47	46
Sex, male/female, %	58/41	67/33
COPD severity, %		
Moderate or less	61	59
Severe or worse	39	41
Duration of COPD, years	6.8 (7.09)	6.8 (6.15)
ICS use, %	35	44
Smoking history		
Ex-/current smoker, %	53/47	55/45
Pack-years	50.0 (24.72)	50.6 (32.33)
FEV_1 pre-albuterol, L	1.33 (0.497)	1.35 (0.478)
FEV_1 pre-albuterol, % predicted	49.0 (14.54)	48.8 (13.99)
FEV_1 post-albuterol, L[a]	1.51 (0.510)	1.52 (0.497)
FEV_1 post-albuterol, % predicted[a]	55.5 (14.13)	55.0 (14.15)
FEV_1/FVC post-albuterol[a]	0.53 (0.099)	0.53 (0.104)
FEV_1 reversibility, %[b]	15.9 (16.07)	14.8 (16.51)

Notes: Data are mean (standard deviation) unless otherwise stated. [a]Post-albuterol measurements taken 30 minutes after patients inhaled albuterol 380 µg (four puffs); [b]Reversibility calculated as difference between pre- and post-albuterol values divided by the pre-albuterol value, expressed as a percentage.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids.

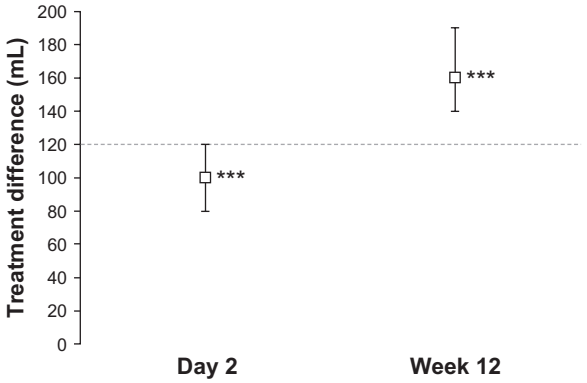

Figure 1 Trough forced expiratory volume in 1 second: differences between indacaterol and placebo treatment after first dose (measured on day 2) and after 12 weeks' treatment. Broken line indicates prespecified level of clinical importance.
Notes: Data are least squares means and 95% confidence intervals. ***Denotes $P < 0.001$ vs placebo.

Serial post-dose measurements of FEV_1 after the first dose and at week 12 are shown in Figure 3. The analysis of the standardized area under the curve showed that FEV_1 was on average 210 mL (95% CI 150–280 mL) higher with indacaterol than with placebo during the first 12 hours post-dose ($P < 0.001$).

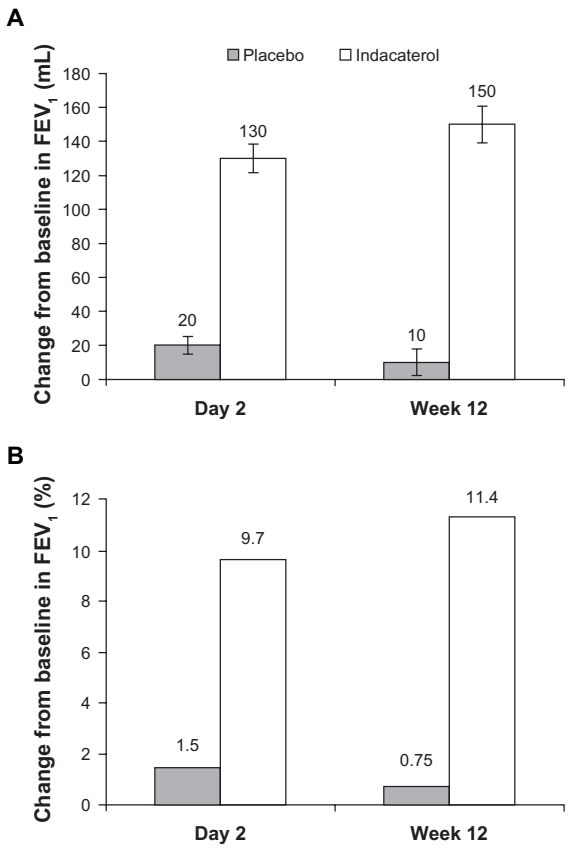

Figure 2 Trough FEV_1 after the first dose (day 2) and after 12 weeks of treatment, expressed as change from baseline (absolute (**A**) and percentage (**B**)).
Note: Data are unadjusted means ± standard error.
Abbreviation: FEV_1, forced expiratory volume in 1 second.

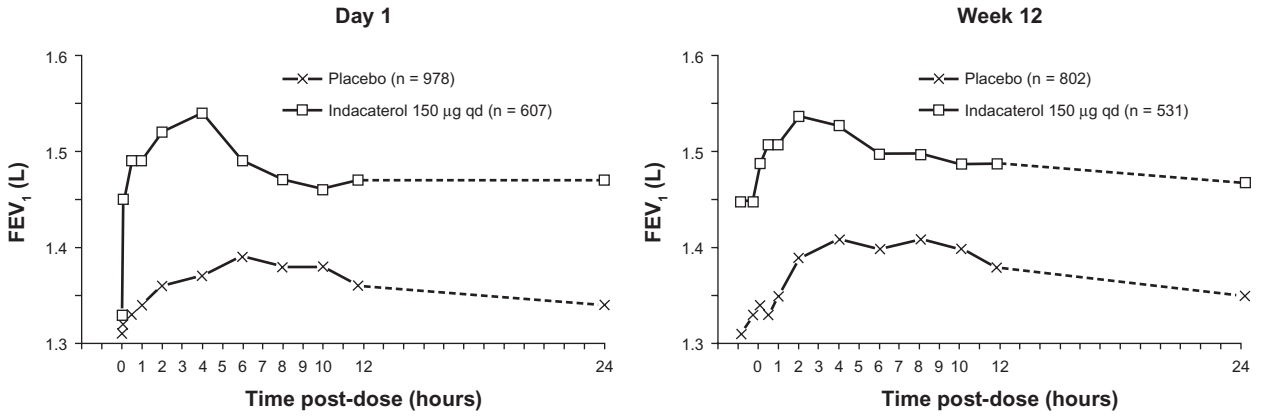

Figure 3 FEV_1 measured at serial time points post-dose on day 1 and week 12.
Note: Data are unadjusted means (error bars omitted for clarity).
Abbreviation: FEV_1, forced expiratory volume in 1 second.

Figure 4 illustrates the bronchodilator effect of treatment during the first hour following dosing on day 1. FEV_1 was significantly higher following indacaterol compared with placebo at each time point ($P < 0.001$), with differences of 120 mL (5 minutes post-dose) and 150 mL (30 and 60 minutes post-dose).

Forced vital capacity (FVC) during treatment was evaluated in only one of the studies comparing indacaterol 150 µg qd with placebo.[10] Results after 12 weeks of treatment are shown in Figure 5,[10] demonstrating that indacaterol significantly increased FVC compared with placebo at each time point post-dose ($P < 0.001$).

Days without use of rescue albuterol

Patients treated with indacaterol recorded no use of rescue albuterol on 52.7% of days, a 40% increase compared with the 37.7% rescue-free days among the placebo group (Figure 6).

Safety

Adverse events

The incidence of (percentage of patients with) adverse events is shown in Table 2. In most cases (indacaterol 88%; placebo 87%), the adverse events were mild or moderate in severity. Comparing the two treatment groups, upper respiratory tract infection, headache, and muscle spasms were reported more frequently with indacaterol treatment than with placebo. For upper respiratory tract infection, all but one of the 33 cases (97%) during indacaterol treatment were mild or moderate, and none was considered to be related to the study drug. With indacaterol, headache was mild or moderate in most patients (26/28; 93%), and was considered related to the study drug in six patients (21%). The episodes of muscle spasms with indacaterol were generally mild or moderate (13/18; 72%), and were considered related to the study drug in six patients (33%). Only one of these cases (the episode of severe upper respiratory tract infection) was

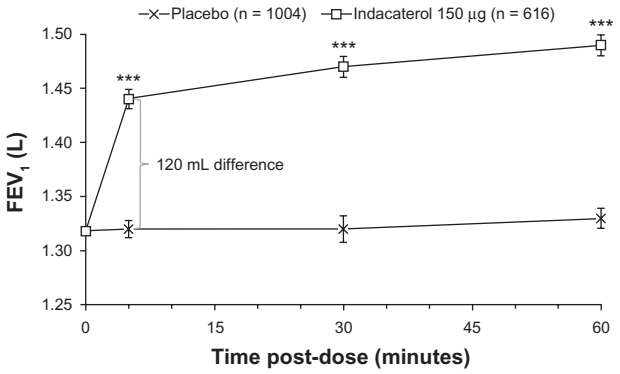

Figure 4 FEV_1 measured at serial time points up to 60 minutes post-dose on day 1.
Notes: Data are least squares means ± standard error. ***Denotes $P < 0.001$ vs placebo.
Abbreviation: FEV_1, forced expiratory volume in 1 second.

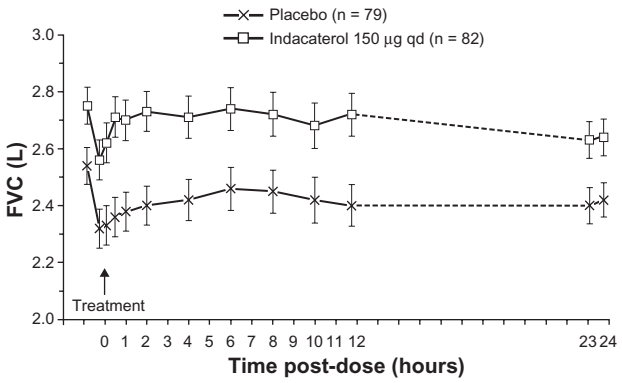

Figure 5 FVC measured at serial time points post-dose after 12 weeks in a single study.[10]
Notes: Data are least squares means ± standard error. Differences between indacaterol and placebo were statistically significant ($P < 0.001$) at each time point.
Abbreviation: FVC, forced vital capacity.

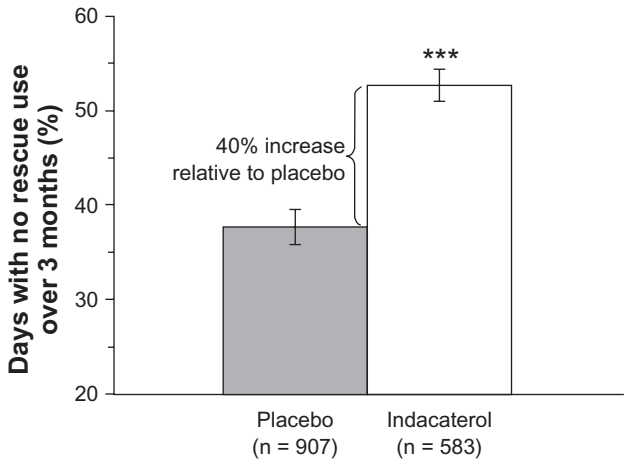

Figure 6 Percentage of days with no use of rescue albuterol over 3 months of treatment.
Notes: Data are least squares means ± standard error. ***Denotes $P < 0.001$ vs placebo.

classed as a serious adverse event. Other events associated with β_2-agonist treatment were uncommon. Tremor occurred in one patient (0.16%) receiving indacaterol and in five receiving placebo (0.47%). Tachycardia was reported for five patients (0.80%) receiving indacaterol and five (0.47%) receiving placebo.

Table 2 Adverse events overall and most commonly occurring (≥2% of indacaterol treatment group) (3-month safety population)

	Indacaterol 150 µg (%) N = 627	Placebo (%) N = 1055
Patients with ≥1 adverse event	51.7	46.3
COPD worsening	10.2	15.1
Cough	5.3	4.3
Upper respiratory tract infection	5.3	2.6
Nasopharyngitis	4.8	5.8
Headache	4.5	2.6
Muscle spasms	2.9	1.1
Diarrhea	2.4	1.5
Dyspnea	2.2	2.7
Back pain	2.1	1.7
Bronchitis	2.1	2.4
Dizziness	1.9	1.6
Nausea	1.9	1.4
Lower respiratory tract infection	1.8	2.2
Pharyngolaryngeal pain	1.8	0.8
Sinusitis	1.8	0.8
Urinary tract infection	1.8	1.2
Viral upper respiratory tract infection	1.6	1.5
Arthralgia	1.3	0.7
Influenza	1.3	0.8
Edema peripheral	1.1	0.4

Abbreviation: COPD, chronic obstructive pulmonary disease.

Overall, serious adverse events occurred in 33 (3.9%) and 47 (4.5%) of patients receiving indacaterol and placebo, respectively. The most common serious adverse event was "COPD worsening" (which includes disease progression and COPD exacerbations) (indacaterol, 0.6% of patients; placebo, 1.6% of patients). Two patients died during the 3-month treatment period, and both of them were in the placebo group.

The incidence of abnormal values for blood chemistries, vital signs, and ECG (QTc interval) is shown in Table 3. The one patient with a QTc interval > 500 milliseconds also had a high baseline value (515 milliseconds) and a history of cardiac insufficiency, and was being treated with amiodarone, an anti-arrhythmic known to prolong QTc interval.

Discussion

The studies that comprised the data for this analysis had identical entry criteria and followed the same methodologies. Despite their differing durations, the three studies shared a common primary efficacy outcome that was assessed at the same 12-week time point. The pooled dataset used here therefore provides a much larger database to report on the

Table 3 Incidence of clinically notable values for blood glucose, serum potassium, blood pressure, pulse rate and QTc interval, recorded at any time post-baseline (3-month safety population)

	Indacaterol 150 µg n (%) N = 627	Placebo n (%) N = 1055
Blood glucose >9.99 mmol/L (179.8 mg/dL)	34 (5.4)	49 (4.7)
Serum potassium <3 mmol/L	0	3 (0.3)
Systolic blood pressure		
Low[a]	1 (0.19)	13 (1.23)
High[b]	4 (0.64)	15 (1.42)
Diastolic blood pressure		
Low[c]	4 (0.64)	7 (0.66)
High[d]	5 (0.80)	12 (1.14)
Pulse rate		
Low[e]	4 (0.64)	15 (1.42)
High[f]	0	5 (0.47)
QTc interval[g] absolute value		
>450 (M) or >470 (F) ms	20 (3.2)	33 (3.1)
>500 ms	1 (0.2)	0
QTc interval[g] increase from baseline		
30–60 ms	48 (7.7)	59 (5.7)
>60 ms	0	1 (0.1)

Notes: [a]<75 mmHg, or ≤90 and decrease from baseline of ≥20 mmHg; [b]>200 mmHg, or ≥180 and increase from baseline of ≥20 mmHg; [c]<40 mmHg, or ≤50 and decrease from baseline of ≥15 mmHg; [d]>115 mmHg, or ≥105 mmHg and increase from baseline of ≥15 mmHg; [e]<40 bpm, or ≤50 bpm and decrease from baseline of ≥15 bpm; [f]≥120 bpm and increase from baseline of ≥15 bpm, or >130 bpm; [g]Calculated using Fridericia's formula.
Abbreviation: QTc, corrected QT interval.

efficacy, tolerability, and safety of indacaterol 150 µg qd. Once-daily dosing with indacaterol 150 µg provided a bronchodilator effect at 24 hours post-dose (trough FEV_1) that was 160 mL greater than with placebo. This level of bronchodilation exceeded the 120 mL difference prespecified in the clinical studies as denoting clinical importance, and is also in excess of the 100–140 mL range that has been reported to be clinically significant in patients with COPD.[13] The bronchodilator effect of indacaterol on trough FEV_1 after the first dose was 100 mL greater than that observed with placebo.

Circadian variation in lung function is a normal process that also occurs in obstructive airway diseases, including COPD, and results in the lowest FEV_1 levels in the early hours of the morning.[14–17] In COPD, the normal early-morning decrease in FEV_1 is thought to be increased by the airflow obstruction in this disease and may be worsened by increased morning sputum production.[18] Reduced β_2-adrenergic receptor stimulation due to decreased levels of endogenous catecholamines has also been proposed as a contributing factor.[19] It is therefore important to provide effective bronchodilation over the entire day, especially during the early morning. Treatment with a long-acting β_2-agonist bronchodilator may represent an appropriate therapeutic approach. The early morning is also the time of day when symptoms are worse or the worst, and shortness of breath is often limiting for the patient's routine and daily activities in life.[20] Trough FEV_1 is a measure of early-morning efficacy of a long-acting β_2-agonist, and the excellent bronchodilation still provided by indacaterol at this critical time of day may be helpful to COPD patients, facilitating improved levels of activity and resulting in improved quality of life.

The 160 mL difference in week 12 trough FEV_1 with indacaterol compared with placebo is similar or slightly better than previous reports of the effect of tiotropium in placebo-controlled studies (difference of 120–137 mL in trough FEV_1 for tiotropium compared with placebo).[21–24] Reported differences in trough FEV_1 between tiotropium and the twice-daily β_2-agonist salmeterol are approximately 20–50 mL in favor of tiotropium.[22,24,25] Thus, indacaterol appears to have a greater effect on trough FEV_1 than other available long-acting bronchodilator treatments for COPD. The bronchodilator efficacy of indacaterol increased from the first dose to the measurements performed at the end of 12 weeks of treatment. In longer-term studies, the efficacy of indacaterol 150 µg qd was not reduced with repeated dosing for 6 or 12 months, showing persistence of bronchodilator response without tachyphylaxis.[10,26,27] In contrast, a decline in bronchodilator effectiveness over time has been reported with both the twice-daily β_2-agonists.[28,29]

The bronchodilator effect of indacaterol was also demonstrated in terms of its improvement of FVC. Effects on FVC generally reflect effects on FEV_1 but can also be useful in patients with COPD, specifically those with hyperinflation, to identify a therapeutic response in the absence of effects on FEV_1.[13] This reduction in hyperinflation may represent an important mechanism through which indacaterol reduces symptoms in COPD.

A very important finding of this analysis is that treatment with indacaterol showed improvement in disease control, since the bronchodilation provided by indacaterol occurred in association with a 40% increase in rescue-free days compared with placebo. This reduction in the requirements for albuterol use for symptom relief suggests that patients receiving indacaterol were experiencing reduced symptoms.[30] Extrapolated to longer-term use, the difference in rescue use between treatments equates to 55 more days per year in which patients with moderate-to-severe COPD did not use albuterol while taking indacaterol, compared with those treated with a placebo.

While comparisons with placebo are a necessary step for approval of new treatments, it is relevant for practicing clinicians to judge the efficacy of a new treatment against other agents that are available for the treatment of COPD patients. Direct comparisons with other long-acting bronchodilators have been published recently. They show that indacaterol 150 µg qd had a bronchodilator effect similar to that of the once-daily anticholinergic, tiotropium, while providing greater improvements in symptoms and health status.[31] In comparison with the twice-daily β_2-agonist, salmeterol, indacaterol proved to be a superior bronchodilator and had a greater effect in reducing dyspnea even though indacaterol-treated patients used less rescue medication.[32]

The overall frequency of adverse events and serious adverse events was similar between active and placebo treatments in the present analysis. The most common adverse event, "COPD worsening," occurred more often in the placebo group, which suggests a potential beneficial effect of indacaterol on COPD exacerbations. Those adverse events occurring more frequently with indacaterol were mostly mild or moderate, and indacaterol was well tolerated. The side effects of tremor and tachycardia that would be expected to result from β_2-adrenergic stimulation were less common with indacaterol than with placebo. Muscle spasms were more common with indacaterol than with placebo (2.9% vs 1.1%), but these events were generally mild or moderate in severity.

The incidence of changes in glucose and potassium, and prolongation of QTc interval, were very low and similar with indacaterol and placebo treatments. Thus, in a large analysis of patients with COPD, therapy with indacaterol was well tolerated with a side-effect profile similar to placebo.

Adherence with treatment is often poor among patients with chronic respiratory diseases, including COPD.[33–35] Adherence in chronic diseases is reported to be inversely related to the number of doses per day, and poor adherence may contribute to the poor control of many medical disorders.[36] Once-daily dosing provides a simplified dosing regimen that should improve adherence and ensure more persistent medication use.[37,38] Thus, the development of an effective treatment for COPD with a simplified treatment regimen (eg, infrequent dosing, simple delivery), rapid onset of action and durable effect should improve patient adherence.[39]

Conclusion

Consistent with international evidence-based treatment guidelines, the COPD patients included in the present analysis are appropriate candidates for regular maintenance treatment with one or more long-acting bronchodilators.[1,7] In view of its efficacy and the safety profile described in this report, once-daily indacaterol represents an appropriate treatment for patients with moderate-to-severe COPD.

Acknowledgments

The authors thank the patients and investigators involved in the studies contributing to the present analysis. They were assisted by Sarah Filcek (ACUMED), a professional medical writer funded by Novartis, and David Young (Novartis).

Disclosure

Eugene Bleecker has performed clinical trials (all negotiated through Wake Forest University Health Sciences) with Actelion, Aerovance, AstraZeneca, Boehringer Ingelheim, Centocor, Ception, Genentech, GlaxoSmithKline, MedImmune, Novartis, and Pfizer. He has served as a consultant with Aerovance, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Merck, and Pfizer. He has grant support from the following studies: Principal Investigator – R01 HL69167 – Genotype-Phenotype Interactions in Severe Asthma; Co-Principal Investigator – U10 HL74225 – Asthma Clinical Research Network (ACRN); Principal Investigator – U01 HL65889 – Pharmacogenetics of Asthma Treatment; Co-Principal Investigator – R01 HL087665 – Genome Wide Association for Asthma and Lung Function; Co-Principal Investigator – K12 HL089992 – Scholars' Program for Genetics and Genomics of Lung Disease; PrincipaI Investigator – R01091762 – SARP; Principal Investigator – HHSN268200900019C – Spiromics Clinical Center; Co-Principal Investigator – U10 HL098103 – Atlantic Coast Consortium for Asthma (ACC-A) AsthmaNet Clinical Site; Co-Principal Investigator – RC2 HL101487 – Linking Genetics, Genomics and Phenomics to Better Understand Asthma Severity; Co-Principal Investigator – R01 HL069116 – SARP Substudy, and Co-Investigator – RC2 HL101651 – The EVE Asthma Genetics Consortium: Building upon "GWAS."

Thomas Siler declares research support paid to Midwest Chest Consultants, PC, for clinical trials for: GSK, Sepracor/Sunovian, Daiichi-Sankyo, Novartis Pharmaceuticals, Forest Research Institute, Boehringer Ingelheim, Genentech, Arena Pharmaceuticals, AstraZeneca, and Schering Plough. He is on Speakers Bureaus for: GSK, Boehringer Ingelheim, AstraZeneca, and Pfizer.

Roger Owen and Benjamin Kramer are employees of Novartis, the manufacturers of indacaterol.

Statement of authorship

RO and BK made substantial contributions to the conception and design of the individual studies from which the data were pooled for this analysis. ERB and TS were involved in the acquisition of data. RO was responsible for analysis of data. All authors were involved in the concept and design of this article and the interpretation of the data, and had full access to the primary study data. All authors revised the article critically for important intellectual content and gave their final approval of the version to be published.

Note

ClinicalTrials.gov identifiers: NCT00463567, NCT00624286, and NCT00393458 (placebo data only).

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2010. Available from: http://www.goldcopd.com. Accessed March 17, 2011.
2. Centers for Disease Control and Prevention (CDC). Deaths from chronic obstructive pulmonary disease – United States, 2000–2005. *MMWR Morb Mortal Wkly Rep.* 2008;57:1229–1232.
3. Centers for Disease Control and Prevention (CDC). Summary health statistics for US adults: National Health Interview Survey, 2008. *Vital and Health Statistics* [serial on the Internet]. Series 10, Number 242. December 2009. Available from: http://www.cdc.gov/nchs/data/series/sr_10/sr10_242.pdf. Accessed May 12, 2010.
4. Thompson WH, St-Hilaire S. Prevalence of chronic obstructive pulmonary disease and tobacco use in veterans at Boise veterans affairs medical center. *Respir Care.* 2010;55:555–560.

5. Schneider KM, O'Donnell BE, Dean D. Prevalence of multiple chronic conditions in the United States' Medicare population. *Health Qual Life Outcomes.* 2009;7:82.
6. Barr RG, Celli BR, Mannino DM, et al. Comorbidities, patient knowledge, and disease management in a national sample of patients with COPD. *Am J Med.* 2009;122:348–355.
7. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004;23:932–946. Erratum in: *Eur Respir J*. 2006;27:242.
8. Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. *BMC Pulm Med.* 2010;10:11.
9. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily LABA, indacaterol, versus the twice-daily LABA, formoterol, in COPD. *Thorax.* 2010;65:473–479.
10. Donohue JF, Fogarty C, Lötvall J, et al; INHANCE Study Investigators. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care Med.* 2010;182:155–162.
11. Barnes PJ, Pocock SJ, Magnussen H, et al. Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. *Pulm Pharmacol Ther.* 2010;23:165–171.
12. Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J.* 2005;26:319–338.
13. Cazzola M, MacNee W, Martinez FJ, et al; American Thoracic Society; European Respiratory Society Task Force on outcomes of COPD. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J.* 2008;31:416–469.
14. Connolly CK. Diurnal rhythms in airway obstruction. *Br J Dis Chest.* 1979;73:357–366.
15. Dawkins KD, Muers MF. Diurnal variation in airflow obstruction in chronic bronchitis. *Thorax.* 1981;36:618–621.
16. Petty TL. Circadian variations in chronic asthma and chronic obstructive pulmonary disease. *Am J Med.* 1988;85:21–23.
17. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. *Thorax.* 2003;58:855–860.
18. Ramsdale EH, Morris MM, Hargreave FE. Interpretation of the variability of peak flow rates in chronic bronchitis. *Thorax.* 1986;41:771–776.
19. Meurs H, Postma DS, Koëter GH, et al. The beta-adrenergic system of non-allergic patients with chronic airflow obstruction and early morning dyspnoea. *Ann Allergy.* 1987;59:417–421.
20. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. *Curr Med Res Opin.* 2009;25:2043–2048.
21. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J.* 2002;19:217–224.
22. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax.* 2003;58:399–404. Erratum in: *Thorax*. 2005;60:105.
23. Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. *Eur Respir J.* 2006;27:547–555. Erratum in: *Eur Respir J.* 2006;27:1076.
24. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest.* 2002;122:47–55.
25. Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. *Pulm Pharmacol Ther.* 2005;18:397–404.
26. Kornmann O, Dahl R, Centanni S, et al; for INLIGHT-2 (Indacaterol Efficacy Evaluation Using 150-µg Doses with COPD Patients) study investigators. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J.* 2011;37:273–279.
27. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B. Long-term safety and efficacy of indacaterol, a novel long-acting β_2-agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest.* 2011;140:68–75.
28. Tsagaraki V, Amfilochiou A, Markantonis SL. Evidence of tachyphylaxis associated with salmeterol treatment of chronic obstructive pulmonary disease patients. *Int J Clin Pract.* 2006;60:415–421.
29. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J.* 2003;22:912–919. Erratum in: *Eur Respir J*. 2004;24:1075.
30. Partridge MR, Miravitlles M, Ståhl E, Karlsson N, Svensson K, Welte T. Development and validation of the Capacity of Daily Living during the Morning questionnaire and the Global Chest Symptoms Questionnaire in COPD. *Eur Respir J.* 2010;36:96–104.
31. Buhl R, Dunn LJ, Disdier C, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Eur Respir J.* 2011. Epub ahead of print. doi: http://dx.doi.org/10.1183/09031936.00191810
32. Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C; for the INSIST study group. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. *Respir Med.* 2011;105:719–726.
33. Rand CS, Nides M, Cowles MK, Wise RA, Connett J. Long-term metered-dose inhaler adherence in a clinical trial. The Lung Health Study Research Group. *Am J Respir Crit Care Med.* 1995;152:580–588.
34. James PN, Anderson JB, Prior JG, White JP, Henry JA, Cochrane GM. Patterns of drug taking in patients with chronic airflow obstruction. *Postgrad Med J.* 1985;61:7–10.
35. Corden ZM, Bosley CM, Rees PJ, Cochrane GM. Home nebulized therapy for patients with COPD: patient compliance with treatment and its relation to quality of life. *Chest.* 1997;112:1278–1282.
36. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296–1310.
37. Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers JW, Herings RM. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. *Respir Med.* 2007;101:1398–1405.
38. Tamura G, Ohta K. Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch. *Respir Med.* 2007;101:1895–1902.
39. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax.* 2008;63:831–838.

International Journal of COPD Dovepress

Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols.

This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/international-journal-of-copd-journal