NOVARTIS

Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease

(NDA 22-383)

Briefing Document

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List of abbreviations

AC	adjudication committee
AE	adverse event
APTC	Anti-Platelets Trialist Collaboration
AUC	area under the curve
BDI	baseline dyspnea index
b.i.d.	bis in diem (twice a day)
CI	confidence interval
CCV	cardio- and cerebrovascular
COPD	chronic obstructive pulmonary disease
EU	European Union
DMC	Data Monitoring Committee
DPI	dry powder inhaler
EDxx	dose to achieve xx% of the maximum effect
FAS	full analysis set
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCP	health care provider
IC	inspiratory capacity
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
Ind	indacaterol (QAB149)
ITT	intent to treat
LABA	long-acting β_2-adrenergic receptor agonist
LFT	liver function test
LLN	lower limit of normal
LOCF	last observation carried forward
LSM	least squares means
MACE	Major Cardiovascular Events
MCID	minimal clinically important difference
mITT	modified intent-to-treat
MG	medication guide
NDA	new drug application
NOAEL	no-observed-adverse effect level
o.d.	omnia die (once a day)
PASS	post-authorization safety study
Pbo	placebo
PD	Pharmacodynamic(s)
pMDI	pressurized metered dose inhaler
PSP	patient support program

q.o.d.	quaque altera die (once every other day)
REMS	Risk Evaluation and Mitigation Strategy
SABA	short-acting β_2-agonist
SAE	serious adverse event
SDDPI	single-dose dry powder inhaler
SE	standard error
SGRQ	St George's Respiratory Questionnaire
Sme	salmeterol
SMQ	standard MedDRA queries
SOC	System organ class
SR	spontaneous report
SRMP	Safety risk management plan
TDI	Transition Dyspnea Index
TORCH	Towards a Revolution in COPD Health
ULN	upper limit of normal

1 Executive summary

1.1 Introduction

Indacaterol maleate (R-enantiomer), QAB149 (proposed tradename Arcapta™ Neohaler™), referred to throughout this document as indacaterol (abbreviated to 'Ind' in data tables where necessary), is a novel inhaled long-acting β_2-adrenergic agonist (LABA). Indacaterol is delivered using a single-dose dry powder inhaler (Concept1) which has low air flow resistance, making it particularly suitable for patients with limited inspiratory capacity, such as COPD patients.

The proposed indication for indacaterol is long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

COPD is a major global health problem which has a profound impact on patients, healthcare systems and society at large, and is predicted to increase in prevalence. There is a need for new, more effective, and more convenient therapies.

Bronchodilators, including LABAs, are central to the treatment of COPD. They reduce airflow limitation, improve emptying of the lungs, tend to reduce hyperinflation, and improve exercise performance, as well as relieving distressing symptoms such as breathlessness (dyspnea).

Indacaterol provides a fast onset of action and sustained 24-hour bronchodilation with once-daily dosing. It is a safe and well-tolerated new treatment option for patients with COPD. The minimum effective dose of indacaterol is 75 µg once daily, and this dose provides clinically meaningful improvements in lung function. The 150 µg dose provides additional bronchodilation from the first dose onwards with better symptom control, particularly with respect to dyspnea. The 150 µg dose has also been shown to be at least as effective as tiotropium and salmeterol.

1.2 Regulatory history

First worldwide approval for indacaterol was granted by the European Commission in November 2009 for the indication of maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). Since then additional regulatory approvals have been granted by Health Authorities worldwide. Currently indacaterol is approved in more than 50 countries at doses of both 150 µg and 300 µg once-daily.

Following the submission of a New Drug Application (NDA) in December 2008, FDA issued a Complete Response letter in October 2009 and requested additional information on the dose and dose regimen of indacaterol. Specifically, the Agency requested further characterization of the lower part of the dose response curve, i.e. doses of indacaterol lower than 150 µg, and evaluation of dose regimens other than once-daily, i.e. less than and more than once-daily, in a bronchoreactive population as FDA considered such a population to be more sensitive to the bronchodilatory effects of β_2-adrenergic agonists than the target population of COPD patients. In addition, FDA commented in their letter on higher frequencies of cardiovascular and

cerebrovascular (CCV) serious adverse events (SAE) observed in a 1-year study, Study B2334, at doses of 300 and 600 µg once-daily compared to placebo and to formoterol in patients with COPD, and possible asthma-related deaths compared to salmeterol in patients with asthma.

In the response to FDA, Novartis submitted in September 2010 the results of new clinical studies performed in patients with asthma to address the FDA's specific requests with respect to dose-ranging and dose regimen, together with results of replicate pivotal studies of indacaterol 75 µg o.d. plus data from other studies that were completed since the NDA had been submitted. The additional safety data and analyses demonstrate that there is no evidence for a significantly increased risk of CCV events under treatment with indacaterol compared to placebo and other marketed bronchodilators or for an increase in the frequency of CCV adverse events with time. Events causing long term disability or end organ damage (i.e. APTC and MACE events) are balanced between indacaterol and comparators, including placebo.

In December 2010, FDA requested Novartis to conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control. To meet this request, Novartis implemented an adjudication committee (AC) to provide an independent, external, systematic, standardized and unbiased assessment of all SAEs occurring during the development of indacaterol (COPD and asthma). An Addendum detailing the methodology and the results of this safety analysis will be provided to this Briefing Document.

1.3 Clinical development program and efficacy

Dose selection is based on the results of three dose-ranging studies:

- Study B2335S, a 26-week adaptive seamless design study in patients with COPD where Stage 1 was the 2-week dose-ranging phase of the study
- Study B2357, a 2-week dose-ranging study in patients with asthma, a more bronchoreactive population, as requested by FDA in the Complete Response letter
- Study B2356, a 2-week dose-ranging study in patients with COPD to further explore the lower part of the dose-response relationship.

One additional study, B2223, a 2-week dose regimen study in patients with asthma, was conducted to study various dosing frequencies to support the proposed once daily dosing of indacaterol.

When considered together, the results of Studies B2357, B2223, B2356, and B2335S indicate that indacaterol provides bronchodilation with increasing efficacy in a dose-range of 75 µg to 300 µg. The 75 µg dose, administered once-daily, provides a minimum clinically relevant level of bronchodilation in patients with COPD. In response to the FDA request to explore lower doses, Novartis proposes indacaterol doses of 75 and 150 µg once-daily for approval in the United States. Doses of indacaterol of 18.75 µg o.d. and 37.5 µg o.d. were sub-optimal because they demonstrated a less robust bronchodilator response across the different dose-ranging studies. Dosing twice daily was demonstrated to be less effective than once daily dosing, and the bronchodilator activity of indacaterol was shown to have a duration of at least 24 hours irrespective of dose.

The key confirmatory efficacy studies include 6 placebo-controlled, parallel-group, randomized studies (B2354, B2355, B2335S (plus its extension B2335SE), B2336, B2346 and B2334) assessing the efficacy and safety of indacaterol in a range of doses from 75 µg to 600 µg once daily with treatment periods of 12 weeks (B2354, B2355, B2346), 26 weeks (B2335S, B2336) or 52 weeks (B2335SE, B2334). Several studies included an approved and marketed bronchodilator as active comparator: formoterol (B2334), salmeterol (B2336), or tiotropium (B2335S).

These pivotal studies were identical in terms of key design features: the study population was defined with the same key inclusion and exclusion criteria, and the same primary endpoint and generally the same secondary endpoints were evaluated. The primary endpoint for these studies was the 24-hour trough FEV_1 at Week 12. Trough FEV_1 was defined in these studies as the mean of the 23 h 10 min and 23 h 45 min post-dose values. A Least Square (LS) mean treatment - placebo difference of 0.12 L was considered to be the minimal clinically important difference (MCID) for trough FEV_1.

Across these confirmatory studies, patients treated with either the 75 or 150 µg doses of indacaterol met the MCID versus placebo of 0.12 L. Treatment with the 150 µg dose resulted in generally greater improvements in trough FEV_1 than the 75 µg dose. Trough FEV_1 improvements achieved with the 150 µg dose also exceeded the improvement observed in the active control treatment arms (0.05 L versus tiotropium 18 µg o.d. in B2335S and 0.06 L versus salmeterol 50 µg b.i.d. in B2336).

The relief of dyspnea was measured using the transition dyspnea index (TDI). Only the 150 µg dose of indacaterol showed a consistently statistically significant effect across studies that approached or exceeded the MCID of more than 1 unit versus placebo.

The effect on health status was measured using the St George's Respiratory Questionnaire (SGRQ). The 150 µg dose of indacaterol showed a statistically significant benefit across studies that exceeded the MCID of an improvement of ≥ 4 units versus placebo in two of the three studies with this dose, whereas the 75 µg dose of indacaterol, although showing a statistically significant difference to placebo, did not achieve the MCID in both pivotal studies that were performed with this dose (B2354, B2355).

The improvements in 24 hour trough FEV_1, dyspnea, and health status with the 150 µg dose of indacaterol also exceeded the improvements observed in the active control treatment arms of the studies. The pivotal studies evaluating the 75 µg dose did not have an active control.

The rescue medication use was similar across studies for the 75 and 150 µg doses except in Study B2355; the percentage of days of no rescue medication use appeared to show a dose response. For percentage of days able to perform usual activities, the 75 and 150 µg doses appeared to be comparable in effect.

Approval for the 300 µg dose of indacaterol is not being sought in the United States, although this dose is approved and marketed in the EU and other countries worldwide. In the key confirmatory studies, 300 µg indacaterol showed incremental benefits over the 150 µg dose across a range of endpoints, particularly a more pronounced and consistent improvement of breathlessness than the 150 µg dose, and a greater reduction of rescue medication use and higher percentage of days able to perform usual activities.

Additional information on efficacy is provided by an integrated study level analysis of summary level data from over 8000 patients across 12 studies, with 10 different indacaterol dose levels ranging from 18.75 to 600 μg, and by an integrated patient level analysis of data from two studies with a total of 1835 patients with 6 different dose levels (18.75 to 600 μg). These analyses also suggest that 75 μg is the minimum effective dose of indacaterol, that higher doses provide greater bronchodilation, and that indacaterol 150 μg o.d. or higher provides a more consistent bronchodilatory effect that is largely independent of baseline FEV_1, and in consequence may provide additional benefit in patients with more severe disease.

1.4 Safety

The clinical development program for indacaterol includes a large number of studies at a range of doses. The clinical safety database includes doses up to four times the highest dose submitted for approval in the US and treatment durations up to 12 months. Together with the substantial post-marketing experience in other countries, the available safety data provide sufficient and convincing evidence to support the safety of indacaterol at the doses recommended for use.

In total, over 15,000 subjects (healthy volunteers and patients) were included in the clinical development program. Of these, 9243 patients were treated with indacaterol, with 4764 patients treated for at least 12 weeks at doses between 75 and 600 μg. Overall exposure to indacaterol was 2470.3 patient years. The key indacaterol COPD studies range from 12 weeks to 52 weeks in duration, with the 75 μg dose evaluated in two studies of 12 weeks in duration. Long term (1-year) safety was evaluated with 150, 300 and 600 μg indacaterol. The systematic evaluation of indacaterol safety is based on three pooled populations, including patients with exposure up to 3 months (3-month COPD safety population), up to 12 months (12-month COPD safety population) and from all COPD studies with a duration of 12 weeks or more (COPD safety population).

Adverse events (AEs) observed in the registration program were as expected, for the disease indication (COPD) and the β_2-agonist drug class. There appeared to be no notable differences between the AE profile of indacaterol o.d. and other LABAs given b.i.d. The most common AEs reported with both the 75 and 150 μg doses of indacaterol were COPD (worsening or COPD exacerbations), nasopharyngitis, cough, and headache. Incidences for these events in the 3-month COPD population ranged from 2% to 12% in the 75, 150, 300 or 600 μg indacaterol treatment groups versus 2% to 13% on placebo. There was no dose dependency noted for AEs in the indacaterol groups regardless of safety dataset analyzed.

The majority of AEs were mild or moderate in severity. In the 3-month COPD safety population, only 2-5% of patients in any treatment group had severe AEs. The highest incidence of severe AEs occurred in the placebo group.

The overall frequency of SAEs in the 3-month COPD safety population was similar across all indacaterol treatment groups (3.1% to 3.8%) and was lower than placebo (4.4%). There was no dose-response relationship between the indacaterol doses and SAEs, with the most frequent SAEs being COPD (including disease progression and exacerbations) and pneumonia. No relationship between indacaterol dose and SAEs was seen for the 12 month COPD safety population with the 150 and 300 μg treatment groups.

Overall, deaths were rare in the indacaterol clinical studies, and no risk associated with indacaterol use was seen in these data. Exposure adjusted death rates were lower for all indacaterol groups (75 µg: none, 150 µg: 0.005, 300 µg: 0.003, 600 µg: 0.003 deaths per patient-year) than for formoterol (0.01 deaths per patient-year), tiotropium (0.011 deaths per patient-year), and placebo (0.015 deaths per patient-year) and similar to the rate for salmeterol (0.004 deaths per patient-year).

The overall rates of discontinuation due to AEs in the 3-month COPD safety population were lower than for placebo for all indacaterol treatment groups with no dose response apparent for the indacaterol treatment groups (4.0%-4.5% on indacaterol 75, 150, or 300 µg treatment groups versus 5.1% on placebo). A similar pattern was seen in the 12 month COPD safety population with the 150 and 300 µg treatment groups.

Indacaterol had no clinically relevant effect on laboratory or ECG values, or on vital signs measures compared to placebo. It has a low potential for drug-drug interactions with other COPD and cardiovascular medications.

Although an imbalance between treatment groups in CCV events was noted in Study B2334, the totality of data from the COPD safety population does not indicate an increase in cardiovascular or cerebrovascular events, including the endpoints of myocardial infarction, stroke and vascular death. All-cause death rates in the COPD safety population were lower for all indacaterol doses than for placebo, further supporting the absence of any significant adverse cardiovascular effect.

Post-marketing data from countries where indacaterol (at doses of 150 and 300 µg) is approved for the treatment of COPD do not reveal any new safety concerns and have not led to any regulatory or manufacturer actions being taken for safety reasons.

1.5 Benefit-risk

COPD is a major public health problem associated with high levels of mortality, chronic morbidity, impact on quality of life and healthcare costs, and the prevalence of COPD is forecasted to increase. There is a need for more effective treatments with a convenient dosing regimen (e.g., once-daily) that achieve their therapeutic effect rapidly and have robust, sustained effects on lung function and symptoms (particularly dyspnea).

Optimizing bronchodilation is essential to the management of COPD. Indacaterol, administered once daily at doses of 75 and 150 µg, provides clinically relevant bronchodilation in COPD with a rapid onset of effect and sustained 24-hour bronchodilator efficacy. While the 75 µg doses of indacaterol provides a minimum effective bronchodilation, only the higher dose of 150 µg achieves its optimal effect from the first dose. Improvements in a range of symptomatic endpoints, particularly dyspnea (BDI/TDI) and SGRQ were also more robust with the 150 µg dose. In addition, 150 µg indacaterol provided gains in health-related quality of life of COPD patients that were as good as or better than those from currently available bronchodilators. Thus, the aggregate data from the extensive clinical development program of indacaterol suggest that the 75 µg dose is clinically effective in terms of bronchodilation whereas the 150 µg dose offers additional benefits to patients.

Overall, the safety profile of once-daily indacaterol (at doses up to 600 µg) is similar to that of other LABAs. Adverse events, laboratory results, vital signs and ECG data suggest a safety

profile that is comparable to approved LABAs and often is similar to placebo. This is consistent with the inhaled route of administration resulting in low systemic exposure to β_2-agonist stimulation and reduced potential for systemic adverse effects.

In conclusion, indacaterol at doses of 75 and 150 µg once daily shows a magnitude and consistency of efficacy that is sufficient to support approval as a long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD. The safety and tolerability profile of indacaterol has been thoroughly characterized, and suggests that the compound has a wide and reassuring therapeutic margin. Post-marketing experience in countries where indacaterol has been approved also contributes to support the positive benefit-risk assessment of indacaterol. This novel bronchodilator has the potential to contribute significantly to the treatment armamentarium available for patients with COPD, given the sustained 24-hour efficacy on once-daily dosing.

2 Introduction and regulatory history

2.1 COPD: Burden of disease and unmet need

Chronic obstructive pulmonary disease (COPD) is a progressive disease in which pathological changes in the lung, a combination, varying between individual patients, of obstructive bronchiolitis and parenchymal destruction (emphysema), are associated with air flow limitation that is not fully reversible. COPD primarily occurs following exposure to tobacco smoke, but exposure to some chemicals and dusts also increases the risk of COPD. The diagnosis of COPD is considered in patients over 40 years of age who present with dyspnea, chronic cough or sputum production, and/or history of exposure to risk factors (GOLD 2009).

COPD is a major public health problem, and is currently the leading cause of chronic morbidity and mortality in the USA. In 2006, there were an estimated 12-24 million people in the USA with COPD, with approximately 2 million emergency room visits and 661,000 hospitalizations (CDC 2010). In 2005, there were 120,970 deaths due to COPD (American Lung Association 2010).

COPD has a considerable impact on patients. Symptoms such as breathlessness, cough, wheezing, chest tightness, sputum production and fatigue are associated with activity limitation which may lead to a loss of independence and to anxiety and depression. COPD is also associated with a major economic burden, in terms of the direct costs to healthcare systems and indirect costs due to disability, economic inactivity and costs to family and caregivers. In the USA, in 2002, it was estimated that the direct costs of COPD were $18 billion, with indirect costs of $14.1 billion (GOLD 2009).

The aims of maintenance treatment in COPD, as described in current treatment guidelines (GOLD 2009), are to prevent and control symptoms, to reduce the frequency and severity of exacerbations, to improve health status, and to improve exercise tolerance. Bronchodilators, which reduce airflow limitation, are central to the relief of symptoms in COPD, and improve exercise tolerance. Regular use of a long-acting bronchodilator can reduce the rate of exacerbations, which, although not prospectively demonstrated, could potentially reduce the risk of mortality (GOLD 2009). Indeed, optimizing bronchodilation is essential to the overall management of COPD.

Inhaled β_2-agonists are widely used as bronchodilators in the treatment of COPD. Long-acting inhaled β_2-agonists (LABAs) such as formoterol and salmeterol have been available to patients for over 10 years, and are recommended to be used twice daily (b.i.d.) for regular maintenance treatment in COPD. They are often used in combination with other classes of medication, such as anticholinergic bronchodilators (for example tiotropium) or inhaled corticosteroids (ICS) and their use is regarded as the cornerstone of modern COPD management. These inhaled medications are used to enhance long-term control of COPD symptoms (GOLD 2009).

Following a review of the safety of LABAs that revealed an increased risk of severe exacerbation of asthma symptoms in patients with asthma, the FDA recently issued recommendations restricting the use of LABAs in the treatment of asthma. No recommendation was made for a change in use of LABAs in COPD (FDA 2010), and there is

some evidence to suggest that these risks do not apply in COPD. In a 3 year study in approximately 6000 patients with COPD (TORCH trial, Calverley et al 2007), the proportion of deaths with salmeterol monotherapy did not differ from that of salmeterol/fluticasone, and was lower than that of placebo. Although the study did not meet the primary efficacy endpoint (reduction in any-cause mortality versus placebo meeting a predefined level of statistical significance), the data suggest that the risk of death in the salmeterol group did not differ from that in the placebo group and that risk of death in the combination therapy group did not differ from the salmeterol alone group. This helps to underscore the safety of LABA monotherapy over 3 years in COPD patients. In addition, a meta-analysis of randomized trials comparing LABAs with placebo or anticholinergics in COPD patients did not confirm an increased risk of respiratory deaths with LABAs (Rodrigo et al 2008).

In view of the increasing prevalence of COPD and the negative impact of the disease on patients, healthcare systems and society at large, there is a pressing need for new, more effective, and more convenient therapies. In addition to new treatments, which should offer better efficacy with respect to improvements in lung function and symptom relief, it has been noted that an important step in simplifying COPD management and improving compliance with prescribed therapy would be to reduce the dose frequency, making treatment more convenient for patients (Bourbeau and Bartlett 2008). Currently, once-daily bronchodilator treatments in the United States are limited to a single therapy, the anti-muscarinic tiotropium. Thus, a once-daily inhaled LABA with improved efficacy is considered a significant advance in the treatment of COPD (Cazzola and Matera 2008).

Indacaterol provides once-daily dosing, fast onset of action and sustained efficacy assuring optimal bronchodilation throughout 24 hours. Its efficacy has been shown to be maintained for up to 1 year with no evidence of tolerance or tachyphylaxis to the bronchodilator effect, unlike the current LABAs on the market, e.g., salmeterol and formoterol. Indacaterol also has a wide therapeutic margin, with doses up to 600 µg o.d. being safe and well-tolerated in 1-year studies. It has demonstrated efficacy similar to or better than that of current standard bronchodilators, and potentially has an improved therapeutic index compared with b.i.d. LABAs such as salmeterol (Boyd 1997, Jones and Bosh 1997). Thus, it offers a new profile that differs from other LABAs and anticholinergics that are indicated for the treatment of COPD.

2.2 Regulatory history

In December 2008, Novartis submitted marketing applications for indacaterol at doses of 150 and 300 µg in the European Union (EU) and the United States and subsequently in many other countries worldwide.

In the EU, marketing authorization was granted in November 2009 for 150 and 300 µg doses of indacaterol (under the tradename Onbrez® Breezhaler®), for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). The EU approval covers 27 countries plus Norway, Liechtenstein, and Iceland.

Further approvals have been obtained in a number of other countries (including Switzerland, Australia, India, Korea, Brazil, and Russia). In total, indacaterol is approved in more than 50 countries.

In the United States, the New Drug Application to the Food and Drug Administration (FDA) sought approval for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. In October 2009, Novartis received a Complete Response letter in which FDA requested additional information on the dose and dose regimen.

This request was based on FDA's review of data from the adaptive seamless design Study B2335S which combined a Phase II dose-ranging study (Stage 1) and a Phase III pivotal study (Stage 2) seamlessly into a single protocol. In Stage 1, lung function improvements with doses of 75, 150, 300 and 600 µg indacaterol administered once daily were compared with placebo and active comparators after 2 weeks of treatment (dose-ranging Stage 1 of the study). Based on pre-defined dose selection criteria, the 150 and 300 µg once-daily doses were selected by an independent Data Monitoring Committee to continue into Stage 2 of the study. However, due to the seamless design of the study, patients in Stage 1 continued until all patients had been treated for at least 2 weeks and the interim analysis had been completed, which resulted in some patients being treated beyond 2 weeks. FDA had requested trough FEV_1 data at specific time points beyond 2 weeks, including data from patients who were originally randomized for treatment with the discontinued doses (75 µg, 600 µg and formoterol). On review of the data out to 12 weeks treatment for both Stage 1 and Stage 2 patients combined, it appeared that the dose response was less pronounced than for Stage 1 patients alone, with trough FEV_1 at 12 weeks for the 75 µg dose appearing to be similar to some higher doses. It should be noted that there were only 66 patients on the 75 µg dose at 12 weeks, and that this time point (12 weeks) was not a pre-defined endpoint for Stage 1.

In the Complete Response letter, FDA also noted that there were higher frequencies of cardiovascular and cerebrovascular (CCV) serious adverse events (SAE) compared to placebo and to formoterol in patients with COPD. This comment was based on data from Study B2334, a 1-year, placebo-controlled study of indacaterol 300 µg o.d. and 600 µg o.d., and formoterol 12 µg b.i.d.

Novartis discussed with FDA steps to address the questions raised in the Complete Response letter. FDA requested that Novartis assess the dose and dose regimen (including doses lower than 150 µg and dosing intervals both less than and greater than once daily) in a bronchoreactive population, such as patients with asthma, to further characterize the lower part of the dose response curve and to support the dose and dose regimen in patients with COPD.

Studies B2357 (dose-ranging) and B2223 (dose regimen) in asthma patients were subsequently conducted to address these FDA requests. Novartis also conducted Study B2356 (a dose-ranging study to further explore the dose response at lower doses in COPD patients) and two pivotal, placebo-controlled efficacy and safety studies with 75 µg once daily in patients with COPD (B2354 and B2355). Details of these studies are found in Section 5.

In addition, Novartis submitted other new data, including results from two studies (Study B2335SE and Study B2336) which were not part of the original NDA, to provide additional safety data which demonstrate that there is no evidence for an association between indacaterol treatment and CCV event rates higher than those from comparators or for an increase in the frequency of CCV events with time. The data also show that events causing long term

disability/end organ damage (APTC events and - analyzed subsequently - MACE events) are balanced between indacaterol and comparators, including placebo (Section 6.5.1).

The results of the above studies, as well as previously and recently completed studies, support the proposal of the 75 and 150 µg once daily doses for registration in COPD.

To address the risk of possible asthma-related deaths with LABAs, FDA also requested a Risk Evaluation and Mitigation Strategy (REMS) to communicate the risks of indacaterol. The proposed REMS includes a Medication Guide to communicate the risks and appropriate use of indacaterol to healthcare providers and patients. In addition, per company policy, a Global Safety Risk Management Plan was submitted with the original NDA that includes a pharmacovigilance plan for individual identified or potential safety risks and a risk minimization action plan regarding the potential risk of an off-label use in asthma, i.e. a Post-Authorization Study and Risk Minimization Action Plan (Section 7). The Post-Authorization Study is currently ongoing in the United Kingdom.

3 Product description

Indacaterol inhalation powder hard capsules contain indacaterol maleate: (IUPAC name, (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate) as the active pharmaceutical ingredient.

Indacaterol has been developed with dosage strengths of 75 and 150 µg as inhalation powder hard capsules for inhalation using the Concept1 inhalation device (Figure 3-1).

Figure 3-1 Concept1 inhaler and indacaterol inhalation capsules

The active component indacaterol maleate is a micronized drug substance in the particle size range of 1 to 5 µm for optimal delivery to the lungs.

Indacaterol inhalation powder hard capsules contain lactose monohydrate and gelatin as excipients. Both are well accepted and widely used in pharmaceutical formulations.

The inhalation capsules are stored in aluminum blisters as moisture occlusive primary pack. Stability data confirmed that the packaging material is adequately protective and compatible with the indacaterol inhalation powder hard capsules.

The dry powder inhaler (DPI) referred to as ‘Concept1’ during development was consistently used throughout the clinical Phase 3 program of indacaterol.

The Concept1 device is a redesign of the Novartis Aerolizer® device, a capsule-based dry powder inhaler used for the marketed product Foradil® 12 µg inhalation powder hard capsules.

The low air flow resistance (0.07 cm $H_2O^{½}$/L/min) of the Concept1 inhaler device facilitates high inspiratory airflow rates. A study with 26 patients with mild to very severe COPD demonstrated that all of them were able to build up high peak inspiratory flow rates of approximately 50 L/min at minimum. *In vitro* testing demonstrated consistent dose delivery at flow rates of 50 L/min and above (investigated range: 50 – 100 L/min).

The Concept1 exhibits a number of other advantageous inhaler characteristics, including feedback on correct use: the capsule makes a whirring sound in the inhalation chamber in response to an adequate inspiratory effort; patients can taste lactose following successful inhalation; the capsules are transparent, so that patients can check visually that the indacaterol powder has been delivered from the capsule.

4 Pharmacology and toxicology

4.1 Non-clinical Pharmacology

Indacaterol is a potent β_2 adrenoceptor agonist (EC_{50} value of 8.7 nM) with high intrinsic efficacy demonstrated in various *in vitro* assays, including the recombinant human β_2 adrenoceptor (Battram et al 2006), the isolated guinea pig trachea (Battram et al 2006), isolated human bronchus (Naline et al 2007) and human lung slices (Sturton et al 2008). Similarly, high intrinsic activity has been reported *in vivo* in the guinea pig and the rhesus monkey (Battram et al 2006). At the recombinant human adrenoceptor expressed in Chinese hamster ovarian cells, indacaterol is a partial and full agonist at the β_1 and β_2 adrenoceptor, respectively. The functional selectivity profile of indacaterol over β_1 human adrenoceptors was similar to that of formoterol, whereas its β_3 adrenoceptor selectivity profile was similar to that of formoterol and albuterol (Battram et al 2006). A fast onset of action, similar to albuterol and formoterol, was demonstrated for indacaterol in the isolated guinea pig trachea (Battram et al 2006), human bronchus (Naline et al 2007) and human lung slices (Sturton et al 2008). The potential for once daily dosing was demonstrated in *in vitro* models by a longer duration of action when compared to salmeterol and formoterol in the electrical field-induced contraction of the isolated guinea pig trachea (Battram et al 2006) and human bronchus (Naline et al 2007). Similarly, a longer duration of action than formoterol and salmeterol was demonstrated in isolated human lung slices contracted with carbachol (Sturton et al 2008). *In vivo* studies have shown a 24-hour duration of action against serotonin-induced bronchoconstriction in the guinea pig (Battram et al 2006). In the Rhesus monkey, for an equivalent degree of bronchoprotection, indacaterol had a better cardiovascular safety profile compared to albuterol, salmeterol and formoterol (Battram et al 2006).

4.2 Toxicology

An extensive preclinical safety program has been completed for indacaterol in a number of species. Inhalation toxicity studies with indacaterol in dogs show the typical alterations expected for inhaled β_2-agonists where high systemic exposure has been achieved (e.g. increase of heart rate at most doses, heart lesions at higher doses and and/or glycogen

mediated periportal hepatocellular vacuolation). These changes are in-line with the known exaggerated pharmacological responses to β-adrenoceptor agonists as a result of systemic activity and are not a result of direct toxicity. β_2-receptor mediated vasodilation and associated hypotension is known to result in a reflex tachycardia, which when excessive causes ischemic damage in the heart. A dose-dependent increased heart rate was seen in all treated groups (doses ≥ 0.01 mg/kg/day) during a 2-week inhalation toxicity study in dogs and at doses ≥ 0.10 mg/kg/day in a 4-week study and at 0.31 mg/kg/day in a 39-week study. Excessive heart rate increases, accompanied by subsequent heart lesions were observed in dogs treated with doses ≥ 0.47 mg/kg/day in the 2-week study and 0.97 mg/kg/day (highest dose) in the 4-week study.

Histopathology changes observed in the nasal cavity or larynx during the rodent inhalation toxicity studies were considered to be associated with mild irritation due to the high amount of drug substance inhaled. The innate sensitivity of rodents to the pathologic effects of inhaled compounds is a well-recognized phenomenon and is probably related to differences in airflow dynamics as well as regional epithelial sensitivity in comparison with non-rodents and humans. Rats are obligate nose breathers with a highly convoluted upper airway tract that tends to trap and concentrate inhaled materials and they are more susceptible to nasal cavity changes associated with inhaled mild irritants than humans who can readily switch between nose and mouth breathing. Laryngeal lesions are also frequently observed during rodent inhalation toxicity studies and can be produced with a wide range of chemical substances. The well-differentiated character of the alterations, the reversibility and lack of progression over time indicates that this response is adaptive without significant human risk.

Embryo-fetal development studies by subcutaneous administration in rats and rabbits showed no evidence of teratogenicity. In rabbits, there were limited fetal effects at 3 mg/kg/day, namely an increased incidence of one skeletal variation. No effects of indacaterol were observed during a fertility and early embryonic development study or a pre- and postnatal development study in rats by subcutaneous administration.

In vitro and *in vivo* genotoxicity studies did not indicate any evidence of a genotoxic potential of indacaterol. In a 26-week oral carcinogenicity study in CB6F1/TgrasH2 hemizygous mice, indacaterol was not carcinogenic at doses up to 600 mg/kg/day. There were no neoplastic findings associated with indacaterol treatment during a 104-week rat carcinogenicity study that were considered relevant for humans during therapeutic use. Increased incidences of ovarian leiomyoma and focal hyperplasia of the ovarian smooth muscle in females were observed at the highest dose of the rat carcinogenicity study. These findings are consistent with the known response of rodents to treatment with high doses of β-agonists and are considered a consequence of an exaggerated pharmacodynamic effect. An apparent statistically increased incidence of pituitary adenoma was also noted among animals treated at the highest dose in this study when compared with one of the two concurrent control groups. The incidences of pituitary tumors in indacaterol-treated animals were within spontaneous incidences observed in historical data for the same strain of rat. A similar finding observed in rats following treatment with salmeterol hydroxynapthoate was considered to be indirectly attributable to expected pharmacologically-related increases in body weight and/or food consumption as these are also known to be associated with higher incidences of pituitary tumors in rats (Owen et al 2010). Murine progressive cardiomyopathy is a rodent specific effect that increases in incidence and severity with age. An increased incidence but not

severity of this change among high dose females in comparison with controls during the rat carcinogenicity study is most likely associated with the exaggerated pharmacological effects of indacaterol on the rodent vascular system.

Clear safety margins were demonstrated based on systemic exposure to indacaterol in rats and dogs at the no-observed-adverse effect levels (NOAEL) compared with humans at therapeutic doses (Table 4-1). Based on the papillary lesions in the heart, the dog is considered to be the most sensitive toxicology species. A NOAEL in the dog was demonstrated in the 39-week chronic toxicity study that was devoid of any heart lesions at the highest dose tested (0.31 mg/kg/day), which corresponds to systemic exposures based on steady state mean AUC(0-24h) of approximately 46 or 23- fold higher than those observed in humans at doses of 75 or 150 µg, respectively.

Table 4-1 Indacaterol exposure multiples in toxicity studies

					Exposure multiples [a/aa]			
					Based on AUC(0-24h)		Based on Cmax	
Species/ Study number	NOAEL (mg/kg)	Sex	AUC(0-24h)[+] (ng·h/mL)	Cmax[+] (ng/mL)	75 µg[aa]	150 µg[a]	75 µg[aa]	150 µg[a]
26-week rat [0220064]	1.02	male	37.20	12.20	19	10	56	28
		female	39.90	12.70	21	10	58	29
39-week dog [0220065]	0.31	male	90.1	9.79	46	23	45	22
		female	87.2	9.24	45	22	42	21
Rat embryo-fetal development [0270037]	1[#]	female	345	26.1	178	89	119	60
Rabbit embryo-fetal development [0270038]	1[#]	female	795	168	410	205	766	383
Mouse carcinogenicity [0470002]	600	male	399	47.7	206	103	218	109
		female	862	71.0	444	222	324	162
Rat carcinogenicity [0320002]	2.09	male	114[$]	38.2[$]	59	29	174	87
	0.62	female	55.6[$]	31.4[$]	29	14	143	72

[a] based on 150 µg, multiple dose (Study B2339), Cmax = 0.4386 ng/mL, AUC(0-24h) = 3.882 ng·h/mL;
[aa] exposure values at 75 µg based on 50% of values obtained at 150 µg, multiple dose (Study B2339), Cmax = 0.2193 ng/mL, AUC(0-24h) = 1.941 ng·h/mL. ;
NOAEL = No-Observed-Adverse-Effect-Level; [+] Values at the end of the stated treatment-period; [$] week 52; [#] NOAEL for effects on the embryo-fetus

4.3 Pharmacokinetics and pharmacodynamics

4.3.1 Summary

From a pharmacokinetic point of view, indacaterol represents a typical inhaled drug product with low systemic concentrations reached early after inhalation and a lack of clinically relevant drug-interaction potential. In general, dose-proportionality of key pharmacokinetic parameters is given at least over a range of doubling doses. Biliary clearance appears to be the major contributor to elimination of drug-related material. The impact of age, gender and race on the pharmacokinetics of indacaterol in COPD patients does not warrant dose-adjustments. Mild or moderate hepatic impairment does not alter the pharmacokinetics of indacaterol.

From a pharmacodynamic perspective, indacaterol is an inhaled, long-acting β_2-adrenergic agonist, which when administered once daily at doses of 75 µg or 150 µg to patients with COPD, has a rapid onset of bronchodilator action, which is sustained over the dosing interval and without evidence of tolerance to this effect after repeated dosing for up to a year. It is generally safe and well tolerated, with small, non-clinically relevant effects on heart rate, QT interval, serum potassium and blood glucose with a broad safety margin for these secondary pharmacodynamic effects at the recommended therapeutic once-daily doses of 75 µg to 150 µg.

4.3.2 Clinical pharmacokinetics

Pharmacokinetic information has been collected from 50 clinical studies conducted in healthy volunteers, patients with COPD and asthma patients.

Except where noted, the pharmacokinetic properties of indacaterol in this summary are described on the basis of study results where indacaterol was inhaled via Concept1.

Some studies in healthy subjects have used other routes of administration, namely: oral route by swallowing inhalation capsules (Studies A2106, A2214 and A2223), oral route by swallowing the contents of inhalation capsules (Study B2106) and intravenous infusions (Studies B2103 and B2106).

Studies in healthy subjects included the four drug interaction studies: (Studies A2311, B2107, B2216 and B2220). Special populations were investigated in Study A2307 which studied hepatic impairment (mild [Child-Pugh 5-6] and moderate [C-P 7-9]) and Study A2221 which investigated UGT1A1 genotype (Gilbert's disease). Ethnic differences between Japanese and Caucasian subjects were addressed in healthy subjects (Study A2215) as well as in asthmatics (Study A2219) and a dedicated PK study in healthy Chinese subjects was also performed (Study B2101).

Information about covariates that may have an impact on pharmacokinetics such as age, gender, body weight, body mass index and race were investigated using a population PK modeling approach with pooled pharmacokinetic data from Studies B2212, A2228, B2334, B2335S and B2338. The population PK analysis and report were updated based on additional data from Studies B1202, B1302, B2331, and B2335SE.

4.3.3 Clinical pharmacokinetics: summary of results

After oral inhalation, indacaterol was rapidly absorbed and achieved peak serum levels (Cmax) within the first 30 minutes after administration. Thereafter, indacaterol concentrations declined in a multi-phasic manner with an apparent terminal half-life that ranged from 45.5 to 126 hours. From the multiple dose inhalation studies (Studies A2221, B2339 and B2223) the effective half-life for accumulation was determined to be in the range of 40 to 56 hours for once-daily doses of indacaterol between 75 µg and 600 µg. This was consistent with the observation that steady state was achieved between 12 and 15 days of o.d. dosing. As evidenced by the results of Study B2339, the increase in steady state indacaterol AUC and Cmax was dose-proportional in the dose range of 150 µg to 600 µg and the data from Study B2356, which compared doses of 150 µg and below, did not indicate any substantial deviation from dose-proportionality in the dose range between 37.5 µg and 150 µg. There was no change in the clearance of indacaterol on repeated once-daily dosing via Concept1.

Accumulation factors (Racc; i.e. Day 14/Day 1 or Day 15/Day 1 ratios) for AUC and Cmax were in the range of 2.9 to 3.8 and 1.6 to 2.8, respectively, at steady state of once-daily dosing with doses between 75 µg and 600 µg.

Absolute bioavailability was determined in two independent studies (Study B2103 and B2106) where the inhaled bioavailability was on average 43% (n=4) and 45% (n=8), respectively. There was no clinically meaningful difference in systemic exposure when comparing dosing via Concept1 in the morning versus evening. After intravenous administration, serum clearance was moderate (18.8 to 23.3 L/h), and a large volume of distribution was observed (Vz=2361 to 2557 L: Studies B2103 and B2106). Study B2106 also included an investigation of the concomitant administration of oral activated charcoal with an inhaled dose of indacaterol. The comparison of the inhaled dose of indacaterol together with charcoal versus an inhaled dose alone indicated that the majority of systemic exposure after oral inhalation is a result of absorption via the lungs. Relative bioavailability of an oral dose compared to an inhaled dose was 46% (Study A2106). The bioavailability data together suggest that systemic exposure to indacaterol after inhalation is a composite of pulmonary and intestinal absorption.

Since indacaterol is an inhaled drug, a formal food effect study was not conducted. In the pivotal studies of the clinical development program indacaterol was administered as a morning dose regardless of the timing of food intake.

Indacaterol is highly bound to plasma and serum proteins. The *in vitro* human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2%, respectively. *In vitro* protein binding results were consistent with *ex vivo* protein binding measurements. Mild-to-moderate hepatic impairment did not alter the protein binding of indacaterol (Study A2307). Indacaterol had an *in vitro* blood-to-plasma concentration ratio of 1.2 (Study R00-594).

Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. After inhaled administration of indacaterol, generally less than 2% of the inhaled dose was excreted into urine. In a human ADME study (Study A2223) the majority of the orally administered radioactive dose was excreted into feces and only a minor fraction was found in the urine. Mass balance in the human ADME study was complete. Because renal clearance plays a very minor role in elimination of indacaterol a study in renally impaired subjects was not conducted.

Indacaterol does not undergo stereoconversion *in vivo*. Analysis of urine samples from Study A2211 provided evidence that stereochemical conversion of indacaterol (the pure R-enantiomer) to the S-enantiomer *in vivo* does not occur to any significant extent.

The primary metabolic pathways of indacaterol in humans involved monohydroxylation, O- and N-glucuronidation, and both C- and N-dealkylation. After oral administration of indacaterol in the human ADME study (Study A2223) unchanged indacaterol was the main circulating component in human serum, accounting for 32.5% of the total drug-related AUC0-24h. The contribution of individual metabolites to the total drug-related AUC0-24h in human serum ranged from 4.2% to 12% with the hydroxylated metabolite P26.9 being the most prominent. All of the metabolites identified in humans were found in one or more of the

animal species tested. Conversely, there were no metabolites observed in the animal species investigated that were not detected in human.

The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. *In vitro* investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic-O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6 and CYP3A4. CYP3A4 was predicted to be by far the most predominant isoenzyme responsible for hydroxylation of indacaterol. The hydroxylated metabolites P26.9 and P30.3 were found to have similar *in vitro* affinity to human β_2-receptors than indacaterol itself. However the hydroxylated metabolites could not compete with indacaterol's duration of action in functional assays. The hydroxylated metabolites were found to represent no more than 11% of the steady state AUC0-24h and 6% of Cmax of parent indacaterol after inhalation via Concept1 (Study B2339). Given the inferior activity profile and low *in vivo* abundancy, the hydroxylated metabolites are not expected to contribute significantly to pharmacological activity of indacaterol. *In vitro* investigations of enzyme and transporter induction indicated that indacaterol has negligible potential to act as an inducer at clinically relevant serum levels (Study R0900287).

Indacaterol is a low affinity substrate for the efflux pump P-gp. *In vitro* investigations in Caco-2 monolayer systems characterized indacaterol as a medium to high permeability drug substance that is also a low affinity substrate for P-gp mediated efflux (Study R0500761). Studies *in vitro* indicate that, *in vivo*, indacaterol is unlikely to significantly inhibit transporter proteins such as P-gp, MRP2, BCRP, the cationic substrate transporters hOCT1 and hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K (Study R0900759) and (Study R0900394).

The pharmacokinetics of indacaterol was studied in populations with different UGT1A1 genotypes – the fully functional [(TA)6,(TA)6] genotype and the low activity [(TA)7, (TA)7] genotype (i.e. Gilbert Syndrome genotype) (Study A2221). The study demonstrated that steady state AUC0-24h and Cmax were 1.2-fold higher in the low activity UGT1A1 genotype group, indicating that systemic exposure to indacaterol is not significantly affected by UGT1A1-genotype.

Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e. ketoconazole (Study A2311), erythromycin (Study B2220), ritonavir (Study B2107) and verapamil (Study B2216)). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to 2-fold increase in AUC and 1.5-fold increase in Cmax. Co-administration of erythromycin resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for Cmax. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and Cmax respectively. Concomitant treatment with another dual inhibitor of CYP3A4 and P-gp, ritonavir, resulted in a 1.6-fold to 1.8-fold increase in AUC, whereas Cmax was virtually unaffected. Taken together the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Given the safety data of Study B2339 and of Study B2334 (which confirmed safe use of a 600 µg dosage regimen up to one year), the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses of 75 µg or 150 µg.

Indacaterol pharmacokinetics show no difference between Japanese and Caucasian subjects (Studies A2215 and A2219) or Chinese subjects (Study B2101). Further exploration of ethnic factors as covariates of systemic exposure in COPD patients and patients with asthma was done using a population PK modeling approach. Within the limits of the sensitivity of that analysis, no ethnic factor was identified in the COPD analysis population that would cause major changes in systemic exposure to indacaterol after inhalation via Concept1. Also, covariate analysis on age, gender, body weight and body mass index did not indicate a need for change in dose. These findings were supported by an updated population PK analysis.

Mild and moderate hepatic impairment does not alter indacaterol pharmacokinetics or protein binding. Study A2307 studied the impact of mild and moderate (Child Pugh 5-6 and 7-9 respectively) hepatic impairment on the pharmacokinetics of single inhaled doses of 600 µg indacaterol delivered via Concept1. The study could not detect any relevant changes in pharmacokinetics or ex-vivo protein binding of indacaterol in either of the two groups when compared to healthy, demographically-matched control subjects. The effect of severe hepatic impairment on indacaterol pharmacokinetics was not studied.

4.3.4 Pharmacodynamics

The bronchodilator effect of indacaterol has been well established in a number of clinical trials in patients with COPD or asthma. These include the dose-ranging and confirmatory efficacy trials, which provide the most extensive data on the bronchodilatory effect of indacaterol. In addition, a number of studies evaluated specific aspects of bronchodilation and assessed secondary pharmacodynamic (PD) effects.

4.3.5 Pharmacodynamics: summary of results

Bronchodilator effects of indacaterol

The bronchodilator effect of indacaterol has been investigated in patients with COPD both in the efficacy studies and in earlier clinical pharmacology studies. The most extensive data on bronchodilation are provided by efficacy studies and are discussed in Section 5.

Other studies evaluated specific aspects of bronchodilation:

- No clinically meaningful difference in bronchodilator effect was observed with 300 µg indacaterol administration in the morning compared with the evening (Study B2305).
- Pharmacogenetic analysis showed that common ADRB2 polymorphisms did not appear to affect bronchodilator response to indacaterol (pharmacogenetic analysis from Studies B2335S and B2336)
- The onset of bronchodilator action of inhaled indacaterol was shown to be rapid: 150 µg and 300 µg single doses of indacaterol were superior to single doses of 50/500 µg salmeterol/fluticasone in FEV_1 response, showing clinically relevant activity within five minutes of inhalation (Study B2307).
- The full bronchodilator effect of indacaterol was achieved within 30 minutes of inhalation, showing a response profile similar to that of the short-acting β_2-agonist albuterol (Study B2307).
- Indacaterol 300 µg increased dynamic inspiratory capacity (IC) under peak exercise compared to placebo and improved exercise endurance, as well as showing an increase in

resting IC. The improvement in dynamic IC relates to a reduction in dynamic hyperinflation and an improvement in exercise capacity (Studies B2318 and 2311).

Secondary pharmacodynamic effects

Throughout the clinical development program, particular attention has been paid to monitoring expected secondary pharmacodynamic β-agonist effects, namely increases in heart rate, QT interval and plasma glucose and decreases in serum potassium levels.

The effects of indacaterol on QT intervals were assessed in healthy subjects, COPD patients and asthma patients.

QTc study in healthy subjects

Study B2339 was a thorough QTc study conducted in compliance with current ICH E14 Guidance (ICH 2005). It was a single-center, randomized, multiple-dose, placebo-controlled and positive-controlled parallel group study to evaluate the effects of indacaterol on cardiac safety. The primary objective was to characterize the maximum mean prolongation of QTcF following multiple doses of indacaterol o.d. for 14 days (pharmacokinetic steady state) in healthy subjects.

Multiple daily doses of indacaterol (150, 300 and 600 µg delivered using the Concept1 device) resulted in mean maximum time matched differences versus placebo that were lower than 5 ms for delta QTcF versus baseline. The upper limit of the 90% CIs were below 10 ms for all time matched comparisons. This shows that there is no concern for a pro-arrhythmic potential (related to QTc prolongation) in the investigated dose range. There was no clinically relevant evidence of a concentration-delta QTcF relationship in the dose range 150 µg to 600 µg in this study.

Dose escalation study in COPD patients

Study B2202 investigated single doses of indacaterol up to 3000 µg in patients with COPD. The maximal increase from baseline in QTcF in this study was 9.10 ms at 8 hours after the inhalation of 2000 µg indacaterol. In this study there was a dose-dependent increase in heart rate up to 3000 µg indacaterol which produced a maximum heart rate change versus placebo of 12.4 bpm.

Multiple-dose study in COPD patients

In Study B2201, patients with COPD received indacaterol at doses of 400 and 800 µg for 28 days. There was a maximum heart rate change versus placebo of 2.9 bpm 1 hour post-dose with the 800 µg dose.

Summary of secondary pharmacodynamic effects

At recommended therapeutic doses, there is no clinically relevant effect on the QTcF interval. Overall, the effects on heart rate appeared to be marginal with doses up to 800 µg indacaterol, so that it is unlikely that doses up to 800 µg will produce relevant effects on heart rate. There is an indication of potential heart rate effects at very high overdoses such as 3000 µg indacaterol.

Changes in blood glucose and serum potassium associated with indacaterol administration in COPD were small, variable and not dose-related in all doses close to the clinical dose level.

5 Clinical efficacy

5.1 Dose selection

The key studies contributing to dose and dose regimen selection are shown in Table 5-1. The results of each study are discussed in Section 5.1.2 to Section 5.1.5.

Table 5-1 Summary of dose-finding trials

Study	Study population	N (Randomized)	Treatment duration	Dosage
B2335S Stage 1	COPD	801	2 weeks	Indacaterol 75, 150, 300, 600 µg o.d. Tiotropium 18 µg o.d. Formoterol 12 µg b.i.d. Placebo b.i.d
B2357	Asthma	511	2 weeks	Indacaterol 18.75, 37.5, 75, 150 µg o.d. Salmeterol 50 µg b.i.d. Placebo b.i.d
B2223	Asthma (dose regimens)	191	2 weeks	Indacaterol 37.5 µg b.i.d. Indacaterol 75 µg o.d. Indacaterol 150 µg q.o.d. Placebo b.i.d.
B2356	COPD	552	2 weeks	Indacaterol 18.75, 37.5, 75, 150 µg o.d. Salmeterol 50 µg b.i.d. Placebo b.i.d

The dose-ranging study in COPD patients, Study B2335S (Stage 1), a seamless adaptive design study, was the original basis for dose selection in the NDA (Table 5-1). The study aimed to identify a dose in COPD patients that was at least as effective as comparators and met the Minimal Clinically Important Difference (MCID) versus placebo. However, following the FDA's review of the NDA, two studies were performed (Table 5-1):

- A dose-ranging study in asthma patients: Study B2357. Asthma patients were studied in order to meet the FDA's request that the study be performed in a bronchoreactive population. This study was performed with the intention of identifying the minimum effective dose of indacaterol in this population.
- A dose-regimen study in asthma patients: Study B2223 was performed to meet the FDA's request to compare the efficacy and safety of indacaterol once daily with more and less frequent dosing, again in a bronchoreactive population.

In addition, the Sponsor conducted a third study:

- Study B2356 was performed in COPD patients, employing a similar design to the asthma dose-ranging study (Study B2357), with the intention of further exploring the dose response at lower doses (i.e., to complement Stage 1 of B2335S).

5.1.1 General features of dose-ranging studies (B2335S, B2356, B2357)

Primary efficacy endpoint

The primary endpoint was 24-hour post-dose trough FEV_1 after 14 days of treatment. Trough FEV_1 was defined as the average of the 23 h 10 min and the 23 h 45 min values taken in the clinic on Day 15. The area under the curve (AUC) 1-4h of FEV_1 on Day 14 was also used to measure dose response in Study B2335S.

Statistical methods

In all three studies, the primary variable(s) was analyzed using a mixed model for the Full Analysis Set (FAS) based on the intention to treat principle. The model contained treatment as a fixed effect with the baseline FEV_1 measurement, FEV_1 prior to inhalation and FEV_1 10-15 min (30 min in B2335S) post inhalation of albuterol (components of SABA reversibility at Visit 2), FEV_1 prior to inhalation and FEV_1 1 hour post inhalation of ipratropium (components of anti-cholinergic reversibility) at Visit 3 (B2335S and B2356 only) as covariates. To reflect the randomization scheme the model for Study B2335S included baseline smoking status (current smoker/ex-smoker) as a fixed effect with center as a random effect nested within country. The model for Study B2356 also included baseline smoking status (current smoker/ex-smoker), as well as ICS use at trial entry (yes/no) as fixed effects with center as a random effect and for B2357 the model included asthma severity (mild persistent/moderate persistent/severe persistent) as a fixed effect and center as a random effect.

Study populations

COPD studies (B2335S, B2356): the study population consisted of a representative group of male and female patients aged 40 years and above, with a clinical diagnosis of moderate to severe COPD, according to the GOLD guidelines at the time of study design (GOLD 2005, GOLD 2008), with a post-bronchodilator $FEV_1 < 80\%$ and $\geq 30\%$ of the predicted normal value, and a post-bronchodilator $FEV_1/FVC < 70\%$, as well as a smoking history of at least 20 pack years (Study B2335S) or 10 pack years (Study B2356).

Patients were excluded if they had a history of asthma, prolonged QTc interval, a history of a respiratory infection or (with the exception of Study B2335S) a COPD exacerbation in the past 6 weeks prior to the screening visit, or patients who, in the judgment of the investigator had a clinically relevant laboratory abnormality or a clinically significant condition which might compromise patient safety or compliance. Concurrent respiratory medication were not allowed during the study with the exception of short-acting β-agonists for rescue and inhaled corticosteroids if the patient was receiving therapy before entering the study.

Asthma study (B2357): the study population included males and females aged 18 years and older with persistent asthma (according to GINA guidelines 2008). Additionally, patients had to (1) be receiving daily treatment with inhaled corticosteroids (ICS) up to the maximum dose per day indicated in the package leaflet, in a stable regimen for the month prior to the study; (2) present with an $FEV_1 \geq 50$ and $\leq 90\%$ of the predicted normal value; (3) demonstrate an increase of $\geq 12\%$ and ≥ 0.2 L in FEV_1 over their prebronchodilator value within 30 minutes after inhaling a total of 360 µg of albuterol via a metered dose inhaler (reversibility test).

Patients were excluded if they had a history of COPD, a smoking history greater than 10 pack years, current smokers who smoked greater than 10 cigarettes per day, a severe asthma attack/exacerbation requiring hospitalization in the 6 months prior to the study, previous intubation for a severe asthma exacerbation, an emergency room visit for an asthma attack/asthma exacerbation within 6 weeks prior to screening, or required the use of ≥ 8 inhalations per day of SABA (90 µg albuterol via pMDI) on any two consecutive days from screening to randomization, or had a lower respiratory tract infection within six weeks prior to

the first study visit. Concurrent respiratory medications were not allowed during the study with the exception of short-acting β_2-agonists for rescue and inhaled corticosteroids.

5.1.2 B2335S (Stage 1): seamless adaptive design dose-ranging study in COPD patients

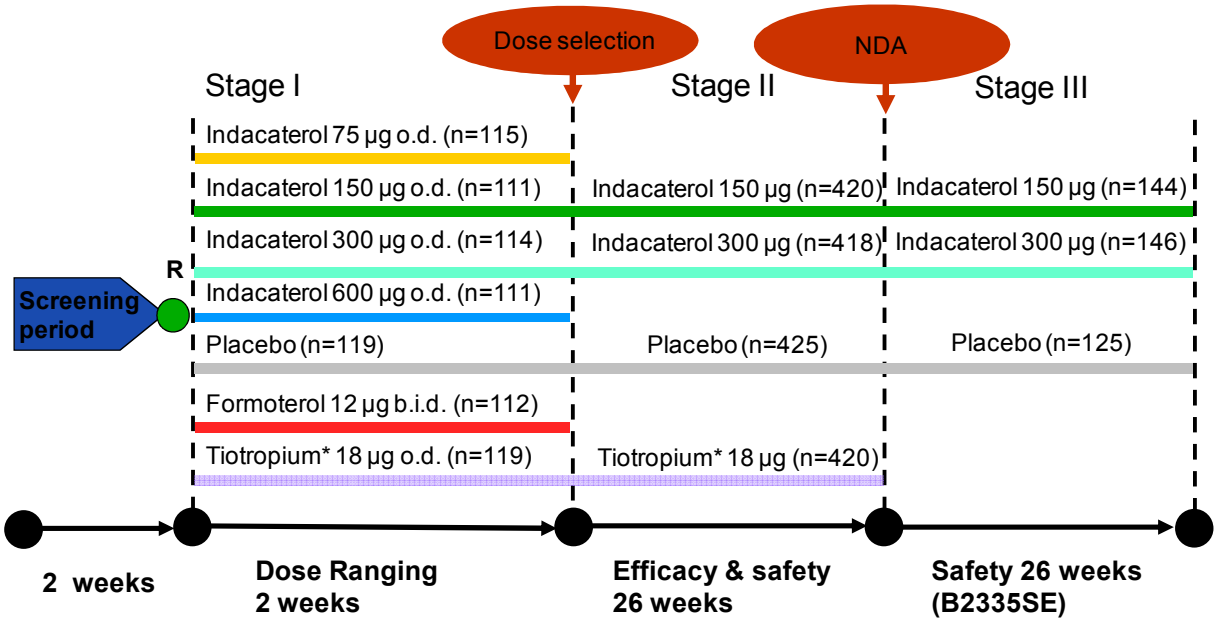
Purpose

Stage 1 of this study was designed to identify two doses of indacaterol, on the basis of meeting the MCID for trough FEV_1 versus placebo after 14 days and providing numerically superior bronchodilator efficacy to formoterol and tiotropium, to take forward into Stage 2.

Study design

Study B2335S was a 26-week treatment, multicenter, randomized, double-blind, double-dummy, placebo- and active controlled, adaptive, seamless, parallel-group study to assess the efficacy, safety and tolerability of two doses of indacaterol (selected from 75, 150, 300 & 600 µg o.d.) in patients with COPD using blinded formoterol (12 µg b.i.d. via the Aerolizer®) and open-label tiotropium (18 µg o.d. via the HandiHaler®) as active controls. Patients were randomized in equal allocation to each treatment. Randomization was stratified by smoking status. The study was conducted at 334 centers in 11 countries, with 185 centers in the US. The study was performed in 2 stages, plus an extension (Figure 5-1): Stage 1 was designed to identify two doses to be carried forward for use in Stage 2 (the pivotal efficacy stage). Stage 2 is discussed in Section 5.2.3. The original dose selection for the NDA was made on the basis of Stage 1 of this study.

Figure 5-1 Study B2335S study design



*Open-label. All drugs were delivered via proprietary single-dose dry powder inhalers (SDDPI)

The dose selection was made by an independent external Data Monitoring Committee (DMC), using unblinded data to which only the DMC had access, and pre-defined criteria, which were discussed in advance with Health Authorities. The study remained blinded to the Sponsor throughout the study.

The pre-defined decision rules for dose selection were:

- The mean effect of the selected dose (versus placebo) needed to be 0.12 L greater than placebo (minimal clinically important difference, MCID (Cazzola 2008)) in terms of trough FEV_1 (the primary endpoint) and numerically higher than the mean effect of tiotropium and formoterol (versus placebo).
- The mean effect of the selected dose (versus placebo) needed to be numerically higher than the mean effect of tiotropium and formoterol (versus placebo) in terms of FEV_1 standardized AUC (1-4h) (as opposed to AUC (5min-4h) in order to not bias selection given the fast onset of indacaterol).

The pre-defined interim analysis of Stage 1 of the study was to be performed when 770 patients (approx. 110 evaluable patients per treatment group) had each completed at least 2 weeks of treatment. Those patients who had already been randomized continued to receive treatment beyond 2 weeks until the independent DMC review of the interim analysis was complete. Patients whose dose was not selected for Stage 2 were then discontinued, although the study blind was maintained.

Primary efficacy endpoints

As noted in Section 5.1.1, the primary endpoints for dose selection were trough FEV_1 and FEV_1 AUC (1 h-4 h) after 14 days of treatment The use of the latter was intended to reflect an active part of the day and ensure a comparable level of bronchodilation in this period and to avoid bias resulting from the slower onset of action of tiotropium. The mean effect was calculated using the mixed model described in Section 5.1.1. The DMC were asked to select the lowest dose that met the specified criteria and the next highest dose (unless the 600 µg dose was selected, in which case the 300 µg dose also had to be chosen) provided there were no safety concerns. In case of unexpected results, for example an absence of dose response or lack of efficacy for the active controls, the DMC had discretion to deviate appropriately from the decision criteria.

Study results

Patient disposition

A total of 805 patients were randomized in Stage 1. Of these, 94% of patients completed the 2 weeks of trial medication.

Baseline characteristics

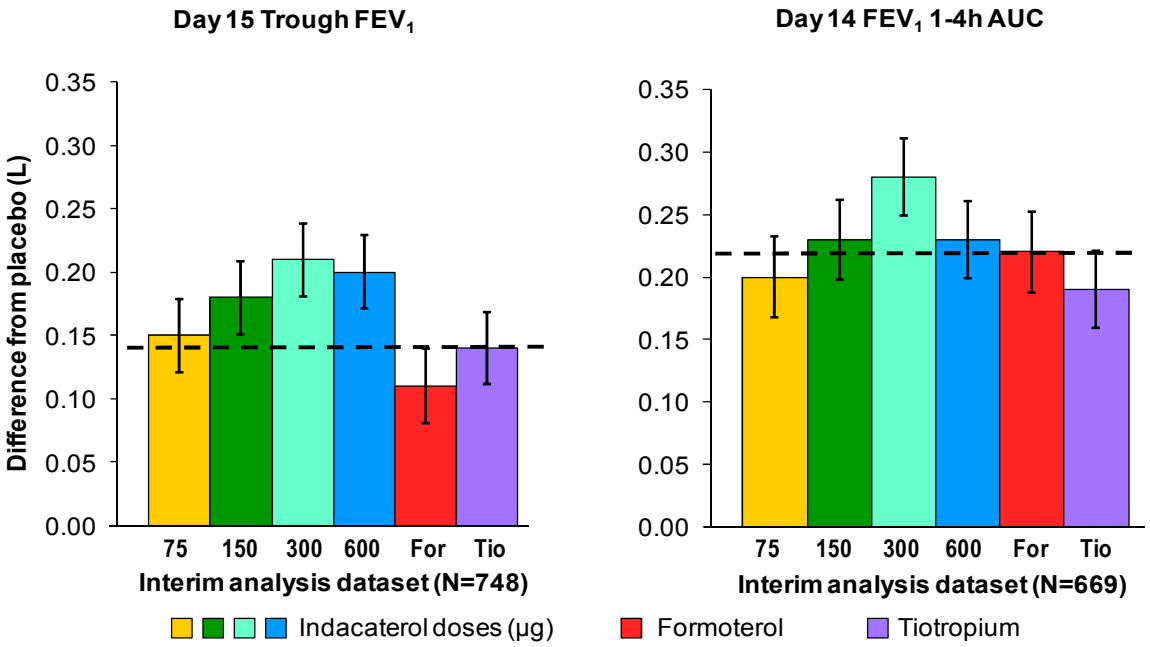
The Stage 1 randomized patients' mean age across treatment groups ranged from 63 to 66 years and the majority of patients were male (53 to 63%) and Caucasian (90 to 94%). Approximately 2% of patients in the study population were Black. There was a higher proportion of ex-smokers than current smokers (59% vs. 41%). Approximately 62% of patients were taking concurrent ICS therapy at baseline and during the study. Baseline lung function values were similar across treatment groups with a post bronchodilator FEV_1 53% of

the predicted value. The study population appeared to be generally representative of the COPD patient population.

Primary efficacy analyses

The results of the interim analyses are presented in Figure 5-2 and Table 5-2. Following the dose selection guidelines described above, the reference value (for selection of the 2 doses of indacaterol) used for trough FEV_1 was 0.14 L (tiotropium vs. placebo difference) and for FEV_1 standardized AUC (1 h-4 h) was 0.22 L (formoterol vs. placebo difference). After 2 weeks of treatment; the lowest dose to surpass these reference values was the indacaterol 150 µg dose, with the next highest dose being 300 µg: these doses were therefore selected for Stage 2 of the study by the DMC. The DMC did not report any safety findings that impacted its independent selection of the indacaterol 150 µg and 300 µg doses for Stage 2 of the study.

Figure 5-2 B2335S: Dose response (interim ITT population)



Dotted lines show reference values used to select doses

Interim analysis dataset: basis for independent Data Monitoring Committee dose selection decision, imputed with LOCF. Data are least squares means ± SE. N = sum of all arms including placebo. Average number of patients per treatment group N=107 (trough) and N=97 (AUC)

Table 5-2 B2335S: Dose response (interim ITT population)

		Treatment			Treatment difference		
Treatment	**N**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**
Trough FEV_1 (L)							
Ind 75 µg	104	1.46	0.024	Ind 75 µg - Placebo	0.15	0.029	(0.09, 0.20)
Ind 150 µg	105	1.49	0.024	Ind 150 µg - Placebo	0.18*	0.029	(0.12, 0.24)
Ind 300 µg	110	1.52	0.024	Ind 300 µg - Placebo	0.21*	0.029	(0.15, 0.27)
Ind 600 µg	108	1.51	0.024	Ind 600 µg - Placebo	0.20	0.029	(0.14, 0.25)
For	105	1.42	0.024	For - Placebo	0.11	0.029	(0.06, 0.17)
Tio	112	1.45	0.023	Tio - Placebo	0.14	0.028	(0.08, 0.19)
Placebo	104	1.31	0.024				
AUC 1 h-4 h FEV_1 (L)							
Ind 75 µg	95	1.50	0.034	Ind 75 µg - Placebo	0.20	0.032	(0.14, 0.27)
Ind 150 µg	96	1.53	0.034	Ind 150 µg - Placebo	0.23*	0.032	(0.16, 0.29)
Ind 300 µg	99	1.58	0.034	Ind 300 µg - Placebo	0.28*	0.031	(0.22, 0.34)
Ind 600 µg	97	1.53	0.034	Ind 600 µg - Placebo	0.23	0.031	(0.17, 0.29)
For	93	1.52	0.035	For - Placebo	0.22	0.032	(0.16, 0.28)
Tio	99	1.49	0.034	Tio - Placebo	0.19	0.031	(0.13, 0.25)
Placebo	90	1.30	0.033				

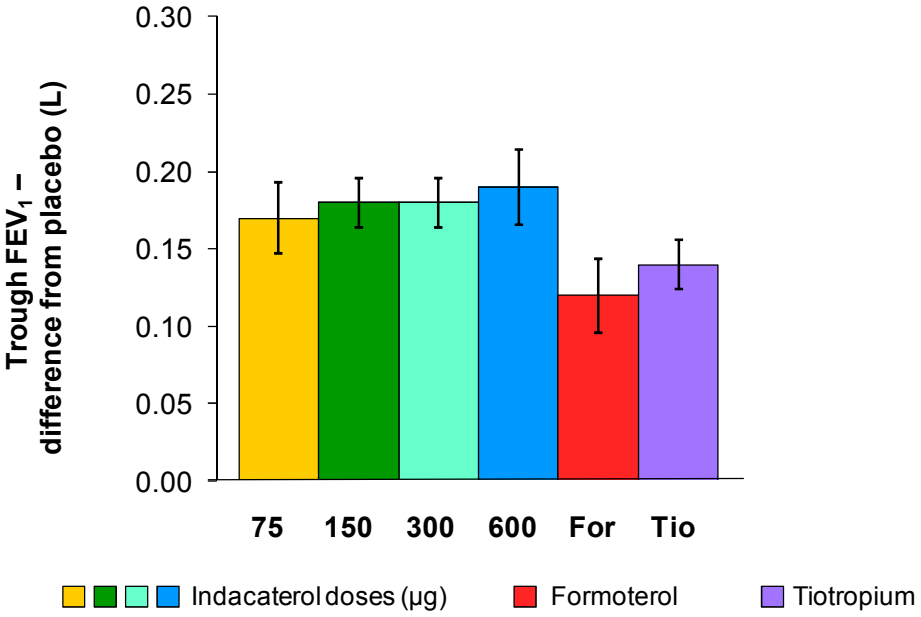
LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center(country), with center(country) as a random effect. For = formoterol, Tio = tiotropium
Bold LS mean differences were those identified as reference values by dose selection criteria
* = selected doses

Additional efficacy analysis

During the review of the NDA, the FDA requested additional data on trough FEV_1 for all patients treated with the seven study arms from Stage 1 at four time points: Day 2, Day 15, Week 12 (Day 85), and Week 26, i.e. beyond the time point used by the DMC for dose selection. Patients who had completed the 2-week treatment period for Stage 1 continued on their assigned treatments until the DMC review of the interim analysis was complete. Approximately 50% of patients in the discontinued treatment arms (75 µg, 600 µg, and formoterol) were exposed to study drug beyond 2 weeks as a result.

Figure 5-3 shows the results for trough FEV_1 at 12 weeks in the extended ITT population (i.e. all patients combined whether randomized in Stage 1 or 2).

Figure 5-3 B2335S: Dose response at Day 85 for dose-ranging population



ITT dataset N=1,898: i.e. all patients randomized who received at least one dose of study drug, imputed with LOCF.
Data are least squares means ± SE.

FDA concluded from these data that a clinically meaningful efficacy difference between the 75 µg and the 150 µg or 300 µg once daily doses was not demonstrated and requested further investigation of the efficacy of indacaterol at doses less than 150 µg in bronchoreactive patients (as a more sensitive population to differentiate between doses) to better characterize the lower end of the dose response curve. Study B2357, in patients with asthma (Section 5.1.3), was performed to address this request, and Study B2356, although not specifically requested by the FDA, also explored the lower end of the dose response curve, but in COPD patients (Section 5.1.5).

5.1.3 B2357: dose-ranging study in asthma patients

Purpose

This study was performed with the intention of identifying the minimum effective dose in a bronchoreactive population, as per the request from FDA.

Study design

Study B2357 was a double-blind, double-dummy placebo- and active-controlled dose-ranging study conducted in patients with persistent asthma (as defined by the GINA guidelines 2008). Patients were randomized in equal numbers to indacaterol 18.75, 37.5, 75, 150 µg o.d., placebo, or salmeterol 50 µg b.i.d. Patients were stratified by asthma severity (all patients were required to use inhaled corticosteroids). The study was conducted at 73 centers in the United States. The treatment period was 2 weeks.

Primary efficacy endpoint

The primary efficacy endpoint was trough FEV_1 on Day 15 and analyzed using the model described in Section 5.1.1. The MCID in asthma for comparisons of trough FEV_1 with placebo was pre-defined as 0.20 L (Reddel 2009).

Secondary efficacy endpoint

Secondary efficacy variables included trough FEV_1 at Day 2 and Day 14, peak FEV_1, standardized (with respect to time) AUC for FEV_1 (5 min – 4 h), and standardized (with respect to time) AUC for FEV_1 (5 min – 23 h 45 min) for the serial spirometry subgroup at Day 14.

Study results

Patient disposition

A total of 511 patients were randomized. Of these, 94.5% completed the study. The percentage of patients who discontinued from the study was slightly higher in the salmeterol treatment group compared with the indacaterol treatment groups. The most common reason for discontinuation overall was AE(s) (1.8%), followed by withdrawal of consent (1.0%), administrative problems (1.0%) and protocol deviation (1.0%).

Baseline characteristics

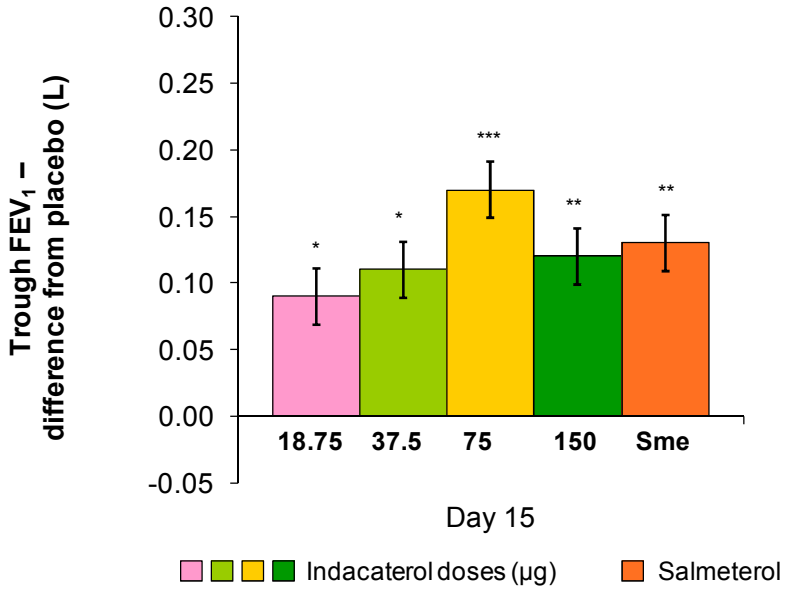
The treatment groups were generally well matched in terms of baseline demographics and disease characteristics. The mean age of the study population was 41.1 years with a range of 18 to 82 years. More than half (55.4%) of patients were female and most were Caucasian. The majority of the patients had never smoked (79.7%); 17.7% were ex-smokers and 2.6% were current smokers. The overall smoking history in terms of the mean number of pack years for all patients was 3.6.

All patients had persistent asthma as defined in the protocol according to GINA guidelines (2008) with 68.3% of the patients presenting with moderate persistent asthma and 24.5% presenting with mild persistent asthma. The overall mean duration of asthma was 26.8 years (range, 0.5 – 68.7 years), and most patients (61.4%) had asthma for more than 20 years. All patients were required to use ICS at baseline and during the study. At Visit 2, the screening visit, where baseline lung function was measured, the mean percentage of predicted FEV_1 before SABA bronchodilation ranged from 68.9% to 71.4% across the treatment groups. Overall, the mean FEV_1/FVC ratio after bronchodilation was 71.3%. The mean percentage increase in FEV_1 after SABA bronchodilator was 22.4%.

Primary efficacy results - trough FEV_1

For trough FEV_1 at Day 15, 75 and 150 µg were more effective than lower doses. The greatest difference versus placebo in trough FEV_1 was seen for the 75 µg dose (Figure 5-4, Table 5-3).

Figure 5-4 Trough FEV_1 (L) at Day 15, B2357, dose ranging in asthma patients



*p<0.05, **p<0.01, ***p<0.001 vs placebo; Data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=80

Table 5-3 Trough FEV_1 (L) at Day 15, B2357, dose ranging in asthma patients

		Treatment			Treatment difference			
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**	**p-value**
Ind 18.75 µg	82	2.50	0.036	Ind 18.75 µg - Pbo	0.09	0.044	(0.00, 0.17)	0.048*
Ind 37.5 µg	77	2.52	0.037	Ind 37.5 µg - Pbo	0.11	0.045	(0.02, 0.19)	0.020*
Ind 75 µg	82	2.59	0.036	Ind 75 µg - Pbo	0.17	0.045	(0.08, 0.26)	<0.001*
Ind 150 µg	80	2.54	0.037	Ind 150 µg - Pbo	0.12	0.045	(0.04, 0.21)	0.006*
Sme	78	2.54	0.037	Sme - Pbo	0.13	0.045	(0.04, 0.21)	0.005*
Pbo	81	2.42	0.036					

Sme = salmeterol, Pbo = placebo
LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + asthma severity + center, with center as a random effect. Analyzed for Full Analysis Set, imputed with LOCF.
* In this analysis the testing does not control for the type I error and in addition there is no power for contrasts between active doses. Hence all p-values are to be regarded as descriptive and interpreted in this context.
A missing trough FEV_1 value at Day 15 was imputed with the Day 14 trough value if available.

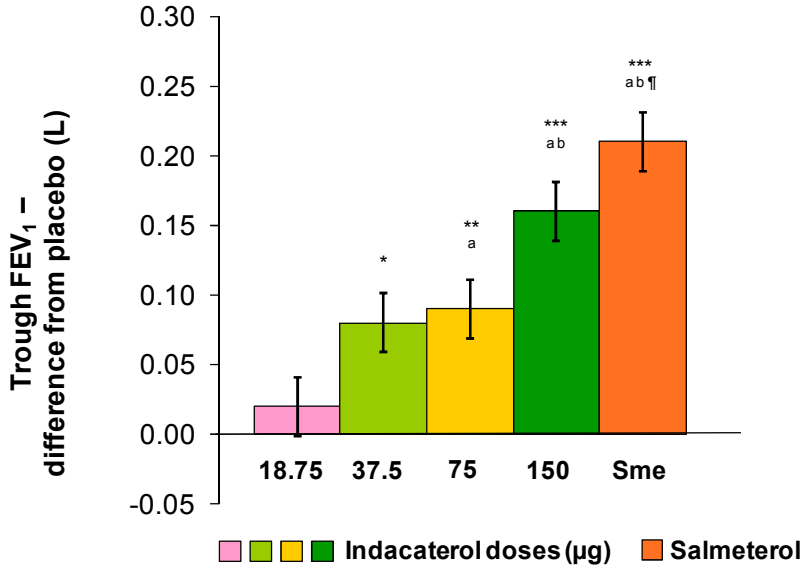
Treatment differences versus placebo were similar for 150 µg and salmeterol. The smallest differences to placebo were seen for indacaterol 18.75 µg and 37.5 µg. All doses of indacaterol showed statistically significant differences versus placebo, as did salmeterol, but none of the differences reached the MCID for asthma of 0.2 L.

Secondary efficacy endpoints

Trough FEV_1 from first dose

For trough FEV_1 after the first dose (i.e. at Day 2) a dose response was observed between the indacaterol treatment groups (18.75 µg up to 150 µg) for the LS mean trough FEV_1 (Figure 5-5, Table 5-4).

Figure 5-5 Trough FEV_1 (L) at Day 2, B2357, dose ranging in asthma patients



*p<0.05, **p<0.01, ***p<0.001 vs placebo; [a]p<0.05 vs 18.75 µg; [b]p<0.05 vs 37.5 µg; ¶p<0.05 vs 75 µg; Data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=80

Table 5-4 Trough FEV_1 (L) at Day 2, B2357, dose ranging in asthma patients

		Treatment			Treatment difference			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Day 2								
Ind 18.75 µg	83	2.46	0.026	Ind 18.75 µg - Pbo	0.02	0.034	(-0.05, 0.08)	0.623
Ind 37.5 µg	77	2.52	0.027	Ind 37.5 µg - Pbo	0.08	0.035	(0.01, 0.15)	0.027
Ind 75 µg	81	2.54	0.026	Ind 75 µg - Pbo	0.09	0.034	(0.03, 0.16)	0.006
Ind 150 µg	82	2.60	0.026	Ind 150 µg - Pbo	0.16	0.034	(0.09, 0.22)	<0.001
Sme	79	2.65	0.027	Sme - Pbo	0.21	0.034	(0.14, 0.27)	<0.001
Pbo	80	2.45	0.027					

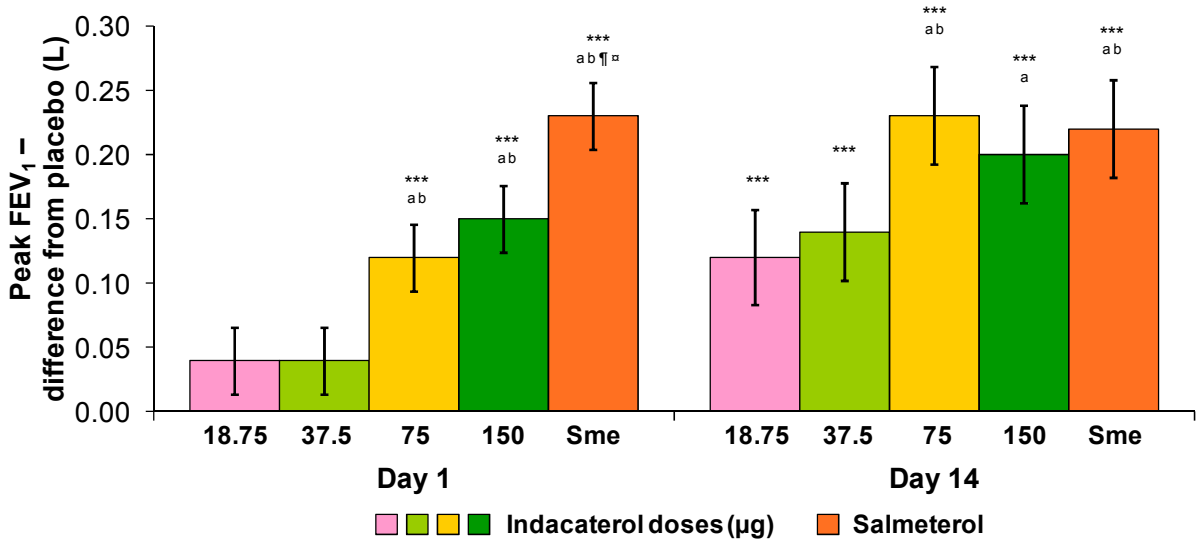
LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + asthma severity + center, with center as a random effect. Analyzed for Full Analysis Set. Sme = salmeterol, Pbo = placebo

The greatest treatment difference between any indacaterol treatment group and placebo was observed in the indacaterol 150 µg treatment group, showing that this dose attained its optimal bronchodilator effect from the first dose. Lower doses appear to require further doses in order to achieve their optimal effect.

Peak FEV_1 after first dose and at Day 14

After the first dose (i.e. at Day 1) a dose response was observed between the indacaterol treatment groups (37.5 µg up to 150 µg) for the LS mean peak FEV_1 in the first four hours following the morning dose (Figure 5-6 and Table 5-5).

Figure 5-6 Peak FEV_1, B2357, dose ranging in asthma patients



***p<0.001 vs placebo; [a]p<0.05 vs 18.75 mcg; [b]p<0.05 vs 37.5 µg; ¶p<0.05 vs 75 µg; [¤]p<0.05 vs 150 µg; Data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=82 (Day 1) and N=80 (Day 14)

The greatest difference between indacaterol and placebo was observed in the indacaterol 150 µg treatment group; the smallest such differences were observed in the indacaterol 18.75 and 37.5 µg treatment groups.

At Day 14, the treatment differences in LS mean peak FEV_1 compared with placebo were clinically relevant in the indacaterol 75 µg and 150 µg groups and the salmeterol group, but not in the indacaterol 18.75 and 37.5 µg groups, suggesting that even at steady state, doses lower than 75 µg are suboptimal.

Table 5-5 Peak FEV_1, B2357, dose ranging in asthma patients

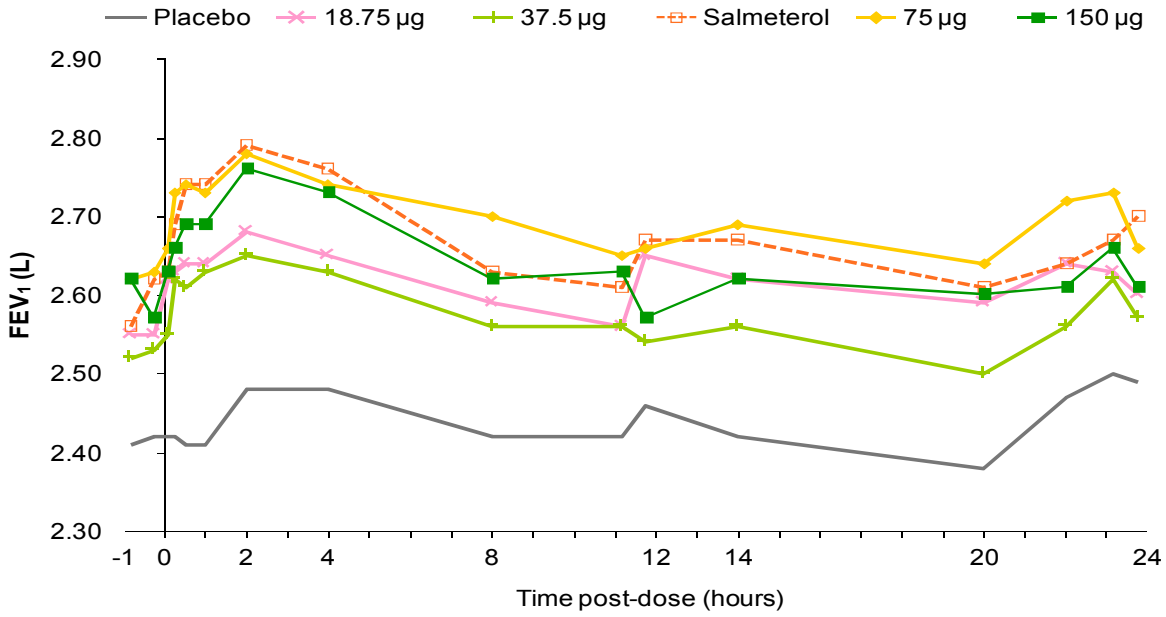
	Treatment				Treatment difference			
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**	**p-value**
Day 1								
Ind 18.75 µg	84	2.62	0.021	Ind 18.75 µg - Pbo	0.04	0.026	(-0.01, 0.09)	0.080
Ind 37.5 µg	80	2.62	0.021	Ind 37.5 µg - Pbo	0.04	0.026	(-0.01, 0.09)	0.101
Ind 75 µg	82	2.69	0.021	Ind 75 µg - Pbo	0.12	0.026	(0.07, 0.17)	<0.001
Ind 150 µg	84	2.72	0.021	Ind 150 µg - Pbo	0.15	0.026	(0.10, 0.20)	<0.001
Sme	82	2.81	0.021	Sme - Pbo	0.23	0.026	(0.18, 0.28)	<0.001
Pbo	84	2.58	0.021					
Day 14								
Ind 18.75 µg	82	2.68	0.030	Ind 18.75 µg - Pbo	0.12	0.037	(0.05, 0.20)	<0.001
Ind 37.5 µg	77	2.69	0.031	Ind 37.5 µg - Pbo	0.14	0.038	(0.06, 0.21)	<0.001
Ind 75 µg	82	2.78	0.030	Ind 75 µg - Pbo	0.23	0.038	(0.15, 0.30)	<0.001
Ind 150 µg	80	2.75	0.030	Ind 150 µg - Pbo	0.20	0.038	(0.13, 0.27)	<0.001
Sme	78	2.77	0.031	Sme - Pbo	0.22	0.038	(0.15, 0.30)	<0.001
Pbo	81	2.55	0.030					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: peak FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + asthma severity + center, with center as a random effect. Analyzed for Full Analysis Set. Sme = salmeterol, Pbo = placebo

Effect on for FEV_1 over 24 hours at Day 14 (subset of patients)

The 24-hour profiles of FEV_1 for indacaterol 75 and 150 µg and salmeterol (the latter dosed b.i.d.) were similar (Figure 5-7). All indacaterol doses showed a 24-hour duration of effect, indicating that the long duration of effect of indacaterol is not dose-dependent.

Figure 5-7 24 hour serial spirometry Day14/15, B2357, dose ranging in asthma patients



Data are least squares means (LSM)

Conclusions

- Study B2357 indicates that 75 µg indacaterol is the minimum effective dose.
- Doses of 75 and 150 µg were more effective than doses of 18.75 and 37.5 µg. On most efficacy parameters the 75 and 150 µg doses showed greater treatment effects versus placebo than lower doses, in most cases similar or superior to those observed with salmeterol (which was not the case for the lower indacaterol doses).
- On Days 1 and 2, the 150 µg dose was more effective with respect to lung function parameters than the 75 µg dose, attaining an optimal bronchodilatory effect more rapidly.
- All doses of indacaterol showed a 24-hour duration of bronchodilatory effect.

5.1.4 B2223 - dose regimen study in asthma patients

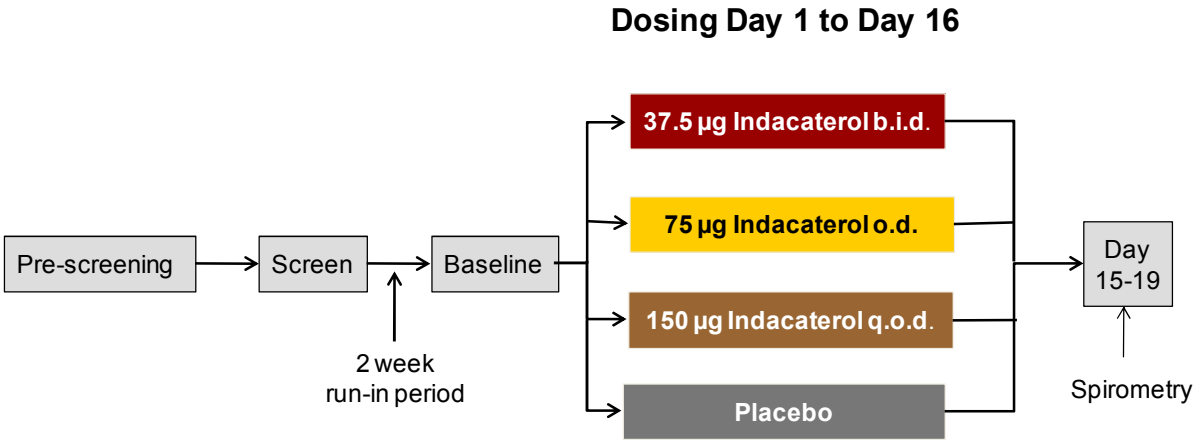
Purpose

This study aimed to evaluate the efficacy of indacaterol when dosed more frequently or less frequently than once daily, in bronchoreactive (asthma) patients, and was performed as per the request from the FDA.

Study Design

This was a parallel-group study that evaluated three different indacaterol regimens utilizing a mean total daily dose of 75 µg indacaterol: 37.5 µg twice daily (b.i.d.), 75 µg once daily (o.d.) or 150 µg every other day (q.o.d.). Patients were recruited from 28 centers in 6 countries with 19 centers in the US. A diagrammatic representation of the study is shown in Figure 5-8.

Figure 5-8 Study Design, B2223, dose regimen study in asthma patients



Primary efficacy

The primary efficacy variables were the trough FEV_1 change from baseline measured after 2 weeks of study treatment, and the time-standardized AUCs (or weighted mean) for FEV_1 change from baseline versus time over the time period 0-24 h (for o.d./b.i.d./placebo), 0-48 h (for o.d./q.o.d./placebo) and 24-48 h (for o.d./q.o.d./placebo). The analysis of these variables was performed using an analysis of variance with treatment as a fixed effect and baseline value as a continuous covariate.

Secondary efficacy

Key secondary efficacy endpoints were FEV_1 and FVC at each post-dose time point on Days 1/2 and Days 16/17/18/19 (o.d. and b.i.d. treatment), FEV_1 and FVC at each post-dose time point on Days 1/2/3 and Days 15/16/17/18/19 (q.o.d. treatment) and to assess peak FEV_1 on Days 1 and 16.

Patient population

The study enrolled male and female patients aged 18 years or above, with a diagnosis of persistent asthma (FEV_1 at screening of 50-90% predicted normal). Patients had to be on a stable dose of inhaled corticosteroids (ICS) one month prior to first study visit and had to demonstrate reversibility to albuterol with an increase in $FEV_1 \geq 12$ % and ≥ 0.2 L.

Key exclusion criteria included: patients who had previous intubation for a severe asthma attack/exacerbation, patients who required the use of ≥ 8 inhalations per day of the short-acting β_2-agonist (90 µg albuterol MDI or equivalent dose of DPI) on any 2 consecutive days from screening to randomization; and patients diagnosed with COPD.

Study results

Disposition

A total of 191 patients were enrolled, of whom 189 patients were dosed and included in the analysis. Thirteen (6.8%) patients discontinued during the treatment phase of the study. Two (1.0%) patients were withdrawn for adverse events (one of which was an SAE), and 2 (1.0%) due to protocol deviations.

Baseline characteristics

Patients had a mean age of 40 years (range: 18 - 80 years). The study included more male than female patients (58% versus 42%). The majority of patients (80%) were Caucasian The treatment groups were fairly well balanced for baseline characteristics with the exception of slight imbalances in sex and race distribution, which were unlikely to impact the results.

Baseline FEV_1 was numerically higher for the 37.5 µg b.i.d and placebo groups than for the other two groups with the means ranging from 2.51 L for the 75 µg o.d group to 2.84 L for the 37.5 µg b.i.d group with an overall mean of 2.67 L (range: 1.20 - 4.59 L). FEV_1 reversibility averaged 21.6% with a range from -20.1 to 50.0 %.

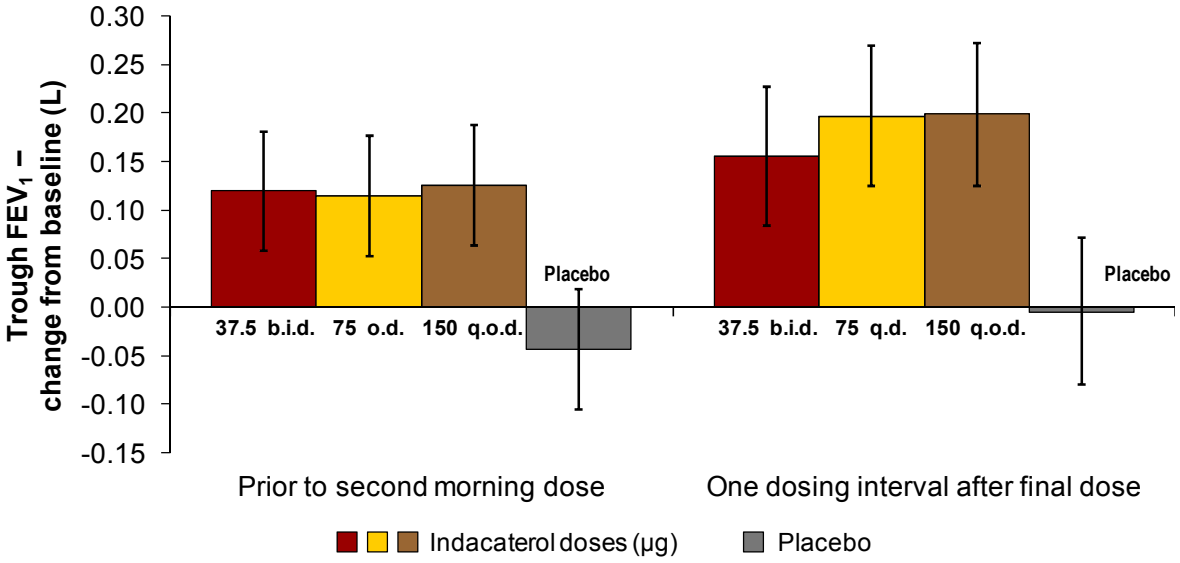
Primary efficacy

Trough FEV_1

Mean increase from baseline in trough FEV_1 was similar for all three regimens at Day 1 (when assessed prior to the second morning dose) but at Day 15/16 (one dosing interval after the final dose) trough FEV_1 was higher for the 75 µg o.d. and 150 µg q.o.d. regimens than for the 37.5 µg b.i.d. regimen (Figure 5-9 and Table 5-6).

The difference versus placebo for the LS mean change from baseline in trough FEV_1 was 0.202 L and 0.203 L for the 75 µg o.d. and 150 µg q.o.d. regimens respectively, meeting the MCID of 0.2 L in asthma patients. The 37.5 µg b.i.d. regimen was less effective than the other regimens, showing a 0.16 L difference to placebo at Day 16.

Figure 5-9 Trough FEV_1, B2223, dose regimen study in asthma patients



Data are unadjusted means and 90% confidence intervals: Baseline = mean of D-1 profiles matching D15+16/D1 pre-dose; Trough = mean of 23h 10m and 23h 50m on D17 48 h after last qod dose, 24h after last qd dose and 12h after last bid dose. Average number of patients per treatment group N=47 (left hand plot) and N=44 (right hand plot)

Table 5-6 Trough FEV_1, B2223, dose regimen study in asthma patients

			Change from baseline		
Trough FEV_1	**Day**	**Treatment**	**Mean**	**Lower 90% CI**	**Upper 90% CI**
	1	37.5 µg b.i.d..	0.120	0.058	0.181
	(prior to	75 µg o.d.	0.115	0.052	0.177
	Second morning	150 µg q.o.d.	0.126	0.064	0.188
	dose)	Placebo	-0.044	-0.106	0.018
	15/16	37.5 µg b.i.d.	0.156	0.083	0.228
	(one dosing interval	75 µg o.d.	0.197	0.125	0.269
	after final	150 µg q.o.d.	0.199	0.125	0.272
	dose)	Placebo	-0.005	-0.080	0.071

Linear model: trough FEV_1 = treatment + baseline FEV_1; analyzed for PD analysis set

Time-standardized AUC for FEV_1

The (LS) mean change from baseline in AUC (0-24 h) for FEV_1 was similar in all indacaterol groups. AUC (0-48 h) and AUC (24-48 h) for FEV_1 were numerically greater in the indacaterol 75 µg o.d. treatment group than in the indacaterol 150 µg q.o.d. group (Table 5-7, Table 5-8).

Table 5-7 Change from baseline in trough FEV_1 and time-standardized AUCs on Days 15/16, B2223, dose regimen study in asthma patients

		Change from baseline		
PD parameter	**Treatment**	**Mean**	**Lower 90% CI**	**Upper 90% CI**
Trough FEV_1 (L)	37.5 µg b.i.d.	0.156	0.083	0.228
	75 µg o.d.	0.197	0.125	0.269
	150 µg q.o.d.	0.199	0.125	0.272
	Placebo	-0.005	-0.080	0.071
AUC 0-24h (L)	37.5 µg b.i.d.	0.196	0.127	0.266
	75 µg o.d.	0.198	0.127	0.269
	Placebo	0.030	-0.044	0.103
AUC 0-48h (L)	75 µg o.d.	0.218	0.148	0.288
	150 µg q.o.d.	0.198	0.135	0.260
	Placebo	0.059	-0.012	0.129
AUC 24-48h (L)	75 µg o.d.	0.216	0.144	0.288
	150 µg q.o.d.	0.201	0.138	0.265
	Placebo	0.085	0.013	0.156

Analyzed for PD Analysis set

Table 5-8 Contrasts with placebo, change from baseline in trough FEV_1 and time-standardized AUCs on Days 15/16, B2223, dose regimen study in asthma patients

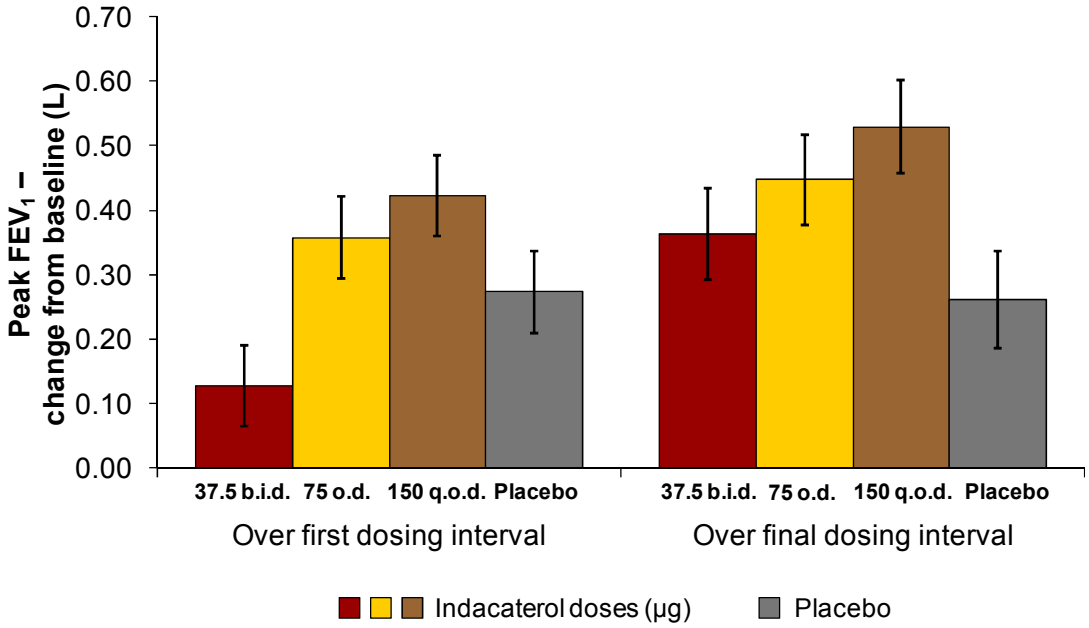
		Contrast with placebo		
PD parameter	**Treatment**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
Trough FEV_1 (L)	37.5 µg b.i.d.	0.160	0.036	0.284
	75 µg o.d.	0.202	0.077	0.327
	150 µg q.o.d.	0.203	0.077	0.329
AUC 0-24h (L)	37.5 µg b.i.d.	0.167	0.046	0.287
	75 µg o.d.	0.168	0.046	0.291
AUC 0-48h (L)	75 µg o.d.	0.159	0.040	0.279
	150 µg q.o.d.	0.139	0.026	0.252
AUC 24-48h (L)	75 µg o.d.	0.131	0.009	0.253
	150 µg q.o.d.	0.117	0.002	0.231

Analyzed for PD Analysis set

Peak FEV_1 after first dose and on Day 16

Change from baseline in peak FEV_1 on Day 1, i.e. over the first dosing interval, was highest for the 150 µg q.o.d. group (0.423 L) and much lower for the 37.5 µg b.i.d. group (Figure 5-10 and Table 5-9); this was also the case at Day 16, i.e. over the final dosing interval though the difference was smaller.

Figure 5-10 Peak FEV_1 (L), B2223, dose regimen study in asthma patients



Data are unadjusted means and 90% confidence intervals; Baseline = mean of D-1 profiles matching D15+16/D1 pre-dose. Average numbers of patients per treatment group N=47 (left hand plot) and N=44 (right hand plot)

Table 5-9 Peak FEV_1 (L), B2223, dose regimen study in asthma patients

			Change from baseline		
PD parameter	**Day**	**Treatment**	**Mean**	**Lower 90% CI**	**Upper 90% CI**
Peak FEV_1	1	37.5 µg b.i.d	0.127	0.065	0.190
	(over first dosing	75 µg o.d	0.357	0.294	0.421
	interval)	150 µg q.o.d	0.423	0.361	0.485
		Placebo	0.273	0.209	0.336
	15/16	37.5 µg b.i.d	0.364	0.293	0.435
	(over final dosing	75 µg o.d	0.447	0.376	0.518
	interval)	150 µg q.o.d	0.529	0.457	0.602
		Placebo	0.261	0.187	0.336

Analyzed for PD analysis set

Conclusions

- This study in a bronchoreactive asthmatic population provides clear evidence that once-daily dosing is appropriate for indacaterol.
- Although the b.i.d. and q.o.d. regimens of indacaterol do provide bronchodilation in asthma patients, the 37.5 µg b.i.d. regimen did not reach the same peak FEV_1 and had a lower trough FEV_1 than 75 µg o.d. (which also suggests that a 37.5 µg o.d. regimen would not be effective), and 150 µg q.o.d. had lower AUC (0-48 h) and AUC (24-48 h) for FEV_1 than 75 µg o.d., suggesting a diminishing effect after the first 24 hours after dosing.

5.1.5 B2356 - dose ranging study in COPD

Purpose

This study was performed with the intention to further explore dose-response at lower doses in COPD patients, to complement Stage 1 of Study B2335S.

Study design

This was a double-blind, double-dummy placebo- and active-controlled trial with a 14-day treatment period, performed in patients with moderate to severe COPD and a smoking history of at least 10 pack years. Patients were randomized to indacaterol 18.75, 37.5, 75, 150 µg o.d., placebo, or salmeterol 50 µg b.i.d. in a ratio of 1:1:1:1:1:1. Patients were stratified by smoking status and ICS use.

Primary efficacy endpoint

The primary efficacy endpoint was trough FEV_1 on Day 15, analyzed using the model described in Section 5.1.1. The MCID for comparisons with placebo of trough FEV_1 was pre-defined as 0.12 L.

Secondary efficacy endpoint

Secondary efficacy variables included trough FEV_1 at Day 2 and Day 14, peak FEV_1, standardized AUC FEV_1 (5 min – 4 h), standardized AUC FEV_1 (5 min – 11 h 45 min), and standardized AUC FEV_1 (5 min – 23 h 45 min) for the serial spirometry subgroup at Day 14.

Study results

Disposition

A total of 552 patients were randomized, 547 patients exposed to treatment and 531 (96.2%) completed the study as planned. The percentage of patients who discontinued prematurely was highest in the indacaterol 18.75 µg group (8.7%). The most common reason for discontinuation was for adverse events, which occurred more frequently in the indacaterol 18.75 µg treatment group (5.4%) compared with the other treatment groups. Protocol deviations accounted for 0.4% (2 patients) of withdrawals.

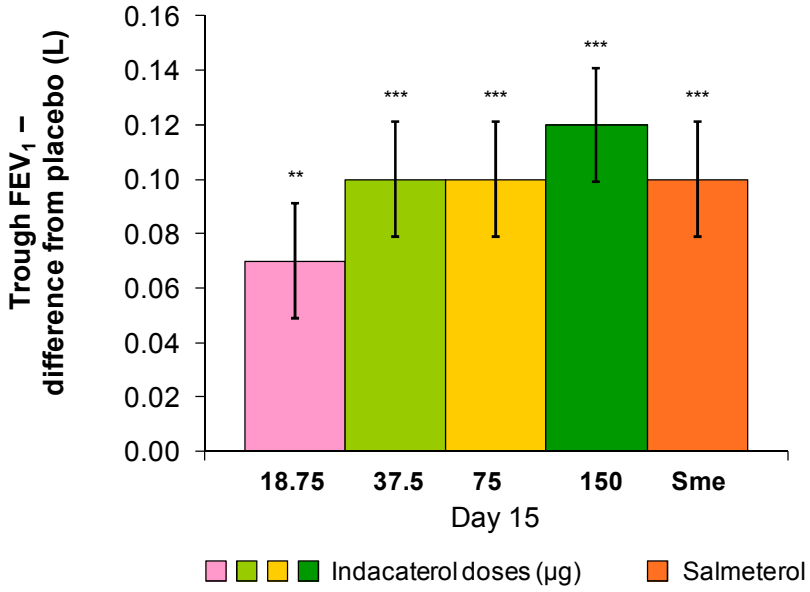
Baseline characteristics

Treatment groups were generally well matched for demographic and baseline disease characteristics. Overall, mean age was 62.6 years, with a range of 40 to 87 years, approximately 54% of patients were male and the majority were Caucasian. Less than half of patients (37%) were using inhaled corticosteroids at entry into the study. A greater proportion (55%) of patients were current smokers than ex-smokers and the overall smoking history in terms of the mean number of pack years for all patients was 51.5. Baseline lung function at screening was similar across treatment groups.

Primary efficacy- trough FEV_1

The greatest LS mean trough FEV_1 value was observed in the indacaterol 150 µg group, together with the greatest LS mean difference to placebo (0.12 L, meeting the MCID, Figure 5-11, Table 5-10).

Figure 5-11 Trough FEV_1 (L) at Day 15, B2356, dose-ranging in COPD



*p<0.05, **p<0.01, ***p<0.001 vs placebo; Data are least squares means ± standard errors (Full analysis set).
Average number of patients per treatment group N=86

Table 5-10 Trough FEV_1 (L) at Day 15, B2356, dose-ranging in COPD

		Treatment			Treatment difference			
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**	**p-value**
Ind 18.75 µg	82	1.35	0.020	Ind 18.75 µg – Pbo	0.07	0.027	(0.02, 0.12)	0.008*
Ind 37.5 µg	84	1.38	0.019	Ind 37.5 µg – Pbo	0.10	0.027	(0.05, 0.16)	<0.001*
Ind 75 µg	87	1.38	0.019	Ind 75 µg – Pbo	0.10	0.026	(0.04, 0.15)	<0.001*
Ind 150 µg	90	1.40	0.019	Ind 150 µg – Pbo	0.12	0.026	(0.07, 0.17)	<0.001*
Sme	88	1.39	0.019	Sme – Pbo	0.10	0.026	(0.05, 0.16)	<0.001*
Pbo	86	1.28	0.019					

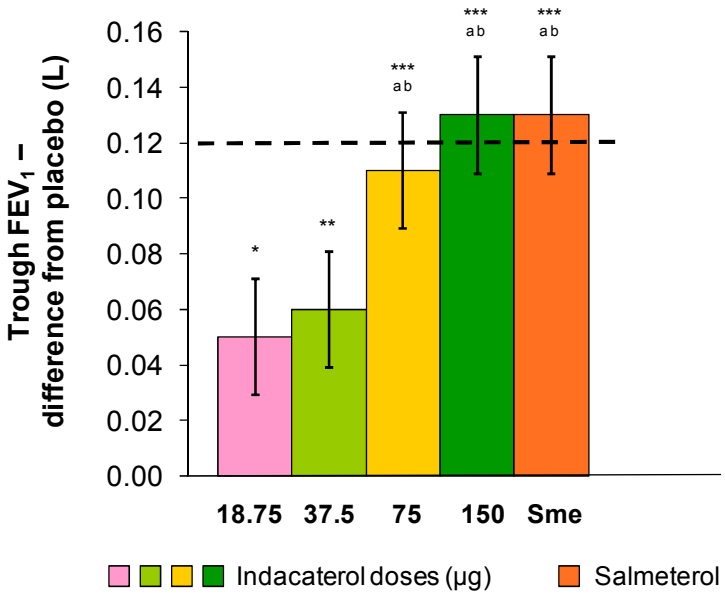
LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval. Imputed with LOCF
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + ICS use + smoking history + center, with center as a random effect. Analyzed for Full Analysis Set. Sme = salmeterol, Pbo = placebo
* In this analysis the testing does not control for the type I error and in addition there is no power for contrasts between active doses.
Hence all p-values are to be regarded as descriptive and interpreted in this context.
A missing trough FEV_1 value at Day 15 was imputed with the Day 14 trough value if available.

Secondary efficacy

Trough FEV_1 after first dose

At Day 2 (i.e. after the first dose), the LS mean difference to placebo in trough FEV_1 exceeded the MCID only for indacaterol 150 µg and salmeterol, indicating that of the indacaterol doses, only 150 µg provided optimal bronchodilation from the first dose (Figure 5-12 and Table 5-11).

Figure 5-12 Trough FEV_1 (L) at Day 2, B2356, dose-ranging in COPD



Dotted line shows prespecified 120 mL level of clinically important difference.
*p<0.05, **p<0.01, ***p<0.001 vs placebo; [a]p<0.05 vs 18.75 µg; [b]p<0.05 vs 37.5 µg; Data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=88

Table 5-11 Trough FEV_1 (L) at Day 2, B2356, dose-ranging in COPD

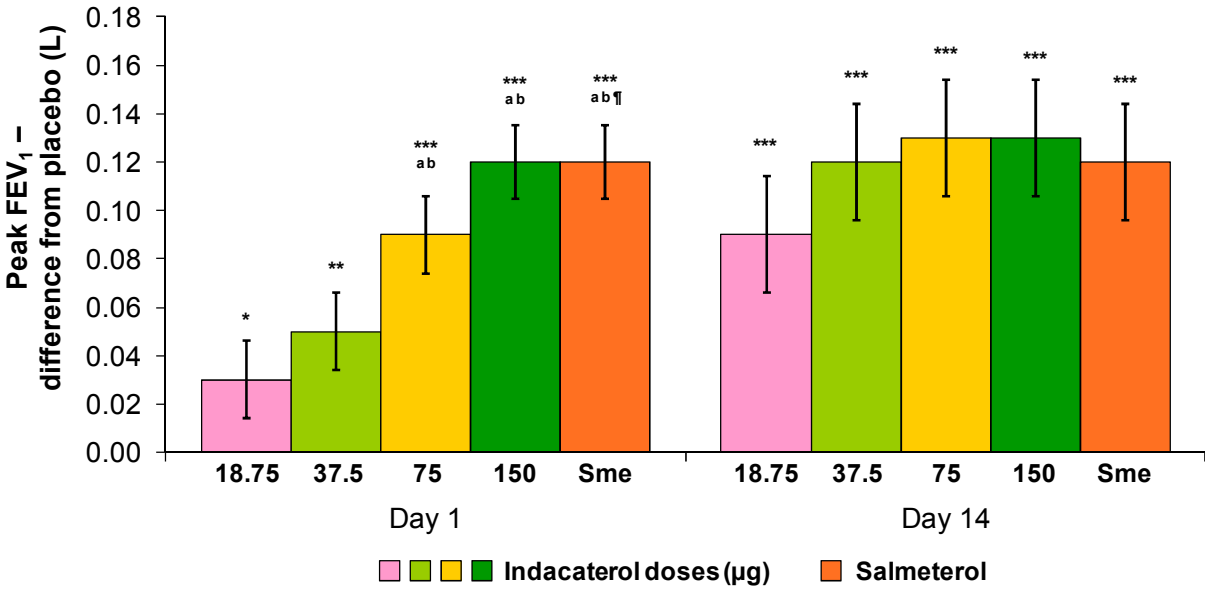
		Treatment			Treatment difference			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Day 2								
Ind 18.75 µg	85	1.33	0.015	Ind 18.75 µg - Pbo	0.05	0.021	(0.01, 0.09)	0.016
Ind 37.5 µg	86	1.34	0.015	Ind 37.5 µg - Pbo	0.06	0.021	(0.02, 0.10)	0.004
Ind 75 µg	88	1.38	0.015	Ind 75 µg - Pbo	0.11	0.021	(0.06, 0.15)	<0.001
Ind 150 µg	91	1.40	0.014	Ind 150 µg - Pbo	0.13	0.021	(0.09, 0.17)	<0.001
Sme	88	1.41	0.015	Sme - Pbo	0.13	0.021	(0.09, 0.17)	<0.001
Pbo	86	1.28	0.015					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + ICS use + smoking history + center, with center as a random effect. Analyzed for Full Analysis Set. Sme = salmeterol, Pbo = placebo

Peak FEV_1 after first dose and at Day 14

The LS mean difference versus placebo after the first dose (i.e. at Day 1) for peak FEV_1 was greatest for indacaterol 150 µg (0.12 L, similar to that for salmeterol), again indicating that 150 µg was the only indacaterol dose to achieve its optimum effect from the first dose (Figure 5-13 and Table 5-12).

Figure 5-13 Peak FEV_1 (L) in first 4 hours post morning dose, B2356, dose-ranging in COPD



*p<0.05, **p<0.01, ***p<0.001 vs placebo; [a]p<0.05 vs 18.75 µg; [b]p<0.05 vs 37.5 µg; ¶p<0.05 vs 75 µg; data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=89 (Day 1) and N=86 (Day 14)

Table 5-12 Peak FEV_1 (L) in first 4 hours post morning dose, B2356, dose-ranging in COPD

		Treatment			Treatment difference			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Day 1								
Ind 18.75 µg	87	1.42	0.011	Ind 18.75 µg - Pbo	0.03	0.016	(0.00, 0.06)	0.043
Ind 37.5 µg	88	1.44	0.011	Ind 37.5 µg - Pbo	0.05	0.016	(0.02, 0.08)	0.001
Ind 75 µg	89	1.48	0.011	Ind 75 µg - Pbo	0.09	0.016	(0.06, 0.12)	<0.001
Ind 150 µg	90	1.51	0.011	Ind 150 µg - Pbo	0.12	0.015	(0.09, 0.15)	<0.001
Sme	90	1.51	0.011	Sme - Pbo	0.12	0.015	(0.09, 0.15)	<0.001
Pbo	87	1.39	0.011					
Day 14								
Ind 18.75 µg	82	1.48	0.018	Ind 18.75 µg - Pbo	0.09	0.024	(0.04, 0.13)	<0.001
Ind 37.5 µg	84	1.52	0.017	Ind 37.5 µg - Pbo	0.12	0.024	(0.08, 0.17)	<0.001
Ind 75 µg	87	1.52	0.017	Ind 75 µg - Pbo	0.13	0.024	(0.08, 0.18)	<0.001
Ind 150 µg	90	1.52	0.017	Ind 150 µg - Pbo	0.13	0.024	(0.08, 0.18)	<0.001
Sme	88	1.51	0.017	Sme - Pbo	0.12	0.024	(0.07, 0.17)	<0.001
Pbo	83	1.39	0.018					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: peak FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + ICS use + smoking history + center, with center as a random effect. Analyzed for Full Analysis Set. Sme = salmeterol, Pbo = placebo

Conclusions

- This study suggests that indacaterol doses of 75 µg and 150 µg were more effective than lower doses in COPD patients.
- The 150 µg dose appeared to achieve optimal bronchodilation more rapidly than the 75 µg dose (from the first dose onward) and tended to show better bronchodilation at most time points.

5.1.6 Conclusions from dose ranging and dose regimen studies

The dose-ranging and dose regimen studies aimed to identify an optimal dose of indacaterol for the treatment of COPD, to identify a minimum effective dose, and to confirm that the once-daily dose regimen is appropriate.

Stage 1 of Study B2335S was designed to identify optimal doses of indacaterol for the treatment of COPD, by evaluating efficacy relative to current therapies. Stage 1 of this study, following its pre-defined selection rules, identified doses of 150 and 300 µg o.d. to take forward into Stage 2 for further evaluation, on the basis that these doses met the MCID versus placebo for COPD and were numerically more effective than formoterol and tiotropium.

Evaluation of lower doses of indacaterol in Studies B2357 and B2356 aimed to identify a minimum effective dose. Both studies showed a dose response for indacaterol, but in Study B2356, which was conducted in COPD patients, a less pronounced dose response was noted from the 37.5 µg to 150 µg doses, whereas in Study B2357, where a bronchoreactive population (asthmatics) was evaluated, there appeared to be a better differentiation of the lower doses of indacaterol. For trough FEV_1 on Day 15 in Study B2357 (the primary endpoint), the indacaterol 75 µg and 150 µg treatment groups had greater LS mean treatment differences compared with placebo than the 18.75 µg and 37.5 µg groups. Taken together, these studies suggest that the 18.75 and 37.5 µg doses are less likely to provide sufficient bronchodilation in a clinical setting to adequately manage COPD.

The 150 µg dose achieved optimal bronchodilation more rapidly than the 75 µg dose (from the first dose onward), which may be an advantage in COPD patients. Trough FEV_1 on Day 2 (i.e. after the first dose) showed a dose response in both B2356 (in COPD patients) and B2357 (in asthma patients). In the former study, the greatest differences to placebo were for indacaterol 150 µg o.d. (the only dose to achieve the MCID). In Study B2357, differences to placebo were much greater for 75 and 150 µg than for lower doses. Other spirometry assessments in Studies B2356 and B2357 support these findings, as do the results of Study B2335S.

The dose-regimen study in bronchoreactive (i.e. asthma) patients, Study B2223, demonstrated that a once-daily dose regimen is appropriate for indacaterol. This is further supported by 24-hour spirometry in Study B2357, which showed that the bronchodilator effects of indacaterol are sustained over 24 hours regardless of dose.

When considered together, the results of Studies B2357, B2223, B2356, and B2335S indicate that the dose response relationship has been well characterized and that the 75 and 150 µg doses, administered once daily, provide clinically relevant levels of bronchodilation in patients with COPD. Doses of indacaterol of 18.75 µg o.d. and 37.5 µg o.d. were sub-optimal because they demonstrated a less robust bronchodilator response across the different dose-

ranging studies. The 75 µg dose is the minimum effective dose with the 150 µg dose providing incremental benefits in terms of effects on lung function.

5.2 Key confirmatory efficacy studies: the Phase 3 program

5.2.1 Purpose of key confirmatory efficacy studies

The core of the indacaterol clinical development program consists of 6 placebo-controlled, parallel group, randomized studies (with an additional placebo-controlled safety extension to one study) that characterized the efficacy and safety of indacaterol in a range of doses from 75 µg to 600 µg o.d. for treatment periods of up to 1 year.

The 75 µg o.d. dose is supported by two 12-week pivotal studies, Study B2354 and Study B2355, and the 150 µg o.d. dose by three key pivotal studies, Study B2335S (26 weeks), Study B2336 (26 weeks) and Study B2346 (12 weeks). In addition, a long-term (52 week) efficacy and safety study using 300 and 600 µg o.d. indacaterol was conducted (B2334) and there was a 26-week extension to Study B2335S, giving a total duration of 52 weeks for doses of 150 and 300 µg o.d. (B2335SE).

Several studies included active comparators such as formoterol (delivered via the Aerolizer®), salmeterol (via the Diskus®), and tiotropium (via the HandiHaler®). The key studies supporting the efficacy of indacaterol are shown in Table 5-13.

Table 5-13 Summary of key confirmatory efficacy studies

Study	Randomized patients	Treatment duration	Dosage
B2355	318	12 weeks	Indacaterol 75 µg o.d. Placebo o.d.
B2354	323	12 weeks	Indacaterol 75 µg o.d. Placebo o.d.
B2335S*	1683	26 weeks	Indacaterol 150 & 300 µg o.d. Tiotropium 18 µg o.d. Placebo o.d.
B2336*	1002	26 weeks	Indacaterol 150 µg o.d. Salmeterol 50 µg b.i.d. Placebo b.i.d.
B2346	416	12 weeks	Indacaterol 150 µg o.d. Placebo o.d.
B2334*	1732	52 weeks	Indacaterol 300 & 600 µg o.d. Formoterol 12 µg b.i.d. Placebo b.i.d.
B2335SE	415	26 weeks (additional to initial 26 weeks)	Indacaterol 150 & 300 µg o.d. Placebo o.d.

* Study was both placebo-controlled and active-controlled

Although the 300 µg dose is not proposed for the United States, data from this dose are included here for completeness, given that this dose is approved in over 50 countries. Efficacy data for the 600 µg dose in Study B2334 are not presented: this dose has not been submitted to any regulatory authority for approval.

5.2.2 Study design, key confirmatory efficacy studies

The general study designs for the key efficacy studies were very similar, with the exception of Study B2335S. The studies were parallel-group, placebo or placebo and active controlled, with treatment duration of 12, 26 or 52 weeks. Patients were equally allocated between treatment groups in each study.

As described in Section 5.1.2, B2335S was the adaptive seamless design study where a 2 week dose selection (Stage 1) was followed by the core study (Stage 2) for 26 weeks and then an extension in a subset of patients of the core study for an additional 26 weeks.

Study populations

Patients included were: male or female ≥ 40 years of age, a diagnosis of COPD (moderate to severe as classified by the GOLD Guidelines with a post-bronchodilator FEV_1 < 80% and ≥ 30% of the predicted normal value and a post-bronchodilator FEV_1/FVC < 70%, and a history of cigarette smoking for ≥ 20 pack-years (except for studies B2354 and B2355 where it was ≥ 10 pack-years).

Patients were excluded if they had a history of asthma, prolonged QTc interval, a history of a respiratory infection or (except in Study B2335S) a COPD exacerbation in the past 6 weeks prior to the screening visit, or patients who, in the judgment of the investigator had a clinically relevant laboratory abnormality or a clinically significant condition which might compromise patient safety or compliance. Concurrent respiratory medications were not allowed during the study with the exception of short-acting β_2-agonists for rescue and inhaled corticosteroids if the patient was receiving therapy before entering the study.

Primary efficacy endpoint

The primary endpoint was the 24 hour trough FEV_1 after 12 weeks of treatment. Trough FEV_1 was defined as the mean of two measurements, the 23 h 10 min and the 23 h 45 min post-dose values. In all of the studies, a treatment-placebo difference in trough FEV_1 of 0.12 L was pre-specified in the protocol as being the MCID. The 0.12 L value exceeds the 0.10 L described by Donohue et al (2005) as a difference which patients can perceive, and is also the midpoint of the 0.10 - 0.14 L range proposed by the ATS/ERS taskforce as a minimal important difference in FEV_1 (Cazzola et al 2008).

Secondary efficacy endpoints

Secondary endpoints included:

- BDI/TDI: dyspnea was assessed at baseline using the baseline dyspnea index (BDI) and during the treatment period using the transition dyspnea index (TDI), which captures changes from baseline. The TDI has three domains; functional impairment, magnitude of task and magnitude of effort and is administered by a trained assessor. The defined difference from placebo of +1.0 unit is the validated minimally clinically important difference (MCID).
- Area under the curve (AUC) of FEV_1 standardized (with respect to time) for various intervals of interest, peak FEV_1, FEV_1 and FVC at each post-baseline time point, the percentage of COPD 'days with poor control', total Saint George's Respiratory

Questionnaire (SGRQ) score, use of rescue medication, COPD exacerbations, and daytime and nighttime symptoms.

- The SGRQ was used to measure health status. It is a self-administered questionnaire comprised of 16 questions that assess disease symptoms, disturbances to patients' daily physical activity, and the impact of the disease on the patient. It is frequently used as a quality of life assessment in clinical trials conducted in drug development programs. The defined difference from placebo that is the validated minimal clinically meaningful effect is -4.0 units (Jones 2002).
- Use of rescue medication, and daytime and nighttime symptoms were recorded by the patient using a daily diary. Daytime and nighttime symptoms were then used to calculate the percentage of 'days of poor control'.

Statistical methods

Statistical analyses

Unless stated otherwise all analyses were pre-planned and included in analysis plans that were finalized prior to database lock.

The primary variable (imputed with LOCF) was summarized by treatment and analyzed using a mixed model for the Full Analysis Set (FAS) in B2354, B2355, the Intention-to-Treat population (ITT) in B2335S, B2336, B2346 or the modified Intention-to-Treat population (mITT) in B2334). The FAS/ITT/mITT included all randomized patients who received at least one dose of study drug. Following the ITT principle patients were analyzed according to the treatment to which they were randomized. The mITT population used for B2334 excluded patient data from Egypt after the discovery of GCP violations; however, the conclusions from this population were the same as for the ITT.

The model contained treatment as a fixed effect with the baseline FEV_1 measurement, FEV_1 prior to inhalation and FEV_1 10-15 min post inhalation of albuterol (components of SABA reversibility) as covariates. Additionally FEV_1 prior to inhalation and FEV_1 1 hour post inhalation of ipratropium (components of anti-cholinergic reversibility) were included in the model for studies where collected. Additionally, to reflect the randomization scheme in the specific study the model also included the baseline smoking status (current/ex-smoker) and inhaled corticosteroid use at trial entry (yes/no) as fixed effects with center or center within country as a random effect.

A strategy for dealing with missing data was included in the analysis plan.

Methods used to handle multiple hypothesis testing

In each of the key confirmatory trials, secondary endpoints were categorized according to their relative importance (Table 5-14). The probability of a false positive conclusion (alpha) was controlled across the primary and selected secondary endpoints within studies by using a hierarchical testing procedure (i.e. test the primary endpoint, if that is statistically significant, test the key secondary endpoint etc).

Table 5-14 Summary of end points with alpha protection, key confirmatory studies

	Study				
	B2334	**B2335S**	**B2336**	**B2354**	**B2355**
Dose supported	150 µg	150 µg	150 µg	75 µg	75 µg
Primary endpoint	Trough FEV_1 at Week 12	Trough FEV_1 at Week 12 (superiority versus placebo)	Trough FEV_1 at Week 12	Trough FEV_1 at Week 12	Trough FEV_1 at Week 12
Key Secondary endpoint	COPD days of poor control over 52 weeks	Trough FEV_1 at Week 12 (non-inferiority versus tiotropium)	SGRQ total score at Week 12	TDI focal score at Week 12	TDI focal score at Week 12
Important Secondary endpoint	Time to first COPD exacerbation	COPD days of poor control over 26 weeks	COPD days of poor control over 26 weeks		
Important Secondary endpoint	SGRQ total score at Week 12				

Secondary efficacy endpoints

Secondary efficacy endpoints were pre-defined in the study protocol and the methods of analysis described in the analysis plan signed-off prior to database lock. These endpoints were analyzed and summarized by treatment for the FAS/ITT/mITT populations (depending on the study) only and in most cases analyzed using a similar mixed model to the primary endpoint replacing the baseline value with an appropriate one for the selected end point.

5.2.3 Results of key confirmatory efficacy studies

Patient disposition

Similar percentages of patients completed treatment across treatment groups within studies and across different studies: in most cases 80-90% of patients completed the studies. The majority of discontinuations were due to adverse events (3-5%) followed by withdrawing consent (2-6%) and protocol deviations (1-2%).

Baseline characteristics

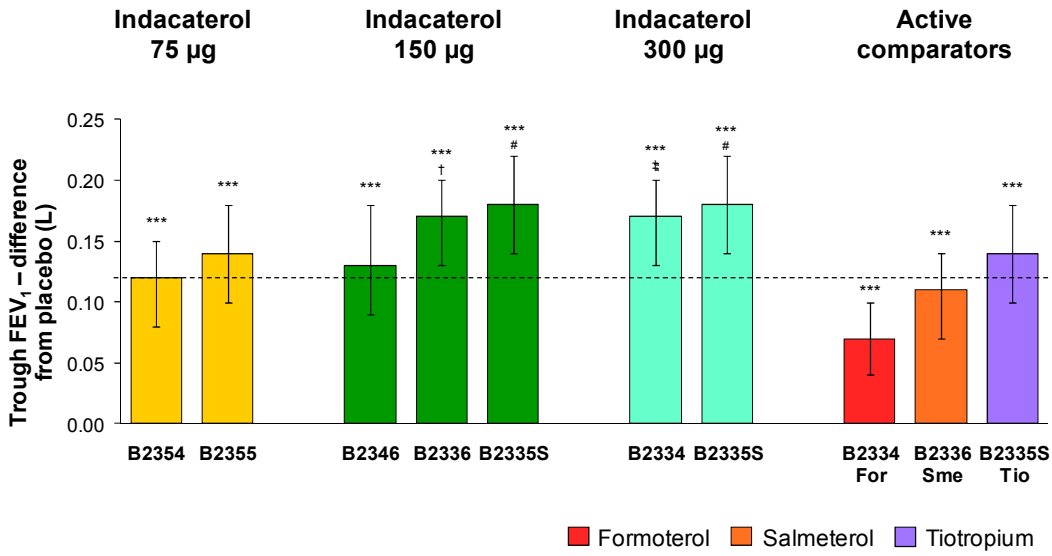
In the studies with 75 and 150 µg indacaterol, the randomized patients ranged in age from 40 to 90 years with means in each study of 61-64 years. The majority of patients in each study were male (52 to 75%) and Caucasian (≥ 76%). There was a higher proportion of current smokers than ex-smokers in most studies with the exception of Studies B2355 and B2346. Baseline lung function values were similar between treatment groups within and across studies. Mean post-bronchodilator FEV_1 was between 53% and 56% predicted, consistent with the GOLD definition of moderate to severe COPD for the study population. Approximately 32% - 45% of patients in studies received concomitant ICS. Previous and concurrent diseases were comparable across treatment arms. In all key efficacy studies, the most commonly reported diseases, besides COPD, included hypertension, gastroesophageal reflux disorder, depression, osteoarthritis and hyperlipidemia. Approximately 40% of patients in studies had 3 or more cardiovascular risk factors. There were no differences in baseline characteristics between treatment groups in the studies that would be expected to significantly

affect the outcomes of the studies. The study populations were representative of patients with moderate to severe COPD.

Primary efficacy: trough FEV_1 at Week 12

Both 75 and 150 µg of indacaterol met the MCID versus placebo of 0.12 L (Figure 5-14, Table 5-15).

Figure 5-14 Primary efficacy results (Trough FEV_1 at Week 12), key confirmatory efficacy studies



Dotted line shows prespecified 120 mL level of clinically important difference.
Data are least squares means with 95% confidence intervals. ***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study); #p<0.05 vs tiotropium (within study); ‡p<0.05 vs formoterol (within study)

Table 5-15 Primary efficacy results (Trough FEV_1 at Week 12), key confirmatory efficacy studies

Study	Treatment	LS mean difference from placebo (L) (95% CI)	LS mean difference from active comparator (L)
B2355	Indacaterol 75 µg	**0.14** (0.10, 0.18)	N/A
B2354	Indacaterol 75 µg	**0.12** (0.08, 0.15)	N/A
B2335S	Indacaterol 150 µg	**0.18** (0.14, 0.22)	**0.05*** (0.01, 0.09) (Tio)
B2336	Indacaterol 150 µg	**0.17** (0.13, 0.20)	**0.06** (0.02, 0.10) (Sme)
B2346	Indacaterol 150 µg	**0.13** (0.09, 0.18)	N/A
B2335S	Indacaterol 300 µg	**0.18** (0.14, 0.22)	**0.04*** (0.00, 0.08) (Tio)
B2334	Indacaterol 300 µg	**0.17** (0.13, 0.20)	**0.10** (0.07, 0.13) (For)
B2335S	Tiotropium	**0.14** (0.10, 0.18)	N/A
B2336	Salmeterol	**0.11** (0.07, 0.14)	N/A
B2334	Formoterol	**0.07** (0.04, 0.10)	N/A

*results are from the non-inferiority analysis for trough FEV_1, other endpoints are from the superiority analyses.
Values in bold p < 0.05.

Across the studies there was a trend for increasing magnitude of effect at higher doses: differences to placebo for the 75 µg dose ranged from 0.12 L to 0.14 L whereas those for the

150 µg dose ranged from 0.13 L to 0.18 L. Treatment with the 150 µg dose resulted in generally greater improvements in trough FEV_1 than the 75 µg dose, although there is variability between studies, despite their similar design and entry criteria. This issue is discussed further in Section 5.3.

Secondary efficacy: lung function parameters

Lung function after first dose and at Week 12

Similar trends to those seen with trough FEV_1 at week 12 were observed with trough FEV_1 at Day 2 (Table 5-16) and peak FEV_1 on Day 1 and at Week 12 (Table 5-17).

Table 5-16 Trough FEV_1 Day 2, key confirmatory efficacy studies

Study	Treatment	LS mean difference from placebo (L) (95% CI)	LS mean difference from active comparator (L)
B2355	Indacaterol 75 µg	**0.08** (0.05, 0.11)	N/A
B2354	Indacaterol 75 µg	**0.08** (0.06, 0.15)	N/A
B2335S	Indacaterol 150 µg	**0.11** (0.08, 0.13)	0.01* (-0.01, 0.03) (Tio)
B2336	Indacaterol 150 µg	**0.13** (0.10, 0.15)	0.00 (-0.02, 0.03) (Sme)
B2346	Indacaterol 150 µg	**0.08** (0.05, 0.12)	N/A
B2335S	Indacaterol 300 µg	**0.14** (0.12, 0.16)	**0.04*** (0.02, 0.07) (Tio)
B2334	Indacaterol 300 µg	**0.14** (0.11, 0.16)	**0.02** (0.00, 0.04) (For)
B2335S	Tiotropium	**0.10** (0.07, 0.12)	N/A
B2336	Salmeterol	**0.12** (0.10, 0.15)	N/A
B2334	Formoterol	**0.11** (0.09, 0.13)	N/A

*results are from the non-inferiority analysis for trough FEV_1, other endpoints are from the superiority analyses.
Values in bold p < 0.05.

The 150 µg dose generally provided greater bronchodilation than the 75 µg dose from Day 1 onward.

Table 5-17 Peak FEV_1 Day 1 & Week 12, key confirmatory efficacy studies

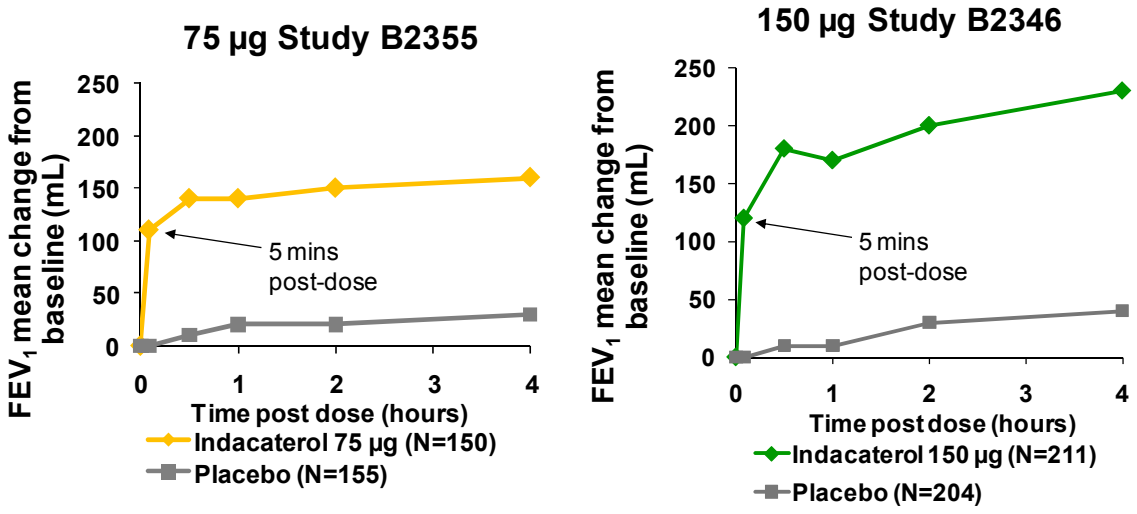
		LS mean difference (L) (95% CI)			
		Day 1		Week 12	
Study	Treatment	Vs. placebo	Vs active comparator	Vs. placebo	Vs active comparator
B2355	Ind 75 µg	**0.11** (0.08, 0.13)	N/A	**0.17** (0.13, 0.22)	N/A
B2354	Ind 75 µg	**0.11** (0.09, 0.13)	N/A	**0.16** (0.13, 0.20)	N/A
B2335S	Ind 150 µg	**0.14** (0.12, 0.17)	-0.01 (-0.03, 0.02) (Tio)	**0.21** (0.14, 0.28)	0.05 (-0.02, 0.11) (Tio)
B2336	Ind 150 µg	**0.12** (0.09, 0.16)	0.02 (-0.02, 0.06) (Sme)	**0.19** (0.12, 0.25)	0.01 (-0.06, 0.07) (Sme)
B2346	Ind 150 µg	**0.19** (0.14, 0.25)	N/A	**0.16** (0.10, 0.21)	N/A
B2335S	Ind 300 µg	**0.17** (0.15, 0.20)	0.02 (0.00, 0.05) (Tio)	**0.21** (0.14, 0.28)	0.05 (-0.01, 0.12) (Tio)
B2334	Ind 300 µg	**0.18** (0.14, 0.22)	0.02 (-0.02, 0.06) (For)	**0.21** (0.15, 0.28)	0.05 (-0.01, 0.11) (For)
B2335S	Tio	**0.15** (0.12, 0.18)	N/A	**0.16** (0.09, 0.23)	N/A
B2336	Sme	**0.10** (0.07, 0.14)	N/A	**0.18** (0.12, 0.25)	N/A
B2334	For	**0.16** (0.12, 0.20)	N/A	**0.16** (0.10, 0.23)	N/A

Ind = indacaterol, Tio = tiotropium, Sme = salmeterol, For = formoterol
Values in bold p < 0.05.

Onset of action

Both the 75 and 150 µg doses of indacaterol had a rapid onset of action. Figure 5-15 shows FEV_1 for the first 4 hours after dosing in Studies B2355 and B2346.

Figure 5-15 Onset of action on Day 1, Studies B2355 and B2346



Data are unadjusted means

Feldman et al. BMC Pulmon Med 2010

FEV_1 5 minutes after dosing was 0.09-0.10 L greater than placebo for the 75 µg dose and 0.10-0.13 L greater than placebo for the 150 µg dose (Table 5-18). The 150 µg dose of indacaterol had a greater magnitude of effect immediately after dosing than the 75 µg dose on Day 1 and attains optimal bronchodilation from the first dose onward.

Table 5-18 FEV_1 5 min post-dose on Day 1 (L), key confirmatory efficacy studies

Study	Treatment	LS mean difference from placebo (L)
B2355	Indacaterol 75 µg	**0.10** (0.08, 0.12)
B2354	Indacaterol 75 µg	**0.09** (0.07, 0.10)
B2335S	Indacaterol 150 µg	**0.12** (0.10, 0.14)
B2336	Indacaterol 150 µg	**0.11** (0.09, 0.13)
B2346	Indacaterol 150 µg	**0.13** (0.10, 0.16)
B2335S	Indacaterol 300 µg	**0.12** (0.10, 0.14)
B2334	Indacaterol 300 µg	**0.13** (0.11, 0.15)
B2335S	Tiotropium	**0.06** (0.03, 0.08)
B2336	Salmeterol	**0.06** (0.04, 0.08)
B2334	Formoterol	**0.14** (0.12, 0.16)

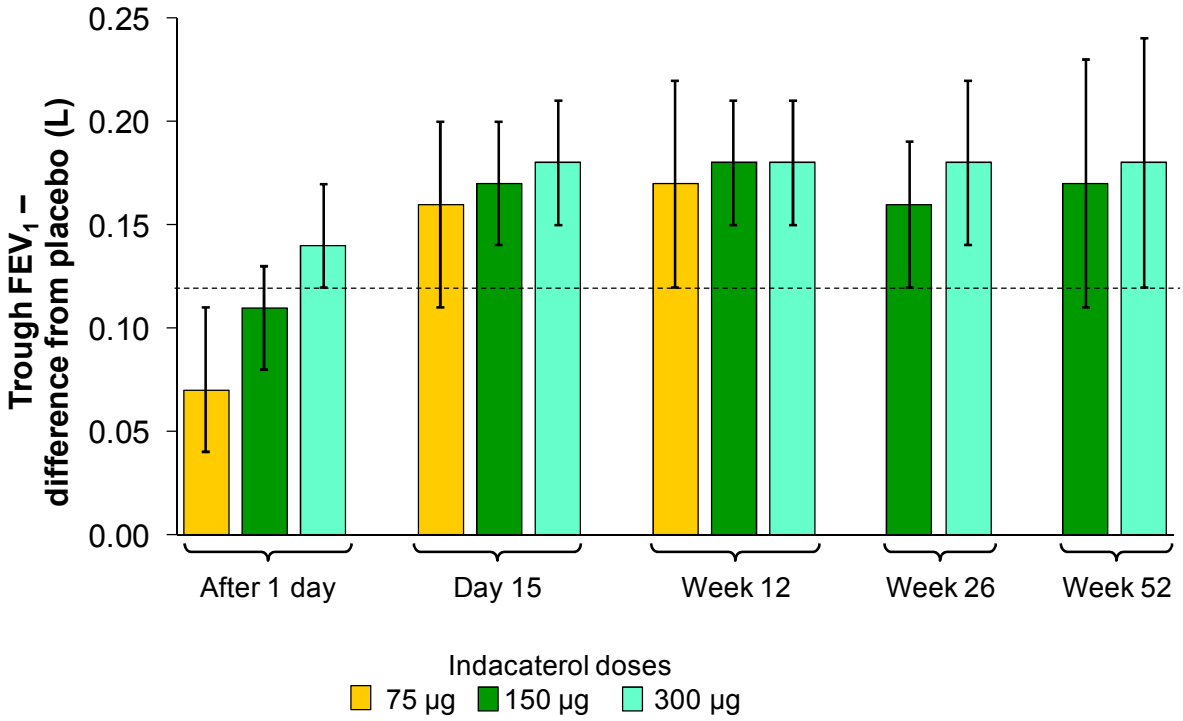
Values in bold $p < 0.05$.

Evaluation of potential for tachyphylaxis

Tolerance has been observed with b.i.d. LABAs such as formoterol (as noted in the Prescribing Information) and salmeterol (Donohue et al 2003). There was no evidence of

tachyphylaxis or tolerance over 52 weeks of treatment for either the 150 or the 300 µg doses of indacaterol with no loss of efficacy from Day 15 to Week 52 in Study B2335SE (Figure 5-16). There was no indication of any decrease in effect over time for the 75 µg dose up to 12 weeks (the maximum duration of treatment with this dose).

Figure 5-16 Trough FEV_1 over 52 weeks, Study B2335S/B2335SE



Dotted line shows prespecified 120 mL level of clinically important difference.
Data are least squares means with 95% confidence intervals. All p<0.001 vs placebo
Trough FEV_1 = mean of measurements at 23 h 10 min and 23 h 45 min post-dose

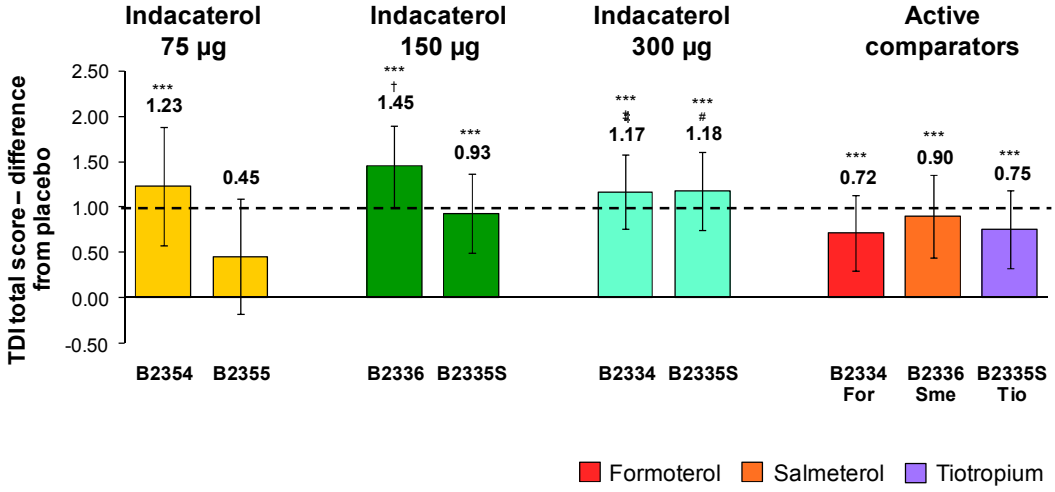
Secondary efficacy: symptomatic endpoints

Transition Dyspnea Index (TDI)

The effect of indacaterol on the relief of dyspnea was measured using the TDI. The validated MCID for this instrument is a difference from placebo of ≥ +1 unit.

The mean TDI total scores for the 75 and 150 µg doses of indacaterol in the key confirmatory efficacy studies (excluding B2346, where TDI was not measured) are presented in Figure 5-17. The 150 µg dose of indacaterol showed a consistently statistically significant effect across studies that approached or exceeded the MCID of ≥ +1 unit. The 75 µg dose only exceeded the MCID in Study B2354. In Study B2355, the difference to placebo of + 0.45 units was neither statistically significant nor clinically meaningful.

Figure 5-17 Transition Dyspnea Index total score at Week 12, key confirmatory efficacy studies



Dotted line indicates MCID (≥1.0).
Data are least squares means with 95% confidence intervals. TDI not assessed in B2346.
***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study); #p<0.05 vs tiotropium (within study); ‡p<0.05 vs formoterol (within study)

Responder analyses for TDI (Table 5-19), with response defined as a TDI of ≥ 1 unit, were performed using logistic regression. Results across studies generally favored the 150 µg dose over the 75 µg dose.

Table 5-19 Transition Dyspnea Index responder analysis at Week 12, key confirmatory efficacy studies

		Odds ratio for responder rate (95% CI)	
Study	**Treatment**	**vs. placebo**	**vs. active control**
B2355	Indacaterol 75 µg	1.58 (0.97, 2.57)	N/A
B2354	Indacaterol 75 µg	**2.19** (1.33, 3.60)	N/A
B2335S	Indacaterol 150 µg	**2.19** (1.58, 3.04)	1.16 (0.84, 1.59) (Tio)
B2336	Indacaterol 150 µg	**2.79** (1.92, 4.06)	1.31 (0.92, 1.87) (Sme)
B2335S	Indacaterol 300 µg	**2.89** (2.08, 4.01)	**1.52** (1.11, 2.09) (Tio)
B2334	Indacaterol 300 µg	**2.80** (2.02, 3.89)	**1.61** (1.17, 2.21) (For)
B2335S	Tiotropium	**1.90** (1.37, 2.62)	N/A
B2336	Salmeterol	**2.13** (1.47, 3.10)	N/A
B2334	Formoterol	**1.74** (1.26, 2.40)	N/A

TDI was not assessed in Study B2346
Values in bold p < 0.05.

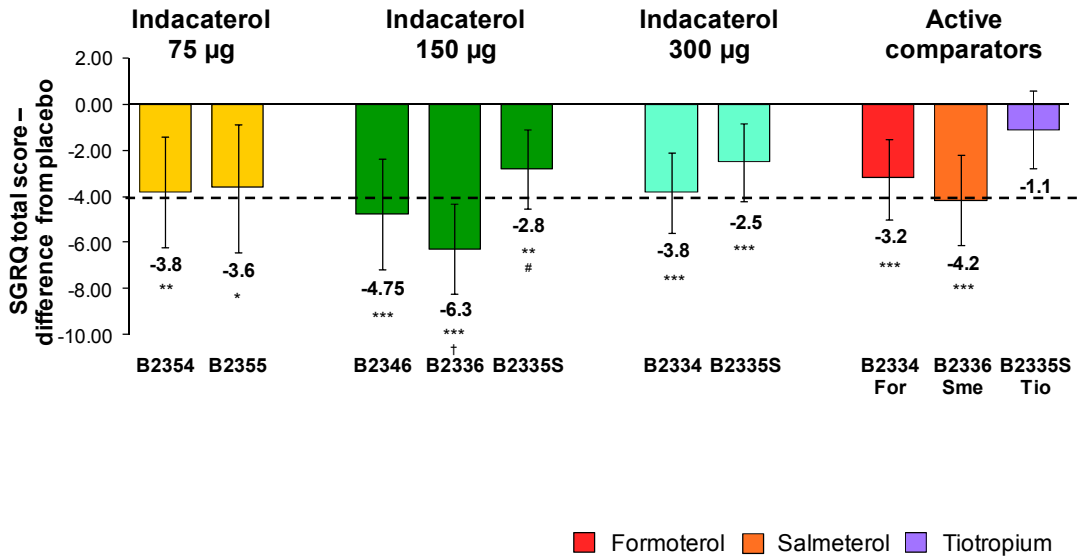
The 150 µg dose also demonstrated incremental benefit over tiotropium and salmeterol. Although not shown in Table 5-19, the 300 µg dose provided a more consistent effect than the 150 µg dose over 6 months. At 3 months, the LS mean difference from placebo was 1.25 versus 1.26; at 6 months, the LS mean difference from placebo was 1.00 versus 1.26, for the 150 and 300 µg doses, respectively. All values were statistically significant versus placebo, p<0.001.

Health status scores: St George's Respiratory questionnaire (SGRQ)

The SGRQ is one of the most commonly used measures of health status in patients with COPD. In the SGRQ a decrease is viewed as an improvement and the validated defined difference versus placebo that represents the minimal clinically meaningful effect is -4.0 units.

Mean differences versus placebo and active comparators in SGRQ total scores for the 75 and 150 µg doses of indacaterol in the key confirmatory efficacy studies are presented in Figure 5-18. The 150 µg dose of indacaterol showed a statistically significant effect across studies that mostly exceeded the MCID, whereas the 75 µg dose of indacaterol failed to achieve the MCID in both studies. In Study B2335S there was a higher placebo response than in the other studies and this likely contributed to the lower magnitude of effect of 150 µg versus placebo. Indacaterol 150 µg was associated with greater improvement in health status than either tiotropium or salmeterol in Studies B2335S and B2336, respectively.

Figure 5-18 St George's Respiratory Questionnaire total score at Week 12, key confirmatory efficacy studies



Dotted line indicates MCID (≤–4.0).
Data are least squares means with 95% confidence intervals.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study);
#p<0.05 vs tiotropium (within study)

Responder analysis for SGRQ, with response defined as having a decrease of ≥ 4 units, is shown in Table 5-20. Response rates for all indacaterol doses in all of the key confirmatory studies were statistically significantly higher than for placebo, except for the 300 µg dose in Study B2335S, where there was a higher placebo response than seen in other studies.

Table 5-20 St George's Respiratory Questionnaire, responder analysis at Week 12, key confirmatory efficacy studies

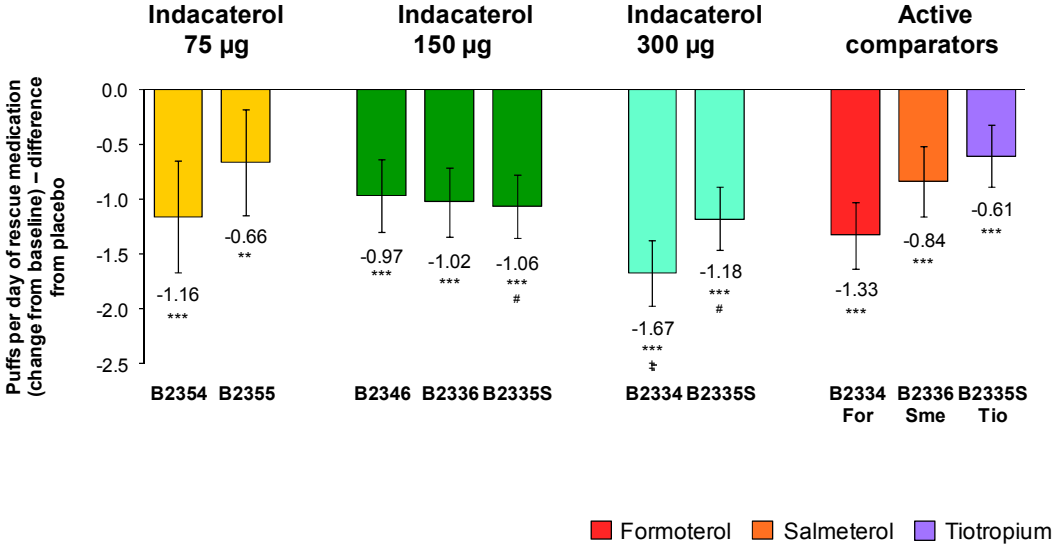
		Odds ratio for responder rate (95% CI)	
Study	**Treatment**	**vs. placebo**	**vs. active control**
B2355	Indacaterol 75 µg	**1.71** (1.05, 2.78)	N/A
B2354	Indacaterol 75 µg	**1.80** (1.08, 2.98)	N/A
B2335S	Indacaterol 150 µg	**1.40** (1.03, 1.91)	1.31 (0.97, 1.78) (Tio)
B2336	Indacaterol 150 µg	**2.41** (1.69, 3.42)	**1.59** (1.12, 2.25) (Sme)
B2346	Indacaterol 150 µg	**2.15** (1.39, 3.32)	N/A
B2335S	Indacaterol 300 µg	1.32 (0.97, 1.79)	1.23 (0.91, 1.67) (Tio)
B2334	Indacaterol 300 µg	**1.59** (1.16, 2.18)	1.00 (0.74, 1.36) (For)
B2335S	Tiotropium	1.07 (0.79, 1.45)	N/A
B2336	Salmeterol	**1.52** (1.06, 2.16)	N/A
B2334	Formoterol	**1.59** (1.16, 2.17)	N/A

Values in bold p < 0.05.

Rescue Medication Use and Daytime and Nighttime Symptoms

Rescue medication use was similar across studies for the 75 and 150 µg doses except in Study B2355 in which the mean decrease from baseline in the number of daily puffs of rescue medication was less than 1.0 puff per day for 75 µg (Figure 5-19).

Figure 5-19 Rescue medication use, change from baseline in puffs/day over the study duration, key confirmatory efficacy studies



Data are least squares means with 95% confidence intervals. **p<0.01, ***p<0.001 vs placebo (within study); #p<0.05 vs tiotropium (within study); ‡p<0.05 vs formoterol (within study)

A dose relationship for the percentage of days without rescue medication use was observed with increasing doses of indacaterol (Table 5-21). Across studies, the 150 µg dose of indacaterol appeared to be superior to the 75 µg dose with respect to percentage of nights with no nighttime awakenings, and the 300 µg dose appeared to be more effective than the 150 µg

dose. For the percentage of days able to perform usual activities, the 75 and 150 µg doses appeared to be comparable, with a slightly increased effect with the 300 µg dose (Table 5-22).

Table 5-21 Rescue medication use, % days with no rescue use over the study duration, key confirmatory efficacy studies

		LS mean difference in % days with no rescue use (95% CI)	
Study	**Treatment**	**vs. placebo**	**vs. active control**
B2355	Indacaterol 75 µg	**8.4** (2.7, 14.1)	N/A
B2354	Indacaterol 75 µg	**13.7** (7.3, 20.0)	N/A
B2335S	Indacaterol 150 µg	**15.0** (10.6, 19.3)	**10.6** (6.4, 14.9) (Tio)
B2336	Indacaterol 150 µg	**17.5** (12.8, 22.2)	**5.1** (0.4, 9.8) (Sme)
B2346	Indacaterol 150 µg	**13.4** (7.9, 18.8)	N/A
B2335S	Indacaterol 300 µg	**16.0** (11.7, 20.3)	**11.7** (7.4, 15.9) (Tio)
B2334	Indacaterol 300 µg	**23.6** (19.0, 28.1)	**6.2** (1.7, 10.7) (For)
B2335S	Tiotropium	4.3 (0.0, 8.6)	N/A
B2336	Salmeterol	**12.4** (7.7, 17.2)	N/A
B2334	Formoterol	**17.3** (12.8, 21.9)	N/A

Data for % days no rescue use are mean differences between treatment groups and not % differences.
Values in bold p < 0.05.

Table 5-22 Symptomatic endpoints based on patient diary data over the study duration, key confirmatory efficacy studies

		LS mean difference in % nights no awakenings (95% CI)		LS mean difference in % days no symptoms (95% CI)		LS mean difference in % days able to perform usual activities (95% CI)	
Study	**Treatment**	**vs. placebo**	**vs. active control**	**vs. placebo**	**vs. active control**	**vs. placebo**	**vs. active control**
B2355	Ind 75 µg	1.9 (-2.9, 6.7)	N/A	2.8 (-0.5, 6.1)	N/A	**8.7** (3.7, 13.7)	N/A
B2354	Ind 75 µg	2.7 (-2.3, 7.6)	N/A	**4.6** (1.5, 7.6)	N/A	5.1 (-0.6, 10.8)	N/A
B2335S	Ind 150 µg	**4.9** (1.5, 8.3)	1.7 (-1.7, 5.1) (Tio)	**3.2** (0.7, 5.7)	1.2 (-1.3, 3.7) (Tio)	**7.1** (3.1, 11.1)	1.9 (-2.0, 5.8) (Tio)
B2336	Ind 150 µg	**6.3** (2.6, 10.1)	0.9 (-2.9, 4.6) (Sme)	**4.2** (1.6, 6.9)	1.5 (-1.1, 4.2) (Sme)	**7.7** (3.7, 11.7)	**4.4** (0.4, 8.3) (Sme)
B2346	Ind 150 µg	3.65 (-0.17, 7.48)	N/A	**3.0** (0.18, 5.85)	N/A	**5.39** (0.66, 10.13)	N/A
B2335S	Ind 300 µg	**5.0** (1.6, 8.5)	1.8 (-1.6, 5.2) (Tio)	**3.1** (0.6, 5.6)	1.1 (-1.4, 3.6) (Tio)	**8.0** (4.0, 12.0)	2.8 (-1.2, 6.7) (Tio)
B2334	Ind 300 µg	**6.6** (3.1, 10.1)	2.4 (-1.0, 5.8) (For)	**2.7** (0.3, 5.1)	-0.2 (-2.6, 2.2) (For)	**8.5** (4.6, 12.5)	2.3 (-1.6, 6.2) (For)
B2335S	Tiotropium	3.2 (-0.2, 6.6)	N/A	2.0 (-0.5, 4.5)	N/A	**5.2** (1.2, 9.2)	N/A
B2336	Salmeterol	**5.5** (1.7, 9.2)	N/A	**2.7** (0.0, 5.4)	N/A	3.4 (-0.7, 7.4)	N/A
B2334	Formoterol	**4.2** (0.8, 7.7)	N/A	**2.9** (0.5, 5.3)	N/A	**6.2** (2.3, 10.2)	N/A

Data for % days no symptoms are mean differences between treatment groups and not % differences.
Sme = salmeterol, Pbo = placebo, Tio = tiotropium, For = formoterol.
Values in bold p < 0.05.

5.2.4 Conclusions from key confirmatory efficacy studies

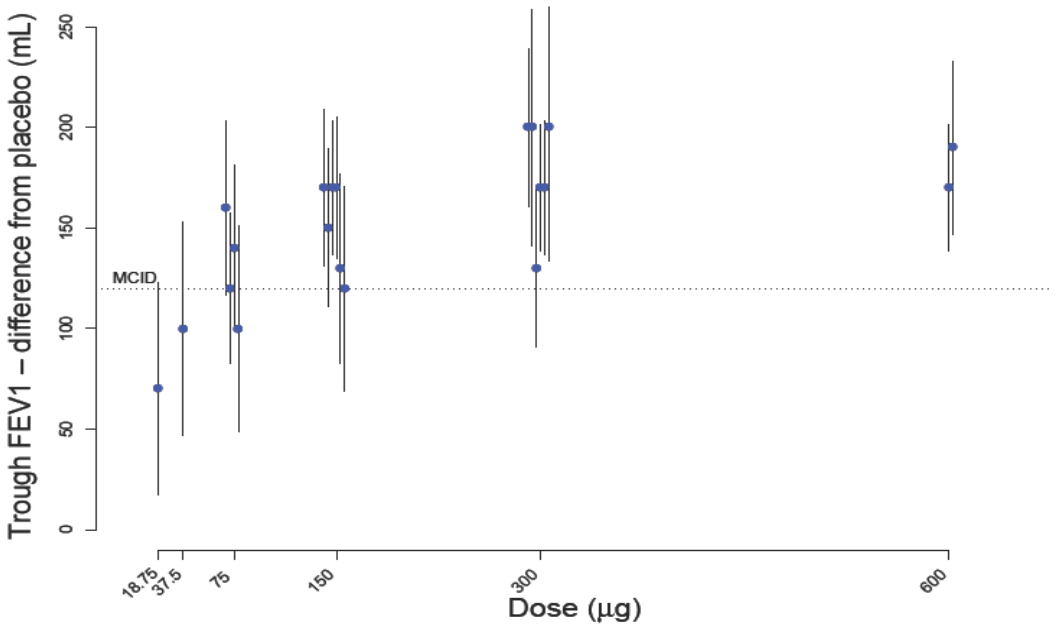
In conclusion, both 75 and 150 µg indacaterol, administered once daily, provide effective bronchodilation in patients with COPD. The totality of the evidence from the key confirmatory efficacy studies indicates that 150 µg is the optimal dose of indacaterol, providing incremental and clinically relevant benefits over the 75 µg dose for patients with COPD.

- The 75 and 150 µg doses provided effective bronchodilation, in both cases consistently meeting the MCID for the primary endpoint and having a fast onset of action.
- The 150 µg dose attained its optimal bronchodilatory effect from the first dose, whereas the 75 µg dose did not achieve its optimal effect so rapidly.
- 150 µg indacaterol demonstrated at least similar and often better efficacy than tiotropium, formoterol and salmeterol.
- The 150 µg dose showed more consistent efficacy on symptomatic endpoints (notably relief of dyspnea as measured by the TDI) than the 75 µg dose.

5.3 Integrated analysis of efficacy data

In addition to the analyses of efficacy data in individual studies, integrated analyses of efficacy across studies were performed. Based on the typical variability observed in the FEV_1 endpoint, it is difficult to differentiate active doses using both standard hypothesis tests and typical trial sizes due to the large uncertainty in the point estimates. This is illustrated in Figure 5-20 where the points correspond to the reported least-squares mean values from the primary statistical analysis of 12 studies (B2205, B2305, B2334, B2335S, B2340, B2346, B1302, B2333, B2336, B2354, B2355, B2356) and the vertical lines represent the associated 95% confidence intervals of the point estimates.

Figure 5-20 Least-square mean contrasts (versus placebo) of trough FEV_1 pooled across studies



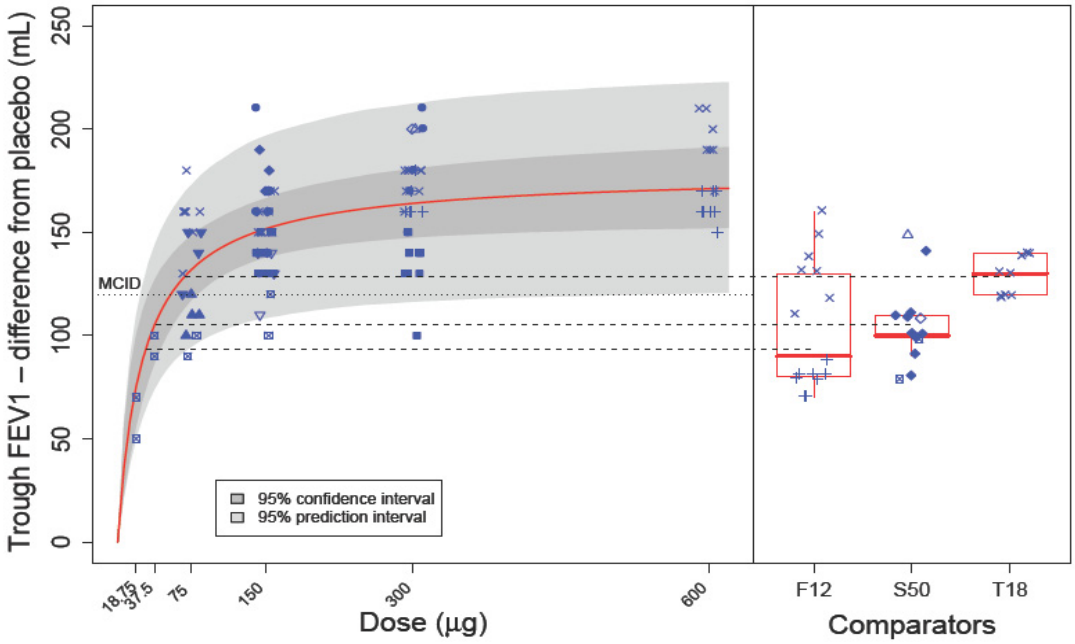
At the dose levels where more than one trial result is available, the considerable trial to trial variability is apparent in the spread of points and the large uncertainty in these points is described by the over-lapping confidence intervals.

In other words, attaining an accurate prediction of the response at any single dose level using the results of any one trial depicted in the figure is not possible. Integrated analyses were used to overcome this issue and exploit the information available in the totality of the data, appropriately pool information across trials. By integrating information, it is possible to achieve accurate and precise predictions of the mean response at each dose level.

Two different analyses were used: a study-level analysis which integrated the reported study-level results for trough FEV_1 across relevant studies and a patient-level analysis which integrated the individual patient level results for trough FEV_1 from the dose-ranging trials. The objective of the study level analysis was to characterize the dose response using the extensive study level data collected across the program; this analysis integrates the statistical summaries of all the included trials. The objective of the patient level analysis was to investigate the impact of patient characteristics on the dose-response relationship using individual patient trough FEV_1 data from the dose-ranging trials; this analysis identifies covariates which may impact dose recommendations.

The study level analysis provide predictions of the bronchodilatory dose-response of indacaterol with respect to three separate steady-state metrics: trough FEV_1, observed peak FEV_1 and AUC(5 min-4 h) FEV_1. Data from 8111 patients from 12 studies with dose levels ranging from 18.75 to 600 µg were included. Data on formoterol, salmeterol and tiotropium were included to allow a direct comparison between indacaterol and the comparators. Figure 5-21 shows a summary of the study-level meta-analysis.

Figure 5-21 Study-level dose-response relationship for trough FEV_1 at steady state in COPD patients

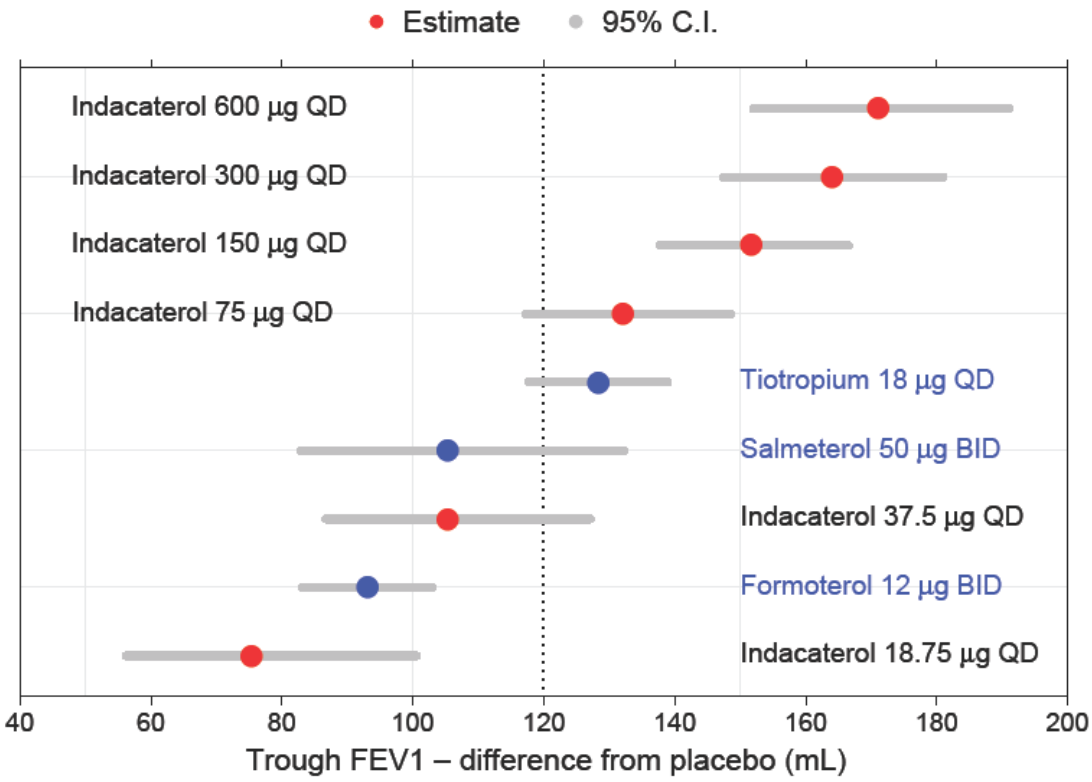


F12: Formoterol; S50: Salmeterol; T18: Tiotropium

The points correspond to the reported least-squares mean values for each study visit. The solid line in the left panel represents the predicted dose-response curve, and the grayed areas the associated (pointwise) 95% confidence (darker) and prediction (lighter) regions. The box-plots in the right panel present the distributions of responses predicted for the comparators. The predicted curve captures the apparent trend in the data which shows that with increasing dose, the response increase to a plateau which is about 0.06 L in excess of the MCID. In contrast, the responses of the comparators are clustered at or below the MCID.

Figure 5-22, which ranks the predicted responses of each of the indacaterol doses and comparators, provides a precise numerical summary of the relative performance. Each dot is the predicted point estimate of a particular treatment and the gray lines are the corresponding confidence intervals.

Figure 5-22 Ranked predicted improvement in trough FEV_1 at steady state for indacaterol doses and comparators



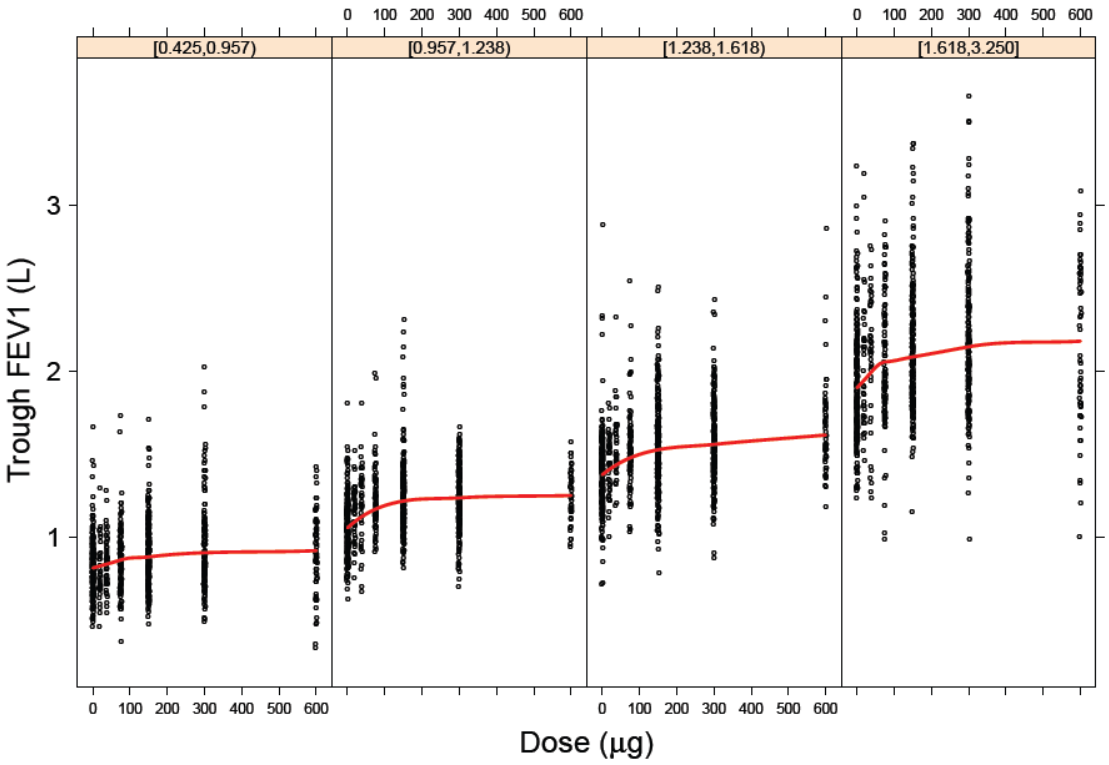
The analysis showed that the response of the 18.75 µg and 37.5 µg doses are inferior to the MCID, with the doses corresponding to the ED42 (dose to achieve 42% of the maximum effect) and ED59, respectively. 75 µg at the ED74 is just superior to the MCID and similar to tiotropium. 150 µg, at the ED85 with a predicted response of 0.15 L, is numerically higher than both the MCID and all comparators but does not reach the predicted maximum response of 0.180 L. 300 µg at the ED92 with a predicted response of over 0.16 L approaches the maximum response.

Similar study level analyses were carried our using the peak FEV_1 and AUC(5 min-4 h) for FEV_1 as responses, predicted similar dose response curves in terms of relative potency.

A nonlinear mixed-effects approach was also used to integrate patient-level data from studies B2335S and B2356 (including data from 1835 patients at 6 different indacaterol dose levels ranging from 18.75 to 600 µg) and characterize the impact of patient characteristics on the dose-response for trough FEV_1. These two studies were chosen as they provided dose-ranging data in COPD patients. Although this analysis used patient level data from a subset of the all trials, the predicted dose-response was very similar to the study level analysis.

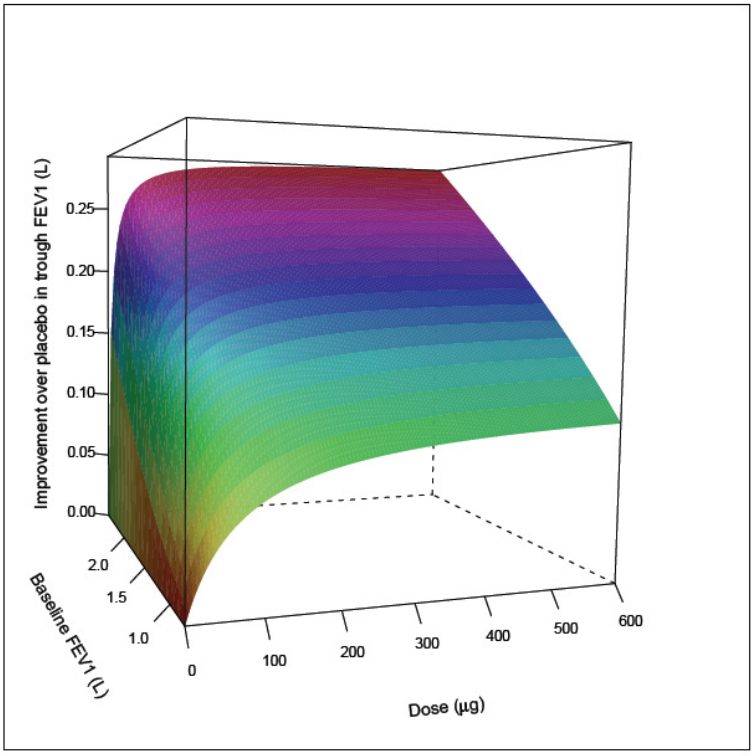
The patient characteristics explored for their impact on the dose response were: baseline FEV_1, age, gender, corticosteroid use, reversibility and smoking. Once baseline FEV_1, as a marker of disease severity, was included as a covariate, no other covariates were found to be significant. Careful scrutiny of the raw data itself supports this finding. Figure 5-23 divides up the analysis population into quartiles by the baseline FEV_1. The dots represent the individual patient responses at each dose level. The red lines are nonparametric smooths of each respective data set and provide a rough estimate of the dose response in each group. As the baseline increases, from the more severe patients on the left to the least severe patients on the right, both the shape and the extent of the dose response increase. In particular, the 25 % of the population with a baseline FEV_1 of less than 1 L have a much flatter dose response than less severe patients. Thus, the data show that the observed response changes with both dose and disease severity.

Figure 5-23 Trough dose response data of individual patients divided into quartiles of increasing baseline FEV_1



The patient level analysis quantifies the significant interrelationship between dose, baseline and response. Figure 5-24 presents the prediction of the response surface which is determined by both dose and baseline FEV_1 which is a surrogate for disease severity. Patients with less severe disease (higher baseline) not only have a larger maximum response but can achieve this response at a lower dose than more severe patients. By the same token, more severe patients require higher doses to achieve their overall lower maximum response. In patients with moderate disease, the 75 µg dose is predicted to correspond to ED85, whereas in patients with severe disease it is ED67. Corresponding potency estimates for 150 µg were ED92 in moderate COPD and ED80 in severe disease. Therefore, while the 75 µg dose may provide a clinically relevant improvement, patients with severe disease may benefit more from 150 µg or higher doses.

Figure 5-24 Patient-level analysis prediction of relationship between response, dose and baseline FEV_1



In summary, both the study level and the patient level analysis provide similar precise predictions of the dose response. Both analyses support 75 µg as the minimum effective dose, but show the benefit of higher doses in terms of both trough and peak FEV_1 responses. Doses of 150 µg or higher provide greater bronchodilation than the tested comparators. In the patient level analysis, the dose response was found to change with disease severity. Specifically, as disease severity increases, additional benefit is achieved with doses of 150 µg or higher.

5.4 Efficacy conclusions

Indacaterol represents a significant advance in bronchodilator therapy for COPD. It has once-daily dosing, a fast onset of action and sustained efficacy throughout 24 hours that was maintained in studies of up to 52 weeks in duration. This is combined with a positive impact on key symptoms of the disease, in particular dyspnea, and associated improvement in health status. Indacaterol offers a new profile that differs from other LABAs and anticholinergics that are currently indicated for the treatment of COPD.

Dose-ranging studies suggested that doses of 75 and 150 μg had a similar bronchodilatory effect after 14 days of dosing and that doses less than 75 μg were suboptimal in this respect. Importantly, the 150 μg dose achieved its optimal bronchodilatory effect more rapidly than the 75 μg dose, from the first dose onwards on the basis of spirometry on Days 1 and 2. Regimens of twice-daily and every other day dosing were suboptimal compared with once-daily dosing in terms of the profile of bronchodilation, indicating that once-daily dosing is appropriate for indacaterol.

The data from several studies show that indacaterol, at doses of 75, 150 and 300 μg, provides effective bronchodilation. Taken as a whole, the data suggest an incremental increase in effect on lung function with increasing dose. Indacaterol 75 μg provided effective bronchodilation, with a trough FEV_1 after 12 weeks statistically significantly higher than that for placebo and meeting or exceeding the minimal clinically important difference (MCID). The bronchodilator efficacy of the 150 μg dose of indacaterol has been well-established in several adequate and well-controlled studies, typically showing greater improvements in trough FEV_1 than observed in studies with the 75 μg dose. Indacaterol 150 μg demonstrated at least similar and often better efficacy than tiotropium and the b.i.d. LABAs formoterol and salmeterol with regard to measures of bronchodilation.

In addition to lung function outcomes, results from symptomatic endpoint instruments confirmed the effectiveness of indacaterol in the treatment of COPD. The positive impact on important patient symptoms is indicated by its statistically significant impact versus placebo on measures such as dyspnea and rescue medication use. In studies with the 75 μg dose, statistically significant differences to placebo were observed for rescue medication use (although in one study the decrease in rescue medication use was less than previously observed in studies with the 150 μg dose) and SGRQ score: the difference for the latter did not reach the MCID, however. In one of the two studies, the TDI total score was statistically significantly higher for indacaterol 75 μg than placebo, and the difference exceeded the MCID. In the other study the difference was neither statistically significant nor exceeded the MCID. The 150 μg dose demonstrated more robust effects on TDI, SGRQ and rescue medication use. Since dyspnea is a key symptom of COPD, and the need for rescue medication use is driven by dyspnea episodes, the findings of both improved TDI total scores and reduction of rescue use provide strong evidence for the beneficial effects of the 150 μg dose over the 75 μg dose.

The integrated analysis of study-level efficacy data showed that both the 75 and 150 μg doses provided effective bronchodilation, and the 150 μg dose was predicted to be more effective than the 75 μg dose. The integrated analysis of patient-level efficacy data demonstrated that doses of 150 μg or higher offer additional benefit to patients with more severe disease.

In summary, indacaterol, when dosed once daily, provides clinically effective bronchodilation in patients with moderate or severe COPD, together with clinically relevant improvements in dyspnea, health-related status and symptomatic endpoints. Once-daily dosing is optimal for indacaterol. The 75 and 150 µg doses provide greater bronchodilation than lower doses. The 75 µg dose is regarded as the minimum effective dose while the 150 µg is considered the optimal dose and may provide greater benefit in certain patients, particularly those with more severe COPD, and where more rapid attainment of optimal bronchodilation (from the first dose onwards), and greater effects on dyspnea and health-related quality of life are required.

6 Clinical safety

The clinical development program for indacaterol includes a large number of studies evaluating a range of doses up to 600 µg, in trials up to 12 months in duration.

The safety presentation in this document will begin with a definition of the key safety populations as well as information on the types of evaluations included in the clinical studies. Data on patient exposure are also provided.

The presentation of adverse events will begin with a presentation on the common adverse events seen in the clinical trials, followed by displays of adverse events leading to discontinuation, serious adverse events, and patient deaths. Because evaluation of cardio- and cerebrovascular events is important for a compound of this class, analyses that focus on these events are summarized.

In addition, a number of analyses were performed to evaluate specific safety aspects of relevance to this class of medication. Details are given in each of the respective sections below.

The safety profile of indacaterol supports the benefit risk profile of the product at all doses studied.

6.1 Safety populations, evaluations and patient exposure

Pooled safety populations

The indacaterol COPD safety studies range from 12 weeks to 52 weeks in duration, with the 75 µg dose evaluated in studies 12 weeks in duration and long term safety (up to 52 weeks) evaluated with 150, 300 and 600 µg doses.

Three key safety populations were defined (Table 6-1):

- The COPD safety population includes patients from all COPD studies with a treatment duration of at least 3 months and includes all observed data
- The COPD 3-month safety population provides pooled 3-month data.
- The COPD 12-month safety population provides pooled 12-month data.

It should be noted that the 3- and 12-month populations are overlapping, so that the 3-month population includes 3-month data from patients who may also be in the 12-month population. For each of these populations, the data summarized are for the whole of the respective period, from baseline to 3 and 12 months.

Table 6-1 Key safety populations

Dataset	Studies included	Safety evaluations
COPD 3-month population	B2346, B2349, B1302, B2350, B2355, B2354, B2334 (up to day 91), B2335S/SE (up to day 91), B2333 (up to day 91), B2336 (up to day 91)	Exposure, disposition, demographics, baseline disease characteristics, deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, vital signs, ECGs, special safety topics, subgroup analyses
COPD 12-month population	B2334, B2335SE	As for COPD 3-month safety population
COPD safety population	B2346, B2349, B1302, B2350, B2355, B2354, B2334, B2335S, B2335SE, B2333, B2336	Exposure, disposition, demographics, baseline disease characteristics, deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, vital signs, ECGs, special safety topics, subgroup analyses

Each of these pooled datasets consisted of adult patients, ≥ 40 years of age, with moderate or severe COPD. The majority of patients were male and Caucasian.

A substantial proportion of patients (35-48%) reported 3 or more cardiovascular risk factors including age > 65, BMI > 30 kg/m^2, current smoking, diabetes mellitus, current cardiovascular and cerebrovascular conditions, hypertension and hyperlipidemia. Similar demographic and disease characteristics were found between treatment groups.

Evaluations

The safety populations were used to assess safety in terms of the rate, type, severity and drug relationship of adverse events; deaths, serious adverse events and other clinically significant adverse events; changes in clinical laboratory parameters; effects on vital signs; and ECG evaluations.

Adverse effects reported with marketed β_2-agonists were carefully evaluated in the analyses conducted in the registration program. Adverse effects reported for other compounds in this class include: anxiety, back pain, chest pain, muscle cramps and myalgia, diarrhea, dizziness, dyspnea, headache, insomnia, musculoskeletal pain, nasal congestion, nausea, peripheral edema, pruritus, rash, rhinitis, sinusitis, throat irritation, tremor, and upper respiratory tract infection. In addition, laboratory abnormalities such as hypokalemia and hyperglycemia, and effects on vital signs and ECG intervals (specifically QTc) have been reported for other LABA compounds, and were evaluated for indacaterol.

Serum glucose (here as a marker of glycogen metabolism) and liver function tests (LFTs) were monitored in all clinical studies and analyses of serum glucose comparing treatments over time, and detailed evaluations of LFTs were performed in the key pooled safety populations. The decision to closely monitor these parameters was in response to a finding in dog inhalation toxicity studies, where increased levels of hepatocellular glycogen (a known class effect of LABAs) were observed.

To assess possible effects on cardiac electrophysiology, in addition to evaluations of ECG data in the key pooled safety populations, a thorough QT study (as defined in the ICH E14 guideline) was performed in healthy subjects (Study B2339), and Holter monitoring data were collected in a sub-set of patients in Study B2335S.

Since some patients experienced a cough of brief duration after inhalation of indacaterol, this was evaluated in the pooled safety populations.

The asthma indication is not being sought for indacaterol monotherapy. In addition, while exposure to LABAs may pose certain risks to patients with asthma, there is some evidence to suggest that this is not the case in COPD (Calverley et al 2007; Rodrigo et al 2008). Safety information on the use of indacaterol in patients with asthma is available primarily from the Phase 3 safety study in asthma patients, Study B2338.

Patient exposure

In total, over 15,000 subjects (healthy volunteers and patients) were included in the entire clinical development program and have been used to assess safety. Of these, 9243 patients were treated with indacaterol, 4764 treated for at least 12 weeks at doses between 75 and 600 µg. Study drug exposure in the COPD safety population is summarized in Table 6-2.

Table 6-2 Duration of exposure to study drug after randomization in COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449	150 µg N=2611	300 µg N=1157	600 µg N=547	For N=556	Tio N=1214	Sme N=895	Pbo N=2012
Exposure (days)								
median	85.0	85.0	183.0	364.0	363.0	85.0	85.0	176.0
range	2 - 179	1 - 385	1 - 420	1 - 407	1 - 397	1 - 208	1 - 215	1 - 403
Patient-years	105.06	859.72	736.97	394.49	396.21	357.97	274.93	923.60
Exposure - n(%)								
≤ 26 wks	449 (100.0)	2141 (82.0)	469 (40.5)	192 (35.1)	201 (36.2)	1038 (85.5)	730 (81.6)	1250 (62.1)
26-52 wks	0	393 (15.1)	432 (37.3)	188 (34.4)	187 (33.6)	176 (14.5)	165 (18.4)	522 (25.9)
> 52 wks	0	77 (2.9)	256 (22.1)	167 (30.5)	168 (30.2)	0	0	240 (11.9)

Includes studies B1302, B2333, B2334, B2335S, B2335SE, B2336, B2346, B2349, B2350, B2354, and B2355.
For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo

6.2 Adverse clinical events

Overall, the AEs observed in the registration program were as expected, given the disease indication (COPD) and the β_2-agonist drug class. It should be noted that the adverse event tables include all adverse events: fatal and non-fatal serious adverse events (SAEs) and non-serious AEs. Study Investigators rated the individual adverse events on a scale of mild, moderate, and severe; Serious adverse events (fatal or life threatening events, events leading to hospitalization or disability) are predefined based on definitions provided by the regulatory authorities.

In the COPD safety population, exposure duration varies so events are presented in an exposure-adjusted manner as number of events per patient-year. A comparison of events per patient-year is only valid if the incidence of a specific event is constant over time. As some events may occur earlier in the course of treatment, and other events occur after long exposure, events are also presented in 3- and 12-month pools where exposure is more homogeneous and are displayed in terms of incidence (% patients experiencing the event).

Common AEs for the 3-month population are shown for those occurring in at least 1.0% of patients and for the 12-month safety populations in at least 2.0% of patients in any of the indacaterol 75 or 150 µg treatment groups. The 2.0% cut off allow for a more efficient presentation of data without excluding any clinically meaningful information.

Total adverse events (AEs) in the COPD safety population

Table 6-3 displays overall rates of AEs in the COPD safety population. There is no dose response apparent for the indacaterol treatment groups; the absolute difference in the overall rate between the indacaterol 75 µg group and placebo is just above one event per patient year, while the event rates for the indacaterol 150 µg and 300 µg treatment groups are similar to placebo, and the event rate for the indacaterol 600 µg treatment group is less than placebo. Thus, the overall rates can be considered comparable between the indacaterol and control treatment groups.

Table 6-3 AE episodes adjusted for exposure by primary system organ class in COPD safety population - # of AEs per patient-year (n/total patient years)

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449	150 µg N=2611	300 µg N=1157	600 µg N=547	For N=556	Tio N=1214	Sme N=895	Pbo N=2012
Patients with > = 1 AE	237	1226	767	351	352	576	340	1093
Total patient years	105.062	859.715	736.966	394.489	396.208	357.971	274.932	923.603
AE episodes/patient year	5.387	4.096	3.924	3.562	2.945	4.450	3.019	3.876

For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo
Exposure in patient years = (sum of the duration of exposure over patients, in days)/365.25
n = The total number of events observed over time from all patients. A patient may have multiple occurrences of the same AE; all occurrences are counted.

Most frequently occurring AEs in the COPD 3-month safety population

The frequencies of the individual common AEs are displayed in Table 6-4.

The incidence of AEs was higher with indacaterol 75 µg o.d. compared with placebo in the pooled 3-month safety population. This is most likely to be an artifact of the pooling process. This treatment group contains data from Study B2354, Study B2355, and patients randomized into Stage 1 of Study B2335S. The differences relative to placebo were less prominent in individual studies. In Studies B2354 and B2355 the incidence of AEs was 3-4% higher with indacaterol 75 µg o.d. versus placebo (49.1% vs. 46.3% in Study B2354 and 44.7% vs. 40.9% in Study B2355) and there were no relevant differences in terms of the primary SOCs affected. In Study B2335S, the incidence of any AE was 67.7% in the indacaterol 75 µg o.d. group versus 57.9% in the placebo group. This study had a higher AE rate overall than other studies, and as it contributed around one-third of patients to the pooled indacaterol 75 µg group but only approximately one-fifth of the pooled placebo group, it had a disproportionate effect on AE rates in the 75 µg group.

Table 6-4 Common AEs (>=1.0% of patients in the 75 or 150 µg indacaterol group) by preferred term in COPD 3-month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Patients with ≥1 AE	231 (51.5)	1067 (40.9)	556 (48.1)	252 (46.1)	246 (44.2)	526 (43.3)	299 (33.4)	867 (43.1)
Preferred term								
COPD †	38 (8.5)	239 (9.2)	136 (11.8)	56 (10.2)	71 (12.8)	120 (9.9)	65 (7.3)	269 (13.4)
Nasopharyngitis	24 (5.4)	114 (4.4)	67 (5.8)	43 (7.9)	31 (5.6)	67 (5.5)	29 (3.2)	89 (4.4)
Cough	29 (6.5)	104 (4.0)	60 (5.2)	27 (4.9)	15 (2.7)	43 (3.5)	20 (2.2)	72 (3.6)
Headache	23 (5.1)	80 (3.1)	26 (2.3)	16 (2.9)	16 (2.9)	42 (3.5)	22 (2.5)	44 (2.2)
Upper RTI	16 (3.6)	59 (2.3)	41 (3.5)	17 (3.1)	8 (1.4)	36 (3.0)	7 (0.8)	54 (2.7)
Muscle spasms	6 (1.3)	38 (1.5)	25 (2.2)	22 (4.0)	14 (2.5)	6 (0.5)	12 (1.3)	15 (0.8)
Dyspnea	8 (1.8)	37 (1.4)	19 (1.6)	13 (2.4)	7 (1.3)	26 (2.1)	13 (1.5)	53 (2.6)
Bronchitis	12 (2.7)	35 (1.3)	11 (1.0)	7 (1.3)	7 (1.3)	12 (1.0)	6 (0.7)	31 (1.5)
Influenza	2 (0.5)	32 (1.2)	14 (1.2)	10 (1.8)	3 (0.5)	19 (1.6)	5 (0.6)	14 (0.7)
Upper RTI bacterial	5 (1.1)	32 (1.2)	22 (1.9)	10 (1.8)	14 (2.5)	17 (1.4)	4 (0.5)	33 (1.6)
Back pain	6 (1.3)	31 (1.2)	12 (1.0)	8 (1.5)	9 (1.6)	17 (1.4)	10 (1.1)	25 (1.2)
Oropharyngeal pain	10 (2.2)	30 (1.2)	13 (1.1)	4 (0.7)	2 (0.4)	16 (1.3)	8 (0.9)	13 (0.7)
Lower RTI	1 (0.2)	28 (1.1)	24 (2.1)	5 (0.9)	8 (1.4)	18 (1.5)	17 (1.9)	36 (1.8)
Nausea	11 (2.5)	28 (1.1)	8 (0.7)	4 (0.7)	5 (0.9)	7 (0.6)	5 (0.6)	19 (0.9)
Diarrhea	7 (1.6)	27 (1.0)	14 (1.2)	5 (0.9)	8 (1.4)	13 (1.1)	9 (1.0)	24 (1.2)
Dizziness	4 (0.9)	25 (1.0)	16 (1.4)	5 (0.9)	3 (0.5)	5 (0.4)	5 (0.6)	24 (1.2)
Hypertension	6 (1.3)	24 (0.9)	10 (0.9)	5 (0.9)	0	12 (1.0)	7 (0.8)	32 (1.6)
Sinusitis	5 (1.1)	24 (0.9)	15 (1.3)	2 (0.4)	4 (0.7)	11 (0.9)	4 (0.5)	21 (1.0)
Arthralgia	8 (1.8)	23 (0.9)	10 (0.9)	6 (1.1)	2 (0.4)	7 (0.6)	4 (0.5)	11 (0.6)
Viral upper RTI	5 (1.1)	21 (0.8)	20 (1.7)	2 (0.4)	5 (0.9)	8 (0.7)	4 (0.5)	22 (1.1)
Fatigue	8 (1.8)	16 (0.6)	5 (0.4)	6 (1.1)	4 (0.7)	6 (0.5)	2 (0.2)	16 (0.8)
Urinary tract infection	15 (3.3)	16 (0.6)	10 (0.9)	1 (0.2)	5 (0.9)	14 (1.2)	8 (0.9)	21 (1.0)
Vomiting	6 (1.3)	12 (0.5)	10 (0.9)	3 (0.6)	2 (0.4)	7 (0.6)	2 (0.2)	11 (0.6)
Pneumonia	6 (1.3)	11 (0.4)	14 (1.2)	1 (0.2)	3 (0.5)	7 (0.6)	2 (0.2)	11 (0.6)
Nasal congestion	6 (1.3)	9 (0.3)	4 (0.4)	3 (0.6)	1 (0.2)	10 (0.8)	3 (0.3)	6 (0.3)

Includes all data from Studies B1302, B2346, B2349, B2350, B2354, and B2355, plus data up to 3 months from studies B2333, B2334, B2335S/SE, and B2336.
For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo
Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg treatment group. A patient with multiple AEs is counted only once in the total row.
† Includes COPD exacerbations.

The most frequent AEs (≥3.0% in any group over all severities) are summarized by preferred term and showing the proportions of patients with severe events in Table 6-5. With all treatments, the majority of AEs were mild or moderate in severity. Only 2-5% of patients in any treatment group had severe AEs. The highest incidence of severe AEs occurred in the placebo group.

COPD (including disease progression and exacerbations) was the most frequent severe AE. The incidence of severe COPD in the indacaterol groups was lowest with 300 µg o.d. and salmeterol (both 0.6%) and highest in the placebo group (1.3%). The majority of cough, nasopharyngitis and muscle spasm AEs were mild in severity.

Table 6-5 Most frequent AEs (>= 3.0% of patients in any group over all severities) by preferred term in COPD 3-month safety population, showing proportions of patients with severe events

	Indacaterol treatment groups				Control treatment groups			
Preferred term:	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
≥1 AE								
Total	231 (51.5)	1067 (40.9)	556 (48.1)	252 (46.1)	246 (44.2)	526 (43.3)	299 (33.4)	867 (43.1)
severe	17 (3.8)	100 (3.8)	37 (3.2)	22 (4.0)	19 (3.4)	56 (4.6)	17 (1.9)	101 (5.0)
COPD †								
Total	38 (8.5)	239 (9.2)	136 (11.8)	56 (10.2)	71 (12.8)	120 (9.9)	65 (7.3)	269 (13.4)
severe	5 (1.1)	25 (1.0)	7 (0.6)	5 (0.9)	5 (0.9)	12 (1.0)	5 (0.6)	27 (1.3)
Nasopharyngitis								
Total	24 (5.4)	114 (4.4)	67 (5.8)	43 (7.9)	31 (5.6)	67 (5.5)	29 (3.2)	89 (4.4)
severe	1 (0.2)	3 (0.1)	0	0	0	1 (0.1)	0	0
Cough								
Total	29 (6.5)	104 (4.0)	60 (5.2)	27 (4.9)	15 (2.7)	43 (3.5)	20 (2.2)	72 (3.6)
severe	1 (0.2)	1 (0.0)	1 (0.1)	1 (0.2)	1 (0.2)	2 (0.2)	0	7 (0.4)
Headache								
Total	23 (5.1)	80 (3.1)	26 (2.3)	16 (2.9)	16 (2.9)	42 (3.5)	22 (2.5)	44 (2.2)
severe	1 (0.2)	4 (0.2)	2 (0.2)	0	0	4 (0.3)	3 (0.3)	1 (0.1)
Upper RTI								
Total	16 (3.6)	59 (2.3)	41 (3.5)	17 (3.1)	8 (1.4)	36 (3.0)	7 (0.8)	54 (2.7)
severe	0	1 (0.0)	0	1 (0.2)	0	0	0	0
Muscle spasms								
Total	6 (1.3)	38 (1.5)	25 (2.2)	22 (4.0)	14 (2.5)	6 (0.5)	12 (1.3)	15 (0.8)
severe	0	7 (0.3)	0	2 (0.4)	2 (0.4)	0	0	1 (0.1)
Urinary tract infection								
Total	15 (3.3)	16 (0.6)	10 (0.9)	1 (0.2)	5 (0.9)	14 (1.2)	8 (0.9)	21 (1.0)
severe	0	0	0	0	0	0	0	0

Includes all data from Studies B1302, B2346, B2349, B2350, B2354 and B2355, plus data up to 3 months from studies B2333, B2334, B2335S/SE and B2336.
† Includes COPD exacerbations
For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo
Preferred terms are sorted in descending order of frequency (over all severities) in the indacaterol 150 µg group.
A patient with multiple AEs is counted only once in the total row.
Selected frequency cut-off of ≥3.0% of patients in any group.

Most frequently occurring AEs in the COPD 12-month safety population

When compared with the 3-month safety population, the overall AE incidences for the 12-month safety population (Table 6-6) were higher for each treatment group. The overall incidence of AEs was higher in the indacaterol 150 µg o.d. group (76.4%) compared with the

indacaterol 300 µg o.d. (72.4%) and 600 µg o.d. (64.9%) and formoterol (65.2%) groups, and lowest in the placebo group (63.1%). Note that the indacaterol 150 µg o.d. treatment group is not as large as the other four groups, and is derived from a single study, B2335SE, where AE rates were higher for both the indacaterol 300 µg o.d. treatment group and the placebo group compared with the pooled data reported here (76.7% and 67.7%, respectively). There was no dose dependency for the indacaterol groups.

Table 6-6 Common AEs (>=2.0% of patients in the indacaterol 150 µg group) by preferred term in COPD 12-month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with ≥1 AE	110 (76.4)	422 (72.4)	276 (64.9)	283 (65.2)	351 (63.1)
Preferred term					
COPD †	35 (24.3)	179 (30.7)	117 (27.5)	134 (30.9)	184 (33.1)
Nasopharyngitis	24 (16.7)	99 (17.0)	80 (18.8)	62 (14.3)	75 (13.5)
Cough	17 (11.8)	47 (8.1)	27 (6.4)	17 (3.9)	27 (4.9)
Upper RTI	17 (11.8)	41 (7.0)	20 (4.7)	18 (4.2)	21 (3.8)
Headache	15 (10.4)	25 (4.3)	21 (4.9)	15 (3.5)	24 (4.3)
Muscle spasms	12 (8.3)	27 (4.6)	25 (5.9)	12 (2.8)	8 (1.4)
Oropharyngeal pain	10 (6.9)	18 (3.1)	4 (0.9)	5 (1.2)	12 (2.2)
Sinusitis	10 (6.9)	18 (3.1)	5 (1.2)	6 (1.4)	8 (1.4)
Dyspnea	9 (6.3)	21 (3.6)	19 (4.5)	12 (2.8)	18 (3.2)
Influenza	8 (5.6)	23 (4.0)	19 (4.5)	13 (3.0)	16 (2.9)
Viral upper RTI	7 (4.9)	24 (4.1)	8 (1.9)	12 (2.8)	14 (2.5)
Electrocardiogram QT prolonged	6 (4.2)	8 (1.4)	4 (0.9)	3 (0.7)	5 (0.9)
Hypertension	6 (4.2)	11 (1.9)	9 (2.1)	7 (1.6)	19 (3.4)
Arthralgia	5 (3.5)	17 (2.9)	9 (2.1)	6 (1.4)	9 (1.6)
Bronchitis	5 (3.5)	23 (4.0)	16 (3.8)	11 (2.5)	24 (4.3)
Diarrhea	5 (3.5)	13 (2.2)	11 (2.6)	14 (3.2)	15 (2.7)
Dizziness	5 (3.5)	15 (2.6)	8 (1.9)	3 (0.7)	10 (1.8)
Fall	5 (3.5)	5 (0.9)	3 (0.7)	4 (0.9)	0
Lower RTI	5 (3.5)	38 (6.5)	23 (5.4)	22 (5.1)	30 (5.4)
Musculoskeletal pain	5 (3.5)	13 (2.2)	2 (0.5)	5 (1.2)	7 (1.3)
Nasal congestion	5 (3.5)	4 (0.7)	3 (0.7)	2 (0.5)	2 (0.4)
Pyrexia	5 (3.5)	15 (2.6)	3 (0.7)	7 (1.6)	7 (1.3)
Upper RTI bacterial	5 (3.5)	35 (6.0)	25 (5.9)	23 (5.3)	40 (7.2)
Urinary tract infection	5 (3.5)	17 (2.9)	2 (0.5)	5 (1.2)	9 (1.6)

Includes data from Studies B2334 and B2335SE.
Ind=indacaterol, For=formoterol, Pbo=placebo
Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg group. A patient with multiple AEs is counted only once in the total row.
† Includes COPD exacerbations

Table 6-6 Common AEs (>=2.0% of patients in the indacaterol 150 ug group) by preferred term in COPD 12-month safety population (continued)

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with ≥1 AE	110 (76.4)	422 (72.4)	276 (64.9)	283 (65.2)	351 (63.1)
Preferred term					
Back pain	4 (2.8)	19 (3.3)	15 (3.5)	13 (3.0)	26 (4.7)
Gastroenteritis viral	4 (2.8)	2 (0.3)	0	0	3 (0.5)
Insomnia	4 (2.8)	3 (0.5)	3 (0.7)	5 (1.2)	10 (1.8)
Muscle strain	4 (2.8)	6 (1.0)	3 (0.7)	0	4 (0.7)
Myalgia	4 (2.8)	6 (1.0)	2 (0.5)	2 (0.5)	4 (0.7)
Nausea	4 (2.8)	7 (1.2)	4 (0.9)	4 (0.9)	15 (2.7)
Pain in extremity	4 (2.8)	10 (1.7)	2 (0.5)	3 (0.7)	5 (0.9)
Rhinorrhoea	4 (2.8)	7 (1.2)	0	1 (0.2)	2 (0.4)
Abdominal discomfort	3 (2.1)	0	2 (0.5)	0	2 (0.4)
Dry mouth	3 (2.1)	1 (0.2)	1 (0.2)	3 (0.7)	0
Ear pain	3 (2.1)	0	1 (0.2)	1 (0.2)	0
Neck pain	3 (2.1)	4 (0.7)	1 (0.2)	3 (0.7)	2 (0.4)
Edema peripheral	3 (2.1)	11 (1.9)	9 (2.1)	6 (1.4)	2 (0.4)
Postnasal drip	3 (2.1)	1 (0.2)	0	0	0
Procedural pain	3 (2.1)	4 (0.7)	1 (0.2)	0	4 (0.7)
Sneezing	3 (2.1)	3 (0.5)	0	0	0
Tooth abscess	3 (2.1)	3 (0.5)	2 (0.5)	0	1 (0.2)
Vertigo	3 (2.1)	4 (0.7)	3 (0.7)	2 (0.5)	1 (0.2)

Includes data from Studies B2334 and B2335SE.
Ind=indacaterol, For=formoterol, Pbo=placebo
Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg group. A patient with multiple AEs is counted only once in the total row.
† Includes COPD exacerbations

The most common AE in all treatment groups was COPD (includes disease progression and exacerbations), which occurred less often with all doses of indacaterol than with formoterol or placebo.

The most frequent AEs (≥ 4.0% in any group over all severities) are summarized by preferred term and severity in Table 6-7. With all treatments, the majority of AEs were mild or moderate in severity. The overall rates of severe AEs were comparable among the treatment groups.

The most frequent severe AE was COPD (includes disease progression and exacerbations); however, this occurred less often with all 3 doses of indacaterol (150, 300 and 600 µg o.d.) compared with formoterol and placebo. Severe muscle spasms occurred in 3 (2.1%) patients on indacaterol 150 µg o.d. and 1 (0.2%) patient on indacaterol 300 µg o.d., but were not reported in the indacaterol 600 µg o.d. or control groups. Severe cough was experienced by only 1 patient in each of the indacaterol 150 µg o.d., 300 µg o.d., 600 µg o.d. and placebo groups (0.2-0.7%), and 2 (0.5%) patients on formoterol. Severe nasopharyngitis was reported for 1 (0.7%) patient on indacaterol 150 µg o.d. and 2 (0.4%) patients on placebo, but none in the indacaterol 300 µg o.d., 600 µg o.d. and formoterol groups.

Table 6-7 Most frequent AEs (>=4.0% of patients in any group over all severities) by preferred term in COPD 12-month safety population, showing proportions of patients with severe events

Preferred term:		Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
≥1 AE	Total	110 (76.4)	422 (72.4)	276 (64.9)	283 (65.2)	351 (63.1)
	severe	19 (13.2)	60 (10.3)	43 (10.1)	52 (12.0)	64 (11.5)
COPD †	Total	35 (24.3)	179 (30.7)	117 (27.5)	134 (30.9)	184 (33.1)
	Severe	3 (2.1)	17 (2.9)	11 (2.6)	22 (5.1)	22 (4.0)
Nasopharyngitis	Total	24 (16.7)	99 (17.0)	80 (18.8)	62 (14.3)	75 (13.5)
	Severe	1 (0.7)	0	0	0	2 (0.4)
Cough	Total	17 (11.8)	47 (8.1)	27 (6.4)	17 (3.9)	27 (4.9)
	Severe	1 (0.7)	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)
Upper RTI	Total	17 (11.8)	41 (7.0)	20 (4.7)	18 (4.2)	21 (3.8)
	Severe	2 (1.4)	0	0	2 (0.5)	0
Headache	Total	15 (10.4)	25 (4.3)	21 (4.9)	15 (3.5)	24 (4.3)
	Severe	2 (1.4)	0	0	0	1 (0.2)
Muscle spasms	Total	12 (8.3)	27 (4.6)	25 (5.9)	12 (2.8)	8 (1.4)
	Severe	3 (2.1)	1 (0.2)	0	0	0
Oropharyngeal pain	Total	10 (6.9)	18 (3.1)	4 (0.9)	5 (1.2)	12 (2.2)
	Severe	0	0	0	0	1 (0.2)
Sinusitis	Total	10 (6.9)	18 (3.1)	5 (1.2)	6 (1.4)	8 (1.4)
	Severe	1 (0.7)	0	1 (0.2)	0	0
Dyspnea	Total	9 (6.3)	21 (3.6)	19 (4.5)	12 (2.8)	18 (3.2)
	Severe	1 (0.7)	1 (0.2)	2 (0.5)	1 (0.2)	1 (0.2)
Influenza	Total	8 (5.6)	23 (4.0)	19 (4.5)	13 (3.0)	16 (2.9)
	Severe	0	1 (0.2)	0	0	0
Viral RTI	Total	7 (4.9)	24 (4.1)	8 (1.9)	12 (2.8)	14 (2.5)
	Severe	0	4 (0.7)	0	1 (0.2)	0
Electrocardiogram QT prolonged						
	Total	6 (4.2)	8 (1.4)	4 (0.9)	3 (0.7)	5 (0.9)
	Severe	0	0	0	1 (0.2)	0
Hypertension	Total	6 (4.2)	11 (1.9)	9 (2.1)	7 (1.6)	19 (3.4)
	Severe	0	0	0	0	1 (0.2)
Bronchitis	Total	5 (3.5)	23 (4.0)	16 (3.8)	11 (2.5)	24 (4.3)
	Severe	0	1 (0.2)	0	0	1 (0.2)
Lower RTI	Total	5 (3.5)	38 (6.5)	23 (5.4)	22 (5.1)	30 (5.4)
	Severe	0	0	0	4 (0.9)	4 (0.7)
Upper RTI bacterial	Total	5 (3.5)	35 (6.0)	25 (5.9)	23 (5.3)	40 (7.2)
	Severe	0	3 (0.5)	2 (0.5)	4 (0.9)	4 (0.7)
Back pain	Total	4 (2.8)	19 (3.3)	15 (3.5)	13 (3.0)	26 (4.7)
	Severe	0	0	1 (0.2)	1 (0.2)	2 (0.4)

Includes data from Studies B2334 and B2335SE.
Ind=indacaterol, For=formoterol, Pbo=placebo
Preferred terms are sorted in descending order of frequency (over all severities) in the Indacaterol 150 µg group.
A patient with multiple AEs is counted only once in the total row.
† Includes COPD exacerbations.

Other severe AEs were reported in 0% to 1.4% of patients in any treatment group, with no discernable trends.

6.3 Serious adverse events, deaths and other clinically significant adverse events

SAEs and patient deaths would be expected in the patient populations studied. These events occurred during the registration program but there were no patterns suggestive of a unique effect of indacaterol on these serious events.

6.3.1 Serious adverse events

Serious adverse events in the COPD safety population

In the COPD safety population a total of 325 indacaterol-treated patients had SAEs (fatal or non-fatal). The SAE rates were less for each indacaterol treatment group compared to the placebo, formoterol, and tiotropium treatment groups. The highest rate of events was found in the SOC of Respiratory, thoracic, and mediastinal disorders (Table 6-8).

Table 6-8 SAE episodes adjusted for exposure by primary system organ class in COPD safety population - # of SAEs per patient-year (n/total patient years)

	Indacaterol treatment groups				Control treatment groups			
Primary system organ class - Total	**75 µg**	**150 µg**	**300 µg**	**600 µg**	**For**	**Tio**	**Sme**	**Pbo**
Total Population	449	2611	1157	547	556	1214	895	2012
Patients with ≥ 1 SAE	17	135	117	56	73	64	35	155
Total patient years	105.062	859.715	736.966	394.489	396.208	357.971	274.932	923.603
# of SAEs per patient-year	0.247	0.235	0.244	0.205	0.318	0.332	0.182	0.270
Blood & lymphatic system disorders	0.019	0.002	0.001	0.003	0	0	0	0.002
Cardiac disorders	0.038	0.034	0.034	0.030	0.018	0.047	0.033	0.028
Congenital, familial & genetic disorders	0	0	0	0	0	0	0	0.001
Ear & labyrinth disorders	0	0	0	0	0	0.003	0.004	0.001
Endocrine disorders	0	0.001	0	0	0	0	0	0
Eye disorders	0.010	0.001	0.004	0	0.015	0.006	0	0.003
Gastrointestinal disorders	0.010	0.014	0.005	0.025	0.008	0.017	0.011	0.018
General disorders & administration site conditions	0.019	0.006	0.003	0.003	0.003	0.008	0.004	0.011
Hepatobiliary disorders	0	0.003	0.005	0	0.003	0	0	0.004
Immune system disorders	0	0.001	0	0.003	0.003	0	0.004	0.001
Infections & infestations	0.048	0.040	0.035	0.023	0.076	0.053	0.036	0.048
Injury, poisoning & procedural complications	0	0.020	0.016	0.018	0.013	0.036	0.004	0.01
Investigations	0	0.003	0.003	0.005	0.005	0.008	0.004	0.001
Metabolism & nutrition disorders	0	0.002	0	0.003	0.003	0.003	0.004	0.003
Musculoskeletal & connective tissue disordersl	0.010	0.007	0.004	0.005	0.008	0.014	0.004	0.010
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	0.010	0.014	0.020	0.023	0.018	0.017	0.004	0.015
Nervous system disorders	0.019	0.019	0.014	0.008	0.010	0.028	0.015	0.011
Psychiatric disorders	0	0.003	0.003	0.003	0.003	0.003	0	0.001
Renal & urinary disorders	0	0	0.005	0	0.008	0.003	0	0.003
Reproductive system & breast disorders	0	0.003	0	0.005	0	0	0	0.002
Respiratory, thoracic & mediastinal disorders	0.067	0.052	0.087	0.035	0.121	0.061	0.055	0.086
Skin & subcutaneous tissue disorders	0	0	0	0	0	0	0	0.001
Surgical & medical procedures	0	0	0	0	0	0.003	0	0.001
Vascular disorders	0	0.008	0.004	0.015	0.008	0.022	0.004	0.008

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354, and B2355.

† Includes COPD exacerbations; For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo; Exposure in patient years = (sum of the duration of exposure over patients, in days)/365.25; n = The total number of serious events observed over time from all patients. A patient may have multiple occurrences of the same SAE; all occurrences are counted; Primary system organ classes are sorted alphabetically.

Serious adverse events in the COPD 3-month population

Table 6-9 summarizes SAEs by preferred term in the COPD 3-month safety population.

Table 6-9 SAEs affecting >= 2 patients in any treatment group by preferred term in COPD 3-month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Patients with SAE(s)	15 (3.3)	98 (3.8)	38 (3.3)	17 (3.1)	21 (3.8)	51 (4.2)	27 (3.0)	89 (4.4)
Preferred term								
COPD †	4 (0.89)	30 (1.15)	8 (0.69)	4 (0.73)	9 (1.62)	12 (0.99)	11 (1.23)	32 (1.59)
Pneumonia	2 (0.45)	7 (0.27)	4 (0.35)	0	2 (0.36)	3 (0.25)	0	4 (0.20)
Angina pectoris	0	4 (0.15)	1 (0.09)	0	0	0	0	2 (0.10)
Acute myocardial infarction	0	3 (0.11)	1 (0.09)	0	0	0	1 (0.11)	0
Cholelithiasis	0	3 (0.11)	0	0	1 (0.18)	0	0	1 (0.05)
Coronary artery disease	0	3 (0.11)	1 (0.09)	1 (0.18)	0	1 (0.08)	1 (0.11)	0
Fall	0	3 (0.11)	0	0	0	1 (0.08)	0	1 (0.05)
Lower RTI	0	3 (0.11)	1 (0.09)	0	1 (0.18)	0	2 (0.22)	4 (0.20)
Myocardial infarction	0	3 (0.11)	1 (0.09)	1 (0.18)	0	0	1 (0.11)	4 (0.20)
Atrial fibrillation	0	2 (0.08)	0	0	0	3 (0.25)	1 (0.11)	1 (0.05)
Cellulitis	0	2 (0.08)	0	0	0	0	0	2 (0.10)
Cerebral infarction	0	2 (0.08)	0	0	0	0	0	0
Cerebrovascular accident	1 (0.22)	2 (0.08)	0	0	0	2 (0.16)	0	0
H1N1 influenza	0	2 (0.08)	0	0	0	0	0	0
Hemiparesis	0	2 (0.08)	0	0	0	0	1 (0.11)	0
Lung adenocarcinoma	0	2 (0.08)	0	0	0	1 (0.08)	0	0
Pancreatitis acute	0	2 (0.08)	0	0	0	0	0	0
Syncope	0	2 (0.08)	3 (0.26)	0	0	2 (0.16)	1 (0.11)	0
Upper RTI bacterial	1 (0.22)	2 (0.08)	0	0	1 (0.18)	0	2 (0.22)	4 (0.20)
Benign prostatic hyperplasia	0	1 (0.04)	0	1 (0.18)	0	0	0	2 (0.10)
Dyspnea	0	1 (0.04)	2 (0.17)	0	0	3 (0.25)	0	3 (0.15)
Foot fracture	0	1 (0.04)	1 (0.09)	2 (0.37)	0	0	0	0
Non-cardiac chest pain	2 (0.45)	1 (0.04)	0	1 (0.18)	0	1 (0.08)	0	1 (0.05)
Colonic polyp	0	0	0	0	0	0	0	2 (0.10)
Coronary artery occlusion	0	0	0	0	0	2 (0.16)	0	0
Diverticulitis	0	0	0	0	0	0	0	3 (0.15)
Inguinal hernia	0	0	0	0	0	0	0	2 (0.10)
Lobar pneumonia	0	0	0	0	0	2 (0.16)	0	0
Presyncope	0	0	2 (0.17)	0	0	0	0	0
Respiratory failure	0	0	1 (0.09)	0	1 (0.18)	1 (0.08)	2 (0.22)	1 (0.05)
Rib fracture	0	0	2 (0.17)	0	1 (0.18)	2 (0.16)	0	0
Road traffic accident	0	0	1 (0.09)	0	0	2 (0.16)	0	0
Volvulus	0	0	0	2 (0.37)	0	0	0	0

Includes all data from Studies B1302, B2346, B2349, B2350, B2354 and B2355, plus data up to 3 months from Studies B2333, B2334, B2335S/SE and B2336; † Includes COPD exacerbations; For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo. Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg group. A patient with multiple SAEs is counted only once in the total row.

The overall frequency of SAEs was similar across the 8 treatment groups, with rates ranging from 3.0% (salmeterol) to 4.4% (placebo). There was no positive dose-response relationship between the indacaterol doses.

The most frequent SAEs reported in the COPD 3-month safety population were COPD (including disease progression and exacerbations) and pneumonia. For the event of COPD, the highest incidences were found in the formoterol and placebo treatment groups. Pneumonia cases were infrequent; in treatment groups where there was at least one case, the incidences were comparable.

Serious adverse events in the COPD 12-month population

The overall frequency of SAEs in the COPD 12-month safety population is shown in (Table 6-10). The frequency of SAEs was comparable between indacaterol treatment groups and placebo with SAEs most common in the formoterol group. There was no positive dose-response relationship between the indacaterol doses. The most frequent SAE across all treatment groups was COPD (including disease progression and exacerbations) which was more common in the placebo group than in any indacaterol group.

Table 6-10 SAEs affecting >=2 patients in any treatment group by preferred term in COPD 12-month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with SAE(s)	15 (10.4)	81 (13.9)	51 (12.0)	69 (15.9)	61 (11.0)
Preferred term:					
COPD†	4 (2.8)	23 (4.0)	12 (2.8)	32 (7.4)	23 (4.1)
Atrial fibrillation	1 (0.7)	3 (0.5)	0	1 (0.2)	1 (0.2)
Syncope	1 (0.7)	2 (0.3)	0	0	0
Upper RTI	1 (0.7)	0	0	3 (0.7)	0
Angina pectoris	0	2 (0.3)	1 (0.2)	0	1 (0.2)
Aortic aneurysm	0	2 (0.3)	0	0	1 (0.2)
Benign prostatic hyperplasia	0	0	1 (0.2)	0	2 (0.4)
Cardiac arrest	0	0	0	0	2 (0.4)
Cardiac failure congestive	0	2 (0.3)	0	0	1 (0.2)
Cataract	0	3 (0.5)	0	2 (0.5)	1 (0.2)
Cholelithiasis	0	2 (0.3)	0	1 (0.2)	2 (0.4)
Convulsion	0	0	0	2 (0.5)	0
Coronary artery disease	0	0	3 (0.7)	0	1 (0.2)
Dyspnea	0	3 (0.5)	0	1 (0.2)	0
Femoral neck fracture	0	0	0	1 (0.2)	2 (0.4)
Foot fracture	0	1 (0.2)	2 (0.5)	0	1 (0.2)
Gastric cancer	0	0	0	0	2 (0.4)
Hypertensive crisis	0	0	0	2 (0.5)	0
Inguinal hernia	0	0	1 (0.2)	0	2 (0.4)
Lower RTI	0	3 (0.5)	2 (0.5)	5 (1.2)	4 (0.7)
Lower RTI bacterial	0	1 (0.2)	0	2 (0.5)	0
Myocardial infarction	0	2 (0.3)	2 (0.5)	1 (0.2)	2 (0.4)
Myocardial ischemia	0	2 (0.3)	0	0	0
Pneumonia	0	4 (0.7)	2 (0.5)	5 (1.2)	2 (0.4)
Prostate cancer	0	2 (0.3)	1 (0.2)	1 (0.2)	0
Respiratory arrest	0	0	0	0	2 (0.4)
Respiratory failure	0	3 (0.5)	0	5 (1.2)	1 (0.2)
Respiratory tract infection	0	0	1 (0.2)	2 (0.5)	0
Rib fracture	0	2 (0.3)	1 (0.2)	1 (0.2)	0
Road traffic accident	0	2 (0.3)	0	0	0
Sudden death	0	1 (0.2)	0	0	3 (0.5)
Upper RTI bacterial	0	4 (0.7)	0	5 (1.2)	4 (0.7)

Includes data from Studies B2334 and B2335SE; † Includes COPD exacerbations; Ind=indacaterol, For=formoterol, Pbo=placebo; Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg group. A patient with multiple SAEs is counted only once in the total row.

6.3.2 Deaths

Overall, deaths were rare in the indacaterol studies. The data do not suggest that the risk of death is elevated by indacaterol treatment.

In the placebo group (n = 2012) there were 14 deaths: these were due to aortic aneurysm rupture (2 cases), cardiac arrest, sudden death (3 cases), cardio-respiratory arrest, COPD, head injury, multiorgan failure, myocardial infarction (3 cases) and in 1 case the cause was unknown.

Seven of 4764 patients in the COPD safety population who received indacaterol died, as did 23 of 4677 patients in control groups (4/556 for formoterol, 4/1214 for tiotropium, 1/895 for salmeterol and 14/2012 for placebo). In the 150 µg indacaterol group, there was 1 patient who experienced sudden death, 1 patient who died due to cardiac arrest, 1 patient who died due to myocardial infarction and 1 death due to gastric cancer. Two patients in the 300 µg group died, 1 as a result of cardiac arrest, 1 due to myocardial infarction. Among patients who received 600 µg indacaterol, 1 died due to a COPD exacerbation 25 days after the last dose of study medication. The rates of death were lower in all indacaterol groups than in the placebo group. There were no deaths in the indacaterol 75, 37.5 or 18.75 µg groups.

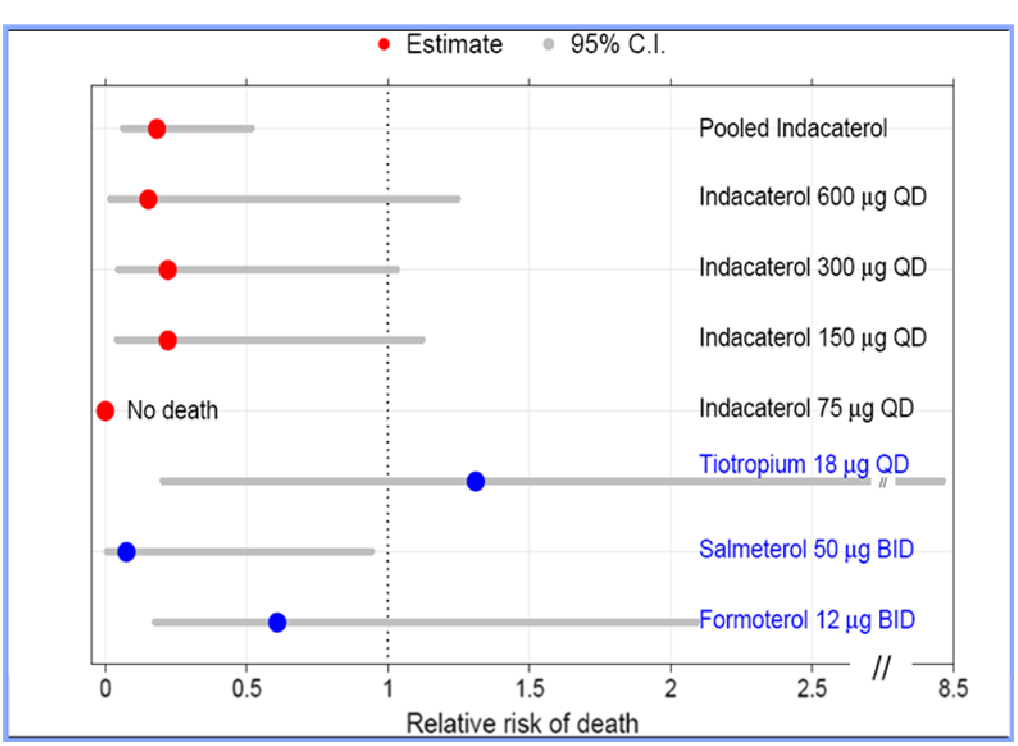
In comparator treatment groups, 4/556 patients who received formoterol at a dose of 12 µg b.i.d. died: causes of death were multi-organ failure, respiratory failure, sudden death, plus 1 death due to unknown causes. Four of 1214 patients who received tiotropium at a dose of 18 µg o.d. died: causes of death were arteriosclerosis, bronchopneumonia, cardiac arrest, septic shock. There was 1 death, due to respiratory failure in the salmeterol group (n = 895).

As shown in Figure 6-1, exposure adjusted death rates were lower for all indacaterol groups (75 µg: 0, 150 µg: 0.005, 300 µg: 0.003, 600 µg: 0.003 deaths per patient-year) than for formoterol (0.010 deaths per patient-year), tiotropium (0.011 deaths per patient-year), and placebo (0.015 deaths per patient-year) and similar to that for salmeterol (0.004 deaths per patient-year). It should be noted that 18.75 and 37.5 µg doses of indacaterol are not presented in this figure, as patient exposure was very low (these doses were only used in 2-week studies) and there were no deaths in patients taking these doses.

The relative risk (calculated using a Poisson regression model including treatment and study as class effects) compared to placebo for exposure adjusted deaths is presented in Figure 6-1. For all indacaterol groups the point estimate of the risk ratio was less than 1 and although the upper limit of the confidence interval includes 1 for each comparison, the data suggests that for patients treated with indacaterol at any dose, it is unlikely that the risk of death exceeds placebo.

Patient deaths also occurred in two studies that were not included in the COPD safety population: these were Studies B2341 and B2351, in which COPD patients were treated concurrently with indacaterol and tiotropium or with tiotropium monotherapy; a total of 2276 patients were included in these studies. There were 4 deaths in patients receiving indacaterol concurrently with tiotropium (2 cases of myocardial infarction, 1 anaphylactic reaction with COPD exacerbation, and 1 death due to unknown cause). One patient on tiotropium monotherapy in these studies also died, due to acute renal failure.

Figure 6-1 Relative risk of death versus placebo



Relative risks (to placebo) adjusted for time on treatment.

6.3.3 Adverse events leading to discontinuation

The presentation of adverse events leading to discontinuation begins with a display of the discontinuation rates for the treatment groups in the COPD safety population overall, then for the 3- and 12- month populations, overall incidence rates are displayed along with the most common individual events leading to discontinuation.

AEs leading to discontinuation in the COPD safety population are displayed in Table 6-11.

Table 6-11 Overall rate of AE episodes leading to discontinuation adjusted for exposure in COPD safety population - # of AEs per patient-year (n/total patient years)

	Indacaterol treatment groups				Control treatment groups			
Primary system organ class - Total	75 µg	150 µg	300 µg	600 µg	For	Tio	Sme	Pbo
Total Population	449	2611	1157	547	556	1214	895	2012
Patients with ≥ 1 AE	21	120	72	34	46	45	29	142
Total patient years	105.062	859.715	736.966	394.489	396.208	357.971	274.932	923.603
# of AEs per patient-year	0.257	0.191	0.129	0.134	0.164	0.260	0.145	0.209

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354, and B2355.
For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo
Exposure in patient years = (sum of the duration of exposure over patients, in days)/365.25
n = The total number of events observed over time from all patients. A patient may have multiple occurrences of the same AE; all occurrences are counted.

Overall, the rates for AE-related are quite low and comparable across the treatment groups. For the indacaterol treatment groups, there is no dose response.

AEs leading to discontinuation in COPD 3-month safety population

The overall rates of AE-related discontinuation for all indacaterol groups are lower than for placebo with no dose response evident for indacaterol (Table 6-12). The most frequently reported AE leading to discontinuation was COPD (including disease progression and exacerbations) which occurred at a rate of 1.6% with both placebo and formoterol, compared to indacaterol 75 µg o.d. (1.1%), 150 µg o.d. (0.8%), 300 µg o.d. (1.0%), 600 µg o.d. (0.4%) and tiotropium (0.7%). Dyspnea was the second most frequent AE leading to discontinuation occurring at similar rates with indacaterol 75 and 300 µg o.d. (both 0.7%), and placebo (0.6%) compared to the other groups (0 to 0.3%).

Table 6-12 AEs leading to discontinuation in >=2 patients in any treatment group by preferred term in COPD 3-month safety population

	Indacaterol treatment groups				Control treatment groups			
Preferred term:	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Any AE(s) leading to discontinuation	20 (4.45)	102 (3.91)	49 (4.24)	15 (2.74)	22 (3.96)	42 (3.46)	24 (2.68)	103 (5.12)
COPD †	5 (1.11)	22 (0.84)	11 (0.95)	2 (0.37)	9 (1.62)	8 (0.66)	7 (0.78)	33 (1.64)
Dyspnea	3 (0.67)	8 (0.31)	8 (0.69)	1 (0.18)	0	4 (0.33)	3 (0.34)	12 (0.60)
Cough	1 (0.22)	4 (0.15)	0	1 (0.18)	1 (0.18)	1 (0.08)	2 (0.22)	5 (0.25)
Nausea	0	4 (0.15)	0	0	0	0	0	0
Ventricular tachycardia	2 (0.45)	4 (0.15)	0	0	0	1 (0.08)	0	0
Acute myocardial infarction	0	3 (0.11)	1 (0.09)	0	0	0	0	0
Atrial fibrillation	0	3 (0.11)	1 (0.09)	1 (0.18)	0	3 (0.25)	1 (0.11)	2 (0.10)
Coronary artery disease	0	3 (0.11)	0	1 (0.18)	0	0	0	0
Muscle spasms	0	3 (0.11)	1 (0.09)	1 (0.18)	0	0	0	0
Pneumonia	1 (0.22)	3 (0.11)	2 (0.17)	0	1 (0.18)	0	0	5 (0.25)
Upper RTI bacterial	0	3 (0.11)	1 (0.09)	0	0	1 (0.08)	1 (0.11)	3 (0.15)
Lung adenocarcinoma	0	2 (0.08)	0	0	0	1 (0.08)	0	0
Myocardial infarction	0	2 (0.08)	1 (0.09)	1 (0.18)	0	0	0	3 (0.15)
Edema peripheral	0	2 (0.08)	0	0	0	1 (0.08)	0	1 (0.05)
Syncope	0	2 (0.08)	0	0	0	0	0	0
Viral infection	0	2 (0.08)	0	0	0	0	0	0
Angina pectoris	0	1 (0.04)	2 (0.17)	0	1 (0.18)	0	1 (0.11)	2 (0.10)
Dizziness	0	1 (0.04)	0	1 (0.18)	0	0	0	4 (0.20)
Electrocardiogram QT prolonged	0	1 (0.04)	0	1 (0.18)	1 (0.18)	3 (0.25)	1 (0.11)	2 (0.10)
Fatigue	0	1 (0.04)	1 (0.09)	2 (0.37)	0	1 (0.08)	0	0
Lower RTI	0	1 (0.04)	3 (0.26)	0	2 (0.36)	0	2 (0.22)	2 (0.10)
Ventricular extrasystoles	1 (0.22)	1 (0.04)	0	0	0	0	0	2 (0.10)
Bronchitis	2 (0.45)	0	0	1 (0.18)	0	1 (0.08)	0	0
Chest pain	0	0	1 (0.09)	0	0	0	0	2 (0.10)
Dry mouth	0	0	0	0	0	2 (0.16)	0	0
Nasopharyngitis	0	0	0	0	0	0	0	2 (0.10)
Rib fracture	0	0	2 (0.17)	0	0	1 (0.08)	0	0
Upper RTI	0	0	0	1 (0.18)	1 (0.18)	0	0	2 (0.10)
Vertigo	0	0	2 (0.17)	0	0	1 (0.08)	0	0
Volvulus	0	0	0	2 (0.37)	0	0	0	0

Includes all data from studies B1302, B2346, B2349, B2350, B2354 and B2355, plus data up to 3 months from Studies B2333, B2334, B2335S/SE and B2336.
For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo, RTI=respiratory tract infection
Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg group.
† Includes COPD exacerbations

AEs leading to discontinuation in COPD 12-month safety population

The overall rates of discontinuation are less than placebo for all indacaterol treatment groups with no dose response present for the indacaterol treatment groups (Table 6-13). The most frequently reported AE leading to discontinuation was COPD (including disease progression and exacerbations) which was 3 times higher in both the placebo and formoterol treatment groups than any indacaterol treatment group.

Table 6-13 AEs leading to discontinuation in >=2 patients in any treatment group by preferred term in COPD 12-month safety population

	Indacaterol treatment groups			Control treatment groups	
Preferred term:	150 µg N=144 n (%)	300 µg N=583 n (%)	600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Any AE(s) leading to discontinuation	4 (2.78)	38 (6.52)	24 (5.65)	42 (9.68)	47 (8.45)
Chronic obstructive pulmonary disease †	1 (0.69)	5 (0.86)	4 (0.94)	17 (3.92)	19 (3.42)
Dyspnea	0	4 (0.69)	2 (0.47)	1 (0.23)	3 (0.54)
Asthenia	0	3 (0.51)	0	0	0
Atrial fibrillation	0	2 (0.34)	0	1 (0.23)	2 (0.36)
Lower respiratory tract infection	0	2 (0.34)	1 (0.24)	4 (0.92)	2 (0.36)
Myocardial infarction	0	2 (0.34)	1 (0.24)	0	2 (0.36)
Rib fracture	0	2 (0.34)	0	0	0
Upper respiratory tract infection bacterial	0	2 (0.34)	1 (0.24)	0	2 (0.36)
Vertigo	0	2 (0.34)	0	0	1 (0.18)
Pneumonia	0	1 (0.17)	1 (0.24)	2 (0.46)	2 (0.36)
Sudden death	0	1 (0.17)	0	0	3 (0.54)
Cardiac arrest	0	0	0	0	2 (0.36)
Cardiac failure	0	0	0	2 (0.46)	0
Muscle spasms	0	0	2 (0.47)	0	0
Prostate cancer	0	0	2 (0.47)	1 (0.23)	0
Respiratory arrest	0	0	0	0	2 (0.36)
Respiratory failure	0	0	0	4 (0.92)	1 (0.18)
Respiratory tract infection	0	0	0	2 (0.46)	0
Upper respiratory tract infection	0	0	0	2 (0.46)	1 (0.18)

Includes data from Studies B2334 and B2335SE.
Ind=indacaterol, For=formoterol, Pbo=placebo
† Includes COPD exacerbations
Preferred terms are sorted in descending order of frequency in the indacaterol 300 µg group.

6.4 Adverse events - overall assessment

The adverse events observed in the registration program were as expected for a patient population with COPD, and for the drug class. For all individual events, the rate, when corrected for exposure, was less than 1 event per patient-year. The most common AE in all treatment groups was COPD (including disease progression and exacerbations). For example, taking the COPD 3-month population as a representative pool that includes all dose groups and all key studies, the most frequent common adverse events were COPD, nasopharyngitis, cough, headache, and upper respiratory tract infection; all of which could be considered to be expected events in a population of patients with moderate or severe COPD.

Adverse events leading to discontinuation from study were infrequent; event incidences for patients treated with indacaterol were either lower or comparable to those seen for comparable placebo controls.

Across the safety populations, the overall incidence of SAEs was similarly low for all treatment groups. No dose dependence was observed for SAEs in the indacaterol groups. The most common SAE was COPD (includes disease progression and exacerbations) which occurred with lower incidence in all indacaterol groups than in the placebo group. In addition, across the populations, no consistent trend was observed in SAEs when examined by the subgroups of age, sex, race, COPD severity, smoking history and use of ICS; there were no patterns suggestive of any unique effect of indacaterol on the incidence of these events.

The exposure-adjusted rate of death for all indacaterol treatment groups was lower than that for the placebo group. There were seven patients treated with indacaterol who died compared with fourteen deaths under placebo administration.

In summary, the data on individual adverse events, events leading to discontinuation, serious adverse events, and deaths support the safety of the indacaterol doses recommended for use in COPD patients.

6.5 Areas of special interest

In this section, safety issues of interest will be presented. These include cardio- and cerebrovascular (CCV) events and events of cough occurring post-inhalation.

6.5.1 Cardiovascular and cerebrovascular events

To assess potential effects of beta-adrenergic stimulation on the cardiovascular system, two search approaches were defined in the analysis plan and used to explore the pooled safety databases: standard MedDRA queries (SMQs) for cardio- or cerebrovascular (CCV) events, and events defined using Anti Platelet Trialist Collaboration (1994) (APTC) criteria. A further search approach, performed subsequently, was to perform analyses based on MACE (Major Cardiovascular Events) criteria.

CCV events are identified by a search using Standard MedDRA Queries (SMQs) on cardiac arrhythmias, cardiac failure, ischemic heart disease and cerebrovascular disorders, including overall 257 preferred terms. SMQs are groupings of terms from one or more System Organ Classes that relate to a defined medical condition or area of interest, approved by ICH.

The APTC search criteria includes terms from the MACE search plus terms for cardiac death, cerebrovascular occlusions and hemorrhages and unstable angina.

The MACE (Major Cardiovascular Events) analyses are based on search criteria designed by the Division of Metabolic and Endocrine Drug Products of the FDA. Two MACE searches have been developed, a Broad MACE and a Custom MACE. The Broad MACE includes all preferred terms in the Standardised MedDRA Queries (SMQs) for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents”, and it also includes cardiac deaths identified by independent adjudication. The “Custom MACE” is a subset of “Broad MACE”. Search terms in the custom MACE were selected by medical reviewers at the FDA and represent the preferred terms that most closely describe myocardial

infarction and stroke. The APTC search criteria includes terms from the MACE search plus terms for cardiac death, cerebrovascular occlusions and hemorrhages and unstable angina.

In the original submission, data from Study B2334 alone comprised the 12-month safety population and a higher frequency of cardiovascular and cerebrovascular (CCV) SAEs was observed with 300 and 600 µg indacaterol compared to placebo and to formoterol in this single study (Study B2334: Table 6-14).

Table 6-14 Number of cardio- or cerebrovascular (CCV) SAEs during the treatment period (Study B2334)

	Indacaterol treatment groups		Control treatment groups	
	300 µg	600 µg	Formoterol	Placebo
Total population, N	437	425	434	432
Patients with ≥ 1 event, n	15	11	6	4
(%)	3.43	2.59	1.38	0.93
Total pt-yr	372.21	361.58	361.38	338.05
# of event per pt-yr	0.04836	0.03872	0.02490	0.01479

Only treatment-emergent cases considered.

This imbalance was not seen in an additional 12-month study, Study B2335SE, in which patients were exposed to the 150 µg, 300 µg or placebo for up to one year (Table 6-15).

Table 6-15 Number of cardio- or cerebrovascular (CCV) SAEs during the treatment period (Study B2335SE)

	Indacaterol treatment groups		
	150 µg	300 µg	Placebo
Total population, N	144	146	124
Patients with ≥ 1 event, n	1	3	4
(%)	0.69	2.05	3.23
Total pt-yr	140.70	143.54	120.21
# of event per pt-yr	0.0071	0.0209	0.0333

Only treatment-emergent cases considered.

CCV SAEs were also analyzed in pooled data. In the COPD safety population, there was a slight excess of CCV SAEs for indacaterol compared with placebo (0.057, 0.043. 0.039, 0.035 events per patient year for 75, 150, 300 and 600 µg, respectively versus 0.028 on placebo). However, the rates were similar to the active controls tiotropium (0.056) and salmeterol (0.036).

The time to first CCV SAE (based on event rates calculated from Kaplan-Meier estimates) shows no statistically significant differences between any indacaterol dose and placebo (based on a Cox proportional hazards regression model stratified by study and country with treatment, ICS use, study, and seven baseline CV risk factors included as covariates). The hazard ratios for the 75, 150, 300 and 600 µg indacaterol doses were 1.87 (0.54, 6.45), 1.14 (0.61, 2.14), 1.38 (0.75, 2.53) 1.05 (0.48, 2.29) versus placebo and comparable with those seen for the active controls (HR=0.54 (95%CI 0.21-1.41); 1.25 (0.56-2.78); 0.61 (0.23-1.58) for formoterol, tiotropium and salmeterol, respectively).

APTC events were rare in all treatment groups and rates observed on indacaterol were similar to those seen for placebo and the active controls (Table 6-16). The most common events, across all treatment groups, expressed as number per patient year were myocardial infarction, acute coronary syndrome, and cerebrovascular accident. The hazard ratios for the 75, 150, 300 and 600 µg indacaterol doses suggest the risk of an APTC event is similar to placebo.

Table 6-16 Antiplatelet Trialists' Collaboration (APTC) AE episodes adjusted for exposure by primary system organ class and preferred term in the COPD safety population: number of APTC AEs per patient-year (n/total patient years)

Primary system organ class	Indacaterol treatment groups				Control treatment groups			
Preferred term	**75 µg**	**150 µg**	**300 µg**	**600 µg**	**For**	**Tio**	**Sme**	**Pbo**
Total Population	449	2611	1157	547	556	1214	895	2012
Patients with ≥1 APTC AE	1	14	7	3	2	4	5	13
Total patient years	105.062	859.715	736.966	394.489	396.208	357.971	274.932	923.603
# of APTC AEs per patient-year	0.010	0.016	0.011	0.010	0.008	0.011	0.018	0.014
Cardiac disorders - Total	0	0.009	0.004	0.005	0.005	0.006	0.015	0.009
Acute myocardial infarction	0	0.005	0.001	0	0	0	0.004	0.001
Myocardial infarction	0	0.003	0.003	0.005	0.005	0	0.007	0.008
Acute coronary syndrome	0	0.001	0	0	0	0.006	0.004	0
General disorders & administration site conditions - Total	0	0.001	0.001	0	0	0	0	0.003
Sudden death	0	0.001	0.001	0	0	0	0	0.003
Nervous system disorders - Total	0.010	0.006	0.005	0.005	0.003	0.006	0.004	0.002
Cerebral infarction	0	0.002	0.001	0	0	0	0	0
Cerebrovascular accident	0.010	0.002	0	0.003	0.003	0.006	0	0
Lacunar infarction	0	0.001	0	0	0	0	0	0
Carotid artery occlusion	0	0	0.003	0.003	0	0	0	0
Cerebellar infarction	0	0	0	0	0	0	0	0.001
Cerebral haemorrhage	0	0	0.001	0	0	0	0	0
Ischaemic stroke	0	0	0	0	0	0	0.004	0.001

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354 and B2355
n= The total number of events observed over time from all patients. A patient may have multiple occurrences of the same AE. All the occurrences are counted.
For = formoterol, Tio = tiotropium, Sme = salmeterol, Pbo = placebo
Total patient years= (sum of the duration of exposure over patients, in days)/365.25
# of APTC AEs per patient year = n/ Total patient years
Primary system organ classes are sorted alphabetically; preferred terms are sorted within each primary system organ class in descending order of (# of APTC AEs per patient-year) in the Indacaterol group (150 µg)

In the COPD safety population using both the Broad and Custom MACE criteria (Table 6-17), no imbalance was seen between all of the indacaterol doses (75, 150, 300, and 600 µg) and placebo. The frequency of events with all doses of indacaterol was lower than placebo. There were no statistically significant differences between the indacaterol doses and placebo and the point estimate of the hazard ratio was less than 1 in all cases.

Table 6-17 Broad and Custom MACE episodes by patient and patient year of exposure, COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg	150 µg	300 µg	600 µg	For	Tio	Sme	Pbo
Total Population	449	2611	1157	547	556	1214	895	2012
Total patient years	105.062	859.715	736.966	394.489	396.208	357.971	274.932	923.603
Broad MACE								
Patients with ≥1 MACE event	4	21	8	6	7	11	7	29
(%)	0.89	0.80	0.69	1.10	1.26	0.91	0.78	1.44
# of events per patient-year	0.038	0.035	0.014	0.023	0.020	0.036	0.029	0.040
HR*	0.56	0.74	0.49	0.62	0.74	1.43	0.49	
96% CI	0.17-1.84	0.37-1.50	0.21-1.13	0.23-1.65	0.29-1.87	0.55-3.69	0.18-1.38	
Custom MACE								
Patients with ≥1 MACE event	1	14	5	3	4	4	4	19
(%)	0.22	0.54	0.43	0.55	0.72	0.33	0.45	0.94
# of events per patient-year	0.010	0.019	0.008	0.008	0.013	0.011	0.015	0.024
HR*	0.41	0.75	0.44	0.45	0.53	1.23	0.43	
96% CI	0.04-3.99	0.31-1.82	0.16-1.24	0.12-1.68	0.16-1.75	0.27-5.64	0.11-1.62	

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354 and B2355
Total patient years= (sum of the duration of exposure over patients, in days)/365.25
# of MACE events per patient year = n/ Total patient years
For = formoterol, Tio = tiotropium, Sme = salmeterol, Pbo = placebo
* HR versus placebo from a Cox proportional hazards regression model (stratified by study and country with treatment, ICS use, study, and 7 baseline CV risk factors included as covariates)

There were no statistically significant differences between the indacaterol doses and placebo and the point estimate of the hazard ratio was less than 1 in all cases in both the Broad and Custom MACE analyses.

In summary, although a numerical imbalance in CCV SAEs was seen in Study B2334, the totality of data from the indacaterol program demonstrates no dose relationship for CCV events with the time to first event not significantly different between indacaterol groups and controls. CCV events were also analyzed according to the presence/absence of cardiovascular risk factors. Very few indacaterol-treated patients without baseline cardiovascular risk factors reported CCV events.

For the most objective and serious cardiovascular and cerebrovascular events, APTC and MACE analyses demonstrate these events occurred in very small numbers of patients with no evidence of any relationship to indacaterol.

The lack of excess cardiovascular and cerebrovascular events for indacaterol is consistent with death rates in the COPD population, which were lower for all indacaterol doses than for placebo; this would seem to strongly support the absence of any adverse cardiovascular effect that would contribute to mortality.

Cardiac arrhythmias

Cardiac electrophysiological effects were investigated by 1) a dedicated QT study in healthy subjects using active and placebo controls, 2) repeated ECG measurements before and after inhalation to assess the immediate post-dose and the long-term effects in COPD patients, 3)

Holter 24-hour ECG monitoring to assess the effects on heart rate and arrhythmias in COPD studies. Results did not show any clinically relevant effects on heart rate, the ECG intervals, morphology and interpretation, nor on pro-arrhythmia indicators.

Study B2339 was a thorough QT study in 404 healthy subjects. The primary objective of the study was to characterize the maximum mean QTcF prolongation following multiple doses of indacaterol for 14 days. The mean maximum time matched differences versus placebo of the QTcF interval for doses of indacaterol up to 600 µg o.d. were below 5 msec.

In the COPD safety population, the mean QTcF values at baseline were comparable across treatments ranging from 400.3 to 410.3 msec. The mean difference from baseline across all time points and doses ranged between -0.6 to 4.2 msec. No dose response relationship for QTcF duration was seen for indacaterol. The largest mean increase from baseline (4.2 msec) was seen with formoterol on day 1 at 30-minutes post-dose.

In the COPD safety population acute notable increases in the QTcF interval from 25 min pre-dose to ≤ 75 min post-dose were rare. Acute prolongations by 30-60 msec were seen in 2.22 to 4.51% of patients on indacaterol and in 2.45% on placebo. The frequencies of notable QTcF increases of 30-60 msec were lower on indacaterol than on formoterol (5.26%), and higher on indacaterol than on tiotropium (2.39%) and salmeterol (1.68%). QTcF increases of >60 msec were rare (Table 6-18).

Table 6-18 Clinically notable increases in QTcF at any visit in COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75µg n (%) N = 449	150µg n (%) N = 2611	300µg n (%) N = 1157	600µg n (%) N = 547	For n (%) N = 556	Tio n (%) N = 1214	Sme n (%) N = 895	Pbo n (%) N = 2012
Increase from 25 min pre-dose to ≤ 75 min post-dose								
Total	449	2607	1153	543	551	1211	895	2004
30-60 msec	16 (3.56)	58 (2.22)	52 (4.51)	22 (4.05)	29 (5.26)	29 (2.39)	15 (1.68)	49 (2.45)
>60 msec	0	4 (0.15)	1 (0.09)	0	1 (0.18)	1 (0.08)	1 (0.11)	1 (0.05)

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354 and B2355
Total = patients with available data. For = formoterol, Tio = tiotropium, Sme = salmeterol, Pbo = placebo

Subsets of COPD patients in Study B2335S underwent continuous 24-hour ECG recording to provide further information on cardiac function and to monitor for occurrences of short lived arrhythmias. Overall, there were no significant differences in mean heart rate between patients receiving 150 or 300 µg indacaterol (the two doses evaluated in the studies), tiotropium and placebo, or between doses of indacaterol over 24-hour ECG recording periods at Week 2 (Visit 5), Week 12 (Visit 9) and Week 26 (Visit 13). Changes in the mean 24 hourly minimum and maximum heart rate across all visits and treatments were similar, small and not clinically relevant. All active treatments showed little difference from placebo and the diurnal variation was maintained. For both doses of indacaterol, tiotropium and placebo no meaningful changes from baseline in the number of sinus pauses were seen at Weeks 2, 12 or 26. The rates of atrial fibrillation were similar between the active drugs and placebo all throughout the study. To look at the rates of ventricular ectopic beats and the associated ventricular tachycardia an analysis was performed looking at 'proarrhythmic criteria' (based on changes from baseline in the number of 1) ventricular extrasystoles and 2) "runs" of ventricular extrasystoles). It was

found that the rates of proarrythmia were similar for the 150 and 300 μg doses of indacaterol, tiotropium and placebo, indicating that there was no evidence of a proarrythmic effect.

6.5.2 Respiratory-related deaths, hospitalizations and intubations

In December 2010, FDA requested Novartis to conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control. To meet this request, Novartis implemented an adjudication committee (AC) to provide an independent, external, systematic, standardized and unbiased assessment of all SAEs occurring during the development of indacaterol (in studies in COPD and asthma). An Addendum detailing the methodology and results of this analysis will be provided to this Briefing Document.

6.5.3 Cough experienced post-inhalation

Some patients experienced a cough of brief duration after inhalation of indacaterol, so this was evaluated further in the pooled safety populations. In Studies B2334, B2335S, B2346, B1302, B2336, and B2333 information about any post-inhalation events at the clinic visits as observed by the study staff was proactively solicited. A patient was said to be experiencing cough post-inhalation if the cough occurred within 5 minutes following inhalation of study medication at a study visit. In Phase III clinical studies, health care providers observed during clinic visits on average 14-15% of patients experienced a sporadic cough at the recommended doses that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds.

In general, cough post-inhalation was not associated with poor tolerability: only 2 patients discontinued treatment due to this (one treated with indacaterol 150 μg and the other with 600 μg). No safety signals associated with cough post-inhalation were detected: the overall incidence of AEs; rate of discontinuation due to AEs; FEV_1 decrease of ≥20% within 30 minutes of dosing; bronchospasm reported as an AE; and exacerbations of COPD were unaffected by the presence of cough post-inhalation. Cough post-inhalation did not affect the efficacy of indacaterol. Subgroup analyses suggested that patients < 75 years of age were more likely to experience cough post-inhalation than older patients, as were female patients relative to males, and smokers relative to ex-smokers. No consistent effect was observed with regard to COPD severity, ICS use, and duration of COPD.

Although dosing with indacaterol is associated with a transient cough in some patients, these events do not negatively impact tolerability, efficacy or safety.

6.6 Vital signs

The mean changes on sitting BP and pulse were small and not clinically relevant showing that for up to 12 months of treatment, there were no meaningful chronic effects of indacaterol 75, 150, 300 and 600 μg o.d. on sitting BP and pulse compared with formoterol, tiotropium, salmeterol and placebo treatment.

The percentage of patients with low clinically notable SBP values was broadly similar across all treatment groups in the COPD safety population, ranging from 0.58% for indacaterol 150 μg to 2.7% for formoterol (1.54% for placebo). High clinically notable SBP values ranged in incidence from 0.45% for indacaterol 75 μg to 3.3% for 600 μg (1.64% for placebo); the 150

and 300 µg indacaterol groups each had a lower incidence than placebo (0.65% and 1.47%, respectively).

For DBP in the COPD safety population, low clinically notable values were most common for indacaterol 600 µg (2.01%) and least common for salmeterol (0.34%); the rate for placebo was 0.95%. High clinically notable DBP was also seen most commonly for indacaterol 600 µg (1.83%), and was lowest for indacaterol 150 µg (0.65%), with 1.54% for placebo.

In the COPD safety population, clinically notable low pulse rates occurred most frequently for placebo group (1.39% of patients) while the largest percentage of patients with clinically notable high pulse rate occurred for formoterol (0.9%); the incidence for placebo was 0.35%. The incidence of clinically notable high and low pulse rates showed no relationship to indacaterol dose, and for most indacaterol doses neither occurred in more than 1% of patients – the exceptions were notable low rates for 75 µg (1.34%) and 300 µg (1.04%), also for formoterol (1.08%) and placebo (1.39%) (Table 6-19).

Table 6-19 Clinically notable pulse rate values at any time post-baseline in COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg n (%) N = 449	**150 µg n (%) N = 2611**	**300 µg n (%) N = 1157**	**600 µg n (%) N = 547**	**For n (%) N = 556**	**Tio n (%) N = 1214**	**Sme n (%) N = 895**	**Pbo n (%) N = 2012**
≥ 120 bpm and increase from baseline of ≥ 15 bpm and/or ≥ 130 bpm								
Total N	449	2607	1156	546	556	1214	895	2009
n (%)	1 (0.22)	5 (0.19)	6 (0.52)	2 (0.37)	5 (0.90)	1 (0.08)	1 (0.11)	7 (0.35)

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354 and B2355
Total = number of patients with a value at any time post-baseline. For = formoterol, Tio = tiotropium, Sme = salmeterol, Pbo = placebo

6.7 Clinical laboratory evaluations

Evaluation of laboratory data included shift analyses, analyses of central tendency (change from baseline) by parameter, evaluation of the rate of notably abnormal laboratory values, as well as more detailed reviews of data for selected parameters.

There was little change over time in hematology, chemistry and urinalysis values overall, and no meaningful differences between treatment groups were seen. Mean and median values were within normal ranges. There were no clinically relevant differences between treatment groups for shifts from normal at baseline to low (< LLN) or high (> ULN) post-baseline in the whole COPD safety population. The laboratory analyses did not reveal any trends in the data that indicated a clinically important effect on hematology, chemistry or urinalysis.

Glucose and potassium were analyzed extensively:

Glucose

The percentages of patients with shifts from normal glucose at baseline to high glucose values post-baseline were comparable among the indacaterol groups and placebo for the COPD 3-month, 6-month, 12-month and COPD safety populations.

The incidence of newly occurring or worsening notably high glucose values (> 9.99 mmol/L) in the indacaterol treatment groups ranged from 4.7 to 8.4% compared to formoterol 5.8%, tiotropium 4.3% and placebo 6.7% for the COPD safety population (Table 6-20). The differences in incidence rates between the indacaterol groups and placebo were small.

Analysis of between treatment comparisons of glucose by visit and time point in the COPD safety population showed that least squares means (LSMs) were similar at all visits among treatment groups; LSM differences were not clinically relevant although some comparisons, especially against placebo were statistically significant. The largest numerical difference between any pair was 0.41 mmol/L (7.4 mg/dL) for indacaterol 600 µg o.d. versus placebo (Month 3 at 1 hour post-dose). At week 12, the LS mean differences to placebo for 75 and 150 µg indacaterol were 0.07 and 0.15 mmol/L, respectively.

Table 6-20 Clinically notable high glucose at any time post-baseline in COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75µg N=449 n (%)	150µg N=2611 n (%)	300µg N=1157 n (%)	600µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Glucose - Total	448	2574	1147	545	553	1191	878	1999
> 9.99 mmol/L (180 mg/dL) n(%)	22 (4.9)	122 (4.7)	90 (7.8)	46 (8.4)	32 (5.8)	51 (4.3)	58 (6.6)	134 (6.7)

Includes data from Studies B1302, B2333, B2334, B2335S/SE, B2336, B2346, B2349, B2350, B2354 and B2355
Total = number of patients with a value at any time post-baseline. For = formoterol, Tio = tiotropium, Sme = salmeterol, Pbo = placebo

Potassium

Mean changes from baseline were small and not clinically significant for all treatment groups at all visits and time points. Maximum and minimum changes from baseline were comparable among groups at all visits. Few patients had clinically notable low potassium levels (Table 6-21).

Potassium changes from baseline to post-baseline by visit and time point were summarized in the COPD safety population for subgroups by age, race, smoking history and ICS use. Changes from baseline were comparable among treatment groups regardless of age, race (Caucasians, other race subgroups were too small for evaluation), smoking history, and ICS use. There does not appear to be a clinically significant effect on potassium by indacaterol in any of the evaluable subgroups.

Potassium mean changes from 25 minutes pre-dose to 1 hour post-dose for all visits were small and comparable among treatment groups. The greatest mean change from 25 minutes pre-dose at any visit (-0.11 mmol/L) was seen in the indacaterol 600 µg o.d. group at Day 1, 1 hour post-dose. At Week 12, the LS mean differences to placebo in change from 25 minutes pre-dose to 1 hour post-dose for 75 and 150 µg indacaterol were zero and -0.04 mmol/L, respectively.

Between-treatment comparisons of potassium by visit and time point in the COPD safety population revealed that, at various visits, there were some LSM differences between

treatments that were statistically significant, but the numerical differences between the treatment groups were too small to be considered clinically relevant.

Table 6-21 Clinically notable low potassium at any time post-baseline in COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75µg N=449 n (%)	150µg N=2611 n (%)	300µg N=1157 n (%)	600µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Potassium - Total	447	2573	1148	544	554	1191	878	1999
< 3 mmol/L	1 (0.2)	4 (0.2)	4 (0.3)	0	0	1 (< 1)	2 (0.2)	5 (0.3)

Total = number of patients with a value at any time post-baseline. For = formoterol, Tio = tiotropium, Sme = salmeterol, Pbo = placebo

6.8 Safety in asthma

Although an asthma indication is not being sought for indacaterol, the FDA requested an evaluation of safety in asthma. Study B2338 was a 26-week, randomized, multi-center, double-blind, double-dummy, parallel-group study designed to assess the safety of indacaterol 300 and 600 µg o.d. Salmeterol 50 µg b.i.d. was an active control. Patients were instructed to continue concomitant inhaled corticosteroids. The randomized, safety and ITT populations included 805 asthmatics (268 on indacaterol 300 µg o.d, 268 on indacaterol 600 µg o.d. and 269 on salmeterol 50 µg b.i.d.), aged 12 to 85 years (mean 43.5 years) using a daily dose of at least 100 µg beclomethasone dipropionate (BDP) or equivalent dose of an alternative inhaled corticosteroid (ICS), and with screening $FEV_1 \geq 50\%$ of the predicted normal value. Two deaths occurred in the study, one cardiac arrest and the other an inadequately-treated asthmatic crisis that was initially reported as sudden death. Both occurred in subjects treated with indacaterol 300 µg o.d. There were no deaths in the other treatment groups. The frequency of SAEs was 1.9% in the indacaterol 300 µg o.d. group, 3.0% in the salmeterol group and 4.1% in the indacaterol 600 µg o.d. The most frequently affected primary system organ class (SOC) was respiratory, thoracic and mediastinal disorders, and the most frequent SAE reported was asthma. Two patients on indacaterol had SAEs suspected to be related to the study medication according to the investigators, the fatal asthmatic crisis (initially reported as sudden death) described above, and a case of atrial fibrillation.

There were 6 non-fatal SAEs related to asthma exacerbation (none of which were suspected to be related to study medication). Five were in patients on indacaterol (3 in the 300 µg group and 2 in the 600 µg group). Of these, 4 cases were triggered/confounded by other events, (i.e. food allergy, external stress, chemical agents, and bacterial respiratory tract infection), and the time point of the asthma exacerbation was very variable (38 to 169 days); 2 patients continued study medication after the event was resolved and completed the study as planned. The one SAE related to asthma exacerbation in a patient receiving salmeterol was an asthma exacerbation triggered by aspirin ingestion, which led to hospitalization.

The dose-finding Study B2357 (Section 5.1.3) and the dose regimen Study B2223 (Section 5.1.4) were performed in patients with asthma and provide some additional safety data in this population. Both studies, however, had treatment periods of only 2 weeks. Cough and headache were the most common AEs in these studies and there did not appear to be any relationship between tolerability and dose or dose regimen of indacaterol. There were no

deaths in either of the studies. In Study B2357, asthma exacerbations occurred in a total of 11 patients and were most common in the placebo and salmeterol control groups; none of these events were serious. In Study B2223, there was one SAE (hospitalization), in a patient taking indacaterol 150 μg q.o.d, an exacerbation of asthma secondary to viral influenza and exposure to pollen.

In addition to the completed studies in asthma, some data are available from ongoing study (QMF149A2210) with QMF149 (a fixed dose combination of indacaterol 500 μg plus mometasone furoate 400 μg). Recruitment was completed in April 2010 with 1519 patients enrolled. Treatment remains blinded. To date, 5 serious asthma events have occurred, all non fatal hospitalizations that did not require intubation. One death, unrelated to asthma or to treatment has been reported.

6.9 Post-marketing experience

Indacaterol (under the tradename Onbrez® Breezhaler®) was approved in the EU in November 2009 as a once-daily long-acting β_2-agonist for adults with chronic obstructive pulmonary disease. Onbrez® Breezhaler® is now approved in more than 50 countries and marketed in major countries which include Germany, Greece, Ireland, Mexico, Portugal, Slovenia, Spain, Switzerland, The Netherlands, United Kingdom, Italy, Lebanon, Malta, Norway, Denmark and India with additional launches planned in 2011. Indacaterol is also co-marketed in Germany and Portugal.

Exposure

For the time period from 30 November 2009 to 30 November 2010 the estimated patient exposure calculated based on worldwide sales volume of capsules (20.7 million) was approximately 56,000 patient-years, although this is likely an overestimation as it is based on sales from the wholesalers to retailers, and the stocking at retailers is unknown.

Distribution of cases by report type

A total of 275 spontaneous reports were received during the review period. Spontaneous reporting of adverse events is voluntary for patients, healthcare providers and other reporters. All reports of AEs received by Novartis are included in the safety database. Patients who submit adverse event reports are requested to provide contact information for their health care providers so that the sponsor can attempt to obtain additional follow up information. In the current database 220 reports were received from Health Care Providers (HCPs) and 55 reports from non-HCPs. Details on the distribution of the reports are presented in Table 6-22.

Table 6-22 Overview of spontaneously reported cases by case seriousness

Report type	Non-serious	Serious	Total
Spontaneous HCP	168	52	220
Spontaneous non-HCP	52	3	55
Total	220	55	275

The majority of the SRs were reported from Germany (184 reports = 66.9%), which has far greater patient exposure than other countries. Other contributing countries were Denmark (20), Greece (10), Ireland (9), The Netherlands (9), United Kingdom (8), Switzerland (7), and

Spain (6) and (in alphabetical order, all with 5 or less reports) Belgium, Malta, Mexico, Norway, Portugal, Sweden, and Venezuela.

Distribution of adverse reactions by MedDRA SOC

A total of 562 reactions (455 HCP + 107 non-HCP) were reported in these 275 reports. The distribution of the reactions by MedDRA System Organ Class, report type and seriousness classification is presented in Table 6-23.

Table 6-23 Distribution of spontaneous adverse reactions by MedDRA SOC

	Non-serious		Serious		
Body System	**HCP**	**non-HCP**	**HCP**	**non-HCP**	**Total**
Blood and lymphatic system disorders	1		2		3
Cardiac disorders	14	1	19	2	36
Ear and labyrinth disorders	2				2
Eye disorders	6	2	3		11
Gastrointestinal disorders	19	3	7	1	30
General disorders and administration site conditions	55	19	18	1	93
Infections and infestations	10	1	4		15
Injury, poisoning and procedural complications	6	6	2		14
Investigations	10	3	15		28
Metabolism and nutrition disorders	5		3		8
Musculoskeletal and connective tissue disorders	24	2	1		27
Nervous system disorders	34	7	15	3	59
Psychiatric disorders	8	8	6		22
Renal and urinary disorders	2		7		9
Reproductive system and breast disorders	1				1
Respiratory, thoracic and mediastinal disorders	85	39	28	2	154
Skin and subcutaneous tissue disorders	23	5	3		31
Social circumstances			2		2
Surgical and medical procedures		1	6		7
Vascular disorders	1	1	8		10
Total	306	98	149	9	562

Most frequent serious adverse reactions reported

The most frequent SRs of SAEs reported by HCP included COPD and dyspnea (n = 6 each) angina pectoris (n=5), circulatory collapse (n=5), arrhythmia, blood pressure decreased, dizziness and syncope (each n=3) (Table 6-24).

Table 6-24 Spontaneous reports of serious adverse events reported by Health Care Professionals (reports with n= >1)

Preferred Term	Total
Chronic obstructive pulmonary disease	6
Dyspnoea	6
Angina pectoris	5
Circulatory collapse	5
Arrhythmia	4
Blood pressure decreased	3
Dizziness	3
Syncope	3
Acute myocardial infarction	2
Asthenia	2
Asthma	2
Bronchospasm	2
Chest discomfort	2
Concomitant disease progression	2
Cough	2
Death	2
Disease progression	2
Hyperhidrosis	2
Oedema peripheral	2
Tachycardia	2

Spontaneous reports with fatal outcome

There were nine deaths reported of which four were related to disease progression (COPD exacerbation). The other causes of death were sepsis, acute myocardial infarction, possible pulmonary embolism, sudden death, and unknown. Deaths occurred between 2 and 128 days after treatment initiation with indacaterol (one case unknown) (Table 6-25).

Table 6-25 Spontaneous reports with fatal outcome

PHHY 2010...	Age/Sex	Case description	TTE (d)	Report Type
DE17342	96F	On Day 15 circulatory collapse following severe diuresis. Increased blood glucose. Discontinuation of indacaterol medication. Pt died 14 days later.	15	HCP/s
DE18208	66F	On Day 1 nausea and dizziness leading to discontinuation of indacaterol on Day 4. After recovery at unknown date, indacaterol treatment restarted. Progression of underlying disease / diabetes. Fatal sepsis following cosmetic surgery of toe nails. Date of death not available.	1/ unk	HCP/s
DE38896	Unk	On Day 17 death due to disease progression / COPD. MedHx: Hypertension, cardiac failure.	17	HCP/s
DE55413	44F	Approx. 6 weeks prior to the fatal event series of exacerbations requiring i.v. prednisolone (no oxygen therapy; no hospitalization). Initiation of systemic prednisolone therapy and switch from fluticasone + tiotropium to indacaterol + tiotropium. After 6 weeks of treatment with indacaterol fatal status asthmaticus. MedHx included both COPD and asthma. No autopsy performed.	6 wks	HCP/s
DK36692	81M	On Day 13 acute myocardial infarction documented by ECGs and troponin level. Med Hx: myocardial ischemia. Death on Day18.	13	HCP/s
IE56067	69M	On Day 2 death due to respiratory failure. Conc. medication: tiotropium + Seretide and daily oxygen therapy. No details available.	2	HCP/s
CH75996	Unk F	Approx 2 months after initiation of Onbrez patient became comatose. Diagnoses: COPD exacerbation, Pulmonary embolism cannot be excluded.	~2 mths	HCP/s
DK62694	55M	Respiratory distress and bronchospasm resulting in hospitalization, discharged 9 days later. 44 days later patient was found dead at home. Heavy smoker and misuse of alcohol.	128	HCP/s
ES73994	84M	On Day 1 concomitantly with Onbrez patient received immunization with influenza virus vaccine. The following day sudden death. Hx of myocardial infarction and diabetes mellitus.	2	HCP/s

Source: ARGUS database; cutoff Nov 30, 2010; HCP = Health Care Provider; s = serious, ns = non-serious;
TTE = time to event in days after start of indacaterol therapy Unk = unknown

Reports with fatal outcome from Patient Support Programs

In addition to the nine deaths shown in Table 6-25, Novartis received reports of the deaths of 17 patients who were participating in Patient Support Programs (PSPs) in Mexico. Sixteen of these patients were participating in a PSP known as “Sentir, Expressar, Respirar” or SER. Patients enrolled into the PSP on starting indacaterol treatment. A call center contacted people at baseline and 2 and 4 weeks to ask them to complete surveys on ongoing symptoms and satisfaction with medication. If the call center received information that the patient had experienced an adverse event (including death), the call center transferred this information to

Novartis pharmacovigilance. Additional follow-up information was then obtained, where possible, from relatives and prescribing physicians.

The SER PSP enrolled 1316 patients between September 26, 2010 and January 4, 2011. As of January 19, 2011, 729 patients had completed all 3 surveys, and 546 had completed 2 surveys. The last patient is expected to complete the final survey on February 7, 2011. Patients in SER tended to have severe or very severe COPD, with significant co-morbidities.

Among the 16 fatal cases that were detected through solicitation by the call center, the most common causes of death were pneumonia and COPD progression (5 patients). The ages of the patients who died ranged from 56 to 98 years. Seven were female. All but one of the patients had significant co-morbidities. Eight patients had underlying cardiac disease, 3 had diabetes, 3 had additional respiratory conditions and 10 had other significant co-morbid conditions including Wegener's disease (2), anemia (2), renal insufficiency (2), infections (3), seizure disorder (1), thromboembolic disorder (1).

Of the patients who died secondary to respiratory causes, all had severe or very severe COPD. Their ages ranged from 57-98 years. All five were taking additional COPD medications, 3 of the 5 reported taking inhaled corticosteroids concomitant with or prior to starting indacaterol. One of the patients had developed pneumonia prior to starting indacaterol. In none of the cases was pneumonia or COPD progression clearly related to indacaterol therapy.

Three patients died secondary to cardiac disease. The patients ranged in age from 70-86 years. All patients had preexisting cardiac disease: congestive heart failure, an unspecified cardiac disorder and cor pulmonale. The duration of indacaterol exposure prior to death ranged from 12-18 days.

Three patients died from complications of malignancy. The patients ranged in age from 78-91 years with indacaterol exposure ranging from 13-41 days. The patients with breast and GI cancer had end stage disease prior to starting indacaterol. One patient was diagnosed with lymphoma approximately 41 days after starting indacaterol.

Of the 5 remaining patients, one died from preexisting Wegener's disease, one from a GI bleed, one from a massive pulmonary embolus and for 2, the cause of death is unknown.

None of the prescribing physicians suspected that indacaterol was related to the events described.

In addition to the patients from the SER PSP who died, Novartis also received one report of a death in another PSP, also in Mexico known as CONTACTO. Again, the death was reported following solicitation by a call center. The patient (PHHY2011MX01484) was a female aged 65 years, with a history of both COPD and asthma, thrombocytopenia and DVTs. Approximately 3 days after starting indacaterol, the patient was hospitalized due an upper GI bleed, anemia and dyspnea. Baseline anticoagulant therapy was discontinued. She died 4 days after hospitalization due to massive pulmonary embolus.

Reports from patients with COPD with asthma co-morbidity/history

There were 5 (1.8%) SRs from patients in whom indacaterol was prescribed for patients with COPD in association with, or with a history of, asthma. Two of them were classified by HCP as serious: fatal status asthmaticus, and upper GI hemorrhage (PHHY2010DE15532), three

were classified as non-serious: 1) numbness in legs, 2) muscle cramps/spasms and 3) tendinitis. In one case the accuracy of the term "asthma" as indication for use is questionable; the case description rather suggests dyspnea than "asthma" as the patient did not have a history of asthma (Table 6-26).

Table 6-26 Spontaneous reports of adverse reactions in patients in whom indacaterol was for COPD in association with asthma or a history of asthma

PHHY 2010...	Age/Sex	Case description	TTE (d)	Report Type
DE37373	58F	Indication: "Dyspnoe". Medical Hx and current condition COPD and asthma. On Day 3 numbness of legs. Co-medication not specified.	3	HCP/ns
DE54292	70M	Indication: "Asthma". Medical Hx of COPD stage IV; no mention of asthma in Hx. On Day 1 dyspnea, palpitation, and tachycardia. On Day 5 restlessness and nausea. Co-medication Symbicort.	1	HCP/ns
DE55413	44F	MedHx included both COPD and asthma. Fatal status asthmaticus, see Table 6-25.	6 wks	HCP/s
DE59220	69M	Indication: COPD stage 2b. Concomitant allergic asthma. On Day 2 muscle cramps and muscle pain on 300 µg indacaterol. MedHx: Coronary artery disease, arterial occlusive disease, diabetes mellitus. Co-medication including Viani, tiotropium, insulin.	2	HCP/ns
DE15532	67M	Indication: COPD with a history of asthma. Day 4 report of upper gastrointestinal hemorrhage and vomiting	4	HCP/s
DE77829	UnkF	Indication: COPD and asthma. Day 135 report of tendinitis, joint inflammation, pain in thumb	135	HCP/ns

Source: ARGUS database; cutoff Nov 30, 2010; HCP = Health Care Provider; s = serious, ns = non-serious; TTE = time to event in days after start of indacaterol therapy. Unk = unknown.

Reports from patients in whom indacaterol was prescribed for asthma

There were 12 (4.4%) SRs from patients in whom indacaterol was prescribed for "pure" asthma, (without any mention of COPD in case descriptions). The main adverse reactions reported were cough (n = 4) exacerbation of the underlying asthma (n=3), and (in alphabetical order) cold/nasopharyngitis/rhinitis, hypertensive crisis, nasopharyngeal pain, and urinary urgency (each n=1). Four of them were classified by HCP as serious: heavy coughing with positive re-challenge (PHHY201001345), asthma exacerbation requiring hospitalization (PHHY2010MT36241), dyspnea and respiratory tract infection (PHHY2010DE80635) and hypertensive crisis (PHHY2010DE80636). (Table 6-27).

Table 6-27 Spontaneous reports of adverse reactions in patients in whom indacaterol was prescribed for asthma.

PHHY 2010...	Age/Sex	Case description	TTE (d)	Report Type
DE01345	28F	On Day 1 dyspnea and heavy coughing of 2-3 mins. D/c of treatment on Day 3. Positive re-challenge.	1	HCP/s
DE08423	54F	On Day 6 cold, nasopharyngitis and rhinitis. Upon re-administration of indacaterol outcome was "positive".	6	HCP/ns
DE29554	UnkM	Indication: "Dyspnoea"; medical history of allergic asthma. On Day 3 increased urinary urgency. Co-medication: Combivir.	3	HCP/ns
DE35188	UnkM	Exacerbation of asthma specified as dyspnea in the 2 nights following inhalation of indacaterol. Treatment with cortisone and fenoterol.	?	Non-HCP/ns
IE13822	UnkM	On an unknown date cough. Had experienced shaking in the past while taking other β_2 agonists; pt was aware that asthma is not labeled indication for indacaterol.	?	HCP/?
MT36241	54M	On Day 5 asthma exacerbation while on co-medication with low dose budesonide, requiring hospitalization.	5	HCP/s
DE54292	72M	Palpitations, tachycardia and dyspnea on Day 1. Restlessness and nausea on Day 5.,	1	HCP/ns
DE80635	49F	Day 1 acute dyspnea and infection of respiratory tract requiring hospitalization. Onbrez continued for 21 days.	1	HCP/s
DE80636	63F	On unknown date start of Onbrez. Report of hypertensive crisis (200/100 mmHg) and dyspnea. Hx of hypertension, thyroiditis, atrial fibrillation and coagulation disorder	unk	HCP/s
GR79881	35M	Chronic bronchial asthma. Intense cough after inhalation of Onbrez since begin of therapy. Event abated after stopping Onbrez.	1	HCP/ns
IE13822	Unk M	Cough	unk	HCP/ns
CH67387	Unk F	Physician with personal Hx of asthma made a tolerability test: oropharyngeal pain, tracheal pain.	1	HCP/ns

Source: ARGUS database; cutoff Nov 30, 2010; HCP = Health Care Provider; s = serious, ns = non-serious; TTE = time to event in days after start of indacaterol therapy. Unk = unknown.

Cardiovascular events

Overall 32 SR were received with 38 cardiovascular adverse reactions; there were no SRs of cerebro-vascular events. Twenty-five of the 38 adverse reactions were classified as serious. The most frequent reactions were palpitation, tachycardia, angina pectoris and arrhythmia (Table 6-28).

Table 6-28 Spontaneous reports of cardiovascular adverse events by report type and seriousness

	Non-serious		Serious		Total
Preferred Term	**HCP**	**Non-HCP**	**HCP**	**non-HCP**	
Acute coronary syndrome			1		1
Acute myocardial infarction			2		2
Angina pectoris			5		5
Arrhythmia			3	1	4
Atrial fibrillation			1		1
Bradycardia		1			1
Cardiac arrest			1		1
Cardiac failure			1		1
Coronary artery embolism			1		1
Extrasystoles			1		1
Heart rate increased	1	1			2
Palpitations	5			1	6
Sinus tachycardia	1				1
Sudden death			1		1
Syncope			3		3
Tachycardia	4		2		6
Troponin T increased			1		1
Total	11	2	23	2	38

Discussion

In the 12-month observation period, 562 adverse reactions were reported in 275 patients, approximately 80% of them by HCP. The most frequently affected SOC across all types of reports related to Respiratory, thoracic and mediastinal disorders (n=154 adverse reactions). There were nine deaths, four of which were related to progression of the respiratory disorder (COPD) and the others related to sepsis, acute myocardial infarction, possible pulmonary embolism, sudden death and in one case the cause of death was unknown.

The type and frequency of the SR with serious cardiovascular events was as expected for a high risk population as COPD, there were no reports of cerebrovascular events.

Within the serious spontaneous HCP reports, adverse reactions occurring in more than one patient were COPD and dyspnea (each n = 6), angina pectoris (n=5), circulatory collapse (n=5), arrhythmia, blood pressure decrease, dizziness and syncope (each n=3). Circumstances and symptomatology of the cases with “circulatory collapse” were rather different, e.g. one patient experienced massive headache associated with high blood pressure and one patient reported increased blood glucose. Another patient with known alcohol abuse and liver

cirrhosis experienced drop in blood pressure, sweating, weakness and dizziness following the first dose. These cases do not suggest a common pathophysiology.

There were 5 (1.8%) SRs from patients with an underlying diagnosis COPD plus asthma co-morbidity, one of whom suffered a fatal status asthmaticus, and one required a hospitalization for an upper GI tract hemorrhage, while the other three cases were non-serious. There were 12 SRs (4.4%) of patients treated with indacaterol for "pure" asthma. Four of them were classified by HCP as serious: heavy coughing with positive re-challenge, asthma exacerbation requiring hospitalization, dyspnea and respiratory tract infection and hypertensive crisis. The remaining SRs were non-serious (one not classified). The data do not allow assessment of whether the safety profile in these subpopulations is different from that in patients without (concomitant) asthma.

Conclusion

Overall the pattern of safety events reported in the post-marketing setting is similar to that observed in Phase 3 studies. The low number of spontaneous reports so far does not allow an assessment of whether there is a different frequency or severity of safety events in the post-marketing population as compared to the clinical trials. The information on the indication for use and/or the case descriptions document an off-label use according to the current labeling, i.e. a use by patients with asthma or patients with COPD with asthma co-morbidity. The small number of SRs in cases of off-label use are not conclusive regarding the safety profile of indacaterol in asthma in general.

6.10 Safety conclusions

Indacaterol doses of up to 600 μg appear to be safe for patients with COPD studied up to 1 year of exposure. There appeared to be no notable differences between the safety profile of indacaterol o.d. and other LABAs given b.i.d. There was no consistent evidence of a dose response for indacaterol with respect to rates of AEs and other safety events typically associated with LABAs. The two proposed doses, 75 and 150 μg, appeared to have comparable safety and tolerability profiles.

There were no unique findings related to cardiovascular or hepatic function in indacaterol treated patients compared to patients treated with other β_2-agonists, as reflected in the adverse event data, in the definitive QT study, in the thousands of ECGs recorded throughout the pivotal studies, in the Holter monitor data recorded in a subset of study patients or the extensive profile of liver function tests analyzed. Extensive analysis of cardio- and cerebrovascular (CCV) events did not reveal a consistent excess of such events compared with placebo or active comparators. The lack of excess CCV events for indacaterol is consistent with death rates in the COPD population, which were lower for all indacaterol doses than for placebo.

In some patients, indacaterol can be associated with a short cough post-inhalation that typically lasted for 5 seconds. This did not impact the efficacy or safety profile afforded by the drug, nor did it lead to premature study discontinuations. Patients who experienced this "cough" responded to indacaterol in a similar manner to those who did not experience this post-inhalation event.

Post-marketing data from countries where indacaterol is approved for the treatment of COPD do not reveal any new safety concerns and have not led to any regulatory or manufacturer actions being taken for safety reasons.

7 Risk evaluation and mitigation plans

The post-marketing safety management strategy for indacaterol has three components 1) the global risk management strategy as defined in the global Safety Risk Management Plan" (SRMP) which is - according to Novartis policy - mandatory for all countries where indacaterol is marketed 2) the US-specific risk management strategy (as defined by the "Risk Evaluation and Mitigation Strategy" (REMS) and 3) additional safety strategies to further evaluate the safety of indacaterol in "real world" use. Characteristics of these complementary plans are as follows:

7.1 Safety Risk Management Plan (SRMP)

The objective the Global SRMP is to optimize safe use of the compound in the post-marketing setting.

- To specify what is and is not known about safety of a drug at the time of submission (Safety Specification)
- To make a plan defining known and potential risks and define how safety information related to these events will be collected post authorization (Pharmacovigilance Plan)
- To define appropriate measures to minimize known and potential risks and monitor their success (Risk Minimization Plan and Evaluation of Effectiveness)

In view of the known risks associated with the use of LABA monotherapy in asthma, the major focus of the SRMP is on minimizing off-label use. The SRMP includes periodic assessments of off-label use and a plan for remediation of root causes if required.

Other identified or potential important risks include for example: QTc prolongation, cardiovascular safety, hyperglycemia, hypokalemia, serious respiratory events in case of off-label use in asthma, and paradoxical bronchospasm (Table 7-1).

Table 7-1 Risk management strategy based on global Safety Risk Management Plan

Risk	PV actions	Risk Minimization Actions
Asthma off-label use (hospitalization, intubation, respiratory deaths in asthma patients)	Routine PV activities including cumulative analysis in PSUR	Routine: Label, including patient information.
	Additional: Post-authorization safety study (PASS) to evaluate for any trends in off-label use in asthma[1]	Additional: Educational measures included as part of all launch activities Remediation in case activities are insufficient[2]:
Other risks: QTc prolongation, cardiovascular events, diabetes mellitus, hyperglycemia, hypokalemia, paradoxical bronchospasm, pharmacokinetic and pharmacodynamic interactions, safety in non-Caucasians, in COPD with significant CV co-morbidity, long-term safety	Routine PV activities incl. cumulative analysis in PSUR	Routine: Label including Patient information
	Additional: Post-authorization safety study (PASS) for signal detection[1]	

1) PASS to be conducted in USA (using a healthcare database) and in UK (GPRD database). Includes survey with off-label prescribers to identify reasons and circumstances of off-label use.
2) Will only be implemented if "off-label" use in asthma has been established and exceeds a predefined limit

7.2 Risk Evaluation and Mitigation Strategy (REMS)

REMS are mandated by the FDA for certain products for which they have determined that measures in addition to product labeling are necessary to ensure that the benefits of the drug outweigh the risks. Novartis has proposed the following REMS, which is under review by the FDA.

The goals of the proposed REMS are to inform:

- Healthcare providers about the increased risk of asthma-related death in patients taking LABAs and the appropriate use of indacaterol in patients with COPD
- Inform patients of other serious risks associated with the use of indacaterol

The components of the proposed REMS are 1) Medication Guide and 2) Communication Plan. The key features are summarized below (Table 7-2):

Table 7-2 REMS elements for Indacaterol

REMS elements	Description
Medication Guide (MG)	MGs are paper handouts. They contain FDA-approved information A MG will be included in each finished package. It will be provided to each patient with each new prescription and refill. The MG will be available on a Novartis website
Communication plan	DHCP letter will be distributed to potential prescribers Will include the key safety information (risks, indication/proper use of indacaterol) Printed or web-based information for health care providers (risk, prescribing information, MG) Communication via letter to leadership of professional societies

Knowledge, Attitude, and Behavior (KAB) surveys will be conducted with patients and HCPs in order to assess their awareness and knowledge of items that are components of the REMS goals. The surveys will also assess receipt of and attention to the Medication Guide. The methodology and protocol for the KAB surveys, and the survey instrument, will be developed after the product labeling and Medication Guide are finalized and will be provided to the FDA at least 60 days before the surveys are administered.

The questions and statements in the survey address the goals of the REMS. They are to be answered either on an unaided basis (without a multiple-choice list or prompts from the interviewer) or by selecting options from multiple-choice lists that include statements of the specific goals. These will be field tested with potential patients and potential prescribers for comprehension. Any items that impact understanding by the targeted users will be modified accordingly. The survey protocol will describe the sample size and confidence intervals associated with that sample size, how the sample will be determined, the expected number of patients to be surveyed, how the participants will be recruited, how and when the surveys will be administered, and explains controls used to minimize bias. A copy of the survey questionnaire will be included with the protocol.

The survey period will begin approximately 13 months after approval of the REMS in order to provide an assessment to FDA at 18 months, and will be repeated at 2.5 years and 6.5 years after launch so that REMS evaluations can be submitted to FDA at 3 years and 7 years after REMS approval.

Progress towards any goal that is not being achieved will be reviewed for potential root causes and remedial actions will be discussed with the FDA.

7.3 Additional studies to evaluate indacaterol safety

Apart from the formal risk evaluation and mitigation plans, Novartis has initiated additional interventional and observation studies to better understand the benefit risk profile of indacaterol. An asthma safety study (QMF149A2210) of 1500 patients followed for 12-21 months is powered to rule out a risk difference in asthma related hospitalization >1% between indacaterol and an ICS in fixed combination vs ICS alone. In addition to voluntary pharmacovigilance, Novartis has designed two observational studies. The first Post Authorization Safety Study (PASS) is being conducted in the UK (GPRD database). A second PASS would be conducted in the US.

The PASS in the UK will include a retrospective analysis comparing the incidence of defined events among patients treated with indacaterol compared to other COPD products. There will also be an assessment of off-label use in asthma and prospective collection of information from prescribers whereby reasons and circumstances for off-label use will be explored by prescriber survey. A PASS for the US would be similarly designed in consultation with the FDA.

Review periods for the PASS and the effectiveness results of the SRMP are 6-month intervals for the first 2 years and at the end of year 3 following the product launch in UK and US, respectively.

Seven single nation observational studies have been planned for initiation soon after the launches of indacaterol in these countries to evaluate the “real world” safety and effectiveness

of indacaterol. These post authorization safety studies will provide safety information from approximately 20,000 patients enhancing our signal detection activities.

Summary

The SRMP and the REMS are complementary risk management tools to assure safe use of indacaterol.

- While the SRMP specifies all important risks associated with indacaterol use and distinguishes between routine and extra pharmacovigilance and routine and extra risk minimization activities, the REMS is focusing on the risk of off-label use in asthma; for the other risks the reader is referred to the Medication Guide.
- Since the SRMP is to be implemented in many countries, the description of the risk minimization activities is kept more general, while the REMS provides details e.g. of the communication plan, tailored to one single country, USA.
- The SRMP defines a threshold for off-label use, beyond which an escalation of the risk minimization activities have to be explored, while the REMS comments on the possible impact of the assessments results (survey data) on pharmacovigilance and risk minimization activities.
- While the SRMP's effectiveness is exclusively based on the percentage of off-label use observed in the two post-authorization safety studies, effectiveness of the REMS is based on the patient's and prescriber's understanding of the Medication Guide including the knowledge about safety risks associated with the compound.
- It is planned to implement in the US post-approval both the SRMP and the REMS.

8 Benefit and risk conclusions

8.1 Summary of benefits, summary of risks

8.1.1 Summary of benefits

COPD is a major global public health problem, and is associated with high levels of mortality and chronic morbidity and a considerable burden of both direct (healthcare) costs and indirect costs. COPD has a profound impact on patients through both distressing symptoms, particularly dyspnea, and limitations to their daily activities that lead to deconditioning. The prevalence of COPD is forecast to increase over the next decade. This, together with the increasing prevalence of COPD, and the high impact of the disease on patients and healthcare systems indicates the need for new, more effective treatments with a convenient dosing regimen (e.g., once-daily) that achieve their therapeutic effect rapidly and have robust effects on lung function and symptoms (particularly dyspnea).

The efficacy, safety, and clinical pharmacology of indacaterol have been investigated in an extensive clinical development program that comprises more than 70 studies, including single dose studies of up to 3000 μg and multiple-dose studies with doses up to 800 μg and durations (with doses up to 600 μg) up to 1 year.

Doses of 150 and 300 μg once daily have been approved in the European Union and in several other countries for the treatment of COPD.

Indacaterol has consistently demonstrated 24-hour bronchodilator efficacy on once-daily dosing, with a rapid onset of action (within 5 minutes) following the first dose, and no loss in efficacy on repeated dosing up to one year. Indacaterol doses of 75 μg, 150 μg and 300 μg consistently demonstrated both statistically significant and clinically relevant differences to placebo on 24-hour trough FEV_1, a parameter that indicates the persistence of bronchodilator effect throughout a treatment's once-daily dosing interval.

An incremental increase in efficacy with increasing dose was observed. The 75 μg dose was shown to provide effective bronchodilation in two pivotal studies. Across the range of studies, the 150 μg dose tended to show greater differences to placebo than the 75 μg dose. For the primary efficacy variable of trough FEV_1, differences to placebo were often well in excess of the protocol defined 0.12 L MCID for the 150 μg dose. Also, optimal bronchodilation was observed from the first dose for 150 μg indacaterol. With the 150 μg dose, efficacy was maintained on once daily dosing for treatment periods of up to a year, with good safety and tolerability. Integrated analyses across key studies supported the bronchodilator efficacy of the 75 and 150 μg doses, and predicted that the 150 μg dose may provide additional benefit, particularly in patients with more severe disease.

Trough FEV_1 data were supported by detailed FEV_1 profiling, with assessments at multiple time points across the 24-hour dosing interval. Indacaterol consistently demonstrated superior bronchodilation to placebo at all time points, including at 5 minutes post-dose (which has the potential to provide prompt reassurance to patients of the efficacy of treatment) and at approximately 12 hours post-dose. Efficacy on once-daily dosing was at least as good as, and often greater than, that of the twice-daily LABAs. The 150 μg dose achieved its optimal bronchodilatory effect from the first dose onwards.

The sustained 24-hour bronchodilator efficacy of indacaterol accompanied improvements in a range of symptomatic endpoints, particularly dyspnea (as measured using the BDI/TDI) but also health-related quality of life (measured using the SGRQ) and rescue medication use. These endpoints showed better responses to the 150 μg dose than the 75 μg dose. These data as a whole suggest that the 75 μg dose is an effective dose, and the 150 μg dose may offer additional benefit to some patients, particularly those with severe COPD or for whom dyspnea is a particular issue.

Also, 150 μg indacaterol (dosed once daily) appears to be at least as effective as currently available therapies on this wide range of spirometric and symptomatic endpoints. This provides further evidence of the potential benefit of indacaterol in treating patients with COPD.

8.1.2 Summary of risks and unanswered risk questions

Overall, the safety of indacaterol was similar to placebo on many assessments. Doses of 300 and 600 μg indacaterol (higher than the proposed doses) demonstrated a good overall safety profile for COPD patients studied up to 1 year of exposure. The two proposed doses, 75 and 150 μg have very similar safety and tolerability profiles. A detailed evaluation of cough experienced post-inhalation demonstrated that this event is not associated with any safety concerns such as COPD exacerbation or bronchospasm.

The safety profile of 75 and 150 μg indacaterol dosed once daily is comparable to those of currently available twice-daily LABAs, with a therapeutic index that is at least as good (Boyd 1997; Jones & Bosh 1997). Dose-related effects on the predicted pharmacologically mediated systemic safety parameters (heart rate, QTc interval, serum glucose and potassium) were only evident at doses much higher than the proposed clinical doses. The current evidence does not suggest that indacaterol is associated with an increased risk of major cardiovascular events or death.

Post-marketing data (with an estimated exposure of over 56,000 patient-years) from other countries do not reveal any additional safety concerns and have not led to any regulatory or manufacturer actions being taken for safety reasons.

8.2 Recommended use and overall benefit/risk relation

8.2.1 Recommended use

Indacaterol is a long-acting β_2-agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD. The recommended dosage of indacaterol is the once-daily inhalation of the content of one 75 μg or 150 μg capsule using the Concept1 inhalation device.

The 75 μg dose of indacaterol provides effective bronchodilation, essentially representing the minimum effective dose. The dose of 150 μg may provide additional clinical benefit, achieving optimal bronchodilatory effect from the first dose and having stronger beneficial effects on symptomatic endpoints, particularly the key COPD symptom of dyspnea. An integrated analysis of patient level data predicted that the effectiveness of the 150 μg dose or higher of indacaterol was less influenced by disease severity and may provide additional benefit in patients with severe disease. No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment or renal impairment. Given that safety has been demonstrated in doses of up to 600 μg o.d. for 1 year and that efficacy is not directly related to systemic exposure, dose adjustment on the basis of these factors is not indicated.

In accordance with current Global Initiative for Asthma (GINA) guidelines (GINA 2009) and recent FDA recommendations (FDA 2010) that recommend the use of a LABA only in combination with an inhaled glucocorticosteroid, indacaterol as a monotherapy has not been developed for asthma. Therefore in the current submission, no claim is made for an asthma indication. A Risk Evaluation and Management Strategy (REMS) is being proposed by the Sponsor to communicate any risks of indacaterol and that the product is not recommended for use in asthma, together with a Safety Risk Management Plan (SRMP).

8.2.2 Overall benefit/risk

Throughout the development program, in studies of up to 1 year in duration, indacaterol has clearly demonstrated full, sustained 24-hour bronchodilator efficacy. The once-daily dosing that this permits is a potential advantage over currently available twice-daily LABAs – as are the improvements observed in a range of efficacy assessments, including dyspnea.

The proposed 75 μg o.d. dose provides effective bronchodilation and may be regarded as the minimum effective dose. The proposed 150 μg dose may offer more benefit, as it is associated with a more rapid achievement of optimal bronchodilatory effect than the 75 μg dose, and

showed greater improvements in symptom-related endpoints (particularly with respect to the key COPD symptom of dyspnea) and health-related quality of life. In addition, a population-based meta-analysis predicted that the efficacy of the 150 μg dose is not affected by disease severity, so may provide additional benefit in patients with severe disease.

Given that indacaterol is intended for chronic dosing, the observation that there is no loss in efficacy on repeated once-daily dosing for up to a year is important. Of note, the 600 μg dose of indacaterol (which is not being proposed for approval) demonstrated a good overall safety profile following up to 1 year of exposure. This good therapeutic margin offers confidence in prescribing doses of 75 or 150 μg; this is supported by 1-year data for the 150 μg dose. In addition, no signal has been observed to suggest any issues in terms of drug-drug or drug-condition interactions, which is particularly important in a patient population with a high prevalence of comorbid diseases who are consequently likely to be using multiple medications. There is no identified subset of patients at increased adverse risk for this compound. Post-marketing data from other countries have revealed no new safety concerns.

In conclusion, indacaterol at doses of 75 and 150 μg once daily has the potential to contribute significantly to the treatment armamentarium for patients with COPD, given the clear evidence of sustained 24-hour efficacy with once-daily dosing. Further, the safety and tolerability profile of indacaterol has been thoroughly characterized, and suggests that the compound has a wide and reassuring therapeutic margin.

9 References

American Lung Association (2010) Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality. February 2010. Available from: http://www.lungusa.org/finding-cures/our-research/trend-reports/copd-trend-report.pdf

Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomized trials of antiplatelet therapy, I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J; 308:81-106.

Battram C, Charlton SJ, Cuenoud B et al (2006). In vitro and in vivo pharmacological characterization of 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one (indacaterol), a novel inhaled beta(2) adrenoceptor agonist with a 24-h duration of action. J Pharmacol Exp Ther 317: 762-70.

Bourbeau J and Bartlett SJ (2008) Patient adherence in COPD. Thorax; 63: 831-838.

Boyd G, Morice AH, Pounsford JC et al (1997) An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J; 10: 815-821.

Calverley PMA, Anderson JA, Celli B et al (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med; 356: 775-89.

Cazzola M and Matera MG (2008) Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol; 155: 291-299.

Centers for Disease Control and Prevention (2010) Healthy People 2010. Progress Review: Respiratory Diseases. May 22, 2008. Available from: http://www.cdc.gov/nchs/healthy_people/hp2010/focus_areas/fa24_rd2.htm

Donohue J, Menjoge S, Kesten S (2003) Tolerance to bronchodilating effects of salmeterol in COPD. Resp Med; 97: 1014-20.

Donohue JF (2005) Minimal clinically important differences in COPD lung function. COPD; 2: 111-24.

Feldman G, Siler T, Prasad N et al (2010). Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med 10: 11.

Food & Drug Administration (2010) FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs) Available from:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm.

GINA: Global Initiative for Asthma (2008) Global strategy for asthma management and prevention. Available from http://www.ginasthma.org.

GINA: Global Initiative for Asthma (2009) Global strategy for asthma management and prevention. Available from http://www.ginasthma.org.

GOLD: Global Initiative for Chronic Obstructive Lung Disease (2005) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated 2005. Available from http://www.goldcopd.org.

GOLD: Global Initiative for Chronic Obstructive Lung Disease (2008) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated 2008. Available from http://www.goldcopd.org.

GOLD: Global Initiative for Chronic Obstructive Lung Disease (2009) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated 2009. Available from http://www.goldcopd.org.

ICH (2005) Note for Guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. European Medicines Agency (EMEA). ICH E14 Guidance 2005.

Jones PW (2002). Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 19: 398-404.

Jones PW, Bosh TK (1997) Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med; 155: 1283-1289.

Naline E, Trifilieff A, Fairhurst RA et al (2007) Effect of indacaterol, a novel long-acting beta2-agonist, on isolated human bronchi. Eur Respir J; 29: 575-81.

Owen K, Beck SL, Damment SJP (2010). The preclinical toxicology of salmeterol hydroxynapthoate. Hum Exp Toxicol; 29: 393-407.

Reddel HK, Taylor DR, Bateman ED, et al (2009) An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med; 180: 59-99.

Rodrigo G, Nannini L, Rodriguez-Roisin R et al (2008) Safety of long-acting β-agonists in stable COPD: a systematic review. Chest; 133: 1079-1087.

Sturton RG, Trifilieff A, Nicholson AG, Barnes PJ (2008). Pharmacological characterization of indacaterol, a novel once daily inhaled beta2 adrenoceptor agonist, on small airways in human and rat precision-cut lung slices. J Pharmacol Exp Ther; 324: 270-5.