

**PULMONARY-ALLERGY DRUGS ADVISORY  
COMMITTEE MEETING**

**March 8, 2011**

**FDA White Oak Campus, the Great Room, White Oak  
Conference Center  
Silver Spring, Maryland**

**NDA 022-383: indacaterol maleate (Arcapta™ Neohaler™) 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.**

**Disclaimer Statement**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application (NDA) 022-383, indacaterol maleate (Arcapta™ Neohaler™) by Novartis Pharmaceuticals Corporation, 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 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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  - 2. Jones, PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19: 398-404.
  - 3. FDA Draft Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007.

## **DIVISION DIRECTOR MEMORANDUM**

Date: February 8, 2011

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary, Allergy, and Rheumatology Products,  
CDER, FDA

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for New Drug Application (NDA) 22-383, Arcapta Neohaler (indacaterol inhalation powder), at a dose of 75 or 150 mcg every day (once-daily), for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema

### **Introduction**

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on March 8, 2011. As members of the PADAC you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss the New Drug Application (NDA) from Novartis Pharmaceuticals, seeking approval for indacaterol inhalation powder, at a dose of 75 or 150 mcg every day (once-daily), 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. The proposed trade name for the product is Arcapta Neohaler.

Novartis originally submitted this application to the Agency on December 15, 2008, for the use of indacaterol inhalation powder at a dose of 150 mcg or 300 mcg once-daily for the same indication. The proposed dose of 150 mcg had a qualifier that administration of a 300 mcg dose provided additional clinical benefit in some patients. A Complete Response action on the original submission was taken on October 16, 2009, because of clinical deficiencies. The clinical review concluded that the doses proposed for marketing were high and not supported by the submitted efficacy and safety data. There were higher frequencies of cardiovascular and cerebrovascular adverse events compared to placebo and formoterol in patients with COPD, and possible asthma-related deaths compared to salmeterol in patients with asthma. The submitted data did not show meaningful efficacy differences between the proposed doses and a lower dose of 75 mg. The submitted data also did not provide substantial evidence to support use of two different doses in patients with COPD with no demonstrated clinically meaningful advantage of the 300 mg dose over the 150 mg dose. Novartis was asked to explore efficacy and establish safety of lower doses and various dosing frequencies, to provide replicate data showing clinically

meaningful advantage of a higher dose compared to a lower dose, and to provide balancing safety data to show no unacceptable safety disadvantage with the higher dose.

Novartis submitted a complete response on October 1, 2010, with results from additional clinical studies to address these deficiencies. The proposed dose of indacaterol is lowered to 75 mcg or 150 mcg once daily based on data from additional clinical studies. Two doses are proposed with the reasoning that the higher dose will provide additional benefit in patients with more severe bronchial obstruction, and the claimed advantage of 150 mg dose over 75 mg based on pharmacodynamic modeling analysis and results of St George's Respiratory Questionnaire (SGRQ) results.

There are several efficacy issues for discussion at the PADAC meeting. Major discussion points are: a) whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data, b) whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data, c) whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses. In the United States, no bronchodilators are approved in more than one dose, and none have claims for improvement in SGRQ. Thus, the indacaterol application represents some new regulatory and scientific paradigms.

The major safety issue with indacaterol is linked to selection of appropriate dose, because beta-adrenergic agonist bronchodilators, particularly at high doses, have the safety concern of severe asthma exacerbations and asthma related deaths in patients who use these drugs to treat asthma. Although such a risk or worsening disease has not been shown in patients with COPD, it is nevertheless important to select the appropriate and safe dose for a bronchodilator.

This memorandum provides an overview of the original submission and the subsequent complete response submission. The content of this document and the materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Novartis. These represent preliminary findings and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive at this PADAC meeting.

The materials to be discussed at this PADAC meeting and the opinions we are seeking are primarily related to the clinical and statistical issues of the indacaterol study results. In the regulatory decision making process to determine approvability of a product, the Agency takes into consideration various other factors in addition to clinical and statistical issues, including manufacturing and controls of a product and preclinical considerations. These will not be the focus of this PADAC meeting.

Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Clinical Briefing Document, Statistical Briefing Document, Clinical Pharmacology Summary, US Professional Drug Product Labels of some approved short-acting and long-acting beta-adrenergic agonists,



some relevant publications, and FDA Draft Guidance on Chronic Obstructive Pulmonary Disease (COPD): Developing Drugs for Treatment.

## Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-adrenergic agonists, anticholinergic agents, combination products containing beta-adrenergic agonists and anticholinergic agents, combination of long-acting beta-adrenergic agonists and corticosteroids, and methylxanthines.

Indacaterol is a new molecular entity that belongs to the class called beta-adrenergic agonists. Due to its longer duration of action, indacaterol belongs to the subclass called long-acting beta-adrenergic agonists (LABA). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, and R,R formoterol. These are marketed either as single ingredient products or as combination products with inhaled corticosteroids. All are dosed twice daily, and all are marketed at one dose level. Indacaterol is proposed to be dosed once daily, and proposed to be marketed at two dose levels, 75 mcg and 150 mcg once daily.

Inhaled beta-adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma related deaths in patients who use these drugs to treat the symptoms asthma. Severe asthma exacerbations and asthma related deaths have been described with short-acting inhaled beta-adrenergic agonists for over the last 50 years.<sup>1, 2, 3, 4</sup> More recently, inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths.<sup>5</sup> This has been discussed at various FDA Advisory Committee meetings,<sup>6</sup> has led to publications expressing concerns on safety,<sup>7, 8, 9</sup> and a safe use strategy outlined by the FDA.<sup>10</sup> The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma related deaths are not

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<sup>1</sup> Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. *J Allergy* 1948; 19:129-140.

<sup>2</sup> Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproterenol in spontaneous and induced asthma. *N Eng J Med* 1949; 240:45-51.

<sup>3</sup> Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. *Thorax* 1991; 46:105-111.

<sup>4</sup> Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. *N Eng J Med* 1992; 326:501-506.

<sup>5</sup> US Professional drug label for Serevent (salmeterol xinafoate), Foradil (formoterol fumarate), Advair (fluticasone propionate and salmeterol), Symbicort (budesonide and formoterol fumarate), and Dulera (mometasone furoate and formoterol fumarate). Rockville, MD: U.S. National Library of Medicine (<http://dailymed.nlm.nih.gov/dailymed/about.cfm>).

<sup>6</sup> Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.

<sup>7</sup> Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. *New Eng J Med* 2005; 353:2637-2639.

<sup>8</sup> Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. *New Eng J Med* 2009; 360:1952-1955.

<sup>9</sup> Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. *New Eng J Med* 2009; 360:1671-1672.

<sup>10</sup> Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *New Eng J Med* 2010; 362:1169-1171.

known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists is a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.<sup>11</sup> Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for development of all LABAs, including indacaterol, which is proposed to be marketed for COPD. The dose and dosing frequency for all marketed beta-adrenergic agonists in the United States for asthma and COPD are the same, and most of these drug products have both asthma and COPD indications.

The indication claims of short-acting beta-adrenergic agonists, such as albuterol (Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, ProAir HFA Inhalation Aerosol, Proventil Inhalation solution) are for general bronchodilation (“treatment or prevention of bronchospasm with reversible obstructive airway disease”). The albuterol product labels do not mention a specific disease, such as asthma or COPD, in the indication section. Clinical studies supporting approval of these products were conducted in patients with asthma. Nevertheless, albuterol is used in patients with asthma and COPD. The indication claims of long-acting beta-adrenergic agonists, such as salmeterol (Serevent Diskus, Serevent Inhalation Aerosol) and formoterol (Foradil Aerolizer) are also for general bronchodilation, but the product labels mention asthma and COPD as specific diseases in the indication section. Clinical trials supporting the dose and dosing frequency for these two long-acting beta agonists were done in patients with asthma, and the same bronchodilatory dose was carried forward to studies in COPD. The regulatory precedence of performing dose ranging and dose regimen studies for bronchodilators in asthma patients has been established in order to demonstrate large separation between doses because the range of response is greatest in a bronchoresponsive population, such as patients with asthma. A COPD population with some degree of fixed obstruction has a smaller response range to a bronchodilator.

### **Relevant Regulatory History for Indacaterol**

Novartis studied three different inhalation indacaterol products. These were the single-dose dry powder inhaler (IND 48,649), an HFA propelled inhalation aerosol (IND 66,337), and a multi-dose dry powder inhaler using the Certihaler device (IND 69,754). IND 48,649 was submitted on February 13, 2004, and IND 69,754 was submitted on April 27, 2004, both to study persistent asthma. An end-of-phase 2 meeting was held on August 1, 2005, to discuss the development of indacaterol multi-dose dry powder product for asthma and COPD. Most of the questions and ensuing discussions were on the asthma program. Novartis later suspended the development of the HFA propelled inhalation aerosol product for technical reasons. The multi-dose dry powder inhaler using the Certihaler device was also suspended due to excessive delivery of dose because of a possible Certihaler device related problem. With the suspension of these delivery devices, which would provide for multiple dose products, the development of the single-dose dry powder product was continued. A second end-of-phase 2 meeting was held on October 10, 2006, to discuss the development of

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<sup>11</sup> Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. *Chest* 2003; 124:70-74.

indacaterol single-dose dry powder product for COPD. There was some discussion on asthma, but most of the questions and ensuing discussions were regarding COPD. Novartis proposed a COPD study (Study 2335, discussed further below) with an adaptive design to build dose ranging assessment and determination into a pivotal efficacy and safety study. The Division cautioned that initiating such a phase 3 study was risky when using a single-dose dry powder product with limited prior information and Agency review of relevant data. On December 20, 2006, Novartis submitted the COPD study with adaptive design for Special Protocol Assessment (SPA). In a letter dated February 1, 2007, the Division expressed various concerns with the study, such as the role of the data monitoring committee (DMC), use of open-label tiotropium as an active comparator, selection of the non-inferiority margin to compare to tiotropium, definition of secondary endpoint of days of COPD exacerbation, and emphasis on trough FEV1 as dose selection criterion. While several discussions occurred between the Division and Novartis on the study, there were no formal SPA agreements. There were no agreements on dose selection criteria.

Novartis submitted an NDA on December 15, 2008, for indacaterol 150 mcg and 300 mcg once daily for patients with COPD. A Complete Response action was taken on October 16, 2009, because of concerns with dose selection as described in the Introduction section.

Novartis met with the Agency in November 2009 to clarify the Complete Response action letter comments for the original NDA submission. Novartis agreed to evaluate doses of indacaterol lower than 150 mcg and regimens with dosing frequencies of less than and more than once-daily in bronchoreactive patients, such as patients with asthma and patients with COPD responsive to bronchodilatory effect of short-acting beta-agonists. Results of these new studies led to the selection of lower doses than the doses originally proposed.

### **Product Information**

The product Arcapta Neohaler contains Arcapta (indacaterol maleate inhalation powder) Capsules packaged in aluminum blister cards, and a Neohaler inhaler. Arcapta Capsules are of two strengths, 75 mcg and 150 mcg. The capsules will be packaged as five blister cards with 6 capsules each in a box of 30. Each capsule contains a dry powder blend of either 75 mcg or 150 mcg of indacaterol maleate with approximately 25 mg of lactose monohydrate. The Neohaler inhaler is a plastic device to be used for inhaling Arcapta Capsules. The Neohaler inhaler consists of a white protective cap, a base with mouthpiece, capsule chamber, and two push buttons. To deliver a dose, the patient will place an Arcapta Capsule in the capsule chamber of the Neohaler inhaler, press the push buttons to pierce the capsule on each end, and breathe in rapidly and steadily through the mouthpiece.

### **Nonclinical Pharmacology and Toxicology**

Novartis submitted results from a full preclinical program to the Agency. The program included studies in which animals were dosed with the drug via inhalation to evaluate local and systemic toxicities. Inhalation toxicity studies were conducted in rats for up to 26 weeks and dogs for up to 39 weeks. The target organs of toxicity in the rats were the nasal cavity, where the observed finding was degeneration of the olfactory epithelium, and the larynx, where the observed finding was squamous metaplasia. The target organs of toxicity in the dogs were the cardiovascular system where the observed findings were increased

heart rates, decreased blood pressure, and myocardial necrosis and fibrosis, and liver where the observed finding was periportal liver hepatocyte vacuolation due to glycogen deposition. The cardiovascular and liver findings are known class effects of beta-agonist drugs. For all the observed findings of concern, there were adequate margin of safety for the expected human exposure. Studies addressing genotoxicity, reproductive toxicity, and carcinogenicity did not show any findings of concern. All genotoxicity studies were negative. The reproductive toxicity study in rats did not reveal adverse effects on male and female fertility and reproductive performance. Embryo-fetal development studies in rats and rabbits did not show any teratogenic effects. The pregnancy category was determined to be Class C, which is the same category for many other beta-2 adrenergic agonists. Carcinogenicity was assessed in a 26-week study in C6F1/TgrasH2 hemizygous mice, and in a 24-month study in Sprague-Dawley rats. These studies showed increased incidences of uterine and endometrial stromal polyps and ovarian leiomyomas. These tumors have been observed with other beta-adrenergic agonists and are known to have no human consequence.

### **Clinical Pharmacology and Biopharmaceutics**

Novartis submitted results from a comprehensive clinical pharmacology program to the Agency. The program addressed the key pharmacokinetic issues, including in vitro studies to assess protein binding and metabolism, pharmacokinetics after single and multiple doses, in vitro and in vivo metabolism, effect of hepatic impairment, QTc effect, and drug-drug interaction. Studies in renally impaired patients were not conducted since renal excretion of indacaterol is a minor route of elimination. Clinical pharmacology studies included inhalation, oral, and IV administration to fully characterize the pharmacokinetics of indacaterol maleate. Inhaled indacaterol maleate has approximately 43% bioavailability resulting from both pulmonary and intestinal absorption. Elimination is primarily through the fecal route where over 90% of the dose was recovered in a mass balance study. Approximately 54% of the drug was eliminated unchanged, and approximately 23% was excreted as a hydroxylated indacaterol metabolite. Urinary elimination is a minor route with less than 2% indacaterol excreted unchanged in the urine. Following inhalation of a single 150 mcg dose of indacaterol, C<sub>max</sub> values were generally reached 0.25 hours post-dose. Following multiple inhalations of 150 mcg doses, the elimination half-life of indacaterol was 49.1 hours. In vitro studies showed that indacaterol is a substrate for CYP3A4, and UGT1A1 can metabolize indacaterol to the phenolic O-glucuronide. Indacaterol is a low affinity substrate for the efflux pump P-gp. Population kinetic studies did not show any significant effect of age, race, gender, hepatic impairment, and presence or absence of COPD.

### **Clinical and Statistical**

Some characteristics of the relevant studies are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy and safety findings. The studies are shown in Table 1 in two groupings – those submitted with the original NDA, and those submitted later with the complete response.

Table 1. Relevant clinical studies with indacaterol maleate

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups†	N (ITT)	Primary efficacy variable	Countries
<b>Submitted with original NDA</b>							
<b><i>Dose- ranging studies in COPD patients</i></b>							
<b>B2201</b> [2004]	Parallel arm	4 weeks	40-75	IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	68 67 28	30 minutes post- dose FEV <sub>1</sub> on Day 1, 14, 28	Europe
<b>B2205</b> [2004]	Parallel arm	1 week	38-75	IN MDDPI 50 mcg QD IN MDDPI 100 mcg QD IN MDDPI 200 mcg QD IN MDDPI 400 mcg QD IN SDDPI 400 mcg QD Tio 18 mcg BID Placebo	103 105 105 110 105 107	FEV <sub>1</sub> AUC <sub>22-24 hr</sub> post-dose on Day 1	Europe, North America, South America
<b>B2212</b> [2007]	Crossover	1 day treatment	43-73	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	51	FEV <sub>1</sub> trough at 24 hr	Belgium
<b>1202</b> [2007]	Crossover	1 day treatment	40-75	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Placebo	50	FEV <sub>1</sub> AUC <sub>22-24 hr</sub> post-dose	Japan
<b><i>Pivotal COPD studies</i></b>							
<b>B2335</b> [2008]	Adaptive design, dose ranging, efficacy and safety	Initial 2 weeks, Continue for 26 weeks	40-88	<i>Initial 2 weeks:</i> IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Tio 18 mcg QD Placebo <i>Continue 6 months:</i> IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	107 105 110 102 112 112 104  416 416 415 418	FEV <sub>1</sub> trough at 24 hr at wk 2 FEV <sub>1</sub> AUC <sub>1-4 hr</sub> at wk 2  FEV <sub>1</sub> trough at 24 hr at wk 12	USA, Canada, W Europe, India, S Korea, Argentina, Turkey, Taiwan
<b>B2334</b> [2008]	Long-term Efficacy and safety	52 weeks	40-90	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	437 425 434 432	FEV <sub>1</sub> trough at 24 hr at wk 12	W and E Europe, Russia, C/S America, Mid East, S Korea
<b>B2346</b> [2008]	Efficacy and safety	12 weeks	40-89	IN SDDPI 150 mcg QD Placebo	211 205	FEV <sub>1</sub> trough at 24 hr at wk 12	USA, NZ, Australia, Belgium
<b><i>Short-time profiling studies in COPD patients</i></b>							
<b>B2340</b> [2008]	Crossover 24 hr FEV	2 weeks	≥ 40	IN SDDPI 300 mcg QD Sal 50 mcg BID Placebo	68	FEV <sub>1</sub> trough at 24 hr at day 15	USA, Belgium, Spain
<b>B2331</b> [2008]	Crossover 24 hr FEV	2 weeks	≥ 40	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	169	FEV <sub>1</sub> trough at 24 hr at day 15	Europe, Australia, New Zealand, South Africa
<b>B2305</b> [2008]	Crossover Assess effect of	2 weeks	≥ 40	IN SDDPI 300 mcg QDAM IN SDDPI 300 mcg	96	FEV <sub>1</sub> trough at 24 hr at day 15	France, Germany, Spain

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups <sup>†</sup>	N (ITT)	Primary efficacy variable	Countries
	dosing time			QDPM Sal 50 mcg BID Placebo			
<b>B2307</b> [2008]	Crossover Onset of effect	Single dose	≥ 40	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Advair 50/500 mcg Albuterol 200 mcg Placebo	89	FEV <sub>1</sub> 5 min post- dose on day 1	USA, Belgium, Germany, Hungary
<b>Asthma studies</b>							
<b>A2210</b> [2004]	Safety	4 weeks	12-65	IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	59 59 26	None	Germany, Belgium, Canada, Czech R, Slovakia
<b>B2338</b> [2008]	Safety with ICS	26 weeks	12-85	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Sal 50 mcg BID	268 268 269	None	USA, Canada, Europe, South America
<b>Submitted with complete response</b>							
<b>Dose-ranging and dose-regimen studies in asthma and COPD patients</b>							
<b>B2357</b> [2010]	Dose ranging in asthma	2 weeks	18-82	IN SDDPI 18.75 mcg QD IN SDDPI 37.5 mcg QD IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	84 81 84 85 84 84	FEV <sub>1</sub> trough at 24 hr at day 15	US
<b>B2356</b> [2010]	Dose ranging in COPD	2 weeks	40-87	IN SDDPI 18.75 mcg QD IN SDDPI 37.5 mcg QD IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	89 90 94 92 91 91	FEV <sub>1</sub> trough at 24 hr at day 15	US
<b>B2223</b> [2010]	Dose regimen in asthma	2 weeks	18-80	IN SDDPI 37.5 mcg BID IN SDDPI 75 mcg QD IN SDDPI 150 mcg QOD Placebo	48 48 48 47	FEV <sub>1</sub> trough at 24 hr at wk 2 and FEV <sub>1</sub> AUC <sub>0-24hr</sub>	US, UK, France, Jordan, Germany, Netherlands
<b>Pivotal COPD studies</b>							
<b>B2336</b> [2009]	Efficacy and safety	26 weeks	41-89	IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	330 333 335	FEV <sub>1</sub> trough at 24 hr at wk 12	W and E Europe, Russia, India, Peru, Taiwan, Canada, Columbia, Iceland
<b>B2354</b> [2010]	Efficacy and safety	12 weeks	40-90	IN SDDPI 75 mcg QD Placebo	163 160	FEV <sub>1</sub> trough at 24 hr at wk 12	US
<b>B2355</b> [2010]	Efficacy and safety	12 weeks	40-86	IN SDDPI 75 mcg QD Placebo	159 159	FEV <sub>1</sub> trough at 24 hr at wk 12	US
* Year study subject enrollment ended <sup>†</sup> IN SDDPI = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); IN MDDPI = Indacaterol multiple dose dry powder inhaler; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder):							

As mentioned in the Background section above, Novartis studied three different inhalation indacaterol products – single dose dry powder inhaler, which is the subject of this application, multi dose dry powder inhaler, and an HFA propelled inhalation aerosol. Table 1 above list relevant studies that used both the single dose dry powder inhaler and the multi dose dry powder inhaler. The clinical data generated with the multiple dose dry powder inhaler and the HFA propelled inhalation aerosol have limited value for the single dose dry powder inhaler because the in vitro delivery characteristics for the three products are substantially different.

The pivotal dose-ranging studies for the indacaterol program are: study B2335 (initial 2 weeks), study B2223, study B2357, and study B2356. The doses of indacaterol proposed in the original NDA were 150 mcg and 300 mcg once-daily. The selection of these doses was based on the initial 2 weeks dose-ranging part of the adaptive-design study B2335 in patients with COPD. Dose regimen (once-daily dosing versus other dosing frequencies) was not studied in the original application. The doses of indacaterol proposed in the complete response are 75 mcg and 150 mcg once-daily. The selection of the doses and dose regimen are based on the dose-ranging part of study B2335 (initial 2 weeks) in patients with COPD, dose-ranging study B2357 in patients with asthma, dose-regimen study B2223 in patients with asthma, and dose-ranging study B2356 in patients with COPD. Patients with asthma were studied based on Agency recommendation that patients with asthma are more responsive to bronchodilatory effect of beta-agonists and more likely to show separation of doses.

The pivotal phase 3 efficacy and safety studies submitted with the original NDA and with the complete response to support various doses of indacaterol are listed below:

- Indacaterol 300 mcg once-daily: study B2335 (latter part), study B2334, and study B2346. *Novartis does not seek approval of this dose in the current submission.*
- Indacaterol 150 mcg once-daily: study B2335 (latter part), study B2336, and study B2346.
- Indacaterol 75 mcg once-daily: study B2354 and study B2355.

In subsequent sections, design and conduct of the studies are described following the order the studies appear in Table 1. Thus studies submitted with the original NDA are described first, followed by studies submitted later with the complete response. Efficacy findings and safety findings are described later in this section after description of the design and conduct of the studies.

### Design and conduct of the studies

#### Studies submitted with the original NDA

Short-term dose ranging studies (B2201, B2205, B2212, B1202):

These were the early studies conducted by Novartis to gather some dosing information for indacaterol. These studies used doses ranging from 50 mcg to 800 mcg and used different formulations and delivery devices. These studies did not provide useful dose and dosing

frequency information because the studies were limited in duration, used different devices and formulations, and some had small sample sizes. Since dose selection information was limited, Novartis designed the first pivotal COPD study (Study B2335) to have an adaptive design to build dose-ranging information into a pivotal efficacy and safety study. In these short-term dose-ranging studies, and in other studies, dosing frequency other than once daily was not explored.

Pivotal COPD studies (B2335, B2334, B2346):

Study B2335, the adaptive design study, was randomized, double blind (except for the tiotropium arm, which was open label), parallel group in design conducted in patients with moderate-to-severe COPD. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, post-bronchodilator FEV1/FVC <70%, post-bronchodilator FEV1 ≤80% predicted (post-bronchodilator refers to 30 minutes of inhalation of 400 mcg albuterol), and be a current or previous smoker with a smoking history of ≥20 pack years. The study had a 2-week run-in period, followed by an initial 2-week double-blind treatment period. There were seven treatment arms in this period as shown in Table 1. An independent DMC was chartered to review the 2-week interim data and make a decision on dose selection. *[The guideline given to DMC for dose selection was as follows: 1. The selected dose needed to be 0.12 L greater than placebo for trough FEV1, and should also have higher trough FEV1 than tiotropium and formoterol. 2. The dose needed to have higher FEV1 AUC 1-4 hours than tiotropium and formoterol. 3. The lowest dose that fulfilled the above two criteria and the next highest dose were to be selected.]* Based on these criteria, indacaterol 150mcg and 300mcg were selected to move forward for the remainder of the study. After the dose selection, patients continued on a double blind treatment period for a total of 26 weeks. There were four treatment arms in this period as shown in Table 1. The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. All patients had serial spirometry covering the first 1 hour after dosing (time points 5 minutes, 30 minutes, and 1 hour) and last 1 hour (time points 23 hours 10 minutes and 23 hours 40 minutes) after dosing at clinic visit days 2, 15, 85, and 183. In a subset (about 30 to 40 patients in each treatment arm) 12-hour serial spirometry (time points 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, and 11 hours 45 minutes) were done on day 1, and after 2, 12, and 26 weeks of treatment. Other efficacy variables included days of poor control, COPD exacerbation, other spirometry variables peak expiratory flow measures, SGRQ at baseline and at weeks 4, 8, 12, and 26, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score at weeks 4, 8, 12, and 26, and BODE (body mass, airflow obstruction, dyspnea, and exercise capacity) index at weeks 12 and 26, MMRC dyspnea score, and 6 minute walk at baseline and at weeks 12 and 26. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs in all patients, and Holter monitoring in a subgroup of patients. Blood samples were also collected for sparse sampling PK analysis at baseline and weeks 2, 12, and 26.



Studies B2334 and B2346 were randomized, double blind, parallel-group in design conducted in patients with moderate-to-severe COPD. The patient population, design and conduct of the study, efficacy variables and safety variables were similar to study B2335 with some minor differences, such as Holter monitoring was not conducted in either study and 6-minute walk test was not conducted in study B2346. The study duration and treatment arms were different as shown in Table 1.

Short-term crossover studies (B2340, B2305, B2307):

Studies B2340, B2331, B2305, and B2307 were randomized, double blind, crossover in design conducted in patients with predominately moderate-to-severe COPD. Studies B2340 and B2331 were designed to collect data to construct a 24 hour spirometry profile. Study B2305 was designed to compare the efficacy of morning and evening indacaterol dose. Study B2307 was designed to assess the onset of action of indacaterol. These studies were relatively small and not germane to the major issues for discussion at this meeting. Therefore, these studies will not be described further in this document.

Asthma safety studies (A2210, B2338):

Study A2210 was randomized, double blind, placebo controlled, parallel group in design conducted in patients with stable asthma who were receiving treatment with inhaled beta-agonist with or without inhaled corticosteroids (ICS). The study had a 14-day run-in period, followed by 28-day double-blind treatment period. There were three treatment arms as shown in Table 1. The objective of the study was to assess safety and tolerability of 28 days treatment with indacaterol and to measure pharmacokinetics. For the assessment of safety, particular attention was paid to serum potassium, blood glucose, heart rate, blood pressure, QTc, FEV1, and adverse events such as tremor, headache, and nervousness.

Study B2338 was randomized, double blind, active controlled, parallel group in design conducted in patients with moderate-to-severe persistent asthma. The intent of the study was to evaluate safety of indacaterol compared to salmeterol in patients with asthma using ICS as background treatment. The study had a 14-day run-in period, followed by 26-week double blind treatment period. There were three treatment arms as shown in Table 1. All enrolled patients were on ICS (study required daily ICS of at least 100 mcg beclomethasone or equivalent for at least 1 month prior to enrollment), had mean baseline post-bronchodilator (SABA) FEV1 of 94.6% (study required FEV1 of  $\geq 50\%$ ), had mean FEV1 reversibility of 22.3% (study required an increase of  $\geq 12\%$  and  $\geq 200$  mL in FEV1 over pre-bronchodilator value within 30 minutes after inhaling a total of 180 mcg of albuterol), and had no emergency room treatment or hospitalization for asthma in the 6 months prior to study entry (study requirement). Safety assessments included collection of adverse events, serious adverse events, vital signs, clinical blood chemistry and hematology, urinalysis, ECG, and Holter monitoring in a subset of patients. Key safety variables identified for the study were serum potassium and glucose, heart rate, blood pressure, and QTc measure on ECG. The main efficacy variable was 24-hour post-dose trough FEV1 over 26 weeks with end of week 12 as the time point of interest. Other efficacy measures were PEFr, daytime

symptoms, nighttime awakenings, rescue medication use, and quality of life measurements. Blood samples were also collected for sparse sampling PK analysis at weeks 1 and 12.

#### Studies submitted later with complete response

Dose ranging (B2357, B2356) and dose regimen (B2223) studies:

Study B2357 was randomized, double blind, parallel group in design conducted in patients with persistent asthma 18 years of age and older. The study had a 14-day run-in period, followed by 2-week double blind treatment period. There were six treatment arms in this period as shown in Table 1. All enrolled patients were on inhaled corticosteroids (study requirement), had mean screening FEV1 ranging from 2.23 to 2.40 L in different treatment groups (study required FEV1  $\geq 50\%$  and  $\leq 90\%$  of predicted normal), and mean screening FEV1 reversibility ranging from 20.5% to 24.5% in different treatment groups (study required an increase of  $\geq 12\%$  and  $\geq 200$  mL in FEV1 over pre-bronchodilator value within 30 minutes after inhaling a total of 360 mcg of albuterol via an inhalation aerosol). The primary efficacy variable was 24-hour post-dose trough FEV1 on day 15. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. All patients had serial spirometry at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 11 hour 10 minutes, and 11 hour 45 minutes relative to study drug dosing on days 1 and 15. In a subset of patients (ranging from 44 to 49 patients in different treatment arms) additional time points were added at 14 hours, 20 hours, and 22 hours relative to dosing on day 15. The secondary efficacy variables were 24-hour post-dose trough FEV1 on day 1, peak FEV1 on day 1, FEV1 AUC on days 1 and 14, morning and evening PEFR over 14 days, and use of rescue medication. Safety assessments included adverse event recording including asthma exacerbation, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Study B2356 was similar to study B2357 in design and conduct with the notable difference that patients in this study were required to have moderate-to-severe COPD, with post-bronchodilator FEV1/FVC  $< 70\%$  and post-bronchodilator FEV1  $\leq 80\%$  and  $\geq 30\%$  predicted, and a smoking history of at least 10 pack years. Study treatment arms are shown in Table 1. Enrolled patients had a mean duration of COPD for 6.9 years, mean screening FEV1 ranging from 1.22 to 1.37 L in different treatment groups, and mean screening FEV1 reversibility to albuterol ranging from 14.2% to 16.7% in different treatment groups. Efficacy and safety assessments were the same as study B2357 with one difference of additional blood sampling on the last day of dosing for indacaterol pharmacokinetic analysis.

Study B2223 was randomized, double blind, parallel group in design conducted in patients with persistent asthma 18 years of age and older. The design and conduct of this study was similar to study B2357, but with 3 treatments arms with different dose regimens of the same total daily dose of indacaterol 75 mcg as shown in Table 1. All enrolled patients were on inhaled corticosteroids (study requirement), had mean screening FEV1 ranging from 2.51 to 2.84 L in different treatment groups (which was higher than study B2357), and

mean screening FEV1 reversibility ranging from 20.4% to 22.5% in different treatment groups (same as study B2357). Efficacy and safety assessments were the same as study B2357 with one difference of additional blood sampling on the first and last day of dosing for indacaterol pharmacokinetic analysis.

Pivotal COPD studies (B2354, B2355, B2336):

Study B2336 was randomized, double blind, parallel group in design. This study was ongoing at the time of original NDA submission and subsequently completed and submitted later with the complete response. Patients enrolled in the study were required to be 40 years of age and older, have a clinical diagnosis of COPD, moderate-to-severe by GOLD guideline criteria, smoking history of at least 20 pack years, post-bronchodilator FEV1 <80% and  $\geq 30\%$  of predicted, and post-bronchodilator FEV1/FVC <70% (post-bronchodilator refers to 10-15 minutes post-inhalation of 400 mcg albuterol). The study had a 2-week run-in period, followed by a 26-week double blind treatment with indacaterol 150 mcg QD, salmeterol 50 mcg BID, or placebo (Table 1). The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic after 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. The primary comparison was between indacaterol and placebo. On the first day and after weeks 12 and 26 of treatment, serial spirometry was done at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours (time points 2 hours and 4 hours were done in subgroup of approximately 300 patients) relative to study drug dosing. Other efficacy variables included other additional spirometry measures at various time points, rescue medication use, nighttime awakenings, daytime symptoms, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score after 4, 8, 12 and 26 weeks of treatment, one month recall version SGRQ score at baseline, and after 4, 12, and 26 weeks of treatment, 6 minute walk test at baseline, and after 12 and 26 weeks of treatment, BODE index (composite of % predicted FEV1, distance walked in 6 min, MMRC dyspnea scale, and body mass index) at baseline and after 12 and 26 weeks of treatment, and COPD exacerbation frequency. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. In a subset of patients blood samples were collected at the end of week 12 for indacaterol pharmacokinetic analysis.

Studies B2354 and B2355 were randomized, double blind, parallel group in design. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, moderate-to-severe by GOLD guideline criteria, smoking history of at least 10 pack years, post-bronchodilator FEV1 <80% and  $\geq 30\%$  of predicted, and post-bronchodilator FEV1/FVC <70% (post-bronchodilator refers to 10-15 minutes post-inhalation of 400 mcg albuterol). Both studies had a 2-week run-in period, followed by 12-week double blind treatment with indacaterol 75 mcg QD or placebo (Table 1). The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. On the first day and last day of treatment, serial spirometry was done at time points -50 minutes, -25 minutes, -15

minutes, 5 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 23 hours 10 minutes, and 23 hours 45 minutes relative to study drug dosing. Other efficacy variables included additional spirometry measure at various time points, rescue medication use, nighttime awakenings, daytime symptoms, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score after 4 and 12 weeks of treatment, one month recall version SGRQ score at baseline, and after 4 and 12 weeks of treatment, and COPD exacerbation frequency. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. In a subset of patients blood samples were collected at the end of week 12 for indacaterol pharmacokinetic analysis.

### Efficacy Findings

The clinical program showed that indacaterol at 75 mcg, 150 mcg, and 300 mcg once-daily doses provided statistically significant bronchodilatory effects in patients with COPD with replicate findings for these doses. The issues for discussion are whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data, and whether the higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data. Some pertinent efficacy results, specifically FEV1 based results and SGRQ results are presented in subsequent sections, with some comments.

### *Original NDA*

In the original NDA submission, exploration of dose ranging was limited and primarily based on the first 2 weeks of data from the adaptive design study (Study B2335); and different dosing frequencies were not explored. In the adaptive design dose-ranging study, all active treatment arms provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at the interim analysis time point of 2 weeks, with no significant differences among any of the indacaterol doses (Table 2, Figure 1). Additional spirometry variables and other secondary measures went in the similar direction with trough FEV1 (data not shown in this document). Based on the DMC dose selection criteria using trough FEV1 and FEV1 AUC 1-4 hours (described in previous section), the 75 mcg dose was considered to be suboptimal and the 150 mcg and 300 mcg doses were carried forward for further assessment in the study. At the 2-week time point, the numerical differences between the 75 mcg and higher indacaterol doses were small. It appears that all studied doses were on the plateau of the dose-response curve. The data show that the DMC dose selection criteria, which were geared towards selection of indacaterol dose that would provide numerically higher efficacy versus the active comparators, may have led to the selection of higher than necessary doses.

Table 2. Study B2335, LS Mean for trough FEV1 (in L) at 2 weeks (interim analysis) and 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at Week 2	Treatment comparison	Treatment Difference at 2 weeks LS Mean (95% CI)	Treatment Difference at 12 weeks LS Mean (95% CI)
IN 75 mcg	1.46	IN 75 - Placebo	0.15 (0.09, 0.20)	
IN 150 mcg	1.49	IN 150 - Placebo	0.18 (0.12, 0.24)	0.18 (0.15, 0.21)
IN 300 mcg	1.52	IN 300 - Placebo	0.21 (0.15, 0.27)	0.18 (0.15, 0.21)
IN 600 mcg	1.51	IN 600 - Placebo	0.20 (0.14, 0.25)	
For 12 mcg	1.42	For - Placebo	0.11 (0.06, 0.17)	
Tio 18 mcg	1.45	Tio - Placebo	0.14 (0.08, 0.19)	0.14 (0.11, 0.17)
Placebo	1.31			

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder)

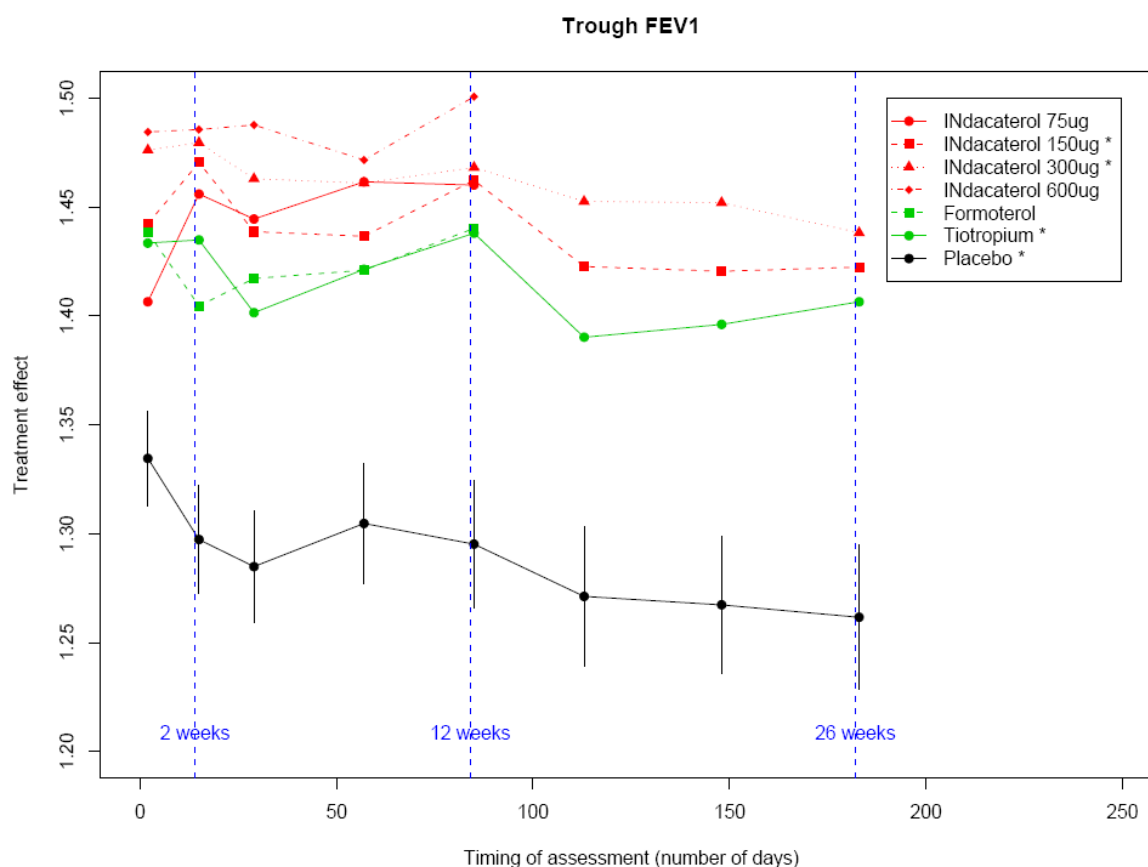


Figure 1. Study B2335, Summary of trough FEV1 in various treatment arms at different assessment times. Note: 2 weeks is interim analysis, 12 weeks is primary efficacy time point, and 26 weeks is end of the study

Table 3. Studies B2334 and B2346, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
<b>Study B2334</b>			
IN 300 mcg	1.48	IN 300 – Placebo	0.17 (0.13, 0.20)
IN 600 mcg	1.48	IN 600 – Placebo	0.17 (0.13, 0.20)
For 12 mcg	1.38	For – Placebo	0.07 (0.04, 0.10)
Placebo	1.31		
<b>Study B2346</b>			
IN 150 mcg	1.49	IN 150 – Placebo	0.13 (0.09, 0.18)
Placebo	1.35		
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder);			

In the other two pivotal studies submitted with the original NDA submission (Studies B2334 and B2436), indacaterol 150 mcg, 300 mcg, and 600 mcg provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo (Table 3). Additional spirometry variables and other secondary measures went in a similar direction to trough FEV1 (data not shown in this review). Similar to the adaptive design study, separation between the indacaterol doses was minimal to none, but the separation between indacaterol and Foradil Aerolizer 12 mcg was numerically large.

Similar concerns were raised by the results of B2338, which was a 26 week study in patients with asthma comparing indacaterol 300 mcg, indacaterol 600mcg, and salmeterol 50 mcg BID, that showed a larger trough FEV1 for both doses of indacaterol compared to salmeterol. The LS mean trough FEV1 at week 12 for indacaterol 300 mcg was superior to salmeterol with LS mean difference of 0.07 L, 95% CI 0.02- 0.12 L, and p-value of 0.006; and LS mean trough FEV1 at week 12 for indacaterol 600 mcg was superior to salmeterol with LS mean difference of 0.08 L, 95% CI 0.02- 0.13 L, and p-value of 0.004.

There were three efficacy questions that were not answered with the data submitted in the original NDA: dose selection, dosing frequency, and efficacy advantages of 300 mcg dose over 150 mcg dose.

The first question was whether the doses of indacaterol proposed to be marketed were optimal, or whether a lower dose may be equally or similarly effective. Since Novartis did not test doses lower than 75 mcg once daily in the original development program, this question could not be answered without further dose exploration. Based on the observation that all doses were at the plateau of the dose-response curve (Table 2, Figure 1, Table 3), it is possible that 75 mcg once-daily or even a lower dose might be effective. Given the general safety concerns with LABAs, specifically the dose-related finding of severe asthma exacerbations and asthma-related deaths, exploration of lower doses was deemed to be necessary. The DMC dose selection criteria that were geared towards selection of an indacaterol dose that would provide numerically higher efficacy versus the active comparators likely resulted in selection of an unnecessarily high dose. The 150 mcg and 300 mcg doses selected appear to provide numerically higher bronchodilator responses

compared to formoterol, another LABA (Table 2, Figure 1, Table 3), but this may not be a safe strategy given the known safety issues with LABAs. It is worth noting that although a higher dose of formoterol (Foradil Aerolizer 24 mcg) provided a numerically superior bronchodilator response compared to the approved dose of formoterol (Foradil Aerolizer 12 mcg) in patients with asthma,<sup>12</sup> the higher dose was not approved for marketing in the United States because of safety concerns noted in the formoterol NDA studies.<sup>13</sup> As with other beta-adrenergic agonists, the dose of formoterol for asthma and COPD are the same.

The second question was whether indacaterol is truly a once-daily drug, or whether it is more appropriate to dose this product twice daily or more frequently. It is possible that similar efficacy might have been achieved with twice daily or a more frequent dosing interval, as compared to a once daily dosing interval, with less of a total daily dose, hence with better safety. Since Novartis did not compare once-daily dosing to a more frequent dosing interval in the original NDA, this question could not be answered without further dose frequency exploration. At the other end of the dosing frequency spectrum, with the half-life of indacaterol being about 49 hours, it seemed a fair question to ask whether indacaterol could even be dosed less frequently than once daily to prevent drug accumulation and alleviate drug accumulation-related safety concerns.

The third question was the proposed labeling statement that the 300 mcg dose provides additional clinical benefit in some patients over the 150 mcg dose. The only study that compared 300 mcg and 150 mcg dose head-to-head was the adaptive design study B2335. In that study at the interim analysis time point of 2 weeks, there was a numerical separation favoring the 300 mcg dose, but at the primary efficacy analysis time point of 12 weeks, there was no difference between the two doses (Table 2, Figure 1). Therefore, it was determined that the proposed labeling statement was not supported. It was determined that to support such a labeling statement, Novartis would need to provide efficacy data showing a clinically meaningful advantage of the 300 mcg dose over 150 mcg, and provide balancing safety data showing no unacceptable safety disadvantages that would negate the efficacy advantage.

### *Complete Response*

These deficiencies were communicated in the Agency's Complete Response action letter of the original NDA submission that was issued on October 16, 2009, and subsequently discussed with Novartis at a meeting held in November 2009. Novartis subsequently conducted further studies (Studies B2357, B2356, and B2223) to evaluate doses of indacaterol lower than 150 mcg and regimens with dosing frequencies of less than and more than once-daily in bronchoreactive patients, such as patients with asthma and patients with COPD responsive to the bronchodilatory effect of short-acting beta-agonists (Table 1). Although indacaterol is proposed to be marketed as a bronchodilator for COPD patients, the Agency recommended that exploration of dose and dose regimen be conducted in patients

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<sup>12</sup> US Professional drug label for Foradil Aerolizer (formoterol fumarate inhalation powder).

<sup>13</sup> Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. *Chest* 2003; 124:7-74.

with asthma who are more responsive to bronchodilatory effect of beta-agonist and more likely to show separation of doses, and in patients with COPD who are tested and identified to be bronchodilator responsive. Novartis also conducted two further pivotal efficacy studies (Studies B2354 and B2355) in COPD patients with indacaterol 75 mcg once-daily dose (Table 1). Based on the results of these studies the proposed dose of indacaterol has been lowered to 75 mcg or 150 mcg once-daily. Two doses are proposed with the reasoning that the higher dose will provide additional benefit in patients with more severe disease. New data submitted with the complete response are presented below with some comments.

In dose-ranging studies in asthma patients (Study B2357) and COPD patients (Study B2356) all indacaterol doses tested (18.75 mcg, 37.5 mcg, 75 mcg, and 150 mcg once-daily) provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at day 15 (Table 4). The effect size of the 18.75 mcg once-daily dose was lower compared to other doses. The effect size did not show clear separation among the other three indacaterol doses at day 15 (Table 4). Other measures of spirometry variables and other secondary measures went in a similar direction with trough FEV1 (data not shown in this document). The FEV1 time profile curves showed some numerical dose ordering after the first dose with indacaterol 75 mcg and 150 mcg once-daily doses separating from the lower doses, but after the last dose at week 2, indacaterol doses 37.5 mcg and above did not show clear separation (Figures 2 and 3). The FEV1 time profile curve for the indacaterol 150 mcg and 75 mcg once-daily doses were essentially superimposable after the first dose in patients with asthma (Figure 2). These FEV1-based data do lend support for the 75 mcg dose, but do not show clear efficacy advantage of the 150 mcg dose over the 75 mcg dose.

Results of study B2223, exploring three different dosing regimens of the same nominal dose are shown in Table 4 and Figure 4. Results of the study do not show clear separation of the different dosing regimen. One limitation of this study was that the screening baseline FEV1 was higher in this study compared to the asthma dose-ranging study (2.51 to 2.84 L in this study compared to 2.23 to 2.40 L in asthma dose ranging study B2357), which may make the study less sensitive to show difference among doses. Nevertheless, the three dosing regimens at day 1 showed some numerical separation (Figure 4) suggesting that even with higher baseline FEV1, the study was adequate to test different dosing regimens.

Table 4. Studies B2357, B2223, and B 2356, LS Mean for trough FEV1 (in L) at day 15 (primary efficacy time point)

Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
<b>Study B2357 (asthma dose-ranging)</b>			
IN 18.75 mcg	2.50	IN 18.75 - Placebo	0.09 (0.00, 0.17)
IN 37.5 mcg	2.52	IN 37.5 - Placebo	0.11 (0.02, 0.19)
IN 75 mcg	2.59	IN 75 - Placebo	0.17 (0.08, 0.26)
IN 150 mcg	2.54	IN 150 - Placebo	0.12 (0.04, 0.21)
Sal 50 mcg	2.54	Sal - Placebo	0.13 (0.04, 0.21)
Placebo	2.42		



Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
<b>Study B2356 (COPD dose-ranging)</b>			
IN 18.75 mcg	1.35	IN 18.75 - Placebo	0.07 (0.02, 0.12)
IN 37.5 mcg	1.38	IN 37.5 - Placebo	0.10 (0.05, 0.16)
IN 75 mcg	1.38	IN 75 - Placebo	0.10 (0.04, 0.15)
IN 150 mcg	1.40	IN 150 - Placebo	0.12 (0.07, 0.17)
Sal 50 mcg	1.39	Sal - Placebo	0.10 (0.05, 0.16)
Placebo	1.28		
<b>Study B2223 (asthma dose-regimen)</b>			
IN 37.5 BID		IN 37.5 BID - Placebo	0.16 (0.08, 0.23)
IN 75 QD		IN 75 QD - Placebo	0.20 (0.12, 0.27)
IN 150 QOD		IN 150 QOD - Placebo	0.20 (0.12, 0.27)
Placebo			
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)			

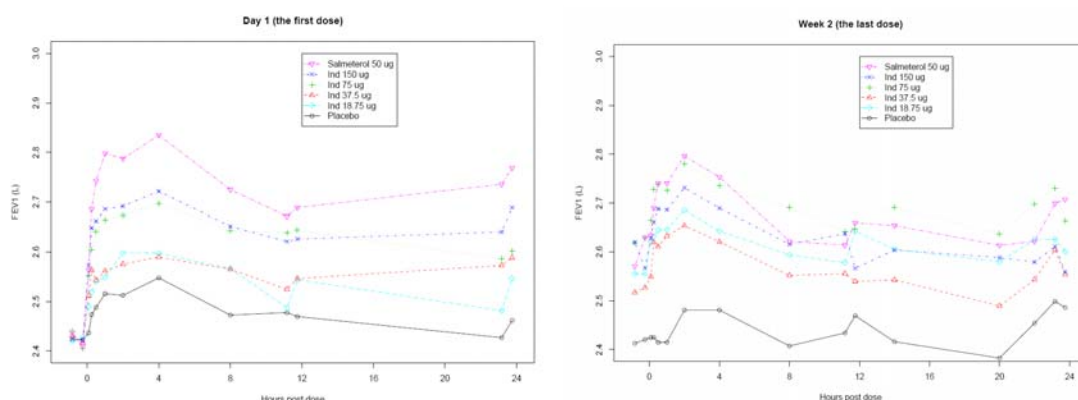


Figure 2. LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2357, asthma dose ranging)

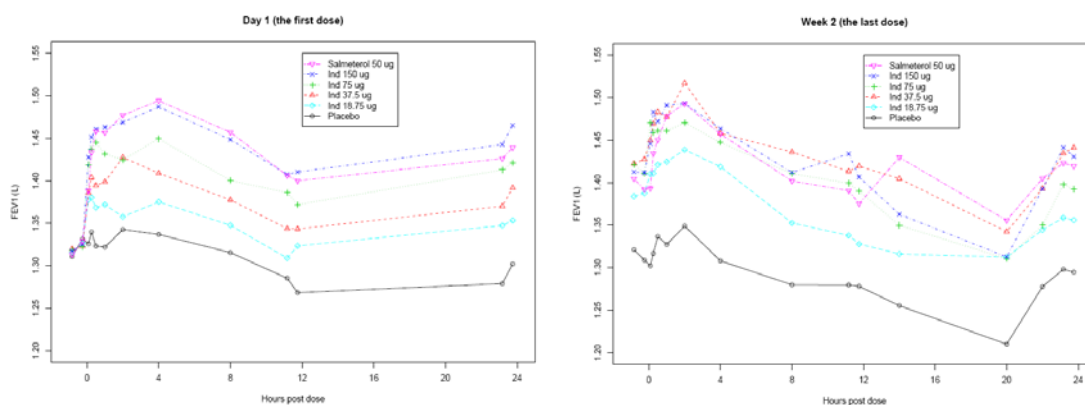


Figure 3. LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2356, COPD dose ranging)

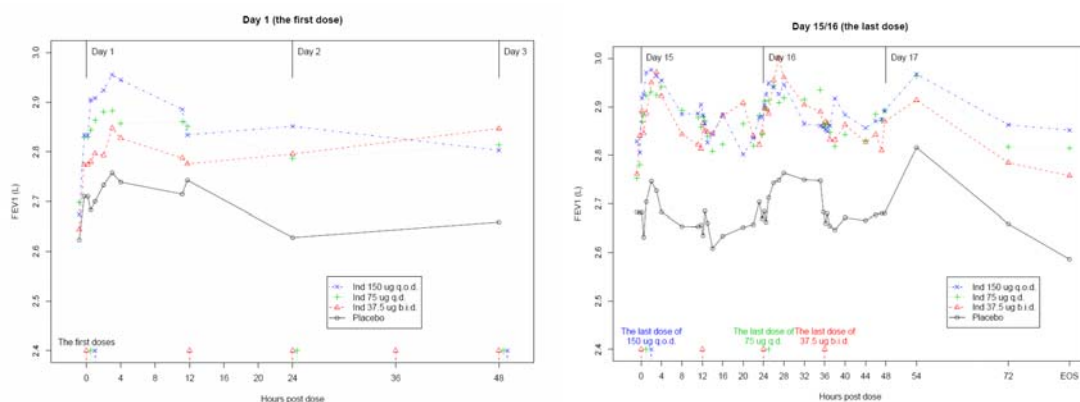


Figure 4. LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2223, asthma dose regimen)

Results of the pivotal efficacy study (Study B2336) that was started when the original NDA was submitted but completed later, and the two pivotal efficacy studies (Studies B2354 and B2355) in COPD patients with indacaterol 75 mcg once-daily dose are shown in Table 5. The results show statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at week 12 in the three studies (Table 5). Additional spirometry variables and other secondary measures went in a similar direction with trough FEV1 (data not shown in this document).

Table 5. Studies B2336, B2354, and B2355, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
<b>Study B2336</b>			
IN 150 mcg	1.45	IN 150 – Placebo	0.17 (0.13, 0.20)
Sal 50 mcg	1.39	IN 150 – Sal 50	0.06 (0.02, 0.10)
Placebo	1.28	Sal - Placebo	0.11 (0.07, 0.14)
<b>Study B2354</b>			
IN 75 mcg	1.38	IN 75 – Placebo	0.12 (0.08, 0.15)
Placebo	1.26		
<b>Study B2355</b>			
IN 75 mcg	1.49	IN 150 – Placebo	0.14 (0.10, 0.18)
Placebo	1.35		
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)			

Novartis is proposing two doses of indacaterol (75mcg and 150mcg) with the reasoning that the higher dose will provide additional benefit in patients with more severe bronchial obstruction, partly relying on comparing the two doses across studies using pharmacodynamic modeling analysis and SGRQ data to support the additional efficacy of the 150 mcg dose. One issue for discussion at the PADAC meeting is whether the second

higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data. In the Complete Response action letter to the original NDA submission, Novartis was asked to provide replicate data showing a clinically meaningful advantage of a higher dose compared to a lower dose and balancing safety data to show no unacceptable safety disadvantage with the higher dose.

From an efficacy standpoint, the FEV1 data and other related efficacy data presented above do not directly provide support for the approval of two doses because there are no 12-week studies that include the 75 mcg dose and the 150 mcg dose in the same study, and therefore, there is no direct comparison of the two doses. In the FDA's COPD draft guidance, it is noted that "if more than one dose is ultimately intended to be marketed, the clinical program design should produce data that allow for a comparative assessment of efficacy and safety between the doses in addition to the usual comparison of the doses of the new drug to placebo." On cross study comparison, which has limitations, the bronchodilatory effect sizes do not show a clear efficacy advantage of the 150 mcg dose over the 75 mcg dose. Furthermore, there is no regulatory precedence for approving more than one dose of a beta-adrenergic bronchodilator. Historically, bronchodilator dosing has been assessed in bronchodilator responsive patients, such as patients with asthma, and later the same dose has been carried forward to patients with COPD. For this reason, Novartis was asked to test dosing in patients with asthma to select the appropriate dose, which they did in studies submitted with the complete response. It is possible that some patients with COPD, who have less bronchial reversibility, may not respond to a typical dose of a bronchodilator, but this does not necessarily justify using higher doses of a bronchodilator in these patients with the intent of achieving a level of bronchodilation, especially given the dose-related safety issues with beta agonists. In addition, Novartis is relying on a meta-analysis and pharmacodynamic modeling to support the claim that the higher dose may provide additional benefit in patients with more severe bronchial obstruction. This is problematic as discussed below.

Pharmacodynamic modeling analysis conducted by Novartis included meta-analysis of data from various COPD and asthma studies. There are potential flaws with such analyses that limit the utility of the findings. The modeling pooled all available FEV1 data from all time points from various studies. It is not appropriate to pool FEV1 data from various time points because it is known that the FEV1 response to beta-adrenergic agonists changes over time. It is also not appropriate to pool different studies for efficacy analysis because of varying demographic and baseline disease characteristics. The peak-to-trough analysis has problems because the trough FEV1 measure is influenced by the normal physiological increase in FEV1 that occurs in the early waking hours in addition to the drug effect. Nevertheless, even the pharmacodynamic modeling analysis did not provide persuasive support of the dose and the dosing frequency and is not discussed further in this review. The clinical data from the dose-ranging studies discussed above remains the more relevant data source to assess the proposed doses.

SGRQ was assessed in all pivotal COPD studies as either one of the key secondary efficacy variables (B2336) or as one of the many efficacy variables (B2335, B2334, B2346, B2354, and B2355). Results of analysis based on the difference in mean total SGRQ scores

between active treatment and placebo are shown in Table 6, and based on the percentage of patients with a minimally important difference (MID) of -4 units or more from baseline in SGRQ total score (defined as responder) are shown in Figure 5. Other than tiotropium, all active treatments, including indacaterol 75 mcg, 150 mcg, 300 mcg, and 600 mcg showed statistically significant separation from placebo. The difference in mean between indacaterol 150 dose and placebo in studies B2336 and B2346 crossed the MID of -4, and the difference in mean between indacaterol 75 mcg dose and placebo did not cross the MID of -4 in studies B2354 and B2355 (Table 6). In part, Novartis is relying on this data to support the 150 mcg dose in addition to 75 mcg dose, and to make an additional labeling claim for the indacaterol 150 mcg dose with respect to SGRQ. It is worth noting that the numerical difference for SGRQ scores between indacaterol 150 mcg dose and 75 mcg dose is small, and the difference in the mean score between indacaterol 300 mcg dose and placebo did not cross the MID of -4 in B2335 and B2334. Based on the analysis of COPD three-month efficacy population pooled data, comparing to placebo, the improvement of SGRQ total scores after 12 weeks treatment was -3.8 with a 95% CI of (-5.3, -2.3) for indacaterol 75 mcg, -4.6 with a 95% CI of (-5.5, -3.6) for indacaterol 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) for indacaterol 300 mcg. Confidence intervals for the three doses overlap considerably. The percentage of patients who had an improvement of SGRQ total score crossing the MID of -4 from baseline was 49% for indacaterol 75 mcg, 52% for indacaterol 150 mcg, 52% for indacaterol 300 mcg, and 40% in placebo (Figure 5). There was no statistically significant difference among different doses. Considering the evidence collectively, a labeling claim based on the improvement in SGRQ scores for the dose of 150 mcg seems to be questionable. The MID of -4 for SGRQ has support in the literature.<sup>14, 15</sup> Whether the -4 difference seen for indacaterol 150 mcg dose and not for 75 mcg and 300 mcg doses supports a unique labeling claim for the 150 mcg dose is an open issue that we would like to be discussed at the PADAC meeting.

Table 6. ANCOVA results of SGRQ total scores in various COPD studies

Treatment	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Change from Baseline (LS mean)	Treatment comparison	Treatment Difference LS Mean (95% CI)
<b>Study B2335</b>					
IN 150 mcg	45.4	38.9	-5.6	IN 150 - Placebo	-2.8 (-4.5, -1.1)
IN 300 mcg	44.8	39.6	-5.2	IN 300 - Placebo	-2.5 (-4.2, -0.8)
Tio 18 mcg	44.6	41.0	-3.5	Tio - Placebo	-1.1 (-2.8, 0.6)
Placebo	45.7	42.7	-3.0		
<b>Study B2334</b>					
IN 300 mcg	44.4	38.6	-5.8	IN 300 - Placebo	-3.8 (-5.6, -2.1)
IN 600 mcg	44.4	38.3	-6.1	IN 600 - Placebo	-4.1 (-5.9, -2.3)
For 12 mcg	44.4	39.2	-5.2	For - Placebo	-3.2 (-5.0, -1.5)
Placebo	43.6	41.6	-2.1		
<b>Study B2346</b>					
IN 150 mcg	50.2	43.7	-6.5	IN 150 - Placebo	-4.8 (-7.2, -2.4)
Placebo	48.7	47.6	-1.1		
<b>Study B 2336</b>					

<sup>14</sup> Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19:398-404.

<sup>15</sup> Jones PW. St. George's Respiratory Questionnaire: MCID. J of COPD 2005; 2:75-79.

Treatment	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Change from Baseline (LS mean)	Treatment comparison	Treatment Difference LS Mean (95% CI)
IN 150 mcg	43.6	35.9	-7.7	IN 150 - Placebo	-6.3 (-8.2, -4.3)
Sal 50 mcg	43.2	37.8	-5.4	Sal - Placebo	-4.2 (-6.1, -2.2)
Placebo	43.6	42.4	-1.2		
<b>Study B2354</b>					
IN 75 mcg	48.4	42.7	-5.8	IN 75 - Placebo	-3.8 (-6.2, -1.4)
Placebo	49.5	47.6	-2.0		
<b>Study B2355</b>					
IN 75 mcg	51.2	46.2	-4.9	IN 75 - Placebo	-3.6 (-6.4, -0.9)
Placebo	50.1	49.2	-0.9		
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder)					

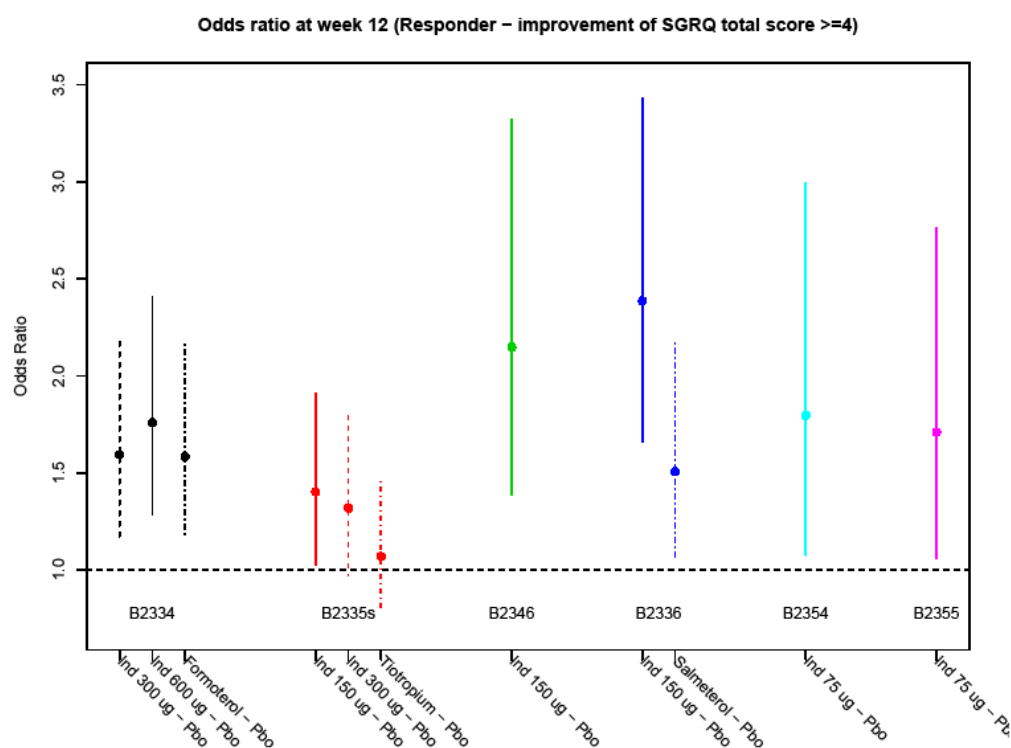


Figure 5. Summary of SGRQ responder analysis in controlled COPD studies.

### Safety findings

The safety assessment of indacaterol is based primarily on studies shown in Table 1. The safety database is reasonably large with approximately 15,000 patients exposed to indacaterol across various development programs. Novartis defined the COPD safety population as patients in all COPD studies with treatment duration of at least 3 months. At

the time of the data lock for the submission of the complete response, there were a total of 9441 patients in this COPD safety population of whom 4764 received indacaterol in the following dose groups: 449 for the 75 mcg dose, 2611 for the 150 mcg group, 1157 for the 300 mcg dose, and 547 for the 600 mcg dose, with duration of exposure varying for different groups.

Deaths and Serious Adverse Events (SAEs)<sup>16</sup> occurred in the COPD program as would be expected in the relatively older and sicker patient population studied. There were 7 deaths out of 4764 patients in the COPD safety population who received indacaterol, and 23 deaths out of 4677 patients in the control group. Exposure adjusted death rates did not show any concerning imbalances raising safety concerns for indacaterol. In the COPD safety population there were 325 SAEs (fatal and non-fatal) in indacaterol treated patients. Review of the SAEs does not show any concerning imbalances or unexpected trends against indacaterol.

In the COPD studies, the adverse event profile was typical for COPD patients with respiratory disorders and cardiac disorders being most common. Adverse events leading to discontinuations and commonly reported adverse events did not raise any specific or unique safety concerns for indacaterol in COPD patients. Adverse events relating to beta-adrenergic effects, such as those in the cardiovascular system, cerebrovascular system, and muscle spasm were seen in indacaterol-treated patients, some occurring more frequently than in placebo-treated patients. These were more prominent in the original NDA review where a higher dose was proposed.

Indacaterol asthma safety studies do raise safety concerns for indacaterol as a bronchodilator because of findings of serious asthma events. A particular safety concern was the 2 deaths seen in the asthma safety study B2338 (26-week study involving about 268 patients per treatment arm), both occurring in patients treated with indacaterol 300 mcg once-daily while they were receiving concurrent ICS.

The first death occurred in a 60-year-old male with a seven-year history of asthma with no other active medical problems. On day 165 of treatment, the patient was hospitalized for one day with “asthmatic crisis” and treated with oral corticosteroid and nebulized medication. Four days later, on day 169, he again developed acute asthma exacerbation and died on his way to the hospital. This patient was on inhaled beclomethasone 500 mcg twice daily for approximately the first six months of the study, and then on inhaled budesonide 400 mcg twice daily for rest of the study until death.

The second death occurred in a 75-year-old woman with a two-year history of asthma, allergic rhinitis, osteoporosis, and past history of respiratory arrest and anaphylactic

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<sup>16</sup> Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

reaction. On day 119 of treatment the patient experienced a cardiac arrest at home. The patient was resuscitated, intubated, and admitted to the hospital. On evaluation, significant findings were a small pneumothorax and pulmonary hyperinflation consistent with asthma. There were no findings consistent with myocardial infarction or other cardiovascular diseases. Life support was withdrawn on day 11 of hospitalization on family request and the patient expired. The patient was on inhaled mometasone 220 mcg once daily for the entire duration of the study.

SAEs related to asthma exacerbation or respiratory events seemed to be more common in patients treated with indacaterol in various asthma studies. In the asthma safety study B2338 (26-week study involving about 268 patients per treatment arm) where two deaths were seen (described above), SAEs related to asthma exacerbation were reported for 2 patients in the indacaterol 300 mcg group, 3 patients in indacaterol 600 mcg group, and for no patients in the salmeterol group. In the other asthma safety study (Study A2210, 4-week study involving 59 patients per active treatment arm) there were more respiratory-related SAEs in the indacaterol treated group compared to placebo (4 in indacaterol versus 0 in placebo). In the 2-week asthma dose regimen study (B2223, 2-week crossover study involving 48 patients) there was one SAE of asthma exacerbation possibly due to viral influenza and pollen exposure reported in one patient while receiving indacaterol 150 mcg every other day.

Although the submitted application for indacaterol is for COPD, the two deaths in patients with asthma while receiving indacaterol with background of concurrent ICS treatment is concerning. The deaths are reminiscent of asthma-related deaths seen with other LABAs. Both the deaths occurred in patients on the 300 mcg dose, which is not very far removed from the 150 mcg dose proposed to be marketed as a bronchodilator. Asthma-related deaths in typical LABA programs for asthma to support NDA submission, even when LABAs were used alone in such studies without concomitant ICS, are very rare to nonexistent. In the indacaterol program, two possible asthma-related deaths occurred in patients receiving indacaterol in a study where there was a salmeterol active comparator and in which the LABAs were administered concomitant with ICS. The possible imbalance of SAEs related to asthma exacerbation further supports the safety concerns for indacaterol.

The major safety concern with indacaterol is linked to selection of appropriate dose, because bronchodilators, particularly at high doses, have the safety concern of severe asthma exacerbations and asthma related deaths in patients who use these drugs to treat asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select the appropriate and safe dose for a bronchodilator. One issue for discussion at the PADAC meeting is whether balancing safety data exists to support the two proposed doses of indacaterol, and if so, what that data show.

In the Agency's Complete Response action letter to the original NDA submission, Novartis was asked to provide replicate data showing a clinically meaningful advantage of a higher dose compared to a lower dose and balancing safety data to show no unacceptable safety disadvantage with the higher dose. Based on our review of the complete response to date, we have determined that further analyses of the existing data will help in the assessment

and balancing the safety risk of the two doses. To that effect, on December 16, 2010, we asked Novartis to conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls by evaluating adverse events of interest (all cause death, asthma-related death, asthma-related intubation, asthma-related intubation, COPD-related death, COPD-related intubation, COPD-related hospitalization, pneumonia-related death, pneumonia-related intubation, pneumonia-related hospitalization) for all parallel-arm controlled trials 7 days or more in duration that used the proposed to-be-marketed product for the treatment of COPD and asthma. We asked for analysis of various study sets (all studies, COPD only studies, asthma only studies, and COPD studies subgroups of bronchodilator responsive patients compared to non-bronchodilator responsive patients). Novartis has developed an adjudication committee charter and analysis plan, and the analysis is currently ongoing. The analysis and subsequent Agency review of the analyses will be submitted as an addendum to this briefing document. This analysis will form a key discussion point at the PADAC meeting.

### **Benefit risk assessment**

Replicate findings of statistically significant differences between indacaterol 75 mcg or 150 mcg once-daily and placebo were shown in COPD patients for the primary efficacy endpoint of 24-hour post-dose trough FEV1 after 12 weeks of treatment, and for various secondary measures of efficacy, including for total SGRQ at 12 weeks. There were no major identified safety concerns with COPD patients; however, there were two asthma related deaths in a relatively small asthma safety study (26-week safety involving about 268 patients per treatment arm) in patients treated with indacaterol 300 mcg once-daily while they were receiving a background of concurrent ICS treatment. SAEs related to asthma exacerbation or respiratory events seemed to be more common in patients treated with indacaterol in various asthma studies. The major safety concern with indacaterol is linked to selection of appropriate dose, because bronchodilators, particularly at high doses, have safety concern of severe asthma exacerbations and asthma related deaths in patients who use these drugs to treat asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select the appropriate and safe dose for a bronchodilator in this population.

### **Summary**

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Novartis to support the approval of indacaterol inhalation powder at a dose of 75 or 150 mcg every day (once-daily), for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. The major issues for discussion at the PADAC meeting are: a) whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data, b) whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data, c) whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses, and finally, d) the safety of the proposed dose and dosing regimen of indacaterol.



At the PADAC meeting, Novartis will present an overview of the clinical program and efficacy and safety data, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following questions that will be discussed and deliberated upon following the presentations and discussion. Some of the questions are for discussion only, and some are for discussion and voting.

### **Draft Questions**

1. Discuss the efficacy data of indacaterol considering the following
  - a) Dosing regimen or dosing frequency
  - b) Total daily dose lower than 75 mcg
  - c) Are there advantages of 150 mcg once-daily dose over 75 mcg once-daily dose
  - d) Claim that 150 mcg once-daily dose improves SGRQ considering the totality of the SGRQ data
2. Discuss the overall safety profile of indacaterol considering the following
  - a) Safety data from asthma studies
  - b) Proposed indication specific to chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
  - c) Comparative safety assessment of 75 mcg and 150 mcg dose for balancing safety risk relative to efficacy
3. Considering the totality of the data, has indacaterol demonstrated substantial evidence of efficacy for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
  - a) For the 75 mcg dose? **(Voting question)**
  - b) For the 150 mcg dose over the 75mcg dose? **(Voting question)**
  - c) If not, what further data should be obtained
4. Is the safety profile of indacaterol adequate for approval for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
  - a) For the 75 mcg dose? **(Voting question)**
  - b) For the 150 mcg dose? **(Voting question)**
  - c) If not, what further data should be obtained

5. Does the totality of the data provide substantial evidence to support a claim that indacaterol improves health-related quality of life as measured using St. George's Respiratory Questionnaire (SGRQ)
  - a) For the 75 mcg dose? **(Voting question)**
  - b) For the 150 mcg dose? **(Voting question)**
  
6. Do the efficacy and safety data provide substantial evidence to support approval of indacaterol inhalation powder for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema? **(Voting question)**
  - a) If yes, should the dose be
    - i. 75 mcg once-daily? **(Voting question)**
    - ii. 150 mcg once-daily? **(Voting question)**
  - b) If not, what further data should be obtained?

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-383
Priority or Standard	Standard-resubmission
Submit Date(s)	September 28, 2010
Received Date(s)	September 28, 2010
PDUFA Goal Date	April 1, 2011
Division / Office	DPARP/ODE II
Reviewer Name(s)	Anya C. Harry M.D., Ph.D.
Review Completion Date	February 8, 2011
Established Name	Indacaterol maleate
(Proposed) Trade Name	Arcapta Neohaler
Therapeutic Class	Long acting $\beta_2$ agonist
Applicant	Novartis Pharmaceuticals
Formulation(s)	Single dose dry powder inhaler
Dosing Regimen	Once daily
Indication(s)	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.
Intended Population(s)	Patients with COPD

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## **1. Executive Summary**

### **1.1 Brief Overview of Clinical Program**

Arcapta Neohaler (indacaterol maleate inhalation powder) is under consideration (NDA 22-383) for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Indacaterol is a beta<sub>2</sub>-adrenergic agonist with proposed once daily dosing, termed a long-acting beta-agonist (LABA). The Applicant, Novartis Pharmaceuticals Corporation, seeks approval of two doses of indacaterol, 75 and 150 mcg. In addition, Novartis is requesting a claim for improvement in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ). Novartis is not currently requesting an asthma claim. Indacaterol is approved for COPD in 30 countries worldwide including the European Union at doses of 150 and 300 mcg once daily.

Novartis initially submitted NDA 22-383 on December 15, 2008, requesting approval of two doses, 150 and 300 mcg once daily, for COPD. To support this application, Novartis submitted three pivotal COPD studies: a 26-week adaptive design dose ranging study (with continuing doses of 150 and 300 mcg), a one-year efficacy and safety study (300 and 600 mcg), and a 12 week study (150 mcg). FDA took a complete response action for this application on October 16, 2009. Key issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma related deaths compared to salmeterol in patients with asthma. In addition, the dose and dosing frequency were not adequately explored, with no clinically meaningful difference between 75 mcg once daily and the proposed doses of 150 and 300 mcg.

In a complete response to regulatory action, Novartis now submits 6 new pivotal studies in addition to 10 Phase 3 supportive studies. The key pivotal studies include dose ranging and dose regimen studies in a bronchodilator-responsive asthma population, a dose ranging study in COPD, two replicative 12-week confirmatory studies in COPD with the 75 mcg dose, and one 26 week confirmatory study in COPD with the 150 mcg dose. Important long-term safety data for the 150 mcg dose comes from a 26 week extension to the adaptive design study, for a total duration of 1 year.

This clinical briefing document includes a review of the results of the 6 new pivotal studies and the safety results from the 26 week extension study. The safety portion of the briefing document will address cardiovascular and cerebrovascular events raised as a potential concern in the original review. At the request of FDA, Novartis is conducting a meta-analysis of asthma and COPD studies with indacaterol to address the issue of possible respiratory-related death. The results of this meta-analysis are not yet available at the time of this review. It is anticipated that the meta-analysis and subsequent review will be submitted as an addendum to the briefing document, as it will form a key discussion point at the PADAC meeting.

### **1.2 Efficacy**

This application raises several efficacy issues for discussion at the PADAC meeting. These issues include: 1) if the proposed 75 mcg dose and dosing frequency has been optimized, 2) if a second, higher 150 mcg dose is supported for more severe patients, and 3) if the SGRQ claim is supported. In the United States, no bronchodilator is approved in more than one dose and none have a claim for improvement in SGRQ. Thus, these claims would represent a new regulatory paradigm.

#### **1.2.1. Dose and dosing frequency**

The asthma dose ranging trial (Protocol B2357) was a 2-week multicenter, randomized, double-blind, placebo-controlled, parallel group trial evaluating 4 different once daily doses of indacaterol (18.75 mcg,

37.5 mcg, 75 mcg, and 150 mcg) compared to salmeterol 50 mcg BID and placebo in persistent asthmatics taking maintenance inhaled corticosteroids (ICS). At the request of FDA, Novartis chose a bronchodilator-responsive asthma population that could show the greatest separation between dose groups. The trial demonstrated that the indacaterol 75 mcg dose showed the most benefit compared to placebo for the primary endpoint, trough FEV1 (tFEV1) at Day 15. Although the 150 mcg indacaterol dose had a larger improvement than 75 or 37.5 mcg after 1 day of treatment, this advantage was lost by Day 14. In this trial, the 37.5 mcg and 18.75 mcg doses offered suboptimal bronchodilator effect.

The COPD dose ranging trial (Protocol B2356) was similar in design to the asthma dose ranging trial (B2357), with the same treatment arms in a population with moderate to severe COPD. There were no clinically meaningful differences in the primary endpoint, tFEV1 at Day 15, among the 37.5, 75, and 150 mcg dose groups. However, the 37.5 mcg dose group showed suboptimal bronchodilator response after the first dose.

The asthma dose regimen trial (Protocol B2223) was a 2-week multicenter, randomized, double-blind, placebo-controlled, parallel group trial evaluating 3 different dosing regimens of indacaterol: 75 mcg once daily, 150 mcg on alternate days, and 37.5 mcg twice daily. Salmeterol 50 mcg BID was also included as an active control arm. There were no clinically meaningful differences among the three indacaterol dosing regimens on FEV1 parameters at Day 15, although the peak effect was higher on Day 1 for the 150 mcg QOD regimen.

Confirmatory support for bronchodilator effect with the 75 mcg dose was shown in Protocols B2354 and B2355. These were 12-week multicenter, randomized, double-blind, placebo-controlled, parallel group trials evaluating the effect of indacaterol 75 mcg once daily on tFEV1. Both trials demonstrated that the indacaterol 75 mcg groups had a significant improvement in 12 week tFEV1 of 120-140 ml. Secondary endpoints of other FEV1 parameters and rescue medication use also showed significant improvement over placebo in both trials.

### **1.2.2. Support for higher dose**

Novartis proposes a 150 mcg once daily dose “to provide additional benefit in patients with more severe bronchial obstruction.” Other than the 2 week dose ranging studies discussed in Section 1.2.1 and the two-week dose ranging portion of the original adaptive design study (B23335s), no studies have included both 75 and 150 mcg arms for direct comparison. In the dose ranging studies, the 150 mcg dose provided no meaningful clinical benefit over the 75 mcg dose. Similarly, a comparison drawn from the pooled 3 month efficacy data from all double-blind, placebo and active controlled trials of at least 12 weeks duration, consisting of 10 trials, does not demonstrate a clinically meaningful benefit in the primary bronchodilator endpoint of tFEV1 at 12 weeks, with difference of only 10 ml between the two dose groups. A subgroup analysis of this data by Global initiative for chronic Obstructive Lung Disease (GOLD) stage likewise did not demonstrate a benefit of the 150 mcg dose over the 75 mcg dose for patients with severe disease.

The sponsor is basing the claim for a 150 mcg dose on two points: modeling data from the dose ranging studies and the SGRQ. According to the sponsor, modeling data demonstrate an advantage of the 150 mcg dose, particularly in more severe patients. However, the sponsor also notes that the model does not match the data from the dose ranging trial in asthma (Protocol B2357), the study with the clearest dose response. In addition, when the modeling data were re-analyzed by the FDA clinical pharmacology reviewer, eliminating uncontrolled Day 14 data, this advantage was lost. See the Clinical Pharmacology Review document in the background package. Therefore, modeling data are not considered further in this review. The SGRQ data are summarized in Section 1.2.3 below.

### **1.2.3. SGRQ**

The SGRQ was evaluated in five pivotal studies—two reviewed in the initial submission (Protocols B2346 and B2335S) and three reviewed in this complete response submission (Protocols B2336, B2354, and B2355). None of these trials included both the 150 mcg and 75 mcg dose groups, so direct comparisons

between the doses cannot be made. At 12 weeks, the 150 mcg dose group met the minimally clinically important difference (MCID) of -4 points change from baseline compared to placebo in the SGRQ total score in two studies. In Protocol B2346 the LS mean difference was -4.8, and in Protocol B2336 the LS mean difference was -6.3, forming the basis of the sponsor's claim that indacaterol 150 mcg improves SGRQ.

This claim is complicated by a number of issues. Firstly, SGRQ did not reach the MCID for doses higher than 150 mcg in Protocol B2346 (300 and 600 mcg), demonstrating a lack of internal consistency in the trial, and did not reach the MCID for 150 mcg or 300 mcg in Protocol B2335S. Further, the MCID was not reached for all time points within the trials. In Protocol B2336, the active comparator salmeterol also reached the MCID at -4.2. Since salmeterol has not been demonstrated to consistently benefit SGRQ, this suggests that the trial may have resulted in larger differences from placebo than is typical. Finally, SGRQ was a secondary endpoint in all studies and no correction for multiplicity was performed, except for Protocol B2336.

Evaluating the SGRQ for the 75 mcg dose (Protocols B2354 and B2355) gives a treatment difference of -3.8 and -3.6, respectively. For all of the trials, the confidence intervals were wide. Between trial comparisons show marked overlap between the 75 and 150 mcg dose groups, suggesting that the results are statistically similar despite different point estimates. Likewise, a responder analysis showed little difference between 75 mcg and 150 mcg, with similar percentages of patients meeting the MCID in both dose groups.

### 1.3 Safety

There were a total of 9441 patients in the 3 month COPD safety dataset, 4764 of whom received indacaterol in the following dose groups—75 mcg (N=449), 150 mcg (N=2611), 300 mcg (N=1157), and 600 mcg (N=547). Twelve month data is available for 2142 patients, 1152 of whom received indacaterol in the following dose groups—150 mcg (N=144), 300 mcg (N=583), and 600 mcg (N=425).

The most common AEs in both the 3 and 12 month safety datasets were COPD exacerbation, nasopharyngitis, cough, headache, upper respiratory infection, and muscle spasms. Both cough and muscle spasms occurred more frequently in the indacaterol groups than in placebo or active comparator groups. Six Phase 3 studies proactively solicited information on post-inhalational cough that occurred at the study center after dosing. Based on this analysis, post-inhalational cough occurred in 23 to 31% of indacaterol treated patients compared to 3 to 6% of placebo treated patients. A small dose effect was seen, with 23% of patients coughing in the 75 mcg group compared to 31% in the 600 mcg group. The odds ratio compared to placebo of 7.75 (95% CI 5.07, 11.86) and 17.62 (95% CI 13.57, 22.87), respectively. However, the cough was generally of very short duration ( $\leq 15$  seconds), did not cause discontinuation from the trial, and did not cause a drop in FEV1.

In the original submission, there were more cardiac or cerebrovascular AEs and serious adverse events (SAEs) in the indacaterol treatment groups compared to placebo (3.4% indacaterol 300 mcg versus 0.9% placebo SAEs) in the 12 month safety evaluation. The 12 month safety data from the complete response, which includes data from the 26 week safety extension to the adaptive design study (Protocol B2335SE), shows that patients with SAEs in any organ system are balanced in the 150 mcg dose group compared to placebo (10.4% of patients in the indacaterol 150 mcg group compared to 11.0% in placebo). There were 0.69% of patients in the 150 mcg indacaterol group with cardiac or cerebrovascular SAEs compared to 1.4% in the placebo group.

The second safety concern raised by the original submission was asthma-related death, with two deaths in the 268 patient 300 mcg dose group of a single 26 week asthma study. As noted above, a specific meta-analysis to address this issue is pending at the time of this background package.

## 2. Introduction and Regulatory Background

### 2.1 Product Information

The proposed product is indacaterol maleate inhalation powder (QAB149), and the proposed trade name is Arcapta™ Neohaler™. The established name, indacaterol (Ind) without specification of the salt will be used throughout the review to refer to the product. Indacaterol is a new molecular entity in the beta-2 adrenergic agonist class of drugs. It is a dry powder for inhalation that is pre-metered with the formulation of approximately 25 mg of lactose monohydrate contained in hard gelatin capsules. A capsule is inserted into the Neohaler device, also called the Concept 1. The device pierces both ends of the capsule, then inhalation causes the capsule to spin and the formulation powder to be entrained into the airstream.

The proposed indication for indacaterol is for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is one inhalation of a 75 mcg capsule once daily, with a qualifier that administration of a 150 mcg capsule once daily has been shown to provide additional clinical benefit in some patients.

### 2.2 Currently Available Treatments for Proposed Indications

Currently available drugs for the treatment of COPD are listed in Table 1. The list includes many pharmacotherapeutics that are used for the treatment of acute bronchospasm.

**Table 1** *Currently available pharmacologic treatment for COPD*

Class		Generic name	Brand name
Beta2-adrenergic agonists	Short-acting <sup>†</sup> (SABA)	Albuterol Albuterol sulfate	Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA
		Levalbuterol Levalbuterol tartrate	Xopenex HFA
		Pirbuterol	Maxair Autohaler
		Terbutaline sulfate	
	Long-acting (LABA)	Salmeterol	Serevent Diskus
		Formoterol	Foradil Aerolizer
		Arformoterol	Brovana
		Formoterol solution	Perforomist
Anti-cholinergics	Short-acting	Ipratropium bromide	Atrovent HFA
	Long-acting	Tiotropium bromide	Spiriva Handihaler
Combination	SABA/anti-cholinergic	Albuterol/ipratropium	Combivent, Duoneb
	Corticosteroid/LABA	Fluticasone/salmeterol	Advair Diskus, Advair HFA
		Budesonide/formoterol	Symbicort
Xanthines		Theophylline	multiple

<sup>†</sup>Products with a general bronchodilator claim, not COPD specific.

### 2.3 Availability of Proposed Active Ingredient in the United States

Indacaterol is currently not marketed in the US. According to the sponsor, it is approved in 30 countries worldwide, including the EU at a dose of 150mcg or 300 mcg once daily.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Indacaterol belongs to a subclass of beta-2 agonists termed long-acting beta agonists or LABAs that include the marketed drugs Foradil and Perforomist (formoterol), Brovana (R,R formoterol), and Serevent (salmeterol). The use of LABAs has come under scrutiny as a result of a safety signal of increased risk of severe exacerbations including death in patients with asthma. The increased risk was demonstrated in the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. SMART was a randomized, double-blind study that enrolled patients with asthma not currently using LABAs to assess the safety of salmeterol (42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). The study was prematurely terminated in January 2003 after a total of approximately 30,000 patients had been enrolled because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including death.

As a result of the findings described above as well findings in smaller safety studies conducted with another LABA, formoterol, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting (PADAC). Subsequent to the meeting, in November, 2005, the FDA released a Public Health Advisory to alert healthcare professionals and patients that LABAs may increase the chance of severe asthma episodes and death. Based on this meeting and a follow up PADAC meeting on December 10, 2008, the existing product labels have been revised and now include a Boxed Warning and a Medication Guide for all marketed LABA products. In addition, the paradigm for asthma treatment has now changed, contraindicating the use of a LABA without a concomitant asthma controller medication, such as an inhaled corticosteroid (ICS)<sup>1</sup>.

Because it is unclear if addition of an inhaled corticosteroid mitigates the risk of LABAs in asthma, sponsors of LABA products indicated for asthma are being required to perform large safety trials to evaluate serious asthma outcomes in patients receiving concomitant ICS and LABA. The design of these trials was discussed at a PADAC meeting held March 10-11, 2010.

While no such safety signal has been observed in patients with COPD, dose-related class effects of beta agonists, especially those affecting the cardiac and central nervous systems, can be deleterious to older patients with COPD, many of whom have increased cerebral and cardiovascular risk factors.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Novartis initially submitted NDA 22-383 on December 15, 2008, requesting approval of two doses, 150 and 300 mcg once daily, for COPD. To support this application, Novartis submitted three pivotal COPD studies: a 26-week adaptive design dose ranging study (with continuing doses of 150 and 300 mcg), a one-year efficacy and safety study (300 and 600 mcg), and a 12 week study (150 mcg). FDA took a complete response action for this application on October 16, 2009. Key issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma related deaths compared to salmeterol in patients with asthma. In addition, the dose and dosing frequency were not adequately explored, with no clinically meaningful difference between 75 mcg once daily and the proposed doses of 150 and 300 mcg.

A post action meeting was held on November 24, 2009. The highlights of the meeting included review of FDA's comments to questions from the November 5, 2009 package as well as a general discussion of the path forward. FDA reviewed recommendations for the use of patients with a significant degree of

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<sup>1</sup> Chowdhury BA, Dal Pan G. FDA and safe use of long-acting beta-agonists in the treatment of asthma. 2010 N Engl J Med 362:1169-71

bronchoresponsiveness to define the dose response profile and for selection of the lowest dose with a tolerable safety profile to be carried forward to patients with COPD.

In a complete response to regulatory action, Novartis now submits 6 new pivotal studies in addition to 10 Phase 3 supportive studies. The key pivotal studies include dose ranging and dose regimen studies in a bronchodilator-responsive asthma population, a dose ranging study in COPD, two replicative 12-week confirmatory studies in COPD with the 75 mcg dose, and one 26 week confirmatory study in COPD with the 150 mcg dose. Important long-term safety data for the 150 mcg dose comes from a 26 week extension to the adaptive design study, for a total duration of 1 year.

### **3. Sources of Clinical Data**

Between the original application [NDA 22383 12/17/08, S0000] and the resubmission [9/28/10, S0027], Novartis has conducted 21 Phase III controlled clinical trials with indacaterol in over 13,500 patients. There were 3 trials identified as pivotal in the original Phase III program: B2335S, B2334 and B2346 and 3 supportive profiling trials: B2305, B2307 and B2340. These trials were summarized in the reviews of the original application by Drs. Lynne Wu and Anthony Durmowicz and are not mentioned further in this review. There were 16 new Phase II and III trials submitted in the complete response. These new trials are summarized in Table 2. Of the 16 new trials, 6 are considered pivotal to the resubmission as they provide data in support of dose selection and dosing frequency as well as confirmation of safety and efficacy of the new proposed doses. The dose finding trials B2357, B2356 and B2223 were the trials submitted in response to concern over the dose and regimen selection described in the CR letter [October 16, 2009]. In addition, two confirmatory trials, B2355 and B2354 were reviewed to evaluate the safety and efficacy of the 75 mcg dose in patients with COPD over a 12 week treatment period. The trial B2336 was ongoing at the time of the initial submission, completed and included as part of the current resubmission. It was a pivotal efficacy and safety trial of indacaterol 150 mcg q.d. with the active comparator, salmeterol over 26 weeks and provides data the sponsor uses to support the SGRQ claim.

Ten additional supplementary controlled trials not included in the original submission were reviewed and briefly summarized as supportive towards efficacy and safety in patients with COPD. Trials B1302 and B2333 were long term studies performed in Asia evaluating the two higher doses of indacaterol 150 mcg and 300 mcg compared to placebo. Trials B2349 and B2350 recruited international patients and evaluated the efficacy of indacaterol 150 mcg and an active comparator, either salmeterol 50 mcg b.i.d or tiotropium 18 mcg q.d. respectively. B2335SE, also an international trial was a 26 week extension to the 26 week adaptive seamless design trial included in the original submission. Although the extension did not include the active control, tiotropium the trial provided long term safety data of indacaterol 150 mcg and 300 mcg compared to placebo after 52 weeks of treatment. Trials B2341 and B2351 compared the efficacies of indacaterol 150 mcg given concurrently with tiotropium HandiHaler (18 mcg q.d.) to tiotropium alone and placebo. Two profiling studies were B2311 and B2331, the former evaluated indacaterol 300 mcg and placebo on exercise endurance time, the latter evaluated the two doses 150 mcg and 300 mcg versus placebo on the 24 hour lung function. The 24 week interim analysis of the ongoing Japanese trial B1303 was also included.

Novartis submitted a Periodic Safety Update Report (PSUR-1) for Onbrez® Breezhaler® (indacaterol maleate) and related products which were first registered in the EU on November 30, 2009 at doses of 150 and 300 mcg covering the time frame of November 30, 2009 to May 31, 2010 that was reviewed. Furthermore, Medwatch reports submitted to the IND 48,649 were also reviewed.



### 3.1 Tables of Studies/Clinical Trials

**Table 2 Clinical trials included in evaluation**

Study	Objective, population	Planned patients	Treatment duration	Dosage	Efficacy endpoint	Safety endpoints
<b>Dose finding trials</b>						
B2335S	Adaptive design dose-ranging in COPD	1945	26 weeks	Indacaterol 75, 150, 300, 600 mcg q.d., Formoterol 12 mcg bid Tiotropium 18 mcg QD (open label) Placebo	FEV <sub>1</sub> trough at 24 hr at wk 2 FEV <sub>1</sub> AUC <sub>1-4</sub> hr at wk 2  FEV <sub>1</sub> trough at 24 hr at wk 12	AE, SAEs, labs, ECGs, VS, PE, weight, COPD exacerbations, 24 hour Holter (subset)
B2357	Dose-ranging in asthma	558	2 weeks	Indacaterol 18.75, 37.5, 75, 150 mcg q.d. Salmeterol 50 mcg bid Placebo bid	tFEV1 after 14 days	AE (including asthma exacerbations), SAEs, labs, ECG, VS, PE, weight
B2223	Dosing regimens in asthma	192	2 weeks	Indacaterol 37.5 mcg bid, 75 mcg q.d., 150 mcg q.o.d	tFEV1 after 14 days	VS, ECG, labs, AEs
B2356	Dose-ranging in COPD	576	2 weeks	Indacaterol 18.75, 37.5, 75, 150 mcg q.d. Salmeterol 50 mcg bid Placebo bid	tFEV1 after 14 days	AE, SAEs, labs, ECG, VS, PE, rescue medication use
<b>Key controlled efficacy trials-75 mcg</b>						
B2355	Efficacy/safety in COPD	326	12 weeks	Indacaterol 75 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE
B2354	Efficacy/safety in COPD	326	12 weeks	Indacaterol 75 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE
<b>Key controlled efficacy trials-≥ 150 mcg</b>						
B2336	Efficacy/safety in COPD	972	26 weeks	Indacaterol 150 mcg q.d. Salmeterol 50 mcg b.i.d Placebo b.i.d	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, medical resource utilization, post inhalation events

Supplementary controlled efficacy trials						
B1302	Efficacy/safety in COPD Hong Kong, India, Japan, Korea, Singapore and Taiwan	336	12 weeks	Indacaterol 150, 300 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events
B2333	Efficacy/safety in COPD, China, Australia and India	558	26 weeks	Indacaterol 150, 300 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AEs, SAEs, VS, ECGs, labs, post inhalation events
B2349	Efficacy/safety in COPD	1084	12 weeks	Indacaterol 150 mcg q.d. Salmeterol 50 mcg b.i.d	AUC (5 min-11h 45 min for FEV1 at Week 12	ECG, labs, blood pressure, heart rate, AEs
B2350	Efficacy/safety in COPD	1568	12 weeks	Indacaterol 150 mcg q.d. Tiotropium 18 mcg q.d.	tFEV1 at Week 12	AEs, SAE, ECG, labs, blood pressure, heart rate, AEs
Long term controlled efficacy trials						
B2335SE	Efficacy/safety in COPD	417	26 weeks (additional to initial 26 weeks)	Indacaterol 150, 300 mcg q.d. Placebo q.d.	tFEV1 at Week 52	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight
Trials with indacaterol given concurrently with tiotropium						
B2341	Efficacy/safety in COPD	1126	12 weeks	Indacaterol 150 mcg q.d. + tiotropium 18 mcg q.d. Placebo to indacaterol + tiotropium 18 mcg q.d.	AUC (5 min-8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG
B2351	Efficacy/safety in COPD	1126	12 weeks	Indacaterol 150 mcg q.d. + tiotropium 18 mcg q.d. Placebo to indacaterol + tiotropium 18 mcg q.d.	AUC (5 min-8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG
Short-term profiling trials						
B2311	Exercise endurance in COPD	83	3 weeks (2 treatment periods separated	Indacaterol 300 mcg q.d. Placebo q.d.	Exercise endurance time (measured	AEs, SAEs, labs, VS, ECG, PE

			by 2 weeks of wash out)		through constant-load cycle ergometry testing) after 3 weeks of treatment	
B2331	24 h lung function profile in COPD	148	14 days (3 treatment periods separated by 2 weeks of wash out)	Indacaterol 150, 300 mcg q.d. Tiotropium 18 mcg q.d. Placebo q.d.	tFEV1 on Day 15	AEs (including COPD exacerbations),, SAEs, labs, VS, ECG, PE
Interim analysis for Japanese trial						
B1303	Efficacy/safety in COPD (Japan)	180	52 weeks (interim analysis at Week 24)	Indacaterol 300 mcg q.d. Salmeterol 50 mcg b.i.d.	tFEV1 on Day 169 (Week 24)	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events

### 3.2 Review Strategy

The two new dose ranging trials (B2357 and B2356) and the dose regimen trial (B2223) were first reviewed for validity and appropriateness of the selected dose and regimen. B2357 and B2223 were conducted in the bronchoreactive population of asthmatics as recommended by FDA. Then the two confirmatory 12 week trials B2355 and B2354 were reviewed for efficacy and safety of the proposed 75 mcg dose. Next, the long term 26 week trial B2336 was examined for safety of the higher proposed dose which could be extrapolated to the lower proposed dose. Overall, safety was judged by the review of many sources including: the Overview of Safety, the PSUR-1 and postmarketing reports. Novartis submission of a meta-analysis of the incidence of respiratory related death is pending at the time of finalization of this background package. It is anticipated that this information will be available at the PADAC meeting

### 3.3 Discussion of Individual Studies/Clinical Trials

### **3.3.1 DOSE FINDING TRIAL IN PATIENTS WITH ASTHMA B2357**

*A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Different Doses of Indacaterol in Adult Patients with Persistent Asthma, Using Salmeterol as an Active Control.*

#### **3.3.1.1 Trial Description**

##### **3.3.1.1.1 Design**

This was a Phase III, multicenter (73), randomized, double-blind, double-dummy, placebo-controlled, parallel group trial conducted in patients with persistent asthma for 14 days with indacaterol once daily at doses of 18.75, 37.5, 75 or 150 mcg, salmeterol 50 mcg twice daily, or placebo. Initially, there was an open label period on Day 15 where all subjects would receive a single dose of indacaterol 300 mcg, this was removed in Amendment #2 dated 2/15/10 along with the associated study objectives and assessments.

##### *Reviewer's Comment:*

*The intention of the Sponsor was that this study would supplement the data from Study CQAB149B2335S and support the selection of an appropriate dose of indacaterol for the treatment of COPD.*

##### **3.3.1.1.2 Duration**

The treatment period was 2 weeks. A two week run-in time preceded the active treatment period.

##### *Reviewer's Comment:*

*The time taken to reach pharmacokinetic steady state is 14 days for indacaterol when administered once daily.*

##### **3.3.1.1.3 Population**

Males and females aged 18 years and older, diagnosed with persistent asthma (according to <sup>2</sup>GINA guidelines, update 2008) were enrolled. The randomization was stratified by asthma severity (GINA guidelines) based on data recorded in the patient's diary during the run-in period. The population was changed in Amendment #2 dated 2/15/10 to include a 24-hour spirometry profiling subgroup. All patients were offered the opportunity

##### *Reviewer's Comment:*

*The targeted asthma population was at the recommendation of the Agency where the rationale was to test in the patient population most sensitive to both the bronchodilator and AE effects of LABAs.*

##### **3.3.1.1.4 Study Sites**

This study was conducted at 73 sites in the United States

##### **3.3.1.1.5 Investigational and Reference Therapy**

The following drugs were used:

- Indacaterol 18.75 mcg dry powder capsules blister batch # VMLK/2009-3018, DP Batch # X223 0909
- Indacaterol 37.5 mcg dry powder capsules blister batch # VMLK/2009-3019, DP Batch # X224 0909
- Indacaterol 75 mcg dry powder capsules blister batch # VMLK/2009-2700, DP Batch # X173GF
- Indacaterol 150 mcg dry powder capsules blister batch # VMLK/2009-2826, DP Batch # X172GF
- Placebo to indacaterol blister batch # VMLK/2008-1409, DP Batch # X039BE
- Salmeterol 50 mcg Diskus® DP batch # R438216
- Placebo to salmeterol Diskus® DP batch # X2780807
- Placebo to salmeterol Diskus® DP batch # X1650608

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<sup>2</sup> Global Initiative for Asthma (GINA) 2008, Available from the website <http://www.ginasthma.org>.

All indacaterol dry powder capsules and placebo-to-indacaterol were inhaled through the Concept1 SDDPI. Salmeterol and the placebo-to-salmeterol were inhaled through the Diskus®.

### 3.3.1.1.6 Objectives

The primary objective was to evaluate the dose response relationship among four doses of indacaterol (18.75, 37.5, 75, and 150 mcg q.d.), placebo and salmeterol 50 mcg b.i.d. as measured by the 24 hr post-dose FEV1 (trough) after 14 days (tFEV1 Day 14) of treatment in adult patients with persistent asthma.

#### *Reviewer's Comment:*

*The doses selected were smaller than those evaluated in study B2335S in the original submission [NDA22-383 S000], 75, 150, 300 and 600 mcg.*

The second secondary objectives were as follows:

- To evaluate the bronchodilator effect for all doses of indacaterol as compared to placebo as measured by:
  - 24-hour post-dose of (trough) FEV1 after 1 day (tFEV1 Day1) of treatment
  - Peak FEV1 on Day 1, this was changed from time to peak FEV1 on Day 1 in Amendment #1, dated 1/15/10
  - AUC for FEV1 5 minutes -11 hours 45 minutes on Days 1 and 14
  - AUC for FEV1 5 minutes-4 hours on Days 1 and 14
- To evaluate the effect of all doses of indacaterol and placebo on morning (premedication) and evening (pre-medication) PEF using data obtained from the eDiary over 14 days
- To evaluate day and night time rescue medication usage for all doses of indacaterol as compared to placebo over 14 days

An exploratory objective to assess the 24-hour (FEV1 and FVC) profile of indacaterol (18.75, 37.5, 75 and 150 mcg q.d.), salmeterol and placebo after 14 days of treatment was added in Amendment #2 dated 2/15/10.

### 3.3.1.1.7 Inclusion Criteria

Key inclusion criteria included:

- Male and female adults aged  $\geq 18$  years
- Diagnosis of persistent asthma per GINA 2008 guidelines
- Stable treatment with inhaled corticosteroid (ICS) for one month
- FEV1  $\geq 50$  and  $\leq 90\%$  of predicted normal
- Reversibility with an increase FEV1 of  $\geq 12\%$  and  $\geq 200$  mL within 30 minutes of albuterol via MDI

The criterion for FEV1 had to be demonstrated after a washout period of at least 6 hours during which no use of short acting  $\beta_2$ -agonist (SABA), and a minimum of 48 hours for a long acting  $\beta_2$ -agonist (LABA). Patients using LABAs (i.e. formoterol or salmeterol) were switched to the PRN use of the SABA (albuterol) at least 48 hours prior to Visit 2, those taking fixed dose combination treatment with ICS plus a LABA were taken off the combined medication and given the equivalent ICS monotherapy replacement of the ICS plus the inhaled SABA (as needed) at least 48 hours prior to Visit 2. Those taking a fixed dose combination anti-cholinergic plus a SABA (i.e., Combivent®) were taken off the combination at least 8 hours prior to Visit 2. Instead, only albuterol was used. In either case where fixed dose combination products were discontinued, regular dosage regimens of albuterol as rescue medication were only permitted during the screening period however, during the treatment period albuterol was taken for rescue ("when required") purposes only. Reversibility could be demonstrated after a washout period of at least 6 hours prior to the evaluation for a SABA and at Visit 2 or between Visits 2 and 3.

### 3.3.1.1.8 Exclusion Criteria

Notable exclusion criteria included:

- Pregnant or lactating women

- Women of child-bearing potential unless use of one or more acceptable method of contraception
- Smoking history of >10 pack years or current smokers who smoke more than 10 cigarettes a day
- Diagnosis of COPD as defined by the <sup>3</sup>Global Initiative for Chronic Obstructive Lung Disease (GOLD guidelines for 2008)
- Patients with seasonal allergic rhinitis whose asthma was likely to deteriorate during the study
- Severe asthma exacerbation requiring hospitalization in the 6 months prior to Visit 1, previous intubation
- Emergency room visit for an asthma attack within 6 weeks prior to Visit 1 or anytime between Visit 1 and 3
- Use of ≥8 inhalations per day of SABA (90 mcg albuterol via MDI) on any 2 consecutive days from screening to randomization
- Respiratory tract infection within 6 weeks prior to Visit 2 however, in Amendment #3, this was changed so that these patients were permitted to reenroll at a later date of at least 6 weeks
- Respiratory tract infection between Visit 2 and Visit 3 must discontinue from the trial
- Concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis
- Patients with diabetes Type I or uncontrolled diabetes Type II including patients with a of blood glucose levels consistently outside the normal range of glycosylated A1c > 8.0% of total hemoglobin measured at Visit 2.
- Clinically relevant laboratory abnormality or a clinically significant condition such as unstable ischemic heart disease, arrhythmia, or other clinically significant ECG findings, uncontrolled hypertension and other significant cardiac disease or conduction defect, uncontrolled thyroid disease, hypokalemia, hyperadrenergic state
- History (or family history) of long QT syndrome or QTc interval (Fridericia) measured at Visit 2 and 3 >450 ms (males) or >470 ms
- Any patient with lung cancer, any active cancer or a history of lung cancer or other cancer with less than 5 years of disease free survival time

### 3.3.1.1.9 Conduct

Table 3 and

Table 4 below outline the overall design of the study and the schedule of study procedures. At the pre-screening visit (Visit 1), informed consent was obtained and current asthma medications were reviewed. Arrangements were made to adjust prohibited asthma therapy prior to Visit 2, and all patients were provided with a SABA (albuterol) which they were to use throughout the study as rescue medication. During the treatment period albuterol was to be taken as rescue (when required) medication only and no other rescue treatment was permitted. The interval between Visits 2 and 3, the 14 day run-in period was used to assess eligibility of patients and to collect baseline patient characteristics and data on PEF measurements and rescue medication use via patient diary entries.

Patients who met inclusion/exclusion criteria at the screening visit returned for the randomization, Visit 3. At Visit 3, patient eligibility was confirmed and the patient was randomized (1:1:1:1:1:1) to one of the 6 blinded treatments as follows:

1. Indacaterol (18.75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
2. Indacaterol (37.5 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
3. Indacaterol (75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or

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<sup>3</sup> Global Initiative for Chronic Obstructive Lung Disease (2001, updated 2007) Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Available from the GOLD website <http://www.goldcopd.com>.

4. Indacaterol (150 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
5. Placebo to indacaterol delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
6. Placebo to indacaterol delivered via SDDPI once daily in the morning and salmeterol 50 mcg via Diskus® in the morning and salmeterol 50 mcg via Diskus® in the evening.

Patients received their first dose of study medication in the clinic on the morning of Day 1 (Visit 3) and were assessed in the clinic on Days 2, 14 and 15.

**Table 3 Protocol B2357 Study Design**

Period	Pre-screen	Screen/ Run-in	14-Day Randomized Treatment			
Visits	1	2	3	4	5	6
Day	-30 to -14	-14	1	2	14	15
<p>Patients are randomized (1:1:1:1:1:1) to receive one of the following six blinded treatments:</p> <p>Indacaterol 18.75 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or</p> <p>Indacaterol 37.5 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or</p> <p>Indacaterol 75 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or</p> <p>Indacaterol 150 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or</p> <p>Placebo to indacaterol o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or</p> <p>Placebo to indacaterol via SDDPI and salmeterol 50 µg b.i.d. via Diskus®</p> <p>Daily ICS monotherapy will be mandatory for all patients to remain stable throughout the duration of the study.</p> <p>Albuterol will be available for rescue use throughout the study.</p>						

Source: Table 3-1 Study No. CQAB149B2357 Amendment #3

The sequence of measurements were to be done in the following order when multiple assessments were required: ECG, vital signs, samples for hematology/blood chemistry, and then spirometry, starting in time to ensure spirometry measurements take place as close as possible to the scheduled time point. The screen period was changed in the Amendment #1 dated January 15, 2010 to only -14 days and an open label period was removed in Amendment #2 dated February 15, 2010.

**Table 4 Protocol B2357 Assessment Schedule**

	Pre-Screen	Screening/ Run-in	Treatment Period			
Treatment period			Double blind treatment			
Visit	1	2	3	4	5	6
Day	-30 to -14	-14	1	2	14	15
Informed consent	XS					
Current medication review	XS					
Inclusion/exclusion Criteria	S	XS	XS			
Medical History	XS					
Demographics	XS					
Smoking History	XS					
Pregnancy Test (serum) <sup>2</sup>		XS				XS
Physical Examination <sup>2</sup>		S <sup>#</sup>				S <sup>#</sup>
Record height (Visit 2 only) and weight <sup>2</sup>		XS				XS
FEV <sub>1</sub> reversibility ( $\beta_2$ agonist) and FEV <sub>1</sub> /FVC		XS				
Contact IVRS/IVRS <sup>2</sup>	S	S	S			S
Randomization via the IVRS <sup>6</sup>			XS			
Provide rescue medication as needed	S	S	S	S	S	
Review/record $\beta_2$ agonist use <sup>2</sup>		XS	XS	XS	XS	XS
ECG <sup>2,3</sup>		XS	XS		XS	XS
Systolic & diastolic blood pressure & radial pulse rate <sup>2,3</sup>		XS	XS		XS	XS
Urinalysis <sup>2,3</sup>		XS	XS		XS	XS
Hematology/blood chemistry <sup>2,3</sup>		XS	XS		XS	XS
Spirometry <sup>2,3</sup>		XS	XS	XS	XS	XS
24-hour spirometry profiling (subset of patients)					XS	XS
AE recording <sup>2</sup>	XS	XS	XS	XS	XS	XS
Concomitant medication <sup>2</sup>	XS	XS	XS	XS	XS	XS
Device training <sup>1</sup>	XS	XS	XS			
PEF & Diary training		XS				
Dispense PEF/Diary		XS				
Review, collect and download PEF/Diary <sup>2,5</sup>			XS	XS	XS	XS
Telephone patient 1 day prior to Visit <sup>4</sup>					S	
Administer study drug at visit			XS	XS	XS	
Dispense study drug <sup>7</sup>			X			
Collect unused study drug <sup>2</sup>						XS

X = assessment to be recorded on clinical data base

S = assessment to be recorded on source documentation

Source: Table 6-1 Study No. CQAB149B2357 Amendment #3



### **Efficacy Assessments**

The scheduling of serial measurements is presented in Table 5 below. Serial spirometry was performed on Days 1 (Visit 3) and Day 14 (Visit 5), at 50 and 15 minutes predose, then 5, 15, 30 minutes, 1, 2, 4, 8 hours and 11 hours 10 min, 11 hours 45 minutes post dose, then on Day 2 (Visit 4) and Day 15 spirometry was performed at 23 hours 10 min and 23 hours 45 minutes post dose. The serial spirometry subgroup continued to have spirometry taken during 14, 20 and 22 hours post dose. Baseline FEV1 was defined as the average of the FEV1 value at 50 and 15 minutes prior to dosing on Day 1. Patients were advised to avoid caffeine, chocolate, ice-cold beverages, strenuous physical activity and alcohol intake for at least 24 hour prior to scheduled study visits. Spirometry was read by a central laboratory.

Patients were provided with a Peak Flow meter and a diary device (Visit 2) to perform morning and evening peak expiratory flow (PEF) measurements, and record clinical symptoms and rescue medication usage (the number of inhalations used of albuterol via MDI) between morning and evening study medication inhalations. Compliance with the diary during the run-in period was encouraged.

Patients were instructed to avoid rescue albuterol within 6 hours of the start of each visit unless absolutely necessary. If rescue medication was taken within 6 hours prior to spirometry at Screening, or prior to the spirometry at Days 1 and 15 (Visits 3 and 6), the visit was rescheduled for the next day. If rescue medication was taken within 6 hours prior to the post-dose spirometry measurements (relative to the previous day's dose) at Days 2 and 14 (Visits 4 and 5 the spirometry measurements were considered invalid). Daily use of rescue medication was recorded once in the morning and once in the evening using their electronic diary.

**Table 5 Protocol B2357 Timed Assessments**

Visit (Day)	Timepoint <sup>1</sup>	Urinalysis	ECG <sup>2</sup>	Vital Signs <sup>3</sup>	Hematology/ blood chemistry	Spirometry (expiratory maneuver FEV <sub>1</sub> ) <sup>4</sup>
Visit 3 (Day 1)	-50 min	X				X
	-25 min		XX	X	X	
	-15 min					X
	5 min					X
	15 min					X
	30 min					X
Visit (Day)	Timepoint <sup>1</sup>	Urinalysis	ECG <sup>2</sup>	Vital Signs <sup>3</sup>	Hematology/ blood chemistry	Spirometry (expiratory maneuver FEV <sub>1</sub> ) <sup>4</sup>
	1 h		XX	X	X	X
	2 h					X
	4 h					X
	8 h					X
	11 h 10 min					X
	11 h 45 min					X
Visit 4 <sup>5</sup> (Day 2)	23 h 10 min					X
	23 h 45 min					X
Visit 5 <sup>6</sup> (Day 14)	-50 min	X				X
	-25 min		XX	X	X	
	-15 min					X
	5 min					X
	15 min					X
	30 min					X
	1 h		XX	X	X	X
	2 h					X
	4 h					X
	8 h					X
	11 h 10 min					X
	11 h 45 min					X
24-hour spirometry subgroup (Day 15)	14 h					X
	20 h					X
	22 h					X
Visit 6 <sup>5</sup> (Day 15)	23 h 10 min	X				X
	23 h 35 min		XX	X	X	
	23 h 45 min					X

Source: Table 6-2 Study No. CQAB149B2357 Amendment #3

### Safety Assessments

ECG, vitals and laboratory evaluations were performed 25 minutes predose and 1 hour post dose on Visits 3 and 5 and then again on Visit 6 at 23 hours 35 minutes. Urinalysis was performed 3 times on Visits 3 and 5 at 50 minutes predose and Visit 6 at 23 hours 10 minutes. AE and concomitant medications were recorded during all clinic visits. Physical exam and serum pregnancy test were performed during the screening and Day 15.

#### 3.3.1.1.10 Concomitant Treatments

Inhaled corticosteroids were required and the dose was to be stable for at least 1 month prior to screening and throughout the study. Other allowed medications included pure SSRIs, inactivated vaccine,

nasal corticosteroids and antihistamines. As mentioned above, only albuterol was to be used as a rescue medication. The following medications were prohibited: non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug), non-selective systemic beta-blocking agents, cardiac anti-arrhythmics Class Ia and Class III, amiodarone, any other drug with potential to significantly prolong the QT interval (i.e. astemizole, terfenadine, mizolastin, macrolides), all antidepressants (except pure SSRI's), anti-psychotics, monoamino-oxidase inhibitors, macrolides and other investigational drugs, mast cell stabilizers, leukotriene antagonists, Varenicline, live attenuated vaccine and intraarticular depot corticosteroids. Prohibited asthma-related medications included: long acting anticholinergics, short acting anticholinergics, fixed combinations of beta2 agonists and ICS, fixed combinations of SABA and short acting anticholinergics, LABAs, SABAs (other than study rescue medication), xanthines, parenteral or oral corticosteroids and intra-muscular depot corticosteroids.

#### **3.3.1.1.11 Ethical Aspects**

The trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki. Eligible patients were included in the study after providing written, IRB/IEC-approved informed consent or, if incapable of doing so, after such consent was provided by a legally acceptable representative of the patient.

#### **3.3.1.1.12 Data Analysis**

##### **Efficacy Variables**

Full details of the statistical analysis of this as well as the other 5 relevant trials will be reviewed by the biostatistician, Dr. Dongmei Liu. Briefly, there were four sets defined for analyses: the randomized set, the full analysis set (FAS), the per-protocol set (PPS) and the safety set. The primary analysis set for efficacy was the FAS and this included all randomized patients who received at least one dose of study drug. The safety set was used in the analysis of all safety variables. In addition, a subset of patients in the FAS with 24 hour serial spirometry was defined. The estimated treatment differences for all treatment comparisons were summarized along with the associated 95% confidence intervals (CIs) and two-sided p-values.

##### *Reviewer comment:*

*For the purposes of this review, only data from the FAS are presented in the efficacy summary.*

##### **Primary endpoint- tFEV1 Day 15**

The primary efficacy endpoint was "trough FEV1" (tFEV1) at Day 15 in the full analysis set (FAS), with trough being defined as the average of the 23 hour 10 minute and the 23 hour 45 minute values taken in the clinic on Day 15.

##### *Reviewer Comment:*

*The trough value characterizes the residual treatment effect prior to the next dose of drug.*

The primary variable with missing values imputed with last observation carried forward (LOCF) was analyzed using a mixed model for the FAS. The model included treatment as a fixed effect with the baseline FEV1 measurement (defined as the average of the FEV1 measurements taken in the clinic at 50 minutes and 15 min prior to first dose of study drug at Visit 3), FEV1 prior to inhalation and FEV1 within 30 minutes post inhalation of albuterol (components of SABA reversibility at Visit 2) all as covariates. The model also included asthma severity (mild persistent/moderate persistent/severe persistent) as a fixed effect and center as a random effect.

The sample size was based on the widths of the two-sided 95% confidence interval (CI) between any pair of treatments. A 95% CI of expected width 200 mL was considered by the sponsor an acceptable level of precision in this dose ranging study. Analysis from a previous indacaterol asthma dose ranging study QAB149A2216 suggested an appropriate standard deviation of trough FEV1 to assume was 320 mL. This led to an estimate of 79 evaluable patients per treatment group required to detect a 95% confidence

interval (two-sided) of expected width 200 mL wide, assuming a standard deviation of 320 mL. A drop out rate of 15% was assumed over 2 weeks of treatment; therefore, a sample size of 558 randomized patients or 93 per treatment group was required.

For the indacaterol and placebo treatment groups, if any of the 23 hour 10 minute and 23 hour 45 minute values contributing to the tFEV1 were collected within 6 hours of rescue medication or if actual measurement times were outside the 22-25 hour post-morning dose time window then the individual FEV1 value was set to missing. This was also done for the salmeterol treatment group. If one of the two values was missing (or set to missing) then the remaining non-missing value was taken as tFEV1. If both values were missing, or if the patient withdrew from the study, regardless of the reason for discontinuation, then tFEV1 was regarded as missing in which case the patient would not contribute to the primary analysis. Other secondary efficacy variables were summarized and analyzed using a similar model to that described for the primary efficacy variable for the FAS only and the estimated treatment difference for all treatment comparisons was displayed along with the associated 95% confidence intervals. In addition to the above, the exploratory efficacy variables were to explore the 24 hour (FEV1 and forced vital capacity (FVC)) profile of indacaterol (18.75, 37.5, 75 and 150 mcg QD), salmeterol and placebo after 14 days of treatment.

Several supportive analyses were conducted: A supportive analysis employing LOCF was performed for the PPS. In addition an analysis employing LOCF was repeated for the log transformed trough FEV1. This analysis was used to assess percentage change from baseline in tFEV1. And as well, a supportive analysis was conducted using a model-based approach to provide a quantitative characterization of the dose-response relationship after 14 days of treatment. This analysis was performed on the FAS and included trough FEV1 values obtained on Day 14 and Day 15. An Emax model was employed to characterize the dose-response relationship:

$$\text{Expected Trough FEV1} = E0 + \frac{Emax \times dose}{ED50 + dose}$$

*Reviewer Comment:*

*The approach of LOCF for missing (or set to missing) trough at Day 15 but not missing at Day 14 was applied as a change in planned analysis pre-database lock. Changes made post-database lock include:*

- 1. Due to the data observed the estimate of an indacaterol dose which yielded the same estimated increase in tFEV1 at Day 15 as treatment with salmeterol 50 mcg b.i.d., and the indacaterol dose which yielded an increase in tFEV1 of 0.2 L, was not possible. Therefore these values were dropped from the analysis outputs.*
- 2. Additional subgroup analyses by a) SABA reversibility (< 12%, 12 - < 15%, 15 - < 20% and ≥ 20%) and b) age group more appropriate to asthma (age < 40 years and ≥ 40 years) for tFEV1 at Day 15 were added to the analysis plan.*
- 3. Responder analyses in tFEV1 at Day 15 for both FAS and PPS were added to the analysis plan. Responders were defined as subjects who had an increase from baseline in tFEV1 of a) ≥ 12 % and ≥ 0.2 L, b) ≥ 15 % and ≥ 0.2 L c) ≥ 20 % and ≥ 0.2 L.*

*These changes were discussed with the Biostatistics team who felt overall, they did not change the conclusions.*

**Secondary endpoints- tFEV1 Day 2 and Day 14**

Trough FEV1 1 day post treatment and at Day 14 (after 13 days of treatment) was analyzed in the same manner and using the same mixed model as specified for trough at 2 weeks. Missing trough FEV1 were not imputed. For Day 2 trough FEV1 was defined as the average of the 23 hour 10 minute and the 23 hour 45 minute values taken in the clinic and for Day 14 as the average of the 50 minute and 15 minute pre-dose values taken at the clinic.

**Secondary endpoints- Peak FEV1 over 5mins-4hours**

Peak FEV1 was defined as the maximum FEV1 during the first 4 hours post morning dosing. It was calculated at Day 1 and Day 14 for all patients in the FAS. FEV1 measurements taken within 6 hours of rescue medication use were set to missing before the peak FEV1 was calculated. If FEV1 measurements were missing at 30 minutes and following time-points up to 4 hours, then the peak FEV1 was not calculated. A similar mixed model to that specified for the primary analysis was used at each visit.

**Secondary endpoints- AUC FEV1 5mins-4hours**

AUC FEV1 was calculated between 5 min and 4 h post morning dose at Day 1 and Day 14 as the sum of trapezoids divided by the length of time for all patients in the FAS. FEV1 measurements taken within 6 h of rescue use were set to missing before the AUC was calculated.

**Secondary endpoints- AUC for FEV1 5 mins – 11 hrs 45 mins**

The AUC for FEV1 will be calculated between 5 minutes and 11 hours 45 minutes post morning dose at Visit 3 (Day 1) and Visit 5 (Day 14). Calculation of AUC and statistical analyses were done in the same way as specified for AUC(5 minutes - 4 hours).

**Secondary endpoints- FEV1 and FVC at all other post-baseline time points**

FEV1 and FVC at each scheduled time-point (5, 15 and 30 minutes, 1, 2, 4, 8 hours, 11 hour 10 minutes, 11 hour 45 minutes, 14, 20, 22 hours, 23 hour 10 minutes and 23 hour 45 minutes after the dose taken at Day 14 (Visit 5)) was analyzed at each post-baseline time point at each visit using the same mixed model as specified for the primary analysis. Least squares means for FEV1 were displayed by treatment group. The estimated treatment difference along with the 95% confidence interval was also displayed.

**Secondary endpoints- AUC for FEV1 5 mins – 23 h 45 min and FEV1 11h 45 min – 23 h 45 min for serial spirometry subgroup**

The AUC for FEV1 was calculated between 5 min and 23 hour 45 min and between 11hour 45 min and 23 hour 45 min post morning dose at Visit 5 (Day 14) for the serial spirometry subgroup. Calculation of AUC and statistical analyses was performed in the same way as specified for AUC(5 min - 4 hour).

**Secondary endpoints- Daily rescue use (number of puffs) over 2 weeks**

The number of puffs of rescue medication taken in the previous 12 hr was recorded in the diary in the morning and evening. The mean change from baseline in the daily number of puffs of rescue medication was analyzed using a similar mixed model to that specified for the primary analysis.

**Secondary endpoints- Daytime and nighttime rescue medication use (number of puffs) over 2 weeks**

The total number of puffs of rescue used over the last 12 hr was recorded in the morning (nighttime use) and in the evening (daytime use) over the two weeks study duration was divided by the total number of days with non-missing rescue data (after imputation was applied) to derive the mean daytime and nighttime number of puffs of rescue medication. Diary data recorded during the 14 day run-in period were used to calculate the baseline values. Change from baseline in mean daytime and nighttime number of puffs of rescue medication was analyzed in the same way as change from baseline in mean daily number of puffs of rescue medication.

**Secondary endpoints- Percentage of days with no rescue use**

A 'day with no rescue use' was defined as any day where the patient did not use any puffs of rescue medication. The total number of 'days with no rescue use' over the 2 week treatment period was divided by the total number of days in order to derive the percentage of 'days with no rescue use'. The percentage of 'days with no rescue use' was summarized by treatment and analyzed using a mixed model similar to that specified for the primary analysis.

### ***Secondary endpoints- Morning and evening PEF over 2 weeks***

Morning and evening (pre-medication) PEF, as recorded in the diary, were averaged separately over the two week study duration for each patient. Diary data recorded during the 14 day run-in period was used to calculate the baseline. Change from baseline in the mean morning and evening PEF was analyzed using a similar mixed model to that specified for the primary analysis.

### **Safety Variables**

All safety data was summarized for the Safety set. The safety assessments included monitoring and recording all AEs, including asthma exacerbations, serious adverse events (SAEs), clinical laboratory (hematology, blood chemistry and urinalysis), and regular assessments of vital signs, physical examination and ECG as well as pregnancy. Asthma exacerbations were recorded on the asthma exacerbation episode eCRF and not on the adverse event eCRF. They were included in the summaries of AEs and additionally summarized separately from other AEs.

Asthma exacerbation was defined as:

- The use of  $\geq 8$  inhalations per day of SABA (90 mcg albuterol via MDI) on any 2 consecutive days from screening to randomization or
- New onset or worsening of respiratory symptoms that required change or increase in asthma related treatment (i.e., use of systemic corticosteroids) or
- Asthma-related hospitalization or emergency room visit that required medical intervention or change to regular treatment

Deaths were summarized by primary system organ class (SOC) and preferred term (PT), also adjusted for exposure. Summaries by primary SOC, high level term and PT were also presented for AEs and SAEs. The summary of all treatment emergent AEs (TEAEs) and of SAEs were repeated by age group. The number and percentage of patients with any asthma exacerbations, with asthma exacerbations requiring treatment with systemic glucocorticosteroids, with asthma exacerbations resulting in an emergency room visit and with asthma exacerbations meeting SAE criteria were displayed.

### ***Adverse Events***

Adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a serious adverse event) after the last inhalation were classified as a TEAE. Any AEs that started during the study but before the time of the first inhalation of study drug were classified as a prior adverse event and not summarized in tables, but only included in listings. The same procedure was followed for AEs which start more than 7 days (30 days in the case of a SAE) after last inhalation of study drug; these were classified as post treatment adverse events. Adverse events were also analyzed using Standard MedDRA queries (version 13.0), restricting to more specific “narrow” terms. The number and percentage of patients with each standardized MedDRA query (SMQ) level were presented for all TEAEs and hepatic disorders AEs. Additionally the number and percentage of patients with cardiac or cerebrovascular (CCV) SAEs were presented by MedDRA primary system organ class and preferred term.

### ***Laboratory Data***

All data were included regardless of rescue medication usage. Serum potassium and blood glucose were summarized by treatment and time-point at Days 1, 14, and 15. The baseline measurement was the measurement taken at 25 minutes pre-dose at Day 1. The maximum (blood glucose) and minimum (serum potassium) post first dosing (i.e. post baseline value) were summarized. Changes from baseline were also summarized by treatment. Summary statistics, standard descriptive statistics including changes from baseline, and shift tables of frequencies (n (%)) of patients relative to the normal ranges between baseline and post baseline time points and between baseline and worst post baseline values were performed. To evaluate potential drug-induced liver injury the numbers of patients with newly occurring or worsening elevations in liver function tests at any time post baseline were summarized. No interim analyses were performed.

### ***Vital Signs, Weight, ECG Data***

All vital signs, body weight and ECG data were included in the analysis regardless of rescue medication usage. All were also summarized with descriptive statistics. Vitals and ECG were also analyzed using a similar mixed model as for the primary analysis.

### **3.3.1.2 Patient Disposition and Demographics**

#### **Disposition**

There were a total of 1200 screening visits, and interestingly, despite planned enrollment, only 511 patients were randomized. A total of 502 (98.2%) patients were exposed to study drug, 500 (97.8%) were included in the FAS and 483 completed the trial as planned. See Table 6. The 511 patients were randomized in a ratio of 1:1:1:1:1 to the following treatment groups: 85 in indacaterol 18.75 mcg; 85 in indacaterol 37.5 mcg; 84 in indacaterol 75 mcg; 86 in indacaterol 150 mcg; 86 in Salmeterol 50 mcg bid; and 85 in placebo. Refer to Table 6 for further details. Overall, 384 patients (75.1%) were included in the PPS. The FAS, including the subset of patients who participated in the 24-hour serial spirometry subgroup, included 279 patients (54.6%). Eleven patients were excluded from the FAS: two were randomized to treatment more than once and the remaining 9 patients were randomized to treatment but discontinued before any study treatment was administered.

**Table 6 Protocol B2357 Patient Disposition**

	Ind 18.75 µg n (%)	Ind 37.5 µg n (%)	Ind 75 µg n (%)	Ind 150 µg n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Screening visits	-	-	-	-	-	-	1200
<b>Patients</b>							
Randomized	85 (100.0)	85 (100.0)	84 (100.0)	86 (100.0)	86 (100.0)	85 (100.0)	511 (100.0)
Exposed	84 (98.8)	81 (95.3)	84 (100.0)	85 (98.8)	84 (97.7)	84 (98.8)	502 (98.2)
Completed	83 (97.6)	78 (91.8)	83 (98.8)	81 (94.2)	78 (90.7)	80 (94.1)	483 (94.5)
Discontinued	2 (2.4)	7 (8.2)	1 (1.2)	5 (5.8)	8 (9.3)	5 (5.9)	28 (5.5)
<b>Primary reason for premature discontinuation</b>							
Adverse event(s)	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)	5 (5.8)	1 (1.2)	9 (1.8)
Administrative problems	1 (1.2)	3 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	5 (1.0)
Subject withdrew consent	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	3 (3.5)	5 (1.0)
Protocol deviation	0 (0.0)	2 (2.4)	1 (1.2)	2 (2.3)	0 (0.0)	0 (0.0)	5 (1.0)
Abnormal test procedure results(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	2 (0.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)

Patients who have screen failed and re-screened under a new patient number will be counted twice in the number of screening visits.

Source: Table 10-1 Study No. CQAB149B2357 Clinical Study Report

The largest percentage of patients discontinued from the salmeterol group (9.3%) and the indacaterol 37.5 mcg (8.2%) groups. The most common reason for discontinuation was AE(s) (1.8%), followed by administrative problems and withdrawal of subject's consent and protocol deviation (1.0% each). The majority of the patients who discontinued due to AE(s) were in the salmeterol treatment group (i.e. 5.8% patients). No patient discontinued from the indacaterol 75 mcg treatment group due to AEs.

#### **Protocol Deviation**

A total of 116 patients (23.2%) in the FAS had at least one major protocol deviation leading to their exclusion from the PPS. The proportion of patients with a protocol deviation leading to exclusion from the PPS ranged from 18.8% of patients in the indacaterol 37.5 mcg treatment group to 28.2% of patients in the indacaterol 150 mcg treatment group. Overall, the most common major protocol deviations leading to

exclusion from the PPS were: postbronchodilator FEV1 < 12% or < 200 mL of the pre-bronchodilator value at screening (5.0% across the 6 treatment groups), non compliance with the morning Dosing of study medication scheduled at the primary endpoint dosing visit (4.0% across the 6 treatment groups), patients not taking inhaled ICS ≥ 1 month pre-screening (3.8% across the 6 treatment groups) and < 80% of study medication doses taken prior to the primary endpoint visit (3.4%).

Four major protocol deviations, reported in 3 patients before the trial database was locked, were retracted by the investigative sites. The sites provided additional information to the sponsor after database lock in order to remove these protocol deviations. Therefore, these patients should have been included in the per protocol (PP) analysis (B2357-0567-00017 [Placebo], B2357-0567-00008 [Indacaterol 75 mcg], and B2357-0578-00014 [Indacaterol 75 mcg]).

### Demographics

While the mean age of the patients with COPD in Study B2356 was 63, the demographics for those with asthma is very different as evidenced by the mean age of 41 years with a range of 18-82 years. Table 7 below summarizes key demographics across treatment groups. There were similar proportions in the 18 – 39 year age range and the 40 – 64 year age range. The majority of the patients were caucasian (78.9%); however, more than half (55.4%) were female.

**Table 7 Protocol 2357 Demographic Summary (Safety Set)**

		Ind 18.75 µg N = 84	Ind 37.5 µg N = 81	Ind 75 µg N = 84	Ind 150 µg N = 85	Salm N = 84	Pbo N = 84	Total N = 502
Age (years)	n	84	81	84	85	84	84	502
	Mean	42.0	41.9	40.2	41.0	40.9	40.6	41.1
	SD	14.64	14.96	14.71	15.20	14.56	14.17	14.65
	Median	43.5	42.0	38.5	42.0	41.0	41.0	41.0
	Min - Max	18 - 74	19 - 74	18 - 77	18 - 82	18 - 75	18 - 70	18 - 82
Age group – n (%)	18 – 39 years	38 (45.2)	34 (42.0)	45 (53.6)	39 (45.9)	39 (46.4)	38 (45.2)	233 (46.4)
	40 – 64 years	41 (48.8)	39 (48.1)	35 (41.7)	42 (49.4)	39 (46.4)	42 (50.0)	238 (47.4)
	65-74 years	5 (6.0)	8 (9.9)	3 (3.6)	3 (3.5)	5 (6.0)	4 (4.8)	28 (5.6)
	≥75 years	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	1 (1.2)	0 (0.0)	3 (0.6)
Sex – n (%)	Male	42 (50.0)	35 (43.2)	35 (41.7)	30 (35.3)	38 (45.2)	44 (52.4)	224 (44.6)
	Female	42 (50.0)	46 (56.8)	49 (58.3)	55 (64.7)	46 (54.8)	40 (47.6)	278 (55.4)
Race – n (%)	Caucasian	68 (81.0)	63 (77.8)	63 (75.0)	69 (81.2)	65 (77.4)	68 (81.0)	396 (78.9)
	Black	13 (15.5)	14 (17.3)	17 (20.2)	11 (12.9)	19 (22.6)	12 (14.3)	86 (17.1)
	Asian	2 (2.4)	0 (0.0)	1 (1.2)	3 (3.5)	0 (0.0)	1 (1.2)	7 (1.4)
	Pacific Islander	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	1 (1.2)	3 (3.7)	3 (3.6)	2 (2.4)	0 (0.0)	3 (3.6)	12 (2.4)
Weight (kg)	n	84	81	84	85	84	84	502
	Mean	81.0	84.5	83.2	80.0	82.2	83.9	82.5
	SD	17.25	17.71	18.94	17.22	18.60	18.23	17.98
	Median	81.1	82.1	83.0	79.4	83.7	82.7	82.0
	Min - Max	45.5-124.1	45.9-131.5	44.4-125.0	46.7-112.0	44.0-128.0	40.0-139.5	40.0 - 139.5
BMI (kg/m²)	n	84	81	84	85	84	84	502
	Mean	28.1	29.5	28.9	28.2	28.2	28.7	28.6
	SD	5.46	5.47	5.75	5.94	5.62	5.24	5.58
	Median	27.5	29.1	28.0	26.9	27.5	28.6	27.8
	Min - Max	17.8 - 39.8	20.1 - 46.7	16.7 - 41.6	17.5 - 42.9	18.3 - 39.5	16.6 - 39.9	16.6 - 46.7

Source: Adapted from Table 11-2 Study No. CQAB149B2357 Clinical Study Report

Baseline disease characteristics overall were similar across the treatment groups, see Table 8 below. The population represented patients with a significant history of disease burden and distribution of severity. All



patients had persistent asthma as defined in GINA guidelines (updated 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 (308 patients, 61.4%) had asthma for more than 20 years. All 502 (100%) patients were using ICS at baseline.

Across all treatment groups, the majority of the patients had never smoked (79.7%), 17.7% were ex-smokers and the remainder were current smokers (2.6%). The number of pack years ( $\pm$  SD) was 3.6 ( $\pm$  2.58) and ranged from 1.0 to 10.0, refer to Table 8. The screening spirometric measurements were comparable across the treatment groups. At Visit 2, the mean percentage of predicted FEV1 before SABA bronchodilation ranged from 68.9% to 71.4% across the treatment groups. The mean percentage of predicted FEV1 after SABA bronchodilation ranged from 83.7% to 86.9%. Overall, the mean FEV1/FVC ratio after bronchodilation was 71.3%. The mean percentage increase in FEV1 after SABA bronchodilator was 22.4%. Baseline values were comparable across the six treatment groups. The mean FEV1 for all patients was 2.36 L and mean FVC was 3.55 L.

**Table 8 Protocol B2357 Disease Characteristics at Screening (Safety Set)**

		Ind 18.75 mcg N=84	Ind 37.5 mcg N=81	Ind 75 mcg N=84	Ind 150 mcg N=85	Salm N=84	Placebo N=84
Asthma Duration (years) n (%)	<10 years	7	8	8	12	10	7
	10-20 years	20	19	22	30	24	27
	>20 years	57	54	54	43	50	50
Asthma Severity (years) n (%)	Mild persistent	19	20	22	21	21	20
	Moderate persistent	59	55	56	58	57	58
	Severe persistent	6	6	6	6	6	6
Smoking History n (%)	Never smoker	63	70	67	68	67	65
	Ex-smoker	19	8	15	17	13	17
	Current smoker	2	3	2	0	4	2

Source: Adapted from Table 11-3 Study No. CQAB1492357 Clinical Study Report

### 3.3.1.3 Efficacy Review

#### 3.3.1.3.1 Primary Endpoint

The primary efficacy variable was tFEV1 at Day 15 which is presented as LS mean and estimated treatment differences in Table 9. The efficacy analysis of the FAS included 500 of the 511 randomized patients (97.8%). Two patients were excluded from the FAS as they were randomized to treatment more than once and the remaining 9 patients were randomized to a treatment group and discontinued before any study treatment was administered. The most common reason for discontinuation was AEs (1.8%), followed by administrative problems, withdrawal of patient's consent and protocol deviation (1% each). None of the treatment differences between an active treatment group and the placebo group reached the pre-specified minimal clinically important difference (MCID) of 0.20 L for asthma. The table below summarizes the treatment group comparisons for the primary efficacy endpoint, tFEV1 Day 15.

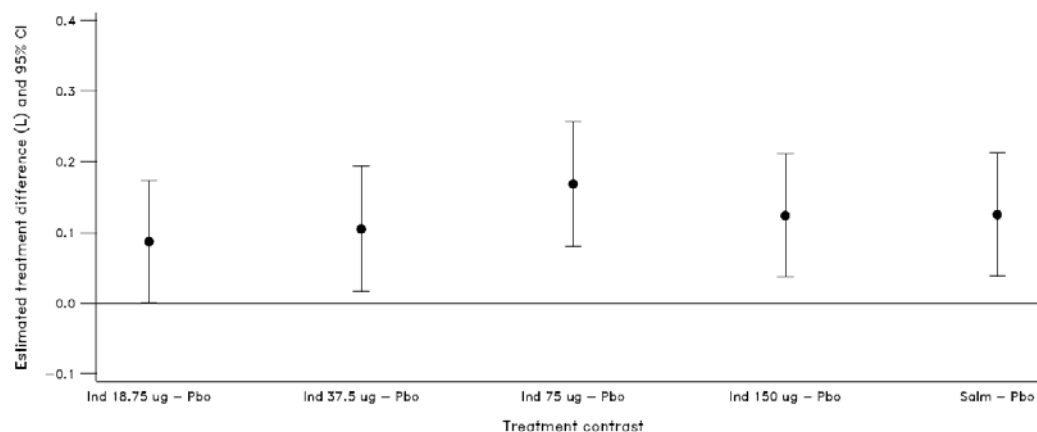
**Table 9 Protocol B2357 Trough FEV1 at Day 15: treatment comparisons (FAS, imputed with LOCF)**

	----- Treatment -----				----- Treatment difference ----			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Full analysis set								
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)	<.001*
Ind 150 µg	80	2.54	0.037	Ind 150 µg - Pbo	0.12	0.045	(0.04, 0.21)	0.006*
Salm µg	78	2.54	0.037	Salm - Pbo	0.13	0.045	(0.04, 0.21)	0.005*
Pbo	81	2.42	0.036					

Source: Adapted from Table 11-5 Study No. CQAB149B2357 Clinical Study Report

All treatment groups on this variable were superior to placebo with the greatest treatment difference in LS mean tFEV1 Day 15 was observed in the indacaterol 75 mcg treatment group (0.17L),  $p < 0.001$  as depicted in the graph below. However, the 150 mcg dose was not superior to the active comparator, Salmeterol 50 mcg bid.

**Figure 1 Protocol B2357 Estimated treatment differences and associated 95% CI of tFEV1 Day 15 (FAS, imputed with LOCF)**



Source: Figure 14.2-1.2 Study no CQAB149B2357 Clinical Study Report

Analysis of the subgroups reveal most patients were caucasian (n=396) versus black (n= 86), asian (n= 7), Pacific Islander (n= 1), or other (n= 12). Most had moderate asthma severity (n= 343) versus mild persistent (n= 123) or severe persistent (n=36). Most never smoked (n=65) versus ex-smoker (n=17) or current smoker (n= 2). Age and gender were generally evenly distributed. Regarding those factors that were unevenly distributed, such as race, it is difficult to comment on the generalizability of any clinically relevant treatment differences. However, some of the key subgroup analyses included the treatment differences found between the three doses of 37.5, 75 and 150 mcg indacaterol amongst mild, moderate and severe asthmatics; never smokers, ex-smokers and current smokers and SABA reversibility. See Table 10.

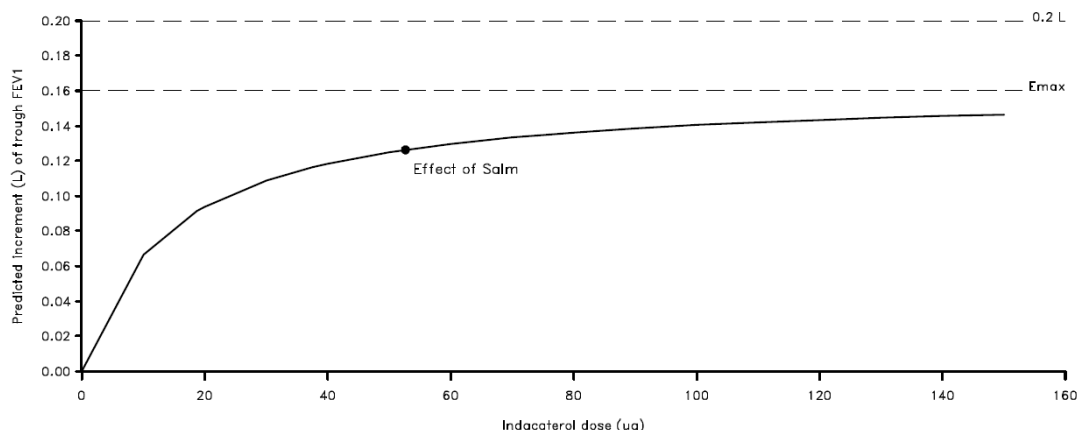
**Table 10 Protocol B2357 Select subgroup analysis of trough FEV1 at Day 15 (imputed with LOCF, FAS)**

		LS mean of treatment differences (n)							
Indacaterol dose		37.5 mcg (n)	p-value	75 mcg (n)	p-value	150 mcg (n)	p-value	Salmeterol (n)	p-value
Severity of asthma	Mild	0.06 (19)	0.482	0.17 (21)	0.054	0.10 (20)	0.29	0.12 (19)	0.177
	Moderate	0.13 (52)	0.022	0.17 (55)	0.002	0.13 (54)	0.018	0.11 (53)	0.042
	Severe	0.06 (6)	0.707	0.16 (6)	0.337	0.19 (6)	0.264	0.27 (6)	0.105
Smoking status	Never smoker	0.09 (67)	0.069	0.18 (65)	<0.001	0.13 (64)	0.009	0.16 (61)	0.002
	Ex-smoker	0.24 (8)	0.053	0.17 (15)	0.097	0.09 (16)	0.367	0.01 (13)	0.934
	Current smoker	0.10 (2)	0.739	-0.09 (2)	0.753	N/A	N/A	0.04 (4)	0.879
SABA reversibility	<12%	0.09 (2)	0.733	0.14 (2)	0.588	0.07 (7)	0.733	0.11 (4)	0.615
	12- <15%	0.12 (20)	0.186	0.15 (17)	0.099	0.13 (16)	0.169	0.11 (19)	0.237
	15- <20%	0.04 (19)	0.620	0.16 (24)	0.059	0.07 (24)	0.374	0.15 (17)	0.100
	> 20%	0.13 (36)	0.077	0.19 (39)	0.006	0.15 (33)	0.031	0.14 (38)	0.044

Source: Table 14.2-1.1 Study no CQAB149B2357 Clinical Study Report

The findings of the Emax model were not supported by the actual data, for example, the largest treatment difference in tFEV1 Day 15 was observed with 150 mcg indacaterol at 0.15 (0.08, 0.24) followed by both indacaterol 75 mcg and salmeterol both at 0.13, refer to. However, results from the trial depict 75 mcg indacaterol exhibiting the largest treatment difference of 0.17 (0.08, 0.26) followed by salmeterol (0.13) and 150 mcg indacaterol (0.12). Refer to Figure 2.

**Figure 2 Protocol B2357 Estimated dose response curve (Emax model) for increase in tFEV1 on Day 15 (imputed LOCF, FAS)**



Source: Figure 14.2-2.1 Study No. CQAB149B2357 Clinical Study Report

Three responder groups were defined post-database lock:

- subjects with an increase in tFEV1 from baseline to day 15 of  $\geq 12\%$  and 200 mL (called the 12% group)
- those with a  $\geq 15\%$  and 200 mL increase (15% group)
- those with an increase of  $\geq 20\%$  and 200 mL (20% group)

The results for the FAS for the 3 groups defined above are given in Table 11. The odds ratios generated were for comparisons of treatment drug with placebo. The highest odds of response were seen in the 75 mcg indacaterol group across the subgroups.

**Table 11 Protocol B2357 Responder analysis of trough FEV1 at Day 15**

	Response by increase from baseline in trough FEV1, n (%), odds ratio, p-value								
	$\geq 12\%$ , 200 mL			$\geq 15\%$ , 200 mL			$\geq 20\%$ , 200 mL		
Indacaterol dose (N)	n (%)	OR	p-value	n (%)	OR	p-value	n (%)	OR	p-value
18.75 mcg (82)	23 (28%)	1.49	0.323	15 (18.3%)	1.07	0.893	11 (13.4%)	6.25	0.002
37.5 mcg (77)	20 (26%)	1.48	0.343	15 (19.5%)	1.24	0.649	7 (9.1%)	3.79	0.033
75 mcg (82)	30 (36.6%)	2.64	0.016	22 (26.8%)	1.88	0.168	15 (18.3)	9.86	< 0.001
150 mcg (80)	24 (30%)	2.09	0.071	18 (22.5%)	1.94	0.159	12 (15%)	8.94	< 0.001
Salmeterol (78)	25 (32.1%)	2.16	0.056	16 (20.5%)	1.29	0.596	12 (15.4%)	6.77	0.002
Placebo (81)	17 (21%)	N/A	N/A	14 (17.3%)	N/A	N/A	4 (4.9%)	N/A	N/A

Source: Table 14.2-1.6 Study No. CQAB149B2357 Clinical Study Report

Odds ratio comparison with placebo

n= the number of patients with a response, N= the number of patients included in the analysis

The highest odds of response in the FAS were achieved in the indacaterol 75 mcg (odds ratio [OR] = 2.64 (12%), OR = 1.88 (15%)) and indacaterol 150 mcg (OR = 2.09 (12%), OR = 1.94 (15%)) treatment groups. In the majority of cases the treatment effects in the indacaterol 75 mcg and 150 mcg treatment groups were similar to the salmeterol group. The smallest treatment differences from placebo were

observed in the indacaterol 18.75 and 37.5 mcg treatment groups. The 20% group had few subjects meeting this definition in the placebo group and this makes the results difficult to interpret.

### 3.3.1.3.2 Secondary Endpoints

#### tFEV1 Day2 and Day 14

The dose with the largest treatment difference in tFEV1 after 1 day of treatment (Day 2) was observed with salmeterol with the LS mean of 0.21 (0.14, 0.27) and for indacaterol it was the 150 mcg dose with 0.16 L (0.09, 0.22). However, a different profile was observed after 13 days of treatment (Day 14) where the largest treatment difference was observed with the 75 mcg dose, 0.17 L (0.08, 0.26) while salmeterol and the 150 mcg indacaterol dose were 0.13 (0.05, 0.22). Again, none of the treatment differences between an active treatment group (i.e. indacaterol or salmeterol) and the placebo group achieved the pre-defined MCID set by the sponsor of 0.20 L for asthma. See Table 12 for summary.

#### Reviewer Comment:

*The 150 mcg dose does not appear to offer benefit over the 75 mcg dose at Day 14 or 15, although a difference is shown on Day 1. Since FEV1 profiles for indacaterol show that 14 days is required for steady state, this suggests that the 150 mcg dose is already on the flat portion of the dosage curve.*

**Table 12 Protocol B2357 Analysis of tFEV1 (L) at Day2 and Day 14 (FAS)**

Treatment	n	--- Treatment ---		Comparison	---- Treatment difference ----			
		LS Mean	SE		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)	<.001
Salm	79	2.65	0.027	Salm - Pbo	0.21	0.034	(0.14, 0.27)	<.001
Pbo	80	2.45	0.027					
Day 14								
Ind 18.75 µg	72	2.51	0.034	Ind 18.75 µg - Pbo	0.10	0.044	(0.02, 0.19)	0.019
Ind 37.5 µg	70	2.51	0.034	Ind 37.5 µg - Pbo	0.10	0.045	(0.02, 0.19)	0.020
Ind 75 µg	69	2.57	0.035	Ind 75 µg - Pbo	0.17	0.045	(0.08, 0.26)	<.001
Ind 150 µg	68	2.54	0.035	Ind 150 µg - Pbo	0.13	0.045	(0.05, 0.22)	0.003
Salm	67	2.54	0.035	Salm - Pbo	0.13	0.045	(0.05, 0.22)	0.003
Pbo	64	2.41	0.035					

Source: Table 11-9 Study No. CQAB149B2357 Clinical Study Report

#### Peak FEV1

At Day1, the greatest treatment difference between the indacaterol groups and the placebo group was observed in the indacaterol 150 mcg treatment group (0.15 L) and was smaller than the treatment difference observed between the salmeterol treatment group and the placebo group (0.23 L). At Day 14, the greatest treatment difference was observed in the 75 mcg indacaterol group. The treatment differences at Day 14 for indacaterol 75, 150 mcg and salmeterol compared to placebo were as follows: 0.23 (95% CI 0.15, 0.30), 0.20 (95% CI 0.13, 0.27) and 0.22 (95% CI 0.15, 0.30).

#### AUC FEV1 5 minutes-4 hours

The results observed for the standardized FEV1 AUC<sub>(5min-4h)</sub> (Table 13) were very similar to those seen for peak FEV1. The LS mean FEV1 AUC<sub>(5min-4h)</sub> at Day 1 was significantly greater in all indacaterol treatments groups than in the placebo group. The greatest treatment difference at Day1 was observed with salmeterol treatment group 0.26 (0.22, 0.31) followed by indacaterol 150 mcg dose with 0.18 (0.14, 0.23) and indacaterol 75 mcg dose 0.15 (0.10, 0.20). Consistent with the previous patterns, on Day 14,

the greatest difference was observed with the indacaterol 75 mcg dose 0.26 (0.19, 0.33) with both salmeterol and indacaterol 150 mcg dose both at 0.24 (0.17, 0.31).

**AUC FEV<sub>1</sub>** *5 minutes-11 hours 45 minutes*

The results observed for the standardized FEV<sub>1</sub> AUC<sub>(5min-11h45min)</sub> were very similar to those for standardized FEV<sub>1</sub> AUC<sub>(5min-4h)</sub> (Table 11). At Day 1, there was a dose response between the indacaterol treatment groups (37.5 mcg up to 150 mcg) for the LS mean FEV<sub>1</sub> AUC<sub>(5min-11h45min)</sub>. The LS mean FEV<sub>1</sub> AUC<sub>(5min-11h45min)</sub> at Day1 was greater in all indacaterol treatments groups than in the placebo group. The greatest treatment difference was observed for salmeterol at 0.23 L (0.18, 0.29) followed by indacaterol 150 mcg dose 0.18 (0.13, 0.23) and indacaterol 75 mcg dose 0.14 (0.09, 0.20). Again, at Day 14, the treatment differences in LS mean FEV<sub>1</sub> AUC<sub>(5min-11h45min)</sub> compared with the placebo group were greatest in the indacaterol 75 mcg dose 0.22 (0.15, 0.30) followed by salmeterol 0.21 (0.14, 0.28) and indacaterol 150 mcg 0.19 (0.11, 0.26).

**Table 13 Protocol B2357 Analysis of secondary endpoints**

	Treatment difference LS mean in Liters (95% CI)				
	Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salmeterol
Peak FEV1 Day 1	0.04 (-0.01, 0.09)	0.04 (-0.01, 0.09)	0.12 (0.07, 0.17)	0.15 (0.10, 0.20)	0.23 (0.18, 0.28)
Peak FEV1 Day 14	0.12 (0.05, 0.20)	0.14 (0.06, 0.21)	0.23 (0.15, 0.30)	0.20 (0.13, 0.27)	0.22 (0.15, 0.30)
AUC FEV1 <sub>5 min- 4hr</sub> Day 1	0.07 (0.02, 0.11)	0.07 (0.02, 0.12)	0.15 (0.10, 0.20)	0.18 (0.14, 0.23)	0.26 (0.22, 0.31)
AUC FEV1 <sub>5 min- 4 hr</sub> Day14	0.15 (0.08, 0.22)	0.17 (0.10, 0.24)	0.26 (0.19, 0.33)	0.24 (0.17, 0.31)	0.24 (0.17, 0.31)
AUC FEV1 <sub>5 min- 12 hr</sub> Day 1	0.06 (0.01, 0.12)	0.06 (0.00, 0.11)	0.14 (0.09, 0.20)	0.18 (0.13, 0.23)	0.23 (0.18, 0.29)
AUC FEV1 <sub>5 min- 12 hr</sub> Day 14	0.11 (0.04, 0.18)	0.14 (0.07, 0.21)	0.22 (0.15, 0.30)	0.19 (0.11, 0.26)	0.21 (0.14, 0.28)

Source: Adapted from Tables 11-10, 11-11, 11-12 Study No. CQAB149B2357 Clinical Study Report

#### **FEV1 and FVC**

Analysis of FEV1 at the following serial time points was conducted: 5, 15, 30 min, 1, 2, 4, 8 hours, 11 hr 10 min, 11 hr 45 min, 23 hr 10 min, 23 hr 45 min. Select values are represented in Table 14 below. Evidence of a dose response relationship was observed with increasing doses as demonstrated in the table below. At the 5 minute time-point on Day 1, the magnitude of the improvements in FEV1 compared with baseline were 0.15 L in the indacaterol 150 mcg treatment group, 0.11 L in the indacaterol 75 mcg treatment group, 0.08 L in the indacaterol 37.5 mcg treatment group and 0.06 L in the indacaterol 18.75 mcg treatment group. These results are consistent with a dose response effect at the early time points measured. As well, the treatment difference for 75 mcg indacaterol at 5 minutes represents 79% of the difference seen at 4 hours, by which time C<sub>max</sub> has been achieved. At 5 minutes, the 150 mcg dose represents 83% of the treatment difference seen at 4 hours. For FVC, overall, a dose response relationship was also evident and the maximum value was reached by 4 hours.

**Table 14 Protocol B2357 Serial FEV1 (FAS)**

	Treatment difference (L) from placebo (95% CI) at Day 1, (FAS)					
	5 min	p-value	4 hr	p-value	8 hr	p-value
Ind 18.75 mcg	0.06 (0.01, 0.11)	0.011	0.05 (0.00, 0.11)	0.071	0.07 (0.01, 0.14)	0.026
Ind 37.5 mcg	0.08 (0.03, 0.12)	0.002	0.05 (-0.11, 0.11)	0.112	0.08 (0.01, 0.14)	0.022
Ind 75 mcg	0.11 (0.06, 0.16)	< 0.001	0.14 (0.08, 0.20)	< 0.001	0.14 (0.07, 0.20)	< 0.001
Ind150 mcg	0.15 (0.10, 0.19)	< 0.001	0.18 (0.12, 0.24)	< 0.001	0.19 (0.12, 0.25)	< 0.001
Salmeterol	0.10 (0.06, 0.15)	< 0.001	0.27 (0.21, 0.33)	< 0.001	0.20 (0.13, 0.26)	< 0.001

Source: Table 14.2-5.1 Study No. CQAB149B2357 Clinical Study Report

**Reviewer Comment:**

*In the proposed label, there is language describing the rapid onset of action at 5 minutes for indacaterol which appears to be supported by this data.*

**Patient Diary Data**

➤ **Use of rescue medication over 2 weeks**

Indacaterol at all doses showed a statistically significant benefit in the mean daily number of puffs, the mean daytime and nighttime number of puffs and the percentage of days with no rescue medication use. Refer to Table 15.

**Table 15 Protocol B2357 Rescue medication use over 14 days: treatment comparisons (FAS)**

Treatment	n	-- Treatment --		Comparison	----- Treatment difference -----			p-value
		LSM	SE		LSM	SE	95% CI	
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 18.75 µg	84	-1.12	0.120	Ind 18.75 µg - Pbo	-0.49	0.155	(-0.79, -0.18)	0.002
Ind 37.5 µg	77	-1.33	0.124	Ind 37.5 µg - Pbo	-0.70	0.159	(-1.01, -0.38)	<.001
Ind 75 µg	82	-1.34	0.120	Ind 75 µg - Pbo	-0.71	0.156	(-1.01, -0.40)	<.001
Ind 150 µg	84	-1.23	0.119	Ind 150 µg - Pbo	-0.59	0.155	(-0.89, -0.29)	<.001
Salm	81	-1.18	0.121	Salm - Pbo	-0.55	0.156	(-0.85, -0.24)	<.001
Pbo	82	-0.64	0.121					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 18.75 µg	83	-0.71	0.068	Ind 18.75 µg - Pbo	-0.29	0.089	(-0.46, -0.11)	0.001
Ind 37.5 µg	77	-0.81	0.070	Ind 37.5 µg - Pbo	-0.39	0.091	(-0.57, -0.21)	<.001
Ind 75 µg	82	-0.76	0.068	Ind 75 µg - Pbo	-0.34	0.089	(-0.52, -0.17)	<.001
Ind 150 µg	83	-0.76	0.068	Ind 150 µg - Pbo	-0.33	0.089	(-0.51, -0.16)	<.001
Salm	79	-0.68	0.069	Salm - Pbo	-0.26	0.089	(-0.43, -0.08)	0.004
Pbo	81	-0.42	0.069					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 18.75 µg	83	-0.43	0.060	Ind 18.75 µg - Pbo	-0.20	0.078	(-0.35, -0.05)	0.011
Ind 37.5 µg	77	-0.54	0.062	Ind 37.5 µg - Pbo	-0.31	0.080	(-0.47, -0.15)	<.001
Ind 75 µg	82	-0.59	0.060	Ind 75 µg - Pbo	-0.36	0.079	(-0.52, -0.21)	<.001
Ind 150 µg	84	-0.48	0.060	Ind 150 µg - Pbo	-0.25	0.078	(-0.40, -0.10)	0.001
Salm	80	-0.53	0.061	Salm - Pbo	-0.30	0.079	(-0.45, -0.14)	<.001
Pbo	82	-0.23	0.061					
Percentage of "days with no rescue use"								
Ind 18.75 µg	82	68.60	3.302	Ind 18.75 µg - Pbo	14.70	4.149	(6.5, 22.8)	<.001
Ind 37.5 µg	76	73.81	3.367	Ind 37.5 µg - Pbo	19.90	4.252	(11.5, 28.2)	<.001
Ind 75 µg	82	69.39	3.269	Ind 75 µg - Pbo	15.50	4.177	(7.3, 23.7)	<.001
Ind 150 µg	83	69.44	3.254	Ind 150 µg - Pbo	15.50	4.139	(7.4, 23.6)	<.001
Salm	78	70.04	3.327	Salm - Pbo	16.10	4.183	(7.9, 24.3)	<.001
Pbo	81	53.93	3.299					

Source: Table 11-13 Study No. CQAB149B2357 Clinical Study Report

➤ **Asthma symptoms**

The percentage of "days with no daytime asthma symptoms" during the 14 days of treatment was reduced in all treatment groups when compared to baseline. The reduction was numerically greater in the active treatment groups than in the placebo group, but the difference was not statistically significant. The mean change from baseline in percentage of days was -24.8 in the indacaterol 18.75 mcg treatment group, -26.7 in the indacaterol 37.5 mcg treatment group, -22.3 in the indacaterol 75 mcg treatment group, -23.3 in the indacaterol 150 mcg treatment group, -23.0 in the salmeterol treatment group and -



13.5 in the placebo group. Similar results were observed for “days with no nighttime asthma symptoms” with the following values: -15.4, -16.6, -13.0, -12.7, -15.9 and -8.2 respectively.

#### ➤ **Peak expiratory flow (PEF) over 2 weeks**

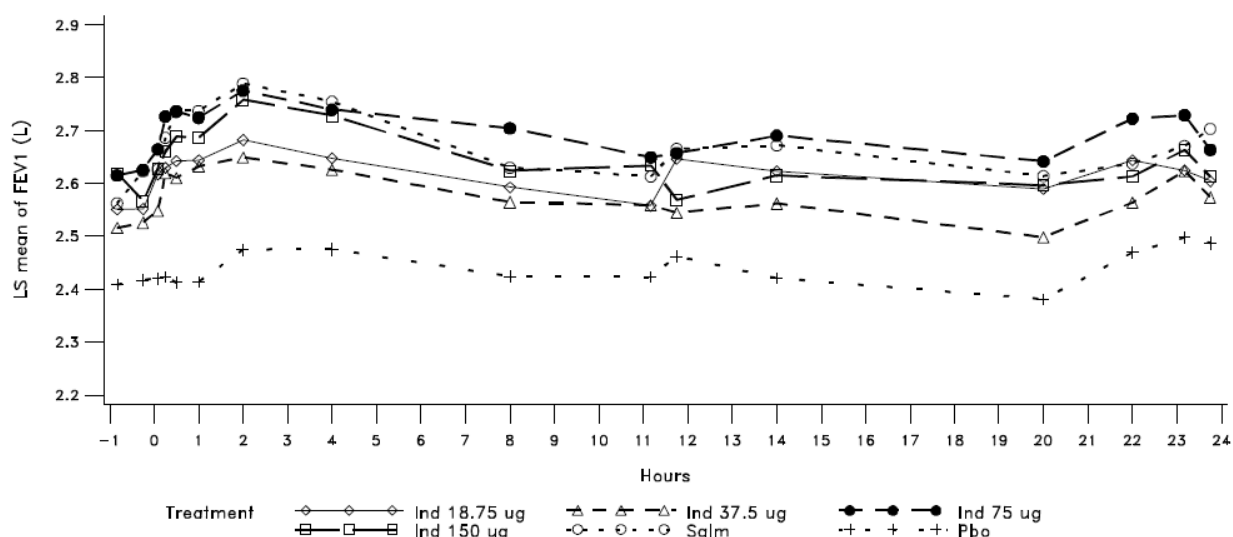
In all indacaterol and salmeterol treatment groups, an increase from baseline in morning and evening PEF was observed compared with the placebo group. All active treatment groups were statistically significantly greater than placebo.

### **Exploratory efficacy results**

#### ➤ **FEV1 and FVC by time-point analyses**

The protocol included exploratory objectives which were to evaluate the 24-hour (FEV1 and forced vital capacity [FVC]) profile of indacaterol (18.75, 37.5, 75, and 150 mcg q.d.), salmeterol and placebo after 14 days of treatment. At each Day 14/15 time-point of the 24 hour FEV1 profile the LS mean FEV1 was greater in all active treatment groups than in the placebo group, see Figure 3. At the majority of time-points, the LS mean FEV1 was similar in the indacaterol 75, 150 mcg and salmeterol treatments groups and smaller in the indacaterol 18.75 mcg and 37.5 mcg treatment groups.

**Figure 3 Protocol B2357 24 hour profile of least squares means of FEV1 (L) after 14 days treatment (FAS)**



Source: Figure 14.2-3.1 Study No. CQAB149B2357 Clinical Study Report

#### ➤ **Standardized (with respect to time) AUC FEV1**

At Day 14/15 the LS mean AUC<sub>(5min-23hr 45min)</sub> FEV1 and FEV1 AUC<sub>(11hr 45min-23hr 45min)</sub> were greater in all active treatment groups (i.e. indacaterol and salmeterol) than in the placebo group. For both spirometry assessments, the FEV1 AUC<sub>(5min-23hr 45min)</sub> and FEV1 AUC<sub>(11hr 45min-23hr 45min)</sub>, the indacaterol 75 mcg treatment group had the greatest magnitude of treatment difference (0.27 L for both). The smallest treatment differences compared with the placebo group were observed in the indacaterol 18.75 and 37.5 mcg treatment groups (0.19 L and 0.15 L, respectively).

### **3.3.1.4 Safety Results**

#### **3.3.1.4.1 Extent of exposure**

All treatment groups had similar exposure to indacaterol with a median of 15 days and a range of 1 to 28 days. Compliance with the Concept1 SDDPI device, assessed as the percentage of doses taken over the whole treatment period, was consistently high across all treatment groups (mean 98.5 - 102.3%).

#### **3.3.1.4.2 Concomitant medication**

Concomitant medications and significant non-drug therapies (asthma-related and non asthma-related) were taken by more than 70% of patients in any treatment group in the safety set. All patients in the salmeterol and placebo groups and most patients (98.8% to 100%) in the indacaterol treatment groups were taking asthma-related concomitant therapy, mostly as inhaled formulations. The most frequently used medications were the corticosteroids. Non asthma-related concomitant medications and significant non-drug therapies were used by 73.8% to 83.5% of all patients in the indacaterol groups and by 78.6% and 81.0% in the salmeterol and placebo group, respectively. Most frequent was the use of ibuprofen, loratadine, mometasone furoate, paracetamol and multivitamins.

### 3.3.1.4.3 Adverse events

Details regarding AEs will be included in the ISS, however a brief summary will be mentioned here. The overall incidence of AEs was higher in the indacaterol 75 mcg treatment group (26.2%), compared with the indacaterol 37.5 mcg treatment group (22.2%) and the salmeterol treatment group (21.4%). Respiratory, thoracic and mediastinal disorders were the most commonly affected system organ classes (SOC) followed by nervous system disorders and infections and infestations. The most frequently reported AE in the total safety set was headache, which occurred at similar frequencies in all treatment groups, but was highest in the indacaterol 75 mcg treatment group (6%). Cough was the second most frequent event and was observed in 9.5% of the patients in indacaterol 75 mcg treatment group, 4.7% in the indacaterol 150 mcg treatment group, and 2.4% in the indacaterol 18.75 mcg treatment group. See Table 16 below for a summary.

**Table 16 Protocol B2357 Most frequent AEs, including exacerbations, (as least 2% in any treatment group) by preferred term, n (%) of patients (Safety set)**

	Ind 18.75 µg N = 84 n (%)	Ind 37.5 µg N = 81 n (%)	Ind 75 µg N = 84 n (%)	Ind 150 µg N = 85 n (%)	Salm N = 84 n (%)	Pbo N = 84 n (%)
Patients with any AE(s)	10 (11.9)	18 (22.2)	22 (26.2)	16 (18.8)	18 (21.4)	14 (16.7)
<b>Preferred term</b>						
Cough	2 (2.4)	0 (0.0)	8 (9.5)	4 (4.7)	1 (1.2)	0 (0.0)
Headache	2 (2.4)	2 (2.5)	5 (6.0)	3 (3.5)	4 (4.8)	4 (4.8)
Asthma	1 (1.2)	2 (2.5)	0 (0.0)	1 (1.2)	3 (3.6)	4 (4.8)
Blood triglycerides increased	0 (0.0)	2 (2.5)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)
Oropharyngeal pain	0 (0.0)	3 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Preferred terms are sorted in descending order of frequency in the Ind 18.75 µg treatment group. Only treatment emergent adverse events are summarized. Adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a serious adverse event) after the last inhalation were classified as a treatment emergent.

Source: Table 12-3 Study No. CQAB149B2357 Clinical Study Report

#### Reviewer comment:

*Cough appears to be dose-related in the indacaterol groups, occurring much more frequently in the 75 and 150 mcg dose groups. Given the large difference from placebo and salmeterol, it is likely that post-inhalational cough is a drug-related side effect. The sponsor specifically evaluates the incidence of cough as part of the Integrated Summary of Safety.*

#### Asthma exacerbations

In total, 10 patients had asthma exacerbations: one patient (1.2%) in the indacaterol 18.75 mcg treatment group; 2 patients (2.5%) in the indacaterol 37.5 mcg treatment group; 3 patients (3.6%) in the salmeterol treatment group and 4 patients (4.8%) in the placebo group]. Six of the 10 patients with asthma exacerbation required treatment; all with systemic glucocorticosteroids. Three patients had to permanently discontinue study drug due to the exacerbation; 2 patients in the salmeterol treatment group and the one patient in the indacaterol 18.75 mcg treatment group.

### **Deaths/SAEs**

There were no deaths and one SAE (substance abuse) which led to premature discontinuation. However, a total of 8 patients discontinued prematurely due to an AE: 3 among the indacaterol treatment groups (1 patient each in indacaterol 18.75 mcg, 37.5 mcg and 150 mcg treatment group); 4 patients in the salmeterol treatment group and 1 patient in the placebo group.

### **Adverse events leading to discontinuation**

A total of 8 patients discontinued prematurely due to an AE, 3 patients among the indacaterol treatment groups (1 patient or 1.2% each in indacaterol 18.75 mcg, 37.5 mcg and 150 mcg, respectively), 4 patients (4.8%) in the salmeterol treatment group and one patient in the placebo group. The AEs leading to discontinuation were asthma exacerbation (indacaterol 18.75 mcg treatment group); ventricular extrasystoles (indacaterol 37.5 mcg treatment group); bronchitis, and sinusitis (salmeterol); headache, nausea and vomiting (salmeterol); asthma exacerbation (salmeterol), flank pain (salmeterol) and sinusitis (placebo). Of note, in the cardiac disorders SOC, there was 1 ventricular extrasystole.

#### **3.3.1.4.4 Laboratory findings**

In the hematology assessment, less than 5% had an abnormal value. The most frequently reported notable value was low hematocrit in the indacaterol 75 mcg treatment group (4 patients, 4.8%) and in the salmeterol treatment group (3 patients, 3.6%). Focus will be on glucose, potassium and liver function assessments within the clinical chemistry assessment. No clinically significant differences were seen in the LS mean serum potassium and mean blood glucose levels between all treatment groups. No patients had a clinically notable low potassium (< 3mmol/L). One patient in salmeterol treatment group had a clinically high (> 6 mmol/L) value for potassium. Notably low (< 2.78 mmol/L) or high (>9.99 mmol/L) glucose levels (non-fasting) were recorded in one patient in the indacaterol 18.75 mcg treatment group, 2 patients in the indacaterol 37.5 mcg treatment group, 1 patient in the indacaterol 75 mcg treatment group, 3 patients in the salmeterol treatment group and for 4 patients in the placebo group. Elevations of liver function tests were reported in 4 patients; one in the indacaterol 75 mcg treatment group, one in the indacaterol 150 mcg treatment group and two in the placebo group.

#### **3.3.1.4.5 ECG findings**

There were no clinically significant abnormal overall ECG interpretations. The incidence of a maximum increase from baseline of 30 ms to 60 ms in Fridericia's QTc was higher in the indacaterol 18.75 mcg treatment group (3 cases) and in the placebo group (2 cases). No patient was recorded with an increase in Fridericia's QTc of > 60ms. Overall, the most frequently recorded ECG abnormalities were changes in rhythm. These occurred more frequently in the salmeterol treatment group (16%) and occurred at a similar frequency in all other treatment groups except for the indacaterol 37.5 mcg treatment group and the indacaterol 150 mcg treatment groups in which the frequency was lower (2.7% and 5.1%, respectively).

#### **3.3.1.4.6 Physical examination (this should be mostly BP and pulse)**

Focus was limited to BP and pulse for the physical examination assessment. There were no clinically relevant differences between treatment groups with respect to LS mean pulse rate or post baseline systolic or diastolic blood pressure. A dose relationship was observed for those with a post-baseline pulse rate above 90 bpm: 2 (2.4%) patients in the indacaterol 18.75 mcg treatment group: 1 (1.2%) patient in the indacaterol 37.5 mcg treatment group; 4 (4.8%) patients in the indacaterol 75 mcg treatment group, 9 (10.6%) patients in the indacaterol 150 mcg treatment group, 8 (9.5%) patients in the salmeterol treatment group and 7 (8.3%) patients in the placebo group. There was not a dose response relationship with SBP > 140 mmHg: 9 (10.7%) in the 18.75mcg treatment group; 11 (13.6%) in 37.5 mcg; 10 (11.9%) in 75 mcg; 8 (9.4%) in 150 mcg; 8 (9.5%) in salmeterol and 16 (19%) in the placebo group. For DBP> 90 mmHg 6 (7.1%) in the 18.75 mcg treatment group; 9 (11.1%) in 37.5 mcg; 11 (13.1%) in 75 mcg; 7 (8.2%) in 150 mcg; 8 (9.5%) in salmeterol and 10 (11.9%) in the placebo group.

#### **3.3.1.5 Summary of Study**

This was a two week, multicenter, randomized, placebo-controlled trial comparing different doses of indacaterol, 18.75 mcg, 37.5 mcg, 75 mcg and 150 mcg, to placebo in adults with persistent asthma. In addition, salmeterol 50 mcg bid was used as an active comparator. There was a dose response in the primary endpoint of tFEV1 at Day 15. The sponsor's predefined minimum clinically important difference (MCID) of 200 ml was not met for any dose of indacaterol. Although this difference is used as a marker of bronchodilator response, an accepted value has not been established. For the primary endpoint, tFEV1 Day 15, the 75 mcg indacaterol dose provided the largest treatment difference of 0.17 L. The key secondary endpoints of tFEV1 at Day 2 and Day 14 demonstrated a larger treatment difference amongst the indacaterol doses compared to placebo. On Day 2, the 150 mcg indacaterol dose group showed the largest difference (0.16 L) although salmeterol was superior with a treatment difference of 0.21 L. However, by Day 14 the 75 mcg dose exhibited the largest treatment difference of 0.17 L. There was a dose response for other secondary endpoints such as peak FEV1 and AUC. Furthermore, the secondary endpoints such as peak FEV1 Day1 and Day 14, AUC FEV1 (5min-4 hr) Day 1 and Day 14, and AUC FEV1 (5 min- 12 hr) Day 1 and Day 14 all exhibited the same pattern with the largest treatment seen early with the 150 mcg indacaterol dose and any superiority lost by Day 14 to the 75 mcg dose.

The most frequent reported AEs were headache and cough. Six of 10 patients with an asthma exacerbation required treatment, all with systemic glucocorticosteroids. Three patients permanently discontinued study drug due to the exacerbation, only one of whom was in an indacaterol group (18.75 mcg). There were no deaths and only one SAE reported (substance abuse) which led to premature discontinuation. There were no clinically meaningful effects of treatment at any of the doses of indacaterol studied on pulse, blood pressure and QTc interval, and no unexpected effects on clinical laboratory parameters were observed.

### 3.3.2 DOSE FINDING TRIAL IN PATIENTS WITH COPD-B2356

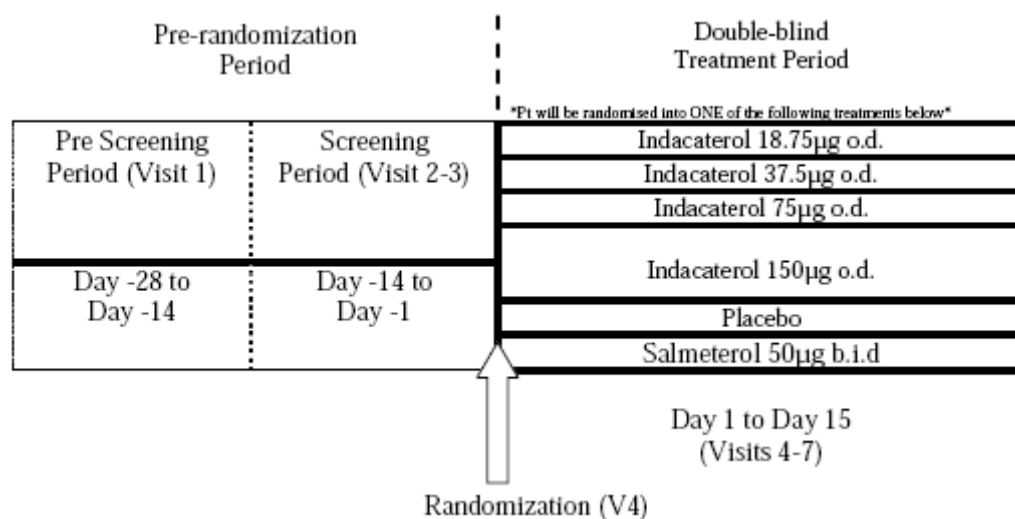
*A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Different Doses of Indacaterol in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD), Using Salmeterol as an Active Control.*

#### 3.3.2.1 Trial Description

##### 3.3.2.1.1 Design

Like the dose ranging Study B2357 in asthmatics, this Phase III multicenter trial was designed as a randomized, double-blind, double-dummy, placebo-controlled, parallel group trial. The study design is represented in Figure 4 below and was very similar to the dose finding study carried out in asthmatics however, ICS therapy was not mandatory for all COPD patients as it was for asthma patients. In addition, PK parameters were collected at the end of the 14-day dosing period.

**Figure 4 Protocol B2356 Study Design**



Source: Figure 3-1, Appendix 16.1.1, Clinical Study Report QAB149B2356

#### Protocol Amendments (Appendix 16.1.1 pg. 1845-6, CSR QAB149B2356):

- Amendment #1 dated February 16, 2010 (prior to study start):
  - Additional spirometry time points were added on Day 14 through Day 15 (at 14 hr, 20 hr and 22 hr post morning dose of Day 14) in the study in order to further characterize the 24-hour bronchodilatory profile of indacaterol at the end of the randomized treatment period. All patients were offered the opportunity to participate in the 24 hour spirometry
  - The open label single dose of indacaterol 300 mcg at Visit 7 was removed
  - Visit 8 (Day16) was removed from the study.
- Amendment #2 dated May 17, 2010:
  - Repeatability criteria at Visit 2 were clarified.
  - Exclusion criteria were amended to give patient s who were eligible to enroll in the study at Visit 2, but had a COPD exacerbation between Visit 2 and Visit 4 (randomization), the ability to re-screen and enroll in the study.
  - Patients who had a respiratory tract infection between Visits 2 and 4 could also re-enroll at a later time of at least 6 weeks after start of infection.

##### 3.3.2.1.2 Duration

The treatment period was 2 weeks. A 2 week run-in time preceded the active treatment period.

##### 3.3.2.1.3 Population

Males and females aged 40 years and older, with a clinical diagnosis of moderate to severe COPD (as classified by the Global Initiative for Chronic Obstructive Lung Disease; GOLD guidelines 2008), and a smoking history of at least 10 pack years were enrolled. The randomization was stratified by the patients' current smoking status (current/ex-smoker) and current ICS use.

#### **3.3.2.1.4 Study Sites**

The study was conducted at 67 centers in the United States.

#### **3.3.2.1.5 Investigational and Reference Therapy**

The following drugs were used:

- Indacaterol 18.75 mcg blister batch # VMLK/2009-3018, DP batch # X223 0909
- Indacaterol 37.5 mcg blister batch # VMLK/2009-3019, DP batch # X224 0909
- Indacaterol 75 mcg blister batch # VMLK/2009-2700, DP batch # X173GF
- Indacaterol 150 mcg blister batch # VMLK/2009-2826, DP batch # X172GF
- Placebo to indacaterol blister batch # VMLK/2009-1409, DP batch # X039BE
- Salmeterol 50 mcg Diskus DP batch # R438216, R438396
- Placebo to salmeterol DP batch # X278 0807, X165 0608

All indacaterol dry powder capsules and placebo to indacaterol were inhaled through the Concept1 SDDPI device. Salmeterol (50 mcg b.i.d.) and placebo to salmeterol were inhaled through a single Diskus® device.

#### **3.3.2.1.6 Objectives**

The primary objective was to evaluate the dose response relationship among four doses of indacaterol (18.75, 37.5, 75, and 150 mcg q.d.), placebo and salmeterol 50 mcg b.i.d. as measured by the 24 h post-dose Forced Expiratory Volume in 1 second (FEV1) (trough) after 14 days of treatment in patients with moderate to severe COPD.

The secondary objective was to evaluate the dose response relationship in the following lung function assessments:

- tFEV1 after 1 day of treatment
- Peak FEV1 on Day 1
- AUC for FEV1 5min-11h 45min on Day 1 and Day 14
- AUC for FEV1 5min-4 h on Day 1 and Day 14
- To evaluate day and night time rescue medication usage for all doses of indacaterol as compared to placebo and salmeterol 50 mcg b.i.d. over 14 days
- To evaluate the pharmacokinetic (PK) profiles of indacaterol in a subset of patients after 14 days of treatment

The safety objective was: to evaluate safety (AEs, ECGs, laboratory tests, vital signs) and tolerability of indacaterol over the course of treatment.

The exploratory objective of this study was: to explore the 24 hour (FEV1 and FVC) profile of indacaterol (18.75, 37.5, 75 and 150 mcg q.d.), salmeterol and placebo after 14 days of treatment.

#### **3.3.2.1.7 Inclusion Criteria**

- Male and female adults aged  $\geq 40$  years
- Moderate to severe diagnosis of COPD as per GOLD guidelines, 2008
- Patients must have a post-bronchodilator FEV1  $<80\%$  and  $\geq 30\%$  of predicted
- Post bronchodilator FEV1/FVC  $<70\%$ .
- Smoking history of at least 10 pack years

#### **3.3.2.1.8 Exclusion Criteria**

Key exclusion criteria were:

- Pregnancy or lactating women
- Women of child-bearing potential unless using two birth control methods
- History of COPD exacerbation requiring glucocorticoid treatment, antibiotics, hospitalization or a respiratory tract infection in the 6 weeks prior to screening
- Concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), clinically significant bronchiectasis or history of lung cancer
- O2 requirement for chronic hypoxia of >15 hours per day (excluding acute COPD exacerbation)
- History of long QT syndrome
- Patients with a history of asthma indicated by (but not limited to): onset of respiratory symptoms (such as cough, wheezing, shortness of breath) suggestive of asthma prior to 40 years of age or a history of a diagnosis of asthma
- Patients involved in the active phase of a supervised pulmonary rehabilitation program or any patients planning to undertake a supervised pulmonary rehabilitation program during the study
- Patients with a known diagnosis of Alpha-1 Antitrypsin deficiency

If there was an exacerbation during the run-in period the patient would be discontinued however, he could be re-screened at a later time.

### 3.3.2.1.9 Conduct

At the pre-screening visit (Visit 1), informed consent was obtained, current COPD medications were reviewed and, if necessary, arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. Patients using LABAs were switched to the “as needed” use of the SABA, albuterol via MDI, at least 48 hours prior to Visit 2. The steroid component of any fixed combination therapy (ICS and  $\beta_2$ -agonist) were replaced with the equivalent ICS monotherapy plus the “as needed” use of a SABA, albuterol via MDI, at least 48 hours prior to Visit 2. A baseline spirometry assessment was to be performed after a washout period of at least 6 hours for SABAs, 48 hours for LABAs and 48 hours for long-acting anticholinergics. However, longer washout periods were acceptable depending on exclusion criteria.

At Visit 2, spirometry measurements were taken to assess eligibility. At Visit 2 FEV<sub>1</sub> and FVC were assessed prior to and 10- 15 minutes after inhalation of 4 x 90 mcg puffs of albuterol via MDI and FEV<sub>1</sub> and FVC within 10-15 min after inhalation of 4 x 90 mcg albuterol via MDI. These FEV<sub>1</sub> assessments were the components of  $\beta_2$ -agonist FEV<sub>1</sub> reversibility.

At Visit 3 the patient was to return in the morning to assess FEV<sub>1</sub> and FVC prior to inhalation of 2 x 21 mcg ipratropium bromide (equivalent to 2 x 17 mcg ipratropium bromide) and FEV<sub>1</sub> and FVC 1 hour post inhalation of the specified anticholinergic medication. The FEV<sub>1</sub> assessments were the components of the anti-cholinergic FEV<sub>1</sub> reversibility. In order to avoid the suggestion of bias in efficacy analysis, the statistical models were to be adjusted with respect to the reversibilities of both anti-cholinergic and beta agonist mechanisms of action so both reversibilities were collected for this purpose and reported. Reversibility was calculated as:

$$100 \times \frac{\text{FEV}_1(\text{post bronchodilator}) - \text{FEV}_1(\text{baseline})}{\text{FEV}_1(\text{baseline})}$$

At Visit 4, eligibility was confirmed and patients were randomized to treatment. The period between Visits 4 to 6 was a 14 day treatment period. Patients were randomized 1:1:1:1:1:1 to one of the six blinded treatments as follows:

1. Indacaterol (18.75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
2. Indacaterol (37.5 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
3. Indacaterol (75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
4. Indacaterol (150 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
5. Placebo to indacaterol delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
6. Placebo to indacaterol delivered via SDDPI once daily in the morning and salmeterol 50 mcg via Diskus® in the morning and salmeterol 50 mcg via Diskus® in the evening

Patients were also randomized to inhale their morning dose of study medication in one of two possible sequences if possible:

- Indacaterol/placebo SDDPI, followed by salmeterol/placebo Diskus® inhaler
- Salmeterol/placebo Diskus® inhaler, followed by indacaterol/placebo SDDPI

The dosing scheme is depicted in Table 17 below.

**Table 17 Protocol B2356 Study treatments (dosing scheme)**

Treatment	Morning		Evening
	Concept1 SDDPI	Salmeterol proprietary inhaler (Diskus®)	Salmeterol proprietary inhaler (Diskus®)
Group 1	Indacaterol 18.75 µg	Placebo	Placebo
Group 2	Indacaterol 37.5 µg	Placebo	Placebo
Group 3	Indacaterol 75 µg	Placebo	Placebo
Group 4	Indacaterol 150 µg	Placebo	Placebo
Group 5	Placebo	Placebo	Placebo
Group 6	Placebo	Salmeterol 50 µg	Salmeterol 50 µg

Source: Table 9-3 Study CQAB149B2356 Clinical Study Report

### Efficacy Assessments

The scheduling of serial measurements were similar to that seen in Study B2357 with the addition of an assessment for FEV1 anticholinergic reversibility at screening and PK profile blood sampling at Days 14 and 15. See

Table 18 below for details.



**Table 18 Protocol B2356 Timed Assessments**

Visit (Day)	Timepoint <sup>1</sup>	Urinalysis	ECG <sup>2</sup>	Vital Signs <sup>3</sup>	Hematology/ blood chemistry	PK profile blood sample <sup>6</sup>	Spirometry (expiratory maneuver FEV <sub>1</sub> ) <sup>4</sup>
Visit 4 (Day 1)	-50 min	X					X
	-25 min		XX	X	X		
	-15 min						X
	5 min						X
	15 min						X
	30 min						X
	1 h		XX	X	X		X
	2 h						X
	4 h						X
	8 h						X
	11 h 10 min						X
	11 h 45 min						X
Visit 5 <sup>5</sup> (Day 2)	23 h 10 min						X
	23 h 45 min						X
Visit 6 <sup>7,8</sup> (Day 14)	-50 min	X					X
	-25 min		XX	X	X	X	
	-15 min						X
	5 min						X
	10 min					X	
	15 min						X
	20 min					X	
	30 min						X
	1 h		XX	X	X	X	X
	2 h					X	X
	4 h					X	X
	8 h					X	X
	11 h 10 min						X
	11 h 45 min					X	X
24 h spirometry subgroup ( Day 15)	14 h						X
	20h						X
	22h						X
Visit 7 (Day 15)	23 h 10 min <sup>5</sup>	X					X
	23 h 35 min		XX	X	X		
	23h 45 min <sup>5</sup>					X	X

Source: Table 9-5 Study No. CQAB2356 Clinical Study Report

**Spirometry measurements:**

As shown in

Table 18 serial spirometry was performed on Day1 (Visit 4) and Day 14 (Visit 6) at 50 and 15 minutes predose, then 5, 15, 30 minutes, 1, 2, 4, 8 hours and 11 hours 10 minutes, 11 hours 45 minutes post dose. On Day 2 (Visit 5) and Day 15 spirometry was performed at 23 hours 10 min and 23 hours 45 minutes post dose. The 24 hour spirometry subgroup continued to have spirometry taken during 14, 20 and 22 hours post dose. These assessments were all similar to the schedule in the B2357 asthma dose finding trial. As in the prior study, patients were advised to avoid caffeine, chocolate, ice-cold beverages, strenuous physical activity and alcohol intake for at least 24 hours prior to scheduled study visits. All spirometry was read at a central laboratory.

#### ***Number of inhalations of albuterol rescue medication***

No rescue medication was permitted other than study-provided albuterol. Patients were instructed to abstain from taking rescue albuterol via MDI within 6 hours of the start of each visit unless absolutely necessary. If rescue medication was taken within 6 hours prior to spirometry at Screening, or the pre-dose spirometry at Day 1 or prior to spirometry at Day 15 (Visits 2, 4 and 7 respectively), the visit was to be rescheduled to the next possible day. The investigator reminded the patients to continue to take their study medication as prescribed. If rescue medication was taken within 6 hours prior to the post-dose spirometry measurements (relative to the previous day's dose) at Days 2 and 14 (Visits 5 and 6), the patient still attended the visit; however, the spirometry measurements taken within the 6 hours of the rescue medication dose were considered invalid for all spirometry analyses. In the event that a patient used a dose of rescue medication after taking study medication at a visit then the visit continued as planned. The time the rescue medication was taken was recorded in the eCRF. All daily usage of rescue medication was recorded once in the morning and once in the evening by the patient using their electronic diary.

#### ***COPD Exacerbations***

COPD exacerbations were defined as:

worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- Dyspnea
- Sputum volume
- Sputum purulence

or

worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- increased cough
- increased wheeze

and

requiring treatment with systemic (oral or parenteral) corticosteroids and/or antibiotic

COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An ER visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not counted as an exacerbation. In the event of a COPD exacerbation matching the above definition occurring at any time after signing of informed consent, patients were to be treated for the exacerbation as deemed necessary by the investigator. All COPD exacerbations, regardless of treatment, was to only be recorded on the COPD exacerbation episode eCRF and not on the AE eCRF.

#### ***Safety Assessments***

ECG, vitals and laboratory evaluations were performed 25 minutes predose and 1 hour post dose on Visits 4 and 6 and then again on Visit 7 at 23 hours 35 minutes. Urinalysis was performed 3 times on Visits 4 and 6 at 50 minutes predose and Visit 7 at 23 hours 10 minutes.

#### ***PK Assessments***

All blood samples (4 mL) will be collected at each of the following time points into polypropylene tubes spray coated with silica ( for serum preparation): Day 14/15: 25 minutes predose and 10, 20 minutes, 1, 2, 4, 8 hours and 11 hour 45 minutes and 23 hour 45 minutes post dose.

#### **3.3.2.1.10 Concomitant Treatments**

Allowed medications included pure SSRIs, inactivated vaccines, ICS, nasal corticosteroids and antihistamines. Prohibited medications include: long acting anticholinergics, short acting anticholinergics, fixed combinations of  $\beta_2$  agonists and ICS; fixed combinations of SABAs and short-acting anticholinergics; LABAs; short acting  $\beta_2$  agonists; xanthines; parenteral or oral corticosteroids and intra-muscular depot corticosteroids. In the event of a COPD exacerbation, the patient was withdrawn from the trial with treatment initiated by the physician.

*Reviewer's Comment:*

*Inhaled corticosteroids were permitted but not required as in the dose finding study in asthmatics because the same concerns of adverse respiratory events associated with the use of LABAs in patients with asthma are not evident for LABAs in the COPD population as described in the <sup>4</sup>TORCH1 study are not evident for LABAs in COPD.*

### **3.3.2.1.11 Ethical Aspects**

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, ( US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

### **3.3.2.1.12 Data Analysis**

#### **Sample size calculation**

The sample size was based on the widths of the two-sided 95% confidence interval (CI) between any pair of treatments for the primary endpoint, trough FEV1. A 95% CI of expected width 120 mL (the sponsor assigned clinically important difference in COPD patients) was considered an appropriate level of precision in this dose ranging study. The estimate for the standard deviation for tFEV1 was 200 mL. This estimate was based on a review of the analysis outputs from the phase III indacaterol studies: QAB149B2334, QAB149B2346, QAB149B2335S and data from the phase IIIb study QAB149B2349. Eighty six evaluable patients per treatment group were required to detect a 95% confidence interval (two-sided) of expected width 120 mL wide, assuming a standard deviation of 200 mL. With a drop- out rate of 10% over 2 weeks of treatment, a sample size of 576 randomized patients (96 per treatment group) in total was required.

#### **Efficacy Variables**

The same four sets defined for analysis in Study B2357; the randomized set, the full analysis set (FAS), the per-protocol set (PPS) and the safety set were defined in addition to a PK set which included all patients with at least one evaluable drug concentration data. The planned analysis of some of the efficacy variables were modified post database lock:

- To estimate an indacaterol dose which yields the same estimated increase in trough FEV1 as the treatment with salmeterol 50  $\mu$ g b.i.d., and the indacaterol dose which yields an increase in tFEV1 by 0.12L, were dropped from the analysis plan.
- Responder analyses in tFEV1 at Day 15 were added to the analysis plan. Responders were defined as patients who had an increase from baseline in trough FEV1 a) = 12 % or = 0.2 L, b) = 12 % or = 0.12 L.

#### **Primary endpoint- tFEV1 Day 15**

The primary efficacy objective was to evaluate the dose response relationship among the four doses of indacaterol (18.75, 37.5 75, and 150 mcg q.d.), placebo and salmeterol as measured by the tFEV1 after 14 days of treatment in patients with COPD and was summarized by treatment group for the FAS. The same statistical analysis and handling of missing data conducted for the B2357 asthma dose ranging trial was carried out for this COPD dose ranging trial. Most of the same supportive analyses were also performed; however, in this case exploratory subgroup analyses were conducted for severity of COPD

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<sup>4</sup> Calverley PD, Anderson JA. Et al. Salmeterol and fluticasone propionate and survival in Chronic Obstructive Pulmonary Disease. NEJM, 2007 Feb; 356(8): 775-789

based on GOLD criteria instead of severity of asthma. As well, the same Emax model was employed to characterize the dose response relationship.

#### **Secondary endpoints- *tFEV1* after one day**

Trough FEV1 after one day of treatment was analyzed the same as above and missing data was not imputed. Peak FEV1 5 mins-4 hrs post morning dose; AUC FEV1<sub>5 mins-4 hrs</sub>; AUC FEV1<sub>5 mins-11hrs 45 mins</sub>; FEV1 and FVC at all other post baseline time points; 24 hour serial spirometry; AUC for FEV1<sub>5 mins - 23 h 45 min</sub> and AUC for FEV1<sub>11h 45 min - 23 h 45 min</sub> for serial spirometry subgroup; daily rescue medication use; daytime and nighttime rescue medication use; percentage of days with no rescue medication use were all defined and analyzed similarly as for the B2357 asthma dose ranging study.

#### **Safety Variables**

All data was summarized for the Safety set. The safety variables included monitoring and recording all treatment emergent AEs, including COPD exacerbations. The same description for prior AE and post treatment AEs were conducted in this trial as performed in the AE section of 5.3.1.1.12. And as mentioned in the COPD Exacerbation Section 5.3.2.1.9, COPD exacerbations were recorded on the COPD exacerbation episode eCRF and not on the AE eCRF. They were included in the summaries of AEs and additionally summarized separately from other AEs. Laboratory data, vital signs and body weight and ECG were all analyzed in a similar manner as in the previous study.

#### **Pharmacokinetic Variables**

Descriptive statistics of pharmacokinetic parameters included mean, SD, and CV, min, median and max. When a geometric mean was presented it was to be stated that way. Since Tmax is generally evaluated by a nonparametric method, only median values and ranges were given for those parameters. An exploratory analysis of the relationship between dose and Cmax as well as AUCtau was carried out on the basis of dose-normalized Cmax and AUCtau values using log transformed geometric means fitted to a "dose-division" model:  $\text{Log(PK parameter/Dose)} = \text{LogB} + (C-1) \cdot \text{log(Dose)}$ , where B was the gradient of the PK parameter versus a possible linear trend and C was the power term. Confidence intervals (90%) was produced for the PK parameters. Changes made in the PK analysis post data lock included the exclusion of the 18.75 mcg treatment group from the exploratory analysis because many patients in the 18.75 mcg treatment group had sample concentration levels which were below the LLOQ and therefore set to zero. This was done in attempt to avoid bias due to the LLOQ artifact.

#### **3.3.2.2 Patient Disposition and Demographics**

##### **Disposition**

Approximately 576 patients (96 per treatment group) were to be randomized with the goal of at least 516 patients (86 per treatment group) to complete the study. Dropouts were not replaced. A total of 1110 screening visits were performed and 552 patients were randomized to the 6 treatment groups (92 in the indacaterol 18.75 mcg group, 91 in the indacaterol 37.5 mcg group, 94 in the indacaterol 75 mcg group, 92 in the indacaterol 150 mcg group, 92 in the salmeterol group and 91 in the placebo group. There were 547 patients exposed to treatment and 531 (96.2%) completed the study as planned (84 in the indacaterol 18.75 mcg group, 86 in the indacaterol 37.5 mcg group, 92 in the indacaterol 75 mcg group, 91 in the indacaterol 150 mcg group, 90 in the salmeterol group and 88 in the placebo group. The percentage of patients who discontinued prematurely was highest in the indacaterol 18.75 mcg group (8.7%) and the next in the 37.5 mcg group (5.5%). Overall, the most common reason for discontinuation was for adverse events, however there was no dose response. Refer to Table 19 below for details. Randomization was stratified by patient's current smoking status and ICS use.

**Table 19 Protocol B2356 Patient disposition (All patients)**

	Ind 18.75 ug n (%)	Ind 37.5 ug n (%)	Ind 75 ug n (%)	Ind 150 ug n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Screening visits	-	-	-	-	-	-	1110
<b>Patients</b>							
Randomized	92 (100.0)	91 (100.0)	94 (100.0)	92 (100.0)	92 (100.0)	91 (100.0)	552 (100.0)
Exposed	89 (96.7)	90 (98.9)	94 (100.0)	92 (100.0)	91 (98.9)	91 (100.0)	547 (99.1)
Completed	84 (91.3)	86 (94.5)	92 (97.9)	91 (98.9)	90 (97.8)	88 (96.7)	531 (96.2)
Discontinued	8 (8.7)	5 (5.5)	2 (2.1)	1 (1.1)	2 (2.2)	3 (3.3)	21 (3.8)
<b>Primary reason for premature discontinuation</b>							
Adverse event(s)	5 (5.4)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	8 (1.4)
Subject withdrew consent	0 (0.0)	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)	2 (2.2)	5 (0.9)
Abnormal test procedure results(s)	2 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Lost to follow-up	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	3 (0.5)
Protocol deviation	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.4)

Patients who have screen failed and rescreened under a new patient number were counted twice in the number of screening visits.

Source: Table 10-1 Study No. CQAB149B2356 Clinical Study Report

### Protocol Deviations

A total of 81 patients (14.8%) in the FAS had at least one major protocol deviation resulting in exclusion from the per-protocol set. The proportion of patients with a protocol deviation leading to exclusion from the PPS included: 11.1% in the indacaterol 37.5 mcg treatment group, 12.8% in the 75 mcg group; 20.7% in the indacaterol 150 mcg group; 15.4% in the salmeterol group and 13.2% in the placebo group. No patient had a non-protocol deviation leading to exclusion. The two most frequent reasons for protocol deviation were:

- “study medication taken < 80% doses prior to the primary endpoint (PEP) visit” (the largest was in placebo, 5.5% and the smallest, indacaterol doses 18.75 and 37.5 mcg at 2.2%) and
- “spirometry for SABA reversibility not acceptable as per American Thoracic Society/ European Respiratory Society (ATS/ERS) criteria” (the largest was in the 18.75 mcg indacaterol dose, 7.9% and the smallest in 37.5, 150 mcg indacaterol and placebo at 1.1%)

The breakdown of the analysis sets show that for the FAS group the range is from 96.7% (18.75 mcg indacaterol) to 100% (75 mcg, 150 mcg indacaterol and placebo) of all randomized patients were included in the analyses.

### Demographics

Similar to most of the trials reviewed, the majority of patients were caucasian (94%) and male (54%) with a mean age of 62.6 years (range of 40 to 87 years) as depicted in Table 20 below. The low numbers of other races, limits any generalizability to non-caucasian demographics.

**Table 20 Protocol B2356 Demographic summary (Safety set)**

		Ind 18.75 ug N=89	Ind 37.5 ug N=90	Ind 75 ug N=94	Ind 150 ug N=92	Salm N=91	Pbo N=91	Total N=547
<b>Age (years)</b>	n	89	90	94	92	91	91	547
	Mean	62.8	61.9	62.6	62.3	62.4	63.6	62.6
	SD	8.95	9.61	9.30	9.50	9.52	8.44	9.20
	Median	62.0	63.5	63.0	62.0	63.0	63.0	63.0
	Min - Max	43 - 84	43 - 83	44 - 87	40 - 84	43 - 83	47 - 85	40 - 87
<b>Age group – n (%)</b>	40-64 years	53 (59.6)	51 (56.7)	52 (55.3)	52 (56.5)	51 (56.0)	54 (59.3)	313 (57.2)
	65-74 years	27 (30.3)	31 (34.4)	33 (35.1)	34 (37.0)	31 (34.1)	26 (28.6)	182 (33.3)
	>= 75 years	9 (10.1)	8 (8.9)	9 (9.6)	6 (6.5)	9 (9.9)	11 (12.1)	52 (9.5)
<b>Sex – n (%)</b>	Male	50 (56.2)	47 (52.2)	54 (57.4)	53 (57.6)	44 (48.4)	48 (52.7)	296 (54.1)
	Female	39 (43.8)	43 (47.8)	40 (42.6)	39 (42.4)	47 (51.6)	43 (47.3)	251 (45.9)
<b>Race – n (%)</b>	Caucasian	86 (96.6)	84 (93.3)	91 (96.8)	84 (91.3)	82 (90.1)	86 (94.5)	513 (93.8)
	Black	2 (2.2)	6 (6.7)	2 (2.1)	6 (6.5)	8 (8.8)	5 (5.5)	29 (5.3)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	2 (0.4)
	Pacific Islander	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Source: Table 11-2 Study No. CQAB149B2356 Clinical Study Report

The population included mainly patients with a short duration of disease with a mean duration of COPD of 6.9 years and approximately 48% of patients diagnosed with COPD for  $\leq 5$  years. Approximately 53% were in the moderate severity category and 46% were in the severe category, no patients had mild COPD. The mean FEV1 for all patients was 1.29 L and the mean FVC was 2.46 L. Across the different treatment groups, the mean baseline FEV1 was similar with the lowest in the placebo group (1.21 L) and the highest in the 75 mcg indacaterol group (1.37 L). The remaining breakdown is as follows: 18.75 mcg with 1.30 L, 37.5 mcg with 1.31 L, 150 mcg with 1.32 L, salmeterol with 1.26 L. Less than half of patients were using ICS on entry to the study. A greater proportion 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. Regarding reversibility, the mean FEV1 before SABA was 1.30 L and after SABA it was 1.47 L. The mean post SABA FEV1 for all patients was 52% of predicted and the mean FEV1/FVC was 52.9%. The mean percentage increase in FEV1 after SABA bronchodilator was 15.7% including a range of 14.2% in the 150 mcg group to 16.7% in the salmeterol group.

Refer to Table 21 below.

**Table 21 Protocol B2356 Baseline disease characteristics (Safety set)**

		Treatment group						
		Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salmeterol	Pbo	Total
Duration of COPD (years)	n	89	90	94	92	91	91	547
	Mean	6.6	6.6	6.8	6.7	7	7.9	6.9
	SD	5.61	5.88	6.27	5.75	6	6.72	6.04
Duration of COPD (years)-n	<1-5 yrs	43	48	46	43	46	38	264
	>5-10 yrs	28	28	27	30	24	29	166
	>10-20 yrs	17	12	19	16	18	19	101
	> 20 yrs	1	2	2	3	3	5	16
Severity of COPD n (%)	Mild	0	0	0	0	0	0	0
	Moderate	47	52	54	45	45	49	292
	Severe	42	37	39	45	46	41	250
	Very Severe	0	1	1	2	0	1	5
FEV1, mean	Pre-BD (L)	1.31	1.32	1.37	1.32	1.26	1.22	1.30
	Pre-BD (%P)	47.2	47.1	47.5	46.5	46.2	45.3	46.6
	Post-BD (L)	1.48	1.50	1.54	1.48	1.44	1.39	1.47
	Post-BD (%P)	53.4	53.8	53.9	52.2	52.7	51.5	52.9
ICS use-n(%)	No	57	55	60	56	59	59	346
	Yes	32	35	34	36	32	32	201
Smoking history-n(%)	Ex smoker	42	40	44	40	39	42	247
	Current smoker	47	50	50	52	52	49	300
Number of pack years	Mean	52.2	51.2	51	50.8	53	51	51.5
	SD	25.19	25.82	21.72	29.34	30.23	25.01	26.25

Legend: Ind: Indacaterol; pbo: placebo; BD: bronchodilator (albuterol)

Source: Adapted from Table 11-3 Study No. CQAB2356 Clinical Study Report

### 3.3.2.3 Pharmacokinetics

Across all treatment groups indacaterol peak serum levels were consistently observed at a median Tmax of 0.33 hours post dose. PK parameters were biased by the fact numerous samples were below LLOQ and therefore the PK parameters calculated for the indacaterol 18.75 mcg treatment group were not included in the statistical analysis of dose-proportionality. Average Cmax increased with increasing dose from 24.80 pg/mL in the 18.75 mcg treatment group, 51.36 in the 37.5 mcg group, 100.36 in the 75 mcg group and 250.53 pg/mL in the 150 mcg treatment group. Average AUC0-23.75hr values increased from 183.8 pg\*hr/mL in the 18.75 mcg treatment group to 2606.3 pg\*hr/mL in the 150 mcg treatment group.

### 3.3.2.4 Efficacy Review

#### 3.3.2.4.1 Primary Endpoint

The primary efficacy variable was tFEV1 at Day 15 which is presented as LS mean and estimated treatment differences as done for Protocol B2357. The overall results are summarized in Table 22 below. The Sponsor predefined MCID for the targeted population was 120 mL. The largest treatment difference was observed for the 150 mcg dose of indacaterol (0.12 L). Salmeterol, and the two lower doses of indacaterol 37.5 and 75 mcg all had the same treatment effect with a treatment difference of 0.10 L.

#### Reviewer Comment:

*Although the Sponsor prespecified a MCID for the targeted population of patients with COPD as 120 mL, this value is not supported.*

**Table 22 Protocol B2356 Trough FEV1 (L) at Day 15: treatment comparisons (FAS and PPS, imputed with LOCF)**

----- Treatment -----				----- Treatment difference ----				
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Full analysis set								
Ind 18.75 ug	82	1.35	0.020	Ind 18.75 ug - Pbo	0.07	0.027	( 0.02, 0.12)	0.008*
Ind 37.5 ug	84	1.38	0.019	Ind 37.5 ug - Pbo	0.10	0.027	( 0.05, 0.16)	<.001*
Ind 75 ug	87	1.38	0.019	Ind 75 ug - Pbo	0.10	0.026	( 0.04, 0.15)	<.001*
Ind 150 ug	90	1.40	0.019	Ind 150 ug - Pbo	0.12	0.026	( 0.07, 0.17)	<.001*
Salm	88	1.39	0.019	Salm - Pbo	0.10	0.026	( 0.05, 0.16)	<.001*
Pbo	86	1.28	0.019					

Source: Table 11-5 Study No. CQAB149B2356 Clinical Study Report

The pre-planned Emax model assumed the absolute increase in trough FEV1 would be at least 0.12L but this was not reflected in the actual data. This resulted in the model producing uninterpretable estimates. Therefore the two estimates were dropped from the analysis plan.

Subgroup analysis is presented in Table 23 below. Most notable findings are that current smokers treatment differences for tFEV1 Day 15 appears to trend lower for all doses. Based on COPD severity those with more severe disease appear to have larger treatment differences in tFEV1 Day15 for doses 37.5, 75 and 150 mcg indacaterol than those with moderate COPD.



**Table 23 Protocol B2356 Summary statistics of change from baseline trough FEV1 (L) at Day 15 imputed with LOCF, FAS**

Subgroup	Ind 18.75 ug		Ind 37.5 ug		Ind 75 ug		Ind 150 ug		Salm		Pbo	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
<b>Age</b>												
< 65 years	50	0.04 ( 0.170)	48	0.08 ( 0.284)	47	0.09 ( 0.271)	50	0.13 ( 0.206)	48	0.10 ( 0.203)	50	-0.01 ( 0.205)
≥ 65 years	32	0.12 ( 0.101)	37	0.08 ( 0.179)	40	0.09 ( 0.124)	40	0.09 ( 0.160)	40	0.10 ( 0.110)	36	0.01 ( 0.181)
<b>Sex</b>												
Male	45	0.06 ( 0.177)	43	0.06 ( 0.309)	50	0.10 ( 0.248)	52	0.15 ( 0.203)	44	0.13 ( 0.189)	45	0.03 ( 0.217)
Female	37	0.08 ( 0.114)	42	0.10 ( 0.149)	37	0.08 ( 0.164)	38	0.06 ( 0.150)	44	0.07 ( 0.135)	41	-0.04 ( 0.160)
<b>Race</b>												
Caucasian	79	0.07 ( 0.153)	79	0.09 ( 0.243)	85	0.09 ( 0.218)	82	0.12 ( 0.184)	79	0.09 ( 0.169)	82	-0.00 ( 0.194)
Black	2	0.06 ( 0.018)	6	0.00 ( 0.239)	2	0.03 ( 0.025)	6	0.13 ( 0.225)	8	0.08 ( 0.094)	4	0.04 ( 0.232)
Asian	0		0		0		1	-0.22 ( )	0		0	
Other	1	0.21 ( )	0		0		1	0.14 ( )	1	0.43 ( )	0	
<b>Inhaled corticosteroid (ICS) use at baseline</b>												
No ICS use	52	0.09 ( 0.143)	53	0.10 ( 0.270)	57	0.08 ( 0.242)	55	0.12 ( 0.208)	56	0.09 ( 0.180)	56	-0.02 ( 0.187)
ICS use	30	0.05 ( 0.165)	32	0.05 ( 0.189)	30	0.12 ( 0.152)	35	0.09 ( 0.148)	32	0.10 ( 0.142)	30	0.03 ( 0.206)
<b>Smoking history</b>												
Ex-smoker	37	0.09 ( 0.114)	39	0.14 ( 0.216)	42	0.10 ( 0.121)	39	0.12 ( 0.183)	39	0.13 ( 0.137)	41	0.01 ( 0.196)
Current smoker	45	0.05 ( 0.175)	46	0.03 ( 0.253)	45	0.08 ( 0.277)	51	0.11 ( 0.191)	49	0.07 ( 0.183)	45	-0.01 ( 0.194)
<b>COPD severity</b>												
Moderate or less	45	0.08 ( 0.142)	49	0.07 ( 0.288)	51	0.07 ( 0.252)	44	0.10 ( 0.204)	44	0.14 ( 0.173)	48	0.02 ( 0.192)
Severe or worse	37	0.06 ( 0.163)	36	0.09 ( 0.165)	36	0.12 ( 0.146)	46	0.12 ( 0.170)	44	0.06 ( 0.150)	38	-0.03 ( 0.197)

Source: Adapted from Table 11-7 Study No. CQAB149B2356 Clinical Study Report

A post hoc analysis was performed after database lock. The responder analysis defined responders as ≥ 12% or ≥ 0.2 L and ≥12% or >0.12 L in the increase in trough FEV1 at Day 15. The odds ratios generated were treatment drug compared to placebo. The highest odds of response were seen in the indacaterol 75 mcg and 150 mcg for both subgroups.

**Table 24 Protocol B2356 Analysis of responders in trough FEV1 at Day 15 (FAS)**

	Response by increase from baseline in trough FEV1, n (%), odds ratio, p-value					
	≥ 12%, 0.2 L			≥ 12%, 0.12 L		
Indacaterol dose (N)	n (%)	OR	p-value	n (%)	OR	p-value
18.75 mcg (82)	29 (35%)	2.52	0.071	39 (48%)	3.45	0.002
37.5 mcg (84)	34 (41%)	4.26	0.005	40 (48%)	4.51	< 0.001
75 mcg (87)	39 (43%)	4.48	0.003	45 (52%)	4.98	< 0.001
150 mcg (90)	32 (43%)	4.28	0.004	46 (51%)	4.71	< 0.001
Salmeterol (88)	25 (36%)	1.09	0.862	41 (47%)	1.09	0.812
Placebo (86)	17 (20%)	N/A	N/A	20 (23%)	N/A	N/A

Source: Table 14.2-1.6 Study No. CQAB149B2356 Clinical Study Report

### 3.3.2.4.2 Secondary Endpoints

#### ➤ tFEV1 Day 2 and Day 14

The largest treatment difference in tFEV1 after 1 day of treatment (Day2) was observed with both indacaterol 150 mcg and salmeterol with a LS mean of 0.13 (0.09, 0.17). At Day 14, again, any advantage demonstrated by the 150 mcg indacaterol dose was lost. The numerical values between the two highest indacaterol doses were similar: indacaterol 75 mcg 0.09 (0.04, 0.13), indacaterol 150 mcg 0.10 (0.05, 0.15) and salmeterol 0.08 (0.03, 0.13). See Table 25 for a summary of the treatment differences.

**Table 25 Protocol B2356 Analysis of trough FEV1 (L) at Day 2 and Day 14 (FAS)**

Treatment	n	--- Treatment ---		Comparison	---- Treatment difference ----			
		LS Mean	SE		LS Mean	SE	95% CI	p-value
Day 2								
Ind 18.75 ug	85	1.33	0.015	Ind 18.75 ug - Pbo	0.05	0.021	( 0.01, 0.09)	0.016
Ind 37.5 ug	86	1.34	0.015	Ind 37.5 ug - Pbo	0.06	0.021	( 0.02, 0.10)	0.004
Ind 75 ug	88	1.38	0.015	Ind 75 ug - Pbo	0.11	0.021	( 0.06, 0.15)	<.001
Ind 150 ug	91	1.40	0.014	Ind 150 ug - Pbo	0.13	0.021	( 0.09, 0.17)	<.001
Salm	88	1.41	0.015	Salm - Pbo	0.13	0.021	( 0.09, 0.17)	<.001
Pbo	86	1.28	0.015					
Day 14								
Ind 18.75 ug	72	1.35	0.018	Ind 18.75 ug - Pbo	0.05	0.025	( 0.01, 0.10)	0.027
Ind 37.5 ug	78	1.38	0.018	Ind 37.5 ug - Pbo	0.09	0.025	( 0.04, 0.14)	<.001
Ind 75 ug	82	1.38	0.017	Ind 75 ug - Pbo	0.09	0.024	( 0.04, 0.13)	<.001
Ind 150 ug	84	1.39	0.017	Ind 150 ug - Pbo	0.10	0.024	( 0.05, 0.15)	<.001
Salm	80	1.37	0.017	Salm - Pbo	0.08	0.024	( 0.03, 0.13)	0.001
Pbo	79	1.29	0.017					

Source: Table 11-9 Study No. CQAB149B2356 Clinical Study Report

A summary of the results of key secondary endpoints is presented in Table 26 below. A brief description of each is presented in the subsequent sections.

**Table 26 Protocol B2356 Treatment differences for secondary endpoints**

	Treatment difference LS mean (95% CI)				
	18.75 mcg	37.5 mcg	75 mcg	150 mcg	Salmeterol
Peak FEV1 1 <sup>st</sup> 4 hrs Day 1	0.03 (-0.00, -0.06)	0.05 (0.02, 0.08)	0.09 (0.06, 0.12)	0.12 (0.09, 0.15)	0.12 (0.09, 0.15)
Peak FEV1 1 <sup>st</sup> 4 hrs Day 14	0.09 (0.04, 0.13)	0.12 (0.08, 0.17)	0.13 (0.08, 0.18)	0.13 (0.08, 0.18)	0.12 (0.07, 0.17)
AUC FEV1 5 min- 4hr Day 1	0.05 (0.02, 0.08)	0.07 (0.04, 0.10)	0.11 (0.08, 0.14)	0.14 (0.11, 0.17)	0.14 (0.11, 0.18)
AUC FEV1 5 min- 4 hr Day14	0.10 (0.05, 0.15)	0.14 (0.09, 0.19)	0.13 (0.09, 0.18)	0.15 (0.11, 0.20)	0.14 (0.10, 0.19)
AUC FEV1 5 min- 12 hr Day 1	0.04 (0.01, 0.08)	0.06 (0.03, 0.09)	0.10 (0.06, 0.13)	0.13 (0.10, 0.17)	0.14 (0.10, 0.17)
AUC FEV1 5 min- 12 hr Day 14	0.08 (0.04, 0.13)	0.14 (0.10, 0.19)	0.13 (0.08, 0.17)	0.14 (0.09, 0.18)	0.13 (0.09, 0.18)

Source: Adapted from Tables 11-10, 11-11 and 11-12

➤ **Peak FEV1**

At Day 1 the treatment difference in LS mean peak FEV1 in the indacaterol 150 mcg treatment group achieved the MCID (0.12L); the same as observed in the salmeterol treatment group. The treatment difference compared to placebo for the indacaterol 37.5 and 75 mcg treatment groups at Day 1 were 0.05L and 0.09L, respectively. However, at Day 14, the LS mean peak FEV1 treatment differences compared with placebo were similar for most indacaterol treatment groups: indacaterol 37.5 mcg 0.12 (0.08, 0.17); indacaterol 75 mcg 0.13 (0.08, 0.18); indacaterol 150 mcg 0.13 (0.08, 0.18) and salmeterol 0.12 (0.07, 0.17).

➤ **AUC for FEV1 5 min – 4 hr and FEV1 5 min – 11 hr 45 min**

The largest treatment differences for AUC for FEV1 5 min-4 hr and FEV1 5 min-11 hr 45 min at Day 1 were largest for the 150 mcg indacaterol group, however, by Day 14 for the same assessments, the difference between 37.5 mcg, 75 mcg and 150 mcg indacaterol were negligible.

➤ **FEV1 and FVC**

At the 5 min time point on Day 1, the magnitude of the improvements in FEV1 compared with baseline are 0.11L for indacaterol 150 mcg, 0.10L for indacaterol 75 mcg and 0.07L for salmeterol. See Table 27 below for a summary. At this same time point on Day 14 the 75 mcg indacaterol dose is observed to have the largest treatment difference. The values are: 0.14L for indacaterol 150 mcg, 0.16L for indacaterol 75 mcg and 0.14L for salmeterol. Consistent with the findings in B2357, at the 5 minute time point on Day 1 indacaterol has achieved 77% of the effect seen at 4 hours when steady state is reached. These results indicate a faster onset of action for the 150 mcg and 75 mcg indacaterol treatment groups compared with the 18.75 mcg and 37.5 mcg treatment groups and salmeterol.

**Table 27 Protocol B2356 Summary statistics of FEV1 (L) at each time point for Days 1 and 14**

Time point	Treatment difference from baseline (L) at Day 1 and 14					
	Day 1			Day 14		
	75 mcg	150 mcg	salmeterol	75 mcg	150 mcg	salmeterol
-0:50	N/A	N/A	N/A	0.1	0.1	0.1
-0:15	N/A	N/A	N/A	0.09	0.11	0.11
0:5	0.10	0.11	0.07	0.16	0.14	0.14
0:15	0.12	0.14	0.11	0.15	0.18	0.18
0:30	0.13	0.15	0.13	0.15	0.17	0.17
1:00	0.12	0.15	0.14	0.15	0.17	0.17
2:00	0.12	0.15	0.16	0.16	0.17	0.17
4:00	0.13	0.16	0.17	0.14	0.15	0.15
8:00	0.09	0.12	0.12	0.09	0.09	0.09
11:10	0.06	0.09	0.08	0.08	0.11	0.11
11:45	0.06	0.1	0.08	0.08	0.09	0.09
11:10	0.09	0.11	0.12	0.08	0.11	0.11
23:45	0.11	0.13	0.13	0.09	0.12	0.12

Source: Adapted from Table 14.2-5.2 Study No. CQAB149B2356 Clinical Study Report

*Reviewer Comment:*

*B2356 represents the second trial providing supportive data for the claim of rapid onset of action within 5 minutes, consistent with language included in the clinical section of the proposed label.*

➤ **Rescue medication use**

All rescue medication assessments including: daily number of puffs of rescue medication; daytime and nighttime number of puffs of rescue medication; and percentage of days with no rescue use statistically significantly improved with all doses of indacaterol as well as salmeterol. Refer to Table 28 below.

**Table 28 Protocol B2356 Rescue medication use over 14 days: treatment comparisons, FAS**

Treatment	n	- Treatment -		Comparison	- Treatment difference -			
		LS Mean	SE		LS Mean	SE	95% CI	p-value
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 18.75 ug	85	-1.58	0.227	Ind 18.75 ug - Pbo	-1.04	0.309	( -1.65, -0.44)	<.001
Ind 37.5 ug	83	-2.07	0.230	Ind 37.5 ug - Pbo	-1.54	0.312	( -2.15, -0.92)	<.001
Ind 75 ug	86	-1.72	0.227	Ind 75 ug - Pbo	-1.18	0.308	( -1.79, -0.58)	<.001
Ind 150 ug	85	-1.84	0.227	Ind 150 ug - Pbo	-1.30	0.309	( -1.91, -0.70)	<.001
Salm	89	-1.72	0.224	Salm - Pbo	-1.19	0.304	( -1.79, -0.59)	<.001
Pbo	89	-0.54	0.223					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 18.75 ug	81	-1.00	0.133	Ind 18.75 ug - Pbo	-0.56	0.180	( -0.91, -0.20)	0.002
Ind 37.5 ug	82	-1.31	0.133	Ind 37.5 ug - Pbo	-0.87	0.180	( -1.22, -0.51)	<.001
Ind 75 ug	84	-1.11	0.132	Ind 75 ug - Pbo	-0.66	0.179	( -1.01, -0.31)	<.001
Ind 150 ug	82	-1.17	0.133	Ind 150 ug - Pbo	-0.72	0.180	( -1.08, -0.37)	<.001
Salm	86	-1.11	0.131	Salm - Pbo	-0.66	0.177	( -1.01, -0.32)	<.001
Pbo	89	-0.45	0.128					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 18.75 ug	83	-0.61	0.110	Ind 18.75 ug - Pbo	-0.49	0.149	( -0.78, -0.20)	0.001
Ind 37.5 ug	83	-0.79	0.110	Ind 37.5 ug - Pbo	-0.67	0.149	( -0.96, -0.38)	<.001
Ind 75 ug	86	-0.64	0.109	Ind 75 ug - Pbo	-0.53	0.148	( -0.82, -0.24)	<.001
Ind 150 ug	85	-0.67	0.109	Ind 150 ug - Pbo	-0.56	0.148	( -0.85, -0.26)	<.001
Salm	88	-0.62	0.108	Salm - Pbo	-0.50	0.146	( -0.79, -0.22)	<.001
Pbo	89	-0.12	0.107					
Percentage of 'days with no rescue use'								
Ind 18.75 ug	81	39.41	3.413	Ind 18.75 ug - Pbo	13.70	4.583	( 4.7, 22.7)	0.003
Ind 37.5 ug	82	44.44	3.389	Ind 37.5 ug - Pbo	18.70	4.581	( 9.7, 27.7)	<.001
Ind 75 ug	85	36.07	3.349	Ind 75 ug - Pbo	10.40	4.523	( 1.5, 19.3)	0.022
Ind 150 ug	83	44.66	3.361	Ind 150 ug - Pbo	19.00	4.554	( 10.0, 27.9)	<.001
Salm	86	40.06	3.336	Salm - Pbo	14.40	4.499	( 5.5, 23.2)	0.001
Pbo	89	25.69	3.260					

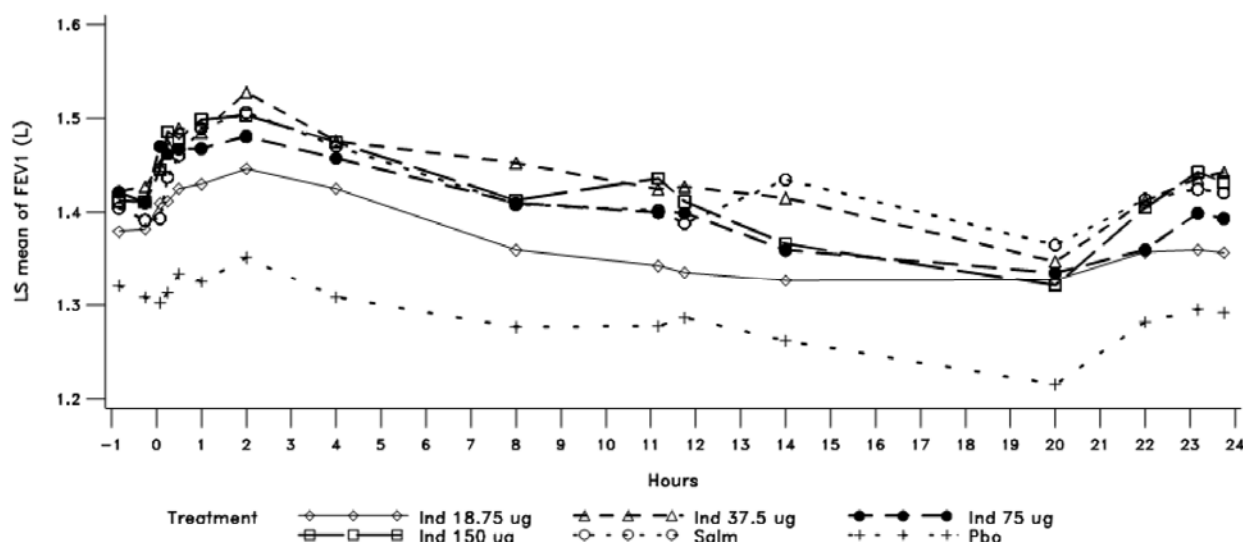
Source: Table 11-13 Study No. CQAB149B2356 Clinical Study Report

### Exploratory efficacy results:

#### ➤ Serial spirometry assessments

After the final dose on Day 14, a subset of 369 patients took part in serial spirometry assessments over 24 hours. The LS mean FEV1 was lower in the 18.75 mcg treatment group at all time points up to 24 hour post-starting on Day 14. While the time points for the 18.75 mcg treatment group during the first half of the dose-response-time curve (5 min-8 hours) were significantly larger than placebo, there were many time points between 11 hr 10 min to 23 hr 45 min that were not. The remaining indacaterol treatment groups, 37.5 mcg, 75 mcg and 150 mcg were statistically greater than placebo at all time points up to 24 hours post dose starting on Day 14. Refer to Figure 5 for a graphical display of the data.

**Figure 5 Protocol B2356 24 hour profile of LS mean of FEV1 after 14 days of treatment (FAS, 24 hour serial spirometry subsets)**



Source: Figure 11-1 Study No. CQAB149B2356 Clinical Study Report

## Pharmacokinetic analysis

Pharmacokinetic assessments were carried out in 135 patients with calculations obtained from 123: 24 patients in the 18.75 mcg dose, 24 the 37.5 mcg, 38 the 75 mcg, and 38 in the 150 mcg dose. Some had too few data points above LLOQ to allow PK parameter calculation. An increase in C<sub>max</sub> (24.8 pg/mL for 18.75 mcg to 250.53 pg/mL for 150 mcg) and AUC (145 pg\*hr/mL for 18.75 to 2606.3 pg\*hr/mL for 150 mcg) was observed with increasing doses. All indacaterol treatment groups demonstrated peak serum levels at a median T<sub>max</sub> of 0.33 hours post dose. Some bias was introduced due to numerous samples being below the LLOQ for the 18.75 mcg treatment group and was not included in the statistical analysis.

### 3.3.2.5 Safety Review

#### 3.3.2.5.1 Extent of exposure

The mean number of days of exposure were similar across all treatment groups (14.4 to 15.5). Compliance over the two week treatment period ranging from 88% of doses taken in the indacaterol 18.75 mcg group to 94% in the 75 mcg group and were identical between the Concept 1 SDDPI and the proprietary device.

#### 3.3.2.5.2 Concomitant medications

Concomitant medications and significant non-drug therapies (COPD-related and non-COPD-related) were taken by greater than 80% of patients in any treatment group in the safety set as follows: indacaterol 18.75 mcg (77 patients, 86.5%), indacaterol 37.5 mcg (80 patients, 88.9%), indacaterol 75 mcg (79 patients, 84.0%), indacaterol 150 mcg (83 patients, 90.2%), salmeterol (74 patients, 81.3%) and placebo (80 patients, 87.9%).

COPD-related concomitant medications were taken by greater than 35% of patients in any treatment group. The most common medications taken were ICSs which were used by a similar percentage of patients in each treatment group (ranging from 35.1% to 38.9%). COPD-related concomitant medications were changed after the start of study medication by a low percentage of patients; 1 patient (1.1%) in the indacaterol 18.75 mcg group, 2 patients (2.2%) in the indacaterol 37.5 mcg group, and 2 patients (2.2%) in the placebo group. Non-COPD-related concomitant medications were taken by a similar percentage of patients in each treatment group. The most commonly used medications overall were acetylsalicylic acid, simvastatin, lisinopril, and multivitamins.

### 3.3.2.5.3 Adverse events

The overall incidence of AEs (including COPD exacerbations) was higher in the placebo group (23.1%) than in any active treatment group (14.6% for indacaterol 18.75 mcg, 18.9% for indacaterol 37.5 mcg, 18.1% for indacaterol 75 mcg, 10.9% for indacaterol 150 mcg, and 15.4% for salmeterol). The system organ classes most frequently affected by AEs were respiratory, thoracic and mediastinal disorders, infections and infestations, gastrointestinal disorders and investigations.

**Table 29 Adverse events overall and by primary system organ class - n (%) of patients (Safety set)**

	Ind 18.75 ug N=89 n (%)	Ind 37.5 ug N=90 n (%)	Ind 75 ug N=94 n (%)	Ind 150 ug N=92 n (%)	Salm N=91 n (%)	Pbo N=91 n (%)
Patients with any AE(s)	13 (14.6)	17 (18.9)	17 (18.1)	10 (10.9)	14 (15.4)	21 (23.1)
Primary system organ class						
Respiratory, thoracic and mediastinal disorders	2 (2.2)	6 (6.7)	7 (7.4)	2 (2.2)	3 (3.3)	4 (4.4)
Infections and infestations	3 (3.4)	2 (2.2)	4 (4.3)	4 (4.3)	2 (2.2)	7 (7.7)
Gastrointestinal disorders	2 (2.2)	3 (3.3)	1 (1.1)	3 (3.3)	4 (4.4)	4 (4.4)

Source: Table 12-2 Study No. CQAB149B2356 Clinical Study Report

The most frequently reported AE in the total safety set was cough, which occurred at similar frequencies in the indacaterol 37.5 and 75 mcg groups (6.7% and 7.4%, respectively) and at lower frequencies in the other treatment groups (none in the indacaterol 18.75 mcg group, 1.1% in the indacaterol 150 mcg group, 1.1% in the salmeterol group and 2.2% in the placebo group). Of the 17 patients with cough, 5 of the 6 in the indacaterol 37.5 mcg group, and 4 of the 7 in the indacaterol 75 mcg group reported the event as occurring after study drug inhalation. No patient in any treatment group discontinued the study drug due to cough.

**Table 30 Most frequent AEs, including COPD exacerbations (at least 2 patients in any treatment group) by preferred term-n (%) of patients (Safety set)**

	Ind 18.75 ug N=89 n (%)	Ind 37.5 ug N=90 n (%)	Ind 75 ug N=94 n (%)	Ind 150 ug N=92 n (%)	Salm N=91 n (%)	Pbo N=91 n (%)
Patients with any AE(s)	13 (14.6)	17 (18.9)	17 (18.1)	10 (10.9)	14 (15.4)	21 (23.1)
Preferred term						
Cough	0 (0.0)	6 (6.7)	7 (7.4)	1 (1.1)	1 (1.1)	2 (2.2)
Chronic obstructive pulmonary disease	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
Headache	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	2 (2.2)
Vomiting	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	1 (1.1)	2 (2.2)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)

Source: Table 12-3 Study No. CQAB149B2356 Clinical Study Report

### Deaths and SAEs

No deaths occurred in any treatment group during the study or 30 day follow up period. SAEs (including COPD exacerbations) were observed in 8 patients in total. Briefly, 1 patient in the indacaterol 18.75 mcg group was a 65 year old male with an AML, symptoms started one day after drug initiation he underwent PTCA two days later. One patient in the indacaterol 75 mcg group, a 55 year old male hospitalized for dyspnea and chest pain 29 days after the last dose.

Three patients in the indacaterol 150 mcg group: a 58 year old female with a history of anemia developed symptomatic anemia 12 days after onset of treatment; a 66 year old female who developed a deep venous thrombosis 23 days after study completion and a 55 year old female hospitalized for a COPD exacerbation 2 weeks after study completion. Three patients in the placebo group reported SAEs: hyperkalemia, COPD exacerbation and esophageal obstruction. There were no significant differences of SAEs by age group (<65 years, ≥ 65 years).

#### **Adverse events leading to discontinuation**

The AEs leading to permanent discontinuation of study drug were observed for 4 patients (4.5%) in the indacaterol 18.75 mcg group, and 1 patient in each of the indacaterol treatment groups. Brief descriptions of the 4 discontinuations in the 18.75 mcg treatment group are as follows: a 56 year old male with atrial fibrillation with rapid ventricular response; a 65 year old male with a myocardial infarction; a 69 year old female with a COPD exacerbation and upper respiratory tract infection and a 62 year old male with increased liver enzymes. One patient in the 37.5 mcg treatment group was a 66 year old male who developed chills, nausea and syncope leading to discontinuation. A 58 year old male in the 75 mcg treatment group developed polycythemia. The one discontinuation in the placebo treatment group was in a 59 year old male with a COPD exacerbation. The 1 patient with the myocardial infarction in the 18.75 mcg group and the one with a COPD exacerbation in the placebo group were also captured in the above SAEs section.

#### **3.3.2.5.4 Laboratory findings**

The notable criteria for the hematology laboratories are for hematocrit, males < 0.37 L/L, and for female < 0.32 L/L. The number of patients with recorded abnormal values was: 3, 3, 4, 2, 2 and 4 in 18.75, 37.5, 75, 150 mcg, salmeterol and placebo respectively. There were no abnormal platelet values and few numbers of patients with white blood cell counts outside of the notable range. Focus will be placed on potassium and glucose levels for the chemistry findings. The numbers of patients with a shift from normal at baseline to low (< 3 mmol/L) post baseline were: 6 patients in the 18.75 mcg, 1 in 37.5 mcg, 4 in 75 mcg, 3 in 150 mcg and 5 each in salmeterol and placebo treatment groups. Notably high glucose levels > 9.99 mmol/L and based on the maximum post-baseline value, the proportion of patients with shifts from normal at baseline to high post-baseline was: 14.8% for indacaterol 18.75 mcg, 11.2% for indacaterol 37.5 mcg, 20.2% for indacaterol 75 mcg, 13.0% for indacaterol 150 mcg, 25.6% for salmeterol and 12.1% for placebo.

#### **3.3.2.5.5 ECG findings**

There were no clinically significant abnormal overall ECG interpretations. The incidence of a maximum increase from baseline of 30 ms to 60 ms in Fridericia's QTc was highest in the indacaterol 75 mcg treatment group (6 cases) and in the 18.75 mcg indacaterol and placebo groups (5 cases in each). Two patients were recorded with an increase in Fridericia's QTc of > 60ms, one in 37.5 mcg and one in salmeterol. Overall, the most frequently recorded ECG abnormalities were ectopy. This occurred the most in the 18.75 and 37.5 mcg treatment groups (23% in each).

#### **3.3.2.5.6 Physical examination**

Focus was placed on systolic and diastolic blood pressure and pulse changes. Low SBP or ≤ 75 mm Hg or ≤ 90 mm Hg and ≥ 20 decrease from baseline was recorded in 1 in the 18.75 mcg and 1 in the salmeterol group. High SBP or >200 mm Hg, or ≥ 180 mm Hg and increase from baseline ≥ 20 mm Hg was observed in: 1 in 18.75 mcg, 1 in 37.5 mcg and 2 in salmeterol groups. Low DBP <40 mm Hg, or ≤ 50 mmHg and decrease from baseline ≥ 15 mm Hg was observed in: 1 in 18.75 mcg, 1 in 37.5 mcg and 1 in salmeterol groups. High DBP or >115 mm Hg, or ≥ 105 mm Hg and increase from baseline ≥ 15



mmHg was observed in: 1 in 37.5 mcg, 1 in 150 mcg and 1 in salmeterol treatment groups.

### 3.3.2.5.7 Summary of Study

This was a two week, multicenter, randomized, placebo-controlled trial comparing different doses of indacaterol, 18.75 mcg, 37.5 mcg, 75 mcg and 150 mcg to placebo in adults with COPD. In addition, salmeterol 50 mcg bid was used as an active comparator. There was a dose response in the primary endpoint of tFEV1 at Day 15. The largest magnitude of treatment difference compared to placebo for the primary endpoint was observed for the 150 mcg indacaterol dose with a value of 0.12 L. This value was statistically significant. The treatment differences observed for indacaterol 37.5 mcg, 75 mcg and salmeterol were all 0.10 L, also statistically significant. For the secondary endpoints of tFEV1 at Day 2 and Day 14, peak FEV1 and AUC, there was a dose response in the LS mean treatment differences for indacaterol doses of 18.75 to 150 mcg. Indacaterol doses 75 mcg and 150 mcg and salmeterol were statistically significant, 0.11, 0.13 and 0.13 L respectively on Day 2 and 0.09, 0.10 and 0.08 L respectively on Day 14. By Days 14/15 the magnitude of effect between the 150 mcg indacaterol and 37.5 mcg, 75 mcg indacaterol and salmeterol treatments for the primary and key secondary endpoints were undetectable.

There were some differences based on subgroup analysis apparent with the primary endpoint. Because of the few numbers of blacks and asians, no quantitative assessments can be made based on race. However, no differences based on age can be concluded. At the higher doses of indacaterol, 75 mcg and 150 mcg males exhibited larger treatment differences than females. Overall, those that were ex smokers had larger treatment differences than current smokers. The higher doses of indacaterol, 75 mcg and 150 mcg displayed larger treatment differences in those who were on ICS at baseline. Those with more severe COPD in the 75 mcg and 150 mcg treatment groups had larger treatment differences of tFEV1 (0.12 each) at Day 15 than the two lower indacaterol 18.75 mcg and 37.5 mcg treatment groups.

Indacaterol demonstrated a rapid onset of action with a treatment difference of 0.10 L for 75 mcg and 0.11 L for 150 mcg indacaterol at the 5 minute post treatment time point on Day1. For the peak FEV1 within 4 hours of the first dose assessment the 150 mcg indacaterol dose along with salmeterol achieved the largest treatment differences of 0.12 L followed by 75 mcg with 0.09 L and 37.5 mcg with 0.05 L. All assessments of rescue medication use showed improvements from baseline for all indacaterol treatment groups and with salmeterol after 14 days of treatment; and all were statistically significantly greater than those seen in the placebo group.

The most frequent reported AE was cough, which occurred at similar frequencies in the indacaterol 37.5 and 75 mcg groups (6.7% and 7.4%, respectively) and at lower frequencies in the other treatment groups (none in the indacaterol 18.75 mcg group, 1.1% in the indacaterol 150 mcg group, 1.1% in the salmeterol group and 2.2% in the placebo group). There were no deaths and 8 patients with SAEs reported. AEs (including COPD exacerbations) leading to permanent discontinuation of study drug were reported for 4.5% of patients in the indacaterol 18.75 mcg group, and 1.1% of patient in the 37.5 mcg and 75 mcg indacaterol treatment groups. There were no clinically meaningful effects of treatment at any of the doses of indacaterol studied on pulse, blood pressure and QTc interval, and no unexpected effects on clinical laboratory parameters were observed.

### **3.3.3 DOSE REGIMEN TRIAL B2223**

*A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel group, Repeated-dose Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of Three Different Dosing Regimens of Inhaled Indacaterol Maleate in Patients with Persistent Asthma*

#### **3.3.3.1 Trial Description**

##### **3.3.3.1.1 Design**

This was a Phase II international multicenter, randomized, double-blind, multiple dose, placebo-controlled, parallel group trial. Patients with persistent asthma were randomized to receive either twice daily 37.5 mcg, once daily 75 mcg, alternate day indacaterol 150 mcg or twice daily placebo from Day 1 to Day 16.

*Reviewer Comment:*

*The dose regimens were selected with a bias of using the mean daily dose of 75 mcg indacaterol.*

*Reviewer Comment:*

*A dosing regimen trial was requested by the FDA to address deficiencies included in the dose selection process of the first cycle.*

##### **3.3.3.1.2 Duration**

A 21 day screening period was followed by a 2 week run-in period and a 19 day treatment period. The end of study evaluation occurred 3 days following the last treatment drug, Day 16. The total study duration per patient was approximately 54 days.

##### **3.3.3.1.3 Population**

Male and female patients aged 18 years or above, who had a diagnosis of persistent asthma diagnosed according to GINA guidelines 2008 (FEV1 at screening of 50-90% predicted normal) were included. Patients had to be on a stable dose of ICS one month prior to first study visit and had to demonstrate reversibility albuterol with an increase in FEV1  $\geq 12\%$  and  $\geq 200$  mL.

*Reviewer Comment:*

*As in trial B2357, an asthmatic population was selected at the recommendation of the Agency where the rationale was to test in the patient population most sensitive to both the bronchodilator and AE effects of LABAs.*

#### **Study Sites**

This trial was conducted at 19 sites in the United States, 3 sites in the United Kingdom, 2 in France, 2 in Jordan, 1 in Germany and 1 in the Netherlands.

*Reviewer's Comment:*

*The two dose finding studies, B2357 and B2356 were carried out solely in the United States. It is unclear if this different population has introduced any unexpected results.*

##### **3.3.3.1.4 Investigational and Reference Therapy**

Investigational therapy was indacaterol capsules as maleate salt in three dose strengths: 37.5 mcg batch number X224 0909, 75 mcg batch number X173GF and 150 mcg batch number X172GF. Matching placebo capsules for inhalation with the batch number X123DF were used. All dry powder capsules were inhaled through the Concept 1 SDDPI device.

##### **3.3.3.1.5 Objectives**

Primary Objectives:

- To evaluate the bronchodilator effect of three different indacaterol dosing regimens (once-daily/q.d., alternate day/q.o.d. and twice daily/b.i.d.) on tFEV1 after two-weeks of treatment in patients with persistent asthma

- To assess the bronchodilator effect of q.d. and b.i.d. indacaterol dosing regimens on FEV1 AUC(0-24hr)
- To assess the bronchodilator effect of q.o.d. and q.d. indacaterol dosing regimens on FEV1 AUC(0-48hr) and FEV1 AUC(24-48hr).

Key Secondary Objectives:

- To assess FEV1 and FVC at each post-dose time-point on days 1/2 and days 16/17/18/19 (q.d. and b.i.d. treatment)
- To assess FEV1 and FVC at each post-dose time-point on days 1/2/3 and days 15/16/17/18/19 (q.o.d. treatment)
- Peak FEV1 on day 1 and 16

Additional Secondary Objectives:

- To assess the bronchodilator effect of three indacaterol dosing regimens on:
  - FEV1 AUC<sub>(0-12hr)</sub> and FEV1 AUC<sub>(12-24hr)</sub> for b.i.d. and q.d. treatment regimens
  - FEV1 AUC<sub>(0-24hr)</sub> and FEV1 AUC<sub>(36-48hr)</sub> for q.d. and q.o.d. treatment regimens
  - Trough FEV1 after 1 day of treatment
  - Time to peak FEV1 on day 1 and day 16
  - FVC (trough, peak and AUCs corresponding to key secondary objective variables defined for FEV1)
  - FEF<sub>25-75</sub> (trough, peak and AUCs corresponding to key secondary objective variables defined for FEV1)
- Morning and evening Peak Expiratory Flow (PEF)
- To assess day and night time rescue medication usage.

Exploratory Objectives:

To explore the relationships between systemic PK (AUC<sub>tau</sub> and C<sub>max</sub>) and heart rate, QTcF interval, serum potassium and plasma glucose of three different indacaterol dosing regimens.

### 3.3.3.1.6 Inclusion Criteria

Patients had to be on a stable regimen of ICS for the month prior to the first study visit. The FEV1 at screening had to be  $\geq 50\%$  and  $\leq 90\%$  of the predicted normal value. As well, patients had to demonstrate reversibility with an increase of  $\geq 12\%$  and  $\geq 200$  mL in FEV1 over their prebronchodilator value within 30 minutes after having inhaled a total of 360 mcg of albuterol MDI (or equivalent dose of DPI) (the reversibility test). This criterion for FEV1 was demonstrated after a washout period of at least 6 hours during which no SABA has been inhaled and a minimum of 48 hours for a LABA and 7 days for tiotropium.

### 3.3.3.1.7 Exclusion Criteria

Key exclusion criteria were:

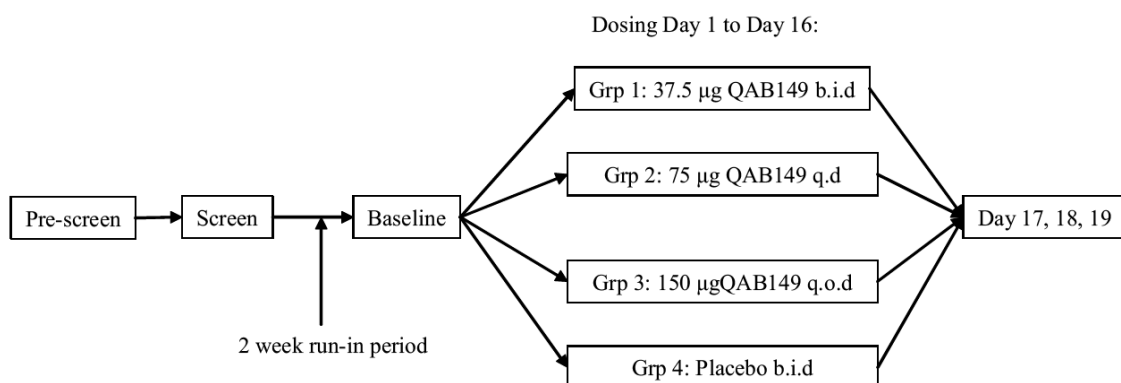
- Prior intubation for a severe asthma attack/exacerbation, a severe asthma attack/exacerbation requiring hospitalization in the 6 months prior to the first study visit or an ER visit for an asthma attack/exacerbation within 6 weeks prior to the first study visit or any time between the first study visit and pre-dose Day 1
- Lower respiratory tract infection within 6 weeks prior to the first study visit or any time between the first study visit and pre-dose day 1
- Seasonal allergy whose asthma was likely to deteriorate during the study period
- Patients who required the use of  $\geq 8$  inhalations per day of the SABA (90 mcg albuterol MDI or equivalent dose of DPI) on any 2 consecutive days from screening to randomization
- Smoking history of greater than 10 pack years, current smokers who smoked greater than 10 cigarettes per day. Smokers had to maintain their usual smoking habits throughout the course of the study
- Patients diagnosed with COPD
- Significant illness within 4 weeks prior to the first study visit

The remainder of the exclusion criteria were similar to the B2357 asthma dose ranging study.

### 3.3.3.1.8 Conduct

Figure 6 and Table 31 below display the overall design and schedule of study procedures. Patients were pre-screened to review their current asthma medication and have it adjusted as appropriate and sign the informed consent. During the pre-screening visit patients were provided with a PEF meter (PiKo®-1 Home Monitoring System) and diary in which they recorded their morning and evening PEF, asthma symptoms and the use of rescue medication throughout the study. Patient eligibility assessments were performed at either the pre-screening or screening visit which included an FEV1 reversibility test to total dose of 400 mcg albuterol. Patients were admitted to the study site by the morning of Day -1. At Visit 3 (Day 1) all eligible patients were randomized to one of the following 4 treatment arms in a ratio of 1:1:1:1 as seen in Figure 6.

**Figure 6 Protocol B2223 Study Design**



Source: Figure 9-1 Study No. CQAB149 B2223 Clinical Study Report

### Efficacy Assessments:

Serial spirometry assessments were performed on a different schedule from the previous dosing ranging studies, B2357 and B2356. The spirometry time points were:

- **Day -1:** 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 8 hrs, 11hrs 10mins, 11hrs 45mins, 12hrs 10mins, 12hrs 30mins, 13, 14, 16, 20 and 22 hrs post dose
- **Day 1:** 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 11hrs 10mins, 11hrs 45mins post dose
- **Day 2:** pre-dose
- **Day 15 and 16:** 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 8 hrs, 11hrs 10mins, 11hrs 45mins, 12hrs 10mins, 12hrs 30mins, 13, 14, 16, 20 and 22hrs post dose
- **Day 17:** 50 and 15 mins pre-dose, 6 hrs post dose
- **Day 18 and 19:** pre-dose

Peak Expiratory Flow Rates were obtained twice daily. Patients were permitted to leave the clinic following the completion of the all post-dose assessments on day 1. Patients returned to the clinic on the morning of days 2, 3, 9, 13, 15, 16, 17, 18 and 19. Patients returned at least 1 hour prior to scheduled dosing for spirometric final study assessments which were performed on day 19.

Placebo capsules were administered to maintain the blind in the 75 mcg q.d. dosing regimen (an evening dose) and 150 mcg q.o.d dosing regimen (an evening dose every other day and morning and evening doses on non-treatment days).

### Safety Assessments:

Blood pressure, heart rate, ECG, potassium and glucose measurements were performed as follows:

- **Day 1:** 50 mins pre-dose, 15 and 30 mins, 1, 2 hrs post dose
- **Day 2 and 3:** pre-dose
- **Day 15, 16:** 50 mins pre-dose, 15 and 30 mins, 1, 2, 13 and 14 hrs post dose

- **Day 17, 18 and 19:** pre-dose

**PK Assessments:**

Timed PK samples were collected on:

- Day 1 at : pre-dose, 0.25, 0.5, 1, 2, 4, 12 hours post dose (before evening dose)
- Day 2, 3, 9, 13 at : pre-morning dose (15 minutes before dosing)
- Day15 at: pre-dose, 0.25, 0.5, 1, 2, 4, 12 hours post dose (before evening dose)
- Day16 at : pre-morning dose (15 minutes before dosing)
- Day17 at : 24 hours post morning dose on day 16

Clinical Review  
Anya Harry  
NDA 22-383  
Arcapta Neohaler (indacaterol maleate)  
Clinical Trials: B2223

**Table 31 Protocol B2223 Evaluation and visit schedule**

	Screening		Baseline	Treatment Period											Study Completion	
Visit numbers <sup>1</sup>		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6		Visit 7		Visit 8	Visit 9	Visit 10	Visit 11	Visit 777
Day	D-35 to D-14	D-1	D-1	D1	D2	D3	D4-8	D9	D10-12	D13	D14	D15	D16	D17	D18	D19
Inclusion /Exclusion criteria		X	X													
Informed consent	X															
Relevant med. History/Current med. Conditions (incl smoking history)		X	X													
Concomitant m eds/Therapies	X	X	As required													
Dem ography		X														
Physical examination		X	X													X
Device instruction			X													
FEV <sub>1</sub> Reversibility test		X														
Hepatitis and HIV screen		X														
Alcohol test & drug screen		X	X													
Pregnancy test (Females only)		X	X													X
FSH testing (post-menopausal females only )		X														
Drug administration at clinic				X	X <sup>2</sup>	X <sup>2</sup>		X <sup>2</sup>		X <sup>2</sup>		X	X			
Drug administration at home					X <sup>2</sup>	X <sup>2</sup>	X	X <sup>2</sup>	X	X <sup>2</sup>	X					
Diary completion					X <sup>2</sup>	X <sup>2</sup>	X	X <sup>2</sup>	X	X <sup>2</sup>	X					
Study completion information																X
Comments	As required															
Vital signs and body measurements																
Body height		X														
Body weight		X	X													X
Body temperature		X	X													
Blood pressure/pulse rate <sup>4</sup>		X	X	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>						X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>
ECG evaluation (12 leads) <sup>4</sup>		X	X	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>						X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>
Spirom etry <sup>3</sup>		X	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>						X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Urine																
Urinalysis		X	X													X
Blood																
Haematology, Biochemistry		X	X													X
Serum Potassium & Plasma Glucose <sup>4</sup>		X	X	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>						X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>
PK Samples <sup>5</sup>				X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>		
PEFR	X <sup>6</sup>															
Adverse Events					As required											

X = visits at which all assessments were performed.

Source: Table 9-4 Study CQAB149B2223 Clinical Study Report

### 3.3.3.1.9 Concomitant Treatments

Prohibited medications were similar to those in B2357, the asthma dose ranging study. The acceptable medications were also similar; primarily a stable dose of ICS was required. However, differences were that inhaled nasal cromolyn was permitted and maintenance immunotherapy was permitted.

### 3.3.3.1.10 Ethical Aspects

This clinical trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### 3.3.3.1.11 Data Analysis

#### Sample size calculation

A sample size of 40 completed patients per treatment arm was planned; with over-recruitment by 20% to allow for drop-outs, 48 patients per treatment arm were to be recruited. The sample size was based on estimating the precision of the treatment contrasts for the primary endpoints tFEV1 and FEV1 AUC 0-24hr, and was based on variability data from study CQAB149A2218 of 290 mL for tFEV1, and 245 mL for AUC 0-24hr, expressed in terms of 95% CI width for treatment differences.

A 95% CI of expected width approximately 250 mL for tFEV1 was considered an acceptable level of precision by the Sponsor in this trial. With the assumption of a standard deviation of 290 mL, Forty (40) evaluable patients per treatment group were required to detect a 95% confidence interval (two-sided) of expected width 250 mL. Over-recruiting by 20% resulted in a total sample size of 192 randomized patients (48 per treatment group) required. This sample size would also allow a 95% CI of expected width of 215 mL for time-standardized FEV1 AUC<sub>0-24</sub> to be detected assuming a standard deviation of 245 mL.

#### Efficacy Variables

The primary efficacy variables were tFEV1 after 2 weeks of study treatment and AUCs for FEV1 change from baseline over the time period 0-24 hr, 0-48 hr and 24-48 hr.

#### Reviewer's Comment:

*Data for the remaining primary endpoints FEV1 AUC<sub>0-48 hr</sub> and AUC<sub>24-48 hr</sub> were not available from previous studies.*

The analysis sets were defined as follows: all patients who were randomized and received at least one dose of study drug were included in the safety and tolerability data set. Different from the dose ranging studies, there was no per protocol analysis. All patients who were dosed, with evaluable data were included in the data analysis set and all patients with evaluable PK data were included in the PK data analysis set.

The analyses of primary endpoints were performed using an analysis of covariance with treatment as a fixed effect and baseline value as a continuous covariate. Baseline values were determined from the baseline spirometry profile (Day -1 and pre-dose Day 1). Treatment contrasts between dosing regimens, and between dosing regimens and placebo, and their 95% confidence intervals, were also derived. Similar analyses were used for secondary endpoints. Change from baseline was analyzed separately for each post-dose time point.

Key secondary endpoints were the FEV1 and FVC change from baseline vs. time over the time periods 0-48 hr, and peak FEV1 on Days 1 and 16. Other endpoints of interest included values of FEV1 and FVC at each time point on Days 1/2/3 and Days 15/16/17/18/19, time-standardized AUC<sub>0-12 hr</sub>, AUC<sub>12-24 hr</sub> and AUC<sub>36-48 hr</sub>; tFEV1 at Day 1; peak and time to peak FEV1 on Day 1 and Day 16; FVC derived endpoints as for FEV1; FEF<sub>25-75</sub> derived endpoints as for FEV1.

The analysis of secondary derived endpoints was the same as for the primary endpoints. Specific treatment contrasts of interest for specified variables are as follows:

- AUC<sub>36-48 hr</sub> for indacaterol b.i.d and q.o.d
- AUC<sub>9-12 hr</sub> and AUC<sub>12-24 hr</sub> for indacaterol b.i.d and q.d.

For the key secondary endpoints, the corresponding confidence interval widths for contrasts between pairs of treatments were: FEV1 at each post-dose time-point on Days 1/2/3 and Days 15/16/17/18/19 would range between 245mL and 408mL. FVC at each post-dose time-point on Days 1/2/3 and Days 15/16/17/18/19 would range between 230mL and 315mL. Peak FEV1 on Day 1 and Day 16 expected confidence interval width was 290mL. A similar approach will be used to analyze other secondary endpoints. Data from the PiKo® device will be listed and summarized only.

PK data were listed and summarized by treatment group.

### **Safety Variables**

Safety data, including adverse events data, vital signs/ECG, chemistry, hematology, and use of rescue and concomitant medications, were and summarized by treatment group. Selected safety data were analyzed formally, including heart rate, QTcF, serum potassium and plasma glucose, using a repeated measures analysis.

### **Pharmacokinetic Variables**

Samples for PK analysis were collected during a dosing interval tau (tau = 12hr, 24hr, and 48hr for 37.5 mcg b.i.d., 75 mcg q.d. and 150 mcg q.o.d. respectively) after the first dose (Day 1) and the dose on Day 15. Trough samples were collected over the treatment period. Indacaterol concentrations in serum were measured by a validated LC/MS/MS method. Pharmacokinetic parameters AUCtau, AUClast, Cmax, Cmin, Tlast and Tmax were calculated after dosing on Day 1 and Day 15.

### **Protocol Amendments**

**Amendment 1** (September 9, 2010), issued before study start (February 23, 2010 – first patient consented), introduced the following changes based on recommendations from Health Authorities:

- The hierarchy of FEV1-based efficacy endpoints was changed, with promotion of AUCs over the dosing intervals of the three regimens to co-primaries to reflect the importance of characterizing the entire FEV1-time course in addition to the residual effect at the dosing interval i.e. trough, when comparing different dosing regimens.
- The addition of spirometry time points, 20 and 22 hours post-dose on days -1, 15 and 16, allowed this time course to be more fully characterized.
- The primary and key secondary efficacy endpoints were analyzed using analysis of covariance of change from baseline at Day 16, with baseline values as a continuous covariate, and treatment as a fixed effect. Treatment contrasts were constructed to compare pairs of treatments, and results expressed as estimates and their 95% confidence intervals, without adjustment for multiple testing.

**Amendment 2** (January 20, 2010), provided clarification for spirometry assessments, urinalysis requirements, device training and on timing of ICS treatment. It also provided small corrections (i.e., correction to the assessment schedule foot note for spirometry and correction to an error in the blood log and estimated total volume of blood). The criteria of two effective methods of contraception for women of child-bearing potential was also changed.

**Amendment 3** (January 20, 2010), clarified the grammar of inclusion 3; acceptable methods of contraception for women of child-bearing potential.

**Amendment 4** (March 31, 2010), issued 37 days after the start of the study when only 7 patients had received their first dose was requested by a Health Authority. An additional exclusion criteria was added



that related to patients being hypersensitive or allergic to indacaterol or other similar drugs in its class or to the excipients (including lactose) of the drug product.

**Amendment 5** (January 20, 2010), clarified the timing of the screening reversibility test to be performed between screening and Day -2.

### 3.3.3.2 Patient Disposition and Demographics

As indicated in Table 32 below, larger numbers of patients discontinued in the indacaterol 150 mcg and placebo (12.5 and 12.8% respectively) treatment groups which also had the largest numbers discontinued due to either abnormal test or subject withdrawal of consent. Few patients used rescue medication in the active treatment groups and most patients used it on a few days. Rescue medication use was higher in the placebo group with up to 19 patients using it on any one day

**Table 32 Protocol B2223 Patient disposition (Safety data set)**

	Indacaterol			Placebo	All patients
	37.5 µg b.i.d	75 µg q.d	150 µg q.o.d		
	N=48	N=48	N=48	N=47	N=191
	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	46 (95.8%)	46 (95.8%)	42 (87.5%)	41 (87.2%)	175 (91.6%)
Discontinued	2 (4.2%)	2 (4.2%)	6 (12.5%)	6 (12.8%)	16 (8.4%)
<b>Main cause of discontinuation</b>					
Adverse Event(s)	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	2 (1.0%)
Abnormal test procedure result(s)	0 (0.0%)	1 (2.1%)	2 (4.2%)	2 (4.3%)	5 (2.6%)
Subject withdrew consent	0 (0.0%)	0 (0.0%)	2 (4.2%)	2 (4.3%)	4 (2.1%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (0.5%)
Administrative problems	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (2.1%)	2 (1.0%)
Protocol deviation	2 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)

Source: Table 10-1 CQAB149B2223 Clinical Study Report

Review of the patient demographics in Table 33 reveal a lack of equal distribution of patients across dosing regimens. For example, there were fewer males in the indacaterol 75 mcg q.d. dose group and fewer blacks in the 37.5 mcg b.i.d dose group. The majority of patients were caucasian. Baseline disease pulmonary function characteristics also appeared to be different for the 75 mcg q.d. regimen with a mean FEV1 of 2.51 L where as the FEV1 for the 37.5 mcg bid regimen was 2.84 L, for 150 mcg q.o.d it was 2.61 L and placebo was 2.72 L.

**Reviewer Comment:**

*Any differences in baseline FEV1 were corrected by using baseline as a covariate in the analysis model.*

**Table 33 Protocol B2223 Demographic summary by treatment group (Safety data set)**

		Indacaterol			Placebo N=46
		37.5 mcg b.i.d N=48	75 mcg q.d N=47	150 mcg q.o.d N=48	
Age (years)	Mean (SD)	37 (11)	41 (14.7)	42 (12.2)	41 (12.7)
	Range	18-68	19-80	19-70	21-73
Gender-N (%)	Male	27 (56%)	23 (49%)	32 (67%)	28 (61%)
	Female	21 (44%)	24 (51%)	16 (33%)	18 (39%)
Race-N (%)	Caucasian	42 (88%)	37 (79%)	29 (60%)	43 (94%)
	Black	3 (6%)	8 (17%)	13 (27%)	2 (4%)
	Asian	1 (2%)	0 (0%)	2 (4%)	0 (0%)
	Pacific Islander	0 (0%)	0 (0%)	1 (2%)	0 (0%)
	Other	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Baseline FEV1 (L)	Mean (SD)	2.84 (0.643)	2.51 (0.624)	2.61 (0.723)	2.72 (0.658)
	Range	1.22-4.59	1.40-3.89	1.22-3.94	1.20-4.19
Reversibility FEV1 (%)	Mean (SD)	22.1 (11.06)	21.4 (8.07)	20.4 (12.75)	22.5 (9.25)
	Range	12.0-49.2	11.7-47.1	-20.1-50.0	11.9-47.1

Source: Adapted from Tables 11-1 and 11-2 CQAB149B2223 Clinical Study Report

#### Protocol deviations

The majority of protocol deviations listed related to missed PK assessments or missed spirometry assessments. For example, one of the protocol deviations included patients not being withdrawn when their PEF readings met the stopping criteria. This impacted 1 patient in the 37.5 mcg b.i.d group, 2 in the 75 mcg q.d. group, 5 patients in the 150 mcg group and 7 patients in the placebo group.

#### Reviewer Comment:

*The protocol deviations described would not change the overall results of the trial.*

### 3.3.3.3 Efficacy Review

#### 3.3.3.3.1 Primary Endpoint

As mentioned earlier in the Efficacy Variables section, the hierarchy of FEV1 related endpoints was changed with the FEV1 AUCs over the three time points being promoted to co-primary endpoints along with tFEV1 after two weeks. However, there was no mention of a multiplicity adjustment made in the analysis of the data. As summarized in Table 34, evaluation of primary endpoints, the treatment differences for all dosing regimens of indacaterol were greater than placebo. The tFEV1 on Days 15/16 for the dosing regimens of 0.197 for 75 mcg q.d. and 0.199 for 150 mcg q.o.d (contrast with placebo 0.202 and 0.203 L, respectively) were larger than 0.156 L for 37.5 mcg bid (contrast from placebo, 0.16 L). The actual values of change from baseline were very similar across treatment regimens ranging from 0.197 to 0.218 however when the widely varied placebo values were subtracted from the treatment differences the resultant values were all also widely spread.

**Table 34 Protocol B2223 Summary of the statistical analysis of change from baseline in trough FEV<sub>1</sub> and time-standardized AUCs on Days 15/16 (PD analysis set)**

PD parameter	Treatment	Change from baseline		
		Mean	Lower 90% CI	Upper 90% CI
Trough FEV <sub>1</sub> (L)	37.5 µg b.i.d	0.156	0.083	0.228
	75 µg q.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 q.d	0.198	0.127	0.269
	Placebo	0.030	-0.044	0.103
AUC 0-48h (L)	75 µg q.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 q.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

Source: Table 11-3 CQAB149B2223 Clinical Study Report

*Reviewer's Comment: Unclear why the placebo mean values varied widely across the different primary endpoints ranging from -0.005-0.08 which when subtracted from the treatment differences demonstrated different trends.*

Here the MCID, predefined as 200 ml was achieved by the 75 mcg q.d. and 150 mcg q.o.d. dosing regimens as demonstrated in Table 35 below of the treatment differences.

**Table 35 Study B2223 Summary of the statistical analysis of contrasts with placebo for change from baseline in trough FEV<sub>1</sub> and time-standardized AUCs on days 15/16 (PD analysis set)**

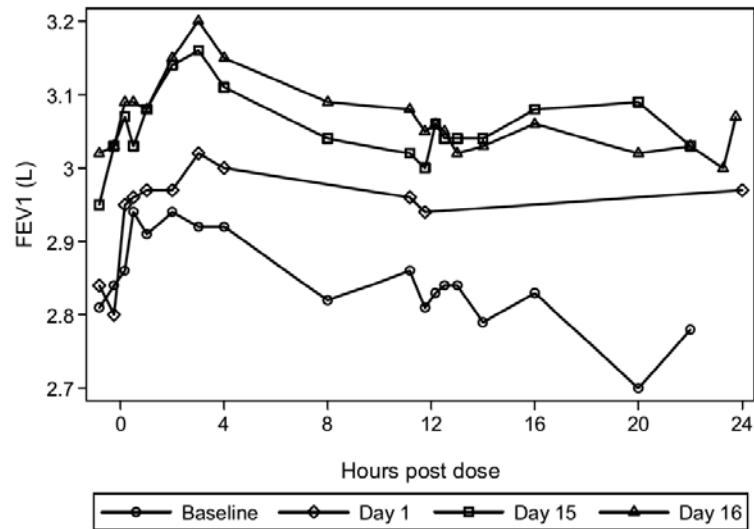
PD parameter	Treatment	Contrast with placebo		
		Mean	Lower 95% CI	Upper 95% CI
Trough FEV <sub>1</sub> (L)	37.5 µg b.i.d	0.160	0.036	0.284
	75 µg q.d	0.202	0.077	0.327
	150 µg q.o.d	0.203	0.077	0.329
AUC 0-24h (L)	37.5 µg b.i.d	0.167	0.046	0.287
	75 µg q.d	0.168	0.046	0.291
AUC 0-48h (L)	75 µg q.d	0.159	0.040	0.279
	150 µg q.o.d	0.139	0.026	0.252
AUC 24-48h (L)	75 µg q.d	0.131	0.009	0.253
	150 µg q.o.d	0.117	0.002	0.231

Source: Table 2 CQAB149B2223 Clinical Study Report

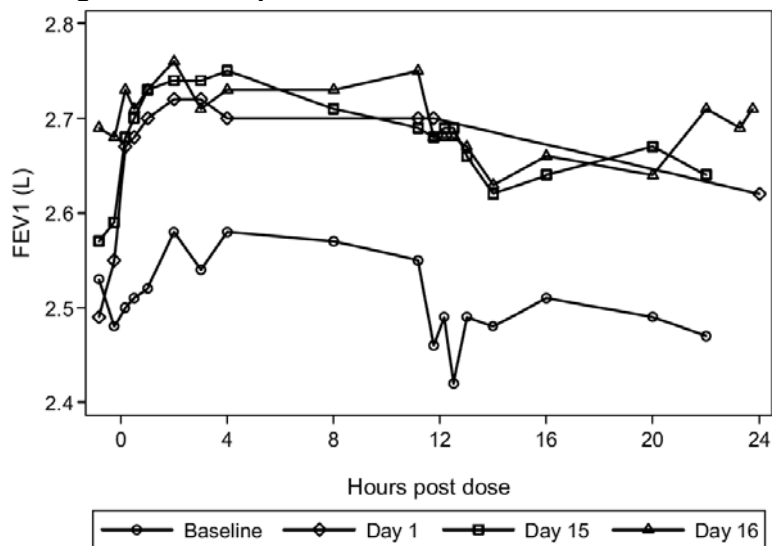
In the 37.5 mcg b.i.d dosing regimen seen in Figure 7 below the Day 1 curve falls in between baseline and Days 15/16. The difference between the Day 1 and Day 15 curves is less marked for the other regimens, 75 mcg q.d. and 150 mcg q.o.d., suggesting that 37.5 mcg b.i.d takes longer to reach maximal benefit than the other regimens.

**Figure 7 Protocol B2223 Mean FEV1 over time for 37.5 mcg b.i.d, 75 mcg q.d. and 150 mcg q.o.d at baseline, Days 1, 15 and 16 (PD analysis set)**

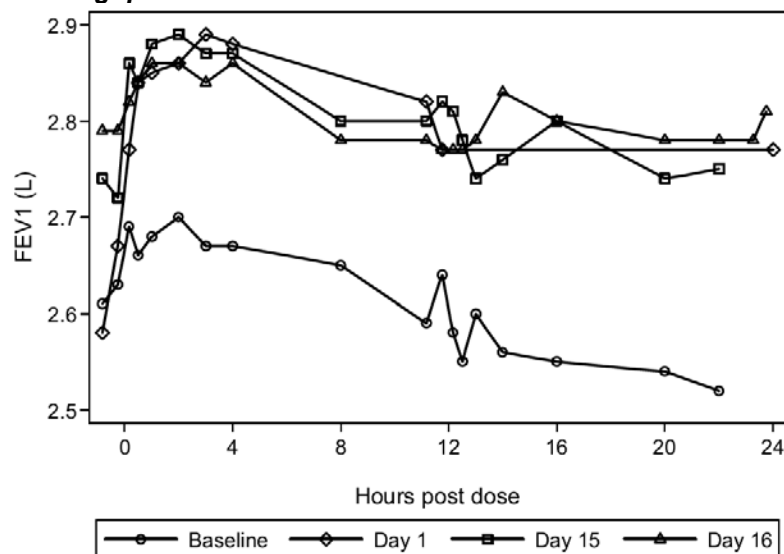
**37.5 mcg indacaterol b.i.d**



**75 mcg indacaterol q.d.**



### 150 mcg q.o.d



Sources: Figures 11-1, 11-2, 11-3 CQAB149B2223 Clinical Study Report

#### Reviewer Comment:

An interesting observation is the baseline between the different dose finding trials conducted in patients with asthma. In B2357 the mean FEV1 for all asthmatic patients was 2.36 L with a tight range of 2.32-2.46 L. In B2223 the mean FEV1 was 2.67 with a wide range from 2.51 L in the 75 mcg q.d group to 2.84 L for the 37.5 mcg b.i.d group. This represents a difference of ~ 0.300 L between the two trial populations. This large difference in baseline FEV1 may perhaps be due to different patient demographics. This absence of homogeneity must be kept in mind when assessing the validity of data from the dose regimen trial, B2223. These patients at baseline already appear to be at a higher level of FEV1 and therefore may not have much room for improvement. Differences between the indacaterol regimens may not be demonstrated due entirely to different baseline FEV1 characteristics.

#### Reviewer Comment:

No adjustments were made for multiple comparisons or multiplicity, and also of note, in Amendment 1 2/19/10, the hierarchy of FEV1-based efficacy endpoints was changed, with promotion of AUCs over the dosing intervals of the three regimens to co-primaries. This was done, according to the Sponsor, to reflect the importance of characterizing the entire FEV1-time course in addition to the residual effect at the dosing interval i.e. trough, when comparing different dosing regimens.

#### 3.3.3.3.2 Secondary Endpoints

A summary of the secondary endpoint analyses is provided in Table 36 below. The largest change from baseline in peak FEV1 at Day 1 was observed with indacaterol 150 mcg q.o.d (0.423 L) followed by 75 mcg q.d. (0.357 L) and 37.5 mcg b.i.d (0.127 L). The largest change from baseline for AUC(0-4 hr) after 2 weeks was observed with indacaterol 150 mcg b.i.d (0.270 L), followed by 37.5 mcg b.i.d (0.256 L) and 75 mcg q.d. (0.249 L). The range of changes from baseline for AUC(0-24 hr) at Day 1 was 0.197 for 75 mcg q.d. to 0.142 L for 37.5 mcg b.i.d. The range of changes from baseline for AUC(0-48 hr) was 0.157 L for 150 mcg q.o.d to 0.144 L for 75 mcg q.d. The largest changes from baseline are seen with either 75 mcg q.d or 150 mcg q.o.d across the different secondary endpoints

**Table 36 Protocol B2223 Select secondary endpoints**

	Change from baseline (90% CI)			
	37.5 mcg b.i.d	75 mcg q.d.	150 mcg q.o.d	Placebo
tFEV1 Day 1	0.120 (0.058, 0.181)	0.115 (0.052, 0.177)	0.126 (0.064, 0.188)	-0.044 (-0.106, 0.018)
Peak FEV1 Day 1	0.127 (0.065, 0.190)	0.357 (0.294, 0.421)	0.423 (0.361, 0.485)	0.273 (0.209, 0.336)
Peak FEV1 Day 15, 16	0.364 (0.293, 0.435)	0.447 (0.376, 0.518)	0.529 (0.457, 0.602)	0.261 (0.187, 0.336)
AUC 0-4h Day 15/16	0.256 (0.185, 0.327)	0.249 (0.178, 0.320)	0.270 (0.197, 0.344)	0.042 (-0.032, 0.116)
AUC 0-12h Day 1	0.138 (0.088, 0.188)	0.193 (0.145, 0.242)	N/A	0.051 (0.001, 0.101)
AUC 0-12h Day 15/16	0.245 (0.170, 0.319)	0.243 (0.168, 0.317)	N/A	0.059 (-0.018, 0.137)
AUC 0-24h Day 1	0.142 (0.090, 0.194)	0.197 (0.143, 0.251)	0.194 (0.144, 0.245)	0.044 (-0.011, 0.098)
AUC 0-48h Day 1	N/A	0.144 (0.087, 0.202)	0.157 (0.109, 0.206)	0.020 (-0.034, 0.074)
AUC 12-24h Day 1	0.130 (0.072, 0.187)	0.188 (0.128, 0.249)	N/A	0.033 (-0.027, 0.093)
AUC 12-24h Day 15/16	0.163 (0.082, 0.244)	0.165 (0.082, 0.247)	N/A	-0.012 (-0.098, 0.073)
AUC 24-48h Day 1	N/A	0.149 (0.079, 0.22)	0.144 (0.089, 0.198)	-0.006 (-0.068, 0.055)

Source: Adapted from Table 14.2-2.2.1 CQAB149B2223 Clinical Study Report

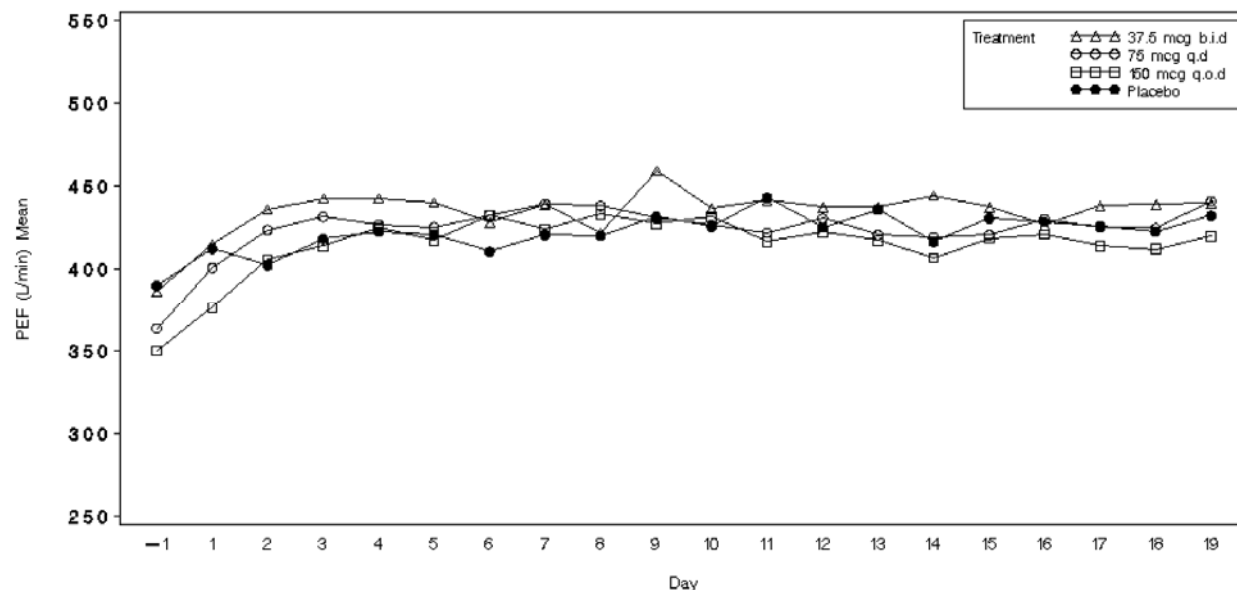
**Reviewer Comment:**

*The peak to trough ratio was close to 1 however, this value has a limited role here with the presence of diurnal variations.*

**PEF**

Peak flow values increased progressively for all three indacaterol dosing regimens through Day 8. After Day 9, all curves including the placebo plateau together, See Figure 8 below for graphical representation of the data.

**Figure 8 Protocol B2223 Mean PEF over time**



Source: Figure 14.2-2.5 CQAB149B2223 Clinical Study Report

### Pharmacokinetic Assessments

Indacaterol was absorbed rapidly following inhalation and the rate of absorption was similar for Day 1 and Day 15 across all regimens. The mean  $T_{max}$  was similar across dosing regimens, 15 to 18 min post-dose on Day 1 and Day 15. The mean  $C_{max}$  increased with dose regimen on Day 1 (18.8 pg/mL for 37.5 mcg b.i.d, 59.6 pg/mL for 75 mcg q.d and 138 pg/mL for 150 mcg q.o.d) and Day 15 (76.2 pg/mL for 37.5 mcg b.i.d, 143 pg/mL for 75 mcg q.d. and 220 pg/mL for 150 mcg q.o.d). Minimum serum indacaterol concentrations on day 15 ( $C_{min}$ ), however, were similar for the three dosing regimens, with means ranging from 34.3 pg/mL to 39.8 pg/mL. Refer to Table 37 and Table 38 for summary of data.

**Table 37 Protocol B2223 Summary statistics of indacaterol PK parameters- Day 1**

Regimen	Statistic	$T_{max}$ (hr)	$C_{max}$ (pg/mL)	$T_{last}$ (hr)	AUC <sub>last</sub> (pg.hr/mL)	AUC <sub>tau</sub> (pg.hr/mL)
37.5 µg b.i.d	N	39	39	39	39	12
	Mean	0.250	18.8	4.00	73.1	162
	SD	0.167-4.00	9.24	0.50-12.0	69.3	59.4
	CV%	-	49.3	-	94.8	36.6
75 µg q.d.	N	45	45	45	45	34
	Mean	0.300	59.6	23.8	389	423
	SD	0.150-23.9	26.9	2.03-25.6	168	137
	CV%	-	45.2	-	43.2	32.5
150 µg q.o.d	N	42	42	42	42	40
	Mean	0.300	138	47.8	1110	1120
	SD	0.183-2.00	48.8	23.8-48.5	293	300
	CV%	-	35.3	-	26.3	26.7

Source: Table 11-8 CQAB149B2223 Clinical Study Report

**Table 38 Protocol B2223 Summary statistics of indacaterol PK parameters- Day 15**

Regimen	Statistic	<sup>1</sup> Tmax (hr)	Cmax (pg/mL)	Cmin (pg/mL)	<sup>1</sup> Tlast (hr)	AUClast (pg.hr/mL)	AUCtau (pg.hr/mL)
37.5 µg b.i.d	N	43	43	43	43	43	39
	Mean	0.267	76.2	34.4	12.0	565	604
	SD	0.217-2.08	37.0	18.5	2.00-12.1	277	255
	CV%	-	48.6	53.8	-	49	42.2
75 µg q.d.	N	40	40	40	40	40	40
	Mean	0.283	143	39.8	23.8	1440	1450
	SD	0.200-4.02	54.2	16.6	22.3-23.8	553	556
	CV%	-	38.0	41.9	-	38.5	38.4
150 µg q.o.d	N	35	35	35	35	36	34
	Mean	0.25	220	34.3	48.0	2920	2970
	SD	0.233-4.03	61.4	12.1	23.8-48.6	774	749
	CV%	-	27.9	35.3	-	26.5	25.2

Source: Table 11-9 CQAB149B2223 Clinical Study Report

### 3.3.3.4 Safety Results

#### 3.3.3.4.1 Extent of exposure

All patients who completed the trial received 16 days of dosing except for one patient in the 37.5 mcg b.i.d group who received 15 days. The range of treatment duration was the lowest in placebo with 89% of patients taking 16 days of treatment drug to the highest in indacaterol 75 mcg q.d. with 98% taking 16 days of trial drug. A summary of the duration of exposure to trial drug is shown in Table 39.

**Table 39 Overall exposure by treatment duration (Safety data set)**

Exposure duration	Indacaterol				Placebo N=46
	37.5 µg b.i.d N=48	75 µg q.d N=47	150 µg q.o.d N=48		
<15 days, n (%)	1 (2)	1 (2)	5 (10)		5 (11)
15 days, n (%)	2 (4)	0 (0)	0 (0)		0 (0)
16 days, n (%)	45 (94)	46 (98)	43 (90)		41 (89)

Source: Table 12-1 CQAB149B2223 Clinical Study Report

#### 3.3.3.4.2 Concomitant medication

Most of the medications used throughout the trial were for asthma and were ongoing from baseline. Few patients used rescue medication in the active treatment groups and most patients used it on a few days. Rescue medication use was much higher in the placebo group with up to 19 patients using it on any one day.

#### 3.3.3.4.3 Adverse events

Adverse events were reported by 10 (21%) patients in the 37.5 mcg b.i.d group, 12 (26%) patients in the 75 mcg q.d group, 19 (40%) patients in the 150 mcg q.o.d group and 14 (30%) in the placebo group. The most common reported AEs were headache and cough. Headaches were observed in 6%, 4%, 6% and 13% in indacaterol 37.5 mcg b.i.d, 75 mcg q.d., 150 mcg q.o.d and placebo, respectively. The largest incidence of cough was observed in 150 mcg q.o.d (15%) and the smallest incidence in placebo (2%).

Headache and cough were the most common AEs reported by patients in this study with a total of 14 patients experiencing each of these AEs. Headache was experienced by patients in all four treatments but more so for patients when receiving placebo [6/46 (13%)] than with the indacaterol dosing regimens (Table 12-3). Cough was mainly experienced by patients when receiving indacaterol with only 1/46 (2%)



patients in the placebo group reporting a cough. The incidence of cough was greatest for the 150 mcg q.o.d group affecting 7/48 patients with 3 (6%) patients affected in the other two dosing regimens. Dizziness and nasopharyngitis were seen with highest incidences of 4% for both in the 75 mcg q.d. group.

#### **Deaths and SAEs**

There were no deaths during the study. Three patients experienced a SAE during the study; two prior to randomization. A third patient in the indacaterol 150 mcg q.o.d group was a 43 year old male, Polynesian, who received a total of three doses of 150 mcg q.o.d and the corresponding 7 matching placebo doses developed flu-like symptoms following exposure to pollen precipitating an asthma exacerbation 5 hours after receiving inhaled placebo requiring hospitalization.

#### **Adverse events leading to discontinuation**

In addition to the above mentioned, a patient in the placebo group was withdrawn due to elevated transaminases.

##### **3.3.3.4.4 Laboratory findings**

*In the hematology assessment, the mean hematocrit values during screening ranged from 0.434 to 0.445 (corresponding hemoglobin values, 142.4 g/L to 146.2 g/L). The mean hematocrit value during end of study ranged from 0.423 to 0.437 (corresponding hemoglobin values, 135.8 g/L to 141.1 g/L). All of the patients had at least one clinical laboratory test result outside of the normal range during conduct of the trial. There were no clinically meaningful events reported for glucose and potassium assessments. There was a reduction in creatinine kinase values over the treatment period as represented by a mean value of 228 U/L on screening to a mean of 161 U/L at the end of the trial in the 150 mcg q.o.d treatment group. Clinically significant effects on transaminases were reported for one patient in placebo with high values at baseline with an increase during the trial leading to discontinuation as mentioned above.*

##### **3.3.3.4.5 ECG findings**

There were no QTcF values flagged as >500 ms. In the 37.5 mcg b.i.d group, 1 patient had an increase of > 30 msec on Days 1, 2 on Day 15; in the 75 mcg q.d. group there was 1 patient on each Day 1 and Day 2, 2 patients at the end of trial and 7 on Day 15 and 3 on Day 16. The 150 mcg group had the greatest numbers of patients with an increase of > 30 msec with the largest number of 8 on Day 15. Values > 60 ms were observed in one patient in the 37.5 mcg b.i.d group, 2 in the 75 mcg q.d. and 1 in the 150 mcg q.o.d group.

##### **3.3.3.4.6 Physical examination**

There was one patient reported with elevated BP resulting in an AE. The patient was a 68 year old black female with a history of hypertension, elevated BP at baseline and increased to a maximum of 209/119 mmHg. This was recorded as an AE. Increases in pulse > 90 bpm were reported in 5 patients in 37.5 mcg b.i.d ranging from 91-102 bpm; 10 patients in the 75 mcg q.d. group ranging from 91-101 bpm; 10 in the 150 mcg q.o.d group ranging from 91-107 bpm and 7 in the placebo group ranging from 91-101 bpm. There were two episodes of bradycardia recorded, one in the 75 mcg q.d. group (39 bpm) and the other in the placebo group (37-39 bpm).

##### **3.3.3.5 Summary of Study**

This trial along with B2356 and B2357 were not included in the Sponsor's summary of safety due to the short duration and different target population. This was a two week, multicenter, international, randomized, placebo-controlled trial comparing different dosing regimens of indacaterol, 37.5 mcg b.i.d, 75 mcg q.d. and 150 mcg q.o.d. to placebo in adults with persistent asthma. Evaluation of the bronchodilatory effects of the different regimens were carried out with spirometry and the systemic levels were measured through the pharmacokinetic assessments. The treatment differences from placebo for the 75 mcg q.d and 150 mcg q.o.d regimens were similar (0.202 L and 0.203 L) and exceeded the Sponsor's predefined MCID of 0.200 L in patients with asthma. The 37.5 mcg b.i.d. regimen had the smallest treatment difference of 0.16 L. The magnitude of mean change from baseline in peak FEV1, FEV1 AUCs

0-24 hr, 1-12 hr and 12-24 hr were greatest for the 75 mcg q.d. regimen when compared to the 37.5 mcg b.i.d regimen. After two weeks of treatment, FEV1 AUC 0-24hr for the 75 mcg q.d, 150 mcg q.o.d and 37.5 mcg b.i.d dosing regimens were similar. The 150 mcg q.o.d regimen had the greatest magnitude of mean change from baseline in the peak FEV1 at Days 1 and 14.

The mean Tmax was similar across dosing regimens; 15 to 18 min post-dose. The mean Cmax increased with dose regimen on Day 1 as well as Day 15. The AUC last and tau increased with dose regimen and from Day 1 to Day 15. Based on the mean AUC tau values the average steady state concentrations of indacaterol were similar for the three dosing regimens. With average steady state concentrations similar across the regimens, the total systemic exposure was similar. Pharmacokinetic steady state was achieved by day 15 for all three dosing regimens as indicated by the trough serum concentrations of indacaterol.

The baseline demographics were generally comparable however the disease characteristics showed the lowest mean baseline FEV1 for the 75 mcg q.d. group (2.51 L) and highest for the 37.5 mcg b.i.d group (2.84 L) a difference of approximately 0.300 L. The degree of reversibility was comparable across groups.

The most frequent reported AEs were cough and headache. There were no deaths during the trial and the one SAE of an asthma exacerbation in the 150 mcg q.o.d. treatment regimen group. There were reports of expected pharmacodynamic effects in glucose, potassium levels, ECG and one event of elevated blood pressure recorded as an AE.

### 3.3.4 CONFIRMATORY TRIAL B2355

*A 12-Week Treatment, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Once Daily Indacaterol in Patients with Chronic Obstructive Pulmonary Disease*

#### 3.3.4.1 Trial Description

##### 3.3.4.1.1 Design

This was a Phase III, multicenter, randomized double-blind, placebo-controlled, parallel group study using 75 mcg indacaterol once daily via an SDDPI for 12 weeks in patients with moderate to severe COPD. The patients were stratified for smoking status and ICS use. The study design is presented in Table 40 below.

**Table 40 Protocol B2355 Study design**

Period	Pre-screen	Screen/ Run-in	Screen/Run -in	12-week Randomized Treatment
Visits	1	2	3	4-9
Day/Week	≥ Day -28 to ≤ -14	Day -14	Day -13	Week 1 – Week 12 (Day 1-85)
				Patients were randomized (1:1) to receive one of the following two blinded treatments: Indacaterol 75 µg o.d. via SDDPI or Placebo to indacaterol o.d. via SDDPI
				Daily ICS monotherapy allowed, if needed, was to remain stable throughout study albuterol was available for rescue use throughout study

Source: Table 9-1 Study No. CQAB149B2355 Clinical Study Report

##### 3.3.4.1.2 Duration

A 14 day run in period was followed by a 12 week treatment period.

##### 3.3.4.1.3 Population

Male and female adults aged ≥ 40 years, outpatients with a diagnosis of COPD, moderate to severe as classified by the GOLD Guidelines 2008. The study also had a 24 hour serial spirometry profiling subgroup, with all patients offered the opportunity to participate.

##### 3.3.4.1.4 Study Sites

The trial was conducted at 54 centers in the United States.

##### 3.3.4.1.5 Investigational and Reference Therapy

Investigational product: indacaterol 75 mcg formulation #6002142.003, batch # X173GF, X297LF and X231KF. Placebo to indacaterol formulation #3760253.004, batch #X123DF. All indacaterol dry powder capsules and placebo to indacaterol were inhaled through the Concept 1 SDDPI device.

##### 3.3.4.1.6 Objectives

The primary objective of the study was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of tFEV1 as compared to placebo after 12 weeks of treatment. Trough FEV1 was defined as the mean of FEV1 measurements at 23hr 10 min and 23hr 45 min after the previous morning's dose.

The key secondary objective was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of transition dyspnea index (TDI) focal score after 12 weeks of treatment as compared to placebo.

Other secondary objectives were:

- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of 24 hour post-dose (trough) FEV1 after a single dose (Day 2) of treatment as compared to placebo

- To evaluate the efficacy of indacaterol (75 mcg q.d.) versus placebo for the standardized AUC of FEV1 5 minutes-4 hours after a single dose (Day 1) and 12 weeks of treatment
- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of health-related quality-of-life as measured by the St George's Respiratory Questionnaire (SGRQ) total score after 12 weeks of treatment compared to placebo
- To evaluate the efficacy on indacaterol (75 mcg q.d.), and placebo in terms of rescue medication use over the 12 week treatment period using data obtained from the eDiary
- To evaluate the efficacy of indacaterol (75 mcg q.d.) and placebo in terms of patient reported symptoms over the 12 week treatment period using data obtained from the eDiary
- To compare indacaterol (75 mcg q.d.) to placebo on spirometry assessments in terms of FEV1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks treatment) and trough response
- To evaluate the safety (in particular regarding ECG, laboratory tests, vital signs, adverse events) of indacaterol (75 mcg q.d.) over 12 weeks, in patients with COPD

Exploratory objectives were:

- To evaluate the effect of indacaterol (75 mcg q.d.) on COPD exacerbations over the 12 week treatment period
- To evaluate the pharmacokinetic profile of indacaterol in a subset of patients after 84 days of treatment. This was added in Amendment 1 dated 2/10/10.
- To explore the 24 hour FEV1 and FVC profile of indacaterol (75 mcg q.d.) and placebo after 12 weeks of treatment
- To explore individual genetic variation in genes relating to drug metabolism, COPD, and the drug target pathway, and how these differences may confer a differential response to indacaterol through pharmacogenetic analysis.

#### **3.3.4.1.7 Inclusion Criteria**

Inclusion criteria were the same as in B2356, the dose ranging study in patients with COPD. Briefly, patients included had a smoking history of at least 10 pack years, post-bronchodilator FEV1 <80% and ≥30% of predicted and post bronchodilator FEV1/FVC <70% of the value at screening. Post bronchodilator refers to within 10-15 minutes of inhalation of 4 x 90 mcg albuterol delivered at the mouthpiece.

#### **3.3.4.1.8 Exclusion Criteria**

The exclusion criteria were the same as in Study B2356, the dose ranging study performed in patients with COPD.

#### **3.3.4.1.9 Conduct**

At prescreening visit (Visit 1) informed consent was obtained and current COPD medications were reviewed. For suitable patients, arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. The adjustments for patients taking LABAs or combinations containing LABAs or SABAs were carried out in the same manner as in Study B2356, the dose ranging trial in patients with COPD. The interval between Visit 1 and Visit 2 was based on the washout period of the prohibited medication that the patient was on. The interval between Visits 2 and 4 was a 14 day run-in period used to assess eligibility of patients for the study and to collect baseline information. The interval between Visits 4 and 9 was the 12-week randomized blinded treatment period. Collection of blood samples for PK measurements after 12 weeks of study treatment was included into the protocol in Amendment 1 dated February 10, 2010. See Table 41 for a schedule of assessments.

**Table 41 Protocol B2355 Assessment schedule**

Period	Pre-screen	Screen / Run-in	Screen / Run-in	12- week Randomized Treatment						
Visit	1	2	3	4	5	6	7	8	9	-
Wk – start of wk (*last day of week)		-2	-2	1	1	5	9	12*	13	13
Day		- 14	- 13	1	2	29	57	84	85	86
Informed consent	XS									
Current medication review/ adjustment	XS	XS								
Incl./Excl. criteria	S	S	S	S						
Medical History, Demographics	XS									
Smoking history/status	XS								XS	
PG Blood (consenting pts)				XS						
Pregnancy Test (serum) <sup>#</sup>		XS							XS	
Concom. Meds <sup>#</sup>		XS	XS	XS	XS	XS	XS	XS	XS	XS
Physical Exam. <sup>#</sup>		S							XS	
ECG <sup>1#</sup>		XS		XS		XS	XS	XS		
Systolic and diastolic BP and radial pulse rate <sup>1#</sup>		XS		XS		XS	XS	XS		
Record Height, waist and hip measurements (Visit 2 only) and Weight <sup>#</sup>		XS							XS	
Review/record $\beta_2$ -agonist use		XS		XS	XS	XS	XS	XS	XS	XS
FEV <sub>1</sub> Reversibility ( $\beta_2$ agonist)		XS								
FEV <sub>1</sub> Reversibility (Anti-cholinergic)			XS							
Spirometry <sup>1#</sup>		XS	XS	XS	XS	XS	XS	XS	XS	XS
Urinalysis <sup>1#</sup>		XS		XS		XS	XS	XS		
Hematology/ Blood Chemistry <sup>1#</sup>		XS		XS		XS	XS	XS		
PG sample <sup>5</sup>				XS						
Device training <sup>3</sup>	S	S		S						
AE Recording <sup>#</sup>	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS

Period	Pre-screen	Screen / Run-in	Screen / Run-in	12- week Randomized Treatment						
Visit	1	2	3	4	5	6	7	8	9	-
Wk – start of wk (*last day of week)		-2	-2	1	1	5	9	12*	13	13
Day		- 14	- 13	1	2	29	57	84	85	86
Provide rescue medication as necessary	S	S	S	S	S	S	S	S		
Issue Patient Diary		S								
Review, collect and download Patient Diary #				S	S	S	S	S	S	
SGRQ #				XS		XS		XS		
BDI				XS						
TDI #						XS		XS		
Randomization				S						
Telephone patients 1 day prior to visit						S	S	S		
Administer study drug at visit				XS	XS	XS	XS	XS	XS <sup>4</sup>	
Dispense study medication <sup>2</sup>				S		S	S			
Collect study medication #						S	S	S		
Call IVRS #	S	S		S		S	S		S	
Record number of capsules taken since previous dispensing visit #						XS	XS		XS	
24 hr profiling at end of study (subset of patients only) <sup>4</sup>										XS
Study completion eCRF #									XS	

S (recorded in source documents only); XS (recorded in database and source documents)

Source: Table 6-1 Study No. CQAB149B23B2355

## Efficacy Assessments

### *Spirometry measurements*

Serial spirometry was performed on:

- Day 1 (Visit 4) at 50 and 15 minutes predose, then 5, 30 minutes, 1, 2 and 4 hours post dose
- Day 2 (Visit 5) at 23 hr 10 min and 23 45 min
- Day 29 (Visit 6) at 50 and 15 minutes predose, then 5, 30 minutes, 1 hour post dose
- Day 57 (Visit 7) at 50 and 15 minutes predose, then 5, 30 minutes, 1 hour post dose
- Day 84 (Visit 8) at 50 and 15 minutes predose, then 5, 30 minutes, 1, 2 and 4 hours post dose
- Day 85 (Visit 9) at 23 hr 10 min and 23 hr 45 min
- Day 85/86 (Visit 9) at 5 and 30 minutes, 1, 2, 4, 6, 12, 16, 22 and 24 hours post dose

### *Daily clinical symptoms and Rescue Medication Use*

At Visit 2 all patients were provided with an electronic Patient Diary to record daily (morning and evening) clinical symptoms and rescue medication (albuterol) use. Questions, which covered the preceding 12

hours included: number of puffs of rescue medication; how would you rate your respiratory symptoms last night: how was your cough; how was your wheeze; how much sputum did you produce; what color was the sputum you produced; and during what activities did you first feel breathless in the past.

#### **Baseline and Transitional Dyspnea Indices**

Dyspnea was measured 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 BDI and TDI each have three domains: functional impairment, magnitude of task, and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired), and the domain scores are summed for the baseline focal score ranging from 0 to 12. Lower scores represented worse dyspnea severity. The TDI domains are rated from -3 (major deterioration) to 3 (major improvement), and the domain scores are summed for the transition focal score ranging from -9 to 9 with minus scores indicating deterioration. Patients were interviewed by an independent, trained assessor who graded the degree of impairment due to dyspnea at Visit 4 (baseline dyspnea index) and Visits 6 and 8 (transition dyspnea index). The same assessor completed both the BDI and TDI assessments for an individual patient, which was undertaken prior to dosing at these visits.

#### **Reviewer comment:**

*The use of the Mahler Baseline Dyspnea Index/Transitional Dyspnea Index (BDI/TDI) to support a dyspnea indication was discussed in a Pulmonary Allergy Drug Advisory Committee (PADAC) meeting held on September 6, 2002 for tiotropium HandiHaler. The committee identified a number of issues with the instrument, making it inappropriate for use to support labeling claims.*

#### **COPD Exacerbations**

COPD exacerbations were defined as:

worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- Dyspnea
- sputum volume
- sputum purulence

**or**

worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- increased cough
- increased wheeze

**and**

requiring treatment with systemic corticosteroids and/or antibiotic

COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An ER visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not counted as an exacerbation. COPD exacerbations were recorded on the COPD exacerbation episode eCRF page only.

#### **Safety Assessments**

ECG, vitals and laboratory evaluations were performed 25 minutes predose and 1 hour post dose on Days 1, 29, 57 and 84. Urinalysis was performed 50 minutes prior to dose on the same days as ECG,

vitals and laboratory evaluations. Serum pregnancy test was performed during screening and again on Day 85 or premature discontinuation visit. AE were recorded at each study visit. A complete physical exam was performed at screening and at Day 85.

An SAE was defined as an event which:

- was fatal or life-threatening
- resulted in persistent or significant disability/incapacity
- constituted a congenital anomaly/birth defect
- required inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- was medically significant, i.e., defined as an event that jeopardized the patient or may have required medical or surgical intervention to prevent one of the outcomes listed above.

## Other Assessments

### SGRQ

The SGRQ was self-administered on paper by the patient at the investigator's site at baseline (Visit 4) and Visit 6 and 8 or at the time of discontinuation for patients who discontinue prematurely. The one month recall version of the SGRQ was used and the questionnaire was to be completed before all other assessments were made to avoid influencing the responses. The completed questionnaires were reviewed and examined by the investigator, before the clinical examination, for responses which may have indicated potential AEs or SAEs. The investigator reviewed the responses as well as the comments written by the patient and then transcribed the answers into the eCRFs.

#### *Reviewer's Comment:*

*The SGRQ contains 50 items divided into three sections: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that caused or were limited by breathlessness; and "Impacts" which covered different aspects of social functioning and psychological disturbances resulting from airway disease. Scores for each section and a "Total" score were calculated, ranging from 0 to 100. Higher values correspond to greater impairment of health-related quality of life. The MCID for the SGRQ is a change from baseline of 4 points over placebo. (<sup>5</sup>Jones PW, 2002, and <sup>6</sup>Jones PW, 2005).*

## PK Assessments

Blood samples (4 mL) were collected at each of the following time points:

- Day 84: -25 min pre-dose, 30 min, 1 hr and 4hr post dose
- Day 85: 23 hr 35 min post the previous days dose

Biofluid concentrations were expressed in mass per volume units. Missing data were labeled as such in the concentration data listings. Data below LLOQ were set to zero and treated as such in the PK analysis and in summary statistics.

### 3.3.4.1.10 Concomitant Treatments

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<sup>5</sup> Jones PW, Eur Resp J 2002; 19:398-404

<sup>6</sup> Jones PW, COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 2: 75-79



The prohibited medications, prohibited COPD-related medications and medications allowed under certain conditions were the same as in Studies B2357 and B2356, the dose ranging studies carried out in patients with asthma and COPD.

#### **3.3.4.1.11 Ethical Aspects**

This clinical trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

#### **3.3.4.1.12 Data Analysis**

##### **Efficacy variables**

The primary variable was 'trough FEV1' after 12 weeks of treatment (Visit 9). Trough FEV1 was defined as the average of the 23 hr 10 min and the 23 hr 45 min values taken in the clinic at Visits 5 and 9 only. At all other visits tFEV1 was defined as the average of the 50 min and 15 min pre-dose values taken at the clinic. The baseline measurement was defined as the average of the FEV1 values taken in the clinic 50 and 15 min prior to dosing at Visit 4 (Day 1/week1). The primary variable (imputed with LOCF) was analyzed using a mixed model for the full analysis set (FAS) which included all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization. The per-protocol set (PPS) included all patients in the FAS without any major protocol deviations. The safety set included all patients who received at least one dose of study drug. The FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who received study drug in error, and the FAS assigns randomized treatment while the safety set assigns received treatment.

The sponsor-defined MCID of 120 mL in the tFEV1 was the same MCID used as in prior trials with patients with COPD. An estimate of the standard deviation of tFEV1 of 225 mL at 12 weeks was obtained from other phase III indacaterol studies, QAB149B2334, QAB149B2346 and QAB149B2335S. Based on these values, the Sponsor calculated 75 evaluable patients per treatment group were required to detect a difference in tFEV1 of 120 mL at Week 12, using a 5% significance level (two-sided) with 90% power, assuming a standard deviation of 225 mL. Assuming a drop out rate of 15% over 12 weeks of treatment, a sample size of 178 randomized patients (89 per treatment group) in total was required.

Missing values and discontinuations were handled as in Studies B2357 and B2356, the dose ranging trials. Furthermore, as in these previous trials, any value contributing to the tFEV1 that were collected within 6 hours of rescue medication or actual measurement times were outside the 22-25 hour post-dose time window then the individual FEV1 value was not analyzed.

Superiority of indacaterol 75 mcg to placebo was demonstrated if the two-sided p-value was less than the 5% significance level and the 95% confidence interval for the mean FEV1 difference of indacaterol minus placebo lay entirely to the right of (higher than) 0 mL.

Supportive analyses include tFEV1 for the PPS imputed with LOCF as well as both FAS and PPS without LOCF. There were numerous exploratory subgroup analyses such as age < 65 and ≥ 65; gender; race; severity of disease; smoking status at baseline; use of ICS; BMI and waist to hip ratio. Analysis of the log-transformed tFEV1 (imputed with LOCF) after 12 weeks of treatment for the FAS was also performed using the same mixed model.

The key secondary variable was the TDI focal score after 12 weeks treatment. This score was analyzed using the same mixed model as specified for the primary analysis with the BDI focal score as baseline. If data was missing or insufficient for any one of the domains a focal score was not calculated. The Sponsor did have a hierarchical testing approach to handle multiplicity for the primary and key secondary comparisons:

1. tFEV1 after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo. If indacaterol 75 mcg was superior to placebo then;
2. TDI focal score after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo.

The treatment comparisons for the other secondary variables were for supportive evidence and no adjustment for multiplicity were made.

Other secondary variables:

- Trough FEV1 following a single dose (Day 2) of treatment
- Standardized AUC (5 min – 4 h) for FEV1 following a single dose and after 12 weeks of treatment
- Peak FEV1 over 5 min - 4 hours post morning dose on Day 1 (single dose) and after 12 weeks of treatment
- FEV1 and FVC at each post-baseline time point
- FEV1 trough response over 12 weeks- rate of change in tFEV1 defined as the average of the 50 min and 15 min pre-dose values from Visit 6 (Day 29) onwards was analyzed using a random coefficients model
- 24 hour Serial Spirometry- FEV1 and FVC at each scheduled time-point (6, 12, 16, 22 and 24 hours) was analyzed using the same mixed model for all patients in the FAS in the 24 hr profiling subgroup. The baseline was defined as the trough measurement at Visit 9 prior to the 24 profiling spirometry
- Daily rescue medication use (number of puffs) over 12 weeks
- Daytime and nighttime rescue medication use (number of puffs) over 12 weeks
- Daily, daytime and nighttime rescue medication use (number of puffs) at approximately 4 weekly intervals
- Percentage of 'days with no rescue use' over 12 weeks
- Percentage of nights with 'no nighttime awakenings' over 12 weeks
- Percentage of days with 'no daytime symptoms' over 12 weeks
- Percentage of 'days able to perform usual daily activities' over 12 weeks
- Symptom scores over 12 weeks
- Percentage of patients with a clinically important improvement of at least 1 in the TDI focal score after 12 weeks treatment
- SGRQ total score after 4 weeks and 12 weeks treatment, percentage of patients with a clinically important improvement of at least 4 units in the total SGRQ score after 4 weeks and 12 weeks treatment.

Exploratory variables:

- COPD exacerbations- For COPD exacerbation related endpoints the comparison between indacaterol and placebo were exploratory endpoints.

All variables were summarized and analyzed by treatment for the FAS unless otherwise specified and where appropriate, utilized the mixed model for analysis.

### **Safety variables**

All safety endpoints were summarized for the safety set. Safety data, including AEs data, vital signs, ECG, chemistry, hematology, and use of rescue and concomitant medications, were listed and summarized by treatment group. Selected safety data were analyzed formally, including heart rate, QTcF, serum potassium and plasma glucose, using a repeated measures analysis. Treatment emergent AEs, prior and post-treatment AE were classified as in Studies B2357 and B2356, the dose ranging studies.

### **Health-related quality of life variables**

***SGRQ total score after 12 weeks of treatment***

The scoring and handling of missing item data for the SGRQ were conducted in accordance with the user guide. The SGRQ total score at Week 12 (Visit 9) were summarized by treatment and analyzed using a mixed model for the FAS. The same model as specified for the primary analysis was used, however, with baseline SGRQ total score instead of baseline FEV1 as covariate.

Missing data of the SGRQ total score were imputed by using LOCF. Scores were carried forward from the last evaluable visit within the previous 8 weeks. Similar analysis as for the SGRQ total score were performed for the symptoms, activities, and impacts component scores.

***Percentage of patients with a clinically important improvement of at least 4 units in the total SGRQ score after 12 weeks treatment***

The proportion of patients who achieved a clinically important improvement of at least 4 units in the total SGRQ was analyzed using logistic regression for the FAS. The model included terms for treatment, baseline smoking status and country as fixed effects with center nested within country as a random effect. The model also contained as fixed effects the baseline total SGRQ score, FEV1 prior to inhalation and FEV1 10-15 min post inhalation of albuterol (components of SABA reversibility at Visit 2), FEV1 prior to inhalation and FEV1 1 hour post inhalation of ipratropium (components of anticholinergic reversibility at Visit 3), and inhaled corticosteroid use at baseline as covariates. The estimated adjusted odds ratios were displayed along with associated 95% confidence interval and two-sided p-values.

### **3.3.4.2 Patient Disposition and Demographics**

#### **Disposition**

Table 42 below outlines the numbers of patients screened, randomized and completed by treatment group. A total of 597 patients were screened, and 318 were randomized equally to the two treatment groups. One hundred forty-eight (93%) of the patients in the indacaterol 75 mcg treatment group and 142 (89%) of patients in the placebo treatment group completed the study. The primary reason for discontinuation in both treatment groups was 'subject withdrew consent', occurring in 5 patients in the indacaterol treatment group and 6 in the placebo group. Overall, the proportion of patients discontinuing for each reason was similar for both treatment groups, with the exception of 'unsatisfactory therapeutic effect' where all (2.5%) the affected patients were in the placebo group. The proportion of patients who discontinued due to AEs was the same in each treatment group and these patients are discussed in Section 3.3.4.3.3.

**Table 42 Protocol B2355 Patient disposition (All patients)**

	Ind 75 µg n (%)	Pbo n (%)	Total n (%)
<b>Patients</b>			
Screened	-	-	597
Randomized	159 (100.0)	159 (100.0)	318 (100.0)
Exposed	159 (100.0)	159 (100.0)	318 (100.0)
Completed	148 (93.1)	142 (89.3)	290 (91.2)
Discontinued	11 (6.9)	17 (10.7)	28 (8.8)
<b>Primary reason for premature discontinuation</b>			
Subject withdrew consent	5 (3.1)	6 (3.8)	11 (3.5)
Adverse event(s)	3 (1.9)	3 (1.9)	6 (1.9)
Abnormal laboratory value(s)	1 (0.6)	0 (0.0)	1 (0.3)
Lost to follow-up	1 (0.6)	2 (1.3)	3 (0.9)
Protocol deviation	1 (0.6)	1 (0.6)	2 (0.6)
Unsatisfactory therapeutic effect	0 (0.0)	4 (2.5)	4 (1.3)
Administrative problems	0 (0.0)	1 (0.6)	1 (0.3)

Source: Table 10-1 Study No. CQAB149B2355 Clinical Study Report

### Protocol Deviations

A total of 69 patients in the FAS had at least one major protocol deviation resulting in exclusion from the PPS, 40 (25%) in the indacaterol treatment group and 29 (18%) in the placebo group. The most frequent protocol deviation resulting in exclusion from the PPS was 'spirometry for SABA reversibility not acceptable as per American Thoracic Society/ European Respiratory Society (ATS/ERS) criteria' and this occurred in a higher proportion of patients in the indacaterol 75 mcg (18%) group than in the placebo (13%) group.

A slightly higher proportion of patients in the placebo group (5%) than in the indacaterol 75 mcg group (2.5%) were 'not compliant with dosing scheduled at the primary endpoint dosing visit(s)'. Other major protocol deviations occurred in 7 patients or fewer overall.

### Demographics

Table 43 summarizes the demographics for the two treatment groups which were generally well matched. Overall the majority of patients were caucasian, approximately 54% were male, and the mean age was 61.4 years, with a range of 40 to 86 years.

**Table 43 Protocol B2355 Demographic summary (Safety set)**

		Ind 75 µg N=159	Pbo N=159	Total N=318
Age (years)	N	159	159	318
	Mean	61.3	61.5	61.4
	SD	9.83	9.85	9.83
	Median	61.0	62.0	62.0
	Min – Max	40 - 82	42 - 86	40 – 86
Age group - n (%)	19-39 years	0 (0.0)	0 (0.0)	0 (0.0)
	40-64 years	96 (60.4)	94 (59.1)	190 (59.7)
	≥65 years	63 (39.6)	65 (40.9)	128 (40.3)
Sex - n (%)	Male	83 (52.2)	89 (56.0)	172 (54.1)
	Female	76 (47.8)	70 (44.0)	146 (45.9)
Race - n (%)	Caucasian	151 (95.0)	147 (92.5)	298 (93.7)
	Black	7 (4.4)	9 (5.7)	16 (5.0)
	Native American	0 (0.0)	1 (0.6)	1 (0.3)
	Other	1 (0.6)	2 (1.3)	3 (0.9)
Weight (kg)	n	159	159	318
	Mean	79.6	82.2	80.9
	SD	17.68	19.17	18.46
	Median	78.0	82.1	80.0
	Min – Max	40.9 - 130.5	35.0 - 132.0	35.0 - 132.0

Source: Adapted from Table 11-2 Study No. CQAB149B2355 Clinical Study Report

Baseline disease characteristics were comparable between treatment groups (Table 44). Overall, the median duration of COPD was 5.0 years, with a range of 0 to 31.2 years. Overall, the severity of COPD was moderate in approximately 62% of patients and severe in 38% of patients. Specifically, in the indacaterol 75 mcg group, 109 (69%) patients were categorized as moderate in severity and in the placebo group, 87 (55%) were moderate. Less than half of patients were using inhaled corticosteroids (ICS) on entry to the study. A greater proportion of patients were current smokers (58.8%) than ex-smokers (41.2%).

**Reviewer Comment:**

*Although, more patients in the placebo group 72 (45%) than in the indacaterol group 48 (30%) were in the severe category, the baseline FEV1 was similar between the groups with an overall pre-bronchodilator FEV1 of 1.30 L, suggesting a more moderate population. This is consistent with the proposed marketing population.*

**Table 44 Protocol B2355 Baseline disease characteristics (Safety set)**

		Ind 75 µg N=159	Pbo N=159	Total N=318
Duration of COPD (years)	n	159	159	318
	Mean	6.7	6.8	6.8
	SD	6.10	6.10	6.09
	Median	5.6	4.7	5.0
	Min - Max	0.0 - 31.2	0.0 - 30.0	0.0 - 31.2
Duration of COPD - n (%)	< 1 year	17 (10.7)	12 (7.5)	29 (9.1)
	1 - 5 years	60 (37.7)	71 (44.7)	131 (41.2)
	> 5 - 10 years	46 (28.9)	45 (28.3)	91 (28.6)
	>10 - 15 years	24 (15.1)	18 (11.3)	42 (13.2)
	>15 - 20 years	5 (3.1)	7 (4.4)	12 (3.8)
	> 20 years	7 (4.4)	6 (3.8)	13 (4.1)
Severity of COPD (GOLD 2008) - n (%)	Mild	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	109 (68.6)	87 (54.7)	196 (61.6)
	Severe	48 (30.2)	72 (45.3)	120 (37.7)
	Very severe	2 (1.3)	0 (0.0)	2 (0.6)
ICS use - n (%)	No	96 (60.4)	103 (64.8)	199 (62.6)
	Yes	63 (39.6)	56 (35.2)	119 (37.4)
Smoking history - n (%)	Ex-smoker	67 (42.1)	64 (40.3)	131 (41.2)
	Smoker	92 (57.9)	95 (59.7)	187 (58.8)
Number of pack years	n	159	159	318
	Mean	52.4	52.4	52.4
	SD	28.06	28.39	28.18
	Median	45.0	45.0	45.0
	Min - Max	11.0 - 180.0	10.0 - 204.0	10.0 - 204.0

Source: Table 11-3 Study No. CQAB149B2355 Clinical Study Report

### 3.3.4.3 Efficacy Review

#### 3.3.4.3.1 Primary Endpoint

The prespecified primary efficacy endpoint was the 'trough FEV1' after 12 weeks of treatment. For the FAS, the LS mean in the indacaterol 75 mcg group was statistically greater than placebo. The number randomized was 318, however, 295 were analyzed. The treatment difference was 0.140 L (0.10, 0.18, p-value of <0.001) consistent with a clinically important bronchodilator effect.

Subgroup analyses for age, sex, COPD severity, smoking history, SABA reversibility and ICS use at baseline were performed for tFEV1 after 12 weeks of treatment. The treatment differences are displayed below in Table 45. Consistent with Study B2354, indacaterol 75 mcg dose had a larger treatment difference in the ≥ 65 age group with 0.16 L as opposed to the < 65 age group with 0.13 L. The treatment difference for indacaterol 75 mcg based on severity were consistent with that seen in B2354 and B2336, larger differences were seen in patients with moderate or less severe COPD (0.16 L) than in those with severe or worse disease with a treatment difference of only 0.13 L. For those who were not on ICS at baseline, the treatment difference was 0.18 L vs. those on a stable ICS regimen with 0.07 L.

**Table 45 Protocol B2355 Analysis of trough FEV1 after 12 weeks treatment (imputed with LOCF), select subgroup analyses**

	Trough FEV1 (L)				
	Ind 75 mcg N=145	Placebo N=150	Treatment difference	95% CI	p-value
Full analysis set	1.49	1.35	0.14	0.10, 0.18	<0.001
<b>Subgroup analyses</b>					
Age					
< 65	1.48	1.35	0.13	0.07, 0.18	<0.001
≥ 65	1.51	1.35	0.16	0.10, 0.23	<0.001
Gender					
Male	1.51	1.34	0.17	0.11, 0.23	<0.001
Female	1.47	1.36	0.11	0.05, 0.17	<0.001
COPD Severity					
Moderate or less	1.49	1.33	0.16	0.10, 0.21	<0.001
Severe or worse	1.49	1.37	0.13	0.05, 0.20	<0.001
Smoking status					
Ex smoker	1.50	1.35	0.14	0.08, 0.21	<0.001
Current smoker	1.49	1.34	0.14	0.09, 0.20	<0.001
SABA reversibility					
≤ 12%	1.49	1.37	0.12	0.06, 0.19	<0.001
>12%	1.49	1.34	0.16	0.10, 0.21	<0.001
ICS					
No	1.51	1.33	0.18	0.13, 0.23	<0.001
Yes	1.46	1.39	0.07	0.01, 0.14	0.035

Source: Adapted from Tables 14.2-1.1b and 14.2-1.1c Study No. CQAB149B2355 Clinical Study Report

### 3.3.4.3.2 Secondary Endpoint

The key secondary efficacy endpoint, the TDI was prespecified by the Sponsor such that a difference of 1 unit was considered a MCID for COPD patients. At Week 12, the difference between treatment groups in LS mean TDI focal score was not statistically significant nor did it meet the MCID of 1 unit. The LS mean TDI treatment difference was 0.45 (-0.18, 1.09).

#### Reviewer comment:

*The Applicant has not included any labeling claims regarding dyspnea or the Mahler TDI instrument.*

### Other Endpoints

- Trough FEV1 on days other than the primary endpoint

The trough FEV1 showed a significant improvement over placebo at all time points tested. A smaller effect was demonstrated after the first dose, consistent with other indacaterol studies..

**Table 46 Protocol B2355 Analysis of tFEV1 over 12 weeks of treatment at visits other than the primary endpoint (FAS)**

tFEV1 alternate visits	Treatment difference Ind 75 mcg – pbo (L)	95% CI	p-value
Day 2	0.08	0.05, 0.11	<0.001
Day 29	0.15	0.11, 0.19	<0.001
Day 57	0.15	0.11, 0.19	<0.001
Day 84	0.12	0.07, 0.16	<0.001

Source: Table 14.2-3.1 Study No. CQAB149B2355 Clinical Study Report

➤ FEV1 AUC 5 min- 4hr following a single dose (Day 1) and Week 12

The FEV1 AUC 5 min- 4 hr after the first dose and week 12 of study medication was analyzed for the full analysis set. The LS mean AUC 5 min- 4 hr at Day 1 and Week 12 were statistically significantly greater in the indacaterol 75 mcg group than in the placebo group. The treatment difference between indacaterol and placebo after Day 1 was 0.12 L (95% CI 0.10, 0.15; p<0.001) and after 12 weeks of treatment, it was 0.18 L (95% CI 0.14, 0.23; p<0.001).

➤ Peak FEV1 over 5 min- 4 hrs Day 1 and Week 12

The maximum FEV1 during the first 4 hours post morning dosing was calculated at Day 1 (Visit 4) and Week 12 (Visit 8). The treatment difference for the peak FEV1 5min- 4 hrs was statistically significant for both time points: for Day1 the value was 0.11 (0.08, 0.13) and Week 12 the value was 0.17 (0.13, 0.22).

➤ FEV1 at post-baseline time points

To evaluate the onset of action, FEV1 was measured at multiple time points on Days 1, 2, 29, 57, 84 and 85. At 5 minutes, the treatment difference represents of 75 mcg indacaterol on FEV1 compared to placebo was 0.10 L which was statistically significant and represented 69% of the mean trough value on Day 85. See Table 47.



**Table 47 B2355 Trough FEV1 at multiple post baseline time points**

Analysis of FEV1 for Indacaterol 75 mcg at multiple time points (FAS)				
		Treatment difference (L)	95% CI	p-value
Day 1	5 min	0.10	(0.08, 0.12)	< 0.001
	30 min	0.12	(0.10, 0.15)	< 0.001
	1 hr	0.12	(0.09, 0.15)	< 0.001
	2 hr	0.12	(0.09, 0.15)	< 0.001
	4 hr	0.13	(0.09, 0.16)	< 0.001
Day 2	23 hr 10 min	0.08	(0.04, 0.11)	< 0.001
	23 hr 45 min	0.07	(0.04, 0.11)	< 0.001
Day 29	-50 min	0.14	(0.11, 0.18)	< 0.001
	-15 min	0.15	(0.11, 0.18)	< 0.001
	5 min	0.18	(0.15, 0.22)	< 0.001
	30 min	0.20	(0.16, 0.23)	< 0.001
	1 hr	0.20	(0.16, 0.24)	< 0.001
Day 57	-50 min	0.15	(0.11, 0.19)	< 0.001
	-15 min	0.14	(0.10, 0.18)	< 0.001
	5 min	0.18	(0.14, 0.22)	< 0.001
	30 min	0.20	(0.15, 0.24)	< 0.001
	1 hr	0.21	(0.17, 0.25)	< 0.001
Day 84	-50 min	0.11	(0.07, 0.15)	< 0.001
	-15 min	0.11	(0.06, 0.15)	< 0.001
	5 min	0.16	(0.11, 0.20)	< 0.001
	30 min	0.19	(0.14, 0.23)	< 0.001
	1 hr	0.18	(0.14, 0.23)	< 0.001
	2 hr	0.19	(0.15, 0.24)	< 0.001
	4 hr	0.17	(0.12, 0.21)	< 0.001
Day 85	23 hr 10 min	0.15	(0.10, 0.19)	< 0.001
	23 hr 45 min	0.14	(0.10, 0.19)	< 0.001

Source: Table 14.2-5.1 Study No. CQAB149B2355 Clinical Study Report

➤ FEV1 trough response over 12 Weeks

To evaluate potential tachyphylaxis over this 12 week study, the protocol called for comparisons of the rate of change in tFEV1 for indacaterol 75 mcg group and placebo from Day 29 to 12 weeks. There was no statistically significant difference in the estimate of the rate of change in tFEV1 from Day 29 to 12 weeks of treatment between the treatment groups. The rate of change (slope) per month was -3.42 for indacaterol 75 mcg group and 4.51 for placebo. The treatment difference was -7.93 (95% CI -25.94, 10.075; p=0.387).

➤ 24 hr serial spirometry

A subset of 239 patients took part in serial spirometry assessments after the final dose of study medication at Week 12. Spirometry measurements were made pre-dose and serially up to 24 hours post-dose. At each time point, both pre-dose and post-dose, the LS mean FEV1 value was statistically significantly greater in the indacaterol 75 mcg group than in the placebo group. The LS mean treatment difference was 0.13 L at all time points, consistent with a bronchodilator effect over the 24 hour dosing period.

➤ Rescue medication use

All patients were provided with albuterol for use as rescue medication from Visit 1. Rescue medication use over 12 weeks of treatment is summarized below in Table 48. The protocol stated that the number of puffs of rescue medication taken in the previous 12 hours would be recorded twice daily in the electronic patient diary. The value was obtained by calculating the total number of puffs of rescue medication per day (over 12 weeks) and dividing that by the total number of days with non-missing rescue medication. The indacaterol 75 mcg group had statistically significant improvement in the LS mean change from baseline over placebo in:

- daily number of puffs of rescue medication
- number of puffs during the day and night compared with placebo over 12 weeks of treatment, and
- days with no rescue medication use

**Table 48 Protocol B2355 Rescue medication use over 12 weeks: treatment comparisons (FAS)**

-- Treatment --				----- Treatment difference -----				
Treatment	n	LSM	SE	Comparison	LSM	SE	95% CI	p-value
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 75 µg	150	-1.15	0.186	Ind 75 µg - Pbo	-0.66	0.247	(-1.15, -0.18)	0.008
Pbo	154	-0.49	0.184					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 75 µg	147	-0.75	0.109	Ind 75 µg - Pbo	-0.41	0.140	(-0.68, -0.13)	0.004
Pbo	152	-0.34	0.107					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 75 µg	149	-0.45	0.091	Ind 75 µg - Pbo	-0.32	0.124	(-0.56, -0.07)	0.011
Pbo	151	-0.13	0.091					
Percentage of 'days with no rescue use'								
Ind 75 µg	149	39.3	2.40	Ind 75 µg - Pbo	8.4	2.91	(2.7,14.1)	0.004
Pbo	150	30.9	2.38					

Source: Table 11-11 Study No. CQAB149B2355 Clinical Study Report

#### ➤ Symptoms

The only symptom category to reach statistical significance was “days able to perform usual daily activities” with a treatment LS mean value of 39 for indacaterol 75 mcg treatment group vs. 30.3 for placebo. The treatment difference was 8.7 with a p-value of <0.001. See Table 49.

**Table 49 Protocol B2355 Percentage of nights with “no nighttime awakenings”, percentage of days with “no daytime symptoms” and percentage of “days able to perform usual daily activities” over 12 weeks: treatment comparisons (FAS)**

Treatment	n	- Treatment -		Comparison	- Treatment difference -			
		LS Mean	SE		LS Mean	SE	95% CI	p-value
Percentage of nights with 'no nighttime awakenings'								
Ind 75 µg	149	63.4	1.82	Ind 75 µg - Pbo	1.9	2.44	(-2.9, 6.7)	0.430
Pbo	151	61.5	1.81					
Percentage of days with 'no daytime symptoms'								
Ind 75 µg	147	8.0	1.20	Ind 75 µg - Pbo	2.8	1.66	(-0.5, 6.1)	0.091
Pbo	152	5.2	1.19					
Percentage of 'days able to perform usual daily activities'								
Ind 75 µg	147	39.0	1.97	Ind 75 µg - Pbo	8.7	2.53	(3.7, 13.7)	<0.001
Pbo	152	30.3	1.94					

Source: Table 11-12 Study No. CQAB149B2355 Clinical Study Report

➤ **Health related quality of life**

The SGRQ was used to provide health-related quality of life measurements during the course of the study. The protocol specified that the SGRQ would be administered at Visits 4, 6 and 8 (Days 1, 29 and 84). Negative changes in scores indicate improvement in health-related quality of life. Comparisons between the indacaterol 75 mcg treatment group and placebo were to be based on the total score, with a difference of 4 points pre-specified as representing a clinically meaningful difference.

The LS mean SGRQ total score treatment difference at Week 12 (imputed with LOCF) was statistically significantly lower in the indacaterol 75 mcg group than in the placebo group. However, the treatment difference of -3.6 (-6.4, -0.9) did not reach the MCID of 4 units. The SGRQ total score treatment difference at Week 4 was -2.0 (-4.3, 0.2). The proportion of patients with a MCID of  $\geq 4$  units in the SGRQ was 51% for the indacaterol 75 mcg group and 37% for the placebo group. Analysis of the individual SGRQ domains was also performed with the only significant findings seen in the symptoms and impact domain as seen in Table 50 below.

**Table 50 Protocol B2355 Analysis of SGRQ component scores after 12 weeks**

	LS Mean score		Treatment difference	95% CI	p-value
	Ind 75 mcg N=148	Placebo N=145			
Symptoms score	56.0	61.9	-6	(-9.8, -2.1)	0.003
Activity score	62.3	65.1	-2.3	(-5.7, 1.1)	0.179
Impacts score	32.8	36.4	-3.6	(-6.7, -0.4)	0.026
Total score	45.9	49.5	-3.6	(-6.4, -0.9)	0.010

Adapted from data in Tables 14.2-9.4, 14.2-9.6 and 14.2-9.8

➤ **COPD exacerbation frequency**

The exploratory efficacy variable of COPD exacerbation frequency was also measured. The mean number of exacerbations over 12 weeks (without imputation) was 0.9 for both the indacaterol 75 mcg group and placebo group. Only one patient had more than 1 COPD exacerbation during the 12 week treatment (1 patient in the placebo group had 2 exacerbations). The rate of exacerbations per year was comparable between the treatment groups (0.39 indacaterol 75 mcg, 0.40 placebo). Imputation was done by adding one exacerbation to the total number of exacerbations for patients who discontinued prematurely unless they had an exacerbation in the 7 days prior to discontinuation. The mean number of exacerbations over 12 weeks with imputation was 0.14 for the indacaterol 75 mcg group and 0.16 for the placebo group and the corresponding rates of exacerbations were 0.64 and 0.74 respectively.

*Reviewer comment:*

*COPD exacerbation frequency is difficult to determine in a 3 month study, so results should be interpreted with caution. The recommended duration for a study designed to show a difference in COPD exacerbations is 12 months.*

**3.3.4.3.3 Safety Review**

All relevant long term trials will be reviewed collectively in the Integrated Summary of Safety. However, a brief synopsis of the safety findings from this trial will be provided here.

**3.3.4.3.4 Extent of Exposure**

The extent of exposure was identical between the indacaterol and placebo groups with a median number of days of exposure as 85 in both. As well, both groups exhibited a high level of compliance with 97 % of the indacaterol 75 mcg doses taken and 98% of placebo doses taken.

**3.3.4.3.5 Concomitant medication**

Most patients were taking both non COPD and COPD related medications. The most commonly taken COPD related medication taken was ICS used in approximately 39% of those on indacaterol and 35% on placebo. The most common non COPD related medications were aspirin, lisinopril, multivitamins and ibuprofen with similar rates in both.

### 3.3.4.3.6 Adverse events

There were more incidences of AEs in the indacaterol group (44.7%) than in placebo (40.9%). The most frequently reported SOC's reported were infections and infestations and respiratory, thoracic and mediastinal. The most common AE was COPD and was reported with similar frequencies in the indacaterol 75 mcg (8.8%) and placebo (8.2%) groups. However, cough, the second most frequent AE overall, was 3x higher in the indacaterol group (9.4%) than placebo (3.1%). Nasopharyngitis, oropharyngeal pain, bronchitis, headache, hypertension were reported in >2% of those on indacaterol and was higher than placebo.

### Deaths and SAEs

There were no deaths in the trial. SAEs occurred with the same rate across the two treatment groups. The most common preferred term The proportion of SAEs leading to discontinuations in either treatment group are summarized in Table 51 below. Using the preferred terms, there were more events of non cardiac chest pain, bronchitis, pneumonia, CVA, COPD and hemoptysis reported in the indacaterol treated groups than placebo.

### Adverse events leading to discontinuation

Two patients in the indacaterol treatment group discontinued, one for hospitalization due to bronchitis and hemoptysis and the other due to hospitalization due to a CVA. One patient discontinued on placebo due to hospitalization for a limb crushing injury.

**Table 51 Protocol B2355 Deaths, other serious adverse events (including COPD exacerbations) and adverse events leading to permanent discontinuation of study drug- n% of patients (Safety set)**

	Ind 75 µg N=159 n (%)	Pbo N=159 n (%)
Patients with any AE(s)	71 (44.7)	65 (40.9)
<b>Serious AEs or AE discontinuations</b>		
Deaths	0 (0.0)	0 (0.0)
SAEs	4 (2.5)	4 (2.5)
Discontinued due to AE(s)	3 (1.9)	3 (1.9)
Discontinued due to SAE(s)	2 (1.3)	1 (0.6)
Discontinued due to non-SAE(s)	2 (1.3)	2 (1.3)

Source: Table 12-4 Study No. CQAB149B2355 Clinical Study Report

### 3.3.4.3.7 Laboratory findings

There were no meaningful differences between groups nor any clinically meaningful shifts from baseline for hematology or chemistry laboratory assessments. Glucose levels greater than 9.99 mmol/L were found in 9 (5.7%) patients in the indacaterol group and 15 (9.4%) in the placebo group. For potassium levels < 3 mmol/L there was 1 patient in each treatment group. There was 1 patient in each the AST, ALT and Gamma GTT with levels > 3x the upper limit of normal (ULN) and 2 patients in placebo with a gamma GT level >3 x the ULN.

### 3.3.4.3.8 ECG findings

There were no events of QTc > 500 ms in either treatment group reported. A maximum increase from baseline of 30-60 ms was observed in 15 patients in the indacaterol group and 12 in the placebo group.

There were no > 60 ms increases from baseline in either group. ECG changes were comparable however there were more conduction abnormalities in the indacaterol group (16.5%) than placebo (10%).

#### **3.3.4.3.9 Physical examination**

Physical examination findings will focus on blood pressure and pulse abnormalities. There were no pulse rates > 130 bpm observed in the indacaterol groups, there was one in the placebo group. There were 2 patients with SBP >200 mm Hg, 1 in placebo, however for diastolic blood pressure, there were 5 with a DBP >115 mm Hg in the indacaterol group and 1 in placebo.

#### **3.3.4.4 Summary of Study**

This was a twelve week, multicenter, randomized, placebo-controlled trial comparing indacaterol 75 mcg q.d. to placebo in adults with moderate to severe COPD. The selected dose of indacaterol 75 mcg achieved the primary endpoint, demonstrating a statistically significant treatment difference of 0.14 L in trough FEV1 from placebo after twelve weeks. Subgroup analyses of the primary endpoint demonstrated larger treatment differences for patients aged  $\geq 65$ , those with moderate or less severe disease and those not on ICS at baseline.

Indacaterol 75 mcg failed to show a statistically significant improvement in the key secondary endpoint, TDI focal score over placebo. Other spirometry based endpoints did demonstrate superiority of indacaterol 75 mcg over placebo including tFEV1 on Days 2, 29, 57 and 84; FEV1 AUC5min-4hr; and peak FEV1 over 5 min-4hr on Days 1 and week 12. At 5 minutes post first dose, the treatment difference was 0.10 L, which was statistically significant and represented 69% of the treatment difference achieved on Day 85. There was no difference in the rate of change in tFEV1 for indacaterol 75 mcg from Day 29 to Week 12, indicating that there was no tachyphylaxis. Rescue medication use was also statistically significantly reduced after 12 weeks of treatment with indacaterol 75 mcg.

Only one category of the patient diary symptoms assessment, 'days able to perform usual daily activities' improved significantly on indacaterol. The quality of life questionnaire, SGRQ, did not meet the predefined clinically meaningful difference of -4 for the total score. However, both the symptom component as well as the impact component achieved statistical significance after 12 week treatment with indacaterol 75 mcg.

COPD and cough were the most frequent reported AEs. There were no deaths reported during the trial and the 3 SAEs 2 in the indacaterol treatment group and the remaining in placebo that led to discontinuation. There were no clinically meaningful differences between treatment groups observed in the hematology, chemistry laboratory or urinalysis assessments, vitals or ECG. There were reports of expected pharmacodynamic effects in glucose, potassium levels, ECG and one event of elevated blood pressure recorded as an AE.

### **3.3.5 CONFIRMATORY TRIAL B2354**

*A Twelve-Week Treatment, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Once Daily Indacaterol in Patients with Chronic Obstructive Pulmonary Disease*

#### **3.3.5.1 Trial Description**

##### **3.3.5.1.1 Design**

This was a Phase III randomized double-blind, placebo-controlled, parallel group trial using 75 mcg indacaterol once daily in patients with moderate to severe COPD. Patients were stratified based on smoking status and ICS use.

##### **3.3.5.1.2 Duration**

The treatment period was 12 weeks following a 14 day run-in period.

##### **3.3.5.1.3 Population**

The population consisted of male and female adults aged  $\geq 40$  years, who were outpatients with a diagnosis of moderate to severe COPD, as classified by the GOLD Guidelines 2008.

##### **3.3.5.1.4 Study Sites**

There were sixty-three centers in the United States

##### **3.3.5.1.5 Investigational and Reference Therapy**

- Investigational product: indacaterol 75 mcg formulation # 6002142.003 batch # X173GF, X297LF, X231KF.
- Placebo to indacaterol formulation # 3760253.004 batch # X171CD, X123DF. Indacaterol and placebo both were delivered via SDDPI, Concept 1 device (Neohaler).

##### **3.3.5.1.6 Objectives**

The primary objective of the study was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of 24 hour post-dose tFEV1 as compared to placebo after 12 weeks of treatment. Trough FEV1 was defined as in the previous trial B2355.

The key secondary objective was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of the TDI focal score after 12 weeks of treatment as compared to placebo.

Other secondary objectives were:

- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of t FEV1 after a single dose (Day 2) of treatment as compared to placebo
- To evaluate the efficacy of indacaterol (75 mcg q.d.) versus placebo for the standardized area under the curve (AUC) of FEV1 5 minutes-4 hours after a single dose (Day 1) and 12 weeks of treatment
- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of health-related quality-of-life as measured by St. George's Respiratory Questionnaire (SGRQ) total score after 12 weeks of treatment compared to placebo
- To evaluate the efficacy on indacaterol (75 mcg q.d.), and placebo in terms of rescue medication use over the 12 week treatment period using data obtained from the electronic diary (eDiary)
- To evaluate the efficacy of indacaterol (75 mcg q.d.) and placebo in terms of patient reported symptoms over the 12 week treatment period using data obtained from the eDiary
- To compare indacaterol (75 mcg q.d.) to placebo on spirometry assessments in terms of FEV1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks treatment) and trough response
- To evaluate the safety (in particular regarding ECG, laboratory tests, vital signs, AEs) of indacaterol (75 mcg q.d.) over 12 weeks, in patients with COPD

The Exploratory objectives were:

- To evaluate the effect of indacaterol (75 mcg q.d.) on COPD exacerbations over the 12- week treatment period
- To evaluate the PK profile of indacaterol in a subset of patients after 84 days of treatment was added in Amendment 1 dated 2/10/10.

#### **3.3.5.1.7 Inclusion Criteria**

The inclusion criteria were the same as those used in trials B2355 and B2356

#### **3.3.5.1.8 Exclusion Criteria**

The exclusion criteria were the same as those used in trials B2355 and B2356

#### **3.3.5.1.9 Conduct**

The trial was conducted almost identically to Study B2355, with the exceptions of no 24 hour spirometry profiling at the end of study as seen in B2355 and the addition of PK profiling obtained on Days 84 and 85. Briefly, the scheduled visits included both a prescreen to obtain informed consent and review and adjust COPD medications that were prohibited. Again, albuterol was to be used during the treatment period for rescue purposes only and rescue use was to be abstained within 6 hours of the start of each visit. The 14 day run-in was to assess eligibility and baseline information which was followed by the interval between Visits 4 and 9, the 12 week randomized blinded treatment period. The assessment schedule was similar with Study B2355.

#### **Efficacy Assessments**

The efficacy assessments included spirometry, daily clinical symptoms and rescue medication use, daily clinical symptoms, number of inhalations of albuterol rescue medication, BDI/TDI, and COPD exacerbations. The scheduling of spirometry measurements were the same as in Study B2355 except for the 24 hour profiling. Daily symptoms and rescue medication were captured with an electronic patient diary provided at Visit 2. Baseline and TDI scores were obtained on a similar schedule. COPD exacerbations were defined and recorded in the same manner as in Study B2355. Furthermore, as in B2355, COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An ER visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not be counted as an exacerbation. COPD exacerbations were recorded on the COPD exacerbations episode eCRF page only.

#### **Safety Assessment**

The safety assessment was the same as conducted in Study B2355.

#### **Other Assessments**

##### **SGRQ**

Similar to the conduct of Study B2355, the SGRQ was self-administered on paper by the patient at the investigator's site at baseline (Visit 4) and Visit 6 and 8 or at the time of discontinuation for patients who discontinue prematurely. The one month recall version of the SGRQ was used in this study. The questionnaire was to be completed before any other assessments were made.

#### **PK Assessments**

The collection of blood samples for PK as well as pharmacogenetic measurements after 12 weeks of study treatment was introduced in Amendment 1 dated February 10, 2010.

#### **3.3.5.1.10 Concomitant Treatments**

The prohibited medications, prohibited COPD-related medications and medications allowed under certain conditions were the same as in Studies B2357 and B2356, the dose ranging studies carried out in patients with asthma and COPD **Section 3.3.2.1.10** and **3.3.1.1.10**

### **3.3.5.1.11 Ethical Aspects**

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

### **3.3.5.1.12 Data Analysis**

The primary variable was 'trough FEV1' after 12 weeks of treatment (Visit 9) with LOCF as in B2355. Five populations were defined for analysis:

- The randomized set, included all randomized patients, whether they received study medication or not, grouped according to the treatment to which they were randomized.
- The full analysis set (FAS), included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were randomized.
- The per-protocol set (PPS), included all patients of the FAS without any major protocol deviations or non-protocol deviations. Patients were analyzed according to the treatment they received in the dispensing period prior to the primary endpoint visit except if a patient incorrectly took more than one treatment in the dispensing period prior to the primary endpoint visit. If this occurred the patient was excluded from the PPS. Major protocol deviations were defined prior to database lock and unblinding of the study.
- The safety set, included all patients who received at least one dose of study drug. Patients were analyzed according to the treatment they received except if a patient incorrectly took more than one treatment. If this occurred the patients was analyzed according to the treatment they were randomized to.
- The PK set included all patients with at least one evaluable drug concentration data sample who consented to participate in the PK subgroup. Patients were analyzed according to the treatment they received.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also, the FAS assigned randomized treatment and the safety set assigned received treatment. The primary analysis set for efficacy was the FAS and was analyzed using the same mixed model as specified in Study B2355. The PPS was used for supportive analysis of the primary objective. The FAS was used for the analysis of all other efficacy variables. The PK set was used for the analysis of all PK data. The safety set was used in the analysis of all safety variables.

For the key secondary objective, the TDI focal score was analyzed using the same mixed model as specified for the primary analysis with the BDI focal score as baseline. If data was missing or insufficient for any one of the domains, the focal score was not calculated. A hierarchical testing approach of the primary and secondary comparisons was the procedure used to handle multiplicity.

1. Trough FEV1 after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo. If indacaterol 75 mcg is superior to placebo then;
2. TDI focal score after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo.

The treatment comparisons for the other secondary variables/comparisons were for supportive evidence and no adjustment for multiplicity was made.

### **3.3.5.2 Patient Disposition and Demographics**

#### **Disposition**

Table 52 below outlines the numbers of patients screened, randomized and completed by treatment group. A total of 755 screenings took place, and 323 patients were randomized into the two treatment groups. The proportion of patients who completed the study was higher in the indacaterol 75 mcg group (88.3%) than in the placebo group (81.3%). The primary reason for discontinuation in both treatment



groups was AEs, primarily COPD exacerbations and pneumonia. A lower proportion of patients in the indacaterol 75 µg group withdrew consent than in the placebo group. Two deaths were reported in the placebo group.

**Table 52 Protocol B2354 Patient disposition (All patients)**

	Ind 75 µg n (%)	Pbo n (%)	Total n (%)
Screenings	-	-	755
<b>Patients</b>			
Randomized	163 (100.0)	160 (100.0)	323 (100.0)
Exposed	163 (100.0)	160 (100.0)	323 (100.0)
Completed	144 (88.3)	130 (81.3)	274 (84.8)
Discontinued	19 (11.7)	30 (18.8)	49 (15.2)
<b>Primary reason for premature discontinuation</b>			
Adverse event(s)	9 (5.5)	10 (6.3)	19 (5.9)
Subject withdrew consent	4 (2.5)	9 (5.6)	13 (4.0)
Protocol deviation	3 (1.8)	4 (2.5)	7 (2.2)
Abnormal test procedure result(s)	1 (0.6)	0 (0.0)	1 (0.3)
Unsatisfactory therapeutic effect	1 (0.6)	3 (1.9)	4 (1.2)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (0.6)
Abnormal laboratory value(s)	0 (0.0)	1 (0.6)	1 (0.3)
Death	0 (0.0)	2 (1.3)	2 (0.6)

Source: Table 10-1 Study No. CQAB149B2354 Clinical Study Report

### Protocol deviations

A total of 39 patients in the FAS had at least one major protocol deviation resulting in exclusion from the per-protocol set. The most frequent protocol deviation resulting in exclusion from the PPS was 'spirometry for SABA reversibility not acceptable as per ATS/ERS criteria' and this occurred in a similar proportion of patients in the indacaterol 75 mcg and the placebo groups. In general, the number of patients with each type of protocol deviation was similar between treatment groups.

### Demographics

Table 53 below summarizes the key demographics of the two treatment groups. Overall, very similar to Study B2355, the majority of patients were caucasian, approximately 55% were male, and the mean age was 64 years.

**Table 53 Protocol B2354 Demographic summary (Safety set)**

		Ind 75 µg N=163	Pbo N=160	Total N=323
Age (years)	n	163	160	323
	Mean	64.0	64.1	64.0
	SD	8.29	9.43	8.86
	Median	64.0	64.0	64.0
	Min - Max	44 - 85	40 - 90	40 - 90
Age group – n (%)	19–39 years	0 (0.0)	0 (0.0)	0 (0.0)
	40–64 years	85 (52.1)	84 (52.5)	169 52.3)
	≥ 65 years	78 (47.9)	76 (47.5)	154 47.7)
Sex – n (%)	Male	89 (54.6)	87 (54.4)	176 (54.5)
	Female	74 (45.4)	73 (45.6)	147 (45.5)
Race – n (%)	Caucasian	145 (89.0)	146 (91.3)	291 (90.1)
	Black	10 (6.1)	10 (6.3)	20 (6.2)
	Asian	5 (3.1)	3 (1.9)	8 (2.5)
	Other	3 (1.8)	1 (0.6)	4 (1.2)

Source: Adapted from Table 11-2 Study No. CQAB149B2354 Clinical Study Report

Baseline disease characteristics were comparable between treatment groups (Table 54). Overall, the median duration of COPD was 5.1 years, with a range of 0 to 35.7 years. Approximately 50% of patients had a diagnosis of COPD for >5 years. The severity of COPD was moderate in approximately 57% of patients overall and the majority of the remaining patients had severe COPD with a balanced distribution between treatment groups. This was also different between the two studies, B2355 and B2354. While both had comparable distribution of severity i.e., B2355 61.6% vs. 37.7% moderate to severe, while in B2354 it was 57.3% vs. 42.1%, Study B2355 had a different pattern of distribution between indacaterol and placebo with 68.6% moderate disease in indacaterol treatment group and 54.7% in placebo; for severe it was 30.2% and 45.3% respectively, however for B2354 both moderate and severe patients were more equally distributed between indacaterol and placebo treatment groups. Overall, approximately 45% patients were using inhaled corticosteroids (ICS) on entry to the study. In contrast to Study B2355, a slightly greater proportion of patients were ex-smokers than current smokers. Overall smoking history in terms of the mean number of pack years for all patients was 52.

Prebronchodilator FEV1 for the combined treatment groups was 1.3 L (47% predicted). The overall mean FEV1 after albuterol was 53.5% of predicted normal, and the FEV1/FVC ratio was 52.4%. The overall mean reversibility of FEV1 after albuterol at Visit 2 and after ipratropium at Visit 3 was approximately 16% in each case.

**Table 54 Protocol B2354 Baseline disease characteristics (Safety set)**

		Ind 75 µg N=163	Pbo N=160	Total N=323
Duration of COPD (years)	n	163	160	323
	Mean	7.2	7.3	7.3
	SD	6.31	6.43	6.36
	Median	5.5	4.7	5.1
	Min - Max	0.0 - 30.7	0.1 - 35.7	0.0 - 35.7
Duration of COPD – n (%)	<1 yrs	13 (8.0)	13 (8.1)	26 (8.0)
	1–5 yrs	65 (39.9)	70 (43.8)	135 (41.8)
	>5–10 yrs	44 (27.0)	39 (24.4)	83 (25.7)
	>10–15 yrs	23 (14.1)	19 (11.9)	42 (13.0)
	>15–20 yrs	10 (6.1)	10 (6.3)	20 (6.2)
	>20 yrs	8 (4.9)	9 (5.6)	17 (5.3)
Severity of COPD (GOLD 2008) – n (%)	Mild	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	96 (58.9)	89 (55.6)	185 (57.3)
	Severe	67 (41.1)	69 (43.1)	136 (42.1)
	Very severe	0 (0.0)	2 (1.3)	2 (0.6)
ICS use – n (%)	Yes	70 (42.9)	76 (47.5)	146 (45.2)
	No	93 (57.1)	84 (52.5)	177 (54.8)
Smoking history – n (%)	Ex-smoker	92 (56.4)	89 (55.6)	181 (56.0)
	Smoker	71 (43.6)	71 (44.4)	142 (44.0)
Number of pack years	n	163	160	323
	Mean	52.9	51.2	52.0
	SD	26.79	24.82	25.81
	Median	48.0	45.0	45.0
	Min - Max	10.0 - 150.0	10.0 - 148.0	10.0 - 150.0

Source: Table 11-3 Study No. CQAB149B2354 Clinical Study Report

### 3.3.5.3 Efficacy Review

All of the 323 randomized patients were included in the Safety set and FAS. Overall, 87.9% of patients were included in the PP set. Approximately 15% of patients in the indacaterol 75 mcg group were included in the PK set.

#### 3.3.5.3.1 Primary Endpoint

The primary variable was 'tFEV1' after 12 weeks of treatment (Visit 9). Of the 323 randomized patients included in the FAS set 297 were evaluated for the primary endpoint. Patients were included in the analysis if a tFEV1 value was available at Day 29 (Visit 6) or later, and values for Week 12 were imputed with a LOCF approach. For the FAS, the LS mean tFEV1 at Week 12 in the indacaterol 75 mcg group was statistically significantly greater to that in the placebo group (Table 55), with a LS mean treatment difference of 0.12 L equal to the pre-defined MCID. This result was comparable to the treatment difference of 0.14 L observed in B2355 and 0.17 L in B2336 which both had less severe COPD patients.. The sensitivity analysis in the per-protocol set showed the same treatment difference in tFEV1 as the FAS.

**Table 55 Protocol B2354 Trough FEV1 (L) at Week 12: treatment comparisons (Full analysis set and per-protocol set, imputed with LOCF)**

		--- Treatment ---		----- Treatment difference -----				
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Full analysis set								
Ind 75 µg	149	1.38	0.013	Ind 75 µg - Pbo	0.12	0.019	(0.08, 0.15)	<.001*
Pbo	148	1.26	0.013					
Per-protocol set								
Ind 75 µg	133	1.39	0.014	Ind 75 µg - Pbo	0.12	0.019	(0.08, 0.16)	<.001
Pbo	129	1.27	0.014					

Source: Table 11-5 No. CQAB149B2354 Clinical Study Report

Subgroup analyses for age, sex, smoking history, COPD severity, SABA reversibility and ICS use at baseline were performed for tFEV1 after 12 weeks of treatment. The treatment differences of select subgroups are displayed below in Table 56. Identical to B2355, but in contrast to B2336, indacaterol 75 mcg dose had a larger treatment difference in the ≥ 65 age group with 0.15 L as opposed to the < 65 age group with 0.09 L. However, the treatment difference for indacaterol 75 mcg based on severity was consistent with that in B2336, where larger differences were seen in patients with moderate or less severe COPD (0.14 L) than in those with severe or worse disease (treatment difference = 0.09 L). Patients who were not on ICS at baseline had a higher the treatment difference of 0.14 L vs. those on a stable ICS regimen with 0.10 L.

**Table 56 Protocol B2354 Analysis of trough FEV1 after 12 weeks treatment (imputed with LOCF), select subgroup analyses**

		Treatment difference (L)		
		Ind 75 mcg	95% CI	p-value
Age	< 65	0.09	0.04, 0.14	< 0.001
	≥ 65	0.15	0.09, 0.20	< 0.001
Gender	Male	0.13	0.08, 0.18	< 0.001
	Female	0.11	0.05, 0.16	< 0.001
COPD Severity	Moderate/less	0.14	0.09, 0.19	< 0.001
	Severe/worse	0.09	0.04, 0.15	= 0.001
Smoking status	Ex smoker	0.13	0.08, 0.18	< 0.001
	Current smoker	0.10	0.05, 0.16	< 0.001
SABA reversibility	>12%	0.12	0.07, 0.16	< 0.001
	≤ 12%	0.12	0.06, 0.18	< 0.001
ICS	No	0.14	0.09, 0.19	< 0.001
	Yes	0.10	0.04, 0.15	< 0.001

Source: Adapted from Tables 14.2-1.1 Study No. CQAB149B2354 Clinical Study Report

### 3.3.5.3.2 Secondary Endpoints

The key secondary objective was to demonstrate that indacaterol (75 mcg q.d.) was superior to placebo with respect to TDI focal score following 12 weeks of treatment. The sponsor considered a difference of 1 unit in TDI to be the MCID for COPD patients. At Week 12, the difference between treatment groups in LS mean TDI focal score was statistically significantly greater in the indacaterol 75 mcg group compared with

the placebo group ( $p < 0.001$ ), with a treatment difference of 1.23 units. The LS mean TDI focal score was statistically significantly higher in the indacaterol 75 mcg group than in the placebo group at Week 4 (LS mean difference 0.97,  $p = 0.001$ ). A responder analysis of the proportion of patients with a MCID of  $\geq 1$  revealed that at Weeks 4 and 12, 42% and 48 % of patients, respectively in the 75 mcg treatment group had a MCID  $\geq 1$ .

A summary of the treatment differences seen between indacaterol and placebo for select secondary endpoints is presented in Table 57 below. Trough FEV1, FEV1 AUC (5 min-4 hr), and peak FEV1 showed a statistically significant difference from placebo at all time points, consistent with the bronchodilator action of the drug.

**Table 57 Protocol B2354 Select secondary efficacy endpoints (FAS)**

		Treatment difference (L)		
		Ind 75 mcg	95% CI	p-value
Trough FEV1	Day 2	0.08	(0.06, 0.1)	$< 0.001$
	Day 29	0.11	(0.08, 0.15)	$< 0.001$
	Day 57	0.10	(0.05, 0.14)	$< 0.001$
	Day 84	0.11	(0.07, 0.15)	$< 0.001$
FEV1 AUC (5 min-4 hr)	Week 12	0.17	(0.14, 0.21)	$< 0.001$
Peak FEV1 1 <sup>st</sup> 4 hr	Day 1	0.11	(0.09, 0.13)	$< 0.001$
	Week 12	0.16	(0.13, 0.20)	$< 0.001$

Source: Adapted from Tables 14.2-3.1, 14.2-3.2, 14.2-4.1, 14.2-4.2, 14.2-4.3, 14.2-4.4 Study No. CQAB149B2354 Clinical Study Report

As described in the protocol, FEV1 was measured at multiple time points on Days 1, 2, 29, 57, 84 and 85. All values were statistically significantly larger than placebo as seen in Table 58. The difference from placebo in FEV1 was 0.09L, consistent with the onset of action claims the sponsor proposes in the label. The values on Day 84 were all larger than the corresponding time points on Day 1. At each time point measured, FVC values in the indacaterol 75 mcg group were also statistically significantly greater than in the placebo group (all,  $p = 0.007$ ), with LS mean differences ranging from 0.10 L to 0.25 L across all time points..

**Table 58 Protocol B2354 Analysis of FEV1 (L) at each time point, by visit (FAS)**

		Treatment differences (L)		
		Ind 75 mcg	95% CI	p-value
Day 1	5 min	0.09	(0.07, 0.10)	< 0.001
	30 min	0.12	(0.10, 0.14)	< 0.001
	1 hr	0.11	(0.09, 0.13)	< 0.001
	2 hr	0.13	(0.10, 0.15)	< 0.001
	4 hr	0.12	(0.10, 0.15)	< 0.001
Day 2	23 hr 10 min	0.08	(0.05, 0.10)	< 0.001
	23 hr 45 min	0.08	(0.06, 0.11)	< 0.001
Day 29	-50 min	0.12	(0.08, 0.15)	< 0.001
	-15 min	0.12	(0.08, 0.15)	< 0.001
	5 min	0.16	(0.13, 0.20)	< 0.001
	30 min	0.17	(0.14, 0.21)	< 0.001
	1 hr	0.17	(0.14, 0.20)	< 0.001
Day 57	-50 min	0.10	(0.05, 0.14)	< 0.001
	-15 min	0.11	(0.06, 0.15)	< 0.001
	5 min	0.15	(0.10, 0.19)	< 0.001
	30 min	0.14	(0.10, 0.19)	< 0.001
	1 hr	0.15	(0.11, 0.20)	< 0.001
Day 84	-50 min	0.12	(0.08, 0.16)	< 0.001
	-15 min	0.13	(0.09, 0.17)	< 0.001
	5 min	0.18	(0.15, 0.22)	< 0.001
	30 min	0.18	(0.14, 0.22)	< 0.001
	1 hr	0.18	(0.14, 0.21)	< 0.001
	2 hr	0.17	(0.14, 0.21)	< 0.001
	4 hr	0.15	(0.11, 0.19)	< 0.001
Day 85	23 hr 10 min	0.11	(0.07, 0.15)	< 0.001
	23 hr 45 min	0.12	(0.07, 0.16)	< 0.001

Source: Adapted from Table 14.2-5.1 Study No. CQAB149B2354 Clinical Study Report

➤ FEV1 trough response

Similar to Study B2355, the protocol called for comparisons of the rate of change in tFEV1 by indacaterol 75 mcg and placebo from Day 29 to Week 12 of treatment to evaluate for evidence of tachyphylaxis. The estimate value for the slope for indacaterol was positive, consistent with no loss of efficacy over time.

➤ Rescue medication use

All patients were provided with albuterol for use as rescue medication from Visit 1 and an electronic diary to record use on Visit 2. The indacaterol 75 mcg group had statistically significant decreases in the LS mean change from baseline in daily number of puffs of rescue medication and the LS mean change from baseline in number of puffs during the day and night compared with placebo over 12 weeks of treatment. The percentage of 'days with no rescue medication use' was statistically significantly higher in the indacaterol 75 mcg group compared with the placebo group. Summary statistics of the mean daily number of puffs of rescue medication, mean number of daytime puffs and mean number of nighttime puffs of rescue medication over 12 weeks of treatment are presented in Table 59 below.

**Table 59 Protocol B2354 Rescue medication use over 12 weeks: treatment comparisons (FAS)**

Treatment	n	-- Treatment --		Comparison	----- Treatment difference -----			
		LS Mean	SE		LS Mean	SE	95% CI	p-value
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 75 µg	153	-1.58	0.186	Ind 75 µg - Pbo	-1.16	0.261	(-1.67, -0.65)	<.0001
Pbo	153	-0.42	0.185					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 75 µg	151	-0.97	0.106	Ind 75 µg - Pbo	-0.64	0.149	(-0.93, -0.35)	<0.001
Pbo	146	-0.33	0.107					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 75 µg	152	-0.65	0.092	Ind 75 µg - Pbo	-0.52	0.129	(-0.77, -0.27)	<0.001
Pbo	151	-0.13	0.091					
Percentage of 'days with no rescue use'								
Ind 75 µg	152	42.4	2.34	Ind 75 µg - Pbo	13.7	3.25	(7.3, 20.0)	<0.001
Pbo	149	28.8	2.36					

Source: Table 11-10 Study No. CQAB149B2354 Clinical Study Report

➤ Symptoms

In contrast to Study B2355 where the only symptom category to reach statistical significance was 'days able to perform usual daily activities', in Study B2354, that category did not reach statistical significance, but instead the category, 'no daytime symptoms' reached statistical significance with a LS mean treatment difference of 4.6 (95% CI 1.5, 7.6; p=0.003).

➤ Health related quality of life

The SGRQ was used to provide health-related quality of life measurements during the course of the trial. The protocol specified that the SGRQ would be administered at Visits 4, 6 and 8 (Days 1, 29 and 84). The LS mean SGRQ total score at Week 12 (imputed with LOCF) was statistically significantly lower in the indacaterol 75 mcg group than in the placebo group, although the treatment difference of -3.8 (95% CI -6.2, -1.4; p=0.002) did not achieve the MCID of 4 units. Analyses of the SGRQ total scores at Week 4 (LS mean difference -2.9, p=0.005) and without LOCF imputation at Week 12 (LS mean difference -3.7, p=0.003) were consistent.

In a responder analysis, the proportion of patients with a clinically important improvement of 4 units in the SGRQ total score at Week 12 (imputed with LOCF) was 47.6% for the indacaterol 75 mcg group and 34.5% for the placebo group, and the odds ratio (1.80) was statistically significant (p=0.024). Analysis of SGRQ components scores after 12 weeks, demonstrated significant improvement in symptoms and activity. See Table 60. This was a different pattern than that seen in B2355 where the symptoms and impact components reached statistical significance but, not the activity component.

**Table 60 SGRQ total score at Week 12 (imputed with LOCF): treatment comparisons (Full analysis set)**

Treatment	n	--- Treatment ---		Comparison	----- Treatment difference -----			
		LS Mean	SE		LS Mean	SE	95% CI	p-value
Ind 75 µg	147	43.4	0.86	Ind 75 µg - Pbo	-3.8	1.21	(-6.2, -1.4)	0.002
Pbo	142	47.2	0.87					

Source: Table 11-12 No. CQAB149B2354 Clinical Study Report

➤ COPD exacerbation frequency

The exploratory efficacy endpoint of number of COPD exacerbations over 12 weeks treatment was also examined. The mean number of exacerbations per patient (without imputation) was 0.2 for the indacaterol 75 mcg group and 0.3 for the placebo group. No patient had more than 1 COPD exacerbation during the 12 week treatment. The rate of exacerbations per year was lower in the indacaterol 75 mcg group than the placebo group (0.8 vs. 1.3).

#### **3.3.5.4 Pharmacokinetic analyses**

PK assessments were measured for a subgroup of 25 patients. Peak serum levels were achieved with a median Tmax of 0.53 hours. The average ( $\pm$ SD) Cmax was 150.44 pg/mL ( $\pm$ 68.26 pg/mL) and average AUClast was 2163.3 pg\*hr/mL)

#### **3.3.5.5 Safety Review**

##### **3.3.5.5.1 Extent of exposure**

The overall exposure and compliance was similar across the two treatment groups. The mean number of days patients in the indacaterol group were exposed to drug was 78.9 and for placebo it was 77 days. Compliance of percent of doses taken over the whole treatment period was over 97% for both groups.

##### **3.3.5.5.2 Concomitant medication**

Concomitant medications and non drug therapies were taken by the majority of patients in both groups. COPD medications were taken by more than half of patients on indacaterol and placebo. The most common COPD related medications were ICSs used by 44.2% of patients in the indacaterol group and 47.5% in the placebo. Non COPD medications were taken by 92.6% of patients in the indacaterol group and 91.9% in the placebo group. The most common were acetylsalicylic acid, multivitamins, simvastatin and lisinopril.

##### **3.3.5.5.3 Adverse events**

The incidence of adverse events reported in the indacaterol group was 49/1% and 46.35 for the placebo group. Similar to other trials the most frequently affected SOC were: infections and infestations, respiratory, thoracic and mediastinal disorders and gastrointestinal disorders. The most commonly reported AE was COPD (8.6% versus 11.1%) for indacaterol vs. placebo treatment groups, respectively. Headache, urinary tract infection nasopharyngitis were observed in higher levels in the indacaterol group than placebo. Cough and dyspnea were also common but had similar rates across treatment groups.

#### **Deaths and SAEs**

There were 2 deaths reported in the trial, both in the placebo group. One patient was a 68 year old female with a history of hypertension, hypercholesterolemia and type II diabetes mellitus died of a myocardial infarction. The other patient, was a 71 year old male with a history of hyperlipidemia, hypertension, anemia and type II diabetes mellitus, died due to a ruptured aortic aneurysm. There were 4 SAEs captured in the indacaterol group (2.5%) and 9 (5.6%) in the placebo group. The SAEs in the indacaterol group include: COPD exacerbation, worsening of chronic anemia, mycosis fungoides and atypical non-cardiac chest pain.

#### **Adverse events leading to discontinuation**

The AEs leading to discontinuation were reported at a lower rate in the 75 mcg indacaterol (4.9%) group than in the placebo (6.9%) group. The most common AE leading to discontinuation was COPD which was higher in the placebo (2.5%) group than in the indacaterol (1.8%) group. Dyspnea was reported more than once and greater in the indacaterol group.

##### **3.3.5.5.4 Laboratory findings**

There were no clinically meaningful changes in the hematology laboratories. Evaluation of the chemistry laboratories revealed a maximum mean change from baseline of creatinine kinase levels higher in the indacaterol 75 mcg group than placebo (65.1 vs. 47.0). Notable elevations of glucose > 9.99 mmol/L were observed in 6.3% of placebo treated patients and 4.9% of indacaterol treated patients. However, based



on the maximum post-baseline value, 19.1% of patients in the indacaterol 75 mcg group and 11.3% of the patients in the placebo group had shifts from normal at baseline to high (above the normal range) post-baseline.

There were no reports of notable potassium < 3 mmol/L in either indacaterol or placebo treatment groups. However, based on the minimum post-baseline value, 6.8% (11 patients) in the indacaterol 75 mcg group and 8.8% (14 patients) in the placebo group had a shift from normal at baseline to low post-baseline.

#### **3.3.5.5.5 ECG findings**

No events of QTc > 500 ms were reported in either treatment group. A maximum increase from baseline of 30- 60 ms in QTc was seen in 8 (4.9%) patients in the indacaterol 75 mcg group and 6 (3.8%) patients in the placebo group. There were no reports of a maximum increase from baseline > 60 ms in either treatment group. Qualitative ECG changes occurred at similar rates between the two groups. Ectopy was reported with the greatest rates of 25.5% in the indacaterol group and 21.8% in the placebo group.

#### **3.3.5.5.6 Physical examination**

There were no reports of pulse rates > 130 bpm in either treatment group. There was 1 event of SBP > 200 mm Hg in the placebo group and 3 events in the placebo group and 1 in the indacaterol group of DBP > 115 mm Hg.

#### **3.3.5.6 Summary of Study**

This was a twelve week, multicenter, randomized, placebo-controlled trial comparing indacaterol 75 mcg q.d. to placebo in adults with moderate to severe COPD. The selected dose of indacaterol 75 mcg achieved the primary endpoint of tFEV1, demonstrating a statistically significant treatment difference from placebo after twelve weeks, 0.12 L.

Consistent with the expected response for a bronchodilator drug, other spirometry based endpoints also demonstrated superiority of indacaterol 75 mcg over placebo including tFEV1 on Days 2, 29, 57 and 84; FEV1 AUC5min- 4hr; peak FEV1 over 5 min-4hr on Days 1 and week 12. As well, at 5 minutes post first dose, the treatment difference was 0.09 L, statistically significant and representing 78% of the treatment difference achieved on Day 85. There was no difference in the rate of change in tFEV1 for indacaterol 75 mcg from Day 29 to Week 12. Rescue medication use was also statistically significantly reduced after 12 weeks of treatment with indacaterol 75 mcg.

A different category from that seen in B2355 of the patient diary symptoms assessment, 'no daytime symptoms' improved significantly to indacaterol. The quality of life questionnaire, SGRQ total score, showed a treatment difference of -3.8, which did not meet the predefined clinically meaningful difference of -4. As seen in B2355, the symptom component reached statistical significance over placebo, however, in this trial the activities component and not the impact component achieved statistical significance after 12 week treatment with indacaterol 75 mcg.

Peak serum levels of indacaterol after administration of a 75 mcg dose reached maximum in approximately 30 minutes

The most frequent AE was COPD with a lower incidence in the indacaterol treatment group than in placebo. Headache, urinary tract infections, nasopharyngitis and arthralgia were also frequently reported AEs. There were two deaths in the placebo group reported during the trial; one due to a myocardial infarction, the other a ruptured aortic aneurysm. There were 7 patients (1 patient in the indacaterol 75 mcg treatment group and 6 patients in the placebo group) with SAEs leading to discontinuation from the trial. There were no clinically meaningful differences reported between treatment groups in the hematology, chemistry laboratory (including serum potassium, blood glucose and transaminases) or urinalysis assessments, vitals or ECG.

### 3.3.6 LONG TERM TRIAL B2336

*A 26-Week Treatment, Multicenter, Randomized, Double Blind, Double Dummy, Placebo Controlled, Parallel Group Study to Assess the Efficacy and Safety of Indacaterol (150 mcg q.d.) in Patients with Chronic Obstructive Pulmonary Disease, Using Salmeterol (50 mcg b.i.d.) as an Active Control*

#### 3.3.6.1 Trial Description

##### 3.3.6.1.1 Design

This was a Phase III, multi center, double blind, double dummy, parallel group study of indacaterol 150 mcg once daily in patients with moderate-to-severe COPD. Eligible patients were randomized 1:1:1 to receive indacaterol 150 mcg q.d., salmeterol 50 mcg b.i.d., or placebo for 26 weeks as detailed in Table 61 below.

**Table 61 Protocol B2336 Study design**

Period	Pre-screen	Screen/Run-in	26- week Randomized Treatment
Visits		1* and 2	3-13
Day/Week		Day -14 to 1	1-26
			↓ Patients were randomized (1:1:1) to receive one of the following three blinded treatments: indacaterol 150 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via a proprietary dry powder inhaler, or salmeterol 50 µg b.i.d. via a proprietary dry powder inhaler and placebo to indacaterol via SDDPI, or placebo to indacaterol via SDDPI and placebo to salmeterol 50 µg b.i.d. via a proprietary dry powder inhaler
		Daily ICS monotherapy, if needed, was to remain stable throughout study Salbutamol/albuterol was available for rescue use throughout study	

Source: Table 9-1 Study No. CQAB149B2336 Clinical Study Report

##### 3.3.6.1.2 Duration

A 14 day run in period was followed by a 26 week treatment period.

##### 3.3.6.1.3 Population

The population included male and female patients aged ≥40 years with a clinical diagnosis of moderate to severe COPD and a smoking history of at least 20 pack years.

##### Reviewer Comment:

*Study B2356 recruited patients with at least 10 pack year history. In this trial only patients with a 20 pack year history were included.*

##### 3.3.6.1.4 Study Sites

The trial was conducted at 142 centers in 15 countries: Canada (4), Colombia (3), Czech Republic (6), Denmark (10), Germany (43), Finland (6), France (4), Hungary (5), India (11), Iceland (1), Italy (15), Peru (6), Russia (15), Slovakia (5), and Taiwan (8).

##### 3.3.6.1.5 Investigational and Reference Therapy

The active comparator was salmeterol 50 mcg b.i.d. delivered via a proprietary drug power inhaler. The indacaterol (150 mcg) placebo product was delivered via SDDPI and the placebo to salmeterol (50 mcg) was delivered via a proprietary dry powder inhalation device. A large number of different batch numbers

were utilized for this trial, which differed by country. These numbers are provided in the Clinical Study Report.

### 3.3.6.1.6 Objectives

The primary objective was to confirm the superiority of indacaterol 150 mcg q.d. via SDDPI in patients with COPD compared to placebo with respect to 24 hr post dose tFEV1 after 12 weeks of treatment..

The key secondary objectives were to: 1) evaluate the effect of indacaterol (150 mcg q.d.) on the total score of the SGRQ after 12 weeks compared with placebo; and 2) evaluate the effect of indacaterol (150 mcg q.d.) on the percentage of “days of poor control” reported over the 26-week randomized treatment period compared with placebo.

Other secondary objectives were to:

- Compare salmeterol with placebo and indacaterol (150 mcg) with salmeterol with respect to all other secondary variables and the tFEV1 at week 12
- Evaluate the effect of indacaterol (150 mcg q.d.) on the total score of the SGRQ, after 4, 8, and 26 weeks compared with placebo
- Evaluate the effect of indacaterol (150 mcg q.d.) on health related quality of life assessments compared with placebo after 12 and 26 weeks of treatment
- Evaluate the effect of indacaterol (150 mcg q.d.) on exacerbation during the 26 week randomized treatment period compared with placebo with respect to:
  - time to first COPD exacerbation
  - COPD exacerbation rate
- Evaluate the effect of indacaterol (150 mcg q.d.) on the TDI focal score compared with placebo measured after 4, 8, 12 and 26 weeks of treatment
- Compare indacaterol (150 mcg q.d.) with placebo on spirometry assessments in terms of:
  - tFEV1 measured on Day 2 and after 26 weeks of treatment
  - FEV1 and FVC measured at all time points, including approximate peak response (Day 1 and after 2, 12 and 26 weeks of treatment) and trough response
  - the standardized AUC for FEV1<sub>(5 min – 1hr)</sub> for all patients and 5 min – 4hr for a sub group) on Day 1 and after 2 (5 min – 1hr), 12 and 26 weeks of treatment
- Evaluate the effect of indacaterol (150 mcg q.d.) vs. placebo on other clinical variables such as morning (pre-medication) and evening (pre-medication) PEF, clinical symptoms and use of rescue medication over 26 weeks of treatment
- Evaluate the effect of indacaterol (150 mcg q.d.) versus placebo on post inhalation events (especially cough) measured over 26 weeks of treatment
- Assess the long-term safety (particularly with regard to ECG, laboratory tests, blood pressure and adverse events) of indacaterol (150 mcg q.d.)
- Evaluate the 24 hour spirometry (FEV1 and FVC) profile of the 150 mcg q.d. dose of indacaterol, placebo and salmeterol after 26 weeks treatment
- Evaluate the response to the patient end of study questionnaire for the 150 mcg q.d. dose of indacaterol, placebo and salmeterol after 26 weeks of treatment

Exploratory objectives were to:

- Conduct (in subjects signing an additional PG consent form) exploratory PG research studies on the effects of human genetic variation on indacaterol (150 mcg q.d.) response and exposure.
- Assess the effect of indacaterol (150 mcg q.d.) on the BODE index (total and individual components) after 12 and 26 weeks of treatment compared to placebo
- Explore the impact of indacaterol (150 mcg) on medical resource utilization
- Evaluate the performance and properties of a new COPD quality of life measure, Living with Chronic Obstructive Pulmonary Disease questionnaire (LCOPD)
- Evaluate the rate of change in trough FEV1 and FVC of indacaterol (150 mcg q.d.) and placebo over 26 weeks of treatment.

#### **3.3.6.1.7 Inclusion Criteria**

Post bronchodilator criteria remained the same as in Study B2355 and B2356.

#### **3.3.6.1.8 Exclusion Criteria**

These were the same as in Study B2355 and B2356 with the addition of further qualification of the diagnosis of asthma for exclusion: blood eosinophil count > 400/mm. However, the protocol did not exclude patients with Alpha-1 Antitrypsin deficiency or those who have ever received omalizumab as in B2355.

#### **3.3.6.1.9 Conduct**

During the prescreening visit, informed consent was obtained, current COPD medications were reviewed and if necessary arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. At Visit 1, eligible patients underwent assessments, including  $\beta$ 2-agonist reversibility testing, and started the 14-day run-in period. At Visit 2, patients underwent anti-cholinergic reversibility testing. At Visit 3 (study day 1), eligible patients were randomized 1:1:1 to receive indacaterol 150 mcg q.d., salmeterol 50 mcg b.i.d., or placebo for 26 weeks. Visits 3 to 12 comprised the 26-week randomized treatment period. Randomization was stratified by smoking status. See Table 62 for details.

**Table 62 Protocol B2336 Assessment Schedule**

Period	Categ- ory <sup>1</sup>	Pre- scree n	Screen / Run-in		26-week randomized treatment									
Visit			1	2	3	4	5	6, 7	8	9	10, 11	12 <sup>2</sup>	13 <sup>2,10</sup>	
Week – start of week <i>(*last day of wk)</i>			- 2	- 2	1	1	3	5, 9	12 *	13	17, 22	26*	27	
Day			- 14	- 13	1	2	15	29,57	84	85	113,148	182	183/184	
Informed consent	DS	X												
PG Informed Consent	DS	X												
Current Medication review	DS	X												
Incl./Excl. criteria	S		X		X									
Medical History, Demographics	DS		X											
Smoking History	DS		X						X			X		
Pregnancy Test (serum)	DS		X						X				X	
Physical exam.	S		X							X			X	
Record height (Visit 1 only) and weight	DS		X						X				X	
Contact IVRS to register patient	DS		X											
FEV <sub>1</sub> Reversibility (β <sub>2</sub> -agonist)	DS		X											
FEV <sub>1</sub> Reversibility (anti-cholinergic)	DS			X										
PG Blood (consenting pts)	DS				X									
Issue Patient Diary	S		X		X			X		X	X			
Review/collect Patient Diary	DS <sup>7</sup>				X	X	X	X	X	X	X	X	X	
Randomization	DS				X									
Provide Rescue Medication as necessary	S		X	X	X	X	X	X	X	X	X	X		
Review/record β <sub>2</sub> - agonist use	DS		X	X	X	X	X	X	X	X	X	X	X	

Period	Categ- ory <sup>1</sup>	Pre- scree n	Screen / Run-in		26-week randomized treatment								
Visit			1	2	3	4	5	6, 7	8	9	10, 11	12 <sup>2</sup>	13 <sup>2,10</sup>
Week – start of week (*last day of wk)			- 2	- 2	1	1	3	5, 9	12 <sup>*</sup>	13	17, 22	26*	27
Day			- 14	- 13	1	2	15	29,57	84	85	113,148	182	183/184
ECG <sup>3</sup>	DS		X		X		X		X			X	X
Systolic & diastolic blood pressure & radial pulse rate <sup>3</sup>	DS		X		X		X		X			X	X
Urinalysis <sup>3</sup>	DS		X		X		X		X				X
Hematology/Blood Chemistry <sup>3</sup>	DS		X		X		X		X			X	X
C-reactive protein <sup>3</sup>	DS				X				X			X	
24 h Spirometry Profiling <sup>8</sup>													X
Spirometry <sup>3</sup>	DS		X	X	X	X	X	X	X	X	X	X	X
Record post inhalation events <sup>4</sup>	DS				X	X	X	X	X	X	X	X	X
AE recording	DS		X	X	X	X	X	X	X	X	X	X	X
Concom. Meds	DS		X	X	X	X	X	X	X	X	X	X	X
Record medical resource utilization	DS		X	X	X	X	X	X	X	X	X	X	X
EQ-5D	DS				X				X			X	
SGRQ	DS				X			X	X			X	
LCOPD	DS				X				X			X	
BDI	DS				X								
TDI	DS							X	X			X	
MMRC dyspnea scale	DS				X				X			X	
Pt end of study questionnaire	DS												X
6 min walk test <sup>5</sup>	DS				X				X			X	
Device training	S		X		X								
Telephone patient <sup>1</sup> day prior to Visit <sup>6</sup>	S						X	X	X		X	X	
Administer study drug at visit	DS				X	X	X	X	X	X	X	X	X <sup>9</sup>
Dispense (excluding Visit 13) and review use of study drug	DS				X			X		X	X		X
Collect unused study drug	S							X		X	X		X
Record total number of capsules taken since the last dispensing visit	DS							X		X	X		X

Period	Categ-ory <sup>1</sup>	Pre-screen	Screen / Run-in		26-week randomized treatment								
Visit			1	2	3	4	5	6, 7	8	9	10, 11	12 <sup>2</sup>	13 <sup>2,10</sup>
Week – start of week (*last day of wk)			- 2	- 2	1	1	3	5, 9	12*	13	17, 22	26*	27
Day			- 14	- 13	1	2	15	29,57	84	85	113,148	182	183/184
Study completion eCRF	DS												X

<sup>1</sup>Source: Table 9-4 Study No. CQAB149B2336 Clinical Study Report

## Efficacy Assessments

### ***Spirometry assessments***

At Visit 1 (Day -14) spirometry was measured to assess eligibility as well as beta agonist reversibility and on the next day anti-cholinergic reversibility testing was performed.

Serial spirometry assessments were performed on a schedule as follows:

- Day 1: 50 and 15 min pre-dose, 5, 30 min, 1 hr post- dose
- Day 2: 23 hr 10 min, 23 hr 45 min post- dose
- Day 15: 50 and 15 min pre-dose, 5, 30 min and 1 hr post- dose
- Day 57: 50 and 15 min pre-dose, 5 min and 30 min post- dose
- Day 84: 50 and 15 min pre-dose, 5, 30 min and 1 hr post- dose
- Day 85: 23 hr 10 min and 23 hr 45 min post- dose
- Day 148: 50 and 15 min pre-dose and 5 and 30 min post- dose
- Day 182: 50 and 15 min pre-dose and 5, 30 min and 1 hr post- dose
- Day 183: 23 hr 10 min and 23 hr 45 min post-dose

As part of Amendment 1 dated 8/7/08, a 24 hr spirometry profiling assessment period (Visit 13 or Day183) was added. For those in the 24 hr serial spirometry subgroup their assessments were extended into Days 183 and 184 to include time points at 6, 12, 16, 22 and 24 hrs post-dose. A subgroup of patients at designated centers also underwent spirometry testing at 2 and 4 hr post- dose at Day 1, 84 and 182.

### ***Patient diaries***

All patients were provided with a Patient Diary to record morning and evening PEF, daily clinical symptoms, rescue medication (albuterol) use, any AEs, and any changes in concomitant medication throughout the study, number of 'days of poor control'. Patient diaries were given out on Days -14, 1, 29, 57, 85, 113 and 148 and patients were instructed to complete the diary twice daily, before taking study drug and again each evening.

### ***Peak expiratory flow (PEF)***

A Peak Flow Meter was given to each patient at Visit 1 (Day -14) for the measurement of morning and evening PEF.

### ***Dyspnea indices***

Patients were interviewed by an independent, trained assessor who graded the degree of impairment due to dyspnea at Visit 3 (Day 1), baseline dyspnea index and at Days 29, 57, 84 and 149 to obtain the transition dyspnea index. The same assessor completed all the BDI/TDI assessments for an individual patient. These assessments were undertaken after completing the EQ-5D, SGRQ and COPDQOL but prior to completion of the MMRC dyspnea scale and the 6 min walk test.

### ***MMRC dyspnea scale***

Investigators assessed patients according to the modified <sup>7</sup>MMRC dyspnea scale at Days 1, 84 and 149. The assessment was performed prior to the 6 min walk test. The MMRC dyspnea score (0-4), together

<sup>7</sup> Mahler DA, et al., (1984) The measurement of dyspnea. Chest; 85:751-8.

with the 6 min walk test, FEV1 (% predicted) and the body mass index were used to calculate the BODE index.

*Reviewer's Comment:*

*The BODE index, a multidimensional 10 point grading system has been shown to be a predictor of the risk of death from any cause and from respiratory causes among patients with COPD (<sup>8</sup>Celli BR et al., 2004). The four factors include: the body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the six-minute-walk test. The higher scores indicate a higher risk of death.*

**Six min walk test**

The 6 min walk test was conducted pre-dose at Day 1 and 90 min post-dose at Days 84 and 182.

**Safety Assessments**

Vitals, laboratory and ECG were taken at 25 min pre-dose and 1 hr post-dose on Days 1, 15, 84, 182 and Day 183 at 23 hr 35 min post-dose. Urinalysis was performed 2 hrs pre-dose on Days 1 and 84, on Day 15 it was performed 35 min pre-dose and on Day 183 23 hrs post-dose. AEs were recorded at all visits and a serum pregnancy test was taken on Days -14, 84 and 183. PE was performed on Days -14, 85 and 183.

All COPD exacerbations, regardless of treatment were recorded on the COPD exacerbation episode eCRF and not on the AE eCRF unless in the opinion of the investigator it should be classified as a SAE (not requiring hospitalization) at which point both the SAE form and the COPD exacerbation episode eCRF was to be completed. A COPD exacerbation was defined as:

- A new onset or worsening of more than one respiratory symptom (i.e. dyspnea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days
- Plus at least one of the following:
  - Documented change or increase in COPD related treatment due to worsening symptoms (e.g., steroids/antibiotics/oxygen)
  - Documented COPD-related hospitalizations or ER visits

**Other Assessments**

Health-related quality of life questionnaires (EQ-5D, SGRQ and LCOPD), assessment of health care resource utilization, and a patient end-of-study questionnaire were used in this study. The EuroQol (EQ-5D) and SGRQ were completed at the investigator's site on the day of randomization and at Days 84 and 182 (or early discontinuation visit), before any treatment had been given or other assessments performed. In addition the new Living with COPD Questionnaire (LCOPD) measure was administered following the EQ-5D and SGRQ. The SGRQ was also completed on Days 29 and 57.

The EQ-5D contained 5 questions asking the patient about their current health and also a visual analogue scale of 0-100 (0= worst imaginable health state; 100 = best imaginable health state) on which the patient marked their health status. The EQ-5D was administered to collect data on health-related quality of life in order to calculate utilities to support economic evaluation.

The SGRQ is divided into three sections: "Symptoms" concerns with respiratory symptoms, their frequency and severity; "Activity" concern activities that caused or were limited by breathlessness; and "Impacts" which cover different aspects of social functioning and psychological disturbances resulting from airway disease. Scores for each section and a "Total" score were calculated, ranging from 0 to 100. Higher values corresponded to greater impairment of health-related quality of life. The LCOPD consisted of 22 statements designed to measure the impact of COPD on patient's lives. Data were collected to

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<sup>8</sup> Celli BR, Cote CG, Marin JM, et al., (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med; 350:1005-12.



support ongoing evaluation of the performance and psychometric properties of available language translations of the LCOPD.

*Reviewer's Comment:*

*Details of the EQ-5D will not be included as economic evaluation is not part of the FDA review and evaluation.*

### **3.3.6.1.10 Concomitant Treatments**

Prohibited and allowed medications were the same as in Study B2355 and B2356.

### **3.3.6.1.11 Ethical Aspects**

This clinical trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **3.3.6.1.12 Data Analysis**

Three populations were defined for analysis:

- The intention-to-treat (ITT) population, including all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were randomized.
- The per-protocol (PP) population, including all patients of the ITT population who had no major protocol deviations. Patients were analyzed according to the treatment they received except if a patient incorrectly received more than one treatment before the primary end point visit. If this occurred the patient was excluded from the PP population. Major protocol deviations were defined prior to database lock and unblinding of the study.
- The safety population, including all patients who received at least one dose of study drug.

The ITT population was used for the primary analysis of efficacy. The PP population was used for supportive analyses of the primary variable. The safety population was used in the analysis of all safety variables. In Amendment 1 dated August 7, 2008, changes were made to the statistical analysis plan, including updating the analyses planned for EQ-5D, post-inhalation events, BODE index, 24 hr spirometry profiling, association of post-inhalation events with a decrease = 20% FEV1 from pre-dose in first 30 min after dosing, and elevating the analysis of SGRQ total score at Visit 8 to an important secondary objective. The amendment also introduced a patient end of study questionnaire to be completed at the end of the study (Visit 13) or at early discontinuation.

There were no changes to the planned analyses post database lock and unblinding. To handle the issue of multiplicity, a hierarchical testing approach to the analyses of primary and important secondary variables was used as follows:

1. Trough FEV1 after 12 weeks treatment - Superiority of indacaterol 150 mcg q.d. over placebo. If indacaterol 150 mcg q.d. was superior to placebo then;
2. SGRQ total score after 12 weeks treatment – Superiority of indacaterol 150 mcg q.d. over placebo. If indacaterol 150 mcg q.d. was superior to placebo then;
3. Percentage of 'days of poor control' over 26 weeks treatment - Superiority of indacaterol 150 mcg q.d. over placebo.

The other treatment comparisons for the other secondary variables/comparisons were for supportive evidence and no adjustment for multiplicity were made.

### **Efficacy Variables**

#### **Primary Efficacy Variables**

The primary efficacy variable was to demonstrate the superiority of indacaterol 150 mcg q.d. over placebo with respect to 24 hour tFEV1 after 12 weeks of treatment measured at Day 85. A difference of 120 mL in

tFEV1 was predefined by the Sponsor to be the MCID for COPD patients. The standard deviation of 270 mL for tFEV1 was based on the weighted average of the estimates from two Foradil pivotal studies, protocols 056 and 058. A sample size of 108 evaluable patients in each treatment group was needed to detect this difference between indacaterol 150 mcg and placebo as statistically significant at the 5% significance level (2 sided) with 90% power. The primary variable was analyzed using a mixed model using the ITT population. The model contained treatment as a fixed effect with the baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 30 min post inhalation of albuterol, FEV1 prior to inhalation and FEV1 one hour post inhalation of ipratropium as covariates. Like with the previous studies, any values contributing to the tFEV1 taken within 6 hours of rescue medication use or the actual measurement times were outside the 22 hr to 25 hr post- dose time window, then the individual FEV1 value was set to missing. For the primary analysis, a missing tFEV1 value at Week 12 was replaced by LOCF as long as the visit was not prior to Day 15.

Exploratory subgroup analyses of trough FEV1 after 12 weeks of treatment (imputed with LOCF) were performed for the ITT population to explore the treatment effect by age (< 65 years / ≥ 65 years), sex (male, female), race (caucasian, black, asian, other), smoking history (current smoker, ex-smoker), severity of disease (moderate or less, severe or worse based on the GOLD Guidelines (GOLD 2005), and the use of ICS at baseline.

### **Secondary Efficacy Variables**

The important secondary objectives were to determine if indacaterol 150 mcg q.d. was superior to placebo with respect to the SGRQ total score after 12 weeks treatment and if indacaterol 150 mcg q.d. was superior to placebo with respect to percentage of COPD 'days of poor control' during 26 weeks treatment. In Amendment 2 dated January 6, 2009, the Sponsor changed the order of testing of secondary efficacy objectives so that the SGRQ total score at Week 12 would be tested after the primary objective had been achieved. In turn, the percentage of 'days of poor control' after 26 weeks of treatment would be tested if the SGRQ total score at Week 12 objective was achieved. The second amendment also elevated comparisons between salmeterol and indacaterol from exploratory to secondary.

#### **SGRQ at 12 weeks**

A detailed description of the statistical analysis will be included in Dr Dongmei Liu's review. The SGRQ total score at 12 weeks was analyzed using a mixed model for the ITT population. The model contained treatment as a fixed effect, baseline total score of SGRQ, smoking status, FEV1 prior to inhalation and FEV1 30 min post inhalation of albuterol, FEV1 prior to inhalation and FEV1 one hour post inhalation of ipratropium as covariates. Missing data was imputed using LOCF.

#### **COPD 'days of poor control'**

A 'day of poor control' was defined as any day in the Patient Diary where a score = 2 (i.e. moderate or severe symptoms) was recorded for at least two out of five symptoms (cough, wheeze, production of sputum, color of sputum, breathlessness). Either the worst of two scores was taken or if one was missing then the existing score was used. If both were missing, then the daily score for that individual symptom was imputed as 0 but otherwise set to missing. The total number of 'days of poor control' over the 26 week treatment period was divided by the total number of evaluable days to calculate the percentage of 'days of poor control'. Diary data recorded during the 14 day run-in period were used to calculate the baseline. The percentage of 'days of poor control' was summarized by treatment and analyzed using the same mixed model as specified for the primary analysis using the ITT population. For the percentage of COPD 'days of poor control', a difference of 8% was considered clinically important. An estimate of 28% for the standard deviation was based on data from the foradil pivotal trials, protocols 056 and 058, over 12 weeks, protocol F2402 over 6 months and protocol 058 over 12 months. A sample size of 259 evaluable patients in each treatment group was needed to detect this difference between indacaterol 150 mcg and placebo as statistically significant at the 5% significance level (2 sided) with 90% power. Assuming a drop out rate of 20% over 26 weeks of treatment and 15% over the first 12 weeks of treatment, a minimum sample size of 972 patients (324 indacaterol 150 mcg: 324 placebo: 324

salmeterol) was chosen that provided >99% power for the primary endpoint (trough FEV1). Since this was so high, the hierarchical procedure only caused a negligible reduction in the unconditional 90% power for the secondary endpoint of the percentage of 'days of poor control'.

*Reviewer's Comment:*

*The sample size above was driven by percentage of 'days of poor control' which was a key secondary endpoint in the original protocol; however, in Amendment 2, SGRQ total score at Week 12 was elevated above the percentage of 'days of poor control' in the hierarchical testing procedure. Recruitment was already complete, so the protocol amendment did not change the sample size or conduct of the trial. According to the Sponsor, this was done because of data coming from other indacaterol pivotal trials. Based on the original hierarchical testing procedure, since 'days of poor control' did not meet statistical significance, SGRQ would not have been measured.*

### **Spirometry assessments**

Assuming a drop-out rate of 15%, a subgroup of 330 randomized patients (110 indacaterol 150 mcg; 110 placebo: 110 salmeterol) was needed to detect a clinically important difference of 120 mL in FEV1 at any serial spirometry time point at the 5% significance level (2 sided) with 80% power. A standard deviation of 290 mL had been assumed based on two Foradil pivotal studies, protocols 056 and 058. No adjustment for multiplicity was carried out for these variables. All spirometry assessments were analyzed using the same mixed model as specified for the primary analysis.

### **COPD exacerbations**

The time to the first COPD exacerbation was displayed for each treatment group with a Kaplan-Meier curve. For COPD exacerbation rate, the number of COPD exacerbations during the 26 week treatment period was analyzed using Poisson regression.

### **Dyspnea**

For the TDI Focal Score after 4, 8, 12, and 26 weeks of treatment, the score was analyzed at each time point (Visits 6, 7, 8, and 12) using the same mixed model as specified for the primary analysis with the BDI focal score as baseline. Missing scores were imputed using LOCF. For percentage of patients with a clinically important improvement of at least 1 in the TDI Focal Score after 4, 8, 12, and 26 weeks of treatment, the proportion of patients who achieved this was analyzed using logistic regression.

### **Symptoms**

The following symptom scores were calculated over the 26 week period. A night with 'no nighttime awakenings' was defined from the diary data as any night where the patient did not wake up due to symptoms. The percentage of nights with 'no nighttime awakenings' was derived and analyzed as for the percentage of 'days of poor control'. That included the imputation of missing nighttime awakening data with a score of 0 (= no awakening) when other symptom data, rescue use, or PEF were available at that morning. A day with 'no daytime symptoms' was defined from the diary data as any day where the patient had recorded in the evening no cough, no wheeze, no production of sputum and no feeling of breathless (other than when running) during the past 12 hours. The percentage of days with 'no daytime symptoms' was derived and analyzed as for the percentage of 'days of poor control'. A 'day able to perform usual daily activities' was defined from the diary data as any day where the patient was not prevented from performing their usual daily activities due to respiratory symptoms (i.e. the question 'Did your respiratory symptoms stop you performing your usual daily activities today?' was answered 'Not at all'). The percentage of 'days able to perform usual daily activities' was derived and analyzed as for the percentage of 'days of poor control' including the imputation of missing data. The mean total symptom scores and individual symptom scores for the patient were calculated for the full 26 weeks. Diary data recorded during the 14 day run-in period were used to calculate the baseline value. The mean change from baseline in the total scores and in the individual scores was summarized with descriptive statistics by treatment. Separate analyses were performed for nighttime, daytime, and the full 24 hours.

### **Rescue medication**

For the daily rescue use or the number of puffs of rescue medication over 26 weeks, the total number of puffs of rescue medication per day over the full 26 weeks was calculated and then divided by the total number of days with non-missing rescue data to derive the mean daily number of puffs of rescue medication taken for the patient. The total number of puffs of rescue medication used over the last 12 hr as recorded in the morning (nighttime use) and in the evening (daytime use) over the full 26 weeks was divided by the total number of days with non-missing rescue data to derive the mean daytime and nighttime number of puffs of rescue medication. The mean daily, daytime and nighttime number of puffs of rescue medication use were calculated for 4 weekly intervals prior to tFEV1 measurements at 12 weeks and 26 weeks and the change from baseline was displayed graphically over time. For the percentage of 'days with no rescue use' over 26 weeks, a 'day with no rescue use' was defined from the diary data as any day where the patient used no puffs of rescue medication. The percentage of 'days with no rescue use' was derived and analyzed as the percentage of 'days of poor control'. The mean change from baseline for all the rescue medication use variables was analyzed using the same mixed model as specified for the primary analysis. Diary data recorded during the 14 day run-in period were used to calculate the baseline.

### **Peak expiratory flow (PEF)**

Morning and evening (pre-medication) PEF, as recorded in the Patient Diary, was averaged separately over the full 26 weeks for each patient. Diary data recorded during the 14 day run-in period were used to calculate the baseline. Change from baseline in the mean morning and evening PEF was analyzed using the same mixed model as specified for the primary analysis.

### **Health related quality of life**

The SGRQ total score at Weeks 4, 8, and 26 was analyzed using the same model as for the total score after 12 weeks. Missing data of the SGRQ total score were imputed by using LOCF. For the percentage of patients with a clinically important improvement of at least 4 in the total SGRQ after 4, 8, 12 and 26 weeks treatment, the proportion of patients who achieved a score of at least 4 in the total SGRQ was analyzed using logistic regression. For the EQ-5D after 12 and 26 weeks of treatment, the questionnaire contained 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with 3 categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of patients in each of the three categories for each question was presented by visit. Standard summary statistics were shown for the self-rated health state assessment.

### **Patient end of study questionnaire**

A patient end of study questionnaire was required to be completed by all patients who completed the study or discontinued early. This questionnaire contained two questions regarding the patients' overall satisfaction with the study drug and their willingness to take the same study medication again in future. Descriptive summary statistics for each item on the patient end of study questionnaire were presented by treatment group.

### **Exploratory variables**

#### **FEV1 and FVC trough response over 26 weeks**

The rate of change in trough FEV1 defined as the average of the 50 min and 15 min pre-dose values from Day 15 (Visit 5) onwards to the end of study was analyzed using a random coefficients model. The random coefficients model was fitted with the same covariates as specified for the primary analysis with the additional fixed effects of time and time by treatment interaction and random effects of patient and patient by time.

### **LCOPD**

This questionnaire was done at baseline, Week 12 and 26. The number and percentage of patients who agree to a statement was presented by visit for each statement.

#### **BODE index after 12 and 26 weeks of treatment**

The BODE index was calculated at baseline (Day 1, Visit 3) and at Weeks 12 (Visit 8) and 26 (Visit 12). The BODE index at each time point was analyzed using the same mixed model as specified for the primary analysis.

#### **Safety Variables**

All treatment emergent AEs, including COPD exacerbations, were summarized and listed. Treatment emergent AEs were summarized with incidences overall, by primary SOC, and by PT. Summaries were provided for all AEs, most frequent AEs, all AEs by maximum severity, suspected drug-related AEs, SAEs, and adverse events leading to permanent discontinuation of study drug.

The assessment of safety was based on the incidence of AEs and abnormal laboratory values as well as on the statistical analysis of vital signs, post-inhalation events, ECG measurements, and time to premature discontinuation due to AE and unsatisfactory therapeutic effect. All safety analyses were based on the safety population and most were summarized with descriptive statistics and listed. However, for VS and ECG changes from baseline were analyzed using a similar mixed model as specified for the primary efficacy variable. Separate analyses were performed for time to premature discontinuation due to the primary reason of adverse event (as some evidence of long-term tolerability) and for time to premature discontinuation due to the primary reason of unsatisfactory therapeutic effect (as some evidence of persistency of efficacy). Kaplan-Meier curves were displayed for each treatment group using the safety population.

#### **3.3.6.2 Patient Disposition and Demographics**

##### **Disposition**

A total of 1518 patients worldwide were screened and 1002 were randomized to study treatment in 142 centers from 15 countries. Approximately 84% of patients completed the study as planned. Of the 3 groups, discontinuation was the highest in the placebo group with 21% compared to 13% in the indacaterol 150 mcg treatment group and 15% in the salmeterol group. The difference in discontinuation rates was largely driven by patients who withdrew consent and had unsatisfactory therapeutic effect, which occurred more frequently in the placebo group. See Table 63.

**Table 63 Protocol B2336 Patient disposition**

	Ind 150 µg n (%)	Salm n (%)	Pbo n (%)	Total n (%)
<b>Patients</b>				
Screened	-	-	-	1518
Randomized	333 (100.0)	334 (100.0)	335 (100.0)	1002 (100.0)
Exposed	330 (99.1)	333 (99.7)	335 (100.0)	998 (99.6)
Completed	289 (86.8)	284 (85.0)	265 (79.1)	838 (83.6)
Discontinued	44 (13.2)	50 (15.0)	70 (20.9)	164 (16.4)
<b>Primary reason for premature discontinuation</b>				
Adverse event(s)	18 (5.4)	16 (4.8)	13 (3.9)	47 (4.7)
Protocol deviation	9 (2.7)	11 (3.3)	13 (3.9)	33 (3.3)
Subject withdrew consent	8 (2.4)	12 (3.6)	22 (6.6)	42 (4.2)
Abnormal lab value(s)	2 (0.6)	1 (0.3)	2 (0.6)	5 (0.5)
Abnormal test procedure result(s)	2 (0.6)	1 (0.3)	1 (0.3)	4 (0.4)
Lost to follow-up	2 (0.6)	5 (1.5)	2 (0.6)	9 (0.9)
Unsatisfactory therapeutic effect	1 (0.3)	2 (0.6)	15 (4.5)	18 (1.8)
Administrative problems	1 (0.3)	1 (0.3)	0	2 (0.2)
Death	1 (0.3)	0	2 (0.6)	3 (0.3)
Patient's inability to use the device	0	1 (0.3)	0	1 (0.1)

Source: Table 10-1 Study No. CQAB149B2336 Clinical Study Report

### Protocol Deviation

Major protocol deviations as well as non-protocol deviations leading to exclusion from the per-protocol (PP) population were reported for 11.5% of patients, with similar frequencies across the treatment groups: 11.2% in indacaterol, 12% in salmeterol and 11.3% in placebo. The most common protocol deviation across all treatment groups was eosinophil count above 400/mm<sup>3</sup> at screening, which was reported in 3.9% of the salmeterol group, 3.0% of the indacaterol and 3.3% of those in the placebo group. The percentage of patients taking <80% of doses of study medication between randomization and the visit of the primary endpoint was highest in the salmeterol, 3.0% and indacaterol, 2.7% groups than in the placebo group with 1.8%. Regarding compliance with dosing schedule, more patients in the indacaterol treated group (1.5%) were not compliant with the dosing schedule. The lower levels of noncompliance were seen in the salmeterol (0.6%) and placebo (0.6%) groups. More patients treated with placebo (2.4%) had a post-bronchodilator FEV<sub>1</sub> < 30% or ≥ 80% of predicted normal value at screening than indacaterol (0.6%) or salmeterol (0.9%).

### Demographics

Overall, the mean age was 63.5 years, the majority were male (75%) and caucasian (76%). Regarding the disease status, the median duration of COPD was 5 years and most patients had moderate (53.6%) or severe (42.6%) COPD based on the GOLD criteria. Mean post- bronchodilator FEV<sub>1</sub> was 1.47 L (53.4% of predicted) and mean FEV<sub>1</sub>/FVC ratio was 52.8%. Mean pre-bronchodilator FEV<sub>1</sub> was 1.34 L. Approximately 44% were using ICS at baseline while 54% were ex-smokers with the remaining as active smokers. The mean number of pack years was 40. Mean FEV<sub>1</sub> reversibility after SABA inhalation at Visit1 was 11.8% and after anticholinergics inhalation at Visit 2 it was 12.5%. Furthermore, nearly 74% of all patients discontinued at least one COPD-related medication prior to the start of study drug, with very similar frequency across the treatment groups. These medications included SABAs (39.9%), predominantly inhaled albuterol (36.2%); LABAs (20.5%), mainly inhaled formoterol (17.6%); combination beta-agonist and steroid (21.8%); long-acting anti-cholinergics (19.2%), mainly inhaled tiotropium (18.3%); combination beta-agonist and anti-cholinergic (12.4%) and xanthines (11.7%). Refer to Table 64 and Table 65 for details.

**Table 64 Protocol B2336 Demographic summary (Safety population)**

		<b>Ind 150 µg N=330</b>	<b>Salm N=333</b>	<b>Pbo N=335</b>	<b>Total N=998</b>
Age (years)	n	330	333	335	998
	Mean	63.2	63.4	63.9	63.5
	SD	8.67	9.19	8.56	8.81
	Median	63.5	64.0	64.0	64.0
	Min - Max	41 - 85	41 - 86	42 - 89	41 - 89
Age group - n (%)	19-39 years	0	0	0	0
	40-64 years	181 (54.8)	178 (53.5)	180 (53.7)	539 (54.0)
	>= 65 years	149 (45.2)	155 (46.5)	155 (46.3)	459 (46.0)
Sex - n(%)	Male	238 (72.1)	249 (74.8)	258 (77.0)	745 (74.6)
	Female	92 (27.9)	84 (25.2)	77 (23.0)	253 (25.4)
Race - n (%)	Caucasian	250 (75.8)	258 (77.5)	251 (74.9)	759 (76.1)
	Black	1 (0.3)	0	1 (0.3)	2 (0.2)
	Asian	53 (16.1)	52 (15.6)	56 (16.7)	161 (16.1)
	Native American	1 (0.3)	0	1 (0.3)	2 (0.2)
	Other	25 (7.6)	23 (6.9)	26 (7.8)	74 (7.4)
Weight (kg)	n	330	332	335	997
	Mean	73.5	73.7	72.0	73.1
	SD	17.06	18.16	17.24	17.49
	Median	72.0	72.0	71.0	72.0
	Min - Max	38.0 - 130.0	34.0 - 138.2	37.0 - 160.0	34.0 - 160.0

Source: Adapted from Table 11-2 Study No. CQAB149B2336 Clinical Study Report

**Table 65 Protocol B2336 Baseline disease characteristics (Safety population)**

		Indacaterol 150 mcg N= 330	Salmeterol N= 333	Placebo N= 335	Total N= 998
Duration of COPD (years)	Mean	6.5	6.4	6.6	6.5
	SD	5.65	5.69	5.79	5.71
Duration of COPD n (%)	< 5 yrs	174 (52.7)	168 (50.4)	158 (47.1)	500 (50.1)
	5-10 yrs	88 (26.7)	109 (32.7)	111 (33.1)	308 (30.9)
	10- 20 yrs	62 (18.7)	47 (14.1)	55 (16.4)	164 (16.4)
	> 20 yrs	6 (1.8)	9 (2.7)	11 (3.3)	26 (2.6)
Severity of COPD n (%)	At risk	2 (0.6)	3 (0.9)	8 (2.4)	13 (1.3)
	Mild	7 (2.1)	7 (2.1)	5 (1.5)	19 (1.9)
	Moderate	182 (55.2)	179 (53.8)	174 (51.9)	535 (53.6)
	Severe	139 (42.1)	141 (42.3)	145 (43.3)	425 (42.6)
	Very severe	0	2 (0.6)	3 (0.9)	5 (0.5)
	Missing	0	1 (0.3)	0	1 (0.1)
ICS use n (%)	No	181 (54.8)	181 (54.4)	200 (59.7)	562 (56.3)
	Yes	149 (45.2)	152 (45.6)	135 (40.3)	436 (43.7)
Smoking history	Ex-smoker	178 (53.9)	179 (53.8)	185 (55.2)	542 (54.3)
	smoker	152 (46.1)	154 (46.2)	150 (44.8)	456 (45.7)
Post bronchodilator (SABA) FEV1 at Visit 1 (% predicted)	Mean	54	53	53	53
	SD	14.0	13.6	14.2	14.0
FEV1 reversibility after SABA at Visit 1 (% increase)	Mean	11.7	11	12.7	11.8
	SD	15.3	13.9	16.4	15.2

Source: Adapted from Tables 11-3 and 11-4 Study No. CQAB149B2336 Clinical Study Report

### 3.3.6.3 Efficacy Review

#### 3.3.6.3.1 Primary Endpoint

The prespecified primary efficacy endpoint was 24 hr post-dose tFEV1 after 12 weeks of treatment with the analysis based on the ITT population. The efficacy analysis was carried out on 953 of the 998 patients of the ITT population. Patients were excluded from the analysis if data were not available on D15 or later. Otherwise a LOCF was utilized for missing data.

The mean percent change from baseline in tFEV1 after 12 weeks of treatment (imputed with LOCF) was 12.5%, 7.7% and -0.7% for indacaterol, salmeterol and placebo, respectively. The treatment differences were statistically significantly different from placebo for both active treatment groups and are summarized in Table 66 below. The numbers were almost identical for the PP group.

Table 66 Study B2336 Trough FEV1 at Week 12: treatment comparisons (ITT and PP populations with LOCF)

Treatment	n	Treatment		Comparison	Treatment difference			
		LS mean	SE		LS mean	SE	95% CI	p-value
ITT population								
Overall baseline	953	1.31						
Ind 150 µg	320	1.45	0.018	Ind 150 µg - Pbo	0.17	0.018	(0.13, 0.20)	<.001*
				Ind 150 µg - Salm	0.06	0.018	(0.02, 0.10)	<.001
Salm	317	1.39	0.018	Salm - Pbo	0.11	0.018	(0.07, 0.14)	<.001

Source: Adapted from Table 11-5 Study No. CQAB149B2336 Clinical Study Report



Subgroup analyses for age, sex, smoking history, COPD severity and ICS use at baseline were performed for tFEV1 after 12 weeks of treatment. Overall, indacaterol was superior to placebo in tFEV1 at Week 12 across all subgroups based on age, sex, smoking history, COPD severity and ICS use at baseline. The treatment differences are displayed below in Table 67. The only significant treatment by subgroup interaction was for age, for which the improvement in the indacaterol group over placebo was smaller in patients who were 65 years of age or older than for the younger age group.

**Table 67 Protocol B2336 Treatment difference from placebo in trough FEV1 after 12 weeks treatment (imputed with LOCF), select subgroup analyses**

		Ind150 mcg	95% CI	p-value	Salmeterol	95% CI	p-value
Age	< 65	0.21	0.16, 0.26	< 0.001	0.15	0.10, 0.19	< 0.001
	≥ 65	0.11	0.06, 0.17	< 0.001	0.06	0.01, 0.11	0.029
Gender	Male	0.17	0.13, 0.21	< 0.001	0.10	0.06, 0.14	< 0.001
	Female	0.14	0.07, 0.21	< 0.001	0.12	-0.04, 0.09	0.002
COPD Severity	Moderate/less	0.19	0.14, 0.23	< 0.001	0.13	0.08, 0.18	< 0.001
	Severe/worse	0.14	0.08, 0.19	< 0.001	0.08	0.02, 0.13	0.006
Smoking status	Ex smoker	0.17	0.12, 0.22	< 0.001	0.10	0.05, 0.15	< 0.001
	Current smoker	0.16	0.11, 0.22	< 0.001	0.11	0.06, 0.17	< 0.001
ICS	No	0.18	0.14, 0.23	< 0.001	0.12	0.07, 0.17	< 0.001
	Yes	0.14	0.09, 0.20	< 0.001	0.09	0.03, 0.14	0.002

Source: Adapted from Tables 14.2-1 Study No. CQAB149B2336 Clinical Study Report

*Reviewer comment:*

*This is the only indacaterol pivotal trial to have a significant subgroup interaction for age, making it most likely to represent a statistical anomaly of multiple testing rather than a real effect. Of note, there is no benefit of indacaterol 150 mcg for patients with severe COPD patients compared to patients with moderate COPD.*

### 3.3.6.3.2 Secondary Endpoints

#### ➤ SGRQ after 12 weeks of treatment

A detailed evaluation of this secondary endpoint is presented in the review by Dr. Dongmei Liu. At baseline, the SGRQ was similar across all treatment groups (43.6, 43.2 and 43.6 units for indacaterol, salmeterol and placebo, respectively). After 12 weeks of treatment the mean change from baseline in SGRQ total score was a decrease (improvement) of 7.7, 5.4 and 1.2 units for indacaterol, salmeterol and placebo, respectively. The LS mean difference between indacaterol and placebo was 6.3 units, which was statistically significant ( $p < 0.001$ ) and exceeded the MCID of 4 units for SGRQ total score. Salmeterol was also significantly different from placebo, with a difference of 4.2 units ( $p < 0.001$ ). Refer to Table 68.

**Table 68 SGRQ total score at Week 12: treatment comparisons (ITT population)**

Treatment	n	Treatment		Comparison	Treatment difference			
		LS Mean	SE		LS Mean	SE	95% CI	p-value
Ind 150 µg	309	36.4	1.04	Ind 150 µg - Pbo	-6.3	0.99	(-8.2,-4.3)	<.001*
				Ind 150 µg - Salm	-2.1	0.99	(-4.0,-0.2)	0.033
Salm	301	38.5	1.04	Salm - Pbo	-4.2	1.01	(-6.1,-2.2)	<.001
Pbo	294	42.6	1.05					

Source Table 11-7 Study No. CQAB149B2336 Clinical Study Report

Evaluation by responder analysis demonstrates that the percentage of patients with a clinically important improvement of 4 units or greater in SGRQ total score was highest in the indacaterol group (57.9%)

compared with the salmeterol (46.8%) and placebo (39.1%) groups. There was a statistically significant difference in the likelihood of achieving a clinically relevant improvement of at least 4 units in SGRQ total score with indacaterol vs. placebo (odds ratio, 2.41; 95% CI, 1.69- 3.42;  $p < 0.001$ ). The validity of this data may be called into question based on the change of sequence in the hierarchical testing that led SGRQ to be tested when originally it would not have been.

➤ **COPD 'days of poor control' over 26 weeks of treatment**

A 'day of poor control' was defined as any day in the Patient Diary where a score = 2 (i.e. moderate or severe symptoms) was recorded for at least two out of five symptoms (cough, wheeze, production of sputum, color of sputum, breathlessness). The total number of 'days of poor control' over the 26 week treatment period was divided by the total number of evaluable days (i.e. the days with 2 or more symptoms with scores) in order to derive the percentage of 'days of poor control'. Diary data recorded during the 14 day run-in period were used to calculate the baseline. Patients were considered as eligible for analysis of the percentage of 'days of poor control' if and only if they had at least 7 evaluable diary days in the baseline period and in the post baseline period they had at least 30% of their diary days evaluable and at least 20 evaluable diary days in total.

Treatment with either indacaterol or salmeterol did not result in a statistically significantly reduced percentage of 'days of poor control'. The treatment difference of indacaterol 150 mcg and placebo was -4, 95% CI (-8.0, 0.1),  $p$ -value 0.058, and for salmeterol it was -4, 95% CI (-8.1, 0.1),  $p$ -value 0.057.

➤ **COPD exacerbation**

The percentage of patients who experienced COPD exacerbations for the indacaterol, salmeterol and placebo groups were 18.2%, 15.3% and 19.4%, respectively. Although indacaterol treated patients exhibited a longer time to first COPD exacerbation compared with placebo treated patients, a Cox regression analysis showed no statistically significant difference between indacaterol and placebo (hazard ratio, 0.78; 95% CI, 0.55-1.12;  $p = 0.177$ ). Rate of exacerbations per year were numerically lower for the indacaterol (0.68) and salmeterol (0.69) groups compared with placebo (1.02); however no treatment comparisons in COPD exacerbation rate ratios were statistically significant.

*Reviewer comment:*

*This analysis does not adjust for overdispersion, so the results presented may overestimate the efficacy of the drug. The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations. The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.*

➤ **Trough FEV1 at Day 2 and after 26 weeks of treatment**

The treatment differences of both indacaterol from placebo and salmeterol from placebo at Day 2 and after 26 weeks of treatment were all statistically significant. Specifically, at Day 2, the treatment difference for indacaterol and placebo was 0.13L, 95% CI (0.10, 0.15),  $p$ -value  $< 0.001$ ; after 26 weeks of treatment, the values were 0.18L, 95% CI (0.14, 0.22)  $p$ -value  $< 0.001$ . The values for salmeterol are as follows: at Day 2, 0.12L, 95% CI (0.10, 0.15)  $p$ -value  $< 0.001$ ; 26 weeks of treatment, it was 0.11L, 95% CI (0.07, 0.15)  $p$ -value  $< 0.001$ . Subgroup analyses for age, sex, smoking history, COPD severity, and ICS use at baseline were performed for tFEV1 after 26 weeks of treatment all showed a statistically significant difference from placebo. The treatment difference by age persisted.

**Table 69 Protocol B2336 Subgroup analyses of trough FEV1 after 26 weeks treatment, imputed with LOCF, ITT population**

		Indacaterol 150 mcg	95% CI	p-value	salmeterol	95% CI	p-value
Age	< 65 years	0.21	(0.16, 0.27)	< 0.001	0.14	(0.08, 0.19)	< 0.001
	≥ 65 years	0.13	(0.08, 0.19)	< 0.001	0.08	(0.02, 0.14)	0.007
Gender	Male	0.18	(0.13, 0.22)	< 0.001	0.10	(0.05, 0.14)	< 0.001
	Female	0.18	(0.10, 0.25)	< 0.001	0.14	(0.06, 0.22)	< 0.001
Smoking history	Ex-smoker	0.16	(0.11, 0.22)	< 0.001	0.12	(0.06, 0.17)	< 0.001
	Current smoker	0.19	(0.14, 0.25)	< 0.001	0.10	(0.05, 0.16)	< 0.001
COPD severity	Moderate/less	0.20	(0.15, 0.25)	< 0.001	0.14	(0.09, 0.20)	< 0.001
	Severe/worse	0.14	(0.08, 0.20)	< 0.001	0.07	(0.01, 0.13)	0.025
ICS use	No	0.17	(0.12, 0.23)	< 0.001	0.13	(0.07, 0.18)	< 0.001
	Yes	0.18	(0.12, 0.24)	< 0.001	0.10	(0.04, 0.15)	0.002

Source: Adapted from table 14.2-4 Study No. CQAB149B2336 Clinical Study Report

➤ **Peak FEV1 and AUC for FEV1**

The LS mean peak FEV1 in the first 4 hr post morning dose at Week 12 was 1.60 L, 1.59 L and 1.41 L for the indacaterol, salmeterol and placebo groups, respectively, based on a subset of the ITT population with 4 hr serial spirometry. The treatment difference for indacaterol compared to placebo was 0.19L, 95% CI (0.12, 0.25) p-value <0.001, and for salmeterol compared to placebo was 0.18L, 95% CI (0.12, 0.25) p-value <0.001. Similar results were seen for peak FEV1 at Day 1 and Week 26 and for AUC<sub>(5min-1hr)</sub> at Week 12. Benefit was demonstrated across all subgroups.

➤ **24 hour serial spirometry**

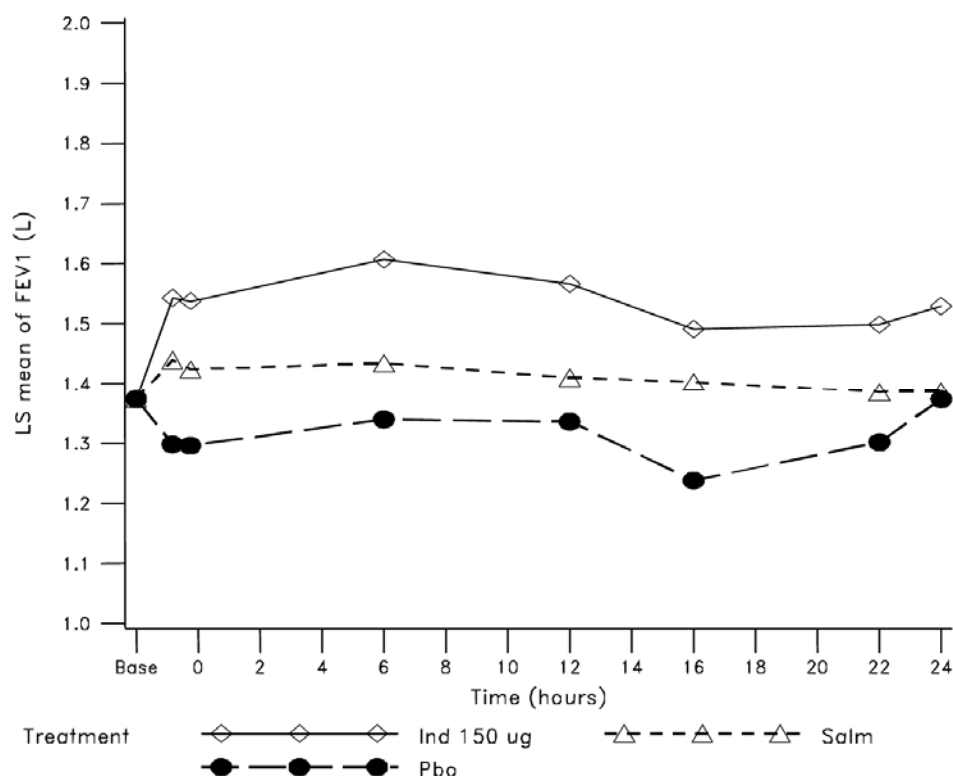
A subset of the ITT population participated in the 24 hr serial spirometry at Week 26. This subset included 53 patients taking indacaterol, 50 patients taking salmeterol, and 48 patients taking placebo. Analysis of FEV1 at each time point up to 24 hr post morning dose for ITT patients in the 24 hr serial spirometry subgroup at Week 26 is presented in Table 70, and the 24-hr profile of LS means of FEV1 is displayed in Figure 9. At all post morning dose evaluations over 24 hr, patients taking indacaterol had significantly higher LS mean FEV1 values compared with patients taking placebo. The difference between indacaterol and placebo was >0.20 L up to 22 hr (all p<0.001) and 0.16 L at 24 hr (p=0.002).

**Table 70 Protocol B2336 FEV1 (L) at each time point up to 24 hours post morning dose at 26 weeks (ITT population, subset with 24 hour serial spirometry)**

Time point	Treatment	n	Treatment		Comparison	Treatment difference			
			LS mean	SE		LS mean	SE	95% CI	p-value
Baseline	All	150	1.37						
-50 min	Ind 150 µg	53	1.54	0.060	Ind 150 µg - Pbo	0.24	0.052	( 0.14, 0.35)	<.001
					Ind 150 µg - Salm	0.10	0.052	( 0.00, 0.21)	0.051
	Salm	50	1.44	0.061	Salm - Pbo	0.14	0.054	( 0.04, 0.25)	0.010
	Pbo	47	1.30	0.061					
-15 min	Ind 150 µg	52	1.54	0.063	Ind 150 µg - Pbo	0.24	0.051	( 0.14, 0.34)	<.001
					Ind 150 µg - Salm	0.11	0.051	( 0.01, 0.22)	0.030
	Salm	50	1.42	0.065	Salm - Pbo	0.13	0.053	( 0.02, 0.23)	0.017
	Pbo	47	1.30	0.064					
6 hours	Ind 150 µg	49	1.61	0.060	Ind 150 µg - Pbo	0.27	0.059	( 0.15, 0.38)	<.001
					Ind 150 µg - Salm	0.17	0.059	( 0.05, 0.29)	0.005
	Salm	48	1.43	0.062	Salm - Pbo	0.09	0.062	(-0.03, 0.22)	0.128
	Pbo	43	1.34	0.062					
12 hours	Ind 150 µg	51	1.57	0.061	Ind 150 µg - Pbo	0.23	0.067	( 0.10, 0.36)	<.001
					Ind 150 µg - Salm	0.16	0.065	( 0.03, 0.29)	0.018
	Salm	48	1.41	0.063	Salm - Pbo	0.07	0.068	(-0.06, 0.21)	0.277
	Pbo	42	1.34	0.064					
16 hours	Ind 150 µg	51	1.49	0.068	Ind 150 µg - Pbo	0.25	0.058	( 0.14, 0.37)	<.001
					Ind 150 µg - Salm	0.09	0.057	(-0.03, 0.20)	0.126
	Salm	48	1.40	0.069	Salm - Pbo	0.16	0.060	( 0.05, 0.28)	0.007
	Pbo	43	1.24	0.070					
22 hours	Ind 150 µg	50	1.50	0.065	Ind 150 µg - Pbo	0.20	0.049	( 0.10, 0.29)	<.001
					Ind 150 µg - Salm	0.11	0.050	( 0.01, 0.21)	0.026
	Salm	47	1.39	0.067	Salm - Pbo	0.08	0.052	(-0.02, 0.19)	0.109
	Pbo	44	1.30	0.066					
24 hours	Ind 150 µg	50	1.53	0.056	Ind 150 µg - Pbo	0.16	0.048	( 0.06, 0.25)	0.002
					Ind 150 µg - Salm	0.14	0.049	( 0.05, 0.24)	0.004
	Salm	46	1.39	0.058	Salm - Pbo	0.01	0.051	(-0.09, 0.11)	0.789
	Pbo	44	1.37	0.057					

Source: Table 11-13 Study No. CQAB149B2336 Clinical Study Report

**Figure 9 Protocol B2336 24 hour profile of least squares means of FEV1 (L) after 26 weeks of treatment (ITT population, subset with 24 hour serial spirometry)**



Source: Figure 11-4 Study No. CQAB149B2336 Clinical Study Report

### ➤ Transitional Dyspnea Index

The protocol called for the evaluation of dyspnea using the TDI. The TDI focal score, ranging from -9 to 9, is the sum of three domains (functional impairment, magnitude of task and magnitude of effort), with negative scores indicating deterioration. The prespecified MCID was 1.0 unit. Mean TDI focal scores increased between Week 4 and Week 26 for all treatment groups including placebo. As seen in Table 71 below, the 1.45 unit difference in LS mean TDI focal score between indacaterol and placebo was significant ( $p < 0.001$ ) and exceeded the MCID of 1.0. Indacaterol was also statistically superior to salmeterol in TDI focal score by a difference 0.55 units ( $p = 0.015$ ). The 0.90 unit difference between salmeterol and placebo was statistically significant ( $p < 0.001$ ) but did not reach the MCID. At Week 26, neither of the active treatments reached the MCID of 1.0 even though they were statistically significantly different from placebo.

**Table 71 Protocol B2336 TDI focal score at Week 12 and Week 26 (LOCF): treatment comparisons (ITT population)**

Treatment	n	Treatment		Comparison	Treatment difference			p-value
		LS Mean	SE		LS Mean	SE	95% CI	
Week 12								
Ind 150 µg	303	2.17	0.246	Ind 150 µg - Pbo	1.45	0.229	(1.00, 1.90)	<.001
				Ind 150 µg - Salm	0.55	0.226	(0.11, 1.00)	0.015
Salm	296	1.62	0.245	Salm - Pbo	0.90	0.231	(0.45, 1.35)	<.001
Pbo	286	0.72	0.250					
Week 26								
Ind 150 µg	297	2.03	0.294	Ind 150 µg - Pbo	0.99	0.244	(0.51, 1.47)	<.001
				Ind 150 µg - Salm	0.02	0.239	(-0.45, 0.49)	0.935
Salm	289	2.02	0.295	Salm - Pbo	0.97	0.247	(0.49, 1.46)	<.001
Pbo	272	1.04	0.300					

Source: Table 11-14 Study No. CQAB149B2336 Clinical Study Report

### ➤ Daytime and nighttime symptoms

The daytime and nighttime symptom treatment effect was evaluated. Specifically, the percentage of nights with 'no nighttime awakenings', percentage of days with 'no daytime symptoms' and percentage of 'days able to perform usual daily activities' over 26 weeks were all measured.

Patients taking either active treatment had a higher percentage of nights with 'no nighttime awakenings' compared with patients taking placebo. The LS mean percentage of nights with 'no nighttime awakenings' over 26 weeks of treatment was 71.6%, 70.8% and 65.3% for indacaterol, salmeterol and placebo, respectively. Differences in the percentage of nights with 'no nighttime awakenings' were statistically significant for comparisons between indacaterol and placebo (difference of 6.3%;  $p<0.001$ ) and between salmeterol and placebo (difference of 5.5%;  $p=0.004$ ).

Patients taking indacaterol had a higher percentage of days with 'no daytime symptoms' compared with patients taking either salmeterol or placebo. The LS mean percentage of days with 'no daytime symptoms' over 26 weeks of treatment was 10.5%, 8.9% and 6.2% for the indacaterol, salmeterol and placebo groups, respectively. Differences in the percentage of days with 'no daytime symptoms' were statistically significant for comparisons between indacaterol and placebo (difference of 4.2%;  $p=0.002$ ) and between salmeterol and placebo (difference of 2.7%;  $p=0.049$ ).

The LS mean percentage of 'days able to perform usual daily activities' over 26 weeks of treatment was 42.5%, 38.2% and 34.8% for the indacaterol, salmeterol and placebo groups, respectively. Differences in the percentage of 'days able to perform usual daily activities' were statistically significant, favoring indacaterol over placebo (difference of 7.7%;  $p<0.001$ ) and over salmeterol (difference of 4.4%;  $p=0.032$ ). Salmeterol provided 3.4% more 'days able to perform usual daily activities' compared with placebo, but this difference was not statistically significant.

### ➤ Rescue medication use

The protocol stated that the daily rescue medication use was calculated by the total number of puffs of rescue medication per day over the full 26 weeks divided by the total number of days of rescue medication use. Baseline rescue medication use was based on patient diary data from the 14 day interval between Visits 1 and 3. The LS mean change from baseline in mean daily number of puffs of rescue medication was a decrease of 1.34, 1.16, and 0.32 puffs for indacaterol, salmeterol and placebo, respectively. Patients taking either indacaterol or salmeterol required significantly fewer daily puffs of rescue medication over 26 weeks compared with placebo patients (both  $p<0.001$ ).

The mean daytime and nighttime number of puffs of rescue medication was also measured. The LS mean change from baseline in mean daytime number of puffs of rescue medication was a decrease of 0.89, 0.74, and 0.22 puffs for indacaterol, salmeterol and placebo, respectively. The decrease from baseline in the mean daytime number of puffs of rescue medication over 26 weeks was significantly higher for

indacaterol and salmeterol vs. placebo (both  $p < 0.001$ ). The LS mean change from baseline in mean nighttime number of puffs of rescue medication was a decrease of 0.47, 0.43, and 0.15 puffs for indacaterol, salmeterol and placebo, respectively. The decrease from baseline in mean nighttime number of puffs of rescue medication over 26 weeks was significantly higher for indacaterol and salmeterol vs. placebo (both  $p < 0.001$ ).

Finally, the percentage of 'days with no rescue use' was measured. A 'day with no rescue use' was defined from the diary data as any day where the patient used no puffs of rescue medication (after imputation of missing data). The percentage of 'days with no rescue use' was derived and analyzed as the percentage of 'days of poor control'. The LS mean percentage of 'days with no rescue use' was 59.7%, 54.7% and 42.2% for indacaterol, salmeterol and placebo, respectively. Compared with placebo, patients taking either active treatment had a significantly higher percentage of days (17.5% more days with indacaterol and 12.4% more days with salmeterol) with no use of rescue medication than patients taking placebo (both  $p < 0.001$ ). Indacaterol treated patients also had a significantly higher percentage of days without using rescue medication compared with salmeterol treated patients (difference of 5.1%;  $p = 0.033$ ).

#### ➤ Peak expiratory flow (PEF)

Patients taking either indacaterol or salmeterol showed improvements from baseline in morning PEF compared with patients taking placebo. The LS mean change from baseline in morning PEF over 26 weeks of treatment was 25.3, 15.2 and -0.8 L/min for indacaterol, salmeterol and placebo, respectively. The corresponding treatment differences were 26.2 (21.0, 31.4) for indacaterol and placebo; 16 (10.8, 21.3) for salmeterol and placebo. Compared with placebo, patients taking either indacaterol or salmeterol had significantly higher increases in change from baseline for morning PEF (both  $p < 0.001$ ). Indacaterol was also significantly superior to salmeterol in the improvement from baseline in morning PEF ( $p < 0.001$ ). Similar results were seen with the evening values and were also statistically significant for both indacaterol and salmeterol.

#### ➤ SGRQ total score and component scores over time

The least squares mean treatment difference for indacaterol over placebo for SGRQ total score over Week 4, 8 and 26 were -3.6, -4.1 and -5.0, all statistically significant over placebo. The component scores are summarized in Table 72.

**Table 72 Analysis of the SGRQ symptoms component score after 4, 8, 12 and 26 weeks of treatment (imputed with LOCF, ITT population)**

	Treatment difference Indacaterol 150 mcg to placebo					
	Symptoms (95% CI)	p-value	Activity (95% CI)	p-value	Impact (95% CI)	p-value
Week 4	-5.6 (-8.1, -3.0)	<0.001	-2.5 (-4.9, -0.2)	0.037	-3.5 (-5.4, -1.6)	<0.001
Week 8	-5.9 (-8.6, -3.2)	<0.001	-3.4 (-6.0, -0.9)	0.008	-4.1 (-6.2, -2.0)	<0.001
Week 12	-7.8 (-10.6, -4.9)	<0.001	-5.4 (-7.9, -2.8)	<0.001	-6.4 (-8.5, -4.3)	<0.001
Week 26	-7.8 (-10.8, -4.7)	<0.001	-4.7 (-7.4, -2.1)	<0.001	-4.4 (-6.8, -2.1)	<0.001

Source: Adapted from Table 14.2-10.4 Study No. CQAB149B2336 Clinical Study Report

#### ➤ Rate of change in FEV1 and FVC response over 26 weeks

Over the 26 week treatment duration, no statistically significant differences between treatment groups in the estimated rate of change per month in tFEV1 or FVC was apparent.

#### ➤ BODE index

At Week 12, the LS mean BODE index score was 2.44, 2.58 and 2.87 for indacaterol, salmeterol and placebo, respectively. At Week 26, the LS mean BODE index score was 2.40, 2.55 and 2.86,

respectively. BODE index scores were significantly lower with both indacaterol and salmeterol compared with placebo after 12 and 26 weeks (all  $p < 0.01$ ).

*Reviewer's Comment:*

*It is unclear if a value has been defined as clinically significant for reduction in BODE score.*

➤ **Six minute walk distance**

The LS mean distance walked in 6 min at Week 12 was 387.3 m, 384.4 m and 382.2 m for the indacaterol, salmeterol and placebo groups, respectively. There were no significant treatment differences at Week 12. The LS mean distance walked in 6 min at Week 26 increased to 395.4 m, 388.9 m and 383.6 m for the treatment groups, respectively. Patients taking indacaterol walked statistically significantly longer distances in 6 min at Week 26 compared with patients taking placebo (difference of 11.8 m;  $p = 0.032$ ). The clinical relevance of such a small improvement has not been demonstrated.

**3.3.6.3.3 Safety Review**

**3.3.6.3.3.1 Extent of exposure**

The extent of exposure was similar across treatment groups. The mean number of days of exposure for indacaterol 150 mcg was 169.2, for salmeterol the mean was 164.3 days and placebo, 155.4 days. Most patients were exposed for over 24 weeks, 88.8% of patients in the indacaterol treatment group and 78.8% in the placebo group. Compliance was demonstrated by > 98% of the planned doses for indacaterol with the SDDPI device and >96% with the proprietary device were taken.

**3.3.6.3.3.2 Concomitant medications**

Slightly more than half of the patients across the treatment groups were taking COPD-related medications, with the most common being ICS. Antibiotics were the second most common COPD-related medication. Non-COPD related medications were taken by 73.9% of patients in the indacaterol group and 69.4% in the salmeterol group and 65.4% in the placebo group. The most common non-COPD medications taken were acetylsalicylic acid, paracetamol, enalapril and simvastatin.

**3.3.6.3.3.3 Adverse events**

Consistent with many of the other trials, the SOC with the highest percent of events were infection and infestations (239 patients) and respiratory, thoracic and mediastinal (230 patients). The most frequent AEs were: COPD with higher rates in placebo (19.4%) than indacaterol (18.2%); nasopharyngitis with similar rates across treatment groups; upper respiratory tract infection, indacaterol (4.2%) higher than placebo (1.5%) lower respiratory tract infection, also with similar rates across treatment groups. Refer to Table 73 for a summary.



**Table 73 Most frequent AEs, including COPD exacerbations, by preferred term (at least 1.0% in any treatment group) (Safety population)**

	Ind 150 µg N=330 n (%)	Salm N=333 n (%)	Pbo N=335 n (%)
Patients with any AE(s)	169 (51.2)	152 (45.6)	156 (46.6)
<b>Preferred term</b>			
Chronic obstructive pulmonary disease	60 (18.2)	51 (15.3)	65 (19.4)
Nasopharyngitis	24 (7.3)	29 (8.7)	21 (6.3)
Upper respiratory tract infection bacterial	14 (4.2)	3 (0.9)	5 (1.5)
Viral upper respiratory tract infection	10 (3.0)	3 (0.9)	7 (2.1)
Lower respiratory tract infection	9 (2.7)	13 (3.9)	8 (2.4)
Cough	8 (2.4)	9 (2.7)	13 (3.9)
Back pain	7 (2.1)	12 (3.6)	6 (1.8)
Dyspnea	7 (2.1)	6 (1.8)	15 (4.5)
Hypertension	7 (2.1)	4 (1.2)	5 (1.5)
Influenza	7 (2.1)	5 (1.5)	4 (1.2)
Pyrexia	7 (2.1)	3 (0.9)	4 (1.2)
Upper respiratory tract infection	7 (2.1)	1 (0.3)	8 (2.4)

Source: Table 12-3 Study No. CQAB149B2336 Clinical Study Report

#### Deaths and SAEs

There were a total of 5 deaths in the trial, 4 occurring during treatment or within 30 of the last dose. One death occurred in a patient on indacaterol, this was reported as a cardiac arrest. There were 2 other deaths not included in the clinical database, 1 in the salmeterol group and 1 in placebo. There were 74 patients with SAEs, of which, 32 led to discontinuation. The most common SAE leading to discontinuation was COPD. In the indacaterol 150 mcg treatment group, 1 patient had a myocardial infarction, another a cardiac arrest, one with a tachyarrhythmia, and one with tachycardia. These events were not reported for salmeterol or placebo. As well, there was 1 patient with a cerebral infarction and 1 with cerebral vascular accident, and none of these events in salmeterol and placebo.

#### Adverse events leading to discontinuation

There were 5 SAEs in indacaterol, 9 in salmeterol and 2 in placebo categorized under the SOC of infections and infestations leading to discontinuation. There were more cardiac disorders leading to discontinuation (4) in indacaterol than placebo (2). AEs leading to discontinuation occurred at similar rates across treatment groups (5.2% in patients treated with indacaterol and 4.8% in patients taking salmeterol and 4.5% in patients treated with placebo).

#### 3.3.6.3.3.4 Laboratory findings

There were no clinically significant changes in hematology or chemistry labs over the treatment groups. There were 1 patient (0.3%) in the indacaterol group, 2 (0.6%) in the salmeterol group and 0 in placebo with potassium levels < 3 mmol/L. For notable glucose levels > 9.99 mmol/L there were 19 (5.8%). 30 (9.0%) and 21 (6.3%) in the indacaterol, salmeterol and placebo groups, respectively.

#### 3.3.6.3.3.5 ECG findings

One patient in the indacaterol treatment group developed a QTcF >500 ms, a 69 year old male who subsequently developed adenocarcinoma of the pancreas. A maximum increase from baseline of 30 – 60 ms in QTcF occurred in more indacaterol treated patients (31 patients, 9.1%) than salmeterol (15 patients, 4.5%) and placebo (21 patients, 6.3%). There were 2 patients who developed a maximum increase from baseline > 60 msec, 1 in the indacaterol group and one in the salmeterol group.

### **3.3.6.3.3.6 Physical examination**

Focus was placed on blood pressure and pulse the with known beta2 adrenergic effect. There was a higher percentage of SBP > 200 mm Hg in patients in the placebo group (1.5%) than indacaterol (0.6%) or salmeterol (0.9%). DBP > 115 mm Hg occurred at equal rates in the indacaterol group and placebo group (0.3%). There were no events of notable pulse rate > 130 bpm.

### **3.3.6.3.3.7 Special safety topics**

More patients taking indacaterol versus other treatments experienced a post inhalational (PI) cough event within 5 min after dosing, usually within 15 seconds after dosing with a median duration of 12 seconds. The incidence of PI cough events in the indacaterol group ranged from 17- 19.7% across visits, salmeterol ranged from 0.3- 2% and placebo ranged from 0.9- 3.3%.

### **3.3.6.3.4 Summary of Study**

This was a 26 week, multicenter, international, randomized, placebo-controlled trial comparing the higher proposed dose indacaterol 150 mcg q.d. to placebo in adults with moderate to severe COPD. The selected dose of indacaterol 150 mcg achieved the primary endpoint demonstrating a statistically significant treatment difference from placebo after twelve weeks, 0.170 L.

Indacaterol 150 mcg treatment for 12 weeks achieved the important secondary endpoint, SGRQ, and met the minimum clinically important difference of 4 units. Indacaterol 150 mcg was not shown to be significantly different from placebo in the symptomatic diary assessment of 'days of poor control'.

Consistent with the known bronchodilator mechanism of indacaterol, a significant difference was also shown over placebo for other spirometry based endpoints including tFEV1 on Day 2 and Week 26; peak FEV 5 min-4hr at Day 1, Week 12 and Week 26; FEV1 AUC 5min- 4hr and AUC 5min- 1hr at Day 1, Week 12 and Week 26. Indacaterol 150 mcg also showed benefit over placebo for FEV1 during all the measured time points over 24 hours.

TDI focal scores were statistically significantly improved with indacaterol 150 mcg by 12 and 26 weeks of treatment. Percentage of nights with 'no nighttime awakenings', days with 'no daytime symptoms' and 'days able to perform usual daily activities' over 26 weeks were statistically significant for comparisons between indacaterol and placebo. Patients taking indacaterol 150 mcg showed improvement for all rescue medication use assessments reported; patients required significantly fewer daily, daytime or nighttime puffs of rescue medication and had a significantly higher percentage of 'days with no rescue use' compared with patients taking placebo over 26 weeks of treatment.

The most frequent AEs were COPD, nasopharyngitis, upper respiratory tract infect, lower respiratory tract infection, cough, dyspnea and back pain. The percentage of patients with the AEs of COPD and dyspnea was higher in the placebo group than the indacaterol 150 mcg group. There were a total of 7 deaths in the trial, 4 occurring during treatment or within 30 of the last dose. One death occurred in a patient on indacaterol, this was reported as a cardiac arrest. There were 74 patients with SAEs, of which, 32 led to discontinuation. The most common SAE leading to discontinuation was COPD. In the indacaterol 150 mcg treatment group, 1 patient had a myocardial infarction, another a cardiac arrest, one with a tachyarrhythmia, and one with tachycardia. These events were not reported for salmeterol or placebo. As well, there was 1 patient with a cerebral infarction and 1 with cerebral vascular accident, and none of these events in salmeterol and placebo. There were 5 SAEs in indacaterol, 9 in salmeterol and 2 in placebo categorized under the SOC of infections and infestations leading to discontinuation. There were more cardiac disorders leading to discontinuation (4) in indacaterol than placebo (2).

There were no clinically meaningful differences reported between treatment groups for serum potassium or blood glucose. There were no significant differences between treatment groups regarding vital signs. An increase of >60 ms in Fridericia's QTc was seen in 1 patient in each active treatment group. More

patients taking indacaterol versus other treatments experienced a post inhalational cough event within 5 min after dosing, typically starting within 15 seconds after dosing and lasting with a median duration of 12 seconds. The incidence of PI cough events in the indacaterol group was <20%.

## Supplementary Trials

### Trial B2341

Trial B2341 was a 12 week, randomized, double-blind, parallel group efficacy and safety comparison of indacaterol 150 mcg plus open-label tiotropium HandiHaler (18 mcg) versus placebo plus open-label tio HH18 in patients with COPD. The study was conducted in 186 different centers in 14 countries (including the United States, Central and South America, Europe, Asia, Africa, and Australia). The primary study endpoint was FEV<sub>1</sub> AUC<sub>5min-8hours</sub> after 12 weeks of therapy. The key secondary endpoint was trough FEV<sub>1</sub> after 12 weeks of therapy. Multiplicity for the key secondary endpoint was controlled by hierarchical testing. Other study efficacy endpoints included FEV<sub>1</sub> at other time points, inspiratory capacity (subset only), rescue medication use, and COPD symptoms.

A total of 1134 male and female subjects with moderate to severe COPD (post-bronchodilator FEV<sub>1</sub> 30-65% predicted) were enrolled; 570 in the combination group and 564 in the tio alone group. Of these, 1060 (93.5%) completed the study. Demographics were generally balanced between the treatment groups. Overall, the mean age of patients in the trial was 63.7 years. Most patients were male (68.7%) and caucasian (77.5%). Patients had a mean post-bronchodilator FEV<sub>1</sub> of 1.33L, with 46.7% having moderate COPD and 52.6% with severe disease. Nearly half of patients were taking concurrent inhaled corticosteroids (47.9%), and just over 1/3 were current smokers (38.4%). Six percent of patient had major protocol deviations, primarily not meeting the FEV<sub>1</sub> enrollment criteria (2.4%), SABA reversibility not acceptable (1.1%), or compliance with <80% of study medication doses (0.8%). These deviations are not expected to bias the results significantly as they occurred equally in both treatment groups.

For the primary endpoint, FEV<sub>1</sub> AUC<sub>5min-8hours</sub> after 12 weeks of therapy, the combination group was significantly higher than the tio alone group, with an AUC of 1.50L versus 1.38L. This demonstrated a treatment difference of 0.13L, 95% CI 0.10-0.15, p<0.001. Likewise, for the key secondary endpoint, trough FEV<sub>1</sub>, the combination group showed a significantly different treatment benefit over the tio alone group, with a difference of 0.08L, 95% CI (0.05, 0.10), p<0.001. Day 1 values also showed a significant benefit for the combination group over the tio alone group for all FEV<sub>1</sub> endpoints measured, with separation demonstrated as early as the 5 minute time point. At Week 12, the FEV<sub>1</sub> treatment difference varied from 100 to 140 ml. Rescue medication use, symptom scores, and inspiratory capacity also showed numerical benefit for the combination group over the tio alone group.

The most frequent adverse event was cough, which occurred more frequently in the combination group (10.4% versus 3.7%). Other adverse events occurring more frequently in the combination group were muscle spasms (2.3% versus 0) and abdominal pain (1.2% versus 0.2%). The most common serious adverse events were respiratory, cardiac, and infections. COPD exacerbations occurred more frequently in the combination group, with 6 (1.1%) versus 12 (2.1%). Likewise, discontinuations due to AEs occurred more frequently in the combination group, with 21 (3.7%) versus 9 (1.6%). There were two on-treatment deaths in the trial, both in the combination group. Cause of death was anaphylaxis 30 minutes after receiving ceftriaxone for a COPD exacerbation and myocardial infarction.

#### Reviewer comment:

*This trial demonstrates that indacaterol provides additional bronchodilator benefit in patients receiving a long-acting anticholinergic (tiotropium), a common therapy in COPD. This benefit is tempered by an increased risk of cough and COPD exacerbation. There were also two deaths in the combination group, but the numbers are too small to draw safety conclusions regarding mortality.*

### Trial B2351

Trial B2351 was a 12 week, randomized, double-blind, parallel group efficacy and safety comparison of indacaterol 150 mcg plus open-label tiotropium HandiHaler (18 mcg) versus placebo plus open-label tio HH18 in patients with COPD. The trial design was the same as Protocol B2341. The trial was conducted in 182 different centers in 12 countries (including the United States, Canada, South America, Eastern and

Western Europe, India, and the Philippines). The primary endpoint was FEV1 AUC<sub>5min-8hours</sub> after 12 weeks of therapy. The key secondary endpoint was trough FEV1 after 12 weeks of therapy. Multiplicity for the key secondary endpoint was controlled by hierarchical testing. Other trial efficacy endpoints included FEV1 at other time points, inspiratory capacity (subset only), rescue medication use, and COPD symptoms.

A total of 1142 male and female subjects with moderate to severe COPD (post-bronchodilator FEV1 30-65% predicted) were enrolled; 572 in the combination group and 570 in the tio alone group. Of these, 1076 (94.2%) completed the trial. Demographics were generally balanced between the treatment groups. Overall, the mean age of patients in the trial was 62.9 years. Most patients were male (65.4%) and Caucasian (78.5%). Patients had a mean post-bronchodilator FEV1 of 1.31L, with 45.8% having moderate COPD and 53.2% with severe disease. Nearly half of patients were taking concurrent inhaled corticosteroids (45.9%), and 40% were current smokers. Seven percent of patients had major protocol deviations, primarily not meeting the FEV1 enrollment criteria (2.8%), compliance with <80% of study medication doses (1.1%), or SABA reversibility not acceptable (0.8%). These deviations are not expected to bias the results significantly as they occurred equally in both treatment groups.

For the primary endpoint, FEV1 AUC<sub>5min-8hours</sub> after 12 weeks of therapy, the combination group was significantly higher than the tio alone group, with an AUC of 1.46 L versus 1.34 L. This demonstrated a treatment difference of 0.12 L, 95% CI 0.09-0.14,  $p < 0.001$ . Likewise, for the key secondary endpoint, trough FEV1, the combination group showed a significantly different treatment benefit over the tio alone group, with a difference of 0.07 L, 95% CI (0.05, 0.09),  $p < 0.001$ . Day 1 values also showed a significant benefit for the combination group over the tio alone group for all FEV1 endpoints measured, with separation demonstrated as early as the 5 minute time point. At Week 12, the FEV1 treatment difference varied from 120 to 130 ml at various time points up to 8 hours. Rescue medication use, symptom scores, and inspiratory capacity also showed numerical benefit for the combination group over the tio alone group.

The most frequent adverse event was cough, which occurred more frequently in the combination group (9.1% versus 4.4%). Other adverse events occurring more frequently in the combination group were dry mouth and dyspnea (2.1% versus 0.5% for both AEs). The most common serious adverse events were respiratory and infections. In contrast to Trial B2341, COPD exacerbations and discontinuations due to AEs were balanced between treatment groups. Serious cardiovascular events were also balanced. There were three on-treatment deaths in the trial, one in the combination group and two in the tiotropium group. In the combination group cause of death was myocardial infarction, and in the tiotropium group cause of death was sudden death and cardiac arrest.

*Reviewer comment:*

*This trial demonstrates that indacaterol provides additional bronchodilator benefit in patients receiving a long-acting anticholinergic (tiotropium), a common therapy in COPD, providing replicate data to Trial B2341. This benefit is tempered by an increased risk of cough. Mortality and serious adverse events were generally balanced between treatment groups.*

## **Trial B2335SE**

Trial B2335SE was a 26 week extension to a 26 week, randomized, double-blind, multicenter, placebo-controlled, adaptive design, parallel-group efficacy and safety comparison of indacaterol (150 mcg and 300 mcg) versus placebo in patients with COPD. The trial was conducted in 142 different centers in 9 countries (including the United States, Argentina, Canada, Germany, India, Italy, Spain, Sweden and Turkey). No primary efficacy endpoint was specified. The secondary efficacy endpoints were trough FEV1 at Week 52. Other efficacy endpoints included: FEV1 and FVC at other time points, time to first COPD exacerbation, COPD exacerbation rates, COPD symptoms, post-inhalational cough events, rescue medication use, PEF and SGRQ.

A total of 415 male and female patients with moderate to severe COPD (post bronchodilator FEV1 <80% and  $\geq 30\%$  of predicted) who completed stage 2 of the core trial (B2335S) were enrolled in the extension trial B2335SE. A total of 366 (88.2%) completed the extension trial (126 patients or 87.5%, indacaterol 150 mcg; 135 or 92.5%, indacaterol 300 mcg and 105 or 84% in placebo). Discontinuation was observed at a higher rate in the placebo group (16%) and ranged from 7.5% in indacaterol 300 mcg to 12.5% in the indacaterol 150 mcg group. The most common reasons for discontinuation were withdrawal of consent, lost to follow up and protocol deviations. Demographics were balanced between the treatment groups and consistent with many of the previous trials. The mean age was 62.6 ( $\pm 9.21$  years), most were males (61.4%) and caucasian (81.4%). The patients had a mean post bronchodilator FEV1 of 1.49 L, with 54% having moderate COPD and 41% with severe disease. Inhaled corticosteroids were taken by 35-38% of patients and half were current smokers. Nineteen percent reported major protocol deviations, primarily time of dosing eosinophil count > 400/mm<sup>3</sup> at screening and trough measurement timings not compliant with protocol. These deviations are unlikely to bias the results significantly as they occurred at similar rates across treatment groups.

The treatment difference of trough FEV1 at Week 52 was statistically significantly higher in the indacaterol treatment groups compared to placebo, 150 mcg indacaterol 0.17 L (0.11, 0.23) and 300 mcg indacaterol 0.18 L (0.12, 0.24) for the ITT population. Likewise, the tFEV1 at other time points, Week 12 (Day1), Week 26 (Day 2), and Week 36 and 44 were all statistically significantly higher than placebo with similar numeric values as Week 52.

The Cox regression analysis of time to first COPD exacerbation showed no statistically significant differences between groups. Likewise, there were no significant differences in number of exacerbations per patient and event free rates. The rates of COPD exacerbations over the 52 week total duration of the study for indacaterol 150 mcg, 300 mcg, and placebo were 0.39, 0.38 and 0.54, respectively. While the Sponsors analysis of ratio of rates meets statistical significance, this analysis is not corrected for overdispersion, so may overestimate the treatment effect.

Evaluation of the percentage of patients with “days of poor control” over 52 weeks as well as improvement in daytime and nighttime symptoms did not show any significant difference between indacaterol treatment groups and placebo. All assessments of rescue medication use as well as morning and evening PEF showed statistical significance in comparison between the indacaterol treatment groups and placebo. Assessment of health-related quality of life as measured by the SGRQ did not meet the MCID of -4 at week 52 (treatment difference of -3.2); however, at Weeks 26 and 44 the treatment differences were -4.47 and -5.7 for the 150 mcg indacaterol treatment group. The treatment difference was smaller for the 300 mcg indacaterol treatment group, with a difference of -1.9, -5.4, and -1.7 at Week 26, 44, and 52, respectively.

The most frequent AEs by preferred term were COPD, nasopharyngitis, cough, upper respiratory tract infection, headache, muscle spasms and oropharyngeal pain. The rates were similar between indacaterol and placebo for COPD and nasopharyngitis, and higher for cough, headache, and muscle spasms. Post inhalational cough occurred in 28.5%, 31.5% and 3.2% of patients in the 150 mcg, 300 mcg, and placebo groups, respectively. SAEs were reported at similar rates between indacaterol 150 mcg (10.4%), 300 mcg (13.0%) and placebo (10.5%). SAEs occurred most frequently in the respiratory, thoracic and mediastinal (14 patients), cardiac (9 patients) and infection and infestations (8 patients) SOC. There were two deaths during the trial, one patient in the placebo group and one in the indacaterol 300 mcg group, both from myocardial infarctions.

*Reviewer Comment:*

*The trial demonstrates that indacaterol 150 mcg and 300 mcg were effective bronchodilators in patients with COPD out to 12 months treatment duration. The safety profile was consistent with events described in the pivotal trials.*

## 4. Review of Efficacy

### Efficacy Summary

There is substantial evidence in support of the efficacy of indacaterol as a maintenance bronchodilator in patients with COPD. Both the original submission and the complete response present adequate and well controlled trials showing the superiority of indacaterol to placebo in the change from baseline in 24 hour tFEV1. However the original dose selections of 150 mcg and 300 mcg, currently marketed in the 40 countries were not significantly different from 75 mcg once daily. Furthermore, the 300 mcg doses were associated with cardiac and cerebrovascular events as well as two suspected asthma deaths. The use of an adaptive design trial as well as other supportive data were acceptable approaches towards dose selection however, the criteria used for dose selection to carry forward were flawed. The doses were chosen among four (75 mcg, 150 mcg, 300 mcg and 600 mcg) from the interim analysis of the adaptive design trial B2335s. The Data Monitoring Committee was charged to select dose (s) that were:

- Greater than placebo in trough FEV1 by 120 mL (proposed MCID) and numerically higher than tiotropium and formoterol
- Numerically higher than tiotropium and formoterol in terms of FEV1 standardized AUC (1- 4 hr)

The new supportive evidence comes from 5 simultaneously conducted trials, 3 dose finding and 2 confirmatory (B2357, B2356, B2223, B2355 and B2354). In addition, Novartis now submits one long term safety and efficacy trial, (B2336) which was initiated, but not completed during the original submission. All demonstrate the superiority of indacaterol to placebo in the primary endpoint of tFEV1. The two dose ranging trials B2357 and B2356 demonstrate superiority of the two lower doses, 37.5 mcg and 75 mcg as well as the 150 mcg indacaterol dose over placebo on the primary endpoint. These trials also demonstrate benefit of indacaterol 37.5 mcg, 75 mcg and 150 mcg over placebo for other standard measures of airflow obstruction with only one exception, 37.5 mcg dose in B2357 did not reach statistical significance for peak FEV1 at Day 1 (p-value 0.101). Both dose ranging trials demonstrated benefit of indacaterol compared to placebo in rescue medication use, providing supportive efficacy data.

The trial B2357 conducted in bronchoreactive asthmatic patients revealed two findings:

1. Indacaterol 75 mcg daily showed the greatest numerical benefit compared to placebo than either the 37.5 mcg or 150 mcg indacaterol doses in the primary endpoint –tFEV1 on Day 14
2. Although 150 mcg indacaterol had a larger improvement than the two lower doses after 1 day of treatment in all of the spirometry based secondary endpoints, this advantage is lost by Day 14. At Day 14, 75 mcg indacaterol showed a larger improvement than the other doses.

Trial B2356 was conducted in the predominantly moderate to severe COPD population (mean prebronchodilator FEV1 1.3 L) with a mean percent increase in FEV1 after SABA ranging from 14.2-16.7%. The trial demonstrated superiority of indacaterol to placebo in the primary efficacy endpoint tFEV1. Numerically, the largest treatment difference in tFEV1 after two weeks compared to placebo was observed with indacaterol 150 mcg; however, the values were similar to tFEV1 in the 37.5 mcg and 75 mcg indacaterol treatment groups. The key secondary endpoints, tFEV1 at Day 2 and Day 14 also demonstrated, significant benefit of the 37.5 mcg, 75 mcg, and 150 mcg group. Although the tFEV1 was marginally higher in the 150 mcg dose group, the difference of 20 ml is within the variability of the test and is not likely to be clinically important. The loss of any advantage of 150 mcg indacaterol over 37.5 mcg and 75 mcg doses by Day 14 for the other spirometry based secondary endpoints was apparent.

Overall, the dose regimen trial, B2223 did not reveal significant differences after two weeks between the three regimens evaluated, 37.5 mcg b.i.d, 75 mcg q.d. and 150 mcg q.o.d. The greatest magnitude in treatment differences from placebo in tFEV1 on Days 15/16 was observed with the 75 mcg q.d and 150 mcg q.o.d regimens which were almost identical in value. The magnitude of mean change from baseline in peak FEV1, FEV1 AUCs  $_{0-24 \text{ hr}}$ , AUC  $_{1-12 \text{ hr}}$  and AUC  $_{12-24 \text{ hr}}$  were greatest for the 75 mcg q.d. regimen when compared to the 37.5 mcg b.i.d regimen. The mean Tmax was similar across dosing regimens

ranging from 15 to 18 minutes with pharmacokinetic steady state being achieved by all three regimens by Day 15 as indicated by the trough serum concentrations of indacaterol.

The two 12 week confirmatory trials (B2355 and B2354) evaluating only the 75 mcg indacaterol dose compared to placebo demonstrated statistically significant benefit of indacaterol on the primary endpoint of tFEV1 after 12 weeks as well as other standard measures of airflow obstruction. However, the results of measurements intended to assess disease control using patient or evaluator reported outcome questionnaires were less consistent between trials. Superiority of indacaterol over placebo was observed using the TDI only in trial B2354, not B2355. While the two trials demonstrated superiority of indacaterol to placebo for all assessments of rescue medication use, there was no consistency in superiority for improvement in symptoms. Trial B2355 demonstrated statistically significant improvement in only the percent of 'days able to perform usual daily activities', while B2354 demonstrated statistical significance for indacaterol instead in the percent of days with 'no daytime symptoms'. The MCID of -4 for SGRQ was not achieved in either trial.

The single 26 week efficacy and safety trial, B2336 evaluating solely the indacaterol 150 mcg dose compared to placebo demonstrated statistically significant benefit of this higher proposed dose in the primary endpoint of tFEV1 after 12 weeks. In addition, indacaterol 150 mcg was superior to placebo in other measures of airflow obstruction. In contrast to the other trials measuring SGRQ, in B2336, indacaterol 150 mcg was statistically superior to placebo and also exceeded the MCID of 4. However, there is a concern that the amended protocol resulted in a change in the interpretation of the data. Amendment 2 dated 1/6/09 submitted towards the completion of the trial, called for the elevation of SGRQ over the original key secondary endpoint, percentage of 'days of poor control' in the hierarchical testing procedure. While it is unlikely that the change would alter the final result (change in the "N" needed to detect the significant difference or the MCID), SGRQ would not have been tested originally as 'days of poor control' did not meet statistical significance. The other secondary endpoints such as COPD exacerbation rates and the 6 minute walk, did not demonstrate superiority of indacaterol 150 mcg over placebo. The remaining secondary endpoints of TDI, all rescue medication use assessments, change from baseline in the mean morning and evening PEF, the BODE index after 12 and 26 weeks, daytime and nighttime symptoms and percentage of 'days able to perform usual daily activities' all supported the benefit of indacaterol 150 mcg over placebo. These secondary endpoints provide supportive evidence of efficacy.

The proposed label includes language describing the 'onset of action within 5 minutes' as well as 'no evidence of loss of efficacy (tachyphylaxis)'. A specific definition of 'onset of action' is not provided by the Sponsor. However, two of the pivotal trials reviewed, B2355 and B2354 provide data to support this claim, with significant improvement in FEV1 at 5 minutes after the first dose for both the indacaterol 75 mcg and 150 mcg doses over placebo. As well, these same two trials also provide data of no statistically significant difference in the rate of change in trough FEV1 from 29 days to 12 weeks of treatment between the treatment groups in support of the claim for no evidence of tachyphylaxis.

#### **4.1 Indication**

As a bronchodilator, the therapeutic aim sought for Arcapta Neohaler is to provide benefit through relief of reversible airflow obstruction. The specific labeling claim proposed by Novartis in the product label includes the following language:

*"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."*

##### **4.1.1 Methods**



### Dose finding trials:

To support the complete response, Novartis submitted 3 two week dose finding trials to address the deficiencies in dose selection and dosing frequency in the original NDA. The original trials exploring the dose response profile of indacaterol included: B2201, B2205, B2212, B1202 and B2335S. These trials will not be reviewed here. The three new trials listed in Figure 10 below explored lower doses to identify a dose with an acceptable balance of observed undesired effects and beneficial effects. The designs of the dose finding trials were similar - parallel, randomized, double-blind, placebo controlled, fixed multiple dose, dose response trials assessing trough FEV1 after two weeks to evaluate the efficacy of indacaterol in bronchodilation. An interesting note is that all were carried out concomitantly along with the two 3 month confirmatory trials.

**Figure 10 Relevant dose finding trials**

Study	Objective, population	n	Treatment duration	Treatment Groups	Efficacy endpoint	Safety endpoints	Study year	Countries
Dose finding trials								
B2357	Dose-ranging in asthma	558	2 wks	Ind 18.75 mcg qd Ind 37.5 mcg qd Ind 75 mcg qd Ind 150 mcg qd Salm 50 mcg bid Placebo bid	tFEV1 after 14 days	AE (including asthma exacerbations), SAEs, labs, ECG, VS, PE, weight	2/22/10-7/14/10	United States
B2223	Dosing regimens in asthma	192	2 wks	Ind 37.5 mcg bid Ind 75 mcg q. Ind 150 mcg qod placebo bid	tFEV1 after 14 days	VS, ECG, labs, AEs	3/10/10-7/12/10	France, Germany, Jordan, Netherlands, United Kingdom, United States
B2356	Dose-ranging in COPD	576	2 wks	Ind 18.75 mcg qd Ind 37.5 mcg qd Ind 75 mcg qd Ind 150 mcg q.d. Salm 50 mcg bid Placebo bid	tFEV1 after 14 days	AE, SAEs, labs, ECG, VS, PE, rescue medication use	3/5/10-7/9/10	United States

**Protocol B2357** was a multi-center, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial in a representative broncho-reactive population, those with persistent asthma, classified by GINA guidelines, 2008. The patients were male and female adults age  $\geq 18$  years with a FEV1  $\geq 50$  and  $\leq 90\%$  of the predicted and on a stable dose of ICS for at least one month. Consistent with their diagnosis, patients had to demonstrate an increase of  $\geq 12\%$  and  $\geq 200$  mL in FEV1 over their pre-bronchodilator value within 30 minutes after inhaling a total of 360 mcg of albuterol via a metered dose inhaler. Randomization was stratified by asthma severity. Those patients excluded had: a smoking history greater than 10 pack years; a diagnosis of COPD defined by GOLD, 2008 guidelines; an exacerbation requiring hospitalization 6 months prior, previous intubation for severe asthma exacerbation; ER visits for an asthma attack/exacerbation within 6 weeks; patients with uncontrolled asthma represented by the use of  $\geq 8$  inhalations per day of SABA (90 mcg albuterol via MDI) on any 2 consecutive days; respiratory tract infection within 6 weeks; other pulmonary disease, pulmonary TB or clinically significant bronchiectasis; history of lung cancer and history or family history of long QT syndrome.

**Protocol B2223**, a Phase II trial was a multi-center, randomized, double-blind, placebo-controlled, parallel group study also in patients with persistent asthma comparing three different indacaterol dosing regimens (75 mcg once daily, 150 mcg on alternate days and 37.5 mcg twice daily). Patients were dosed

for a total of 16 days following a 2 week run-in period to allow and monitor patient stability. The inclusion criteria were the same as in B2357, notably patients had to be on a stable dose of ICS for one month and demonstrate reversibility to SABA with an increase in FEV1  $\geq 12\%$  and 200 mL. The key exclusion criteria were identical to B2357.

**Protocol B2356** was a randomized, double-blind, double-dummy, placebo-controlled, parallel group trial. Patients were stratified for smoking status and ICS use. Patients with moderate to severe COPD as per GOLD, 2008 guidelines were treated for 14 days with indacaterol once daily (18.75, 37.5, 75 or 150 mcg), salmeterol 50 mcg twice daily or placebo. Patients were male or female adults aged  $\geq 40$  years with a smoking history of at least 10 pack years, a post bronchodilator FEV1  $<80\%$  and  $\geq 30\%$  of the predicted normal and FEV1/FVC  $<70\%$  of the value. Key exclusion criteria were: COPD exacerbation requiring systemic glucocorticosteroid treatment and/or antibiotics and/or hospitalization in the 6 weeks prior to screening; the requirement of oxygen therapy for chronic hypoxemia (excluding acute COPD exacerbation); patients who had a respiratory tract infection within 6 weeks; patients with concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis; patients with a history of asthma indicated by (but not limited to) onset of respiratory symptoms suggestive of asthma prior to 40 years of age or a history of a diagnosis of asthma.

**Long term efficacy and safety trials:**

**Protocols B2355 and B2354** were identical, Phase III trials, multi-center, randomized, double-blind, placebo-controlled, parallel-group design, using 75 mcg indacaterol once daily via an SDDPI for 12 weeks in patients with moderate to severe COPD with stratification for smoking status and inhaled corticosteroid (ICS) use. There was a 14 day run-in period, and a 12 week treatment period. The study was designed to allow further characterization of the efficacy and safety of the 75 mcg dose of indacaterol in COPD, using placebo as a control. The patients were male or female adults aged  $\geq 40$  years, with smoking history of at least 10 pack years; a post-bronchodilator FEV1  $< 80\%$  and  $\geq 30\%$  of the predicted normal and FEV1/FVC  $< 70\%$ . Key exclusion criteria included: patients who had a COPD exacerbation requiring systemic glucocorticosteroid treatment and/or antibiotics and/or hospitalization in the 6 weeks prior to screening, patients requiring oxygen therapy for chronic hypoxemia (excluding acute COPD exacerbation), patients who had a respiratory tract infection within 6 weeks, concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis, patients with a history of asthma indicated by (but not limited to) onset of respiratory symptoms suggestive of asthma prior to 40 years of age or a history of a diagnosis of asthma.

**Figure 11 Twelve week placebo-controlled efficacy/safety trials**

Key controlled efficacy trials-75 mcg								
Study	Objective, population	n	Treatment duration	Treatment Groups	Efficacy endpoint	Safety endpoints	Study year	Countries
B2355	Efficacy/safety in COPD	326	12 wks	Ind 75 mcg q.d. Pbo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE	1/27/10-6/14/10	United States
B2354	Efficacy/safety in COPD	326	12 wks	Ind 75 mcg q.d. Pbo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE	1/22/10-7/14/10	United States
B2336	Efficacy/safety in COPD	972	26 wks	Ind 150 mcg qd Salm 50mcg bid Pbo b.i.d	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, medical resource utilization, post inhalation events	11/27/07-1/28/09	Canada, Colombia, Czech Republic, Denmark, Germany, Finland, France, Hungary, India, Iceland, Italy, Peru, Russia, Slovakia, Taiwan

**Protocol B2336**, a multi center, double blind, double dummy, parallel group trial of the higher proposed indacaterol dose of 150 mcg q.d. in patients with moderate-to-severe COPD. Eligible patients were randomized and stratified based on smoking status 1:1:1 to receive indacaterol 150 mcg q.d., salmeterol 50 mcg b.i.d., or placebo for 26 weeks. The main criteria for inclusion were male or female adults aged  $\geq 40$  years, with smoking history of at least 10 pack years; a post-bronchodilator FEV1  $< 80\%$  and  $\geq 30\%$  of the predicted normal and FEV1/FVC  $< 70\%$ . They were somewhat different from the above COPD trials in that their smoking history was greater with at least 20 pack years. The exclusion criteria were the same as Protocols B2355 and B2354.

#### Supplementary trials

Submitted under this NDA were 10 supplementary trials that were either trials for registration in other countries or for profiling. These were only briefly reviewed and a summary is listed in Figure 12 below.

**Figure 12 Supplementary controlled trials in patients with COPD**

Supplementary controlled efficacy trials								
Study	Objective, population	n	Treatment duration	Drug	Efficacy endpoint	Safety endpoints	Study year	Countries
B1302	Efficacy/safety in COPD, Asia	336	12 weeks	Ind 150, 300 mcg q.d. Pbo q.d.	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events	11/17/08-10/7/09	Hong Kong, India, Japan, Korea, Singapore, Taiwan
B2333	Efficacy/safety	558	26 weeks	Ind 150,	tFEV1 at	AEs, SAEs, VS,	11/13/08-	Australia,

	in COPD, Primarily China			300 mcg q.d. Pbo q.d.	Week 12	ECGs, labs, post inhalation events	2/26/10	China, India
B2349	Efficacy/safety in COPD	1084	12 weeks	Ind150 mcg q.d. Salm 50 mcg b.i.d	AUC (5 min- 11h 45 min for FEV1 at Week 12	ECG, labs, blood pressure, heart rate, AEs	1/23/09- 10/9/09	Czech Republic, Germany, Hungary, India, Slovakia, Spain, Turkey, United States
B2350	Efficacy/safety in COPD	1568	12 weeks	Ind150 mcg q.d. Tiotropium 18 mcg q.d.	tFEV1 at Week 12	AEs, SAE, ECG, labs, blood pressure, heart rate, AEs	6/1/09- 3/25/10	Austria, Belgium, Canada, Colombia, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Norway, Poland, Russia, Slovakia, Spain, Switzerland, Turkey, United Kingdom, United States
Long term controlled efficacy trials								
B2335SE	Efficacy/safety in COPD	417	26 weeks (additional to initial 26 weeks)	Ind 150, 300 mcg q.d. Pbo q.d.	tFEV1 at Week 52	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight	5/14/08- 3/2/09	Argentina, Canada, Germany, India, Italy, Spain, Sweden, Turkey and United States
Trials with indacaterol given concurrently with tiotropium								
B2341	Efficacy/safety in COPD	1126	12 weeks	Ind 150 mcg q.d. + tiotropium 18 mcg q.d. Pbo to ind + tiotropium 18 mcg q.d.	AUC (5 min- 8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG	3/5/09- 3/17/10	Argentina, Australia, Colombia, Denmark, Germany, Greece, Guatemala, Mexico, Peru, Philippines , South

								Africa, Spain, Turkey, United States.
B2351	Efficacy/safety in COPD	1126	12 weeks	Ind 150 mcg q.d. + tiotropium 18 mcg q.d. Pbo to ind + tiotropium 18 mcg q.d.	AUC (5 min- 8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG	4/8/09-2/9/10	Argentina, Canada, Colombia, Czech Republic, Hungary, India, Netherlands, Philippines, Slovakia, Spain, United States
Short-term profiling trials								
B2311	Exercise endurance in COPD	83	3 weeks (2 treatment periods separated by 2 weeks of wash out)	Ind 300 mcg q.d. Pbo q.d.	Exercise endurance time (measured through constant-load cycle ergometry testing) after 3 weeks of treatment	AEs, SAEs, labs, VS, ECG, PE	4/30/08-1/13/09	Belgium, Canada, Denmark, Italy, Spain, United States
B2331	24 h lung function profile in COPD	148	14 days (3 treatment periods separated by 2 weeks of wash out)	Ind 150, 300 mcg q.d. Tiotropium 18 mcg q.d. Pbo q.d.	tFEV1 on Day 15	AEs (including COPD exacerbations), SAEs, labs, VS, ECG, PE	2/14/08-12/30/08	Australia, Germany, Poland, South Africa, Spain, The Netherlands, New Zealand
Interim analysis for Japanese trial								
B1303	Efficacy/safety in COPD (Japan)	180	52 weeks (interim analysis at Week 24)	Indacaterol 300 mcg q.d. Salmeterol 50 mcg b.i.d.	tFEV1 on Day 169 (Week 24)	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events	3/3/09-3/31/10 (last patient completes 24 weeks treatment)	Japan

#### 4.1.2 Demographics

The populations reviewed were either asthmatics (as recommended by the FDA for evaluation of dose response) to test for bronchodilator efficacy in this known responsive group or patients with COPD, the ultimate marketing target. As such, the different disease characteristics require separate discussions of the demographic data.

The population of patients with asthma used in the dose ranging trial, B2357 and the dose regimen trial, B2223 were comparable in the breakdown of demographic characteristics as well as disease status. Caucasians made up the overwhelming predominate race, > 80% in both trials, however gender distribution varied as there were more males in B2223 (49%-67%) than B2357 (35%-52%). The mean age was consistent at 40-41 in both trials. Although the baseline disease characteristics were not provided in B2223, in B2357, the disease burden for asthma appears adequate with the mean duration of diagnosis of 27 years. Regarding reversibility, the main feature of this pathology, the mean predicted pre SABA FEV1 was 70-71% and post SABA was 85-86% with a high degree of mean reversibility of 22% for both trials. Overall, most patients in B2357 were mild to moderate in severity and approximately 80% never smoked.

The other 4 controlled trials conducted in patients with COPD, B2356, B2355, B2354 and B2336 were reviewed for the distribution of demographics, disease characteristics and generalizability. Overall, the majority, 85% to 94% were caucasian and most studies had between 52-63% males, however, B2356 had a lower range of 48-58% male patients and B2336 had a greater proportion of males 72-77%. The age was expectedly older with a mean ranging from 61 to 64 years. B2355 had a lower percentage of ex-smokers, 41% while B2354 had the highest percentage of ex-smokers, 55%. The median pack years of smoking ranged from 38 in B2336 to 45 pack years in B2356, B2354 and B2355. Across all 4 trials, >95% of the patients fell into the moderate to severe category according to GOLD, 2008 criteria. The trial with the lowest percent increase after SABA was B2336 with a mean percent increase of 11.8% seen for all treatment groups, while B2356, B2354 and B2355 had similar, high percent increases after SABA ranging from 15.7 -16.9%. Baseline ICS use was recorded for a low of 36% in B2355 and a high of 45% in B2354.

#### 4.1.3 Subject Disposition

Patient disposition is described in detail in Sections 5.3 and 7.2.9. An evaluation of the pooled data includes the two dose finding trials in asthmatics which will be analyzed separately from the 4 trials conducted in patients with COPD. Refer to Figure 13.

**Figure 13 Disposition in Trials B2357 and B2223**

	B2357-(n)							B2223- (n)				
	Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salm	Pbo	Total	Ind 37.5 b.i.d	Ind 75 q.d.	Ind 150 q.o.d	pbo	total
Randomized	85	85	84	86	86	85	511	48	48	48	47	191
Discontinued	2	7	1	5	8	5	28	2	2	6	6	16
Analyzed for prim efficacy	82	77	82	80	78	81	480	48	47	48	46	189

In B2357, 1200 patients were screened and 511 were randomized. The top four reasons for screening failure include: failure to meet reversibility criteria; prebronchodilator FEV1 >90%; withdrawal of consent and lost to follow-up. Of the 511 randomized, 502 were exposed to treatment drug, 500 were included in the FAS, 483 completed the trial as planned and 480 analyzed. For B2223, the number screened was not provided however 191 patients were enrolled and 189 were analyzed.

**Figure 14 Disposition in Trials B2356 and B2355**

	B2356- (n)							B2355- (n)		
	Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salm	Pbo	Total	Ind 75 mcg	Pbo	Total
Randomized	92	91	94	92	92	91	552	159	159	318
Discontinued	8	5	2	1	2	3	21	11	17	28
Analyzed for prim efficacy	82	84	87	90	88	86	517	159	158	317

**Figure 15 Disposition in Trials B2354 and B2336**

	B2354 (n)			B2336 (n)			
	Ind 75 mcg	Pbo	Total	Ind 150 mcg	salm	Pbo	Total
Randomized	163	160	323	333	334	335	1002
Discontinued	19	30	49	44	50	70	164
Analyzed for prim efficacy	149	148	297	320	317	316	953

In Protocol B2356, 1110 patients were screened, 552 randomized and 96.2% (531) completed the trial. In the two confirmatory studies, B2355 and B2354 the breakdown was different. In B2355, 597 screenings occurred 318 patients were randomized and 91% completed the trial as planned. In B2354, 755 screenings occurred with 323 patients randomized into the protocol and a lower percentage, 84.8% (274) completed the trial. The top reasons for screening failures were similar across the three trials B2355, B2354 and B2356: 'unacceptable test procedure result'; 'did not meet diagnosis/severity criteria' and 'subject withdrew consent'. The reasons for screen failures were not provided in trial B2336. The percentage of discontinuations was greatest in the placebo group of Studies B2355, B2354, B2336 and B2223. Refer to Figure 14 and Figure 15 for further details.

#### 4.1.4 Analysis of Primary Endpoint(s)

The selection of efficacy endpoints chosen by Novartis includes a wide breadth of objective physiological assessments as well as patient or evaluator reported outcome measures. As described in the <sup>9</sup>FDA Draft Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment, the recommended measure of improvement in airflow obstruction is the change in post-dose FEV1. The 24 hour trough FEV1 was chosen as the primary endpoint with the specific aim of characterizing the end of the dosing interval in their once daily dosing LABA. In addition, several secondary and exploratory endpoints including multiple time points characterizing the entire FEV1 AUC were also evaluated and will be reviewed in the next section.

##### *Reviewer Comment:*

*Novartis proposed the MCID of 200mL tFEV1 compared to placebo for the asthma trials and 120mL for the COPD trials. Support for their choice of a clinically meaningful improvement as the MCID of 200 ml in tFEV1 compared to placebo for the asthma trials and 120 ml for the COPD trials was provided by two referenced COPD review articles, <sup>10</sup>Cazzola, M et al., 2008 and <sup>11</sup>Donahue, JF 2005. Although this difference is used as a marker of bronchodilator response, it is intended to demonstrate peak effect, and does not apply to 24 hour trough, where smaller differences may also be clinically important. While an accepted MCID for FEV1, has yet to be established, the limitations in use of this value is evidenced by a*

<sup>9</sup> November, 2007 available at the website <http://www.fda.gov/cder/guidance/index.htm>

<sup>10</sup> Cazzola M. et al., Eur Respir J 2008; 31: 416–468

<sup>11</sup> Donahue JF. COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 2: 111-124

*quote from Donahue, "an MCID for FEV1 must be anchored to a global or overall assessment when evaluating dose-response". Not only efficacy should go into the balancing equation but the associated toxicities seen with the dose response profile. This concept corresponds appropriately with the ICH E4 guideline on dose-response information where a great emphasis on dose selection is placed on defining the relationship of drug dosage to clinical beneficial as well as undesirable effects. Therefore, the sponsor defined MCID of 120 ml is not further discussed or used in clinical decision making for this review.*

Novartis has submitted significant data in support of the efficacy of indacaterol. In the original submission, doses ranging from 150 mcg to 600 mcg were supported by adequate and well controlled trials with significant p-values for the primary endpoint, trough FEV1 at week 12. See Figure 16 below.

**Figure 16 Summary of primary efficacy endpoint (trough FEV1 at week 12) in pivotal studies, original submission**

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	p-value
B2335s Stage 2	Ind 150 mcg	1.46	0.02	Ind 150-Pbo	0.18	0.02	(0.15, 0.21)	<0.001
	Ind 300mcg	1.46	0.02	Ind 300-Pbo	0.18	0.02	(0.15, 0.21)	<0.001
	Tio 18mcg	1.42	0.02	Tio-Pbo	0.14	0.02	(0.11, 0.17)	<0.001
	Placebo	1.28	0.02					
B2334	Ind 300 mcg	1.48	0.01	Ind 300-Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	Ind 600 mcg	1.48	0.01	Ind 600-Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	For 12 mcg	1.38	0.01	For-Pbo	0.07	0.02	(0.04, 0.10)	<0.001
	Placebo	1.31	0.01					
B2346	Ind 150 mcg	1.49	0.02	Ind 150-Pbo	0.13	0.02	(0.09, 0.18)	<0.001
	Placebo	1.35	0.02					

Source: Table 4, from review of Biostatistician, Dr Dongmei Liu

However, these doses were associated with higher toxicities seen in the combined cardiac and cerebrovascular SMQs as well as unacceptable asthma deaths. Since there was not a significant difference between these doses and the 75 mcg dose in the efficacy for the primary endpoint, it was apparent the selected doses were on or approaching the plateau of the dose response profile. The new adequate and well controlled dose finding studies also show a significant difference of lower doses of indacaterol over placebo in the trough FEV1 primary endpoint at two weeks. Furthermore, the new long term trials, B2336, B2355 and B2354 were all designed to provide a reasonable assessment of benefit and the duration was consistent with FDA guidelines. See Figure 17 for summary.



**Figure 17 Summary of primary efficacy endpoint (trough FEV1 at week 12) in pivotal studies, resubmission**

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	p-value
B2336	Ind 150 mcg	1.45	0.02	Ind 150-Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	Salmeterol	1.39	0.02	Sal-Pbo	0.06	0.02	(0.02, 0.10)	<0.001
	Placebo	1.28	0.02	Ind-Sal	0.11	0.02	(0.07, 0.14)	<0.001
B2354	Ind 75 mcg	1.38	0.01	Ind 75-Pbo	0.12	0.02	(0.08, 0.15)	<0.001
	Placebo	1.26	0.01	---	---	---	---	---
B2355	Ind 75 mcg	1.49	0.02	Ind 75-Pbo	0.14	0.02	(0.10, 0.18)	<0.001
	Placebo	1.35	0.02	---	---	---	---	---

Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

The Applicant proposes two doses of indacaterol for marketing, 75mcg and 150mcg, which would be novel for a LABA, as typically only one dose level is approved for use. The rationale for including a higher dose is “to provide additional benefit in patients with more severe bronchial obstruction.” In addition, the Applicant proposes that the 150mcg dose provides meaningful improvement in SGRQ, which is discussed in the next section. The Applicant would need to provide substantial evidence that the higher dose provides clinically meaningful benefit over the lower dose and that the higher dose has an acceptable safety profile.

Other than two-week dose ranging studies, there are no direct comparisons of 75mcg and 150mcg and thus comparison of the doses at the 12 week time period is cross study comparison, which has some limitations. In the dose ranging studies, the 150 mcg dose provided no meaningful clinical benefit over the 75 mcg dose. Similarly, a comparison drawn from the pooled 3 month efficacy data from all double-blind, placebo and active controlled trials of at least 12 weeks duration, consisting of 10 trials, does not demonstrate a clinically meaningful benefit in the primary bronchodilator endpoint of tFEV1 at 12 weeks, with difference of only 10 ml between the two dose groups. A subgroup analysis of this data by Global initiative for chronic Obstructive Lung Disease (GOLD) stage likewise did not demonstrate a benefit of the 150 mcg dose over the 75 mcg dose for patients with severe disease.

#### 4.1.5 Analysis of Secondary Endpoints(s)

##### SGRQ

The Applicant seeks a labeling claim for improvement in SGRQ, which would be a novel labeling claim for any drug approved for COPD in the United States. The medical literature has suggested a difference of 4 units as the value corresponding to a clinically meaningful improvement of SGRQ. The SGRQ was evaluated in five pivotal studies—two reviewed in the initial submission (Trials B2346 and B2335S) and three reviewed in this complete response submission (Trials B2336, B2354, and B2355). None of these trials included both the 150 mcg and 75 mcg dose groups, so direct comparisons between the doses cannot be made.

The table below shows the results for the SGRQ for the doses proposed by the Applicant. At 12 weeks, the 150 mcg dose group met the minimally clinically important difference (MCID) of -4 points change from baseline compared to placebo in the SGRQ total score in two studies. In Protocol B2346 the LS mean difference was -4.8, and in Protocol B2336 the LS mean difference was -6.3, forming the basis of the sponsor’s claim that indacaterol 150 mcg improves SGRQ.

See Figure 18 for a summary of the results.

**Figure 18 SGRQ total score at Week 12, treatment comparisons (imputed with LOCF, ITT)**

		n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
B2334	Ind 300 mcg	372	37.5	0.70	Ind 300 mcg – Pbo	-3.8	0.90	(-5.6, -2.1)	<.001
	Ind 600 mcg	354	37.2	0.70	Ind 600 mcg – Pbo	-4.1	0.90	(-5.9, -2.3)	<.001
	Form	359	38.1	0.70	For – Pbo	-3.2	0.90	(-5.0, -1.5)	<.001
	Placebo	347	41.3	0.70	---	---	---	---	---
B2335 S	Ind 150 mcg	368	38.3	0.70	Ind 150 mcg – Pbo	-2.8	0.90	(-4.5, -1.1)	0.001
	Ind 300 mcg	375	38.6	0.70	Ind 300 mcg – Pbo	-2.5	0.90	(-4.2, -0.8)	0.003
	Tio	374	40.1	0.70	Tio – Pbo	-1.1	0.90	(-2.8, 0.6)	0.195
	Placebo	347	41.2	0.70	---	---	---	---	---
B2336	Ind 150 mcg	309	36.4	1.04	Ind 150 mcg- Pbo	-6.3	0.99	(-8.2, -4.3)	<0.001
	Salm	301	38.5	1.04	Ind 150 mcg- Salm	-2.1	0.99	(-4.0, -0.2)	0.033
	Pbo	294	42.6	1.05	Salm- Pbo	-4.2	1.01	(-6.1, -2.2)	<0.001
B2346	Ind 150 mcg	199	43.4	0.86	Ind 150 mcg- Pbo	-4.8	1.22	(-7.1, -2.4)	<0.001
	Pbo	187	48.1	0.89	---	---	---	---	---
B2354	Ind 75 mcg	147	43.4	0.86	Ind 75 mcg- Pbo	-3.8	1.21	(-6.2, -1.4)	0.002
	Pbo	142	47.2	0.87	---	---	---	---	---
B2355	Ind 75 mcg	148	45.9	1.00	Ind 75 mcg- Pbo	-3.6	1.40	(-6.4, -0.9)	0.01
	Pbo	145	45.9	1.02	---	---	---	---	---

Source: Adapted from Tables 3-120, 3-121, 3-122 and 3-123 Summary of Clinical Efficacy and adapted from the review of Biostatistician, Dr Dongmei Liu

As shown in the table above, the SGRQ did not reach the proposed MCID for doses higher than 150 mcg in Trial B2334 (300 and 600 mcg) and Trial B2335S, which calls into question any dose response with SGRQ. In Trial B2336, the active comparator salmeterol also reached the MCID at -4.2. Since salmeterol has not been demonstrated to consistently benefit SGRQ, this suggests that the trial may have resulted in larger differences from placebo than expected.

Evaluating the SGRQ for the 75 mcg dose in Trials B2354 and B2355 shows a treatment difference of -3.8 and -3.6, respectively. The confidence intervals were wide, and between trial comparisons show marked overlap between the 75 and 150 mcg dose groups, suggesting that the results are statistically similar despite different point estimates. Likewise, as discussed in Dr. Dongmei Liu's statistical review, a responder analysis showed little difference between 75 mcg and 150 mcg, with similar percentages of patients meeting the MCID in both dose groups.

#### 4.1.6 Other Endpoints

There were a multitude of nonprimary endpoints evaluated for indacaterol, notably tFEV1 at Day 2, tFEV1 after 12 and 26 weeks, peak FEV1 in first 4 hours, serial FEV1 over 24 hours, morning and evening PEF and these endpoints provided supportive evidence of the efficacy of indacaterol. However any conclusions regarding the validity of the data must be examined qualitatively as no statistical adjustments were made for the multiple comparisons of the many endpoints.

#### FEV1 AUC

The standardized AUC measurements for FEV1 (between 5 min- 1 hr and between 5 min-4 hr) after 12 weeks were significantly greater with indacaterol 75 mcg (B2354 and B2355) and 150 mcg (B2336)

compared with placebo (both  $p < 0.001$ ). AUC values were also significantly higher with salmeterol vs. placebo ( $p < 0.001$ ).

### **Rescue Medication Use**

Both indacaterol 75 mcg and 150 mcg demonstrated statistically significant improvements over placebo in rescue medication use.

### **TDI**

Both the indacaterol 75 mcg and 150 mcg treatments in B2354 and B2336, respectively demonstrated statistically significant improvements in the TDI. In B2355 the TDI score difference was not statistically significant.

#### **4.1.7 Subpopulations**

Subgroup analyses for age, sex, race, COPD severity, smoking history, and ICS use at baseline, were performed for trough FEV1 after 12 weeks of treatment for trials B2355, B2354 and B2336. Since the population for the studies was about 80- 94% caucasian, it was difficult to make conclusions about the racial subgroups.

Males had higher trough FEV1 values at Week 12 than for females in the indacaterol 75 mcg and indacaterol 150 mcg treatment groups by approximately 30 mL. Patients without ICS use had a higher trough FEV1 at Week 12 in the indacaterol, 75 mcg (0.04 L) and indacaterol 150 mcg (0.03 L) treatment groups.

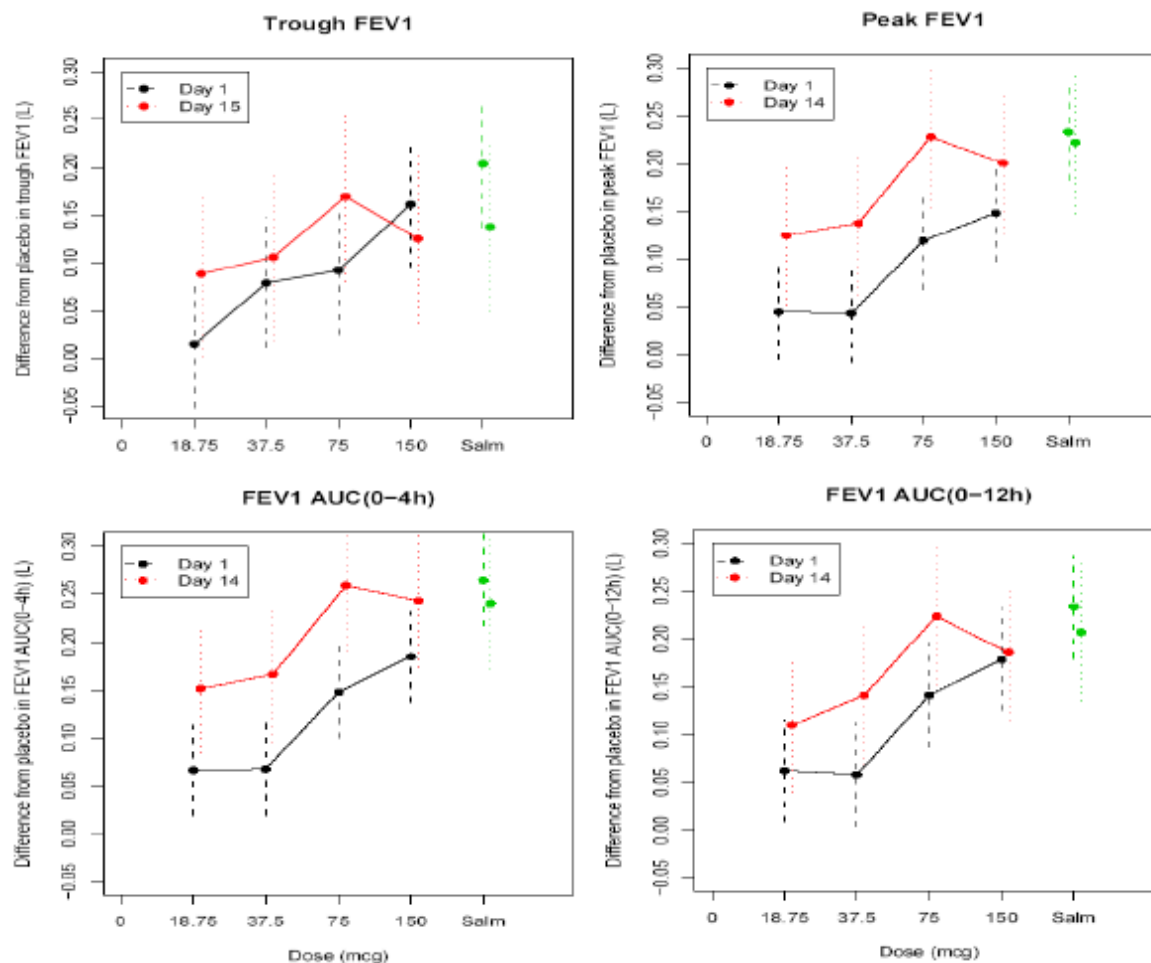
There was little difference in FEV1 response based on COPD severity (moderate/mild versus severe), age  $< 65$  vs.  $\geq 65$ , and ex-smokers versus current smokers. The results do not support the Sponsor's claim that the higher dose, indacaterol 150 mcg may provide additional benefit in severe patients. See individual study reviews for additional information.

#### **4.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

##### **Dose selection**

In addition to the data for trough FEV1, review of other FEV1 variables can inform dose selection. Using the data from Trial B2357 (dose ranging trial in patients with asthma), trough FEV1, peak FEV1, FEV1 AUC0-4hr, FEV1 AUC0-12hr, and serial FEV1 measurements were evaluated. As demonstrated in Figure 19 below, the 75 mcg dose has the largest effect on all four bronchodilator assessments highlighted. The Day 1 (black) curves show a characteristic dose response profile with the largest effect seen with the highest dose (150 mcg). By steady state however, the Day 14/15 curves reveal a maximum effect with the 75 mcg dose and the highest dose not exhibiting the peak effect. The two lowest doses, 18.75 and 37.5 are not very different (slope) in their bronchodilatory effects with the exception of tFEV1 on Day 1.

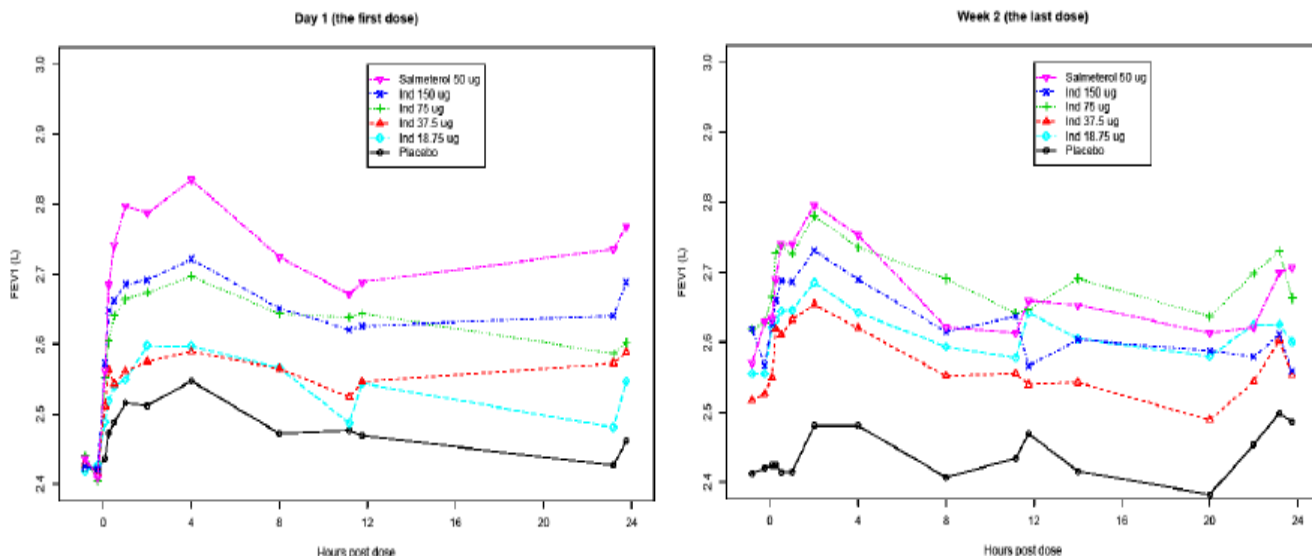
**Figure 19 Protocol B2357, Dose response curves**



Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

The figure below shows the dose response curves over time generated by our biostatistician, Dr. Liu. The curves measuring FEV1 on Day 1 demonstrate the greatest magnitude of effect for most time points, particularly after the first hour by salmeterol. In terms of indacaterol, the 150mcg dose and the 75mcg dose had similar FEV1 profiles on Day 1, while the two lowest doses of indacaterol (18.75mcg and 37.5mcg) have a noticeably smaller effect of FEV1. Similar to the discussion above, by week 2 the FEV1 profile of 75mcg dose was numerically greater than the 150 mcg dose. Also of note, the dose response over time curves for the two lower doses at two weeks also changed their pattern as shown in Figure 20, now with both curves shifting upwards consistent with a greater bronchodilatory effect.

**Figure 20 B2357 FEV1 profiles comparison**



Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

These data show that the indacaterol 75 mcg dose showed the most benefit compared to placebo for the primary endpoint, trough FEV1 (tFEV1) at Day 15. Although the 150 mcg indacaterol dose had a larger improvement than 75 or 37.5 mcg after 1 day of treatment, this advantage was lost by Day 14. In this trial, the 37.5 mcg and 18.75 mcg doses offered suboptimal bronchodilator effect on Day 1.

### Dosing frequency

As indacaterol is proposed for once daily dosing, which is novel for a LABA, sufficient data is necessary to support to once daily dosing. The Agency requested the Applicant explore alternate dosing intervals. Study B2223 compared QD, BID, and QOD dosing regimens for the same nominal dose in patients with asthma. Data from Study B2223 demonstrated no statistical difference between the three dosing regimens examined and supports the proposed once daily dosing interval. The results for trough FEV1 are shown in the table below.

**Table 74 Protocol B2223 Change from baseline in trough FEV1 on Days 15/16 (PD analysis set)**

PD parameter	Treatment	Contrast with placebo		
		Mean	Lower 95% CI	Upper 95% CI
Trough FEV <sub>1</sub> (L)	37.5 µg b.i.d	0.160	0.036	0.284
	75 µg q.d	0.202	0.077	0.327
	150 µg q.o.d	0.203	0.077	0.329

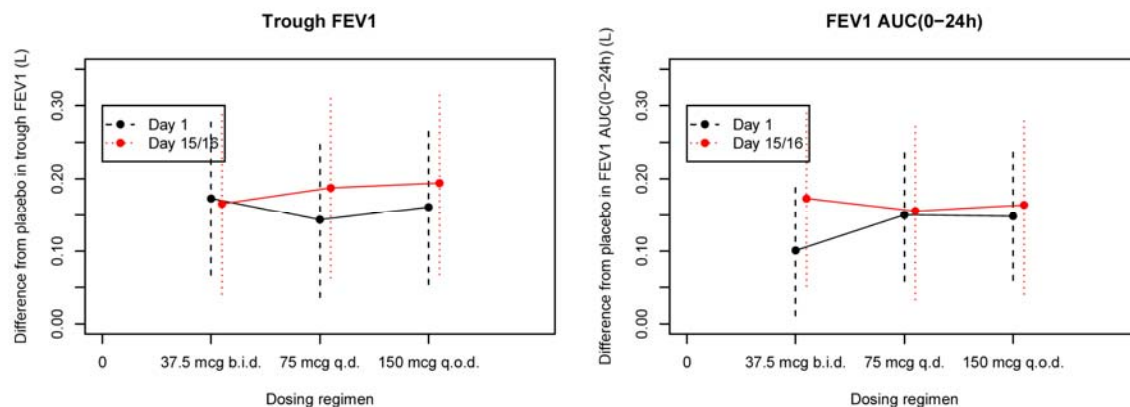
Source: Table 2 CQAB149B2223 Clinical Study Report

Refer to the Figure 21 which displays the trough FEV1 as well as the FEV1 AUC (0-24 hr) for the different dosing regimens and suggests the once daily dosing regimen is supported. The peak/trough ratio for the 37.5 mcg b.i.d regimen was close to 1.0 on day 1 with the 90% CI including 1.0, on days 15/16 it was 1.08 with 90% CI above 1.0. The peak/trough ratio was 1.10 for 75 mcg q.d dosing and 1.13 for 150 mcg q.o.d dosing on both day 1 and days 15/16.

**Reviewer Comment:**

*Limitations to the peak-to-trough analysis are due to the trough FEV1 measures influenced by the normal diurnal rhythm of pulmonary fluctuations resulting in an increase in FEV1 in the early waking hours in addition to the drug effect.*

**Figure 21 B2223 Dosing frequency**

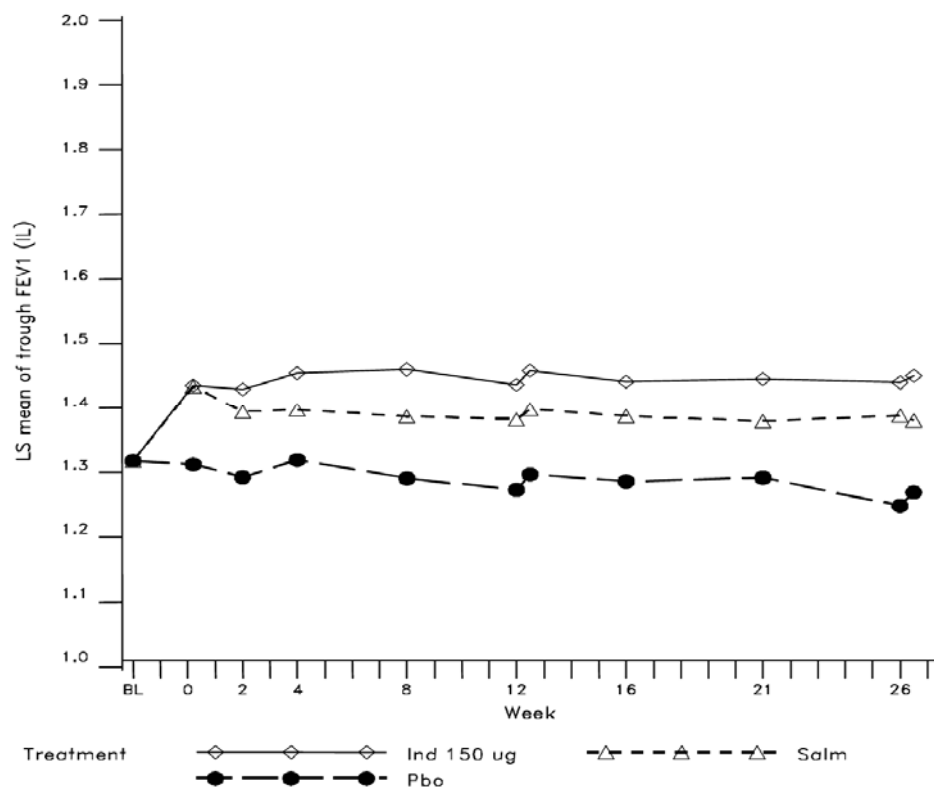


Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

#### 4.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

To evaluate the persistence of efficacy/tolerance claim proposed by the Applicant, examination of the FEV1 response over long term use of indacaterol is necessary. The figure below displays the trough FEV1 (L) over 26 weeks of treatment and shows that the trough FEV1 for indacaterol 150mcg is maintained over the 26 weeks of treatment.

**Figure 22 Protocol B2336 Least squares means of trough FEV1 (L) over 26 weeks of treatment (ITT population)**



Source: Figure 11-2 Study No. CQAB149 B2336 Clinical Study Report

#### 4.1.10 Additional Efficacy Issues/Analyses

##### Onset of Action

The Applicant has proposed an onset of action claim, which is not unusual as many bronchodilators have onset of action claims. Serial spirometry data in Trials B2355 and B2354 is shown in the table below. at the 5 min time point on Day 1, the magnitude of the improvements in FEV1 between indacaterol 75 mcg and placebo was 0.10 L and was statistically significant ( $p < 0.001$ ) and represented 69% of the trough FEV1 on Day 85 refer to Figure 23 for details. In B2354, it was 0.09 L and also statistically significant ( $p < 0.001$ ).

**Figure 23 Analysis of FEV1 (L) 75 mcg indacaterol vs. placebo at each time point, by visit (FAS)**

Analysis of FEV1 (L) 75 mcg indacaterol vs. placebo at each time point, by visit (FAS)									
B2355					B2354				
Time point		Treatment difference (L)	95% CI	p-value	Time point	Treatment difference (L)	95% CI	p-value	
Day 1	5 min	0.10	(0.08, 0.12)	< 0.001	Day 1	5 min	0.09	(0.07, 0.10)	< 0.001
	30 min	0.12	(0.10, 0.15)	< 0.001		30 min	0.12	(0.10, 0.14)	< 0.001
	1 hr	0.12	(0.09, 0.15)	< 0.001		1 hr	0.11	(0.09, 0.13)	< 0.001
	2 hr	0.12	(0.09, 0.15)	< 0.001		2 hr	0.13	(0.10, 0.15)	< 0.001
	4 hr	0.13	(0.09, 0.16)	< 0.001		4 hr	0.12	(0.10, 0.15)	< 0.001
Day 2	23 hr 10 min	0.08	(0.04, 0.11)	< 0.001	Day 2	23 hr 10 min	0.08	(0.05, 0.10)	< 0.001
	23 hr 45 min	0.07	(0.04, 0.11)	< 0.001		23 hr 45 min	0.08	(0.06, 0.11)	< 0.001
Day 84	5 min	0.16	(0.11, 0.20)	< 0.001	Day 84	5 min	0.18	(0.15, 0.22)	< 0.001
	30 min	0.19	(0.14, 0.23)	< 0.001		30 min	0.18	(0.14, 0.22)	< 0.001
	1 hr	0.18	(0.14, 0.23)	< 0.001		1 hr	0.18	(0.14, 0.21)	< 0.001
	2 hr	0.19	(0.15, 0.24)	< 0.001		2 hr	0.17	(0.14, 0.21)	< 0.001
	4 hr	0.17	(0.12, 0.21)	< 0.001		4 hr	0.15	(0.11, 0.19)	< 0.001
Day 85	23 hr 10 min	0.15	(0.10, 0.19)	< 0.001	Day 85	23 hr 10 min	0.11	(0.07, 0.15)	< 0.001
	23 hr 45 min	0.14	(0.10, 0.19)	< 0.001		23 hr 45 min	0.12	(0.07, 0.16)	< 0.001



## 5. Review of Safety

### Safety Summary

The action letter dated October 16, 2009 for the original cycle specified a lack of substantial evidence of safety to support the originally proposed 150 and 300 mcg doses in COPD as one explanation for the complete response action. Key safety issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma related deaths compared to salmeterol in patients with asthma. While there is substantial evidence of adverse respiratory events associated with the use of LABAs in patients with asthma<sup>12</sup> (SMART), it is unclear if this safety concern applies to COPD patients. Furthermore, since the Sponsor is requesting approval for 2 doses for the treatment of COPD, they are tasked in the current cycle to balance the safety data to show no unacceptable safety disadvantages with the higher dose.

Exposure to indacaterol 75 mcg was less than ideal. As described in the E1A-Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions, March 1995, "The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADEs over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300 to 600 patients should be adequate." Furthermore, "100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base." The mean exposure of 75 mcg indacaterol was 85.5 days and for 150 mcg indacaterol it was 120 days. Therefore the sponsor is relying on the extrapolation of the safety data for the 75 mcg dose to the 150 mcg dose. The safety datasets were categorized by 3-, 6-, and 12- month duration of exposure as well as a "COPD safety" population and a "COPD tiotropium combination safety" population. Evaluation of the demographics of the datasets revealed a mean age range of 63-65 years across the indacaterol treatment groups with the majority of patients being caucasian males. The median duration ranged from 4- 7 years across the safety populations and the degree of reversibility was balanced with the mean FEV1% predicted above 50%.

There were a total of 9441 patients in the 3 month COPD safety dataset, 4764 of whom received indacaterol in the following dose groups—75 mcg (N=449), 150 mcg (N=2611), 300 mcg (N=1157), and 600 mcg (N=547). Twelve month data is available for 2142 patients, 1152 of whom received indacaterol in the following dose groups—150 mcg (N=144), 300 mcg (N=583), and 600 mcg (N=425). The sponsor proposes to use long-term (12-month) safety data from the 150 mcg dose group to support safety for the 75 mcg group. The longest duration of exposure for the proposed 75 mcg once daily dose is 3 months.

The most common AEs in both the 3 and 12 month safety datasets were COPD exacerbation, nasopharyngitis, cough, headache, upper respiratory infection, and muscle spasms. Both cough and muscle spasms occurred more frequently in the indacaterol groups than in placebo or active comparator groups. Six Phase 3 studies proactively solicited information on post-inhalational cough that occurred at the study center after dosing. Based on this analysis, post-inhalational cough occurred in 23 to 31% of indacaterol treated patients compared to 3 to 6% of placebo treated patients. A small dose effect was seen, with 23% of patients coughing in the 75 mcg group compared to 31% in the 600 mcg group, with the odds ratio compared to placebo of 7.75 (95% CI 5.07, 11.86) and 17.62 (95% CI 13.57, 22.87), respectively. However, the cough was generally of very short duration ( $\leq 15$  seconds), did not cause discontinuation from the trial, and did not cause a drop in FEV1.

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<sup>12</sup> Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*, 2006 Jan; 129(1):15-26

In the original submission, there were more cardiac or cerebrovascular AEs and serious adverse events (SAEs) in the indacaterol treatment groups compared to placebo (3.4% indacaterol 300 mcg versus 0.9% placebo SAEs) in the 12 month safety evaluation. The 12 month safety data from the complete response, which includes data from the 26 week safety extension to the adaptive design study (Protocol B2335SE), shows that patients with SAEs in any organ system are balanced in the 150 mcg dose group compared to placebo (10.4% of patients in the indacaterol 150 mcg group compared to 11.0% in placebo). There were 0.69% of patients in the 150 mcg indacaterol group with cardiac or cerebrovascular SAEs compared to 1.4% in the placebo group.

The second safety concern raised by the original submission was asthma related death, with two deaths in the 268 patient 300 mcg dose group of a single 26 week asthma study. The Sponsor was asked to conduct a blinded adjudicated analysis comparing indacaterol treated patients to controls by evaluating AE of interest: all cause death, respiratory-related deaths, respiratory-related, respiratory related hospitalizations, pneumonia-related death and pneumonia-related intubation. Results of the meta-analysis are pending at the time of this review.

## **5.1 Methods**

### **5.1.1 Studies/Clinical Trials Used to Evaluate Safety**

The safety review includes a separate analysis of the asthma trials including those in the original submission. See Section 5.6 Additional Safety Evaluations. The data from the two week dose finding trials B2356, B2357 and the 2 week dose regimen trial, B2223 were not included in the Sponsor's pooled safety analyses. The Sponsor suggests that the different doses and dose regimens not used in other trials, the short duration of treatment time and the different population (asthmatics) would not add to the quality of the pooled safety evaluation. The safety results of these trials were reviewed in the individual trial sections and will also be summarized in Section 5.6 Additional Safety Evaluations.

- B2356, 2 weeks of treatment with indacaterol 18.75 mcg q.d., 37.5 mcg q.d., 75 mcg q.d., 150 mcg q.d., placebo, or salmeterol 50 mcg b.i.d in patients with moderate to severe COPD.
- B2357, 2 weeks of treatment with indacaterol 18.75 mcg q.d, 37.5 mcg q.d, 75 mcg q.d, 150 mcg q.d, placebo, or salmeterol 50 mcg b.i.d in patients with persistent asthma.
- B2223, 2 weeks of treatment with indacaterol 37.5 mcg b.i.d, 75 mcg q.d, 150 mcg q.o.d, or placebo, in patients with persistent asthma.

The pivotal COPD trials submitted during this cycle, B2354, B2355 and B2336 were the primary source of safety data that were reviewed.

- B2355, 12 weeks of treatment with indacaterol 75 mcg q.d, or placebo (double-blind)
- B2354, 12 weeks of treatment with indacaterol 75 mcg q.d, or placebo (double-blind)
- B2336, 26 weeks of treatment with indacaterol 150 mcg q.d, salmeterol 50 mcg bid or placebo (double-blind)

The Sponsor's pooled analyses included data from trials submitted during the first cycle as well as 10 supportive trials added during this cycle. Summaries of B2341 and B2351, the largest of the supportive trials, may be found at the end of the individual trial summaries.

- B2346, 12 weeks of treatment with indacaterol 150 mcg q.d, or placebo (double-blind)

- B2334, 52 weeks of treatment with indacaterol 300 mcg q.d, 600 mcg q.d, placebo (double-blind) or formoterol 12 mcg bid (double-blind) and providing long-term safety data
- B2335S, 26 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d, placebo (double-blind) or tiotropium 18 mcg q.d, (open-label)
- B1302, 12 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d or placebo (double-blind)
- B2333, 26 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d or placebo (double-blind)
- B2349, 12 weeks of treatment with indacaterol 150 mcg q.d, or salmeterol 50 mcg b.i.d (double-blind)
- B2350, 12 weeks of treatment with indacaterol 150 mcg q.d, or tiotropium 18 mcg q.d (double-blind)
- B2335SE, 52 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d, or placebo (double-blind) - patients were included only after completion of B2335S.
- B2311, 21 days of treatment in each period with indacaterol 300 mcg q.d, or placebo (double-blind).
- B2331, 14 days of treatment in each period with indacaterol 150 mcg q.d, 300 mcg q.d, or placebo (double-blind); tiotropium 18 mcg q.d was used as a blinded active control (using third party blinding).
- B1303, 24 week interim analysis of a 52 week treatment with indacaterol 300 mcg q.d and salmeterol 50 mcg b.i.d.
- B2341, 12 weeks of treatment with indacaterol 150 mcg q.d via Concept1 device plus tiotropium 18 mcg q.d via Handihaler, vs. placebo via Concept1 device plus tiotropium 18 mcg q.d via Handihaler (double-blind)
- B2351, 12 weeks of treatment with indacaterol 150 mcg q.d via Concept1 device plus tiotropium 18 mcg q.d via Handihaler, vs. placebo via Concept1 device plus tiotropium 18 mcg q.d via Handihaler (double-blind)

Also included in the safety analysis were the PSUR-1 ranging from November, 2009 to May, 2010, additional postmarketing reports and the Mexico Patient Support Program. The metaanalysis of respiratory related adverse events particularly intubations, hospitalizations and deaths was pending at the time of this review.

### 5.1.2 Categorization of Adverse Events

Adverse events were captured into 2 data sets, the AE case report forms (CRF) and the COPD exacerbation-dedicated CRFs. The analysis of AEs involved coding of verbatim terms to preferred terms of the MedDRA medical dictionary system (version 13.0). Treatment emergent AEs (TEAEs) were defined by the Sponsor as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first dose of study drug and up to 7 days after the last dose for non-serious AEs, or up to 30 days after the last dose for SAEs. An exception was for deaths occurring in the 30 days after the last dose in B2335S (these data were in the database for the ongoing extension study B2335SE) were described separately. Medical comorbidities present at baseline were considered AEs if they worsened after starting the study. Abnormal laboratory values or test results were recorded as AEs only if they induced clinical signs or symptoms, were considered clinically significant, or required therapy.

Coding of COPD exacerbations as well as the verbatim term “worsening of COPD” from an investigator were to the preferred term “chronic obstructive pulmonary disease”. The Sponsor also highlighted that if

these “worsening of COPD” AEs did not meet the definition of COPD exacerbation, the AEs were not reported on the COPD exacerbation CRF.

All other events were coded based on preferred term. There was no grouping of similar terms for adverse events of interest, such as cardiovascular. For example, acute myocardial infarction and myocardial infarction were coded separately. Pneumonia was coded under the System Organ Class (SOC) of infections and infestations rather than in the respiratory category. Similar to MI, this under-counts the grouped AE of pneumonia because events for various types of pneumonia may be listed separately depending on the verbatim term listed by the investigator.

For the analysis of cardiac events, the sponsor prospectively grouped events by Standard MedDRA Queries (SMQs) based on published SMQ version 11.0 “narrow”, for the disorders “cardiac failure”, “ischemic heart disease”, and “cerebrovascular disorders” and “cardiac arrhythmias” (broad). The search did not include CV death, i.e. the preferred terms cardiac death, sudden cardiac death and sudden death.

The definition of COPD exacerbation changed during the development program. The original trials included a definition of:

- a new onset or worsening of more than one respiratory symptom (i.e. dyspnea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days,

***plus at least one of the following:***

- documented change or increase in COPD-related treatment due to worsening symptoms (e.g. steroids/antibiotics/oxygen),
- documented COPD-related hospitalizations or Emergency Room visits.

However, in the trials B2341, B2349, B2350 and B2351 conducted more recently, the definition of COPD exacerbation was updated:

worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

***or***

worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- cold (nasal discharge and/or nasal congestion)
- fever without other cause
- increased cough
- increased wheeze

***and***

requiring treatment with systemic corticosteroids and/or antibiotic.

### **5.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

The datasets evaluated by the Sponsor were categorized into the following populations for an integrated summary of safety:

- “COPD 3-month” safety population containing pooled 3-month data from phase III studies B2346, B2349, B2350, B2354, B2355, B1302 (all data), also studies B2333, B2334, B2335S, B2335SE, and B2336 (only the first 3 months).
- “COPD 6 month”, the safety population containing pooled 6-month (26 week) data from phase III studies B2333, B2336, and B2335S, (all data), also studies B2335SE, and B2334 (each up to day 182).
- “COPD 12 month” safety population containing 52 week, pivotal, phase III studies B2334 and B2335SE.
- “COPD safety” populations containing all data from controlled studies in COPD patients of at least 3 months duration, these being B2333, B2334, B2335S, B2335SE, B2336, B2346, B2349, B2350, B2354, B2355, and B1302. The datasets included 449, 2611, 1157 and 547 patients who received treatment with indacaterol 75, 150, 300 and 600 mcg q.d, respectively.
- COPD Tiotropium combination safety population containing pooled data from two studies with indacaterol 150 mcg administered concurrently with open-labeled tiotropium, double-blind, controlled by tiotropium, parallel design, duration of total exposure to study drug of 3 months, studies B2341 and B2351.
- All treated subjects population containing pooled data from all completed COPD, asthma and healthy volunteer studies of indacaterol regardless of study design, excluding post-inhalation cough studies A2222 and D2301, pediatric study C2101, 3 ADME studies A2106, A2214 and A2223, device handling study B2353, formulation/delivery study B2222, special safety single dose study B2102, and studies B2356, B2357, and B2223.

These pooled data contain overlapping populations (i.e. the 3 month population includes patients who may also be included in the 6 month population). The COPD safety population included patients from all COPD trials with a treatment duration of at least 3 months. The COPD tiotropium combination safety population was analyzed because tiotropium is commonly used in the COPD indication, and it is of interest whether the safety profile of concurrently administered indacaterol and tiotropium is likely to differ from tiotropium alone. The dose finding trials, B2356, B2357 and B2223 were not included in the pooled safety analyses because of the doses and dose regimens investigated in these trials and not in others, the short duration and the different target population those with asthma in trials B2357 and B2223. Some special safety topics were identified due to particular concern. Subsets of the events in these special categories include the particularly focused on cardio- and cerebrovascular AEs.

## **5.2 Adequacy of Safety Assessments**

### **5.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

In the COPD safety population, this dataset included 4,764 patients who received indacaterol treatment: 449 received 75 mcg; 2,611 received 150 mcg; 1,157 received 300 mcg and 547 received 600 mcg. The number of patients with COPD and exposure to indacaterol at different doses is summarized in Table 75 below. Of note, the two week dose finding trials, B2357, B2356 and B2223 were not included in these analyses and the extent of exposure for these trials is described in the Safety Results section of the reviews for the individual trials. The largest numbers of patients were treated with the originally proposed doses of 150 mcg and 300 mcg.

**Table 75 Exposure to indacaterol by safety population group**

Safety population	Indacaterol treatment groups (N)			
	75 mcg	150 mcg	300 mcg	600 mcg
COPD 3- month	449	2611	1157	547
COPD 6- month	127	933	1041	547
COPD 12- month	---	144	583	425

Source: Section 1.2 CTD 2.7.4 Summary of Clinical Safety

**Reviewer Comment:**

*For an acceptable safety assessment of a chronically administered drug for the treatment of a non-life threatening condition, ICH guidelines recommend evaluating a minimum of 300 patients for a 6 month duration and 100 for a 3 month duration, provided no concerning safety signals are identified. One-hundred-twenty-seven patients were exposed to the 75 mcg dose for 6 months and no patients were exposed for 12 months. However, 77 patients were exposed to indacaterol 150 mcg for ≥52 weeks and 57 were exposed for 44-52 weeks, giving over a hundred patients with nearly 12 months of data. Exposure numbers were much higher for the higher dose groups of 300 and 600 mcg. See Table 76.*

The exposure of indacaterol amongst the total COPD safety population was heterogeneous across the different treatment groups. This was due to particularly to the variation of duration across the different trials. Data for one of the two proposed doses, 75 mcg group, for example, was drawn from the 3-month studies B2354 and B2355, and the dose-ranging Stage 1 of B2335S, whereas the data for the 150 and 300 mcg groups were drawn from a greater number of trials, with duration of up to 12 months. The Sponsor therefore adjusted the safety data for the COPD safety population for duration of exposure, for comparison across treatment group.

**Table 76 Duration of exposure to study drug after randomization in the COPD safety population**

	Indacaterol treatment groups				Control treatment groups			
	75 mcg	150mcg	300mcg	600mcg	For	Tio	Salm	Pbo
<b>Exposure (days)</b>								
mean	N=449	N=2611	N=1157	N=547	N=556	N=1214	N=895	N=2012
sd	85.5	120.3	232.7	263.4	260.3	107.7	112.2	167.7
min- max	25.81	74.61	123.27	135.27	133.46	49.36	51.45	115.93
	2 - 179	1 - 385	1 - 420	1 - 407	1 - 397	1 - 208	1 - 215	1 - 403
<b>Patient-years</b>	105.06	859.72	736.97	394.49	396.21	357.97	274.93	923.60
<b>Exposure-n(%)</b>								
≥ 3 months	90 (20.04)	257 (9.84)	132 (11.41)	87 (15.90)	101 (18.17)	161 (13.26)	83 (9.27)	204 (10.14)
≥ 6 months	0	583 (22.33)	539 (46.59)	191 (34.92)	190 (34.17)	240 (19.77)	230 (25.70)	687 (34.15)
≥ 12 months	0	77 (2.95)	256 (22.13)	167 (30.53)	168 (30.22)	0	0	240 (11.93)

Source: Adapted from Table 5-2 CTD 2.5 Clinical Overview

**Demographics**

Demographic information for the multiple indacaterol doses in the COPD 3- month, 6- month and 12- month safety population was analyzed. Conclusions about age, gender and race were common across all 3 populations. The mean age was similar across treatment groups, about 63- 65 years of age. Gender distribution was also skewed with the predominate gender being male across all groups with different

ratios between groups. The majority of patients were caucasian, with so few other races, no comment can be made regarding generalizability of trends based on race. See Table 77.

**Table 77 Demographics in COPD 3- month and 6- month populations**

	<b>Indacaterol treatment groups</b>				<b>Control treatment groups</b>			
	75 mcg n=449	150 mcg n=2611	300 mcg n=1157	600 mcg n=547	For n=556	Tio n=1214	Salm n=895	Pbo n=2012
<b>COPD 3 month</b>								
Age mean (years)	63.5	63.5	64.3	63.1	64	63.6	63.3	63.7
Gender- n (%)								
Male	248 (55.23)	1815 (69.51)	908 (78.48)	401 (73.31)	418 (75.18)	807 (66.47)	664 (74.19)	1436 (71.37)
Female	201 (44.77)	796 (30.49)	249 (21.52)	146 (26.69)	138 (24.82)	407 (33.53)	231 (25.81)	576 (28.63)
Race- n (%)								
Caucasian	414 (92.20)	2026 (77.59)	772 (66.72)	503 (91.96)	511 (91.91)	1110 (91.43)	736 (82.23)	1502 (74.65)
Black	19 (4.23)	56 (2.14)	13 (1.12)	6 (1.10)	3 (0.54)	18 (1.48)	11 (1.23)	38 (1.89)
Asian	11 (2.45)	462 (17.69)	348 (30.08)	15 (2.74)	13 (2.34)	52 (4.28)	120 (13.41)	415 (20.63)
Other	5 (1.11)	67 (2.57)	24 (2.07)	23 (4.20)	29 (5.22)	34 (2.80)	28 (3.13)	57 (2.83)
	75 mcg ---	150 mcg n=144	300 mcg n=583	600 mcg n=425	For n=434	Tio ---	Salm ---	Pbo n=556
<b>COPD 12 month</b>								
Age mean (years)	---	62.5	63.6	62.9	63.6	---	---	63.1
Gender- n (%)								
Male	---	87 (60.42)	437 (74.96)	327 (76.94)	348 (80.18)	---	---	433 (77.88)
Female	---	57 (39.58)	146 (25.04)	98 (23.06)	86 (19.82)	---	---	123 (22.12)
Race- n (%)								
Caucasian	---	120 (83.33)	526 (90.22)	393 (92.47)	400 (92.17)	---	---	502 (90.29)
Black	---	4 (2.78)	6 (1.03)	1 (0.24)	0 (0.00)	---	---	3 (0.54)
Asian	---	19 (13.19)	27 (4.63)	8 (1.88)	7 (1.61)	---	---	31 (5.58)
Other	---	1 (0.69)	24 (4.12)	23 (5.41)	27 (6.22)	---	---	20 (3.60)

**Source: Adapted from Tables 1-18, 1-19 and 1-20**

#### **Disease Characteristics**

Disease characteristics such as baseline duration, severity of COPD, smoking status, use of ICS, medical history, concomitant disease characteristics and use of concomitant medications were included for

subgroup analyses in the 3 safety populations. The patterns of distribution of baseline disease characteristics were similar across the 3 safety populations.

#### ***COPD 3- month safety population***

Overall, disease characteristics were balanced across the treatment groups. The median duration of COPD ranged from 4.6 to 5.8 years with >94% of patients across treatment groups categorized as moderate to severe. The degree of reversibility was balanced with the mean FEV1% predicted (after SABA) above 53% in all treatment groups. The mean percent increase after SABA ranged from 10-19%. The mean percent increase ranged from 11% for salmeterol to 19% in the 75 mcg indacaterol group. The majority of patients were on ICS and were ex smokers. Mean lifetime number of pack years ranged from 40 to 57 years across all treatment groups. The presence of comorbidities such as CCV, hypertension or hyperlipidemia at baseline was proportionate across all groups.

#### ***COPD 6- month safety population***

Disease characteristics were balanced across the safety populations. The median duration of COPD ranged from 4.8 to 5.7 years with >94% of patients across treatment groups categorized as moderate to severe. The degree of reversibility was balanced with the mean FEV1% predicted (after SABA) was above 50% in all treatment groups. The mean percent increase after SABA ranged from 12-17%. The mean percent increase ranged from 13% for formoterol to 15% between all treatment groups except indacaterol 75 mcg with the highest of 17%. ICS use ranged from 42% in 75 mcg group to 50% in formoterol group. Most patients were ex-smokers; the lowest percent was in 75 mcg (52%) and the highest in the 300 mcg (60.85%) treatment group. Mean lifetime usage was >40 pack years in all treatment groups with the highest mean usage found in the indacaterol 75 mcg q.d. group (54 pack years) and the lowest (43 pack years) in the salmeterol group. The presence of comorbidities such as CCV, hypertension or hyperlipidemia at baseline was proportionate across all groups.

#### ***COPD 12- month safety population***

Similar to the 3- month and 6- month safety population, the disease characteristics were balanced across the treatment groups. The median duration of COPD ranged from 6.8 to 7.3 years with >93% of patients across treatment groups categorized as moderate to severe. The degree of reversibility was balanced with the mean FEV1% predicted (after SABA) above 52% in all treatment groups. The mean percent increase after SABA ranged from 12-18%. The mean percent increase ranged from 13% for formoterol to 15% between all treatment groups. ICS use ranged from the lowest of 34% in 75 mcg group to 53% in the indacaterol group. Most patients except the 75 mcg group were ex smokers. Mean lifetime usage was 48 to 54 pack years across all treatment groups. The presence of comorbidities such as CCV, hypertension or hyperlipidemia at baseline was proportionate across all groups.

### **5.2.2 Explorations for Dose Response**

Four doses of indacaterol (75 mcg, 150 mcg, 300 mcg and 600 mcg once daily) were assessed in large Phase III clinical trials with the 150, 300 and 600 mcg doses studied for up to 12 months. The safety evaluation for the dose response trials are discussed in the individual sections (B2357, B2356, B2223)..

### **5.2.3 Special Animal and/or In Vitro Testing**

No special animal or in vitro safety assessments were submitted as part of this application.

### **5.2.4 Routine Clinical Testing**

Routine clinical testing conducted in the submitted trials was adequate to assess for systemic effects of indacaterol. Assessments included measurements of vital signs, clinical laboratory testing (with particular focus on potassium, glucose, and LFTs), and ECGs, notably during baseline, time of peak effect and at serial time points post dosing.

### **5.2.5 Metabolic, Clearance, and Interaction Workup**



The metabolic, clearance and drug interaction assessments conducted were adequate. Please see the review by the Clinical Pharmacology reviewer, Dr. Ying Fan. Two trials (B2341 and B2351) were conducted investigating the bronchodilator effects of indacaterol when combined with an often prescribed bronchodilator for COPD, tiotropium. The two 12 week, randomized, controlled trials demonstrated that indacaterol provides additional bronchodilator benefit in patients receiving a long-acting anticholinergic.

## **5.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

The known adverse events reported for LABAs include: anxiety, back pain, chest pain, muscle cramps and myalgia, diarrhea, dizziness, dyspnea, headache, insomnia, musculoskeletal pain, nasal congestion, nausea, peripheral edema, pruritis, rash, rhinitis, sinusitis, throat irritation, tremor, and upper respiratory tract infection. These as well as the established laboratory effects such as hypokalemia and hyperglycemia, effects of tachycardia and increased blood pressure as well as effects on QTc were adequately evaluated across the different indacaterol treatment groups.

## **5.3 Major Safety Results**

### **5.3.1 Deaths**

The fatal events included in the safety analysis conducted by the Sponsor were events which occurred after administration of the first dose of study drug up to and including the last dose [CTD 2.7.4 Summary of Clinical Safety Section 2.1.2.1.1]. Deaths occurring more than 30 days after the last dose or  $\leq 30$  days but not captured in the clinical database i.e. data submitted after database lock were not included in the clinical study database. Narratives for the subjects were reviewed. The deaths of only patients in an indacaterol treatment group are summarized below.

There were a total of 17 deaths of indacaterol treated patients reported, this number does not include 29 deaths from two ongoing trials. The COPD safety population included a total of 7 reported deaths in the indacaterol treatment group, 4 in the formoterol group, 4 in the tiotropium group, 1 in the salmeterol and 14 patients in the placebo group.

There were seven deaths in the indacaterol groups during the double-blind periods in the pivotal trials:

- Patient B2334-0165-00002 (indacaterol 600 mcg q.d.) was 66 year old male who developed gastric ulcer bleeding on Day 164 underwent surgical repair had a severe COPD exacerbation on Day 169 and died on Day 189 25 days after last dose.
- Patient B2334-0214-00004 (indacaterol 300 mcg q.d.) was a 57 year old male with a prior history of respiratory failure 5 months prior to death. The patient was taking concomitant budesonide when he developed a severe COPD exacerbation on Day 47 after a respiratory tract infection. On Day 84 he had a second COPD exacerbation with hyperinflation and 3 days after the last dose he had a cardiac arrest.
- Patient B2335S-0135-00006 (indacaterol 150 mcg q.d.) was a 52 year old male with a history of hypertension who developed cardiac failure on Day 113. He was treated with diclofenac and furosemide. Study medication was discontinued on Day 144 and the next day the patient was found dead at home.
- Patient B2335SE-0043-00046 (indacaterol 300 mcg q.d.) was a 66 year old male with a history of hypertension who on Day 232 developed sudden dyspnea and collapse en route to the hospital with unsuccessful CPR. The principal cause of death was identified as myocardial infarction.
- Patient B2336-0311-00037 (indacaterol 150 mcg q.d.) was a 67 year old male with a history of pedal edema since Day 28. He developed chest pain on Day 171 and was taken to the emergency department where he was declared dead due to sudden cardiac arrest.

- B2349-0403-00008 (indacaterol 150 mcg q.d.) was a 57 year old male with a history of 20 kg weight loss over the span of a few months. He was hospitalized on Day 38 for abdominal pain and was diagnosed with gastric cancer and thrombocytopenia. The patient died on Day 40 due to severe cardiopulmonary failure.
- B2349-0906-00004 (indacaterol 150 mcg q.d.) was a 74 year old male who developed a myocardial infarction on Day 16 and was found dead the following night 2 days after last dose.

Two deaths were reported in the indacaterol more than 30 days from last dose:

- Patient B2334-0376-00003 (indacaterol 600 mcg q.d.) was a 77 year old female who experienced a COPD exacerbation 85 days after the last dose.
- Patient B2334-0400-00027 (indacaterol 600 mcg q.d.) was a 65 year old male who was diagnosed with metastases lung & bone 51 days after the last dose

There were 2 deaths of patients on indacaterol and 1 patient on tiotropium reported after database lock:

- Patient B2205-0083-00005 (indacaterol 400 mcg q.d.) was a 64 year old female found dead at home on Day 40. An autopsy performed indicated that the patient died 29 days after last dose. The cause of death was labeled as pulmonary embolism
- Patient B2305-0031-00002 (indacaterol 300 mcg q.d.) was a 70 year old male with a history of hypertension and stroke who was discontinued due to a diagnosis of lung cancer with metastases to the brain. On Day 68 he was hospitalized with a stroke. On Day 132 (85 days after last dose) he died.

There were 2 deaths in the asthma study B2338 on indacaterol:

- Patient B2338-0549 -00003 (indacaterol 300 mcg q.d.) was a 75 year old female with a history of hypertension who suffered a cardiac arrest on Day 119, the day of her last dose. Cardiopulmonary resuscitation occurred, an ECG was compatible with infarction and life support was withdrawn on Day 129.
- Patient B2338-0099-00002 (indacaterol 300 mcg q.d.) was a 60 year old male with a past medical history of asthma who had a one day hospitalization for an acute asthma exacerbation 165 days into treatment. Four days later he developed an acute asthma exacerbation leading to death *en route* to the hospital.

The COPD tiotropium combination safety population had 7 fatal events reported, 4 for patients receiving indacaterol and tiotropium concurrently and 3 patients on tiotropium alone.

The 4 deaths of patients on the combination indacaterol 150 mcg plus open-label tiotropium HandiHaler, 18 mcg) were:

- Patient B2341-0104-00006 was a 67 year old male with a history of hypertension, CAD, CVA and myocardial infarction who was hospitalized on Day 33 due to a severe COPD exacerbation. The patient received the antibiotic ceftriaxone and 30 minutes later he developed tongue and facial edema, apnea and became pulseless CPR was not successful.
- Patient B2341-0305-00015 was a 58 year old male with a history of diabetes mellitus, hypertension and gastroesophageal reflux. Approximately 28 days after the patient's last study visit (Visit 9 = end of study) he was found dead in the bathroom.
- Patient B2341-0822-00018 was a 62 year old male who was found dead on Day 19, one day after the last dose. The death certificate identified acute myocardial infarction as the cause of death.
- Patient B2351-0509-00014 was a 74 year old female who was found dead on Day 73, one day after last dose. An autopsy identified atherosclerotic cardiovascular disease due to "natural causation (myocardial infarction)" as cause of death.

There were no deaths reported during the trial or within 30 days of last doses in the 2-week dose finding trials, B2356, B2357 and B2223. There was 1 death in the ongoing open label study B1303 and 28 deaths in ongoing study B2348 reported to Novartis as of July 28, 2010. Summaries are included in Table 78 below.

**Table 78 Summaries of deaths reported in ongoing studies with indacaterol monotherapy arm**

Study-center-patient	Age/ sex/ race	Treat- ment	Principal cause of death Description of event & medical history	Study day/ day after LD	Caus- ality †
B1303-0418-00002	77/M/As	Ind 300 µg	Sudden death	211/1	Susp
B2348-0001-00003	79/M/Ca	Blinded	Myocardial infarction	73	NS
B2348-0001-00005	64/M/Ca	Blinded	Completed suicide	184	NS
B2348-0001-00014	62/M/Ca	Blinded	Pneumonia	347	NS
B2348-0001-00032	57/M/Ca	Blinded	COPD	115	NS
B2348-0003-00005	67/M/Ca	Blinded	Pancreatic carcinoma metastatic	167/89	NS
B2348-0023-00031	73/M/Ot	Blinded	Sudden death	8	NS
B2348-0025-00006	74/F/Ot	Blinded	Death, dyspnea	48	NS
B2348-0087-00010	61/M/Ca	Blinded	Cardiac arrest	86	NS
B2348-0101-00001	78/M/Ca	Blinded	Multi-organ failure	99	NS
B2348-0150-00006	63/M/Ca	Blinded	Lung carcinoma cell type unspecified stage IV	6	NS
B2348-0176-00007	66/M/Ca	Blinded	Cardiac failure	Pre-dose	NS
B2348-0183-00006	55/M/Ot	Blinded	COPD	Unk	NS
B2348-0186-00008	62/M/As	Blinded	COPD	68	Susp
B2348-0187-00009	43/M/Ot	Blinded	Cardiopulmonary failure, COPD exacerbation, cardiomegaly, fibrosis, anemia	218	NS
B2348-0189-00004	73/M/Ot	Blinded	COPD exacerbation, lower RTI, fibrobronchiectasis lung, respiratory failure	NA	Susp
B2348-0189-00017	M/Unk/Ot	Blinded	Death	99	NS
B2348-0190-00035	60/M/Ot	Blinded	Death	141	NS
B2348-0190-00054	51/M/Ot	Blinded	Death	64	NS
B2348-0269-00002	69/F/Ca	Blinded	Pulmonary embolism	241	NS
B2348-0292-00021	63/M/Ca	Blinded	Cardiac arrest	144	NS
B2348-0294-00014	75/M/Ca	Blinded	COPD	530	NS
B2348-0315-00005	50/F/Ca	Blinded	Meningitis pneumococcal	40	NS
B2348-0424-00016	70/M/Ca	Blinded	Acute respiratory failure, COPD exacerbation, dyspnea, pneumonia	15	NS
B2348-0440-00015	Unk/M/Ca	Blinded	Aortic stenosis	346/7	NS
B2348-0455-00005	85/M/Ca	Blinded	Cardiac failure	80	NS
B2348-0635-00017	57/M/Ca	Blinded	Cardiac failure	150	NS
B2348-0642-00003	56/M/Ca	Blinded	N. recurrens paresis, disease progression	249	NS
B2348-0818-00008	72/M/Unk	NA	Sudden death	Screening	NS

Source: Table 2-35 CTD 2.7.4 Summary of Clinical Safety

*Reviewer comment:*

*Protocol B2348 is a 3000 patient one year trial enrolling patients with severe COPD and a history of exacerbation. Since this trial includes sicker patients and has a longer duration than most of the trials included in the safety database, it is not unexpected that there would be a greater number of deaths in the trial. Since the data are still blinded, the treatment distribution of these deaths is unknown.*

### 5.3.2 Nonfatal Serious Adverse Events

The SAEs reported in the safety analysis conducted by the Sponsor included events that occurred after administration of the first dose of study drug through to 30 days past the last dose [CTD 2.7.4 Summary of Clinical Safety Section 2.1.2.1.1]. Serious adverse events occurring more than 30 days after the last

dose or  $\leq 30$  days but not captured in the clinical database i.e. data submitted after database lock were not included. Narratives for the subjects were reviewed. The SAEs were categorized by the Sponsor into the same 3-, 6- and 12- month safety groups (not mutually exclusive) and summarized by SOC and preferred term below.

***COPD- 3 month safety population***

The frequency of SAEs in the COPD 3-month safety population was similar across the active treatment groups and placebo. The lowest rate was observed in the salmeterol group with 3% of patients reporting SAEs, the largest was 4.4% for placebo. Amongst the indacaterol doses, the rates of SAEs did not change with increasing doses: 3.3%, 3.8%, 3.3% and 3.1% for 75 mcg, 150 mcg, 300 mcg and 600 mcg. Across the different treatment regimens, the MedDRA System Organ Classes (SOCs) with the greatest rates include respiratory thoracic and mediastinal disorders and infections and infestations. The most commonly reported SAEs in the COPD 3-month group were COPD (which included disease progression as well as exacerbations) and pneumonias. Refer to Table 79 for details.

**Table 79 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)
<b>Preferred term</b>								
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

Source: Table 2.37, CTD2.7.4 Section 2.1.3.1 Summary of Clinical Safety

#### **COPD- 6 month safety population**

This dataset was derived from trials: B2333, B2335S, B2336 and up to 6 months of data from B2334 and B2335SE. The numbers of patients included in the evaluation were smallest for the indacaterol 75 mcg group (n= 127) and largest in the placebo group (n= 1,371). The SOC's with the largest percentage of SAEs include: respiratory, thoracic and mediastinal disorders; infections and infestations; cardiac disorders, nervous system disorders and gastrointestinal disorders. Many of the SAE rates observed in the active treatment groups were similar to placebo. See Table 80 for summary.

**Table 80 SAEs (n (%) of patients) by primary system organ class in COPD 6- month safety population**

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Patients with SAE(s)	9 (7.1)	76 (8.2)	75 (7.2)	34 (6.2)	45 (8.1)	34 (8.2)	19 (5.7)	109 (8.0)
<b>Primary system organ class</b>								
Respir., thoracic and mediastinal disorders†	4 (3.2)	25 (2.7)	26 (2.5)	7 (1.3)	18 (3.2)	8 (1.9)	6 (1.8)	42 (3.1)
Infections and infestations	3 (2.4)	17 (1.8)	15 (1.4)	5 (0.9)	13 (2.3)	9 (2.2)	9 (2.7)	27 (2.0)
Cardiac disorders	2 (1.6)	14 (1.5)	9 (0.9)	7 (1.3)	4 (0.7)	8 (1.9)	5 (1.5)	14 (1.0)
Nervous system disorders	1 (0.8)	6 (0.6)	7 (0.7)	0	3 (0.5)	3 (0.7)	0	9 (0.7)
Gastrointestinal disorders	1 (0.8)	5 (0.5)	3 (0.3)	7 (1.3)	2 (0.4)	3 (0.7)	2 (0.6)	9 (0.7)

Adapted from Table 2-40 CTD2.7.4 Section 2.1.3.1 Summary of Clinical Safety

The frequency of SAEs in the COPD 6-month safety population, ranged from 5.7% in the salmeterol group to 8.2% in the indacaterol 150 mcg and tiotropium treatment groups as detailed in Table 81. A dose response relationship is not apparent with the SAEs reported. However, these safety analyses did not include the lower doses of indacaterol. The most frequent preferred terms reported in the COPD 6-month safety population were COPD, pneumonia, angina, atrial fibrillation, upper respiratory tract infection and acute myocardial infarction. The preferred term, COPD had similar rates compared to placebo however pneumonia and upper respiratory tract infection had higher rates in some of the active treatment groups (i.e., 75 mcg) than placebo. See Table 81 for further details. There were 2 acute myocardial infarctions in the 150 mcg group, 1 in the 300 mcg indacaterol group, 1 in salmeterol and none reported in the placebo group.

**Table 81 SAEs affecting ≥ 2 patients in any treatment group by preferred term in COPD 6- month safety population**

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Patients with SAE(s)	9 (7.1)	76 (8.2)	75 (7.2)	34 (6.2)	45 (8.1)	34 (8.2)	19 (5.7)	109 (8.0)
<b>Preferred term</b>								
COPD †	3 (2.4)	25 (2.7)	24 (2.3)	7 (1.3)	17 (3.1)	7 (1.7)	4 (1.2)	39 (2.8)
Lower RTI	0	4 (0.4)	1 (0.1)	0	1 (0.2)	0	2 (0.6)	5 (0.4)
Angina pectoris	1 (0.8)	3 (0.3)	1 (0.1)	1 (0.2)	0	0	1 (0.3)	2 (0.2)
Atrial fibrillation	1 (0.8)	3 (0.3)	0	0	0	3 (0.7)	1 (0.3)	3 (0.2)
Pneumonia	1 (0.8)	3 (0.3)	4 (0.4)	1 (0.2)	3 (0.5)	4 (1.0)	3 (0.9)	4 (0.3)
Acute myocardial infarction	0	2 (0.2)	1 (0.1)	0	0	0	1 (0.3)	0
Cholelithiasis	0	2 (0.2)	1 (0.1)	0	1 (0.2)	0	0	1 (0.1)
Sinusitis	0	2 (0.2)	0	0	0	0	0	0
Upper RTI bacterial	1 (0.8)	2 (0.2)	4 (0.4)	0	1 (0.2)	0	2 (0.6)	5 (0.4)
Benign prostatic hyperplasia	0	1 (0.1)	0	1 (0.2)	0	0	0	2 (0.2)

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Coronary artery disease	0	1 (0.1)	2 (0.2)	2 (0.4)	0	0	2 (0.6)	1 (0.1)
Myocardial infarction	0	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	1 (0.3)	2 (0.2)
Sudden death	0	1 (0.1)	1 (0.1)	0	0	0	0	2 (0.2)
Cellulitis	0	1 (0.1)	0	0	0	0	0	2 (0.2)
Upper RTI	0	1 (0.1)	0	0	3 (0.5)	0	0	1 (0.1)
Syncope	0	1 (0.1)	3 (0.3)	0	0	2 (0.5)	0	0
Hypertension	0	1 (0.1)	0	0	0	0	1 (0.3)	2 (0.2)
Acute coronary syndrome	0	0	0	0	0	2 (0.5)	0	0
Angina unstable	1 (0.8)	0	2 (0.2)	1 (0.2)	0	0	0	1 (0.1)
Coronary artery occlusion	0	0	0	0	0	2 (0.5)	0	0
Cataract	1 (0.8)	0	2 (0.2)	0	1 (0.2)	0	0	1 (0.1)
Inguinal hernia	0	0	0	1 (0.2)	0	0	0	4 (0.3)
Bronchitis	1 (0.8)	0	2 (0.2)	0	0	1 (0.2)	0	4 (0.3)
Diverticulitis	0	0	0	0	0	0	0	3 (0.2)
Foot fracture	0	0	1 (0.1)	2 (0.4)	0	0	0	0
Rib fracture	0	0	3 (0.3)	0	1 (0.2)	1 (0.2)	0	0
Road traffic accident	0	0	2 (0.2)	0	0	2 (0.5)	0	0
Lung neoplasm malignant	0	0	1 (0.1)	2 (0.4)	1 (0.2)	0	0	0
Convulsion	0	0	0	0	2 (0.4)	0	0	0
Dyspnea	1 (0.8)	0	3 (0.3)	0	0	0	0	5 (0.4)
Respiratory failure	0	0	2 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Hypertensive crisis	0	0	0	0	2 (0.4)	0	0	2 (0.2)
Volvulus	0	0	0	2 (0.4)	0	0	0	0
Loss of consciousness	0	0	0	0	0	1 (0.2)	0	2 (0.2)
Presyncope	0	0	2 (0.2)	0	0	0	0	0
Transient ischemic attack	1 (0.8)	0	0	0	0	0	0	2 (0.2)

Source: Table 2-41 CTD 2.7.4 Summary of Clinical Safety

**Reviewer Comment:**

*Interpretation of the 75 mcg indacaterol 6 month safety data is difficult with the small number of patients included.*

**COPD- 12 month safety population**

Two trials were included in the COPD 12- month safety dataset, B2334 and B2335SE. There were no data for the lower proposed 75 mcg dose of indacaterol included in this analysis. The incidence of SAEs was highest in the formoterol group, at 15.9%, and lowest in the indacaterol 150 mcg group, 10.4%. See Table 82. Consistent with the other safety populations, the SOC with the highest SAE rates included infections and infestations and respiratory, thoracic and mediastinal disorders. The placebo group had comparable SAE rates (4.7%) for respiratory, thoracic and mediastinal disorders to indacaterol 300 mcg and 600 mcg doses (5% and 3.1% respectively) but smaller than formoterol (7.8%). Other SOC with high incidence rates included: injury, poisoning and procedural complications; gastrointestinal disorders and vascular disorders, with indacaterol 150 mcg having higher rates except for gastrointestinal disorders where the rates were comparable with placebo.

**Table 82 SAEs (n (%) of patients) by primary system organ class 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)
<b>Primary system organ class:</b>					
Infections and infestations	4 (2.8)	16 (2.7)	8 (1.9)	23 (5.3)	14 (2.5)
Respir., thoracic and mediastinal disorders†	4 (2.8)	29 (5.0)	13 (3.1)	34 (7.8)	26 (4.7)
Injury, poisoning and procedural complications	3 (2.1)	7 (1.2)	6 (1.4)	5 (1.2)	4 (0.7)
Gastrointestinal disorders	2 (1.4)	3 (0.5)	7 (1.7)	2 (0.5)	8 (1.4)
Vascular disorders	2 (1.4)	3 (0.5)	4 (0.9)	3 (0.7)	2 (0.4)
Cardiac disorders	1 (0.7)	15 (2.6)	8 (1.9)	6 (1.4)	10 (1.8)
Metabolism and nutrition disorders	1 (0.7)	0	1 (0.2)	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.7)	3 (0.5)	1 (0.2)	2 (0.5)	4 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	9 (1.5)	7 (1.7)	7 (1.6)	7 (1.3)
Nervous system disorders	1 (0.7)	5 (0.9)	3 (0.7)	3 (0.7)	4 (0.7)
Blood and lymphatic system disorders	0	0	1 (0.2)	0	0
Congenital, familial and genetic disorders	0	0	0	0	1 (0.2)
Ear and labyrinth disorders	0	0	0	0	1 (0.2)
Eye disorders	0	3 (0.5)	0	5 (1.2)	1 (0.2)

Source: Adapted from Table 2-44 CTD 2.7.4 Summary of Clinical Safety

Consistent with the other 2 safety populations, the most frequent SAE observed for the COPD 12- month group was COPD with the rates highest for the placebo group (4.1%) but comparable to indacaterol 300 mcg (4.0%). Atrial fibrillation, syncope and upper respiratory tract infection all had rates  $\leq 1\%$ , but higher than placebo, refer to Table 83. Note that in the COPD 12-month safety population, there was one additional patient in the indacaterol 300 mcg treatment group with a non-fatal SAE of atrial fibrillation which occurred on Day 197.

**Table 83 SAEs affecting  $\geq 2$  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)
<b>Preferred term:</b>					
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)

Source: Adapted from Table 2-45 CTD 2.7.4 Summary of Clinical Safety

### Other population analyses



Below is a brief evaluation of SAEs for the COPD safety population adjusted for exposure. The rates described are episodes per patient years. The preferred terms with the highest rate for this safety population were COPD, pneumonia and angina with comparable rates between the indacaterol 300 mcg dose and placebo. However, angina was highest for all indacaterol doses: 0.01, 0.007, 0.003 and 0.003 episodes per patient year for 75 mcg, 150 mcg, 300 mcg and 600 mcg vs. placebo with 0.002 episodes per patient year. Acute myocardial infarction, atrial fibrillation, CVA, TIA and dyspnea are events that had higher rates observed during the first cycle also had higher rates over placebo in this analysis.

*Reviewer comment:*

*Although there is a numerical increase in acute myocardial infarction, atrial fibrillation, CVA, TIA, and dyspnea, the difference is small and difficult to interpret. A dose effect is not observed.*

**Table 84 SAEs (fatal and nonfatal) occurring at > 0.005 episodes per patient year in any treatment group by preferred term adjusted for exposure (episodes per patient year) 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 in patient years	105.06	859.72	736.97	394.49	396.21	357.97	274.93	923.60
SAE episodes: n / patient year	0.247	0.235	0.244	0.205	0.318	0.332	0.182	0.270
<b>Preferred term</b>								
COPD †	0.048	0.048	0.061	0.033	0.096	0.039	0.040	0.065
Pneumonia	0.019	0.008	0.011	0.005	0.015	0.017	0.011	0.010
Angina pectoris	0.010	0.007	0.003	0.003	0	0	0.004	0.002
Lower RTI	0	0.006	0.004	0.005	0.013	0	0.007	0.010
Acute myocardial infarction	0	0.005	0.001	0	0	0	0.004	0.001
Atrial fibrillation	0.010	0.005	0.005	0	0.003	0.011	0.004	0.005
Upper RTI bacterial	0.010	0.005	0.008	0	0.013	0	0.007	0.010
Coronary artery disease	0	0.003	0.003	0.008	0	0.003	0.011	0.001
Myocardial infarction	0	0.003	0.003	0.005	0.005	0	0.004	0.005
Cerebrovascular accident	0.010	0.002	0	0.003	0.003	0.006	0	0
Peripheral arterial occlusive disease	0	0.002	0	0	0	0.006	0	0
Transient ischemic attack	0.010	0.002	0	0	0	0	0	0.002
Acute coronary syndrome	0	0.001	0	0	0	0.006	0.004	0
Dyspnea	0.010	0.001	0.007	0	0.003	0.008	0	0.005
Non-cardiac chest pain	0.019	0.001	0	0.003	0	0.003	0	0.001
Small intestinal obstruction	0.010	0.001	0	0	0	0	0	0
Viral upper RTI	0	0.001	0.001	0	0.005	0.003	0	0

Source: Adapted from Table 2-48 CTD 2.7.4 Summary of Clinical Safety

Despite the lower numbers, different designs (controlled and uncontrolled) and disparate treatment populations (i.e., asthma, COPD, healthy subjects), the most frequent SAE reported in the 'short term safety population' was COPD.

The SAEs reported in the asthma safety trial B2338 demonstrated the most frequent was asthma (2 in 300 mcg and 3 in 600 mcg indacaterol and 0 in placebo). There was 1 atrial fibrillation, 1 splenic cyst, 1 cholangitis in the 600 mcg indacaterol group and none in placebo. There was 1 neck abscess and 1 upper respiratory tract infection (bacterial) and none in placebo.

The SAEs in the COPD tiotropium combination safety population were comparable across treatment groups however, consistent with other populations, COPD was the highest reported and similar across the two groups. Pneumonia, angina and upper and lower respiratory tract infections were more frequent in the indacaterol 150 mcg plus tiotropium, 18 mcg group vs. tiotropium 18 mcg group.

### **Subgroup analyses**

For age, the 300 mcg indacaterol group compared to all other indacaterol treatment groups had the most varied percentages of patients with SAEs. For the 3- month COPD: < 65 (2.26%) and ≥ 65-<75 (3.92%) and ≥ 75 (5.3%). This was consistent across the 6- month and 12 month COPD safety groups. There were no apparent trends for gender and no comments of generalizability can be made regarding race due to the low numbers of representation of blacks, asians and other.

The severe population also had the largest numbers of respiratory, thoracic and mediastinal SOC rates across most treatment groups and across all safety populations. Across all safety populations ex-smokers in the placebo and formoterol groups had more frequent respiratory disorder SAEs versus current smokers. SAEs related to infections and infestations were more frequent in patients with severe or worse COPD across most treatment groups. However, many of these subgroup analyses have small numbers making any general statements difficult.

### **5.3.3 Dropouts and/or Discontinuations**

In general, adverse events rates leading to discontinuation were comparable across treatment groups. As seen in other analyses, the most common AEs leading to discontinuation by SOC was respiratory, thoracic and mediastinal. The highest rates were seen in those on placebo (1.6%) vs. the indacaterol doses (ranging from 0.4-1.1%) in the 3 month safety group; placebo (3.4%) vs. indacaterol doses (ranging from 1.57-2.11) in the 6 month group and placebo (4.9%) vs. indacaterol doses (0.7-1.9%) in the 12 month safety group. The two most common AEs leading to discontinuation in preferred terms were COPD and dyspnea across the 3 safety populations. Others included cough, upper and lower respiratory tract infections, ventricular tachycardias and atrial fibrillation.

### **5.3.4 Submission Specific Primary Safety Concerns**

#### **Cardio- and cerebrovascular events**

The safety evaluation during the first cycle highlighted a higher frequency of combined cardio- and cerebrovascular (CCV) events as well as two probable asthma deaths in the indacaterol 300 mcg treatment group (B2338). To further evaluate any potential respiratory related events resulting in intubation, hospitalization or death, the metaanalysis conducted by the Sponsor is intended to assess this safety concern. At the time of this review the results of the metaanalysis are pending.

Regarding the CCV events, the Sponsor utilized two approaches to explore the pooled Phase III safety databases for patients with events meeting the search criteria for: 1). Standard MedDRA queries (SMQs) for cardio- or cerebrovascular events, and 2). Analysis of events using <sup>13</sup>Antiplatelet Trialist' Collaboration (APTC) criteria. In a prospective manner, the Sponsor developed a list of pre-defined search criteria for preferred terms related to CCV disorder based on published SMQ version 11.0 "narrow", for the disorders: cardiac failure; ischemic heart disease; cerebrovascular disorders and "broad" for cardiac arrhythmias. Of note, sudden death or cardiac death was not included in the analysis. A summary of the number and percentage of patients with COPD in the 3-, 6- and 12- month safety populations with AEs or SAEs meeting the criteria is presented below.

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<sup>13</sup> 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. BMJ 1994; 308:81-106.

### CCV AEs in 3- month COPD safety population

The percentage of patients with  $\geq 1$  CCV AE was similar across the different treatment regimens with the highest rate observed in the indacaterol 300 mcg group with 3.11%. Placebo had a rate of 2.58%. See Table 85 below for details.

Of those events reported more than once, ventricular tachycardias, coronary artery disease, atrial flutter and cardiac failure congestive were higher in the indacaterol groups than placebo.

**Table 85 Cardio- and cerebrovascular AEs by preferred term in COPD 3- month 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 (%)
Patients with $\geq 1$ CCV AE	9 (2.00)	62 (2.37)	36 (3.11)	11 (2.01)	11 (1.98)	27 (2.22)	21 (2.35)	52 (2.58)
<b>CCV AEs:</b>								
Electrocardiogram QT prolonged	0	8 (0.31)	4 (0.35)	5 (0.91)	3 (0.54)	4 (0.33)	3 (0.34)	11 (0.55)
Angina pectoris	0	7 (0.27)	6 (0.52)	0	1 (0.18)	2 (0.16)	3 (0.34)	4 (0.20)
Atrial fibrillation	0	6 (0.23)	5 (0.43)	2 (0.37)	0	5 (0.41)	4 (0.45)	5 (0.25)
Coronary artery disease	0	6 (0.23)	1 (0.09)	1 (0.18)	0	1 (0.08)	1 (0.11)	0
Ventricular extrasystoles	1 (0.22)	6 (0.23)	6 (0.52)	1 (0.18)	2 (0.36)	2 (0.16)	1 (0.11)	7 (0.35)
Ventricular tachycardia	2 (0.45)	5 (0.19)	0	0	0	2 (0.16)	0	0
Acute myocardial infarction	0	3 (0.11)	1 (0.09)	0	0	0	1 (0.11)	0
Atrioventricular block first degree	1 (0.22)	3 (0.11)	4 (0.35)	0	0	1 (0.08)	0	3 (0.15)
Cardiac failure congestive	0	3 (0.11)	1 (0.09)	0	0	2 (0.16)	0	0
Myocardial infarction	0	3 (0.11)	1 (0.09)	1 (0.18)	0	0	2 (0.22)	5 (0.25)
Atrial flutter	2 (0.45)	2 (0.08)	1 (0.09)	1 (0.18)	1 (0.18)	0	0	0
Bundle branch block left	0	2 (0.08)	0	0	0	0	1 (0.11)	0
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
Myocardial ischaemia	0	2 (0.08)	1 (0.09)	0	0	0	0	0
Acute coronary syndrome	0	1 (0.04)	0	0	0	1 (0.08)	1 (0.11)	0
Arrhythmia	0	1 (0.04)	0	0	0	2 (0.16)	1 (0.11)	1 (0.05)
Arrhythmia supraventricular	0	1 (0.04)	0	0	0	0	0	0
Bundle branch block right	0	1 (0.04)	1 (0.09)	0	0	0	0	2 (0.10)
Cardiopulmonary failure	0	1 (0.04)	0	0	0	0	0	0
Carotid artery stenosis	0	1 (0.04)	0	0	0	1 (0.08)	0	2 (0.10)
Cerebral ischaemia	0	1 (0.04)	0	0	0	0	0	1 (0.05)
Cerebrovascular insufficiency	0	1 (0.04)	0	0	0	0	0	0
Coronary artery occlusion	0	1 (0.04)	0	0	0	3 (0.25)	0	0
Coronary artery thrombosis	0	1 (0.04)	0	0	0	0	0	0

	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 (%)
Lacunar infarction	0	1 (0.04)	0	0	0	0	0	0
Sick sinus syndrome	0	1 (0.04)	0	0	0	0	0	0
Tachyarrhythmia	0	1 (0.04)	0	0	0	0	0	0
Transient ischaemic attack	1 (0.22)	1 (0.04)	0	0	0	0	1 (0.11)	2 (0.10)
Troponin increased	0	1 (0.04)	0	0	0	0	0	0
Angina unstable	0	0	1 (0.09)	0	0	0	0	1 (0.05)
Atrioventricular block second degree	0	0	2 (0.17)	0	0	0	0	0
Cardiac failure	0	0	0	1 (0.18)	0	1 (0.08)	1 (0.11)	1 (0.05)
Carotid artery occlusion	0	0	1 (0.09)	0	0	0	0	0
Cerebellar infarction	0	0	0	0	0	0	0	1 (0.05)
Cerebral haematoma	0	0	0	0	0	1 (0.08)	0	0
Cerebral haemorrhage	0	0	1 (0.09)	0	0	0	0	0
Cor pulmonale	0	0	0	0	1 (0.18)	0	0	1 (0.05)
Cor pulmonale chronic	0	0	0	0	1 (0.18)	0	1 (0.11)	0
Coronary artery bypass	0	0	0	0	0	1 (0.08)	0	0
ECG PR prolongation	0	0	0	0	0	0	0	1 (0.05)
ECG repolarisation abnormality	0	0	0	0	0	1 (0.08)	0	0
Extrasystoles	0	0	0	0	1 (0.18)	0	0	2 (0.10)
Ischaemic cardiomyopathy	0	0	0	0	0	1 (0.08)	0	0
Ischaemic stroke	0	0	0	0	0	0	1 (0.11)	1 (0.05)
Left ventricular failure	0	0	0	0	0	0	1 (0.11)	0
Sinus bradycardia	0	0	3 (0.26)	1 (0.18)	1 (0.18)	0	0	1 (0.05)
Sinus tachycardia	0	0	0	0	0	0	0	1 (0.05)
Supraventricular extrasystoles	2 (0.45)	0	1 (0.09)	0	1 (0.18)	1 (0.08)	1 (0.11)	1 (0.05)
Supraventricular tachycardia	0	0	0	0	0	1 (0.08)	0	0
Vertebrobasilar insufficiency	0	0	1 (0.09)	0	0	0	0	1 (0.05)

Source: Table 2-81 CTD 2.7.4 Summary of Clinical Safety

There were 5 ventricular tachycardias (VT) in the 150 mcg dose and 2 in the 75 mcg indacaterol dose and none reported in the placebo group. The events were captured on Holter monitoring as nonsustained VT. For the 5 in the 150 mcg group, 3 were 3-10 beats and 2 were >10 beats. One event was reported as a SAE.

CCV SAEs in the 3- month COPD population ranged between 0.18% in formoterol group to 0.92% in indacaterol 150 mcg group. Acute myocardial infarction, coronary artery disease, cerebral infarction and cerebrovascular accident all occurred at higher rates in the indacaterol and specifically more in the 150 mcg dose than placebo, and all these events were numerically greater than one for the indacaterol groups. Refer to Table 86 for a summary.

**Table 86 Cardio- and cerebrovascular SAEs (n(%) of patients) 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 CCV SAE	2 (0.45)	24 (0.92)	8 (0.69)	3 (0.55)	1 (0.18)	11 (0.91)	6 (0.67)	13 (0.65)
<b>CCV SAEs:</b>								
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
Coronary artery disease	0	3 (0.11)	1 (0.09)	1 (0.18)	0	1 (0.08)	1 (0.11)	0
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)
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
Acute coronary syndrome	0	1 (0.04)	0	0	0	1 (0.08)	1 (0.11)	0
Atrial flutter	0	1 (0.04)	0	1 (0.18)	0	0	0	0
Cardiac failure congestive	0	1 (0.04)	0	0	0	1 (0.08)	0	0
Cardiopulmonary failure	0	1 (0.04)	0	0	0	0	0	0
Cerebrovascular insufficiency	0	1 (0.04)	0	0	0	0	0	0
Lacunar infarction	0	1 (0.04)	0	0	0	0	0	0
Myocardial ischaemia	0	1 (0.04)	1 (0.09)	0	0	0	0	0
Sick sinus syndrome	0	1 (0.04)	0	0	0	0	0	0
Transient ischaemic attack	1 (0.22)	1 (0.04)	0	0	0	0	0	1 (0.05)
Troponin increased	0	1 (0.04)	0	0	0	0	0	0
Ventricular tachycardia	0	1 (0.04)	0	0	0	0	0	0
Angina unstable	0	0	1 (0.09)	0	0	0	0	1 (0.05)
Arrhythmia	0	0	0	0	0	2 (0.16)	0	0
Bundle branch block left	0	0	0	0	0	0	1 (0.11)	0
Cardiac failure	0	0	0	1 (0.18)	0	0	0	0
Carotid artery occlusion	0	0	1 (0.09)	0	0	0	0	0
Cerebellar infarction	0	0	0	0	0	0	0	1 (0.05)
Cerebral haematoma	0	0	0	0	0	1 (0.08)	0	0
Cerebral haemorrhage	0	0	1 (0.09)	0	0	0	0	0
Cor pulmonale	0	0	0	0	0	0	0	1 (0.05)
Coronary artery occlusion	0	0	0	0	0	2 (0.16)	0	0
Electrocardiogram QT prolonged	0	0	0	0	1 (0.18)	0	0	0
Ischaemic cardiomyopathy	0	0	0	0	0	1 (0.08)	0	0
Ischaemic stroke	0	0	0	0	0	0	1 (0.11)	1 (0.05)
Sinus bradycardia	0	0	0	0	1 (0.18)	0	0	0
Ventricular extrasystoles	0	0	0	0	0	0	0	1 (0.05)
Vertebrobasilar insufficiency	0	0	1 (0.09)	0	0	0	0	0

Source: Table 2-82 CTD 2.7.4 Summary of Clinical Safety

#### **CCV AEs in 6- month COPD safety population**

The frequency of CCV AEs in the 6- month population ranged from 3.3% (indacaterol 600 mcg) to 5.8% (tiotropium). Of interest, indacaterol 150 mcg had a rate of 5.6% and placebo, 4.0%. ECG QT prolonged, angina pectoris, atrial fibrillation, ventricular extrasystoles, ventricular tachycardia, coronary artery

disease, acute myocardial infarction, left and right bundle branch blocks and cardiac failure congestive all occurred at higher rates in the indacaterol groups and again, particularly the 150 mcg group than placebo. The rates were higher for the 75 mcg indacaterol group for than the 150 mcg group for ventricular extrasystoles, ventricular tachycardia and cardiac failure congestive. All these events had numerical values greater than one in the affected groups

The highest rates of CCV SAEs were in the indacaterol 75 mcg group (2.4%) the lowest were in the indacaterol 300 mcg group (1.2%) and placebo (1.2%) as shown in Table 87. The highest SAEs rates were in angina pectoris, atrial fibrillation, acute myocardial infarction all at higher rates in the indacaterol groups than placebo and all events occurring more than once.

**Table 87 Cardio- and cerebrovascular SAEs by preferred term in COPD 6- month safety population**

	Indacaterol treatments				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Patients with ≥1 CCV SAE	3 (2.36)	16 (1.71)	12 (1.15)	7 (1.28)	3 (0.54)	9 (2.17)	5 (1.50)	17 (1.24)
<b>CCV SAEs:</b>								
Angina pectoris	1 (0.79)	3 (0.32)	1 (0.10)	1 (0.18)	0	0	1 (0.30)	2 (0.15)
Atrial fibrillation	1 (0.79)	3 (0.32)	0	0	0	3 (0.72)	1 (0.30)	3 (0.22)
Acute myocardial infarction	0	2 (0.21)	1 (0.10)	0	0	0	1 (0.30)	0
Cerebral infarction	0	1 (0.11)	0	0	0	0	0	0
Cerebrovascular accident	0	1 (0.11)	0	0	0	0	0	0
Coronary artery disease	0	1 (0.11)	2 (0.19)	2 (0.37)	0	0	2 (0.60)	1 (0.07)
Lacunar infarction	0	1 (0.11)	0	0	0	0	0	0
Myocardial infarction	0	1 (0.11)	1 (0.10)	1 (0.18)	1 (0.18)	0	1 (0.30)	2 (0.15)
Sick sinus syndrome	0	1 (0.11)	1 (0.10)	0	0	0	0	0
Subdural haemorrhage	0	1 (0.11)	0	0	0	0	0	0
Ventricular tachycardia	0	1 (0.11)	0	0	0	0	0	1 (0.07)

Source: Table 2-84 CTD 2.7.4 Summary of Clinical Safety

#### **CCV AEs in 12- month COPD safety population**

The 75 mcg indacaterol dose was not included in this analysis. The CCV AE rates were highest for the indacaterol 150 mcg group (9.7%) and lowest in the placebo group (5.4%). The most common CCV AE preferred terms were atrial fibrillation, ECG QT prolongation, angina pectoris, myocardial ischemia, ventricular extrasystoles, cardiac failure, AV block 1st degree, AV block 2nd degree, bundle branch block left, cardiac failure congestive, sinus tachycardia and ventricular tachycardia (including an additional patient not originally captured) which occurred more frequently in the indacaterol groups than placebo. Refer to Table 88 for a summary. Note that these events are not corrected for patient exposure.

**Table 88 Cardio- and cerebrovascular AEs 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 CCV AE	14 (9.72)	50 (8.58)	26 (6.12)	28 (6.45)	30 (5.40)
<b>Preferred term:</b>					
Atrial fibrillation	1 (0.69)	8 (1.37)	2 (0.47)	2 (0.46)	5 (0.90)
ECG QT prolonged	6 (4.17)	8 (1.37)	4 (0.94)	3 (0.69)	5 (0.90)
Angina pectoris	1 (0.69)	6 (1.03)	2 (0.47)	1 (0.23)	1 (0.18)
Myocardial ischaemia	0	4 (0.69)	0	1 (0.23)	0
Ventricular extrasystoles	0	4 (0.69)	2 (0.47)	2 (0.46)	1 (0.18)
Cardiac failure	0	3 (0.51)	4 (0.94)	6 (1.38)	1 (0.18)
AV block first degree	1 (0.69)	2 (0.34)	0	0	0
AV block second degree	0	2 (0.34)	0	0	0
Bundle branch block left	1 (0.69)	2 (0.34)	0	1 (0.23)	0
Cardiac failure congestive	1 (0.69)	2 (0.34)	0	0	2 (0.36)
Myocardial infarction	0	2 (0.34)	2 (0.47)	1 (0.23)	3 (0.54)
Sinus tachycardia	1 (0.69)	2 (0.34)	0	0	0
Acute myocardial infarction	0	1 (0.17)	0	0	1 (0.18)

Source: Adapted from Table 2-85 CTD 2.7.4 Summary of Clinical Safety

Of note, there was an additional ventricular tachycardia event in the 150 mcg indacaterol group not captured in the 12- month COPD safety group because it occurred 12 days after the patient discontinued from the trial.

The CCV SAEs in the 12- month safety group had a similar pattern as above. The highest rates were seen in the indacaterol 300 mcg group (3%) and the lowest in the indacaterol 150 mcg group. Atrial fibrillation, angina pectoris and cardiac failure congestive all occurred at higher rates in the indacaterol group, particularly, the 300 mcg group than in the placebo group. Refer to Table 89.

**Table 89 Cardio- and cerebrovascular SAEs 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 CCV Serious AE	1 (0.69)	18 (3.09)	11 (2.59)	6 (1.38)	8 (1.44)
<b>Preferred term:</b>					
Atrial fibrillation	1 (0.69)	3 (0.51)	0	1 (0.23)	1 (0.18)
Angina pectoris	0	2 (0.34)	1 (0.24)	0	1 (0.18)
Cardiac failure congestive	0	2 (0.34)	0	0	1 (0.18)
Myocardial infarction	0	2 (0.34)	2 (0.47)	1 (0.23)	2 (0.36)
Myocardial ischaemia	0	2 (0.34)	0	0	0

Source: Adapted from Table 2-86 CTD 2.7.4 Summary of Clinical Safety

#### ***CCV AEs in COPD Tiotropium combination safety population***

The CCV AEs in the COPD tiotropium combination safety group were reported at similar rates between the two treatment groups: 2.0% in the Ind 150 mcg + tiotropium and 1.8% in the placebo + tiotropium group (1.77%). Likewise, CCV SAEs occurred at almost identical rates between the two groups, 0.79% in the ind + tio group and 0.80% in the tio alone group.

Class related toxicities such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, worsening hypertension as well as increase serum glucose, decrease in serum potassium, and QT prolongation are well known and were adequately assessed during the indacaterol development program. Overall, there were no unexpected class related toxicities for indacaterol.

#### **Class effects**

Class related toxicities such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, worsening hypertension as well as increase serum glucose, decrease in serum potassium, and QT prolongation are well known and were adequately assessed during the indacaterol development program. Overall, there were no unexpected class related toxicities for indacaterol.

### **5.4 Supportive Safety Results**

#### **5.4.1 Common Adverse Events**

##### ***3- month COPD safety population***

The frequencies of the common events occurring  $\geq 1\%$  are listed in Table 90. The highest rate was observed in the 75 mcg indacaterol group (51.5%) and the lowest in the salmeterol (33.4%). The rate for those on placebo was 43.1%. COPD was the preferred term with the highest rate but was comparable across different groups. Cough, headache and muscle spasms are key examples of common AE reported at higher rates in the indacaterol groups than placebo. Dyspnea was observed at higher rates in the placebo group than other treatment groups.



**Table 90 Common AEs (>1.0% of patients in any 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)
<b>Preferred term</b>								
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)
Pyrexia	3 (0.7)	21 (0.8)	10 (0.9)	4 (0.7)	6 (1.1)	7 (0.6)	4 (0.5)	14 (0.7)
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)
Odema peripheral	4 (0.9)	19 (0.7)	8 (0.7)	7 (1.3)	6 (1.1)	7 (0.6)	2 (0.2)	9 (0.5)
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)
Dry mouth	4 (0.9)	14 (0.5)	4 (0.4)	1 (0.2)	1 (0.2)	27 (2.2)	3 (0.3)	10 (0.5)
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)
Insomnia	2 (0.5)	11 (0.4)	5 (0.4)	5 (0.9)	3 (0.5)	6 (0.5)	9 (1.0)	14 (0.7)
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)
Rhinorrhea	3 (0.7)	10 (0.4)	13 (1.1)	1 (0.2)	1 (0.2)	6 (0.5)	2 (0.2)	4 (0.2)
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)
Tremor	0	4 (0.2)	3 (0.3)	7 (1.3)	5 (0.9)	3 (0.3)	2 (0.2)	5 (0.3)

Source: Table 2-1 Table 2-86 CTD 2.7.4 Summary of Clinical Safety

#### **6- month COPD safety population**

The most common AEs occurring in the 6- month safety population are similar to the previous safety group. COPD is the most common and rates were comparable across treatment groups including placebo. Cough and headache were observed at higher rates for the indacaterol groups than the placebo groups. The most common SOC was infections and infestations and respiratory, thoracic and mediastinal disorders.

### 12- month COPD safety population

Overall, the highest rates of AE were observed in the 150 mcg group (76.4%) and the lowest in the placebo group (63.1%). The most common AEs in the 12- month COPD safety population was COPD and as observed before, the rates were comparable across all treatment groups. Cough, upper respiratory tract infection, headache, muscle spasms, oropharyngeal pain and sinusitis, ECG QT were seen at higher rates in the indacaterol groups than placebo. The top two SOCs identified were infection and infestations and respiratory, thoracic and mediastinal disorders.

### Subgroup evaluations of AE

Overall, the rates of the reported AE were comparable across subgroups except women who had higher incidences of AE than males. Consistent with other safety analyses, no generalization can be made regarding races as the representative numbers were too low. There were no trends in AE based on age. For baseline disease status, rates of AE were comparable between those with moderate versus severe disease. As well, there were no differences across groups based on ICS use and smoking status.

## 5.4.2 Laboratory Findings

The two known beta2-adrenergic effects of hypokalemia and hyperglycemia were evaluated adequately by the Sponsor during the conduct of clinical trials. A review of the laboratory safety data will first focus on alterations in serum potassium and glucose in the COPD 3- month, 6- month and 12- month safety populations. Evaluation of other laboratory values will follow.

### Potassium assessment

The mean changes in potassium values were similar across all treatment groups. Minimum post-baseline values for patients in the indacaterol groups ranged from 2.50 mmol/L (indacaterol 300 mcg q.d.) to 3.10 mmol/L (indacaterol 600 mcg q.d.). Acute changes in potassium were also assessed, from 25 minutes pre-dose to 1 hour post-dose time points. The largest mean change from 25 minutes pre-dose at any visit (-0.11 mmol/L) was seen in the indacaterol 600 mcg q.d. group at Day 1, 1 hour post-dose. Refer to for a summary of the acute changes in potassium across the different treatment groups.

**Table 91 Acute changes in potassium (mmol/L): mean change from 25 min predose to 1 hr post dose by visit in COPD safety population**

Visit / Time		Indacaterol treatment groups				Control treatment groups			
		75 µg	150 µg	300 µg	600 µg	For	Tio	Sme	Pbo
Day 1 *	n	435	989	884	526	533	401	329	1731
	-25m Pre-dose mean	4.47	4.50	4.45	4.45	4.42	4.48	4.54	4.46
	1h Mean change	-0.04	-0.04	-0.05	-0.11	-0.09	0	-0.00	0.01
Week 2 *	n	117	749	855	508	513	384	309	1116
	-25m Pre-dose mean	4.44	4.46	4.42	4.39	4.41	4.45	4.53	4.42
	1h Mean change	0.02	0.02	-0.00	-0.02	-0.04	0.05	0.03	0.05
Month 3 *	n	356	872	789	439	449	342	287	1415
	-25m Pre-dose mean	4.37	4.46	4.43	4.43	4.43	4.42	4.55	4.42
	1h Mean change	0.04	-0.01	-0.01	-0.02	-0.03	0	0	0.03
Month 6 †	n	0	593	686	341	345	316	279	848
	-25m Pre-dose mean	0	4.48	4.44	4.49	4.48	4.41	4.57	4.42
	1h Mean change	0	0.01	0.01	-0.03	-0.01	0	-0.04	0.01
Month 12 ††	n	0	122	446	307	298	0	0	381
	-25m Pre-dose mean	0	4.39	4.50	4.49	4.50	0	0	4.41
	1h Mean change	0	-0.02	-0.03	-0.04	-0.07	0	0	0.02

Source: Table 3-11 CTD 2.7.4 Summary of Clinical Safety

Reviewer comment:

*These data do not suggest a clinically important affect on potassium at the doses evaluated.*

### **Glucose assessment**

The observed incidences of newly occurring or worsening notably high glucose values as predefined as  $>9.99$  mmol/L in the indacaterol treatment groups were and 4.7-8.4% in the whole COPD safety population. Based on the different safety subgroups the incidence was 4.0-6.4% in the COPD 3-month safety population, 3.9-7.2% in the COPD 6-month safety population and 9.0- 11.1% in the COPD 12-month. The highest incidences of notable high glucose levels within the COPD 3- and 6- months safety populations was observed in the 600 mcg indacaterol group; however for the 12-month safety population, highest incidences were in the indacaterol 150 mcg q.d. group. Acute changes in glucose measured from 25 minutes pre-dose to 1 hour post-dose for all visits were comparable among treatment groups. The greatest mean change from 25 minutes pre-dose at any visit was seen in the indacaterol 600 mcg q.d. group at Day 1, 1 hour post-dose (0.35 mmol/L = 6.3 mg/dL).

### **COPD 3- month safety population**

In the 3- month population there was one patient who developed idiopathic thrombocytopenia purpura in the indacaterol 150 mcg group that was reported as an SAE. Otherwise there were no clinically meaningful differences in hematology and chemistry laboratory data for the indacaterol or placebo treatment groups.

### **COPD 6- month safety population**

There were no clinically meaningful differences in hematology and chemistry laboratory data for the indacaterol or placebo treatment groups. Notable differences from baseline were similar across treatment groups.

### **COPD 12 month safety population**

There were no clinically important differences from placebo in hematocrit or BUN and creatinine.

Overall, there were 18 patients with reported notably low platelets, 10 were in the indacaterol treatment groups. One of these patients had low levels at screening who had the diagnosis of alcoholic hepatitis. A second patient with a history of non-Hodgkin's lymphoma also had low platelets at screening and was subsequently diagnosed with a recurrence of disease, started treatment and later discontinued from the trial with worsening thrombocytopenia while on chemotherapy. Two other patients had low platelets at screening which subsequently worsened by the final visit, one with a history of hepatopathy.

The percentage of patients with notable differences in GGT  $>3$  x ULN ranged from 2.9%-3.6% in indacaterol 75 mcg to 300 mcg groups but higher in the indacaterol 600 mcg group, 5.9%. There were small numbers of patients with AST  $>3$  x ULN and ALT  $>3$  x ULN that were generally comparable between treatment groups and placebo. There were incidences of AST  $>5$  x ULN ranging 0.17 – 0.22% in indacaterol groups vs. 0.1% in placebo. There was one episode of AST  $>10$  x ULN in the 150 mcg group and one in the tiotropium group. There were 6 episodes of ALT  $>10$  x ULN, one in the 75 mcg, one in the 150 mcg group, one in formoterol, two in tiotropium and one in the placebo groups.

## **5.4.3 Vital Signs**

The same safety datasets were utilized in evaluation of the vitals across different treatment regimens.

### **3- month COPD safety population**

As shown in Table 92, Table 93 and Table 94 a small dose response effect is apparent across the indacaterol treatment groups with the exception of the 75 mcg dose for elevations in blood pressure and pulse, consistent with the known beta-agonist effect of the drug. This may likely be due to the smaller numbers of patients in trials treated with 75 mcg meeting the duration criteria of 3- or 6 months to be included in the safety dataset; there were none included in the 12- month safety dataset.

**Table 92 Vital signs: incidence of clinically notable values any time post baseline in COPD 3-month safety population**

		Treatment groups (%)				
		Ind 75 mcg N=449	Ind 150 mcg N=2611	Ind 300 mcg N=1157	Ind 600 mcg N=547	Pbo N=2012
3 month-COPD safety population	SBP $\geq$ 200 mm Hg	0.45	0.61	0.87	2.01	1.14
	DBP $\geq$ 105 mm Hg	1.56	0.58	0.61	0.92	1.09
	Pulse $\geq$ 120 bpm	0.22	0.19	0.26	0.37	0.30

High SBP: >200 mm Hg or  $\geq$  180 mm Hg and increase baseline by >20 mm Hg

High DBP: > 115 mm Hg or  $\geq$  105 mm Hg and increase baseline by > 15 mm Hg

High pulse: >130 bpm or  $\geq$ 120 bpm and increase from baseline by  $\geq$ 15 bpm

Source: Adapted from Table 4-1 CTD 2.7.4 Summary of Clinical Safety

In the COPD 3- month safety population there were 4 cases of intervals for QTcF > 500 ms, 2 in the indacaterol 150 mcg group and 2 in the tiotropium group. For notable increases of QTcF by >60 msec the incidences were higher in the placebo group (6 patients, 0.30%) than in the indacaterol 150 mcg q.d. (3 patients, 0.12%), 300 mcg q.d. (1 patient, 0.09%) and 600 mcg q.d. (1 patient, 0.19%) groups. The frequency of events with a notable QTcF increase by 30-60 msec was higher on indacaterol 150 mcg q.d. (155 patients, 5.96%) than on placebo (105 patients, 5.27%).

#### **6- month COPD safety population**

Increasing doses of indacaterol between 150 mcg and 600 mcg show increasing rates of notable high SBP and DBP. Refer to Table 93.

**Table 93 Vital signs: incidence of clinically notable values any time post baseline in COPD 6-month safety population**

		Treatment groups (%)				
		Ind 75 mcg N=127	Ind 150 mcg N=933	Ind 300 mcg N=1041	Ind 600 mcg N=547	Pbo N=1371
6 month-COPD safety population	SBP $\geq$ 200 mm Hg	0	0.96	1.15	2.20	1.53
	DBP $\geq$ 105 mm Hg	0.79	0.64	0.96	1.28	1.24
	Pulse $\geq$ 120 bpm	0.79	0.21	0.38	0.37	0.44

Source: Adapted from Table 4-2 CTD 2.7.4 Summary of Clinical Safety

In the COPD 6- month safety population, there were 4 cases of intervals for QTcF > 500 ms, 2 in the indacaterol 150 mcg group, 1 case in the 300 mcg indacaterol group and 1 in the tiotropium group. For notable increases of QTcF by >60 msec the incidences were higher in the placebo group (7 patients, 0.50%) than in the indacaterol 150 mcg q.d. (3 patients, 0.30%), 300 mcg q.d. (3 patients, 0.30%) and 600 mcg q.d. (1 patient, 0.20%) groups. The frequency of events with notable increase of QTcF by 30- 60 msec was highest in the tiotropium and placebo group with 0.50% for both.

#### **12- month COPD safety population**

The rates for notable increases in SBP, SBP and pulse were highest in placebo. Refer to Table 94 below.

**Table 94 Vital signs: incidence of clinically notable values any time post baseline in COPD 12-month safety population**

		Treatment groups (%)			
		Ind 150 mcg N=144	Ind 300 mcg N=583	Ind 600 mcg N=425	Pbo N=556
12 month-COPD safety	SBP $\geq$ 200 mm Hg	0.69	2.06	3.54	3.06
	DBP $\geq$ 105 mm Hg	0.69	1.03	2.12	2.52
	Pulse $\geq$ 120 bpm	0	1.03	0.24	0.90

Source: Adapted from Table 4-2 CTD 2.7.4 Summary of Clinical Safety

In the COPD 12- month safety population there were no cases of intervals for QTcF > 500 msec. For notable increases of QTcF by >60 msec there were 6 cases reported: indacaterol 150 mcg q.d. (1 case); indacaterol 300 mcg q.d. (2 cases); indacaterol 600 mcg q.d. (1 case); formoterol (1 case) and placebo (1 case). The frequency of events with notable increase of QTcF by 30- 60 msec was highest in the indacaterol 150 mcg group, 0.70%. The placebo group had a rate of 0.20%.

A thorough QTc study was conducted, B2339 and reviewed by the Clinical Pharmacology team. The trial was a randomized, multiple-dose, placebo and positive-controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects, using the Concept1 device. The primary objective was to characterize the maximum mean prolongation of QTc Fridericia (QTcF) following treatment with indacaterol 150 mcg, 300 mcg and 600 mcg q.d. for 14 days. A total of 404 subjects were randomized with 388 subjects completing the trial. There was no evidence of statistically significant QT prolongation for the 3 doses evaluated.

## 5.5 Other Safety Explorations

### 5.5.1 Dose Dependency for Adverse Events

See Section 5.6 Additional Safety Evaluations for evaluation of dose and post inhalational cough.

### 5.5.2 Time Dependency for Adverse Events

See Section 5.6 Additional Safety Evaluations for evaluation of time of onset and post inhalational cough.

### 5.5.3 Drug-Demographic Interactions

Evaluation of treatment by subgroup interaction for various demographic groups including age, gender and race for the bronchodilatory effect of indacaterol was conducted in the pivotal Phase III COPD trials.

#### **3- month COPD safety population**

There was no clear age by treatment group interaction with respect to SAEs. Although the majority of patients were males, females had higher rates of “all SOC” across the indacaterol treatment groups (ranging 3.61-4.98) than males (2.02-3.58). The majority of patients were caucasian and therefore no conclusions can be drawn by race. Patients with severe disease had higher rates of “all SOC” in the 75 mcg, 150 mcg and 300 mcg indacaterol groups. There was no clear relationship between smoking status and ICS use and SAEs across the indacaterol treatment groups.

#### **6- month COPD safety population**

*In the 6- month COPD safety dataset, there was no clear age by treatment group interaction with respect to SAEs. Females had higher rates of “all SOC” across the indacaterol treatment groups (ranging 6.9 - 11.8) than males (4.0 -7.4). No conclusions can be drawn by race due to the small numbers of blacks,*

*asians and others. There was no clear relationship between disease severity and smoking status and SAEs, however, patients on ICS had higher frequency of SAEs than non-ICS users.*

### **12- month COPD safety population**

There were no clear relationships between the frequencies of SAEs and age and gender. As before, no conclusions can be drawn about race. Overall, there was no consistent pattern between subgroups of disease characteristics and SAEs.

#### **5.5.4 Drug-Disease Interactions**

Drug disease interaction analyses were conducted for patients with CCV conditions (see Section 5.3.4 Submission Specific Primary Safety Concerns), diabetes mellitus 2 and hypertension. Overall, there were no clinically important differences, however in the 12- month COPD population, AE rates in patients with diabetes mellitus 2 were higher for all active treatment groups (indacaterol 150 mcg with 2.08%, indacaterol 300 mcg with 2.06%, indacaterol 600 mcg with 1.41%) than placebo (0.72%).

#### **5.5.5 Drug-Drug Interactions**

*In vitro* data demonstrated two key enzymes responsible for metabolic clearance of indacaterol, UGT1A1 and CYP3A (refer to clinical pharmacology review by Dr. Sandra Saurez, August 25, 2009). Therefore, substrates, inhibitors or inducers of these enzymes may affect the PK of indacaterol and its metabolites. Concomitant administration of indacaterol 300 mcg with ketoconazole 200 mcg BID resulted in a 2-fold increase in the AUC and a 31% increase in C<sub>max</sub>. Concomitant administration of indacaterol 300 mcg with verapamil 80 mcg t.i.d for 4 days showed an increase in the AUC and C<sub>max</sub> of indacaterol of 200% and 50%, respectively. Concomitant administration of a single dose of indacaterol 300 mcg with erythromycin 400 mcg q.i.d for 7 days showed an increase in the indacaterol AUC and C<sub>max</sub> of 60% and 15%, respectively. The indacaterol C<sub>max</sub> and AUC increased by 12% and 41%, respectively following single dose administration of indacaterol 250 mcg via Twisthaler + mometasone furoate 200 mcg dry powder inhaler formulation administered via Twisthaler™ compared to that after indacaterol 250 mcg alone via Twisthaler. Indacaterol did not alter the systemic exposure of mometasone.

### **5.6 Additional Safety Evaluations**

#### **Post inhalational Cough**

The incidence of post inhalational cough (PI) was assessed along with any post inhalation events at the clinic visits as observed by the staff. This was conducted prospectively in pivotal phase III trials, B2334, B2335S, B2346, B1302, B2336, and B2333. The data was collected at each clinic visit, where the investigator completed a CRF page including the time of onset following inhalation of trial medication and duration of PI cough. The percentage of visits with patients having PI cough and the percentage of patients with PI cough were summarized for the safety populations. A patient was identified with a PI cough if the number of visits with PI cough was >1 or the number of visits with PI cough was more than 20% of all attended post baseline visits.

#### **3- month COPD safety population**

The mean percentages of attended visits at which patients experienced PI cough were statistically significantly greater in the indacaterol treatment groups than in the placebo or other active comparator groups. The mean percentage of attended visit with PI cough were as follows: indacaterol 75 mcg, 14%; 150 mcg group, 15.1%; 300 mcg group, 17.5% and the 600 mcg group 16.6%; formoterol, 0.9%; tiotropium, 0.9%, salmeterol, 0.9% and placebo 2%. The percent of PI coughs were: 23.6, 27.9, 29.7, 30.8, 4.3, 2.2, 3.9 and 6.6% for 75 mcg, 150 mcg, 300 mcg, 600 mcg, formoterol, tiotropium, salmeterol and placebo respectively.

#### **6- month COPD safety population**

The mean percentages of attended visits at which patients experienced PI cough were statistically significantly greater in the indacaterol treatment groups (range 14.1 to 17.7%) than in the placebo (1.9%) or other active comparator groups (0.8 to 0.9%). The mean percentage of attended visit with PI cough were as follows: indacaterol 75 mcg, 23.6%; 150 mcg group, 24.3%; 300 mcg group, 28.0% and the 600 mcg group 29.1%; formoterol, 1.6%; tiotropium, 2.2%, salmeterol, 1.5% and placebo 3.6%. The percent of PI coughers were: 23.6, 24.3, 28.0, 29.1, 1.6, 2.2, 1.5 and 3.6% for 75 mcg, 150 mcg, 300 mcg, 600 mcg, formoterol, tiotropium, salmeterol and placebo respectively.

### 12- month COPD safety population

The mean percentages of attended visits at which patients experienced PI cough were statistically significantly greater in the indacaterol treatment groups (range 18.3 to 19.9%) than in the placebo (1.7%) or other active comparator group, formoterol (0.8 %). The mean percentage of attended visit with PI cough were as follows: indacaterol 150 mcg group, 18.3%; 300 mcg group, 19.9% and the 600 mcg group 18.9%; formoterol, 0.8% placebo 1.7%. The percent of PI coughers were: 28.5, 29, 29, 1.2, and 3.1% for 150 mcg, 300 mcg, 600 mcg, formoterol, and placebo respectively.

The time to onset of the PI cough for the majority of patients was within 15 seconds of inhalation and lasted  $\leq 15$  seconds. Subgroup analysis demonstrated that the percentage of patients with PI cough were similar across indacaterol groups. There were no consistent trends between PI cough and age, COPD severity or ICS use however, the percentage of patients with PI cough were higher for females and current smokers.

### Asthma Safety Evaluation

Concern over the 2 asthma deaths in the 300 mcg indacaterol treatment group of trial B2338 in the first cycle prompted a further evaluation of available trials treating patients with asthma for deaths and SAEs at the onset of this cycle review. A summary is available in Table 95 below of deaths, SAEs and asthma exacerbations categorized as AEs leading to discontinuation.

A thorough evaluation of asthma exacerbations as relates to the trial inclusion criteria will be carried out using the Sponsor's metaanalysis of respiratory related intubations, hospitalizations and deaths, however, preliminary review of the asthma trials available reveal 1 asthma exacerbation in the 18.75 mcg group, 0 in the 75 mcg group and the highest numerical value was 10 captured in the 600 mcg indacaterol group. These numbers represent either asthma exacerbations or events labeled as bronchospasm associated with death, SAE or AE leading to discontinuation. Evaluation of these such asthma exacerbations show a range of 1 event occurring in the 18.75 mcg indacaterol group to 9 events in the 600 mcg indacaterol group.

**Table 95 Deaths, SAEs and AEs leading to discontinuation in Asthma trials**

ID Year*	Study type	Study duration	N	Treatment groups <sup>†</sup>	Adverse Event
Randomized, controlled trials					
<b>A2201 [2003]</b>	Safety Efficacy	5 x 1 dose	42	Ind HFA 50 mcg QD Ind HFA 100 mcg QD Ind HFA 200 mcg QD Ind HFA 400 mcg QD Placebo	0 Deaths, SAEs • Pbo (1: hypoglycemia) AE-> d/c: • Gilbert's syndrome
<b>A2205 [2003]</b>	Safety	4 weeks	156	Ind HFA 200 mcg QD Ind HFA 400 mcg QD Ind HFA 600 mcg QD Placebo	0 Deaths, SAEs AE-> d/c: • Ind 400 mcg (1 cough) • Ind 600 mcg (1 asthma exac) • Pbo (1 asthma exac)

ID Year*	Study type	Study duratio n	N	Treatment groups <sup>†</sup>	Adverse Event
<b>A2208 [2006]</b>	Efficacy Safety	4 x 1week	115	Ind SDDPI 100 mcg QD Ind SDDPI 200 mcg QD Ind SDDPI 300 mcg QD Ind SDDPI 400 mcg QD Ind SDDPI 600 mcg QD Formoterol 12 mcg BID OL Pbo	0 Deaths SAEs • Pbo (1: pregnancy) AE-> d/c: • Ind 300 mcg (1 metrorrhagia) • Ind 100 mcg (1 insomnia, nervousness)
<b>A2210 [2004]</b>	Safety	4 weeks	144	Ind SDDPI 400 mcg QD Ind SDDPI 800 mcg QD Placebo	0 Deaths SAEs • Ind 400 mcg (1 bronchospasm, 1 hyperventilation) • Ind 800 mcg (1 bronchospasm, 1 asthma attack, 1 ectopic pregnancy) AE-> d/c: • Ind 800 mcg (1 cough, 1 asthma attack)
<b>A2216 [2006]</b>	Safety Efficacy	1 week	436	Ind MDDPI 50 mcg QD Ind MDDPI 100 mcg QD Ind MDDPI 200 mcg QD Ind MDDPI 400 mcg QD Ind SDDPI 400 mcg QD	0 Deaths SAEs • Pbo (1: ostectomy) AE -> d/c: • Ind 50 mcg (1 2 <sup>nd</sup> degree AV block) • Ind 100 mcg (1 erythema, anxiety) • Ind 400 mcg ( asthma exac, 1 headache, palpitations)
<b>A2218 [2005]</b>	Efficacy Safety	2 weeks	25	Ind SDDPI 400 mcg QD Ind MDDPI 200 mcg QD	0 Deaths, SAEs, AE-> d/c
<b>A2222 [2006]</b>	Safety H2O effects on cough	2 weeks	87	Ind MDDPI 200 mcg QD Salmeterol 50 mcg	0 Deaths, SAEs, AE-> d/c
<b>A2228 [2008]</b>	Safety Efficacy	5 x 1 day each	45	Ind SDDPI 150 mcg QD Ind SDDPI 300 mcg QD Ind SDDPI 600 mcg QD Formoterol 12 mcg BID Pbo	0 Deaths SAEs • Pbo (1 appendicitis) • Ind 50 mcg (1 cellulitis R elbow) AE-> d/c • Pbo (1 asthma exac)
<b>A1202 2008</b>	Safety Efficacy	4 x 1 day each	41	Ind SDDPI 150 mcg QD Ind SDDPI 300 mcg QD Ind SDDPI 600 mcg QD Pbo	0 Deaths, SAEs, AE-> d/c
<b>B2102 [2010]</b>	Safety	4 x 1 day	98	Ind Maleate SDDPI 400 mcg QD Ind Xinafoate SDPPI 400 mcg QD Ind acetate SDDPI 400 mcg QD	0 Deaths, SAEs AE-> d/c • Ind Acetate 400 mcg ( 1 cold, fever) • Ind Acetate 400 mcg (1 fever, laryngitis)
<b>B2223 [2010]</b>	Safety Efficacy	2 weeks	189	Ind SDDPI 37.5 mcg BID Ind SDDPI 75 mcg QD Ind SDDPI 150 mcg QOD Pbo	0 Deaths SAEs • 2 Prerandomization (anxiety attack, anemia) • Ind 150 mcg (1 asthma exac) AE -> d/c: • Pbo elevated transaminases
<b>B2338</b>	Safety	26	805	Ind SDDPI 300 mcg QD	2 Deaths



ID Year*	Study type	Study duration	N	Treatment groups <sup>†</sup>	Adverse Event
[2008]		weeks		Ind SDDPI 600 mcg QD Salmeterol 50 mcg BID Pbo	<ul style="list-style-type: none"> <li>Ind 300 mcg (asthma exac)</li> <li>Ind 300 mcg (cardiac arrest/ asthma exac)</li> </ul> SAEs <ul style="list-style-type: none"> <li>Ind 300 mcg (2 asthma exac, 1 biliary colic, 1 stress, 1 R neck mass, 1 bacterial URTI)</li> <li>Ind 600 mcg ( 2 falls, 1 cholangitis, 3 asthma exac, 1 pneumonia, 1 atrial fibrillation, 1 foot fx, 1 splenic cyst, 1 food allergy)</li> <li>Salm ( 1 asthma exac, 1 cholelithiasis, 1 foot fx, 1 AML, 1 facial paresis, 1 pneumonia, 1 allergic dermatitis, 1 angioedema)</li> </ul> AE->d/c <ul style="list-style-type: none"> <li>Ind 300 mcg (2 asthma exac)</li> <li>Ind 600 mcg (6 asthma exac,)</li> <li>Salm (4 asthma exac)</li> </ul>
<b>B2357</b> <b>[2010]</b>	Efficacy Safety	2 weeks	502	Ind SDDPI 37.5 mcg QD Ind SDDPI 75 mcg QD Ind SDDPI 150 mcg QD Sal 50 mcg BID Pbo	0 Deaths SAEs <ul style="list-style-type: none"> <li>Substance abuse</li> </ul> AE-> d/c <ul style="list-style-type: none"> <li>Ind 18.75 mcg (1 asthma exac)</li> <li>Ind 37.5 mcg (1 ECG/Cardiac)</li> <li>Salm (2 asthma exac)</li> </ul>
* Year study subject enrollment ended <sup>†</sup> Ind SDDPI = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Ind MDDPI = Indacaterol multiple dose dry powder inhaler; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handilaler (tiotropium bromide inhalation powder); Salm = Serevent Diskus (salmeterol xinafoate inhalation powder); URTI = upper respiratory tract infection; asthma exac = asthma exacerbation AE I-> d/c = AE leading to discontinuation, primarily asthma exac or serious cardiac events					

### 5.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted with indacaterol. There were no apparent trends in cancer events and treatment with indacaterol observed in the safety datasets.

### 5.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported in the indacaterol treatment groups for COPD patients. Therefore no clinical data is available to assess indacaterol use during pregnancy.

There were 7 pregnancies reported during the use of indacaterol in patients with asthma. These include 5 patients in the Phase III trial, B2338: 1 on 300 mcg; 3 on 600 mcg and 1 on salmeterol. In addition, there were 2 patients in the Phase II program: in A2210 there was 1 in the 800 mcg group and in A2208, there was 1 who completed the 5 way crossover. These pregnancies resulted in 3 normal babies, 2 abortions and one ectopic pregnancy with a successful surgical outcome.

### 5.6.3 Pediatrics and Assessment of Effects on Growth

A pediatric waiver was granted because COPD is a disease that does not occur in the pediatric patient population.

#### **5.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

The two trials of indacaterol 75 mcg versus placebo in patients with COPD over 12 weeks, B2355 and B2354 showed no evidence of tachyphylaxis over the duration of the trial. In the 26 week trial of indacaterol 150 mcg versus placebo, B2336 also revealed a lack of tachyphylaxis in the LS means of FEV1 over the 26 week trial duration. As well, higher doses of indacaterol revealed no appreciable evidence of acute toxicity with a single dose of 600 mcg. In Study B2202, not reviewed in this submission, single orally inhaled doses of 3000 mcg were reported to be associated with an increase in pulse rate, blood pressure and QTc interval which is consistent with the expected beta2 adrenergic effects of tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia and hyperglycemia. No formal trials of potential withdrawal and rebound effects of indacaterol have been conducted.

#### **5.7 Additional Submissions / Safety Issues**

The FDA requested information of an analysis to evaluate the incidence of respiratory-related death, intubation and hospitalization in indacaterol treated patients compared to control. At the time of this review the analysis is pending.

### **6. Postmarket Experience**

Patient support program in Mexico

On January 24, 2011, Novartis submitted a summary of fatal cases from a branded patient support program ongoing in Mexico. Mexico approved indacaterol maleate SDDPI (Onbrize Breezhaler) at doses of 150 and 300 mcg once daily for the treatment of COPD on July 30, 2010. Novartis began a branded patient support program on September 26, 2010, with the last of 1316 patients enrolling in the 30 day program on January 4, 2011. In this program, participating physicians, primarily pulmonologists, are asked to enroll patients on starting indacaterol. Upon enrollment, patients are given a 10 day supply of indacaterol 150 mcg and complete a survey regarding COPD symptoms via a centralized call center. Upon completion of the initial survey, patients receive a free 30 day supply of indacaterol 150 mcg. The call center then contacts the patient for follow up surveys 2 weeks and 4 weeks after enrollment. Any adverse events reported in the surveys are transferred to Novartis pharmacovigilance.

Based on baseline survey data, the mean age of patients enrolled in the program was 66 years, and 52% of patients were female. The average symptom score was 6.6-7, on a Likert scale of 1-9, with 9 being the most severe. Based on a survey of participating physicians, the sponsor suggests that the majority of patients enrolled in the program had severe or very severe COPD.

As of January 19, Novartis reports a total of 16 deaths (1.2%) in the Mexican patient support registry. The most common cause of death was respiratory (3 pneumonia, 1 respiratory insufficiency, 1 COPD, and 1 PE), followed by cardiac (1 CHF, 2 cardiac arrest) and cancer (breast, lymphoma, GI). There were also 2 deaths of unknown cause, one GI bleed and one due to progression of Wegener's disease. Of the 16 patients who died, 11 were aged 75 years or older. The three patients who died of cardiac causes reportedly had pre-existing cardiac disease.

*Reviewer comment:*

*While these deaths represent a much larger number than the rest of the post-marketing deaths from over 50 countries put together, it is difficult to determine the clinical meaningfulness of these events in the*

*context of post-marketing reporting. The events in the Mexican patient support program were solicited as opposed to spontaneous reports in the rest of the database, which traditionally results in significant underreporting. In a severe COPD population enrolled in clinical trials, the expected mortality rate 3-5% over a one year period<sup>14, 15</sup>. The causes of death do not appear to be particularly unusual for a severe COPD patient population.*

#### Spontaneous post-marketing reports

Novartis states that the estimated patient exposure to indacaterol based on worldwide sales is approximately 57,000 patient years. Excluding the deaths reported in the Mexican patient support program, there are 10 other fatal cases in post-marketing reports. These cases ranged in age from 44 to 96 years. The most common cause of death was respiratory: COPD exacerbation, status asthmaticus, respiratory failure, and pulmonary embolus. Three patients died of unknown causes, one of which was reported as sudden death. The other three patients died of circulatory collapse following diuresis, sepsis, and myocardial infarction.

In light of the known risk of asthma-related death with LABAs, the one concerning event was the patient who died of status asthmaticus. This was a 44 year old female with a history of asthma and COPD. Approximately 6 weeks prior to the fatal event, she developed a series of exacerbations requiring systemic corticosteroids. In addition, her maintenance regimen was changed from fluticasone plus tiotropium to indacaterol (unknown dose) plus tiotropium. An autopsy was not performed.

#### *Reviewer comment:*

*While all of the details surrounding the case are unavailable, the single report of death from status asthmaticus raises the concern of LABA-related death. Unfortunately, it is not known whether the patient received a 150 mcg or 300 mcg indacaterol dose. Although her ICS was stopped, the patient was reportedly receiving concomitant oral corticosteroids.*

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** NDA 22-383 / 0027

**Drug Name:** Arcapta Neohaler (Indacaterol Maleate Inhalation Power)

**Indication(s):** Treatment of chronic obstructive pulmonary disease (COPD)

**Applicant:** Novartis Pharmaceuticals Corp.

**Date(s):** Receipt date: October 1, 2010  
PDUFA date: April 1, 2011

**Review Priority:** Standard (resubmission)

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Dongmei Liu, Ph.D.

**Concurring Reviewers:** Joan Buenconsejo, Ph.D., Team Leader  
Thomas Permutt, Ph.D., Division Director

**Medical Division:** Division of Pulmonary, Allergy, and Rheumatology Products

**Clinical Team:** Anya Harry, M.D., Ph.D., Medical Reviewer  
Theresa Michele, M.D., Team Leader  
Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director

**Project Manager:** Carol Hill

**Keywords:** NDA review, clinical studies, dose selection

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# **1 EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

Novartis proposes indacaterol maleate, a long-acting beta<sub>2</sub>-agonist (LABA), for long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Based on evaluation of 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment, the applicant claims indacaterol is effective in relieving bronchoconstriction in COPD patients. My review of the statistical evidence suggests support for the claim. However, based on the data from the dose and regimen selection trials submitted, there were no clear separation among the doses and regimens studied. Multiple doses and regimens worked equally well in terms of efficacy. Which dose and regime to approve is up to discussion at the advisory committee meeting.

## **1.2 Brief Overview of Clinical Studies**

In the original submission, the review on dose selection was mainly based on the first stage of key controlled efficacy study B2335s with adaptive design. The review on efficacy was mainly based on B2334, the second stage of B2335s, B2346 and three supportive studies B2305, B2307, and B2340. For detailed information of these studies, please refer to my review in the first cycle.

In this resubmission, the review on dose and regimen selection was mainly based on study B2356 in COPD patients and studies B2223 and B2357 in asthma patients; the review on efficacy was mainly based on studies B2336, B2354, B2355 in COPD patients.

All the three new dose and regimen selection trials were two weeks long, multi-center, randomized, double-blind, parallel-arm, placebo-controlled studies. The primary efficacy endpoint was 24-hour post-dose trough FEV<sub>1</sub> at week 2. Most of the centers that participated in the three dose and regimen selection trials were in USA.

Study B2223 was a dosing regimen study in asthma patients. It had four arms: indacaterol 37.5 mcg b.i.d., indacaterol 75 mcg q.d., indacaterol 150 q.o.d., and placebo. About 48 patients were randomized to each arm. Study B2357 was a dose ranging study in asthma patients. It had six arms: indacaterol 18.75 mcg, 37.5 mcg, 75 mcg, and 150 mcg all given once daily, plus placebo and salmeterol 50 mcg b.i.d. About 85 patients were randomized to each arm. Study B2356 had exactly the same design with Study B2357, but was conducted in COPD patients. About 91 to 94 patients were randomized to each arm.

All the three new key controlled efficacy phase 3 trials were multi-center, randomized, double-blind, parallel-arm, placebo controlled studies. B2336 was also active controlled with salmeterol.

Study B2336 had three arms: indacaterol 150 mcg once daily, salmeterol 50 mcg twice daily, and placebo. About 300 patients were randomized to each arm. The study was 26 weeks long and was conducted outside of USA. Studies B2354 and B2355 were identical in study design. They

both had two arms: indacaterol 75 mcg once daily and placebo. About 160 patients were randomized to each arm. Both studies were 12 weeks long and conducted in USA.

### **1.3 Statistical Issues and Findings**

#### Dose and Regimen Selection

The main statistical issue in this submission is dose and regimen selection.

Based on the dose ranging study B2357 in asthma patients, indacaterol 75 mcg once daily demonstrated the greatest bronchodilatory effect compared to the other indacaterol doses, 18.75 mcg, 37.5 mcg, and 150 mcg once daily. After two weeks of treatment, the 24-hour FEV<sub>1</sub> profile of indacaterol 75 mcg once daily was above the profile of other doses at most of the time points, and in most cases similar to the observed effect of salmeterol.

The dosing regimen study B2223 in asthma patients did not show clear separation among the three dosing regimens, indacaterol 37.5 mcg twice daily, 75 mcg once daily, and 150 mcg once every other day. The difference of the spirometric parameters, including trough FEV<sub>1</sub>, peak FEV<sub>1</sub>, FEV<sub>1</sub> AUC<sub>(0-12h/0-24h/0-48h)</sub>, were similar in the three arms both in day 1 and after two weeks of treatment. There was no separation among the 48-hour FEV<sub>1</sub> profiles after two weeks treatment.

The dose ranging study B2356 in COPD patients showed that the dose of 18.75 mcg once daily was ineffective. After two weeks treatment, the treatment difference of 24-hour post-dose trough FEV<sub>1</sub> between indacaterol 18.75 mcg once daily and placebo was 0.07 L with a 95% CI of (0.02, 0.12), which was way below the minimum clinical important difference (MCID) of 0.12 L (defined by the applicant). The dose of 150 mcg once daily appeared to achieve bronchodilation more rapidly than the other doses, but lost its advantage after two weeks treatment. Considering indacaterol is proposed to be used as a long-term maintenance bronchodilator treatment, the 150 mcg dose's rapid effect in day 1 may not be important, especially balancing with safety concerns on higher dose. On day 1, the 75 mcg dose showed marginal effect and the 37.5 mcg dose showed unsatisfactory effect. From the week 2 data, it appears indacaterol 37.5 mcg, 75 mcg, and 150 mcg once daily worked equally well in terms of bronchodilatory effect.

#### Trough FEV<sub>1</sub>

The primary efficacy endpoint in the key controlled efficacy studies was the 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment.

In Study B2336, the treatment effect of indacaterol 150 mcg once daily measured by the 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment was 1.45 L with a standard error of 0.02 L. Comparing to the placebo arm, the improvement in trough FEV<sub>1</sub> by indacaterol 150 mcg once daily was 0.17 L with a 95% CI of (0.13 L, 0.20 L), which was statistically significant and the improvement exceeded the MCID of 0.12 L. The 12-week trough FEV<sub>1</sub> of indacaterol 150 mcg once daily also exceeded that of salmeterol 50 mcg twice daily (1.39 L with a standard error of

0.02 L). The difference between the two treatments was statistically significant with p value less than 0.001.

In Study B2354, the treatment effect of indacaterol 75 mcg once daily measured by the 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment was 1.38 L with a standard error of 0.01 L. Comparing to the placebo arm, the improvement in trough FEV<sub>1</sub> by indacaterol 75 mcg once daily was 0.12 L with a 95% CI of (0.08 L, 0.15 L), which was statistically significant and the improvement reached the MCID of 0.12 L.

In Study B2355, the treatment effect of indacaterol 75 mcg once daily measured by the 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment was 1.49 L with a standard error of 0.02 L. Comparing to the placebo arm, the improvement in trough FEV<sub>1</sub> by indacaterol 75 mcg once daily was 0.14 L with a 95% CI of (0.10 L, 0.18 L), which was statistically significant and the improvement exceeded the MCID of 0.12 L.

### SGRQ

The indacaterol 150 mcg dose in two key controlled efficacy studies, B2336 and B2346, demonstrated a significant improvement in SGRQ total scores, as well as each component scores, in comparison to placebo. In addition, the improvement exceeded the MCID between indacaterol and placebo of 4 units. After 12 weeks treatment, the improvement of SGRQ total score by indacaterol 150 mcg comparing to placebo was -4.8 with 95% CI of (-7.2, -2.4) in Study B2346; -6.3 with 95% CI of (-8.2, -4.3) in Study B2336. The superiority of indacaterol over placebo in SGRQ scores was confirmed in all doses.

However, the differences among indacaterol doses were small. Based on the analysis of COPD three-month efficacy population pooled data, comparing to placebo, the improvement of SGRQ total scores after 12 weeks treatment was -3.8 with a 95% CI of (-5.3, -2.3) in 75 mcg, -4.6 with a 95% CI of (-5.5, -3.6) in 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) in 300 mcg. The percentage of patients who had an improvement of SGRQ total score greater or equal to 4 units from baseline was 49.1% in 75 mcg, 52.3% in 150 mcg, 51.6% in 300 mcg, and 39.5% in placebo. There was no statistically significant difference among difference doses. Considering the evidence collectively, whether the improvement in SGRQ scores could be claimed as an advantage for the dose of 150 mcg is questionable.

## 2 INTRODUCTION

### 2.1 Overview

#### 2.1.1 Class and Indication

Novartis proposes indacaterol maleate, a long-acting beta<sub>2</sub>-agonist (LABA), for long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). COPD is characterized by air flow limitation that is not fully reversible, is usually progressive, and is associated with pathological changes in the lung — a combination of obstructive bronchiolitis and parenchymal destruction. COPD is a major public health problem and is currently the fourth leading cause of chronic morbidity and mortality in the USA. Inhaled beta<sub>2</sub>-agonists have a bronchodilator effect and are widely used in the treatment of COPD. Currently, they are often used as monotherapy or in combination with other classes of medication, such as anticholinergic bronchodilators or inhaled corticosteroids. In this application, indacaterol is proposed to be used as a monotherapy for COPD.

The developed drug in this application is in dry powder formulation. Inhalation powder hard capsules is administered once daily (Q.D.) via a single dose dry powder inhaler (SDDPI). The applicant is requesting approval for two dosage strengths, 75 mcg and 150 mcg.

#### 2.1.2 History of Drug Development

The original NDA was submitted on December 18, 2008. In the original submission, the applicant proposed indacaterol as a once daily maintenance treatment of COPD, with two dosage strengths — 150 mcg and 300 mcg. The drug formulation was the same as in this resubmission, single dose dry powder inhalation. A few deficiencies were identified in the first review cycle and a complete response letter was issued on October 16, 2009. The reasons for the action were quoted below:

- 1. The submitted data do not provide substantial evidence of safety to support the use of Arcapta Neohaler at the proposed doses of 150 mcg and 300 mcg once daily in patients with chronic obstructive pulmonary disease (COPD). At the proposed doses, there were unacceptable higher frequencies of cardiovascular and cerebrovascular serious adverse events compared to placebo and to formoterol in patients with COPD, and possible asthma related deaths compared to salmeterol in patients with asthma.*
- 2. The submitted studies do not show a clinically meaningful efficacy difference between the 75 mcg once daily dose compared to the 150 mcg or 300 mcg once daily doses or the 150 mcg dose compared to the 300 mcg dose.*
- 3. An appropriate dosing frequency has not been explored in clinical studies.*
- 4. The submitted data do not provide substantial evidence to support use of two different doses in patients with COPD. The data submitted did not show a clinically meaningful*

*advantage of 300 mcg dose over 150 mcg dose, especially in regards to potential safety disadvantages associated with the administration of a higher dose.*

The division requested the applicant to 1) conduct clinical studies to explore efficacy and establish the safety of doses lower than the proposed 150 mcg dose and to study various dosing frequencies to support the proposed dosing frequency; 2) provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose to support approval of two doses of indacaterol in COPD patients.

An End-of-Review meeting was held on November 24, 2009. Further comments on dose selection and dosing frequency were conveyed to the applicant. The meeting minutes were quoted below:

*We consider LABAs as medications which have a narrow therapeutic index and which require careful and precise dose selection in order to balance the risk to benefit ratio of their use both in patients with COPD and asthma. Since asthma patients by definition possess significant bronchoreactivity to beta-2 agonists and are more sensitive to the severe adverse events that have been linked to the use of beta-2 agonists in asthma patients (death, intubations), our thinking has evolved such that we believe that the safety and efficacy of LABAs and other beta-2 agonists are best characterized first in asthma patients, and then in COPD patients. Moving forward, we feel that characterizing the dose, dosing frequency, and safety of indacaterol in the patient population most sensitive to both the bronchodilator and adverse event effects of LABAs will provide for selection of the safest while still effective dose in patients with asthma and COPD both. Thus, prior to further development of indacaterol for patients with COPD we recommend that you:*

- *Assess the dose and dosing frequency fully in patients with asthma (including doses less than 150 mcg and at dosing intervals both less than and greater than once daily)*
- *Assess the long-term safety of a dose or doses of indacaterol in patients with asthma.*

*Once a relatively safe but effective dose and dosing frequency of indacaterol has been determined in patients with asthma, development should then proceed in patients with COPD.*

After the communication, the applicant conducted new clinical studies on dose selection and dosing frequency in both asthma and COPD patients. In this resubmission, the application changed the proposed dosage strengths from 150 mcg and 300 mcg to 75 mcg and 150 mcg. The dosing frequency remains as once daily.

There will be an advisory committee meeting on March 8, 2011 to discuss the approvability of this application.

### **2.1.3 Specific Studies Reviewed**

In the original submission, the review on dose selection was mainly based on the first stage of key controlled efficacy study B2335s with adaptive design. The review on efficacy was mainly based on the second stage of B2335s, B2334 and B2346 and three supportive studies B2305, B2307, and B2340. For detailed information of these studies, please refer to my review in the first cycle, which is available in the appendix.

In this resubmission, the review on dose selection was mainly based on study B2356 in COPD patients and studies B2223 and B2357 in asthma patients; the review on efficacy was mainly based on studies B2336, B2354, B2355 in COPD patients. In some cases, the efficacy results from the new studies were compared to the results from the studies in the original submission.

## **2.2 Data Sources**

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location < <\\CDSESUB1\EVSPROD\NDA022383\022383.enx>>. The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.3.5.

### 3 STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study Design

The design of the dose and regimen selection trials is summarized in Table 1. All three new studies submitted to the complete response were two weeks long, randomized, double blind, parallel-arm, multi-center, placebo controlled clinical trials. Studies B2356 and B2357 were also active controlled with salmeterol. Study B2223 was designed to compare three difference indacaterol dosing regimens (75 mcg once daily, 37.5 mcg twice daily, and 150 mcg once every other day) in patients with persistent asthma. Study B2357 was designed to assess the efficacy and safety of difference doses (ranging from 18.75 mcg to 150 mcg once daily) of indacaterol in patients with persistent asthma. The design of Study B2356 was identical to Study B2357, but was conducted in patients with COPD to assess the dose response of indacaterol in the target population. All three studies had a 2-week run-in period to allow and monitor patient stability.

Table 1 Design of dose and regimen selection trails.

Study ID (Period)	Location	Study population, design and treatment duration	Number of Patients randomized	Treatment arms (Ind=Indacaterol) (For=Formoterol) (Tio=Tiotropium) (Sal=Salmeterol)
<b>B2223</b> (Mar. 2010 – Jul 2010)	USA Europe Jordan	Dosing regimen	48	Ind 37.5 mcg (b.i.d)
		trial in asthma	48	Ind 75 mcg (q.d.)
		patients,	48	Ind 150 mcg (q.o.d.)
		16 days,	47	placebo
		Parallel-arm, Placebo controlled		
<b>B2357</b> (Feb. 2010 – Jul. 2010)	USA	Dose ranging trial	85	Ind 18.75 mcg (q.d.)
		in asthma patients,	85	Ind 37.5 mcg (q.d.)
		2 weeks,	84	Ind 75 mcg (q.d.)
		Parallel-arm,	86	Ind 150 mcg (q.d.)
		Placebo and active	86	Sal 50 mcg (b.i.d)
		controlled	85	Placebo (double dummy)
<b>B2356</b> (Mar. 2010 – Jul. 2010)	USA	Dose ranging trial	92	Ind 18.75 mcg (q.d.)
		in COPD patients,	91	Ind 37.5 mcg (q.d.)
		2 weeks,	94	Ind 75 mcg (q.d.)
		Parallel-arm,	92	Ind 150 mcg (q.d.)
		Placebo and active	92	Sal 50 mcg (b.i.d)
		controlled	91	Placebo (double dummy)

The design of the key controlled efficacy studies is summarized in Table 2. All of the key controlled efficacy studies were multi-center, randomized, double-blind, parallel-arm, placebo controlled studies. Studies B2335s, B2334, and B2346 were submitted in the original NDA. Studies B2336, B2354, and B2355 were new studies submitted to the complete response. B2336 was also active controlled with salmeterol. In all key controlled efficacy studies, following a 2-

week run-in period, patients were randomized into treatment arms with stratification on smoking status (ex-smoker vs. current smoker). Balance of randomization across treatment arms was controlled on the country level in Study B2336.

Table 2 Design of key controlled efficacy studies.

Study ID (Period)	Location	Design and treatment duration	Number of Patients randomized	Treatment arms (Ind=Indacaterol) (For=Formoterol) (Tio=Tiotropium) (Sal=Salmeterol)
<b>B2334</b> (Oct. 2006 - Jul. 2008)	West Europe, East Europe, South and Central America, Asia	52 weeks, Parallel-arm, Placebo and active controlled	405 396 399 400	Ind 300 mcg Ind 600 mcg Placebo (double dummy) For 12 mcg (b.i.d)
<b>B2335s</b> (Apr. 2007 - Aug. 2008)	USA, Canada, South America, West Europe, Asia	1 <sup>st</sup> stage – 2 weeks, (dose selection) 2 <sup>nd</sup> stage – 26 weeks, (efficacy and safety) Parallel arm, Placebo and active controlled	107 105 / 325 † 110 / 341 † 102 104 / 294 † 112 112 / 331 †	Ind 75 mcg Ind 150 mcg * Ind 300 mcg * Ind 600 mcg Placebo (double dummy) * For 12 mcg (b.i.d) Tio 18 mcg * (open-label)
<b>B2346</b> (Feb. 2008 - Jul. 2008)	USA, Belgium, New Zealand	12 weeks, Parallel-arm, Placebo controlled	211 205	Ind 150 mcg Placebo
<b>B2336</b> (Nov. 2007 – Jan. 2009)	Canada, South America, Europe, Asia	26 weeks, Parallel-arm, Placebo and active controlled	333 334 335	Ind 150 mcg Sal 50 mcg b.i.d. Placebo (double dummy)
<b>B2354</b> (Jan. 2010 – Jul. 2010)	USA	12 weeks, Parallel- arm, Placebo controlled	163 160	Ind 75 mcg Placebo
<b>B2355</b> (Jan. 2010 – Jun. 2010)	USA	12 weeks, Parallel- arm, Placebo controlled	159 159	Ind 75 mcg Placebo

- Studies submitted in the original NDA.
- \* Treatment arms that were continued into stage 2.
- † Sample size in stage 2.
- All indacaterol arms were dosed once daily.

### 3.1.2 Efficacy Endpoints and Assessment Schedule

The primary efficacy endpoints in all dose and regimen selection studies were 24-hour post-dose trough FEV<sub>1</sub> after 2 weeks treatment. The 24-hour post-dose trough FEV<sub>1</sub> was defined as the average of two FEV<sub>1</sub> measurements taken in clinic after 23 hour 10 minute and 23 hour 45 minute.



In Study B2223, 24-hour spirometry profiling was assessed in all patients. In Studies B2356 and B2357, 24-hour spirometry profiling was assessed in a subset of patients. The measurements were taken in clinics and patients who consented to participate in the 24-hour spirometry profiling were asked to remain at the clinic overnight or in appropriate accommodation.

Other efficacy endpoints used for dose and regimen selection include peak FEV<sub>1</sub>, weighted mean FEV<sub>1</sub> over 0-4 hours post-dose, weighted mean FEV<sub>1</sub> over 0-12 hours post-dose, etc. Weighted mean FEV<sub>1</sub> over 0-4 hours was defined as standardized AUC for FEV<sub>1</sub> between 0 and 4 hours post-dose. The standardization was calculated as the sum of trapezoids between two time points divided by the length of time.

In Study B2223, the spirometry assessments were taken at the following time points:

- On day -1 at: 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 8 hrs, 11hrs 10mins, 11hrs 45mins, 12hrs 10mins, 12hrs 30mins, 13, 14, 16, 20 and 22 hrs post dose.
- On day 1 at: 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 11hrs 10mins, 11hrs 45mins post dose
- On day 2 and 3 at: pre-dose
- On days 15 and 16 matched timings for day -1.
- On day 17 at: 50 and 15 mins pre-dose, 6 hrs post dose
- On day 18 and 19 at: pre-dose

In Studies B2356 and B2357, the spirometry assessments were taken at the following time points:

- On day 1 at: 50, 25 and 15 min pre-dose, 5, 15, 30 mins, 1, 2, 4, 8 hrs, 11hrs 10mins, 11hrs 45mins post dose
  - On day 2\* at: 23 hrs 10 mins, 23 hrs 45 mins post-dose
  - On day 14 matched timings for day 1.
  - On day 15 (in the 24-h spirometry subgroup) at: 14, 20, 22 hrs post-dose
  - On day 15\* (in all patients) at: 23 hrs 10 mins, 23 hrs 35 mins, 23 hrs 45 mins post-dose,
- \* Time points relative to morning dose at previous day's visit.

The primary efficacy endpoints in all key controlled efficacy studies were 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment. The secondary efficacy endpoints include peak FEV<sub>1</sub>, FVC (forced vital capacity), PEF (peak expiratory flow), SGRQ (St. George's respiratory questionnaire) score, TDI (transitional dyspnea index) focal score, COPD exacerbation, rescue medication use, etc. This review only includes details on trough FEV<sub>1</sub>, serial spirometry profiling and SGRQ score. A brief summary on COPD exacerbations is also available. However, since the division and the applicant did not reach agreement on definition of COPD exacerbation, detailed review on this efficacy endpoint are not included. In this application, COPD exacerbation is defined as a new onset or worsening of more than one respiratory symptom (i.e. dyspnea, cough, sputum purulence or volume, or wheeze) presented for more than 3 consecutive days, and at least one of the following: documented change or increase in COPD related treatment due to worsening symptoms and/or documented COPD-related hospitalizations or emergency room visits.

In Study B2336, 24-hour post-dose trough FEV<sub>1</sub> was measured at clinic visit at day 2, 85, and 183. Four hour serial spirometry was conducted in the clinic, in a subset of patients (about 100 patients in each arm), at day 1 and after 12, and 26 weeks treatment.

In Studies B2354 and B2355, 24-hour post-dose trough FEV<sub>1</sub> was measured at clinic visit at day 2 and 85. Only in Study B2355, 24-hour serial spirometry was conducted in a subset of patients (about 120 patients in each arm) after 12 weeks treatment.

In all key controlled efficacy studies, a patient diary to record daily clinical symptoms, rescue medication use, and any adverse events was provided to all patients. SGRQ scores were derived from the diary information. At each study visit, all COPD exacerbations, regardless of treatment, were recorded on the COPD exacerbation episode electronic Case Report Form.

### **3.1.3 Patient Disposition, Demographic and Baseline Characteristics**

Since the study duration was short in all dose and regimen selection trials, majority of patients (92% to 96%) in those studies completed the trial. In all three studies, treatment groups were evenly matched in terms of baseline demographics. Detailed information on patient disposition, demographic and baseline characteristics summary for dose and regimen selection trials is available in appendix.

The summary of patient disposition in key controlled efficacy studies is given in Table 3. About 84% to 91% enrolled in the key controlled efficacy studies completed the study. The discontinuation occurred more frequently in placebo arm than in other treatment arms in all three studies. The primary reasons for premature discontinuation were adverse events, withdrawal of consent, and protocol deviation. In study B2336, the number of patients who discontinued prematurely due to unsatisfactory therapeutic effect was significantly higher in placebo arm (15 out of 335) than in other arms (1 out of 333 in indacaterol 150 mcg and 2 out of 334 in salmeterol). The premature discontinuation rate in placebo arms due to unsatisfactory therapeutic effect in the other two studies was not as high as that in Study B2336.

The intent-to-treat (ITT) population in Study B2336 was defined as all randomized patients who received at least one dose of study drug. The full analysis set (FAS) in Studies B2354 and B2355 was defined the same. Patients in ITT/FAS population were analyzed according to the treatment to which they were randomized.

The per-protocol (PP) population in all key controlled efficacy studies was defined as all patients of the ITT or FAS population without any major protocol deviations. Patients in PP population were analyzed according to the treatment they received.

The primary analysis for the primary and important secondary efficacy endpoints was based on the ITT population in study B2336, and FAS population in Studies B2354 and B2355. All the efficacy results reported in this review were based on ITT/FAS population.

Table 3 Patient disposition of key controlled efficacy studies.

Study	B2336			B2354		B2355	
Treatment	Ind 150 mcg	Salmeterol	Placebo	Ind 75 mcg	Placebo	Ind 75 mcg	Placebo
Randomized	333	334	335	163	160	159	159
Exposed	330	333	335	163	160	159	159
Completed	289	284	265	144	130	148	142
Discontinued	44	50	70	19	30	11	17
ITT/FAS*	330	333	335	163	160	159	158
PP	293	293	297	145	139	119	129
Primary reason for premature discontinuation							
Adverse events	18	16	13	9	10	3	3
Subject withdrew consent	8	12	22	4	9	5	6
Protocol deviation	9	11	13	3	4	1	1
Lost to follow-up	2	5	2	1	1	1	2
Administrative problems	1	1	0	0	0	0	1
Unsatisfactory therapeutic effect	1	2	15	1	3	0	4
Abnormal lab values	2	1	2	0	1	1	0
Abnormal test procedure results	2	1	1	1	0	0	0
Death	1	0	2	0	2	0	0
Patient's inability to use the device	0	1	0	0	0	0	0

\* FAS = full analysis set.

The study population in all three new key controlled efficacy studies consisted of male and female patients who were 40 years of age or older with moderate to severe COPD (post-bronchodilator FEV<sub>1</sub> < 80% and ≥30% of the predicted normal value; post-bronchodilator FEV<sub>1</sub>/FVC < 70%) and a smoking history of at least 20 pack years. Most patients were Caucasians. In all three key controlled efficacy studies, treatment groups were evenly matched in terms of baseline demographics. The demographic and baseline characteristics summary in the randomized populations of all three new key controlled efficacy studies is given in Table 4.

Table 4 Demographic and baseline characteristics of patients in key controlled efficacy studies.

Study		B2336			B2354		B2355	
Treatment		Ind 150 mcg	Salmeterol	Placebo	Ind 75 mcg	Placebo	Ind 75 mcg	Placebo
Age (years)	N	330	333	335	163	160	159	159
	Mean	63.2	63.4	63.9	64.0	64.1	61.3	61.5
	SD	8.7	9.2	8.6	8.3	9.4	9.8	9.9
	Median	63.5	64	64	64.0	64.0	61.0	62.0
	Min - Max	41 - 85	41 - 86	42 - 89	44 - 85	40 - 90	40 - 82	42 - 86
Age group	19 - 39 yrs	0	0	0	0	0	0	0
	40 - 64 yrs	181 (55)	178 (54)	180 (54)	85 (52)	84 (53)	96 (60)	94 (59)
	N (%) ≥ 65 yrs	149 (45)	155 (47)	155 (46)	78 (48)	76 (47)	63 (40)	65 (41)
Sex	Male	238 (72)	249 (75)	258 (77)	89 (55)	87 (54)	83 (52)	89 (56)
	N (%) Female	92 (28)	84 (25)	77 (23)	74 (45)	73 (46)	76 (48)	70 (44)
Race	Caucasian	250 (76)	258 (78)	251 (75)	145 (89)	146 (91)	151 (95)	147 (93)
	N (%) Black	1 (0.3)	0	1 (0.3)	10 (6)	10 (6)	7 (4)	9 (6)
	Asian	53 (16)	52 (16)	56 (17)	5 (3)	3 (2)	0	0
	Native American	1 (0.3)	0	1 (0.3)	0	0	0	1 (0.6)
	other	25 (8)	23 (7)	26 (8)	3 (2)	1 (0.6)	1 (0.6)	2 (1.3)
Duration of COPD (years)	N	330	333	335	163	160	159	159
	Mean	6.5	6.4	6.6	7.2	7.3	6.7	6.8
	SD	5.7	5.7	5.8	6.3	6.4	6.1	6.1
	Median	4.7	5.0	5.3	5.5	4.7	5.6	4.7
	Min - Max	0 - 39	0 - 31	0 - 30	0 - 31	0 - 36	0 - 31	0 - 30
COPD severity	At risk	2 (0.6)	3 (0.9)	8 (2.4)	0	0	0	0
	Mild	7 (2.1)	7 (2.1)	5 (1.5)	0	0	0	0
	N (%) Moderate	182 (55)	179 (54)	174 (52)	96 (59)	89 (56)	109 (69)	87 (55)
	Severe	139 (42)	141 (42)	145 (43)	67 (41)	69 (43)	48 (30)	72 (45)
	Very severe	0	2 (0.6)	3 (0.9)	0	2 (1.3)	2 (1.3)	0
	Missing	0	1 (0.3)	0	0	0	0	0
ICS use	No	181 (55)	181 (54)	200 (60)	70 (43)	76 (47)	96 (60)	103 (65)
	N (%) Yes	149 (45)	152 (46)	135 (40)	93 (57)	84 (53)	63 (40)	56 (35)
Smoking history	Ex-smoker	178 (54)	179 (54)	185 (55)	92 (56)	89 (56)	67 (42)	64 (40)
	Smoker	152 (46)	154 (46)	150 (45)	71 (44)	71 (44)	92 (58)	95 (60)

### 3.1.4 Statistical Methodologies

The primary (24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment) and secondary (SGRQ scores) efficacy endpoints included in this review were analyzed using a mixed effect model. The model contained treatment as a fixed effect with the baseline variable of interest, FEV<sub>1</sub> prior and post to inhalation of salbutamol/albuterol (components of SABA reversibility), FEV<sub>1</sub> prior and post to inhalation of ipratropium (components of anti-cholinergic reversibility) as covariates. To reflect the randomization scheme, the model also included the smoking status as fixed effects with center as a random effect. In study B2336, since the study centers were located in multiple countries, country was included in the model as a fixed effect. The random effect of center was nested within country. In Studies B2354 and B2355, inhaled corticosteroid use at trial entry was included as a fixed effect.

In addition to the mixed effect model mentioned above, responder analysis was applied to SGRQ scores. Patients with a clinically important improvement of 4 units or greater in SGRQ total score was defined as responders. The responder analysis was based on logistic regression with the same covariates as those in the mixed effect model.

A brief summary of COPD exacerbation is included in this review. The summary statistics reported include the median time to the first exacerbation, the number of exacerbations, total exposure time, and exacerbation rate by treatment arms.

The data imputation method specified by the sponsor was the last observation carried forward (LOCF) method. Any of the 23 hour 10 minute and the 23 hour 45 minute values contributing to the trough FEV<sub>1</sub> that were taken within 6 hours of rescue medication use or that were outside the 22 hour to 25 hour post-dose time window were considered missing values. If both values were missing, or if the patient withdrew from the study, then trough FEV<sub>1</sub> was regarded as missing. A missing trough FEV<sub>1</sub> value at week 12 was replaced by carrying forward trough FEV<sub>1</sub> from the last evaluable visit as long as the visit was not prior to Day 29. The primary analysis on trough FEV<sub>1</sub> at week 12 was based on imputed data. In this case, since majority of patients completed the study, there were not much missing data. The data imputation method does not affect the analysis results significantly. Otherwise, sensitivity analysis with alternative data imputation methods should have been applied.

Missing SGRQ scores were imputed by LOCF as well. A missing SGRQ score at week 12 was replaced by carrying forward SGRQ score from the last evaluable visit as long as the visit was not prior to week 4. The primary analysis was based on imputed data. Since SGRQ is a patient reported outcome, for patients who withdrew from the study due to lack of efficacy or adverse event, imputing data based on LOCF may introduce bias. To avoid the problem, this reviewer also did analysis on both SGRQ data without imputation (i.e. patients who had missing SGRQ score at week 12 were excluded from the analysis) and data imputed by baseline observation carried forward method (BOCF, i.e. patients who had missing SGRQ score at week 12 were included in the analysis and their SGRQ score at week 12 was replaced by carrying forward SGRQ score from baseline). All three sets of results were reported in section 3.1.6.

### **3.1.5 Dose Selection**

One of the major deficiencies identified in the original NDA was dose and regimen selection. After the applicant received the complete response letter, three new dose and regimen selection trials were conducted to address this issue. This section reports the results from these three trials.

Study B2223 was the asthma dosing regimen trial, which included four treatment arms: indacaterol 37.5 mcg b.i.d., indacaterol 75 mcg q.d., indacaterol 150 q.o.d., and placebo. Figure 1 shows the spirometric parameters used for dosing regimen selection. The black curves show the spirometric parameters by treatment arms in day 1 (after the first dose); while the red curves is for day 15/16 (after the last dose). Note that the final dose with indacaterol 150 mcg q.o.d. was administered on day 15; the final doses for indacaterol 75 mcg q.d. and 37.5 mcg b.i.d. were administered on day 16 to ensure an equivalent total dose is administered for all treatment arms.

For all spirometric parameters considered, there were small differences among the three dosing regimens in both day 1 and day 15/16. It is hard to distinguish which dosing regimen is the best.

Other than the spirometric parameters, it is also important to check the FEV<sub>1</sub> time serial profile for dosing regimen selection. Figure 2 and Figure 3 give the FEV<sub>1</sub> time serial profile after the first dose and the last dose in Study B2223. In day 1, there were good separations among treatment arms. From top to bottom, the treatment arms is in order of indacaterol 150 mcg q.o.d., indacaterol 75 mcg q.d., indacaterol 37.5 mcg b.i.d., and placebo. Since FEV<sub>1</sub> data were only available at one time point from 12 hours post-dose to 24 hours post-dose, the curves in the plot do not give us information how indacaterol 37.5 mcg b.i.d. performs comparing to other dosing regimens after the second dose. The trough FEV<sub>1</sub> at the end of day 2 were almost the same for the three indacaterol arms, with indacaterol 37.5 mcg b.i.d. having marginally numeric advantage than the other two. After two weeks treatment, the separations among different dosing regimens were lost. The FEV<sub>1</sub> time serial profile at day 15/16 for all three indacaterol arms intersected.

Study B2357 was the asthma dose ranging trial, which included six treatment arms: indacaterol 18.75 mcg, 37.5 mcg, 75 mcg, and 150 mcg all given once daily, plus placebo and salmeterol 50 mcg b.i.d. The spirometric parameters summary at day 1 and after two weeks treatment was given in Figure 4. In all the parameters, there was a clear dose response in day 1, with the highest dose 150 mcg having the greatest bronchodilatory effect. After two weeks treatment, indacaterol 75 mcg peaked in all the parameters and in most cases similar to those observed in the salmeterol arm. Looking at the FEV<sub>1</sub> time serial profile (Figure 5), in day 1, indacaterol 75 mcg and 150 mcg were more effective than doses of 18.75 and 37.5 mcg. After two weeks treatment, FEV<sub>1</sub> scores improved in all the indacaterol arms compared to day 1, with 75 mcg being the most effective and similar to that observed in the salmeterol arm. In asthma population, it appears that indacaterol 75 mcg is the most effective dose.

One thing need to point out is that the baseline FEV<sub>1</sub> scores in the two asthma studies (Studies B2223 and B2357) were not comparable. As shown in Figure 6, baseline FEV<sub>1</sub> in Study B2223 was around 0.26 to 0.27 L, but the baseline FEV<sub>1</sub> in Study B2357 was around 0.24 L. Patients in Study B2223 reached about 0.3 to 0.35 L improvement in FEV<sub>1</sub> after the first dose; while patients in Study B2357 got about 0.4 to 0.45 L improvement. The patient population had different baseline disease characteristics in the two studies, thus the results in the two studies are not comparable. Patients in Study B2223 were not as sensitive as patients in Study B2357 in terms of response to bronchodilation drugs. It would have been better if the patient population were about the same in the two studies.

Study B2356 was the COPD dose ranging trial, which had exactly the same design with Study B2357, but was conducted in COPD patients. The spirometric parameters summary at day 1 and after two weeks treatment for Study B2356 was given in Figure 7. Again in all the parameters, there was a clear dose response in day 1, with the highest dose 150 mcg having the greatest bronchodilatory effect. After two weeks treatment, indacaterol 37.5 mcg, 75 mcg and 150 mcg reached about the same level in trough and peak FEV<sub>1</sub>. The 18.75 mcg dose was clearly not as effective as the higher doses. In terms of FEV<sub>1</sub> AUC<sub>(0-12h/0-24h/12-24h)</sub>, 37.5 mcg was better than all other doses.

Looking at the FEV<sub>1</sub> time serial profile (Figure 8), in day 1, there was a clear dose response, the higher the dose was, the greater the FEV<sub>1</sub> improvement at all time points reached. In day 1, indacaterol 150 mcg reached the same bronchodilatory effect as salmeterol. After two weeks treatment, there was little change for indacaterol 150 mcg and salmeterol, but indacaterol 18.75 mcg, 37.5 mcg and 75 mcg all being improved and indacaterol 37.5 mcg, 75mcg, and 150 mcg all had the similar effect as that of salmeterol. In COPD population, there was not clear separation among indacaterol 37.5 mcg, 75 mcg and 150 mcg. It is hard to select among the three doses.

Although indacaterol 150 mcg appeared to achieve bronchodilation more rapidly than the lower doses in day 1, this advantage did not appear to persist at Week 2. Given indacaterol is proposed to be used as a long term maintenance treatment, it is important to consider the long term benefit and safety of the product.

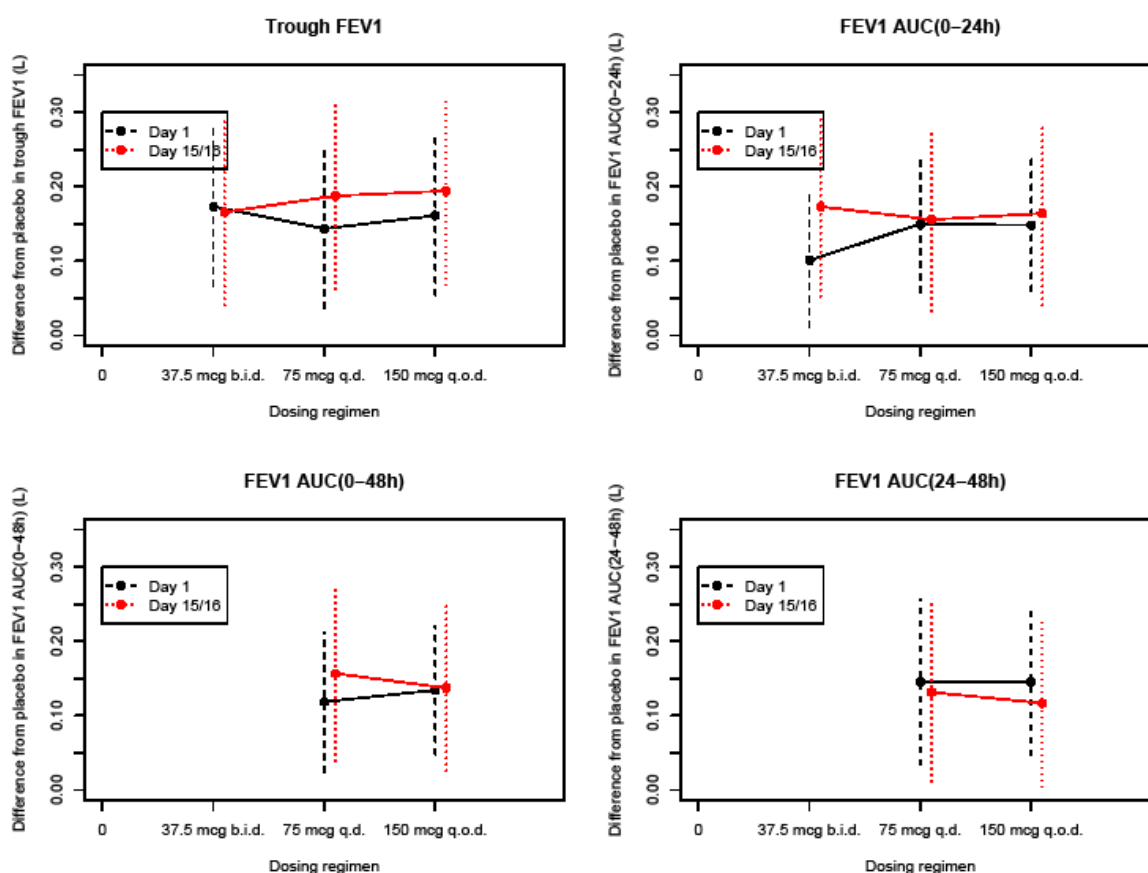


Figure 1 Study B2223 summary of spirometric parameters at day 1 and after 2 weeks treatment.

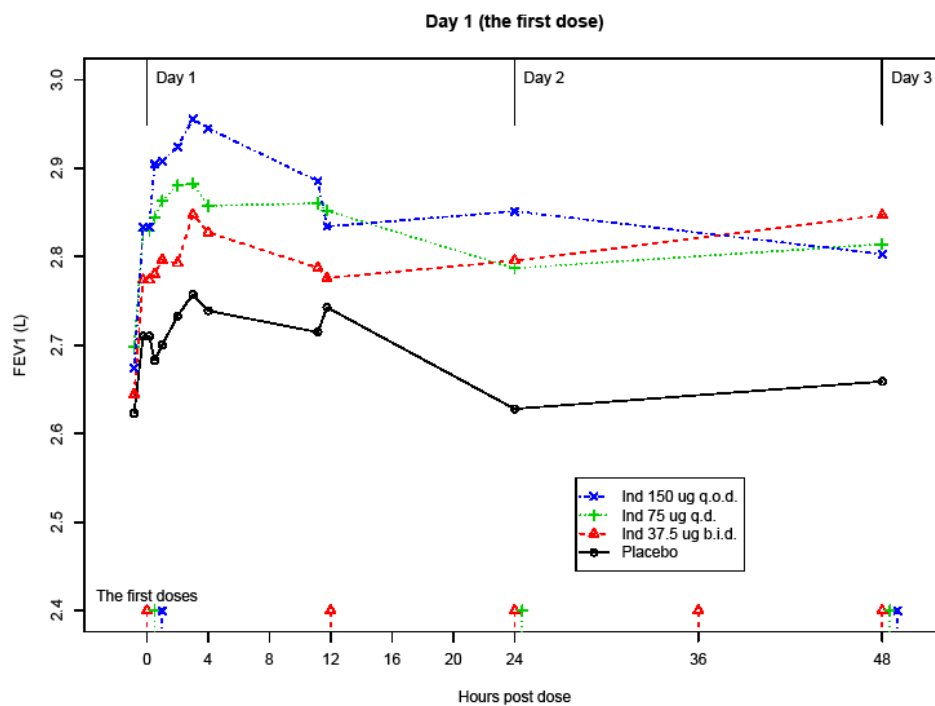


Figure 2 Study B2223 48-hour FEV<sub>1</sub> profile after the first dose.

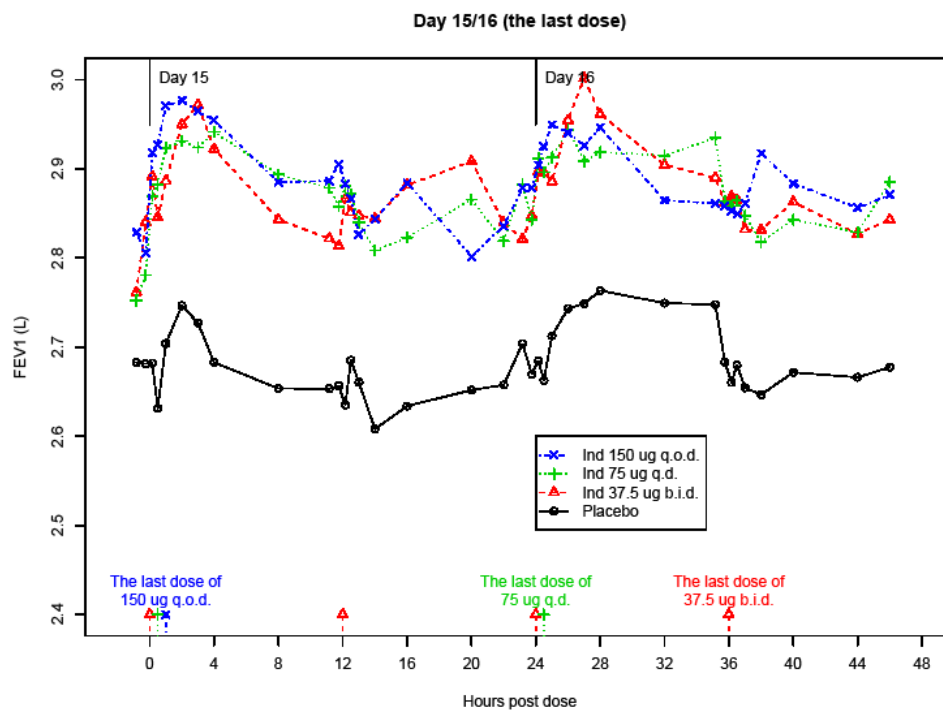


Figure 3 Study B2223 48-hour FEV<sub>1</sub> profile after the last dose.



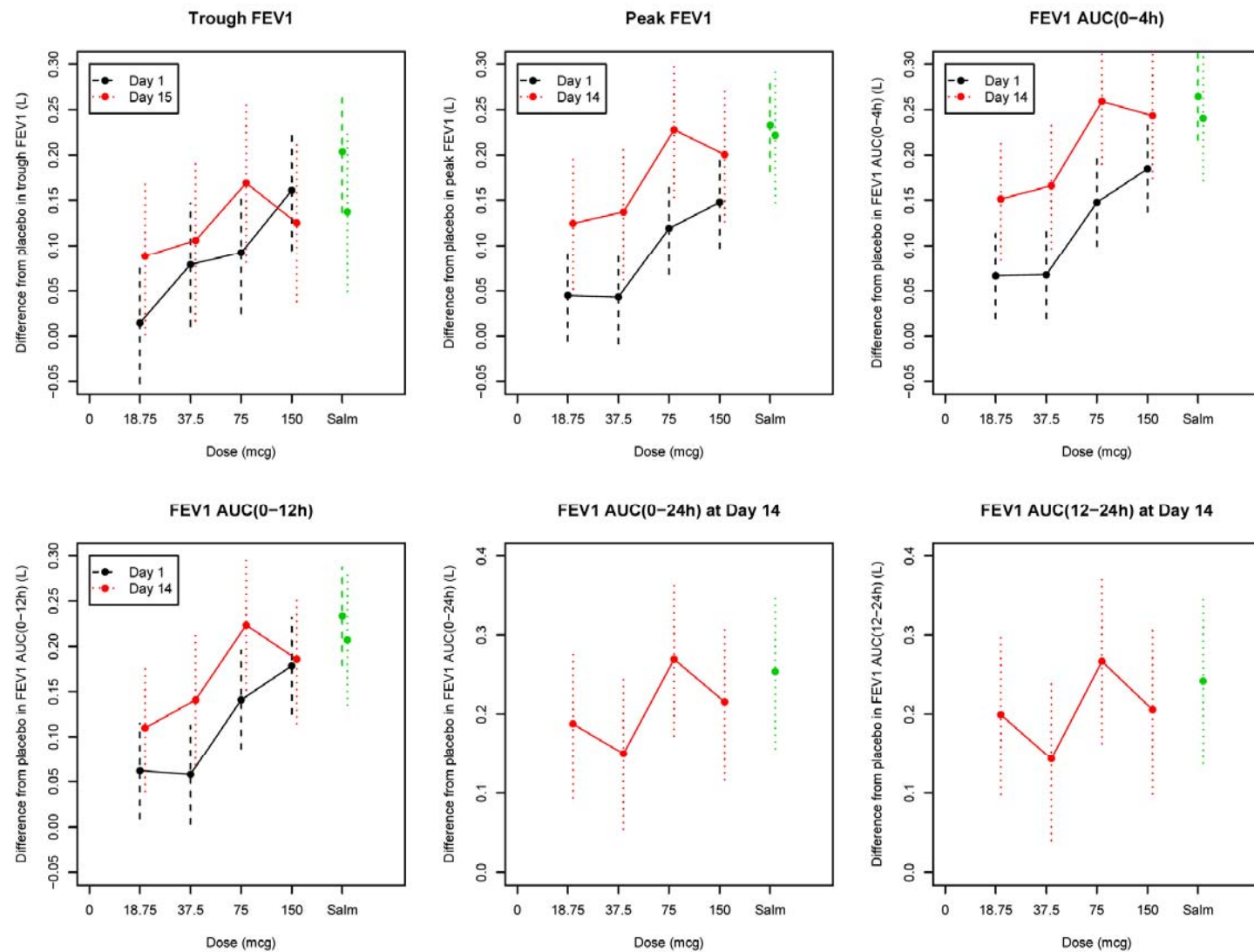


Figure 4 Study B2357 Summary of spirometric parameters at Day 1 and after 2 weeks treatment.

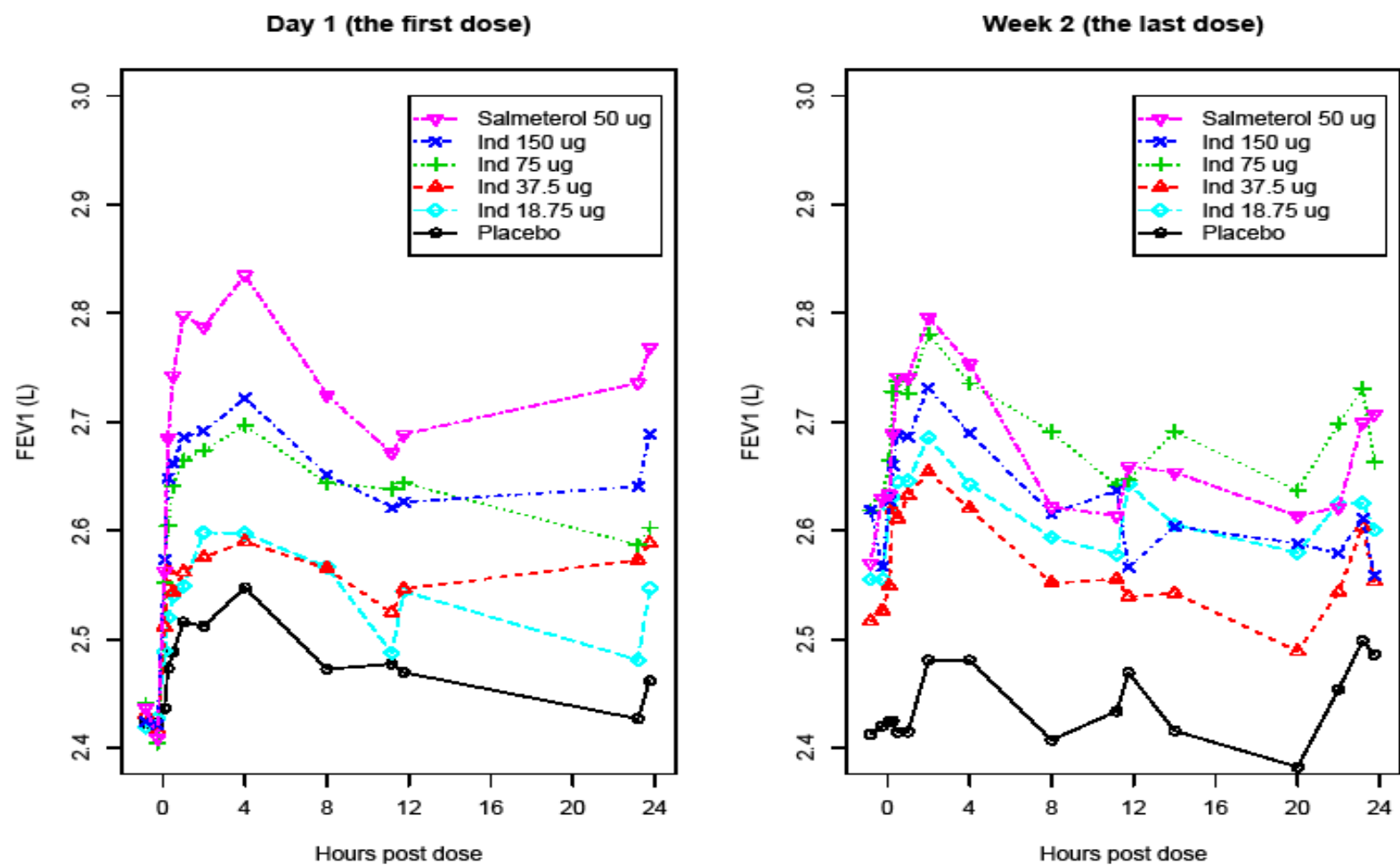


Figure 5 Study B2357 24-hour FEV<sub>1</sub> profile after the first and last doses.

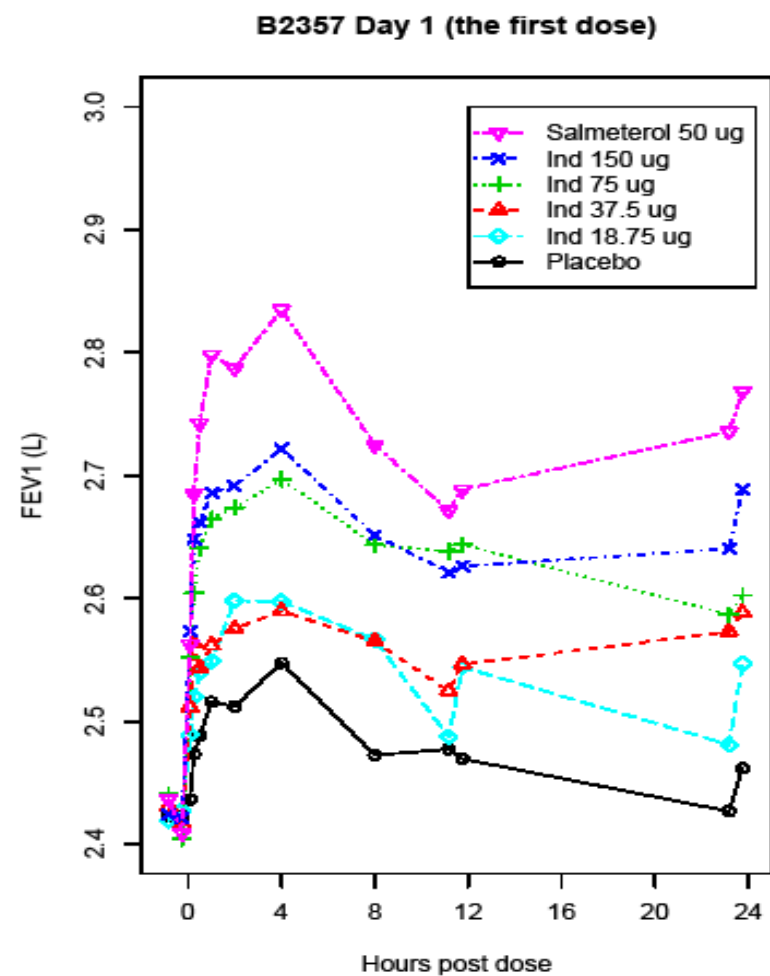
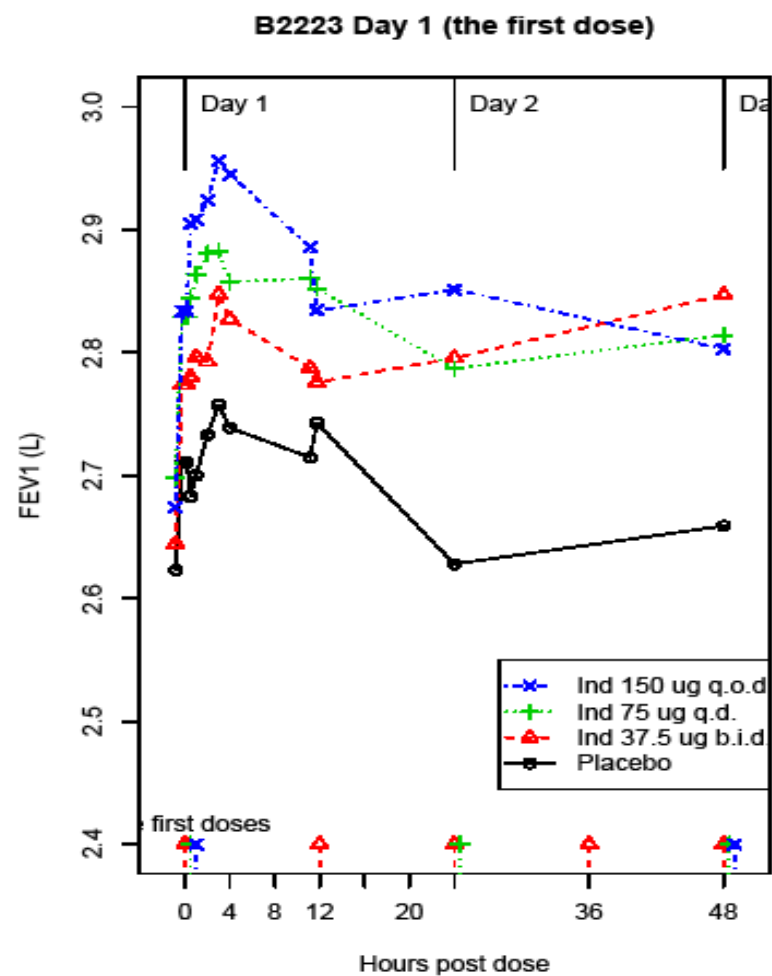


Figure 6 Comparison of baseline FEV<sub>1</sub> in Studies B2223 and B2357.

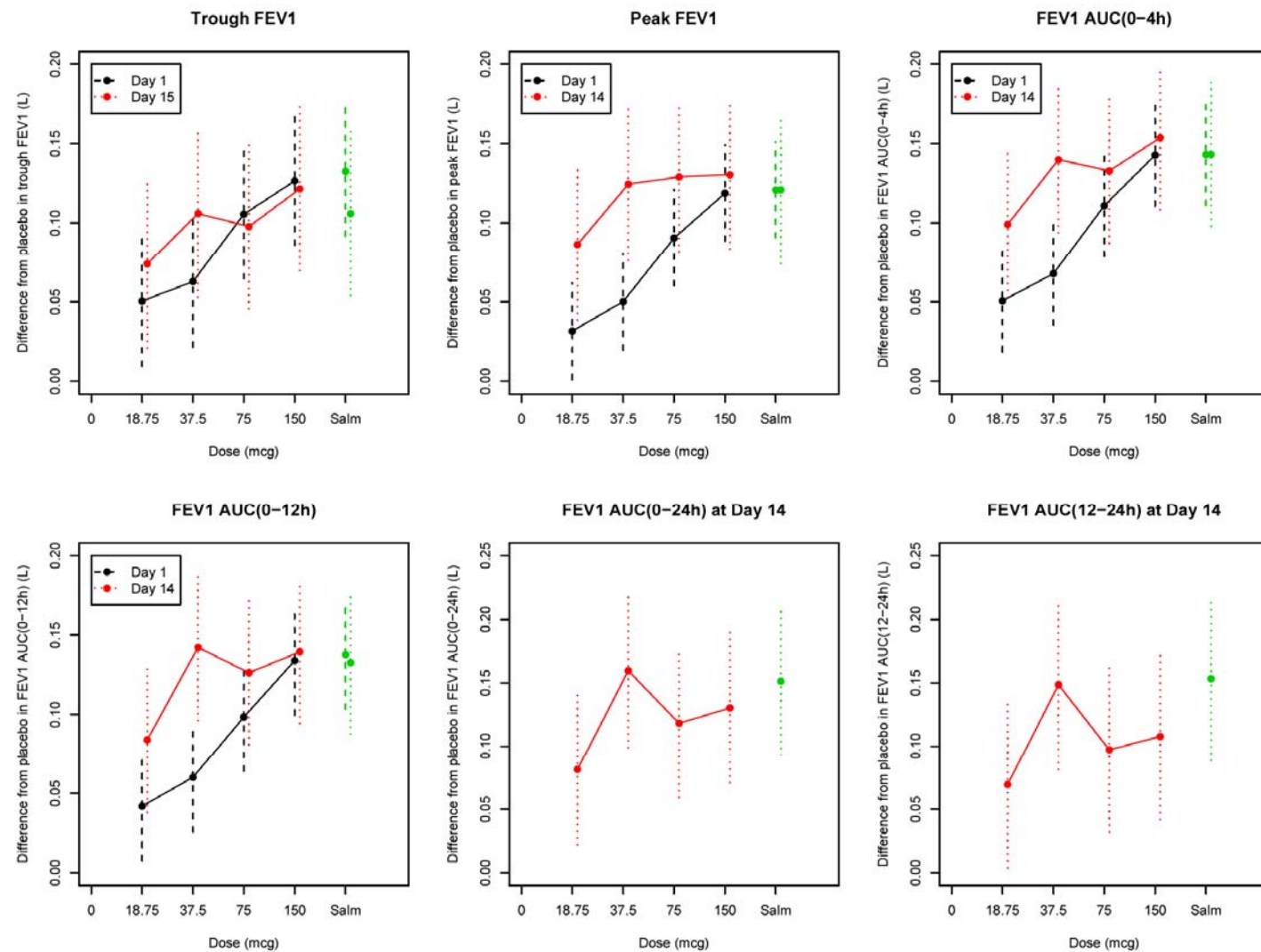


Figure 7 Study B2356 summary of spirometric parameters at Day 1 and after 2 weeks treatment.

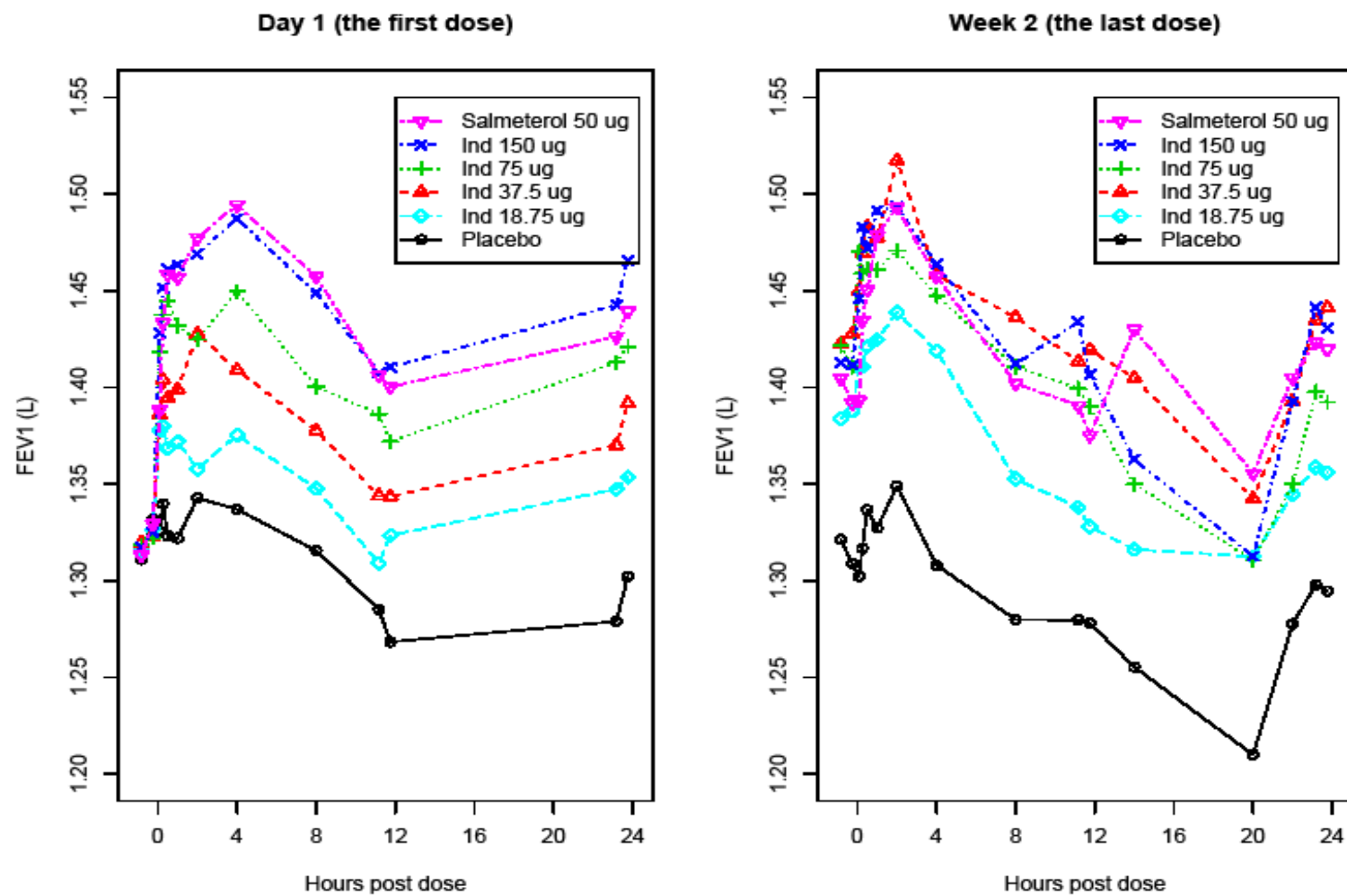


Figure 8 Study B2356 24-hour FEV<sub>1</sub> profile after the first and last doses.

### 3.1.6 Efficacy Results and Conclusions

The summary of primary efficacy endpoint in the three new key controlled efficacy studies is given in Figure 9 and Table 5. The plot on the left in Figure 9 summarizes the least square mean estimate of treatment effect with the 95% confidence interval by the mixed model on 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment. The treatment arms are labeled in the x-axis. The arms in Study B2336 are labeled in black, the arms in Study B2354 are labeled in red, and the arms in Study B2355 are labeled in green. The active control in Study B2336 is indicated by dotted line. It shows that the active control and treatments with indacaterol all had higher trough FEV<sub>1</sub> than the placebo arm after 12 weeks treatment.

The treatment comparisons between indacaterol and placebo are given in the plot on the right. The x-axis indicates the comparisons made. The horizontal dash line indicates the applicant-defined MCID (0.12L). All indacaterol treatment arms were superior to the placebo arms with the mean estimate of treatment difference between indacaterol and placebo above the MCID in all three studies.

The proposed labeling includes claim for advantage of the 150 mcg dose on SGRQ,

*The dose of 150 mcg once daily demonstrated a significantly lower (improved) mean total score in the SGRQ, as well as each component score, in comparison to placebo.*

The summary of ANCOVA analysis result on SGRQ scores in all six key controlled efficacy studies is given in Figure 10 and

Table 7. Figure 10 shows the treatment difference between indacaterol arms and placebo in SGRQ total scores. Each study is labeled in a different color. The x-axis indicates the comparisons made. For each comparison, three estimates were plotted. The point estimate with 95% CI based on SGRQ total score without imputation were labeled in solid line; the ones based on data imputed with LOCF were labeled in dashed lines; the ones based on data imputed with BOCF were labeled in dotted lines. There were little differences among the three sets of analysis results. Since the completion rate was high (80% to 90%), imputation of missing data does not play an important role in the analysis. Out of all the comparisons made in the six studies, except the active control tiotropium in Study B2335s, all other treatments demonstrated a significant improvement in SGRQ total scores. Indacaterol 150 mcg arms in Studies B2346 and B2336 showed an improvement on SGRQ total scores exceeding MCID (defined as a difference of SGRQ changing from baseline at week 12 between indacaterol and placebo greater than or equal to -4). After 12 weeks of treatment, the improvement of SGRQ total score by indacaterol 150 mcg comparing to placebo was -4.8 with 95% CI of (-7.2, -2.4) in Study B2346; -6.3 with 95% CI of (-8.2, -4.3) in Study B2336. Indacaterol 75 mcg arms in Studies B2354 and B2355, indacaterol 300 mcg and 600 mcg arms in Study B2334 showed an improvement on SGRQ total scores close (ranging from -3.6 to -4.1) to MCID.

Table 7 gives the detailed information of analysis results based on SGRQ scores imputed with LOCF. In the two studies B2346 and B2336 where the improvement in SGRQ total score by

indacaterol 150 mcg over placebo exceed the MCID, indacaterol 150 mcg also demonstrated a significant improvement in each of the component scores in comparison to placebo.

In Study B2346, no key secondary efficacy endpoints was specified. The treatment comparisons on the secondary efficacy endpoints were done without any adjustment on multiplicity. In Study B2336, the “days of poor control” (DOPC) were specified as the key secondary efficacy endpoint in the original protocol, but was changed into SGRQ before the database lock and unblinding. Multiple testing was controlled by a hierarchical procedure. The protocol change did not affect the study conduct, but does change data interpretation as it modified the order of how the secondary efficacy endpoints were tested.

Other than ANCOVA analysis, this reviewer also summarized the percentage of patients with a clinically important improvement of 4 units or greater from baseline in SGRQ total score (defined as responders) in all six studies. The result is given in Figure 11. The percentage of responders was highest in the indacaterol group in all the studies. There was a statistically significant difference in the likelihood of achieving a clinically relevant improvement of at least 4 units in SGRQ total score with indacaterol vs. placebo. The results of responder analysis based on logistic regression are given in Figure 12 and Table 6.

It is clear that indacaterol demonstrated an improvement in SGRQ total score over placebo. However, the differences among indacaterol doses were small. Whether the improvement in SGRQ scores could be claimed as an advantage for the dose of 150 mcg is questionable. The major drawback of the clinical program in this submission is that there were no direct comparison between the two proposed indacaterol doses, 75 mcg and 150 mcg, available in any of the phase 3 studies. The only way we can make this comparison is by analyzing the COPD three-month efficacy population pooled data, which consisted of double blind, placebo and/or active controlled studies of at least 12 weeks treatment in COPD patients. Ten studies were included in the COPD three-month efficacy populations, B2335S, B2346, B1302, B2333, B2336, B2349, B2350, B2354, B2355 and B2334. However, Studies B2333 and B2349 were excluded for SGRQ analysis. As B2333 and B2349 did not include an anti-cholinergic reversibility test, data from these studies could not be included in the primary analysis models. Additionally B2349 did not include a patient diary recording symptoms and therefore could not be included in any analysis requiring these endpoints. The results of ANCOVA and responder analysis on SGRQ total scores in COPD three-month efficacy population are given in Table 8 and Table 9. None of the analysis results showed statistically significant difference among indacaterol doses.

A brief summary of COPD exacerbations is given in Table 10. Since the division did not agree on the definition of COPD exacerbation defined by the applicant, no further analysis is done on this efficacy endpoint. The Kaplan-Meier plots on time to the first exacerbation are included in the appendix for reference.

The proposed label contains claim on symptomatic outcomes, including use of rescue medication, percentage of days with no day time symptoms, percentage of days where patients were able to perform their normal daily activities. Based on the consultation with clinical review team, these efficacy endpoints would not be included in the approved label, thus were not reviewed.

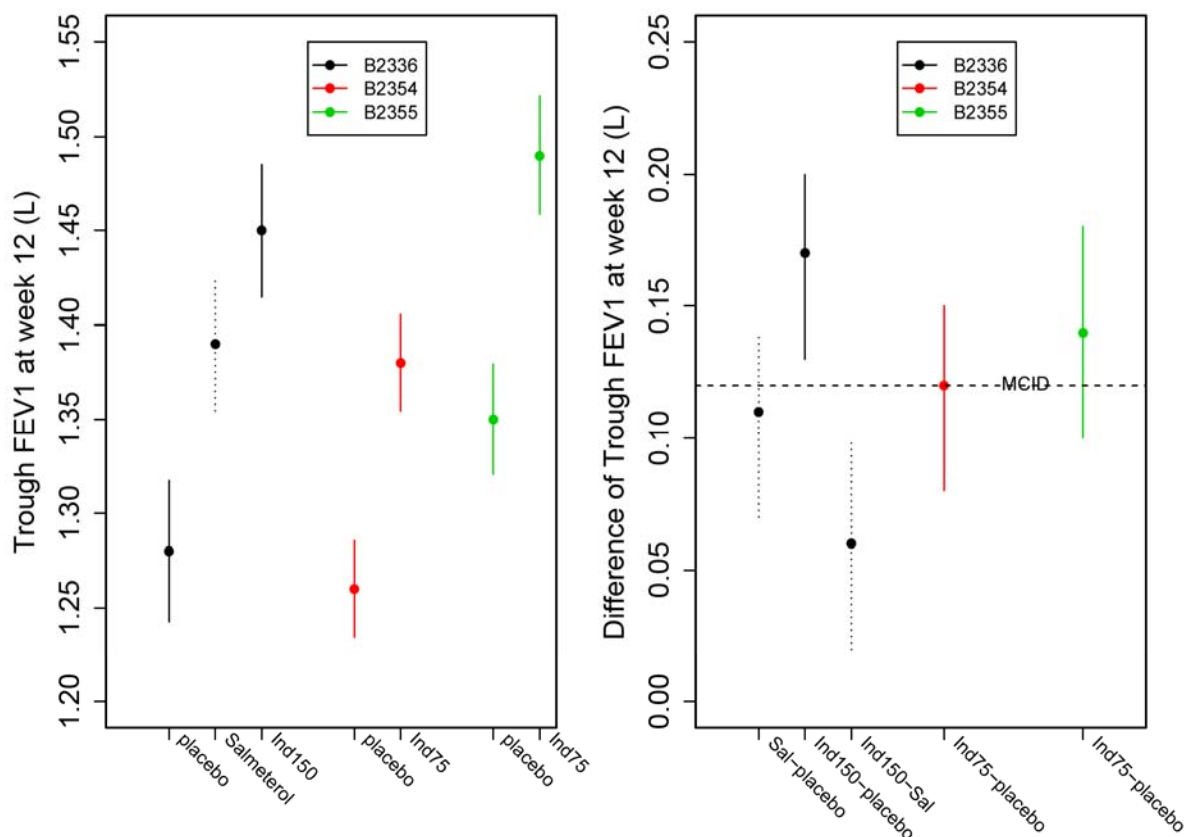


Figure 9 Summary of the primary efficacy endpoint (trough FEV<sub>1</sub> at week 12 imputed with LOCF) in the three new key controlled efficacy studies.

Table 5 Summary of the primary efficacy endpoint (trough FEV<sub>1</sub> at week 12 imputed with LOCF) in the three new key controlled efficacy studies.

Study	Treatment	N	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	P value
B2336	Ind 150 mcg	320	1.45	0.02	Ind 150 mcg – Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	Salmeterol	317	1.39	0.02	Ind 150 mcg – Sal	0.06	0.02	(0.02, 0.10)	<0.001
	Placebo	316	1.28	0.02	Sal – Pbo	0.11	0.02	(0.07, 0.14)	<0.001
B2354	Ind 75 mcg	149	1.38	0.01	Ind 75 mcg – Pbo	0.12	0.02	(0.08, 0.15)	<0.001
	Placebo	148	1.26	0.01	---	---	---	---	---
B2355	Ind 75 mcg	145	1.49	0.02	Ind 75 mcg – Pbo	0.14	0.02	(0.10, 0.18)	<0.001
	Placebo	150	1.35	0.02	---	---	---	---	---



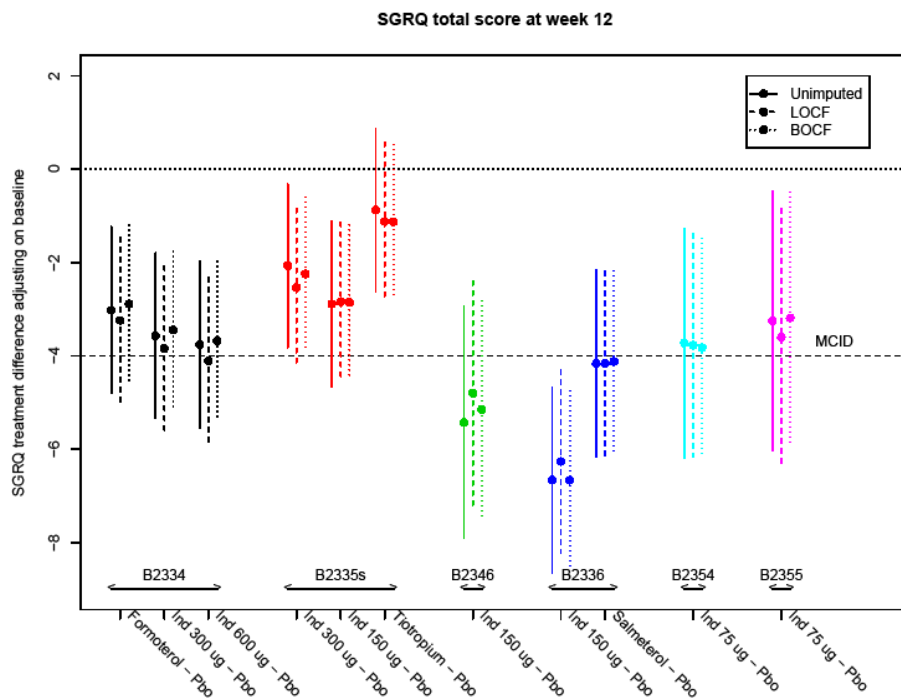


Figure 10 ANCOVA results of SGRQ total scores (imputed with LOCF) in the key controlled efficacy studies.

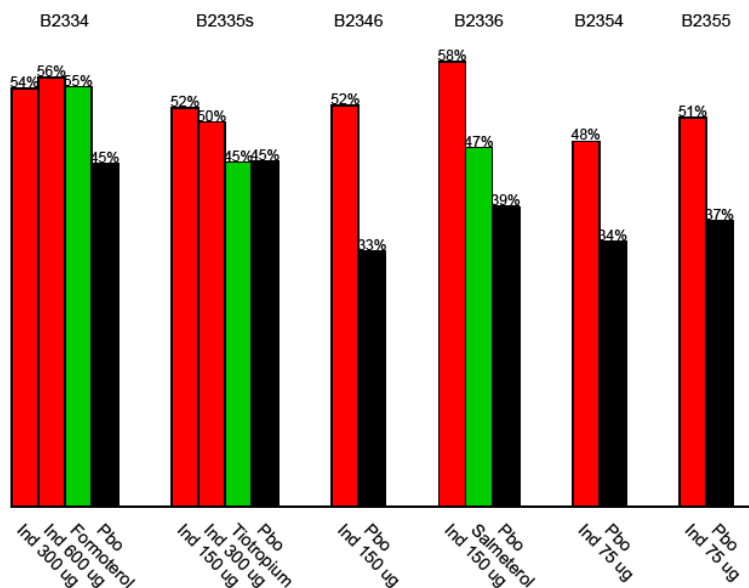


Figure 11 Summary of proportion of SGRQ (imputed with LOCF) responders in key controlled efficacy studies.

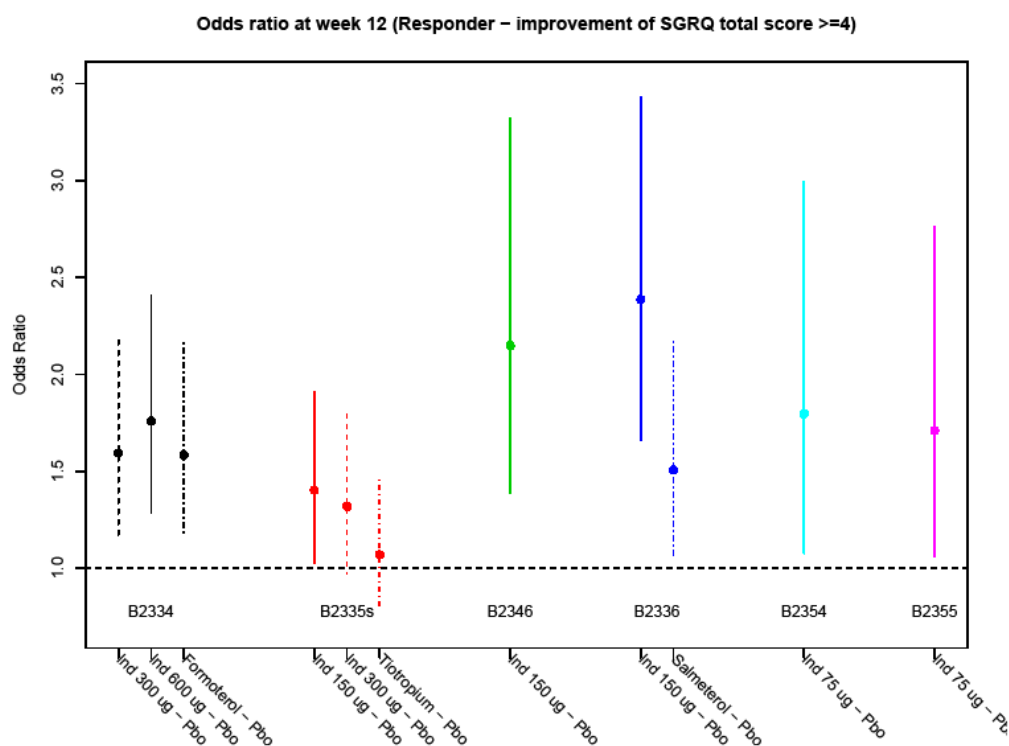


Figure 12 Summary of SGRQ (imputed with LOCF) responder analysis results in key controlled efficacy studies.

Table 6 Summary of SGRQ (imputed with LOCF) responder analysis results in key controlled efficacy studies.

Study	Treatment	n	N	%	Comparison	Odds ratios	95% CI	P value
B2334	Ind 300 mcg	217	398	54.5	Ind 300 mcg vs. Pbo	1.6	(1.2, 2.2)	0.003
	Ind 600 mcg	212	379	55.9	Ind 600 mcg vs. Pbo	1.8	(1.3, 2.4)	<.001
	Formoterol	214	391	54.7	For vs. Pbo	1.6	(1.2, 2.2)	0.004
	Placebo	167	374	44.7	---	---	---	---
B2335s	Ind 150 mcg	191	368	51.9	Ind 150 mcg vs. Pbo	1.4	(1.0, 1.9)	0.033
	Ind 300 mcg	188	375	50.1	Ind 300 mcg vs. Pbo	1.3	(1.0, 1.8)	0.078
	Tiotropium	168	374	44.9	Tio vs. Pbo	1.1	(0.8, 1.5)	0.674
	Placebo	156	347	45.0	---	---	---	---
B2346	Ind 150 mcg	104	199	52.3	Ind 150 mcg vs. Pbo	2.1	(1.4, 3.3)	<.001
	Placebo	62	187	33.2	---	---	---	---
B2336	Ind 150 mcg	179	309	57.9	Ind 150 mcg vs. Pbo	2.4	(1.7, 3.4)	<.001
	Salmeterol	141	301	46.8	Sal vs. Pbo	1.5	(1.0, 2.2)	0.027
	Placebo	115	294	39.1	---	---	---	---
B2354	Ind 75 mcg	70	147	47.6	Ind 75 mcg vs. Pbo	1.8	(1.1, 3.0)	0.025
	Placebo	49	142	34.5	---	---	---	---
B2355	Ind 75 mcg	75	148	50.7	Ind 75 mcg vs. Pbo	1.7	(1.1, 2.8)	0.028
	Placebo	54	145	37.2	---	---	---	---

- n = number of patients with a clinically important improvement of  $\geq 4$  in the SGRQ total score.
- N = total number of patients.

Table 7 ANCOVA results of SGRQ scores (imputed with LOCF) in the key controlled efficacy studies.

Study	Score	Treatment	N	LS mean	SE	Treatment difference	LS mean	SE	95% CI	P value
B2334	Total	Ind 300 mcg	372	37.5	0.7	Ind 300 mcg – Pbo	-3.8	0.9	( -5.6, -2.1)	<.001
		Ind 600 mcg	354	37.2	0.7	Ind 600 mcg – Pbo	-4.1	0.9	( -5.9, -2.3)	<.001
		Formoterol	359	38.1	0.7	For – Pbo	-3.2	0.9	( -5.0, -1.5)	<.001
		Placebo	347	41.3	0.7	---	---	---	---	---
	Activity	Ind 300 mcg	373	53.5	0.8	Ind 300 mcg – Pbo	-3.3	1.1	( -5.5, -1.2)	0.003
		Ind 600 mcg	357	53.1	0.9	Ind 600 mcg – Pbo	-3.8	1.1	( -6.0, -1.6)	<.001
		Formoterol	361	52.7	0.9	For – Pbo	-4.2	1.1	( -6.4, -2.0)	<.001
		Placebo	351	56.9	0.9	---	---	---	---	---
	Impact	Ind 300 mcg	373	25.8	0.8	Ind 300 mcg – Pbo	-3.1	1.0	( -5.1, -1.1)	0.002
		Ind 600 mcg	357	25.8	0.8	Ind 600 mcg – Pbo	-3.1	1.0	( -5.1, -1.1)	0.003
		Formoterol	361	27.4	0.8	For – Pbo	-1.5	1.0	( -3.5, 0.4)	0.129
		Placebo	349	28.9	0.8	---	---	---	---	---
	Symptom	Ind 300 mcg	372	46.4	1.0	Ind 300 mcg – Pbo	-6.0	1.4	( -8.7, -3.4)	<.001
		Ind 600 mcg	359	45.4	1.1	Ind 600 mcg – Pbo	-7.1	1.4	( -9.8, -4.4)	<.001
		Formoterol	364	46.6	1.1	For – Pbo	-5.9	1.4	( -8.6, -3.2)	<.001
		Placebo	353	52.4	1.1	---	---	---	---	---
B2335s	Total	Ind 150 mcg	368	38.3	0.7	Ind 150 mcg – Pbo	-2.8	0.9	( -4.5, -1.1)	0.001
		Ind 300 mcg	375	38.6	0.7	Ind 300 mcg – Pbo	-2.5	0.9	( -4.2, -0.8)	0.003
		Tiotropium	374	40.1	0.7	Tio – Pbo	-1.1	0.9	( -2.8, 0.6)	0.195
		Placebo	347	41.2	0.7	---	---	---	---	---
	Activity	Ind 150 mcg	370	53.7	1.0	Ind 150 mcg – Pbo	-3.4	1.1	( -5.6, -1.3)	0.002
		Ind 300 mcg	375	54.8	0.9	Ind 300 mcg – Pbo	-2.4	1.1	( -4.5, -0.3)	0.027
		Tiotropium	376	55.7	0.9	Tio – Pbo	-1.5	1.1	( -3.6, 0.6)	0.161
		Placebo	348	57.2	1.0	---	---	---	---	---
	Impact	Ind 150 mcg	370	26.5	0.8	Ind 150 mcg – Pbo	-2.0	1.0	( -3.9, -0.1)	0.035
		Ind 300 mcg	376	26.5	0.8	Ind 300 mcg – Pbo	-2.1	1.0	( -4.0, -0.2)	0.030
		Tiotropium	375	27.7	0.8	Tio – Pbo	-0.8	1.0	( -2.7, 1.1)	0.391
		Placebo	348	28.6	0.8	---	---	---	---	---
	Symptom	Ind 150 mcg	372	45.7	1.1	Ind 150 mcg – Pbo	-4.4	1.3	( -6.9, -1.9)	<.001
		Ind 300 mcg	376	46.0	1.1	Ind 300 mcg – Pbo	-4.1	1.3	( -6.6, -1.6)	0.002
		Tiotropium	375	49.0	1.1	Tio – Pbo	-1.1	1.3	( -3.6, 1.4)	0.388
		Placebo	350	50.1	1.1	---	---	---	---	---

B2346	Total	Ind 150 mcg	199	43.2	0.9	Ind 150 mcg - Pbo	-4.8	1.2	( -7.2, -2.4)	<.001
		Placebo	187	48.0	0.9					
	Activity	Ind 150 mcg	199	60.0	1.2	Ind 150 mcg - Pbo	-5.4	1.5	( -8.4, -2.4)	<.001
		Placebo	188	65.4	1.2					
	Impact	Ind 150 mcg	200	30.5	1.1	Ind 150 mcg - Pbo	-4.7	1.4	( -7.5, -1.9)	0.001
		Placebo	188	35.3	1.1					
Symptom	Ind 150 mcg	200	53.7	1.2	Ind 150 mcg - Pbo	-3.7	1.6	( -7.0, -0.5)	0.023	
	Placebo	189	57.4	1.2						
B2336	Total	Ind 150 mcg	309	36.4	1.0	Ind 150 mcg - Pbo	-6.3	1.0	( -8.2, -4.3)	<.001
		Salmeterol	301	38.5	1.0	Sal - Pbo	-4.2	1.0	( -6.1, -2.2)	<.001
		Placebo	294	42.6	1.1	---	---	---	---	
	Activity	Ind 150 mcg	309	51.1	1.3	Ind 150 mcg - Pbo	-5.4	1.3	( -7.9, -2.8)	<.001
		Salmeterol	301	54.7	1.3	Sal - Pbo	-1.7	1.3	( -4.3, 0.9)	0.204
		Placebo	294	56.4	1.3	---	---	---	---	
	Impact	Ind 150 mcg	311	25.3	1.1	Ind 150 mcg - Pbo	-6.4	1.1	( -8.5, -4.3)	<.001
		Salmeterol	301	27.1	1.1	Sal - Pbo	-4.6	1.1	( -6.8, -2.5)	<.001
		Placebo	295	31.7	1.1	---	---	---	---	
	Symptom	Ind 150 mcg	312	44.4	1.4	Ind 150 mcg - Pbo	-7.8	1.4	( -10.6, -4.9)	<.001
		Salmeterol	302	44.6	1.4	Sal - Pbo	-7.6	1.5	( -10.4, -4.7)	<.001
		Placebo	295	52.1	1.4	---	---	---	---	
B2354	Total	Ind 75 mcg	147	43.4	0.9	Ind 75 mcg - Pbo	-3.8	1.2	( -6.2, -1.4)	0.002
		Placebo	142	47.2	0.9					
	Activity	Ind 75 mcg	147	59.6	1.1	Ind 75 mcg - Pbo	-4.0	1.5	( -7.0, -1.0)	0.010
		Placebo	142	63.6	1.1					
	Impact	Ind 75 mcg	147	30.5	1.0	Ind 75 mcg - Pbo	-2.6	1.4	( -5.2, 0.1)	0.060
		Placebo	142	33.1	1.0					
Symptom	Ind 75 mcg	147	55.3	1.3	Ind 75 mcg - Pbo	-7.0	1.8	( -10.5, -3.4)	<.001	
	Placebo	142	62.2	1.3						
B2355	Total	Ind 75 mcg	148	45.9	1.0	Ind 75 mcg - Pbo	-3.6	1.4	( -6.4, -0.9)	0.010
		Placebo	145	49.5	1.0					
	Activity	Ind 75 mcg	150	62.7	1.3	Ind 75 mcg - Pbo	-2.3	1.7	( -5.7, 1.1)	0.179
		Placebo	145	65.1	1.3					
	Impact	Ind 75 mcg	149	32.8	1.1	Ind 75 mcg - Pbo	-3.6	1.6	( -6.7, -0.4)	0.026
		Placebo	148	36.4	1.2					
Symptom	Ind 75 mcg	149	56.0	1.4	Ind 75 mcg - Pbo	-6.0	2.0	( -9.8, -2.1)	0.003	
	Placebo	147	61.9	1.5						

Table 8 ANCOVA results of SGRQ total score after 3 months treatment (imputed with LOCF) in COPD 3 month efficacy population.

Treatment	N	LS Mean	SE	Comparison	LS mean	SE	95% CI	P value
Ind 75 mcg	407	37.9	0.8	Ind 75 mcg - Placebo	-3.8	0.8	(-5.3, -2.3)	<.001
				Ind 75 mcg - For	-0.5	1.0	(-2.5, 1.4)	0.588
				Ind 75 mcg - Tio	-1.4	0.9	(-3.1, 0.4)	0.118
				Ind 75 mcg - Salm	-0.4	1.1	(-2.6, 1.8)	0.726
Ind 150 mcg	1727	37.1	0.5	Ind 150 mcg - Placebo	-4.6	0.5	(-5.5, -3.6)	<.001
				Ind 150 mcg - For	-1.3	0.8	(-2.8, 0.2)	0.085
				Ind 150 mcg - Tio	-2.2	0.5	(-3.1, -1.2)	<.001
				Ind 150 mcg - Salm	-1.2	0.9	(-2.9, 0.5)	0.175
				Ind 150 mcg - Ind 75 mcg	-0.8	0.8	(-2.4, 0.9)	0.358
Ind 300 mcg	853	37.8	0.6	Ind 300 mcg - Placebo	-3.8	0.5	(-4.9, -2.8)	<.001
				Ind 300 mcg - For	-0.6	0.7	(-2.0, 0.8)	0.409
				Ind 300 mcg - Tio	-1.4	0.7	(-2.8, -0.1)	0.032
				Ind 300 mcg - Salm	-0.4	1.0	(-2.4, 1.5)	0.650
				Ind 300 mcg - Ind 75 mcg	0.0	0.9	(-1.8, 1.7)	0.956
				Ind 300 mcg - Ind 150 mcg	0.7	0.6	(-0.4, 1.9)	0.224
Formoterol	471	38.4	0.8	For - Placebo	-3.3	0.7	(-4.6, -1.9)	<.001
				For - Tio	-0.9	0.8	(-2.4, 0.7)	0.289
				For - Salm	0.1	1.1	(-2.0, 2.2)	0.900
Tiotropium	1127	39.3	0.6	Tio - Placebo	-2.4	0.6	(-3.6, -1.2)	<.001
				Tio - Salm	1.0	1.0	(-0.9, 2.9)	0.302
Salmeterol	301	38.3	0.9	Salm - Placebo	-3.4	0.9	(-5.1, -1.7)	<.001
Placebo	1562	41.7	0.5					

Table 9 Analysis of proportion of patients with a clinically important improvement of  $\geq 4$  in the SGRQ total score at 3 months (imputed with LOCF) in COPD 3 months efficacy population.

Treatment	n	N	%	Comparison	Odds Ratio	95% CI	P value
Ind 75 mcg	200	407	49.1	Ind 75 mcg - Pbo	1.7	(1.3, 2.2)	<.001
				Ind 75 mcg - For	1.1	(0.8, 1.5)	0.671
				Ind 75 mcg - Tio	1.3	(1.0, 1.8)	0.076
				Ind 75 mcg - Salm	1.3	(0.9, 2.0)	0.161
Ind 150 mcg	904	1727	52.3	Ind 150 mcg - Pbo	1.8	(1.5, 2.2)	<.001
				Ind 150 mcg - For	1.1	(0.9, 1.5)	0.310
				Ind 150 mcg - Tio	1.4	(1.2, 1.7)	<.001
				Ind 150 mcg - Salm	1.4	(1.0, 1.9)	0.025
				Ind 150 mcg - Ind 75 mcg	0.9	(0.7, 1.3)	0.674
Ind 300 mcg	440	853	51.6	Ind 300 mcg - Pbo	1.6	(1.3, 2.0)	<.001
				Ind 300 mcg - For	1.0	(0.8, 1.3)	0.890
				Ind 300 mcg - Tio	1.3	(1.0, 1.6)	0.061
				Ind 300 mcg - Salm	1.3	(0.9, 1.8)	0.196
				Ind 300 mcg - Ind 75 mcg	1.1	(0.8, 1.4)	0.718
				Ind 300 mcg - Ind 150 mcg	1.1	(0.9, 1.4)	0.260
Formoterol	239	471	50.7	For - Pbo	1.6	(1.2, 2.0)	<.001
				For - Tio	1.2	(0.9, 1.6)	0.151
				For - Salm	1.2	(0.8, 1.8)	0.277
Tiotropium	488	1127	43.3	Tio - Pbo	1.3	(1.0, 1.6)	0.016
				Tio - Salm	1.0	(0.7, 1.4)	0.993
Salmeterol	141	301	46.8	Salm - Pbo	1.3	(1.0, 1.7)	0.098
Placebo	617	1562	39.5				

- n = number of patients with a clinically important improvement of  $\geq 4$  in the SGRQ total score.
- N = total number of patients.

Table 10 Summary of COPD exacerbations (without imputation) in the key controlled efficacy studies.

Study (Treatment duration in days)	Treatment	Number of subjects			Time to the first exacerbation		Exacerbation rate		
		Total	Failed	Censored	Median (Days)	IQR (Days) (25%, 75%)	Number of exacerbations	Exposure (Years)	Rate (Per year)
<b>B2334</b> (364)	Formoterol	400	126	274	NA	(203, ---)	185	332.5	0.56
	Ind 300 mcg	405	133	272	NA	(233, ---)	209	347.4	0.60
	Ind 600 mcg	396	116	280	NA	(220, ---)	191	336.4	0.57
	Placebo	399	145	254	NA	(176, ---)	232	312.3	0.74
<b>B2335s</b> (182)	Ind 150 mcg	416	72	344	NA	NA	90	177.5	0.51
	Ind 300 mcg	416	76	340	NA	NA	97	183.1	0.55
	Placebo	418	91	327	NA	(179, ---)	118	163.8	0.73
	Tiotropium	415	79	336	NA	NA	95	179.2	0.55
<b>B2346</b> (84)	Ind 150 mcg	211	16	195	NA	NA	17	47.0	0.37
	Placebo	204	25	179	NA	NA	26	44.0	0.58
<b>B2336</b> (182)	Ind 150 mcg	330	60	270	NA	NA	72	152.0	0.47
	Placebo	335	65	270	NA	NA	86	141.7	0.62
	Salmeterol	333	51	282	NA	NA	61	149.0	0.40
<b>B2354</b> (84)	Placebo	160	18	142	NA	NA	18	33.3	0.54
	Ind 75 mcg	163	13	150	NA	NA	13	34.8	0.37
<b>B2355</b> (84)	Placebo	158	13	145	NA	NA	14	34.9	0.40
	Ind 75 mcg	159	14	145	NA	NA	14	35.8	0.40

- Studies submitted to the original NDA.

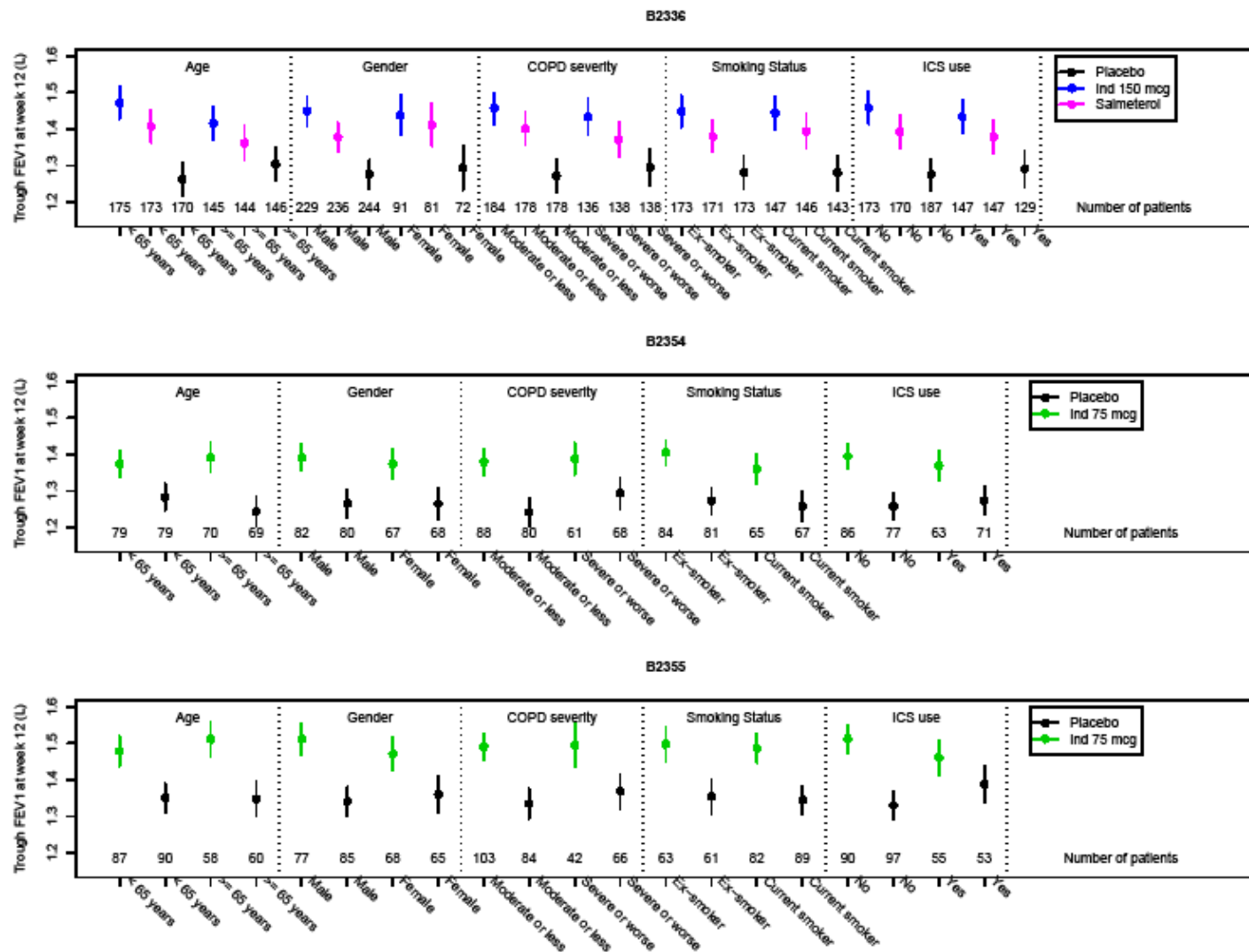


Figure 13 Summary of subgroup analysis on the primary efficacy endpoint in the three new key controlled efficacy studies.



### **3.2 Evaluation of Safety**

The evaluation of safety was conducted by Dr. Anya Harry. Reader is referred to Dr. Anya Harry's review for this section.

## **4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

The summary of subgroup analysis on the primary efficacy endpoint in the three new key controlled efficacy studies is given in Figure 13. The subgroups are categorized by age group, gender, COPD severity, smoking status, and ICS use at baseline, based on the categories summarized in Table 4. The results presented in the plots are from the mixed model, similar to the one used for the primary efficacy analysis, with the additional covariate on the subgroups being analyzed. In general, the subgroup analysis results are consistent with the results of overall population.

Interaction between treatment and subgroups were tested, there were statistically significant interactions between treatment and age group in Study B2336, as well as between treatment and ICS use at baseline in Study B2355. In study B2336, the improvement by indacaterol 150 mcg over placebo was smaller in patients who were 65 years old or above (0.11 L with a 95% CI of (0.06 L, 0.17 L)) than that in patients who were less than 65 years old (0.21 L with a 95% CI of (0.16 L, 0.26 L)). In Study B2336, the improvement by indacaterol 75 mcg over placebo was smaller in patients with ICS use at baseline (0.07 L with a 95% CI of (0.01 L, 0.14 L)) than that in patients without ICS use at baseline (0.18 L with a 95% CI of (0.13 L, 0.23 L)). No significant interaction was detected in other studies. All studies had the similar trends in subgroup analysis results.

## **5 SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

The main statistical issue in this submission is dose and regimen selection. Based on the dose ranging study B2357 in asthma patients, indacaterol 75 mcg once daily demonstrated the greatest bronchodilatory effect compared to other doses. The dosing regimen study B2223 in asthma patients did not show clear separation among the three dosing regimens, indacaterol 37.5 mcg b.i.d, 75 mcg q.d., and 150 mcg q.o.d., thus it is hard to make selections on dosing regimen. The dose ranging study B2356 in COPD patients showed that the 18.75 mcg dose was ineffective. The dose of 150 mcg appeared to achieve its maximum bronchodilation effect more rapidly than the other doses, but lost its advantage after two weeks of treatment. Considering indacaterol is proposed to be used as a long term maintenance bronchodilator treatment, the 150 mcg dose's rapid effect in day 1 may not be important, especially balancing with safety concerns on higher dose. From the week 2 data, it appears indacaterol 37.5 mcg, 75 mcg, and 150 mcg once daily worked equally well in terms of bronchodilatory effect.

The indacaterol 150 mcg dose in two key controlled efficacy studies, B2336 and B2346, demonstrated a significant improvement in SGRQ total scores, as well as each component scores, in comparison to placebo. In addition, the improvement exceeded the MCID between indacaterol and placebo of 4 units. The superiority of indacaterol over placebo in SGRQ scores was confirmed in all doses. However, the differences among indacaterol doses were small. Whether the improvement in SGRQ scores could be claimed as an advantage for the dose of 150 mcg is questionable.

### **5.2 Conclusions and Recommendations**

The review on efficacy supports the claim of using indacaterol as a long term maintenance bronchodilatory treatment for COPD patients. However, based on the efficacy data submitted, there were no clear separation among the doses and regimens studied. This reviewer does not have recommendation for which dose and regimen to approve.

## APPENDICES

Table 11 Patient disposition of Study B2223.

	Indacaterol			Placebo	All patients
	37.5 µg b.i.d N=48	75 µg q.d N=48	150 µg q.o.d N=48	N=47	N=191
	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	46 (95.8%)	46 (95.8%)	42 (87.5%)	41 (87.2%)	175 (91.6%)
Discontinued	2 (4.2%)	2 (4.2%)	6 (12.5%)	6 (12.8%)	16 (8.4%)
<b>Main cause of discontinuation</b>					
Adverse Event(s)	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	2 (1.0%)
Abnormal test procedure result(s)	0 (0.0%)	1 (2.1%)	2 (4.2%)	2 (4.3%)	5 (2.6%)
Subject withdrew consent	0 (0.0%)	0 (0.0%)	2 (4.2%)	2 (4.3%)	4 (2.1%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (0.5%)
Administrative problems	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (2.1%)	2 (1.0%)
Protocol deviation	2 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)

- Quoted from the submitted study report.

Table 12 Demographic summary of Study B2223.

		Indacaterol 37.5 µg b.i.d N=48	Indacaterol 75 µg q.d N=47	Indacaterol 150 µg q.o.d N=48	Placebo N=46
Age (years)	Mean (SD)	37 (11.0)	41(14.7)	42(12.2)	41(12.7)
	Range	18 - 68	19 - 80	19 - 70	21 - 73
Gender - n(%)	Male	27 (56%)	23 (49%)	32 (67%)	28 (61%)
	Female	21 (44%)	24 (51%)	16 (33%)	18 (39%)
Race - n(%)	Caucasian	42 (88%)	37 (79%)	29 (60%)	43 (94%)
	Black	3 (6%)	8 (17%)	13 (27%)	2 (4%)
	Asian	1 (2%)	0 (0%)	2 (4%)	0 (0%)
	Pacific Islander	0 (0%)	0 (0%)	1 (2%)	0 (0%)
	Other	2 (4%)	2 (4%)	3 (6%)	1 (2%)

- Quoted from the submitted study report.

Table 13 Summary of disease characteristics for patients in Study B2223.

		Indacaterol			Placebo
		37.5 µg b.i.d	75 µg q.d	150 µg q.o.d	
		N=48	N=47	N=48	N=46
Baseline FEV <sub>1</sub> (L)	Mean (SD)	2.84 (0.643)	2.51 (0.624)	2.61 (0.723)	2.72 (0.658)
	Range	1.22 - 4.59	1.40 - 3.89	1.22 - 3.94	1.20 - 4.19
Reversibility FEV <sub>1</sub> (%)	Mean (SD)	22.1 (11.06)	21.4 (8.07)	20.4 (12.75)	22.5 (9.25)
	Range	12.0 - 49.2	11.7 - 47.1	-20.1 - 50.0	11.9 - 47.1

- Quoted from the submitted study report.

Table 14 Patient disposition of Study B2356.

	Ind 18.75 ug n (%)	Ind 37.5 ug n (%)	Ind 75 ug n (%)	Ind 150 ug n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Screening visits	-	-	-	-	-	-	1110
<b>Patients</b>							
Randomized	92 (100.0)	91 (100.0)	94 (100.0)	92 (100.0)	92 (100.0)	91 (100.0)	552 (100.0)
Exposed	89 (96.7)	90 (98.9)	94 (100.0)	92 (100.0)	91 (98.9)	91 (100.0)	547 (99.1)
Completed	84 (91.3)	86 (94.5)	92 (97.9)	91 (98.9)	90 (97.8)	88 (96.7)	531 (96.2)
Discontinued	8 (8.7)	5 (5.5)	2 (2.1)	1 (1.1)	2 (2.2)	3 (3.3)	21 (3.8)
<b>Primary reason for premature discontinuation</b>							
Adverse event(s)	5 (5.4)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	8 (1.4)
Subject withdrew consent	0 (0.0)	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)	2 (2.2)	5 (0.9)
Abnormal test procedure results(s)	2 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Lost to follow-up	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	3 (0.5)
Protocol deviation	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.4)

- Quoted from the submitted study report.

Table 15 Demographic summary of Study B2356.

		Ind 18.75 ug N=89	Ind 37.5 ug N=90	Ind 75 ug N=94	Ind 150 ug N=92	Salm N=91	Pbo N=91	Total N=547
<b>Age (years)</b>	n	89	90	94	92	91	91	547
	Mean	62.8	61.9	62.6	62.3	62.4	63.6	62.6
	SD	8.95	9.61	9.30	9.50	9.52	8.44	9.20
	Median	62.0	63.5	63.0	62.0	63.0	63.0	63.0
	Min - Max	43 - 84	43 - 83	44 - 87	40 - 84	43 - 83	47 - 85	40 - 87
<b>Age group – n (%)</b>	40-64 years	53 (59.6)	51 (56.7)	52 (55.3)	52 (56.5)	51 (56.0)	54 (59.3)	313 (57.2)
	65-74 years	27 (30.3)	31 (34.4)	33 (35.1)	34 (37.0)	31 (34.1)	26 (28.6)	182 (33.3)
	>= 75 years	9 (10.1)	8 (8.9)	9 (9.6)	6 (6.5)	9 (9.9)	11 (12.1)	52 (9.5)
<b>Sex – n (%)</b>	Male	50 (56.2)	47 (52.2)	54 (57.4)	53 (57.6)	44 (48.4)	48 (52.7)	296 (54.1)
	Female	39 (43.8)	43 (47.8)	40 (42.6)	39 (42.4)	47 (51.6)	43 (47.3)	251 (45.9)
<b>Race – n (%)</b>	Caucasian	86 (96.6)	84 (93.3)	91 (96.8)	84 (91.3)	82 (90.1)	86 (94.5)	513 (93.8)
	Black	2 (2.2)	6 (6.7)	2 (2.1)	6 (6.5)	8 (8.8)	5 (5.5)	29 (5.3)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	2 (0.4)
	Pacific Islander	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

- Quoted from the submitted study report.

Table 16 Summary of baseline disease characteristics of patients in Study B2356.

		Ind 18.75 ug N=89	Ind 37.5 ug N=90	Ind 75 ug N=94	Ind 150 ug N=92	Salm N=91	Pbo N=91	Total N=547
Duration of COPD (years)	n	89	90	94	92	91	91	547
	Mean	6.6	6.6	6.8	6.7	7.0	7.9	6.9
	SD	5.61	5.88	6.27	5.75	6.00	6.72	6.04
	Median	5.8	4.9	5.1	5.8	4.9	5.9	5.7
	Min	0.2	0.7	0.0	0.0	0.0	0.0	0.0
	Max	29.9	35.8	29.9	29.9	29.8	29.8	35.8
Duration of COPD (years) – n (%)	<1 yrs	9 (10.1)	9 (10.0)	15 (16.0)	12 (13.0)	7 (7.7)	8 (8.8)	60 (11.0)
	1–5 yrs	34 (38.2)	39 (43.3)	31 (33.0)	31 (33.7)	39 (42.9)	30 (33.0)	204 (37.3)
	>5–10 yrs	28 (31.5)	28 (31.1)	27 (28.7)	30 (32.6)	24 (26.4)	29 (31.9)	166 (30.3)
	>10–15 yrs	11 (12.4)	8 (8.9)	10 (10.6)	13 (14.1)	12 (13.2)	14 (15.4)	68 (12.4)
	>15–20 yrs	6 (6.7)	4 (4.4)	9 (9.6)	3 (3.3)	6 (6.6)	5 (5.5)	33 (6.0)
	>20 yrs	1 (1.1)	2 (2.2)	2 (2.1)	3 (3.3)	3 (3.3)	5 (5.5)	16 (2.9)
Severity of COPD ( <a href="#">GOLD 2008</a> ) n (%)	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	47 (52.8)	52 (57.8)	54 (57.4)	45 (48.9)	45 (49.5)	49 (53.8)	292 (53.4)
	Severe	42 (47.2)	37 (41.1)	39 (41.5)	45 (48.9)	46 (50.5)	41 (45.1)	250 (45.7)
	Very severe	0 (0.0)	1 (1.1)	1 (1.1)	2 (2.2)	0 (0.0)	1 (1.1)	5 (0.9)
ICS use – n (%)	No	57 (64.0)	55 (61.1)	60 (63.8)	56 (60.9)	59 (64.8)	59 (64.8)	346 (63.3)
	Yes	32 (36.0)	35 (38.9)	34 (36.2)	36 (39.1)	32 (35.2)	32 (35.2)	201 (36.7)
Smoking history – n (%)	Ex-smoker	42 (47.2)	40 (44.4)	44 (46.8)	40 (43.5)	39 (42.9)	42 (46.2)	247 (45.2)
	Current Smoker	47 (52.8)	50 (55.6)	50 (53.2)	52 (56.5)	52 (57.1)	49 (53.8)	300 (54.8)

- Quoted from the submitted study report.

Table 17 Patient disposition of Study B2357.

	Ind 18.75 µg n (%)	Ind 37.5 µg n (%)	Ind 75 µg n (%)	Ind 150 µg n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Screening visits	-	-	-	-	-	-	1200
<b>Patients</b>							
Randomized	85 (100.0)	85 (100.0)	84 (100.0)	86 (100.0)	86 (100.0)	85 (100.0)	511 (100.0)
Exposed	84 (98.8)	81 (95.3)	84 (100.0)	85 (98.8)	84 (97.7)	84 (98.8)	502 (98.2)
Completed	83 (97.6)	78 (91.8)	83 (98.8)	81 (94.2)	78 (90.7)	80 (94.1)	483 (94.5)
Discontinued	2 (2.4)	7 (8.2)	1 (1.2)	5 (5.8)	8 (9.3)	5 (5.9)	28 (5.5)
<b>Primary reason for premature discontinuation</b>							
Adverse event(s)	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)	5 (5.8)	1 (1.2)	9 (1.8)
Administrative problems	1 (1.2)	3 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	5 (1.0)
Subject withdrew consent	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	3 (3.5)	5 (1.0)
Protocol deviation	0 (0.0)	2 (2.4)	1 (1.2)	2 (2.3)	0 (0.0)	0 (0.0)	5 (1.0)
Abnormal test procedure results(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	2 (0.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)

- Quoted from the submitted study report.

Table 18 Demographic summary of Study B2357.

		Ind 18.75 µg N = 84	Ind 37.5 µg N = 81	Ind 75 µg N = 84	Ind 150 µg N = 85	Salm N = 84	Pbo N = 84	Total N = 502
<b>Age (years)</b>	n	84	81	84	85	84	84	502
	Mean	42.0	41.9	40.2	41.0	40.9	40.6	41.1
	SD	14.64	14.96	14.71	15.20	14.56	14.17	14.65
	Median	43.5	42.0	38.5	42.0	41.0	41.0	41.0
	Min - Max	18 - 74	19 - 74	18 - 77	18 - 82	18 - 75	18 - 70	18 - 82
<b>Age group – n (%)</b>	18 – 39 years	38 (45.2)	34 (42.0)	45 (53.6)	39 (45.9)	39 (46.4)	38 (45.2)	233 (46.4)
	40 – 64 years	41 (48.8)	39 (48.1)	35 (41.7)	42 (49.4)	39 (46.4)	42 (50.0)	238 (47.4)
	65-74 years	5 (6.0)	8 (9.9)	3 (3.6)	3 (3.5)	5 (6.0)	4 (4.8)	28 (5.6)
	≥75 years	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	1 (1.2)	0 (0.0)	3 (0.6)
<b>Sex – n (%)</b>	Male	42 (50.0)	35 (43.2)	35 (41.7)	30 (35.3)	38 (45.2)	44 (52.4)	224 (44.6)
	Female	42 (50.0)	46 (56.8)	49 (58.3)	55 (64.7)	46 (54.8)	40 (47.6)	278 (55.4)
<b>Race – n (%)</b>	Caucasian	68 (81.0)	63 (77.8)	63 (75.0)	69 (81.2)	65 (77.4)	68 (81.0)	396 (78.9)
	Black	13 (15.5)	14 (17.3)	17 (20.2)	11 (12.9)	19 (22.6)	12 (14.3)	86 (17.1)
	Asian	2 (2.4)	0 (0.0)	1 (1.2)	3 (3.5)	0 (0.0)	1 (1.2)	7 (1.4)
	Pacific Islander	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	1 (1.2)	3 (3.7)	3 (3.6)	2 (2.4)	0 (0.0)	3 (3.6)	12 (2.4)

- Quoted from the submitted study report.

Table 19 Summary of baseline disease characteristics of patients in Study B2357.

		<b>Ind 18.75 µg N = 84</b>	<b>Ind 37.5 µg N = 81</b>	<b>Ind 75 µg N = 84</b>	<b>Ind 150 µg N = 85</b>	<b>Salm N = 84</b>	<b>Pbo N = 84</b>	<b>Total N = 502</b>
<b>Duration of Asthma (years)</b>	n	84	81	84	85	84	84	502
	Mean	28.3	28.2	27.4	25.4	26.2	25.3	26.8
	SD	14.77	14.34	14.28	15.53	13.47	13.00	14.24
	Median	24.8	24.9	23.8	20.7	24.9	23.8	23.8
	Min - Max	0.5 - 67.5	3.7 - 65.8	1.1 - 64.9	0.9 - 68.7	2.7 - 61.8	1.7 - 67.8	0.5 - 68.7
<b>Duration of Asthma (years) – n (%)</b>	< 1 year	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	2 (0.4)
	1 – 5 yrs	4 (4.8)	2 (2.5)	5 (6.0)	3 (3.5)	6 (7.1)	5 (6.0)	25 (5.0)
	> 5 – 10 yrs	2 (2.4)	6 (7.4)	3 (3.6)	8 (9.4)	4 (4.8)	2 (2.4)	25 (5.0)
	> 10 – 15 yrs	7 (8.3)	9 (11.1)	8 (9.5)	10 (11.8)	9 (10.7)	10 (11.9)	53 (10.6)
	> 15 – 20 yrs	13 (15.5)	10 (12.3)	14 (16.7)	20 (23.5)	15 (17.9)	17 (20.2)	89 (17.7)
	> 20 yrs	57 (67.9)	54 (66.7)	54 (64.3)	43 (50.6)	50 (59.5)	50 (59.5)	308 (61.4)
<b>Severity of Asthma – n (%)</b>	Mild	19 (22.6)	20 (24.7)	22 (26.2)	21 (24.7)	21 (25.0)	20 (23.8)	123 (24.5)
	persistent							
	Moderate	59 (70.2)	55 (67.9)	56 (66.7)	58 (68.2)	57 (67.9)	58 (69.0)	343 (68.3)
	persistent							
<b>ICS use – n (%)</b>	Severe	6 (7.1)	6 (7.4)	6 (7.1)	6 (7.1)	6 (7.1)	6 (7.1)	36 (7.2)
	persistent							
<b>Smoking history – n (%)</b>	Yes	84 (100.0)	81 (100.0)	84 (100.0)	85 (100.0)	84 (100.0)	84 (100.0)	502 (100.0)
	Never	63 (75.0)	70 (86.4)	67 (79.8)	68 (80.0)	67 (79.8)	65 (77.4)	400 (79.7)
	Smoker							
	Ex-smoker	19 (22.6)	8 (9.9)	15 (17.9)	17 (20.0)	13 (15.5)	17 (20.2)	89 (17.7)
	Current	2 (2.4)	3 (3.7)	2 (2.4)	0 (0.0)	4 (4.8)	2 (2.4)	13 (2.6)
	Smoker							

- Quoted from the submitted study report.



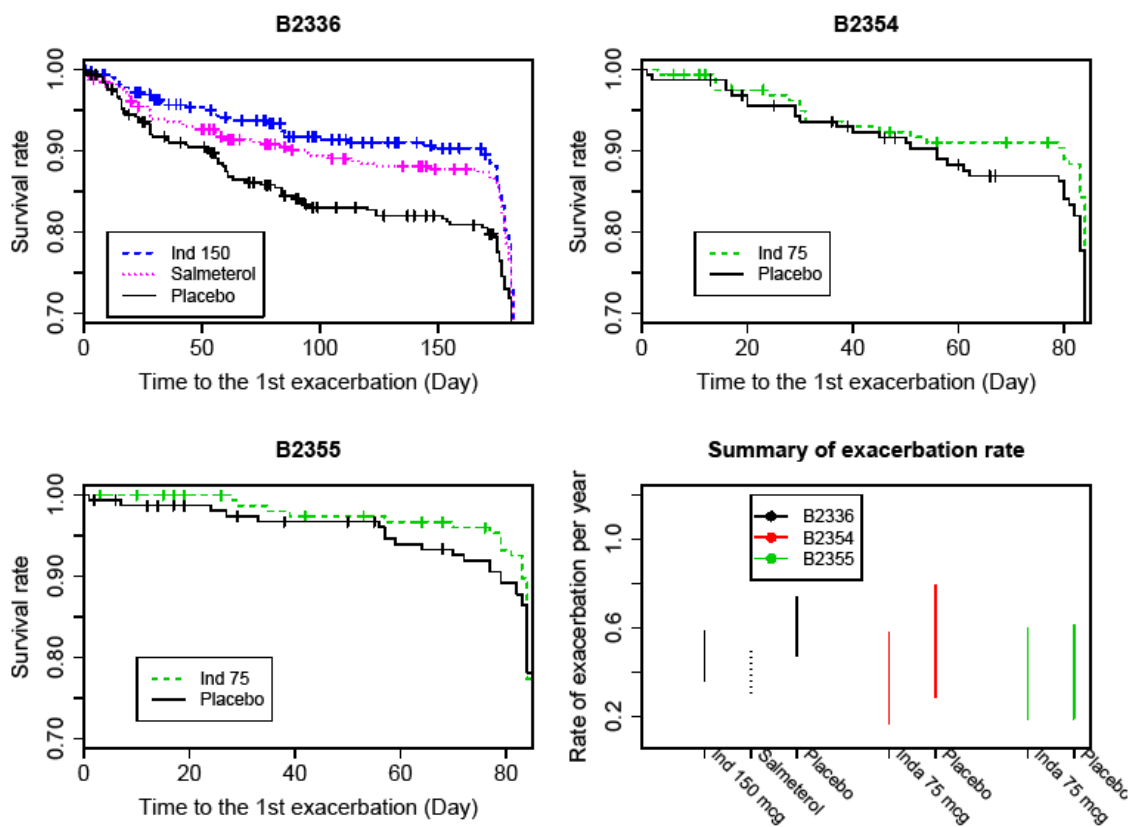


Figure 14 Summary of COPD exacerbations (without imputation) in the three new key controlled efficacy studies.

## **SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Dongmei Liu, Ph.D.  
Date: February 8, 2011

Statistical Team Leader: Joan Buenconsejo, Ph.D.

Biometrics Division Director: Thomas Permutt, Ph.D.



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** NDA 22-383

**Drug Name:** Arcapta Neohaler (Indacaterol Maleate Inhalation Power)

**Indication(s):** Treatment of chronic obstructive pulmonary disease (COPD)

**Applicant:** Novartis Pharmaceuticals Corp.

**Date(s):** Receipt date: December 18, 2008  
PDUFA date: October 18, 2009

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Dongmei Liu, Ph.D.

**Concurring Reviewers:** Qian Li, Sc.D., Team Leader  
Thomas Permutt, Ph.D., Division Director

**Medical Division:** Division of Pulmonary and Allergy Products

**Clinical Team:** Lynne Wu, M.D., Medical Reviewer  
Anthony Durmowicz, M.D. Team Leader  
Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director

**Project Manager:** Carol Hill

**Keywords:** NDA review, clinical studies, dose selection

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# **1 EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

Novartis proposes indacaterol maleate, a long-acting beta<sub>2</sub>-agonist (LABA), for long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed starting dose is 150 mcg, with the option of a higher dose 300 mcg. Based on evaluation of 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment, the applicant claims indacaterol is effective in relieving bronchoconstriction in COPD patients. My review of the statistical evidence suggests support for the claim. However, the support is from efficacy standpoint alone, there are issues on dose selection indicating that doses lower than 150 mcg, such as 75 mcg, may also have similar efficacy. Doses lower than 75 mcg were not adequately studied in the development program. Understanding the dose response of lower doses in efficacy is critical because a few dose-dependent safety signals, including increase in heart rate, muscle spasm and tremor, were identified by the medical reviewer in this application. More cerebro- cardiovascular (CCV) serious adverse events were seen for COPD patients treated with higher dose of indacaterol (starting from 300 mcg) compared to the active comparator formoterol and placebo. This raises the concern of approving a dose level that might be unnecessarily high. In addition, there was not enough data to support indacaterol as a once daily drug. The currently available data on 24-hour lung function profile after treatment, collected in a crossover study with 68 patients, was based on 300 mcg, instead of the proposed starting dose of 150 mcg. Data on 12-hour lung function profile were collected in 31 patients in study B2335s. None of the phase 3 pivotal studies collected 24 hour serial spirometry data. As BID dosing interval may further lower the dose level to achieve adequate efficacy results, additional studies with lower doses to further explore the dose response and dosing frequency need to be done.

## **1.2 Brief Overview of Clinical Studies**

This application includes data from four short term placebo controlled dose ranging studies (B2201, B2205, B2212, B1202); three phase 3 pivotal studies (B2335s, B2334, B2346) to evaluate long term safety and efficacy, one of them with adaptive design (B2335s); and three short term crossover studies (B2305, B2307, B2340) to examine the specific aspects of efficacy. All the indacaterol treatments in these studies were administered once daily (Q.D.).

The short term dose ranging studies (B2201, B2205, B2212, B1202) used varied doses (from 50 mcg to 800 mcg) of indacaterol in varied populations (COPD patients in Japan, Europe, North and South America), as well as different formulations and delivery devices (SDDPI and MDDPI). These studies were designed to explore the dose response of indacaterol and to provide guidance on choosing doses to be studied in the definitive dose selection study.

The first stage of the pivotal study B2335s with adaptive design was served as the definitive dose selection study using the target population and the device with phase 3 supplies. There were seven treatment arms in the first stage of B2335s, indacaterol 75 mcg, 150 mcg, 300 mcg, 600 mcg, placebo, formoterol 12 mcg, and tiotropium 18 mcg, with two-week treatment duration.

After an interim analysis on data collected in stage 1, two indacaterol doses (150 mcg and 300 mcg) were selected to be continued into stage 2. The stage 2 of study B2335s was designed to collect data up to 26 weeks to evaluate the safety and efficacy of two selected doses. Study B2334 was a 52-week long, four parallel arms (indacaterol 300 mcg, 600 mcg, placebo, and formoterol 12 mcg) study, designed to collect further efficacy and safety data for the 300 mcg dose and support for long-term use. Study B2346 was a 12-week long, two parallel arms (indacaterol 150 mcg and placebo) study, designed to provide further efficacy data for indacaterol 150 mcg.

For the short term crossover studies, B2305 was designed to examine the evening dose efficacy of indacaterol; B2307 was designed to examine the fast onset of action of indacaterol; B2340 was designed to examine the 24-hour lung function profile after treatment with indacaterol.

The primary efficacy endpoint for the three pivotal studies was trough FEV<sub>1</sub> at 24 hour post-dose after 12 weeks treatment; the key secondary efficacy endpoint was days of poor control; another secondary efficacy endpoint considered in this review is use of rescue medication. Since the division did not reach agreement with the applicant on the definition of exacerbation, efficacy analyses on exacerbation rate and time to the first exacerbations are not included in this review.

### ***1.3 Statistical Issues and Findings***

#### Findings with the proposed indacaterol doses, 150 mcg and 300 mcg

In all three pivotal studies, indacaterol at the proposed doses, 150 mcg and 300 mcg, was shown to be statistically significantly better than placebo in terms of trough FEV<sub>1</sub> after 12 weeks treatment. The treatment differences between indacaterol 150 mcg and placebo were 0.18L with standard error of 0.016L in study B2335s, 0.13L with standard error of 0.024L in study B2346. The treatment differences between indacaterol 300 mcg and placebo were 0.18L with standard error of 0.016L in study B2335s, 0.17L with standard error of 0.024L in study B2334.

Indacaterol was also shown to be superior over placebo in terms of the key secondary efficacy endpoint, percentage of days of poor control, in two of the three pivotal studies — B2334 and B2346. In the other pivotal study B2335s, there was no statistically significant difference between either of the two indacaterol doses (150mcg and 300 mcg) and placebo. In all three pivotal studies, the daily number of puffs of rescue medication use was significantly lower in the indacaterol arms than in the placebo arms; the percentage of days with no use of rescue medication was significantly higher in the indacaterol arms than in the placebo arms.

#### Dose response issues

About dose selection, all four studied doses (75 mcg, 150 mcg, 300 mcg, and 600 mcg) included in the first stage of study B2335s were shown to be effective, i.e. superior over placebo. In fact, all the four doses have reached the efficacy plateau and exhibit similar efficacy responses. The efficacy of the selected dose 150 mcg does not seem to be significantly different from the next lower dose 75 mcg. Doses lower than 75 mcg has not been sufficiently explored. Such study results do not provide sufficient information in understanding dose response relationship.



Particularly it is not clear that at which dose level, which maybe lower than 75 mcg, the efficacy starts to reach plateau. It is important to understand if the lower indacaterol dose level could achieve an acceptable efficacy response because of the safety concern of the LABA drug class (please refer to the medical officer Dr. Lynne Wu's review for detail).

The applicant used two efficacy criteria to make dose selections, trough  $FEV_1$  at 24 hour post-dose and weighted mean  $FEV_1$  over 1-4 hours after two weeks treatment. The applicant's dose selection rational was aiming at indacaterol showing better efficacy than the active comparator. This criteria became problematic because the study results has shown that all indacaterol doses reached efficacy plateau.

Insufficient dosing interval exploration also became an issue as it is suspected that comparable efficacy could be gained at even lower dose level for BID dosing regimen.

## **2 INTRODUCTION**

### **2.1 Overview**

#### **2.1.1 Class and Indication**

Novartis proposes indacaterol maleate, a long-acting beta<sub>2</sub>-agonist (LABA), for long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). COPD is characterized by air flow limitation that is not fully reversible, is usually progressive, and is associated with pathological changes in the lung — a combination of obstructive bronchiolitis and parenchymal destruction. COPD is a major public health problem and is currently the fourth leading cause of chronic morbidity and mortality in the USA. Inhaled beta<sub>2</sub>-agonists have a bronchodilator effect and are widely used in the treatment of COPD. Currently, they are often used as monotherapy or in combination with other classes of medication, such as anticholinergic bronchodilators or inhaled corticosteroids. In this application, indacaterol is proposed to be used as a monotherapy for COPD.

The developed drug in this application is in dry powder formulation, inhalation powder hard capsules is administered once daily (Q.D.) via a single dose dry powder inhaler (SDDPI). The applicant is requesting approval for two dosage strengths, 150 mcg and 300 mcg.

#### **2.1.2 History of drug development**

The applicant has studied three different indacaterol formulations: Hydrofluoroalkane propellant (HFA; IND 66,337), single dose dry powder inhaler (SDDPI; IND 48, 649), and multi-dose dry powder inhaler (MDDPI; IND 69, 754). The HFA drug product development program was suspended by the applicant due to technical reasons.

IND 48,649 assigned to study indacaterol SDDPI in subjects with persistent asthma was submitted on February 13, 2004. IND 69,754 to study indacaterol MDDPI in subjects with persistent asthma was submitted on April 27, 2004. End-of-Phase-2 (EOP2) meeting was held on August 1, 2005 to discuss the clinical development of indacaterol MDDPI. At that time, Novartis indicated that they planned to focus on the MDDPI formulation. On May 22, 2006, the applicant communicated via General Correspondence plans to substitute indacaterol SDDPI for indacaterol MDDPI in Phase III studies. The Division cautioned that Phase III studies using the SDDPI formulation without prior review were “extremely risky.”

Another EOP2 meeting was held on October 10, 2006 to discuss the clinical development program on indacaterol SDDPI. The applicant proposed the COPD study B2335s with adaptive design. The division raised concerns regarding the data monitoring committee’s (DMC) role, data blinding, dose-selection criteria, selection of appropriate efficacy endpoints, use of open-label tiotropium as an active comparator, and treatment of missing data. On December 20, 2006, the applicant submitted study B2335s to request a special protocol assessment (SPA).

In the SPA review, Division emphasized again trough FEV<sub>1</sub> (forced expiratory volume in one second) alone was not adequate dose-selection criteria, other variables such as peak FEV<sub>1</sub> and

FEV<sub>1</sub> AUC (area under the curve) would be considered in the review of dose selection. While the applicant may base dose selection on trough FEV<sub>1</sub> alone at their own risk, the applicant should also collect 12 hour serial spirometry for all four indacaterol doses at steady state in Stage 1 to provide the necessary supplemental information. Other than the dose-selection criteria, the division also raised concerns on lacking of well-accepted definition on the key-secondary endpoints “days of poor control” and COPD exacerbation. About the non-inferiority comparison of indacaterol and tiotropium, the division made it clear in both the EOP2 meeting on October 10, 2006 and the SPA review on study B2335s protocol that because of the open-label nature of the tiotropium arm, the division would not consider any labeling claims based upon the non-inferiority comparison of indacaterol and tiotropium. In addition, while the applicant provided some justification of the 55mL margin based upon historical studies with tiotropium and placebo, from a clinical standpoint the 55mL margin is quite large and not acceptable.

The applicant submitted NDA 22-383 to request approval of using indacaterol to treat patients with COPD on December 18, 2008.

### **2.1.3 Specific studies reviewed**

The summary of all clinical studies the applicant submitted to support this application was given in section 5.2 (Tabular listing of all clinical studies) of the study report. My statistical review focuses on the short term dose ranging studies (B2201, B2205, B2212, and B1202) for dose selection, the pivotal studies (B2335s, B2334 and B2346) and supportive studies (B2305, B2307, and B2340) for efficacy.

## **2.2 Data Sources**

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location < [\\CDSESUB1\EVSPROD\NDA022383\022383.enx](#) >. The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.3.5.

### 3 STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study Design

The design of the pivotal studies is summarized in Table 1. All of the three pivotal studies were multi-center, randomized, double-blind, parallel-arm, placebo controlled studies. B2334 and B2335s were also active controlled. Tiotropium was administered as an open label treatment in B2335s. Formoterol were administered as blinded treatment in B2335s and B2334. B2335s was a study with adaptive design with two stages, stage 1 for dose selection (phase 2) and stage 2 for efficacy and safety evaluation (phase 3). B2334 and B2346 were simple phase 3 studies for efficacy and safety evaluation. In all three pivotal studies, patients were randomized into treatment arms with stratification on smoking status (ex-smoker vs. current smoker). Balance of randomization across treatment arms was controlled on the country level.

Table 1 Design of pivotal studies.

Study ID (Period)	Location	Design and treatment duration	Number of Patients randomized	Treatment arms (Inda=Indacaterol) (For=Formoterol) (Tio=Tiotropium)
<b>B2334</b> (Oct. 2006 - Jul. 2008)	West Europe, East Europe, South and Central America, Asia	52 weeks, Parallel-arm, Placebo and active controlled	405 396 399 400	Inda 300 mcg Inda 600 mcg Placebo (double dummy) For 12 mcg (b.i.d)
<b>B2335s</b> (Apr. 2007 - Aug. 2008)	USA, Canada, South America, West Europe, Asia	26 weeks, Parallel arm, Placebo and active controlled	107 105 / 325 † 110 / 341 † 102 104 / 294 † 112 112 / 331 †	Inda 75 mcg Inda 150 mcg * Inda 300 mcg * Inda 600 mcg Placebo (double dummy) * For 12 mcg (b.i.d) Tio 18 mcg * (open-label)
<b>B2346</b> (Feb. 2008 - Jul. 2008)	USA, Belgium, New Zealand	12 weeks, Parallel-arm, Placebo controlled	211 205	Inda 150 mcg Placebo

- \* Treatment arms that were continued into stage 2.
- † Sample size in stage 2.

The detail design of B2335s is given in Figure 1. After two weeks run-in period, eligible patients were randomized into one of the seven treatment arms (Indacaterol 75 mcg, 150 mcg, 300 mcg, 600 mcg, placebo, formoterol 12 mcg, and tiotropium 18 mcg) in ratio of 1:1:1:1:1:1:1 with about 110 patients in each arm with stratification for smoking status. Twelve hour serial spirometry data were planned to be collected in a subset of patients. This subset of patients were randomized into each treatment arm in ratio of 1:1:1:1:1:1:1 with about 30 to 40 patients in each arm. When all patients in stage 1 had completed at least two weeks treatment, there was an interim analysis performed by an external independent data monitoring committee (DMC) to

make decisions on dose selection. The dose selection was primarily based on pre-defined criteria comparing the efficacy of indacaterol with placebo and the active control, as well as safety. Based on the result of the interim analysis, two of the four indacaterol doses were continued into stage 2 with the tiotropium and placebo arms. The sponsor's clinical trial team and the investigators were informed of the two chosen doses of indacaterol following the interim analysis but remained blinded to any other information including efficacy results arising from the interim analysis. Moreover, patients, investigators, and the clinical trial team remained blinded to the specific treatments for any individual patient until the stage 2 database lock.

Patients randomized to the discontinued indacaterol dose arms or formoterol continued treatment until the completion visit. The total treatment period for the discontinued stage 1 patients could range from 6 to 26 weeks. Patients randomized to the two selected indacaterol doses, placebo, and tiotropium continued on their assigned study treatments into stage 2 for a total of 26 weeks treatment.

In stage 2, sites re-commenced recruitment for the two chosen indacaterol doses, placebo and tiotropium in a 1:1:1:1 ratio. An additional 285 patients per treatment group were randomized until the total required number (400) of patients had been included. Newly screened patients entered a two-week run-in period in the same manner as those who had continued from stage 1. Each patient in stage 2 went through a total of 26 weeks treatment.

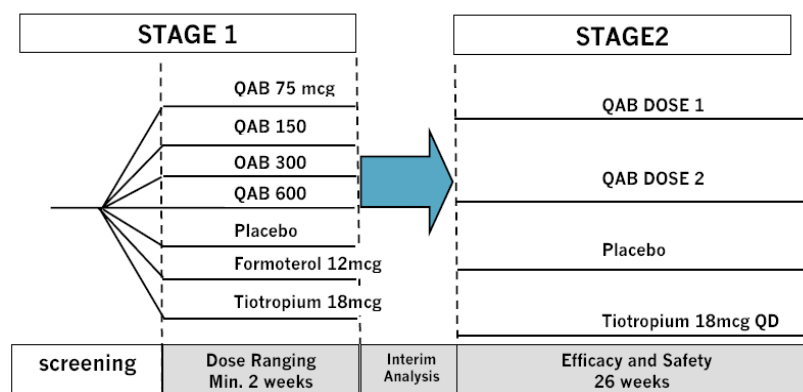


Figure 1 Study design of B2335s (quoted from the clinical study report).

### 3.1.2 Efficacy Endpoints and Assessment Schedule

The primary efficacy endpoints in all three pivotal studies were 24-hour post-dose trough  $FEV_1$  after 12 weeks treatment. The 24-hour post-dose trough  $FEV_1$  was defined as the average of two  $FEV_1$  measurements taken in clinic after 23 hour 10 minute and 23 hour 45 minute. The key secondary efficacy endpoint was days of poor control (DOPC). A “day of poor control” was defined as any day in the patient diary where a score  $\geq 2$  (i.e. moderate or severe symptoms) was recorded for at least two out of five symptoms (cough, wheeze, production of sputum, color of sputum, breathlessness). Another important secondary efficacy endpoint is use of rescue medication (salbutamol/albuterol). Summary on number of daily puffs of rescue medication use and percentage of days with no use of rescue medication during the whole study period is included in this review.

The applicant defined COPD exacerbation as a new onset or worsening of more than one respiratory symptom (i.e. dyspnea, cough, sputum purulence or volume, or wheeze) presented for more than 3 consecutive days, and at least one of the following: documented change or increase in COPD related treatment due to worsening symptoms and/or documented COPD-related hospitalizations or emergency room visits. Since the division and the applicant did not reach agreement on the definition of COPD exacerbation, the efficacy summary on COPD exacerbation is not included in the review, but available in Figure 11 in the appendices. The applicant also collected data on peak FEV<sub>1</sub>, FVC (forced vital capacity), PEF (peak expiratory flow), total SGRQ (St. George's respiratory questionnaire) score, TDI (transitional dyspnea index) focal score, BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, etc. Reviews on these secondary and tertiary endpoints are not included in this document.

The efficacy variables that the applicant used for dose selection were 24-hour post-dose trough FEV<sub>1</sub> and weighted mean FEV<sub>1</sub> over 1-4 hours after 2 weeks of treatment. Weighted mean FEV<sub>1</sub> over 1-4 hours was defined as standardized AUC for FEV<sub>1</sub> between 1 and 4 hours post-dose. The standardization was calculated as the sum of trapezoids between two time points divided by the length of time.

In all pivotal studies, daily clinical symptoms (to derive DOPC), rescue medication use, and any adverse events were recorded in a patient diary.

In B2335s, 24-hour post-dose trough FEV<sub>1</sub> was measured at clinic visit at day 2, 15, 85, and 183. Twelve hour serial spirometry was conducted in the clinic, in a subset of patients (about 30 to 40 patients in each arm), at day 1 and after 2, 12, and 26 weeks treatment. Data from the 12-hour serial spirometry measurements were used to derive weighted mean FEV<sub>1</sub> over 1-4 hours.

In B2334, 24-hour post-dose trough FEV<sub>1</sub> was measured at clinic visit at day 2, 85, and 365. Twelve hour serial spirometry was conducted in the clinic, in a subset of patients, at day 1 and after 12, and 52 weeks treatment.

In B2346, 24-hour post-dose trough FEV<sub>1</sub> was measured at clinic visit at day 2, and 85. Four hour serial spirometry was conducted in the clinic, in all patients, at day 1 and after 12 weeks treatment.

### **3.1.3 Patient Disposition, Demographic and Baseline Characteristics**

The number of patients randomized in each treatment arm in the pivotal studies was given in Table 1 Design of pivotal studies. On average, about 70% enrollment to the pivotal studies completed the study. The discontinuation occurred more frequently in placebo arm than in other treatment arms in both study B2335s (30% in placebo vs. 18~23% in other treatments) and study B2334 (32% in placebo vs. 23~26% in other treatments). The discontinuation rate in study B2346 were comparable in the placebo arm and indacaterol 150 mcg arm (13% in placebo vs. 12% in indacaterol 150 mcg). The primary reasons for premature discontinuation were adverse events and withdrawal of consent. The summary of patient disposition in pivotal studies is given in Table 2.

Table 2 Patient dispositions of the pivotal studies.

Study	B2335s (stage 2)				B2334*				B2346	
Treatment	Inda 150 mcg	Inda 300 mcg	Tio 18 mcg	Placebo	Inda 300 mcg	Inda 600 mcg	For 12 mcg	Placebo	Inda 150 mcg	Placebo
Randomized	420	418	420	425	437	428	435	432	211	205
Exposed	416	416	415	418	437	425	434	432	211	205
Completed	325	341	331	284	338	326	323	295	186	178
Discontinued	95	77	89	131	99	102	112	137	25	27
ITT (mITT*)	416	416	415	418	405	396	400	399	211	204
PP	369	373	351	358	354	338	344	346	199	182
Primary reason for premature discontinuation										
Adverse events	29	26	17	46	35	24	40	35	6	3
Subject withdrew consent	29	22	20	37	27	40	33	50	5	4
Protocol deviation	13	9	14	11	11	11	11	10	7	9
Lost to follow- up	12	6	13	8	5	6	5	3	3	2
Administrative problems	5	3	6	9	7	8	5	2	3	0
Unsatisfactory therapeutic effect	4	9	9	17	12	9	12	30	1	6
Abnormal lab values	1	1	2	1	1	1	0	0	0	0
Abnormal test procedure results	1	1	6	2	0	1	1	2	0	1
Death	1	0	2	0	1	1	5	5	0	1
Subject's condition no longer requires study drug	0	0	0	0	0	1	0	0	0	0
Not stated	0	0	0	0	0	0	0	0	0	1

The intent-to-treat (ITT) population in all pivotal studies was defined as all randomized patients who received at least one dose of study drug, with one exception — in study B2346, one patient randomized to placebo arm was excluded from the ITT population due to lack of signed consent form. The primary analysis for the primary and important secondary efficacy endpoints was based on the ITT population in study B2335s and B2346. In study B2334, patients who enrolled into centers in Egypt (about 5% of the total enrollment) were excluded from the modified intent-to-treat (mITT) population due to serious GCP non-compliance and unreliability of data. The primary analysis in study B2334 for the primary and important secondary efficacy endpoints was thus based on the mITT population. Patients were analyzed according to the treatment to which they were randomized.

The per-protocol (PP) population in all pivotal studies was defined as all patients of the ITT population (mITT in study B2334) without any major protocol deviations.

The study population consisted of male and female patients who were 40 years of age or older with moderate to severe COPD (post-bronchodilator FEV<sub>1</sub> < 80% and ≥30% of the predicted normal value; post-bronchodilator FEV<sub>1</sub>/FVC < 70%) and a smoking history of at least 20 pack years. Most patients were Caucasians. In all three pivotal studies, treatment groups were evenly matched in terms of baseline demographics. The demographic and baseline characteristics summary in the randomized populations of all three pivotal studies is given in Table 8 in the appendices.

All three pivotal studies enrolled both reversible and non-reversible patients. The medical review team pointed out that patient population in B2335s and B2346 consisted of a large proportion of patients with good reversibility, the study population in these two studies were not the right target population, which helps to give indacaterol a good result. This need to be taken into consideration in efficacy evaluation. The detail summary of patient's post-bronchodilator FEV<sub>1</sub>/FVC and FEV<sub>1</sub> reversibility at baseline, quoted from the clinical study report, is given in Table 12, Table 13, and Table 14 in the appendices.

### **3.1.4 Statistical Methodologies**

The primary (24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment) and secondary (DOPC, mean daily number of puffs of rescue medication use, percentage of days with no use of rescue medication) efficacy endpoints included in this review were analyzed using a mixed effect model. The model contained treatment as a fixed effect with the baseline FEV<sub>1</sub> measurement, FEV<sub>1</sub> prior to inhalation of salbutamol/albuterol, FEV<sub>1</sub> 30 minute post inhalation of salbutamol/albuterol (components of SABA reversibility), FEV<sub>1</sub> prior to inhalation of ipratropium, and FEV<sub>1</sub> one hour post inhalation of ipratropium (components of anti-cholinergic reversibility) as covariates. To reflect the randomization scheme, the model also included the smoking status and country as fixed effects with center nested within country as a random effect.

Missing data were imputed with last observation carried forward (LOCF) method. Any of the 23 hour 10 minute and the 23 hour 45 minute values contributing to the trough FEV<sub>1</sub> that were taken within 6 hours of rescue medication use or that were outside the 22 hour to 25 hour post-dose time window were considered missing values. If both values were missing, or if the patient withdrew from the study, then trough FEV<sub>1</sub> was regarded as missing. A missing trough FEV<sub>1</sub> value at week 12 was replaced by carrying forward trough FEV<sub>1</sub> from the last evaluable visit as long as the visit was not prior to Day 15. The primary analysis was based on imputed data.

### **3.1.5 Dose selection**

The applicant conducted four short term placebo-controlled dose ranging studies to explore the dose response of indacaterol. The summary of the study design of the dose ranging studies is available in Table 6 in the appendices. These studies used varied doses (from 50 mcg to 800 mcg) of indacaterol in varied populations, as well as different formulations and delivery devices (MDDPI and SDDPI). Since the dose ranging studies were different in multiple ways, a definitive dose selection study using the target population and the device with phase 3 supplies



was needed. The first stage of the pivotal study B2335s with adaptive design was designed to serve this purpose.

Data from the first stage of study B2335s was analyzed by an independent external data monitoring committee (DMC). Based on the pre-specified dose selection rational defined by the applicant and the interim analysis results, the DMC identified two doses in stage 1 to be carried forward for use in the second stage of the study.

The applicant's dose selection criteria were:

- *The selected dose need to be 120 mL greater than placebo (MCID) in terms of trough FEV<sub>1</sub> and numerically higher than tiotropium and formoterol.*
- *The selected dose needed to be numerically higher than tiotropium and formoterol in terms of weighted mean FEV<sub>1</sub> over 1-4 hours.*

The summary of interim analysis results is given in Table 3.

Based on analysis of weighted mean FEV<sub>1</sub> over 1-4 hours, the sponsor consider the efficacy of indacaterol 75 mcg to be suboptimal because the point estimate of treatment effect of indacaterol 75 mcg was 1.5L, lower than the point estimate of treatment effect of formoterol (1.52L). The lowest dose that satisfied the dose selection criteria was 150 mcg. 150 mcg and 300 mcg were the two doses carried forward to stage 2.

Table 3 Summary of B2335s interim analysis results (Quoted from clinical study report).

Treatment				Treatment difference			
Treatment	N	LS mean	SE	Comparison	LS mean	SE	95% CI
Trough FEV <sub>1</sub> (L)							
Comparisons with placebo							
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	<b>0.14</b>	0.028	( 0.08, 0.19)
Placebo	104	1.31	0.024				
AUC 1h-4h FEV <sub>1</sub> (L)							
Comparisons with placebo							
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	<b>0.22</b>	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				

The issue of dose response analyses raised during the review are discussed here.

First of all, the study showed that all doses has reached efficacy plateau. The dose response curve based on trough FEV<sub>1</sub> and weighted mean FEV<sub>1</sub> over 0-4 hours is given in Figure 2. Given such results, it is not clear at which lower dose level the plateau effect has reached. To understand this, lower dose levels should be studied. Indacaterol doses lower than 75 mcg were not adequately studied in the development program.

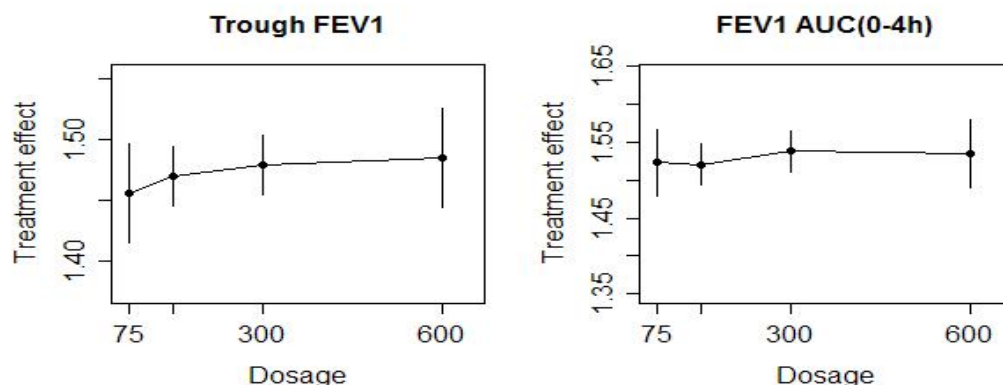


Figure 2 Dose responses by trough FEV<sub>1</sub> and weighted mean FEV<sub>1</sub> over 0-4 hours at Day 15 in B2335s.

Data on week 2 appear to be adequate to conclude that the efficacy of indacaterol 75 mcg and indacaterol 150 mcg are very similar. This is further confirmed by the data on week 12. Since patients were enrolled into stage 1 of the study at different time, when the interim analysis was done, more than half of the patients in the arms that were discontinued after stage 1 already had week 12 assessment. Figure 3 shows the summary of trough FEV<sub>1</sub> by treatment arms at different assessment time. The slight separation among indacaterol 75 mcg, 150 mcg, and 300 mcg at week 2 disappeared at week 12.

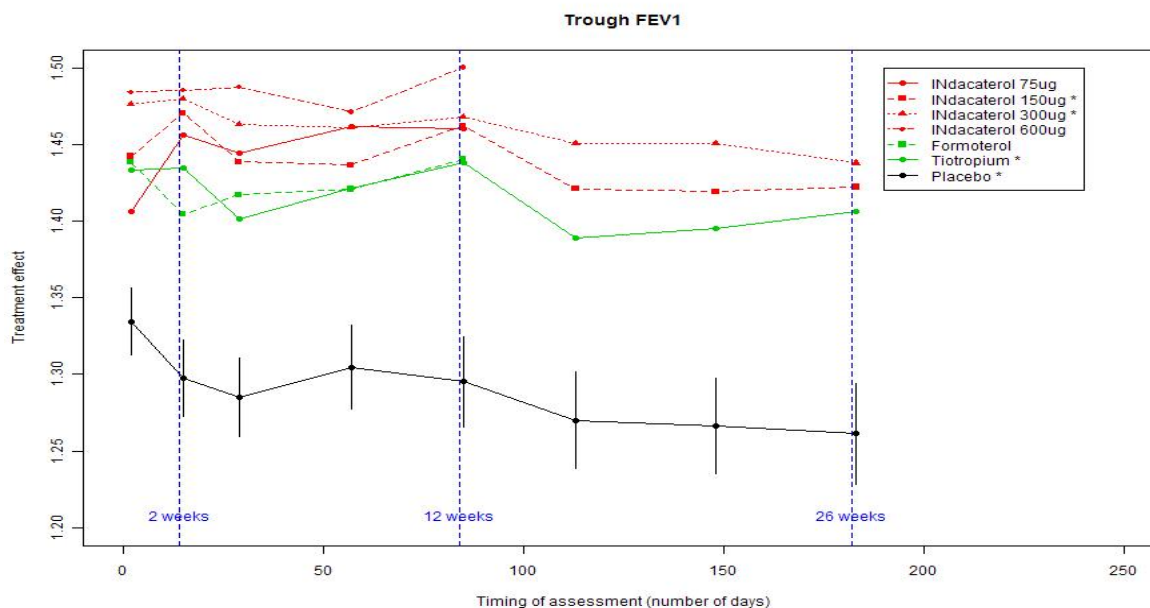


Figure 3 Summary of trough FEV<sub>1</sub> by treatment arms in B2335s at different assessment time.

This reviewer also checked the distribution of change from baseline in trough FEV<sub>1</sub> after two weeks treatment of individual dose groups. The summary plot is given in Figure 4. The plot on the left shows that the distribution of change from baseline in trough FEV<sub>1</sub> is well separated between the placebo arm and the indacaterol arms, but the indacaterol arms are all overlapped with each other with very small difference. The plot on the right highlights the distribution of indacaterol 75 mcg and indacaterol 150 mcg. The almost perfect overlap of the two distributions implies the small difference between the two arms is only due to the difference in the high end of the distribution, which means only a small percentage of patients in indacaterol 150 mcg arm got additional benefit at the increased dose. However, the potential risk for a higher dose increased to all patients in the 150 mcg arm.

Additional comparisons on treatment effect between 150 mcg and 75 mcg with other spirometry measures as efficacy endpoints are available in Figure 11 in the appendices. In general, 75 mcg is not significantly different from 150 mcg. In the early responses (FEV<sub>1</sub> and FVC up to 60 minutes post-dose), 75 mcg was even numerically higher than 150 mcg.

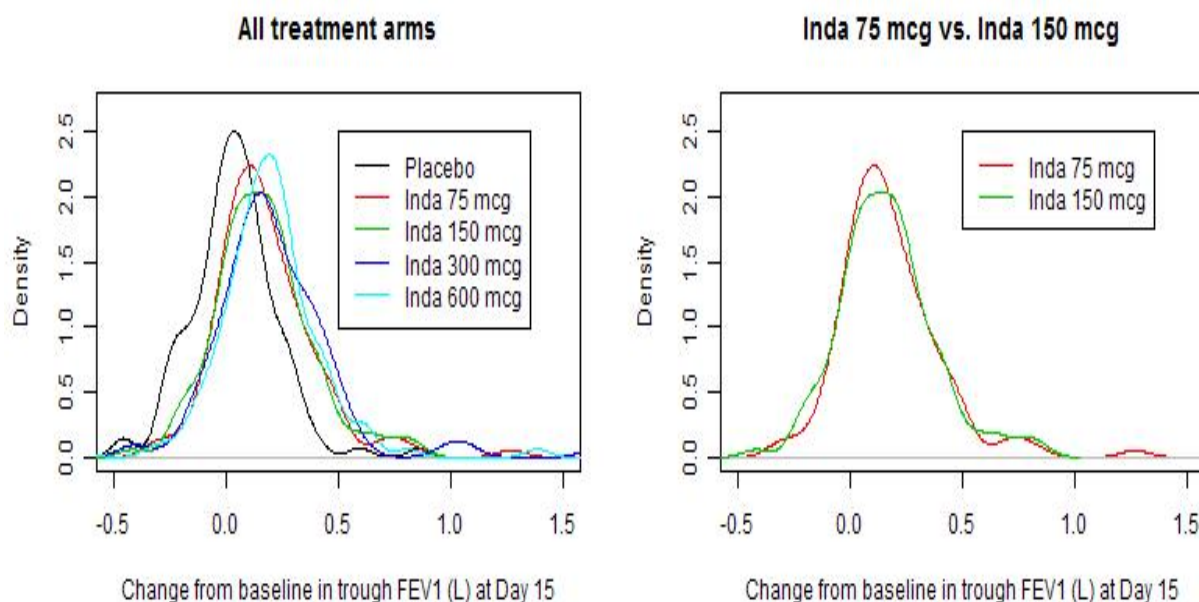


Figure 4 Distribution of change from baseline in trough FEV<sub>1</sub> at Day 15 in study B2335s.

The applicant's dose selection rational was aiming at indacaterol showing better efficacy than the active comparator. Thus higher doses are more likely to be chosen than lower doses with better safety profile and sufficient efficacy. This was reflected by the applicant's dose selection criteria to screen out doses that may have sufficient efficacy, but do not have a numerically higher efficacy result than the active comparator. Such criteria became problematic when the study results showed that all doses studied has reached plateau level.

### 3.1.6 Efficacy Results and Conclusions

#### a) Pivotal studies

The summary of primary efficacy endpoint in pivotal studies is given in Figure 5 and Table 4. The plot on the left in Figure 5 summarizes the least square mean estimate of the treatment effect with the 95% confidence interval by the mixed model on 24-hour post-dose trough FEV<sub>1</sub> after 12 weeks treatment. The treatment arms are labeled in the X-axis. The arms in study B2335s are labeled in black, the arms in study B2334 are in labeled in red, the arms in study B2346 are in labeled in green. The active controls in the first two studies are indicated by dotted line. It shows that the active controls and treatments with indacaterol all had higher trough FEV<sub>1</sub> than the placebo arm after 12 weeks treatment.

The treatment comparisons between indacaterol and placebo are given in the plot on right. The X axis indicates the comparisons made. The horizontal dash line indicates the applicant defined minimum clinical important difference (MCID, which is 0.12L). Although the comparison between indacaterol and active controls are also reported, for the reasons stated in section 2.1.2 History of drug development, the division doesn't consider any labeling claim based on non-inferiority comparisons.

To summarize the analysis results on the primary efficacy endpoint, all arms with treatment of indacaterol were superior to the placebo arms with the mean estimate of treatment difference between indacaterol and placebo above the MCID in all three studies. The purpose of evaluating multiple doses is to understand the dose response relationship. The error rate of wrongly approving an ineffective drug is protected by collective evaluating multiple doses. For these reasons, no multiplicity adjustment is applied in reporting the study results.

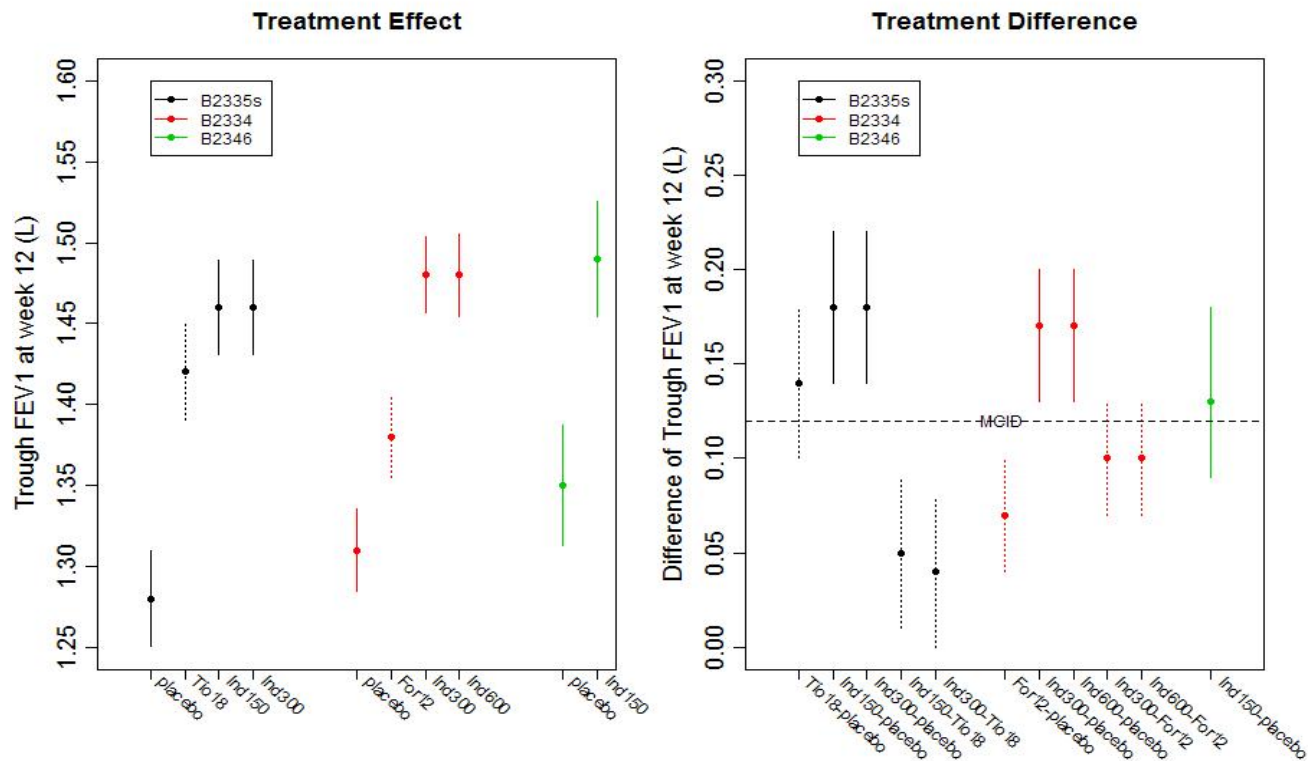


Figure 5 Summary of the primary efficacy endpoint (trough FEV<sub>1</sub> at week 12) in pivotal studies.

Table 4 Summary of the primary efficacy endpoint (trough FEV<sub>1</sub> at week 12) in pivotal studies.

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	P value
B2335s Stage 2	Placebo	1.28	0.015	---	---	---	---	---
	Tio 18 mcg	1.42	0.015	Tio18-placebo	0.14	0.016	(0.11, 0.17)	<0.001
	Inda 150 mcg	1.46	0.015	Ind150-placebo	0.18	0.016	(0.15, 0.21)	<0.001
	Inda 300 mcg	1.46	0.015	Ind300-placebo	0.18	0.016	(0.15, 0.21)	<0.001
B2334	Placebo	1.31	0.013	---	---	---	---	---
	For 12 mcg	1.38	0.013	For12-placebo	0.07	0.016	(0.04, 0.1)	<0.001
	Inda 300 mcg	1.48	0.012	Ind300-placebo	0.17	0.016	(0.13, 0.2)	<0.001
	Inda 600 mcg	1.48	0.013	Ind600-placebo	0.17	0.016	(0.13, 0.2)	<0.001
B2346	Placebo	1.35	0.019	---	---	---	---	---
	Inda 150 mcg	1.49	0.018	Ind150-placebo	0.13	0.024	(0.09, 0.18)	<0.001

The summary of key secondary efficacy endpoint in pivotal studies is given in Figure 6 and Table 5. The legend and axis in Figure 6 are the same with those in Figure 5 with the exception that the Y axis here is the percentage of days in poor control (DOPC). The horizontal dash line in the plot on the right indicates 0, i.e. no difference between treatments. In this case, the patients in the active controls and indacaterol treatments all had a lower percentage of DOPC than those in the placebo arms. In study B2335s, the differences between the indacaterol arms and the placebo arm were not significantly different from 0. The superiority of indacaterol over placebo in terms of DOPC was confirmed in the other two pivotal studies.

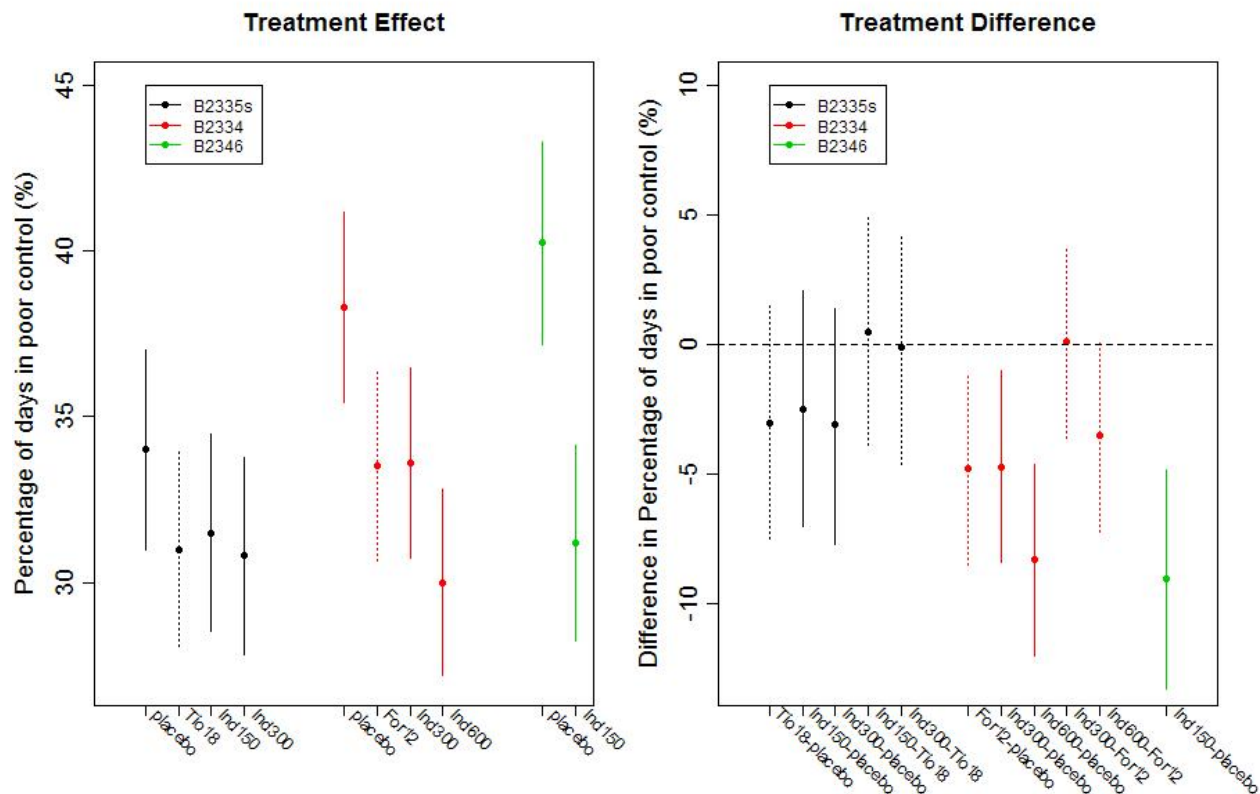


Figure 6 Summary of the key secondary efficacy endpoint (DOPC) in pivotal studies.

Table 5 Summary of the key secondary efficacy endpoint (DOPC) in pivotal studies.

Study	Treatment	Mean (% days)	SE (% days)	Treatment difference	Mean (% days)	SE (% days)	95% CI (% days)	P value
B2335s Stage 2	Placebo	34	1.5	---	---	---	---	---
	Tio 18 mcg	31	1.5	Tio18-placebo	-3	1.8	(-6.5, 0.5)	0.1
	Inda 150 mcg	32	1.5	Ind150-placebo	-2.5	1.8	(-6, 1.0)	0.18
	Inda 300 mcg	32	1.5	Ind300-placebo	-3.1	1.8	(-6.6, 0.4)	0.09
B2334	Placebo	38	1.5	---	---	---	---	---
	For 12 mcg	34	1.5	For12-placebo	-4.8	1.9	(-8.5, -1.1)	0.01
	Inda 300 mcg	34	1.5	Ind300-placebo	-4.7	1.9	(-8.4, -1)	0.01
	Inda 600 mcg	30	1.4	Ind600-placebo	-8.3	1.9	(-12, -4.6)	<0.001
B2346	Placebo	40	1.6	---	---	---	---	---
	Inda 150 mcg	31	1.5	Ind150-placebo	-9.1	2.2	(-13.3, -4.8)	<0.001

Similar summaries on daily number of puffs of rescue medication used and percentage of days with no use of rescue medication are given in Figure 7. Superior of indacaterol over placebo in terms of using rescue medication was confirmed in all three studies.

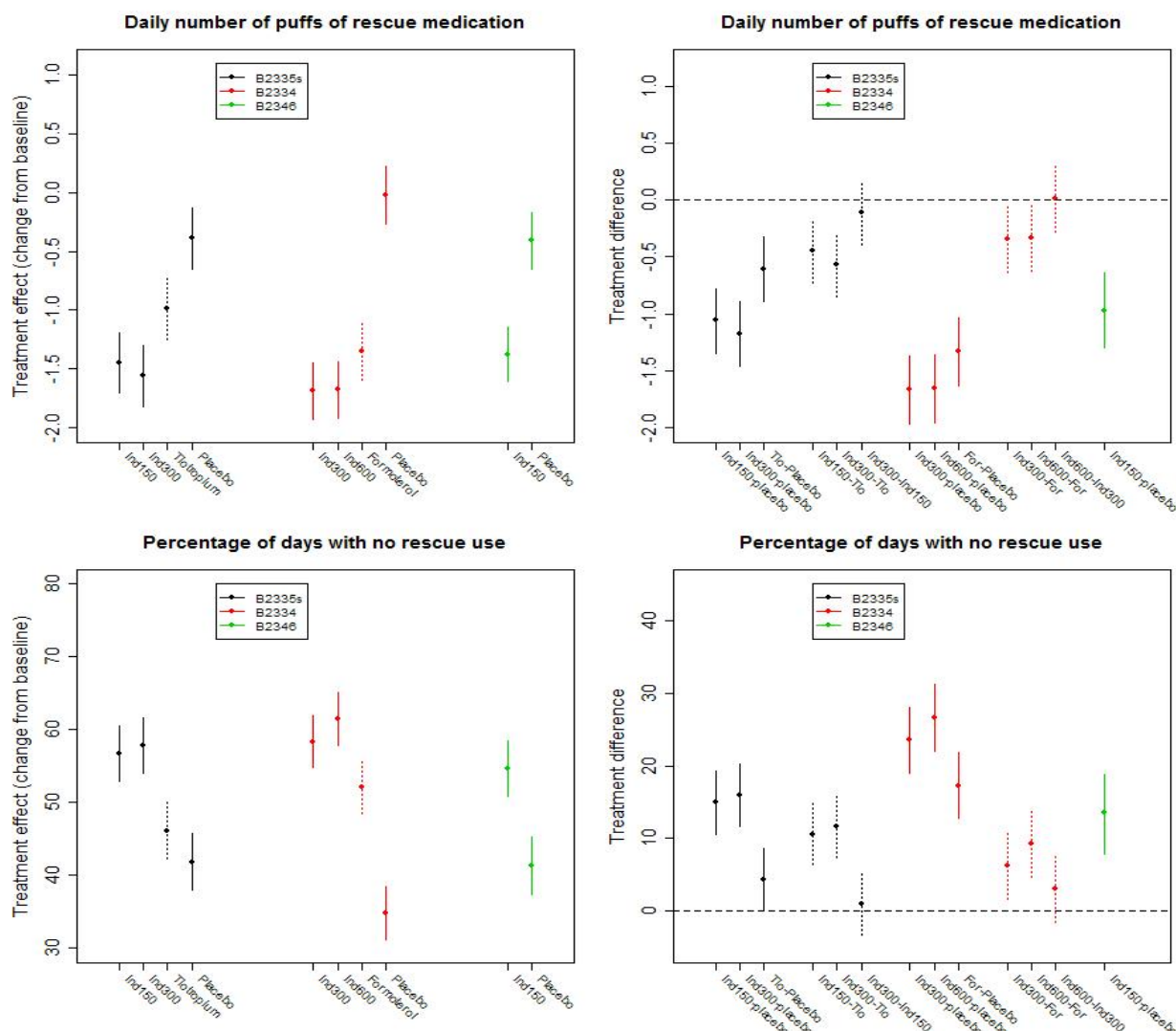


Figure 7 Summary of rescue medication use in pivotal studies.

In conclusion, the superiority of indacaterol at the proposed dose (150 mcg and 300 mcg) over placebo was confirmed by the pivotal studies.

#### b) Supportive studies

The applicant also conducted three supportive studies, B2305, B2307, and B2340, to evaluate the specific efficacy aspects of indacaterol. All three supportive studies were short term, placebo and active controlled, crossover studies with small number of patients (68~96). The detail design of the supportive studies is given in the appendices. The study populations in the three supportive studies were similar to those in the pivotal studies. Summary of the baseline and demographic information on the patient population in the supportive studies is given in appendices as well.

Study B2340 was designed to collect the 24-hour serial spirometry of indacaterol 300 mcg, placebo, and Salmeterol 50 mcg. Study B2305 was designed to compare the efficacy of



indacaterol 300 mcg given at evening to the efficacy of indacaterol 300 mcg given at morning. Study B2307 was designed to assess the fast onset of action, comparing indacaterol 150 mcg and 300 mcg to salbutamol 200 mcg, salmeterol 50 mcg + fluticason 500 mcg, and placebo.

The summary of 24-hour profile of FEV<sub>1</sub> after two weeks treatment in study B2340 is given in Figure 8. Indacaterol (300 mcg) was superior to placebo at each scheduled time point and was higher than salmeterol at all scheduled time points as well, but usually not reaching statistical significance.

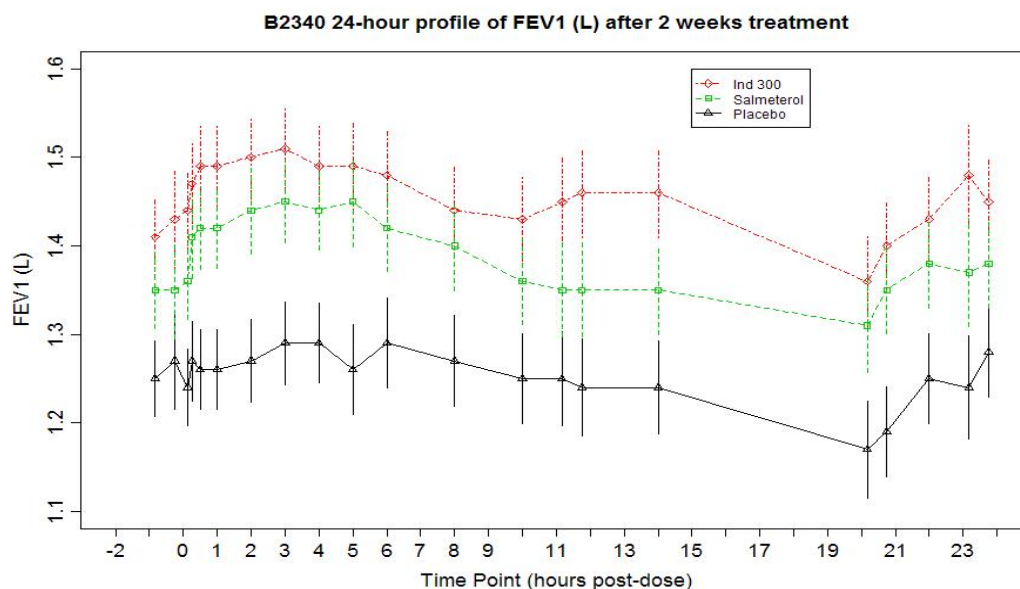


Figure 8 24-hour FEV<sub>1</sub> profile after two weeks treatment in study B2340.

The efficacy results for study B2305 show that after 2 weeks treatment, the evening indacaterol doses were associated with a clinically relevant increase in 24-hour post-dose trough FEV<sub>1</sub> compared to placebo. The estimated treatment difference was 0.2L and was statistically significant. The secondary analyses showed that following 2 weeks treatment, the morning indacaterol dose was associated with a clinically relevant increase in morning trough FEV<sub>1</sub> relative to placebo. The evening and morning indacaterol doses were associated with a similar increase in trough FEV<sub>1</sub>.

The efficacy results in study B2307 show that FEV<sub>1</sub> at 5 minute post-dose for indacaterol treatments (150 mcg and 300 mcg) were significantly higher than those for placebo. Indacaterol had a fast acting onset and was at least as effective as salbutamol at 5 minute post-dose. At most time points up to 2 hours post-dose, there was little difference between indacaterol and other active treatments (i.e. salbutamol, salmeterol + fluticason).

### 3.2 Evaluation of Safety

The evaluation of safety was conducted by Dr. Lynne Wu. No special analysis on safety evaluation was requested by the clinical review team. Reader is referred to Dr. Lynne Wu's review for this section.



## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The summary of subgroup analysis on the primary efficacy endpoint in the pivotal studies is given in Figure 9 and Figure 10. The subgroups in Figure 9 are categorized by age group, gender, COPD severity, smoking status, and ICS use at baseline, based on the categories summarized in Table 8 in the appendices. The subgroups in Figure 10 are categorized by race and study locations. The results presented in the plots are from the mixed model, similar to the one used for primary efficacy analysis, with the additional covariate on the subgroups being analyzed.

In general, the subgroup analysis results are consistent with the results of overall population. There are some slight differences on gender, COPD severity, and smoking status, however none of them is statistically significant.

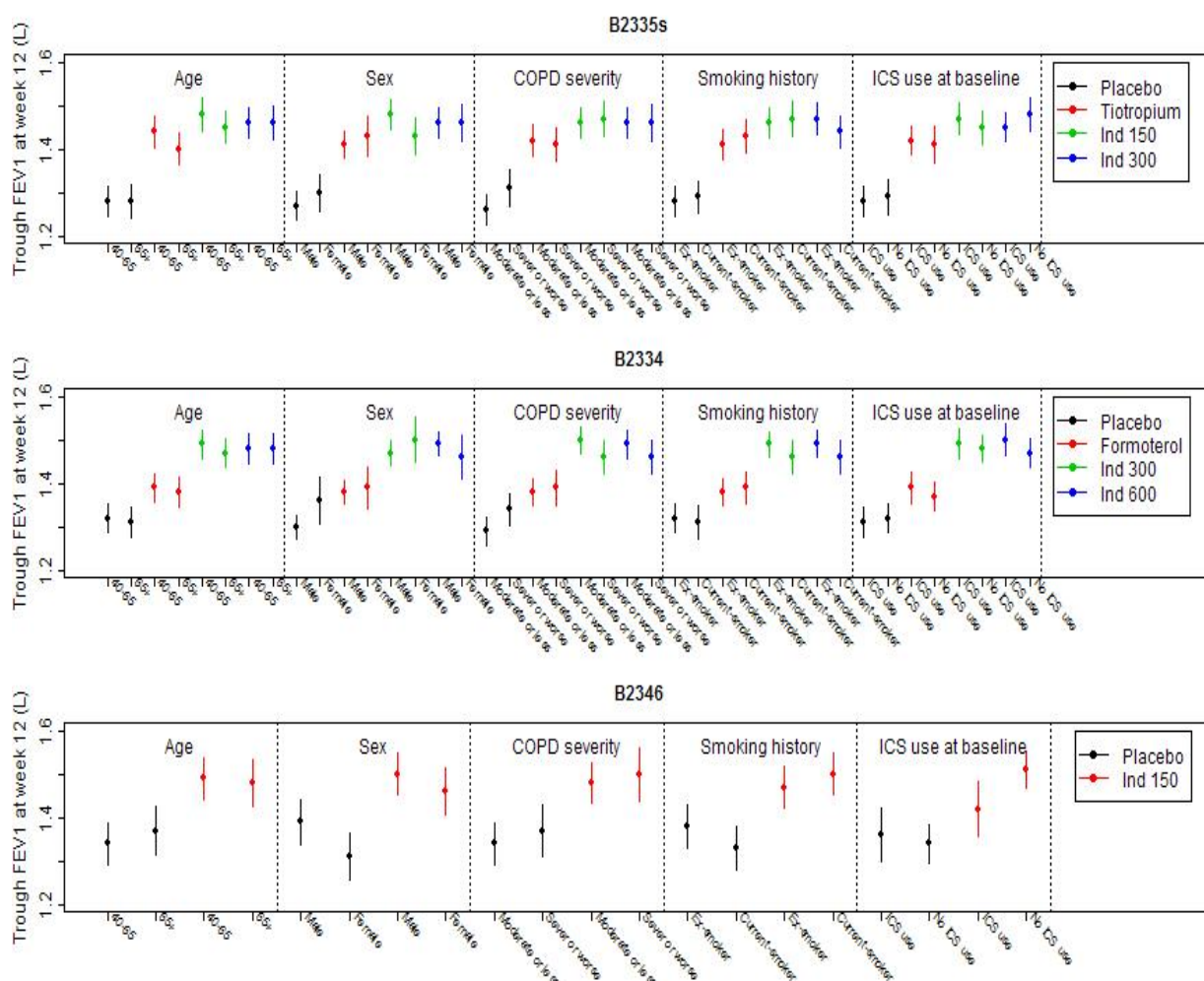


Figure 9 Summary of subgroup analysis (a) in pivotal studies.

Since most patients enrolled in the pivotal studies were Caucasians, there was not enough number of patients in all races in study B2334 and study B2346 to conduct the subgroup analysis on race. The summary on primary efficacy endpoint by race was only done in study B2335s.

Subgroup analysis was also done on study locations. Since over 99% of the study centers in B2346 were in USA, the summary on primary efficacy endpoint by study location was only done in study B2335s and B2334. The results are shown in Figure 10.

The subgroup analysis on race showed that the results in all races are comparable within each treatment arm. The only deviation is the last group in treatment arm of indacaterol 300 mcg. Since there were only two patients in that group, the estimation was not reliable. In general, the result of subgroup analysis on race is consistent with the results of overall population as well.

In study B2334, there was a consistent pattern that the efficacy results in East Europe were always better than that in West Europe. However, this difference was not statistically significant either. In general, the efficacy results in different regions in both study B2335s and study B2334 are comparable.

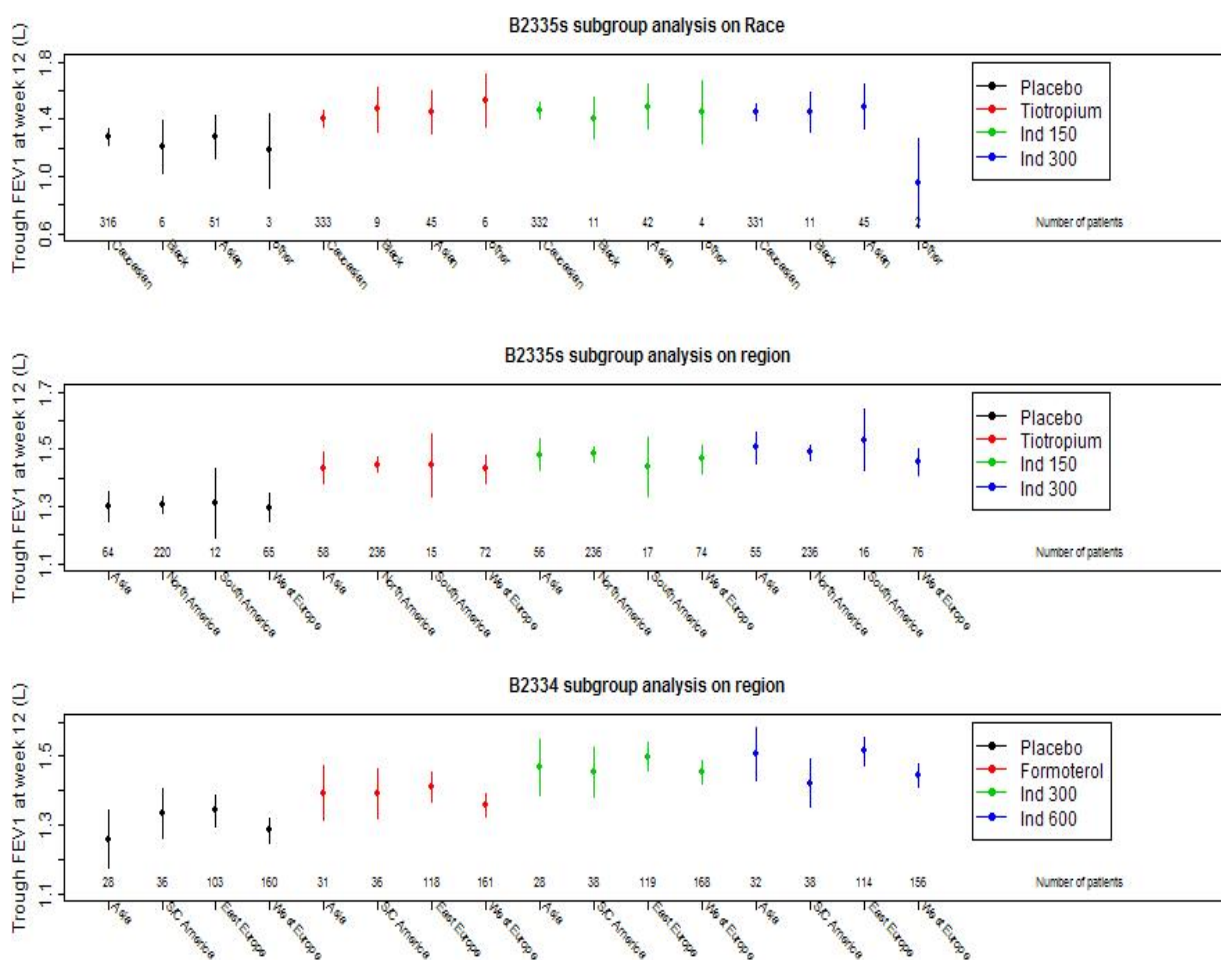


Figure 10 Summary of subgroup analysis (b) in pivotal studies.

## APPENDICES

### Design of short term dose ranging studies

The design of the four short term dose ranging studies is summarized in Table 6. All four studies were multi-center, randomized, placebo-controlled, double-blind studies. Two of the studies, B2201 and B2205, were parallel-arm studies; the other two studies, B2212 and B1202, were complete block cross over studies. In each study, there was a two-week run-in period. In the two crossover studies, each treatment period was followed by a wash out period with no treatment. In all the study arms, except formoterol 12 mcg (B.I.D) in B2212, treatments were administered once daily (Q.D.). B2212 was a double dummy study with placebo matching to both indacaterol (SDDPI) and Formoterol 12 mcg. Tiotropium 18 mcg in B2205 was administered as an open-label treatment.

Table 6 Design of short term dose ranging studies.

Study ID (Period)	Location	Design	# of patients randomized (completed)	Treatment / period duration	Treatment arms (Inda=Indacaterol) (For=Formoterol) (Tio=Tiotropium)
<b>B2201</b> (Jan. 2004 – Jul. 2004)	Europe	Parallel-arm	68 (65) 67 (64) 28 (26)	28-day treatment	Inda 400 mcg (SDDPI) Inda 800 mcg (SDDPI) Placebo (SDDPI)
<b>B2205</b> (Jul. 2004 – Dec. 2004)	Europe, North and South America	Parallel-arm	103 (102) 105 (104) 105 (102) 110 (108) 105 (102) 107 (105)	7-day treatment	Inda 50 mcg (MDDPI) Inda 100 mcg (MDDPI) Inda 200 mcg (MDDPI) Inda 400 mcg (MDDPI) Inda 400 mcg (SDDPI) Placebo (MDPPI & SDDPI) Tio 18 mcg (open-label)
<b>B2212</b> (Oct. 2006 – Jan. 2007)	Belgium	5-period, 5-treatment, Cross over	51 (47)	1-day treatment, 6-day wash out period	Inda 150 mcg (SDDPI) Inda 300 mcg (SDDPI) Inda 600 mcg (SDDPI) Placebo (double dummy) For 12 mcg (b.i.d.)
<b>B1202</b> (Dec. 2006 – Oct. 2007)	Japan	4-period, 4-treatment, cross over	50 (45)	1-day treatment, 14 to 28-day wash out period	Inda 150 mcg (SDDPI) Inda 300 mcg (SDDPI) Inda 600 mcg (SDDPI) Placebo (SDDPI)

Table 7 Patient disposition of treatment arms not continued into stage 2 in B2335s.

Treatment	Indacaterol 75 mcg	Indacaterol 600 mcg	Formoterol 12 mcg
Randomized	130 (100%)	123 (100%)	123 (100%)
Exposed	127 (98%)	122 (99%)	122 (99%)
Completed	107 (82%)	102 (83%)	112 (91%)
Discontinued	23 (18%)	21 (17%)	11 (9%)

Table 8 Demographic and baseline characteristics summary in randomized populations of pivotal studies.

Study		B2335s (stage 2)				B2334				B2346	
Treatment		Inda 150 mcg	Inda 300 mcg	Tio 18 mcg	Placebo	Inda 300 mcg	Inda 600 mcg	For 12 mcg	Placebo	Inda 150 mcg	Placebo
Age	N	416	416	415	418	437	425	434	432	211	205
	Mean	63	63	64	64	64	63	64	63	63	63
	SD	9.4	9.3	8.8	8.9	8.6	8.7	8.5	8.3	9.9	9.6
	Median	64	63	64	64	64	63	64	63	63	63
	Min - Max	40-87	40-88	41-85	41-84	40-87	40-87	40-84	41-90	40-85	42-89
Age group	40-64 years	214 (51%)	230 (55%)	215 (52%)	215 (51%)	220 (50%)	232 (55%)	226 (52%)	239 (55%)	117 (56%)	119 (58%)
	≥65 years	202 (49%)	186 (45%)	200 (48%)	203 (49%)	217 (50%)	193 (45%)	208 (48%)	193 (45%)	94 (44%)	86 (42%)
Gender	Male	259 (62%)	263 (63%)	269 (65%)	255 (61%)	351 (80%)	327 (77%)	348 (80%)	352 (82%)	108 (51%)	110 (54%)
	Female	157 (38%)	153 (37%)	146 (35%)	163 (39%)	86 (20%)	98 (23%)	86 (20%)	80 (18%)	103 (49%)	95 (46%)
Race	Caucasian	353 (85%)	355 (85%)	347 (84%)	355 (85%)	407 (93%)	393 (93%)	400 (92%)	404 (94%)	194 (93%)	191 (93%)
	Black	14 (3%)	12 (3%)	10 (2%)	7 (2%)	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.2%)	12 (6%)	10 (5%)
	Asian	45 (11%)	47 (11%)	51 (12%)	53 (13%)	7 (2%)	8 (2%)	7 (2%)	7 (2%)	1 (0.5%)	1 (0.5%)
	Other	4 (1%)	2 (1%)	7 (2%)	3 (1%)	22 (5%)	23 (5%)	23 (5%)	20 (4%)	4 (2%)	3 (2%)
COPD severity	At risk	0 (0%)	0 (0%)	3 (1%)	0 (0%)	9 (2%)	3 (1%)	7 (2%)	10 (2%)	0 (0%)	1 (0.5%)
	Mild	18 (4%)	19 (5%)	20 (5%)	16 (4%)	2 (0.5%)	6 (1%)	7 (2%)	10 (2%)	7 (3.3%)	10 (5%)
	Moderate	239 (58%)	240 (58%)	213 (51%)	236 (57%)	226 (52%)	212 (50%)	226 (52%)	216 (50%)	119 (56%)	117 (57%)
	Severe	157 (38%)	156 (38%)	176 (42%)	165 (40%)	190 (44%)	188 (44%)	182 (42%)	186 (43%)	84 (40%)	76 (37%)
	Very severe	2 (0.5%)	1 (0.2%)	3 (0.7%)	1 (0.2%)	9 (2%)	15 (4%)	10 (2%)	9 (2%)	1 (0.5%)	1 (0.5%)
ICS use	No	257 (62%)	261 (63%)	270 (65%)	253 (61%)	194 (44%)	199 (47%)	213 (49%)	208 (48%)	150 (71%)	135 (66%)
	Yes	159 (38%)	155 (37%)	145 (35%)	165 (40%)	243 (56%)	226 (53%)	221 (51%)	224 (52%)	61 (29%)	70 (34%)
Smoking history	Ex-smoker	229 (55%)	227 (55%)	230 (55%)	227 (54%)	255 (58%)	246 (58%)	256 (59%)	258 (60%)	103 (49%)	97 (47%)
	Current smoker	187 (45%)	189 (45%)	185 (45%)	191 (46%)	182 (42%)	179 (42%)	178 (41%)	174 (40%)	108 (51%)	108 (53%)

## Design of supportive studies

The design of supportive studies is summarized in Table 9. All of the three supportive studies were multi-center, randomized, double-blind, crossover, placebo and active controlled, short term studies. All the treatments were administered once daily (Q.D.) except salmeterol (B.I.D.). B2340 and B2305 were incomplete block crossover studies. In both B2340 and B2305, there were three treatments in each sequence. Each treatment was 14 days long, followed by a two-week wash out period. In B2307, each sequence had five treatments, each was a single dose one day treatment followed by a one week wash out period. B2340 was designed to collect patients' 24 hour spirometry profile after each treatment. B2305 was designed to compare the efficacy of morning dose and evening dose of indacaterol to the efficacy of placebo control and active control. B2307 was designed to study the fast onset of action of indacaterol, comparing to the active controls (salbutamol, combination of salmeterol and fluticason) and placebo.

Table 9 Design of supportive studies.

Study (Period)	Location	Design	Number of Patients randomized (completed)	Treatment / period duration	Treatment (Inda=Indacaterol) (Salm=Salmeterol) (Salb=Salbutamol) (Flut=Fluticason)	Objective
<b>B2340</b> (Jan. 2008 – Jul. 2008)	USA, Belgium, Spain	crossover	68 (61)	14-days each treatment (Three 28-day periods)	Inda 300 mcg Salm 50 mcg (b.i.d., open label) Placebo	24 hour FEV <sub>1</sub> profile
<b>B2305</b> (Jan. 2008 – Jul. 2008)	France, German, Spain	crossover	96 (83)	14-day each treatment (Three 29-day periods)	Inda 300 mcg am Inda 300 mcg pm Salm 50 mcg (b.i.d.) Placebo (double dummy)	Evening dose efficacy
<b>B2307</b> (Apr. 2008 – Aug. 2008)	USA, Belgium, German, Hungary	crossover	89 (86)	one day single dose treatment (five 7-day periods)	Inda 150 mcg Inda 300 mcg Salb 200 mcg Salm/flut 50/500mcg Placebo (triple dummy)	Fast onset of action

Table 10 Patient disposition of supportive studies.

Study	B2305	B2307	B2340
Randomized	96 (100%)	89 (100%)	68 (100%)
Exposed	95 (99%)	89 (100%)	68 (100%)
Completed	83 (87%)	86 (97%)	61 (90%)
Discontinued	13 (13%)	3 (3%)	7 (10%)
mITT	95 (99%)	89 (100%)	68 (100%)
PP	92 (96%)	85 (96%)	61 (90%)

Table 11 Demographic and baseline characteristics summary in randomized populations of supportive studies.

Study		B2305	B2307	B2340
Age	N	95	89	68
	Mean	64	62	66
	SD	8.7	8.4	9.1
	Median	63	62	67
	Min - Max	43-84	43-79	46-85
Age group	40-64 years	53 (56%)	55 (62%)	27 (40%)
	≥65 years	42 (44%)	34 (38%)	41 (60%)
Gender	Male	80 (84%)	54 (61%)	52 (77%)
	Female	15 (16%)	35 (39%)	16 (24%)
Race	Caucasian	95 (100%)	88 (99%)	65 (96%)
	Black	0 (0%)	1 (1%)	3 (4%)
COPD severity	At risk	0 (0%)	0 (0%)	0 (0%)
	Mild	3 (3%)	2 (2%)	0 (0%)
	Moderate	60 (63%)	49 (55%)	41 (60%)
	Severe	31 (33%)	38 (43%)	27 (40%)
	Very severe	1 (1%)	0 (0%)	0 (0%)
ICS use	No	40 (42%)	40 (45%)	39 (57%)
	Yes	55 (58%)	49 (55%)	29 (43%)
Smoking history	Ex-smoker	53 (56%)	40 (45%)	43 (63%)
	Current smoker	42 (44%)	49 (55%)	25 (37%)

Table 12 Summary of SABA reversibility and anti-cholinergic reversibility on the randomized population in study B2335s (quoted from the clinical study report).

		Ind 150 µg N=416	Ind 300 µg N=416	Tio N=415	Pbo N=418	Total N=1665
<b>Pre-bronchodilator (SABA) FEV1 at Visit 1 (L)</b>	<b>n</b>	416	416	415	414	1661
	<b>Mean</b>	1.34	1.36	1.28	1.33	1.33
	<b>SD</b>	0.485	0.509	0.494	0.471	0.490
	<b>Median</b>	1.31	1.26	1.20	1.27	1.25
	<b>Min - Max</b>	0.53-3.19	0.43-2.95	0.41-2.94	0.44-2.90	0.41-3.19
<b>Post bronchodilator (SABA) FEV1 at Visit 1 (L)</b>	<b>n</b>	416	416	415	418	1665
	<b>Mean</b>	1.52	1.53	1.45	1.51	1.50
	<b>SD</b>	0.497	0.521	0.505	0.490	0.504
	<b>Median</b>	1.48	1.44	1.38	1.43	1.43
	<b>Min - Max</b>	0.62-3.45	0.57-3.14	0.48-3.00	0.53-2.98	0.48-3.45
<b>Post bronchodilator (SABA) FEV1 at Visit 1 (% predicted)</b>	<b>n</b>	416	416	415	418	1665
	<b>Mean</b>	56.1	56.3	53.9	56.1	55.6
	<b>SD</b>	14.47	14.50	15.56	14.27	14.73
	<b>Median</b>	56.0	55.5	52.9	55.1	54.7
	<b>Min - Max</b>	29.3-116.6	21.3-90.0	23.6-132.3	28.4-95.1	21.3-132.3
<b>Post bronchodilator (SABA) FEV1/FVC at Visit 1 (%)</b>	<b>n</b>	416	416	415	418	1665
	<b>Mean</b>	53.0	52.6	52.7	53.4	52.9
	<b>SD</b>	9.97	10.07	10.14	10.11	10.07
	<b>Median</b>	53.9	53.1	53.0	53.6	53.3
	<b>Min - Max</b>	24.4-69.7	25.7-69.5	24.7-72.6	24.0-69.9	24.0-72.6
<b>FEV1 reversibility after SABA at Visit 1 (% increase)</b>	<b>n</b>	416	416	415	414	1661
	<b>Mean</b>	15.6	15.2	15.6	15.5	15.5
	<b>SD</b>	15.43	15.44	17.64	18.03	16.66
	<b>Median</b>	13.2	13.3	12.8	12.8	13.0
	<b>Min - Max</b>	-22.5-88.2	-45.2-89.3	-35.4-81.1	-32.4-222.7	-45.2-222.7
<b>FEV1 reversibility after anti-cholinergic at Visit 2 (% increase)</b>	<b>n</b>	415	412	414	417	1658
	<b>Mean</b>	15.3	15.9	14.8	15.9	15.5
	<b>SD</b>	15.37	21.85	16.05	18.28	18.05
	<b>Median</b>	14.0	13.5	12.5	13.2	13.2
	<b>Min - Max</b>	-72.2-89.6	-35.1-342.9	-36.4-110.3	-59.5-178.3	-72.2-342.9

Table 13 Summary of SABA reversibility and anti-cholinergic reversibility on the randomized population in study B2334 (quoted from the clinical study report).

		Ind 300 µg N=437	Ind 600 µg N=425	For N=434	Pbo N=432	Total N=1728
<b>Pre bronchodilator (SABA)</b> <b>FEV<sub>1</sub> at Visit 1 (L)</b>	n	437	425	434	432	1728
	Mean	1.33	1.32	1.35	1.37	1.34
	SD	0.407	0.452	0.432	0.471	0.441
	Median	2.82	1.28	1.30	1.28	1.29
	Min - Max	0.36-2.87	0.45-2.84	0.48-2.76	0.48-2.92	0.36-2.92
<b>Post bronchodilator (SABA)</b> <b>FEV<sub>1</sub> at Visit 1 (L)</b>	n	437	425	434	432	1728
	Mean	1.48	1.48	1.50	1.52	1.50
	SD	0.449	0.480	0.469	0.502	0.475
	Median	1.44	1.41	1.47	1.44	1.44
	Min - Max	0.44-2.95	0.55-2.91	0.59-3.25	0.58-3.09	0.44-3.25
<b>Post bronchodilator (SABA)</b> <b>FEV<sub>1</sub> at Visit 1 (% predicted)</b>	n	436	424	432	431	1723
	Mean	52.8	51.6	52.9	52.9	52.5
	SD	13.63	13.16	14.20	14.14	13.79
	Median	51.5	50.8	52.5	52.0	51.8
	Min - Max	23.5-101.4	24.0-84.2	20.8-100.5	17.6-96.3	17.6-101.4
<b>Post bronchodilator (SABA)</b> <b>FEV<sub>1</sub>/FVC at Visit 1 (%)</b>	n	437	425	434	432	1728
	Mean	51.1	51.1	51.3	52.1	51.4
	SD	10.72	10.55	10.52	10.56	10.59
	Median	50.7	51.1	51.2	52.0	51.2
	Min - Max	27.7-90.1	15.8-84.4	23.0-96.5	21.5-80.0	15.8-96.5
<b>FEV<sub>1</sub> reversibility after</b> <b>SABA at Visit 1 (% increase)</b>	n	437	425	434	432	1728
	Mean	11.7	13.7	11.8	12.7	12.5
	SD	12.66	14.50	12.73	13.14	13.28
	Median	9.8	10.9	10.1	10.8	10.5
	Min - Max	-34.3-60.9	-19.2-89.6	-23.1-77.0	-23.7-87.4	-34.3-89.6
<b>FEV<sub>1</sub> reversibility after</b> <b>anti-cholinergic at Visit 2</b> <b>(% increase)</b>	n	435	422	433	429	1719
	Mean	15.0	14.1	13.6	13.6	14.1
	SD	15.67	14.49	14.60	13.41	14.57
	Median	12.5	11.5	10.5	11.9	11.8
	Min - Max	-19.0-118.5	-65.2-81.2	-15.5-103.0	-15.8-86.0	-65.2-118.5



Table 14 Summary of SABA reversibility and anti-cholinergic reversibility on the randomized population in study B2346 (quoted from the clinical study report).

		<b>Ind 150 µg N = 211</b>	<b>Pbo N = 205</b>	<b>Total N = 416</b>
<b>Pre-bronchodilator (SABA) FEV<sub>1</sub> at Visit 1 (L)</b>	n	211	205	416
	Mean	1.3	1.4	1.3
	SD	0.52	0.52	0.52
	Median	1.2	1.3	1.3
	Min - Max	0.5-3.0	0.4-3.0	0.4-3.0
<b>Post-bronchodilator (SABA) FEV<sub>1</sub> at Visit 1 (L)</b>	n	211	205	416
	Mean	1.5	1.5	1.5
	SD	0.53	0.51	0.52
	Median	1.4	1.5	1.4
	Min - Max	0.6-3.5	0.6-3.0	0.6-3.5
<b>Post-bronchodilator (SABA) FEV<sub>1</sub> at Visit 1 (% predicted)</b>	n	211	205	416
	Mean	54.4	55.8	55.1
	SD	13.38	14.08	13.73
	Median	53.5	56.0	53.7
	Min - Max	28.1 – 84.1	27.6 – 91.9	27.6 – 91.9
<b>Post-bronchodilator (SABA) FEV<sub>1</sub>/FVC at Visit 1 (%)</b>	n	211	205	416
	Mean	53.5	53.5	53.5
	SD	9.84	10.36	10.09
	Median	55.1	54.7	54.8
	Min - Max	28.6 – 69.8	28.0 – 70.0	28.0 – 70.0
<b>FEV<sub>1</sub> reversibility after SABA at Visit 1 (% increase)</b>	n	211	205	416
	Mean	16.4	16.6	16.5
	SD	17.31	19.44	18.37
	Median	14.0	12.4	13.6
	Min - Max	-34.8 – 80.9	-46.5 – 160.1	-46.5 – 160.1
<b>FEV<sub>1</sub> reversibility after anti-cholinergic at Visit 2 (% increase)</b>	n	210	205	415
	Mean	15.9	15.6	15.7
	SD	17.59	16.67	17.13
	Median	13.8	12.4	12.9
	Min - Max	-31.8 – 156.9	-26.9 - 85.9	-31.8 – 156.9

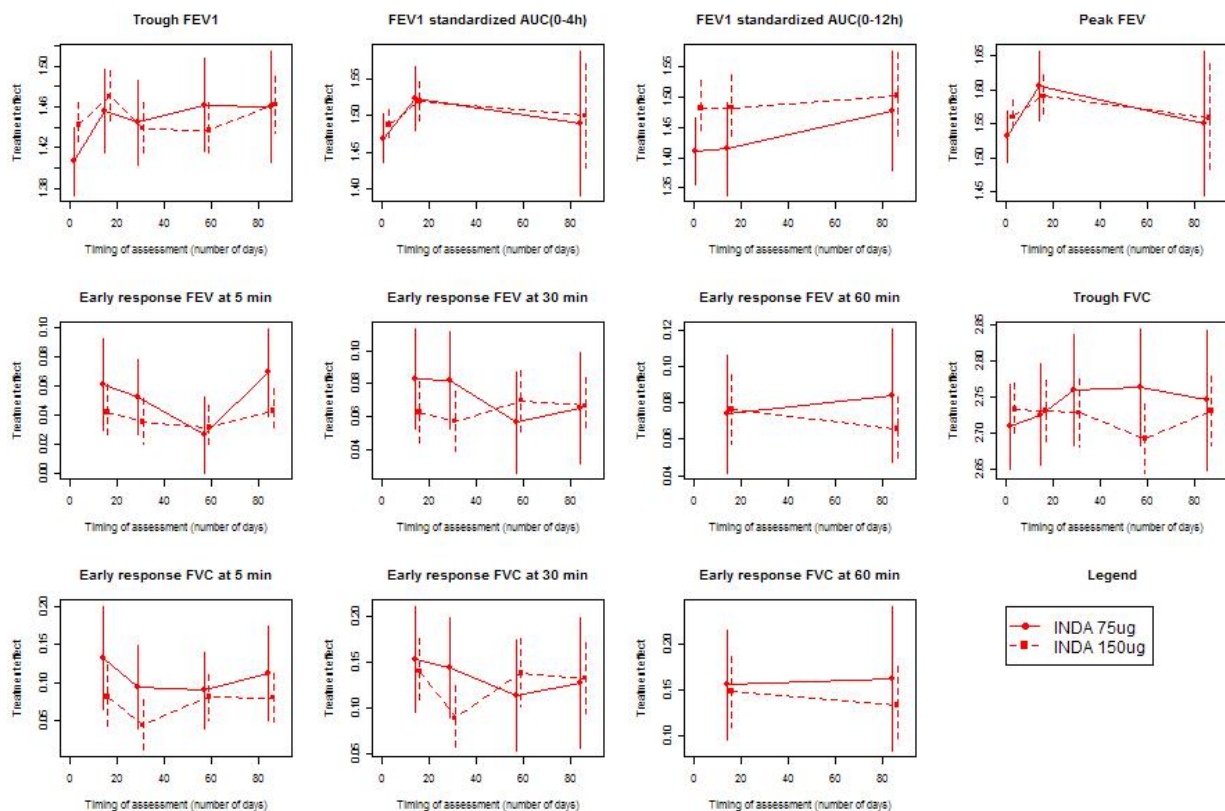


Figure 11 Comparison of spirometry measurements between Indacaterol 75 mcg and 150 mcg at different assessment times in B2335s.

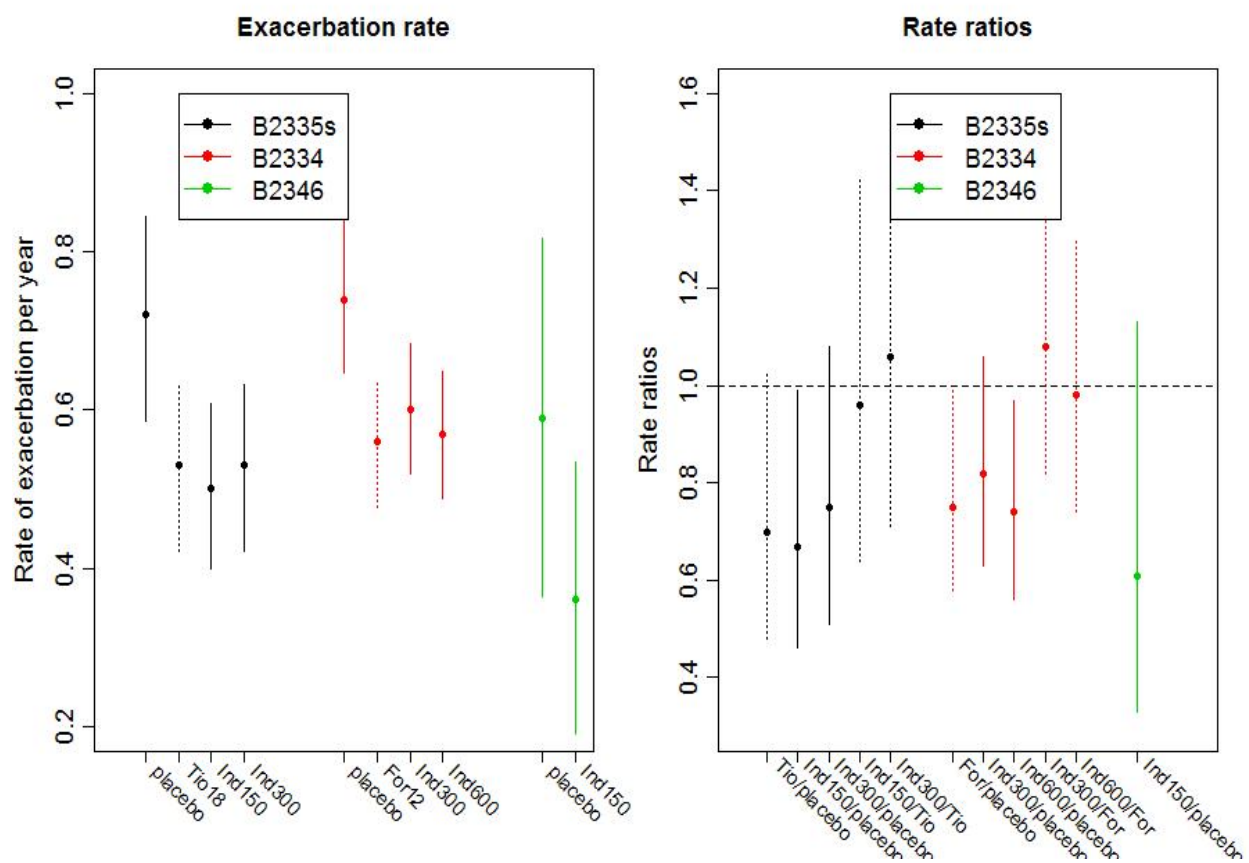


Figure 12 Summary of exacerbation rate in pivotal studies.

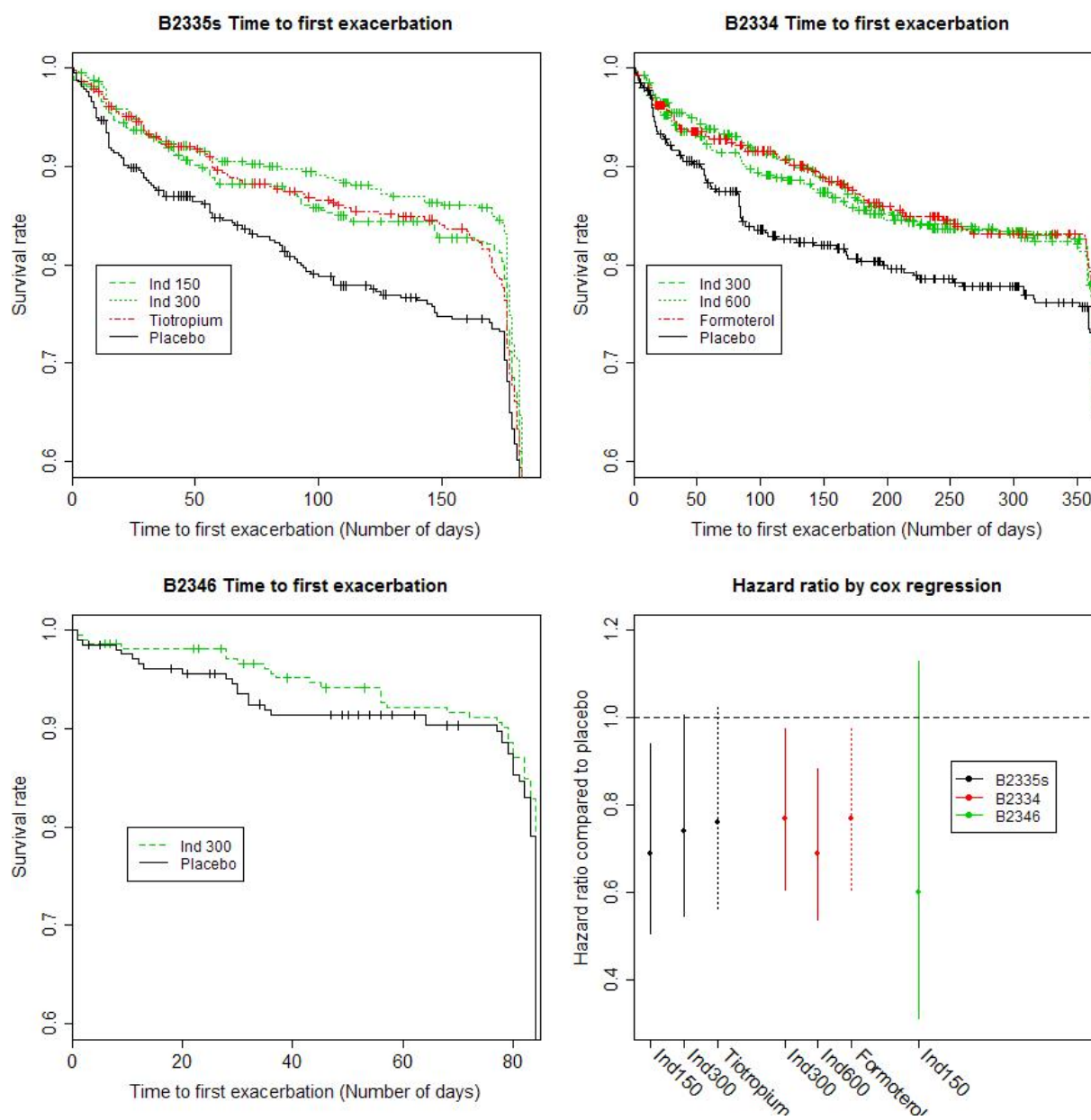


Figure 13 Summary of time to the first exacerbations in pivotal studies.

## **SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Dongmei Liu, Ph. D.  
Date: August 25, 2009

Statistical Team Leader: Qian Li, Sc. D.

Biometrics Division Director: Thomas Permutt, Ph. D.

Office of Biostatistics Associate Director: Sue-Jane Wang, Ph.D.

## **SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS**

The clinical pharmacology studies submitted by the sponsor Novartis (originally submitted on December 15, 2008) included 36 clinical studies that contain pharmacokinetic (PK) information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). The Complete Response letter was issued on October 16, 2009. In the current submission, the clinical pharmacology studies include 3 *in vitro* drug-drug interaction studies, 1 bioavailability study, 1 intrinsic factor PK study in healthy Chinese subjects, and 1 extrinsic factor PK study assessing the PK interaction of indacaterol with ritonavir in healthy adult subjects.

### **Executive Summary**

The median time to reach peak serum concentrations of indacaterol was approximately 15 minutes after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 mcg to 600 mcg) in a dose proportional manner, and was about dose-proportional in the dose range of 75 mcg to 150 mcg. Absolute bioavailability of indacaterol after an inhaled dose was on average 45%. After intravenous infusion the volume of distribution ( $V_z$ ) of indacaterol was 2,361 L to 2,557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1-95.3% and 95.1-96.2%, respectively. *In vitro* investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. Renal clearance of indacaterol was, on average, between 0.46 and 1.2 L/h. Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours.

Regarding to the dose-response relationship based on the data after two weeks, 75 mcg cannot be justified as the minimum effective dose for long term usage even though it was supported as the appropriate dose for fast onset of action after the first dose. The sponsor's claim of additional benefit with 150 mcg over 75 mcg for more severe COPD patients based on minimal clinically important difference (MCID) is not supported by the reviewer's sensitivity analysis.

### **Pharmacokinetics**

#### ***Absorption, Distribution, Metabolism and Elimination***

Following inhalation of indacaterol 150 mcg,  $C_{max}$  values of indacaterol were generally observed within 0.25 hours post-dose. Mean  $C_{max}$  and  $AUC_{0-24hrs}$  values were  $253 \pm 120$  pg/mL and  $1202 \pm 554$  pg\*hr/mL, respectively. Systemic exposure to indacaterol increased with increasing dose (150 mcg to 600 mcg) in a dose proportional manner, and was about dose-proportional in the dose range of 75 mcg to 150 mcg.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e. AUC over the 24-hour dosing interval on day 14 or day 15 compared to day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 mcg and 600 mcg. The absolute bioavailability of indacaterol after an inhaled dose was on average 45%.

Following inhalation of indacaterol in COPD patients and healthy subjects, measurable plasma concentrations of indacaterol were observed in the systemic circulation within 5 minutes post-dose. After intravenous infusion the volume of distribution ( $V_z$ ) of indacaterol was 2,557 L. The plasma protein binding of the compound in humans, determined by ultracentrifugation, ranged from 95.1-96.2%.

*In vitro* studies with indacaterol using recombinant human cytochrome P450 enzymes and recombinant human UGT enzymes showed that the key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. Indacaterol was primarily metabolized in human liver microsomes to the inactive metabolite phenolic o-glucuronide, followed by formation of minor monooxygenation products.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. In a radiolabeled mass-balance study, the overall mean total recovery of radioactivity in feces and urine was 85.3 % and 9.7 % of the dose, respectively. The majority of the dose in the feces was recovered as unmodified indacaterol 54.4 % with a significant portion also being recovered in the form of the oxidative metabolites 23.8 %. The portion of the dose recovered in the urine was distributed between multiple metabolites and unchanged parent drug. In serum, the largest contributor to the exposure ( $AUC_{0-24hrs}$ ) was indacaterol (32.5%).

### **Special population**

Patients with mild and moderate hepatic impairment showed no relevant changes in  $C_{max}$  or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed. The effect of severe hepatic impairment on the PK of the drug and its major metabolites was not evaluated.

The effect of renal impairment on the PK of indacaterol and its metabolites was not evaluated. 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.

### **Drug-drug Interactions**

Indacaterol did not inhibit the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Indacaterol is a low affinity ( $K_m > 150 \mu M$ ) substrate for the efflux pump P-gp. The potential of indacaterol/major metabolites to induce drug metabolizing enzymes is considered negligible based on the low indacaterol serum concentrations (2.2 nM) observed in humans compared to the  $EC_{50}$  levels that are known for typical enzyme inducers. *In vitro* investigation furthermore indicated 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, and that indacaterol has negligible potential to induce P-gp or MRP2.

Concomitant administration of Arcapta Neohaler with ketoconazole, verapamil or erythromycin increased the systemic exposure of indacaterol by less than 2-fold. Concomitant administration with mometasone increased the systemic exposure of indacaterol by 41%. Indacaterol did not alter the PK of mometasone.

### **Genetics**

The relationship between common single nucleotide polymorphisms in the  $\beta_2$ -adrenergic receptor gene (*ADRB2*; -47C/T Arg16Gly, Gln27Glu, Thr164Ile) and Arcapta Neohaler response was retrospectively analyzed in two of the controlled trials (n=626). Pooled analysis did not reveal any significant effect of *ADRB2* genotype on changes in FEV1 or other efficacy endpoints.

### **Thorough QT Study**

The effect of Arcapta Neohaler on the QT interval was evaluated in a double-blind, placebo- and active (moxifloxacin)-controlled study following multiple doses of indacaterol 150 mcg, 300 mcg or 600 mcg once-daily for 2 weeks in healthy volunteers. Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QTcF).

Maximum mean prolongation of QTcF intervals were <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time-matched comparisons versus placebo. This shows that there is no concern for a pro-arrhythmic potential related to QT-interval prolongations at recommended therapeutic doses. There was no evidence of a clinically relevant concentration-delta QTc relationship in the range of doses evaluated.

### **Dose-Response relationship**

The sponsor updated the previous dose-response modeling by adding new studies and submitted a report titled 'Update of the bronchodilatory dose-response analysis of indacaterol in COPD' to justify their proposed doses. The pharmacometric review addresses the questions of 1) whether 75 mcg is the minimum effective dose, 2) whether the sponsor's claim of additional benefit with 150 mcg over 75 mcg for more severe patients based on MCID is appropriate.

#### *Is 75 mcg the minimum effective dose?*

The sponsor's analyses methods are similar to the previous report but two lower doses (18.75 mcg and 37.5 mcg) from new studies are added in the analyses.

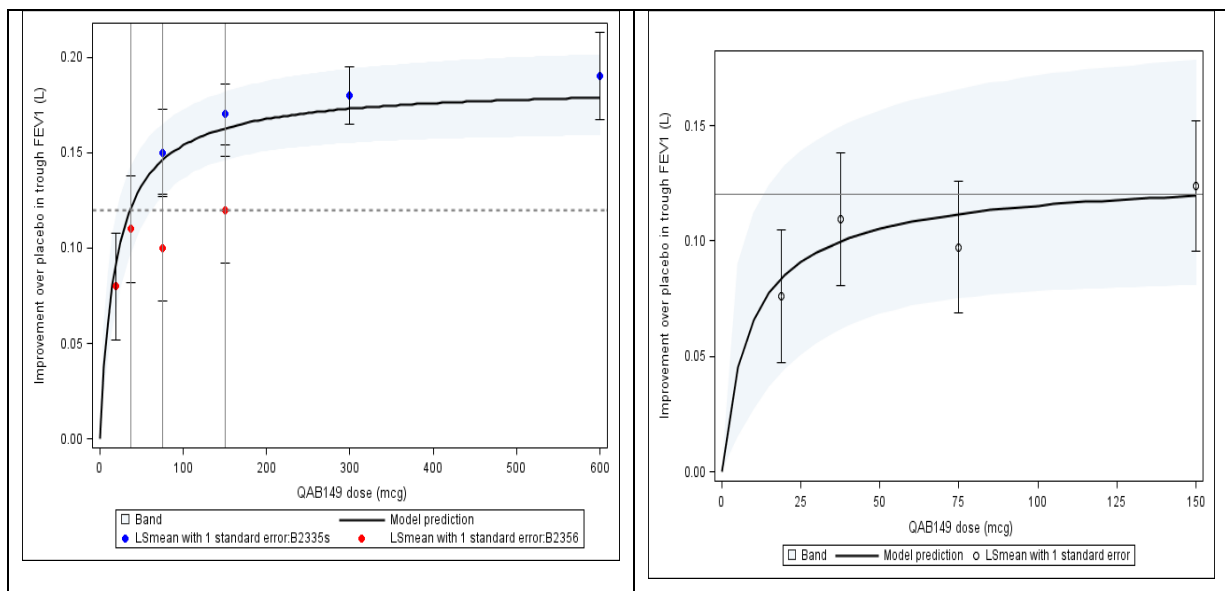
Two separate model-based methods were applied using Emax model: Bayesian meta-analysis and a non-linear mixed effect modeling (hereafter NLME). Least square mean (LSM) contrasts to placebo with standard error for three different endpoints (trough FEV1, observed peak, peak average response (AUC0-4)) at each visit up to 26 weeks from 13 studies were collected and used in the Bayesian meta-analysis. For NLME analysis trough FEV1 on day 14 and 15 from two dose-ranging studies (CQAB149B2335S, CQAB149B2356; hereafter B2335S and B2356) were pooled and analyzed. Both analyses produced similar results.

The sponsor's model predicted that 75 mcg just exceeds MCID of 0.12 L and 150 mcg is located mid-way between the MCID and the maximum response whereas 37.5 mcg is inferior to the MCID of 0.12 L, which resulted in 75 mcg as a minimum effective dose.



However, as shown in Figure 1(left panel), there is little difference in LSM between 37.5 mcg (0.11 L) and 75 mcg (0.10 L) within study B2356 (please notice that B2356 is the only study which includes 18.75 mcg and 37.5 mcg in COPD patients). Noticeable differences were observed between the two dose-ranging studies for the common doses studied (75 mcg and 150 mcg). More importantly, the sponsor's prediction was mainly driven by study B2335S and the covariates identified in the model could not explain the difference between the two studies. Hence, the reviewer reanalyzed the dose-response relationship with study B2356 only, and the result is shown in Figure 1(right panel). The reviewer's reassessment predicted that none of the doses (including 75 mcg and 150 mcg) in study B2356 could achieve FEV1 response above MCID of 0.12 L. Moreover, % maximum effect at both 37.5 mcg and 75 mcg are more than 80%, which are different from the sponsor's prediction (37.5 mcg: 66%, 75 mcg: 79%) based on the pooled analysis. The reviewer's analyses suggested that 37.5 mcg achieved comparable FEV1 response as 75 mcg within the same study. If 37.5 mcg were included in other studies where 75 mcg had larger effect size than that in study B2356, 37.5 mcg would be expected to have larger effect size too.

**Figure 1. Model-predicted dose-response (trough FEV1) relationship. Left panel: the sponsor's analysis using pooled two studies with LSM with standard error for each study. Right panel: the reviewer's analysis using study B2356 only.**

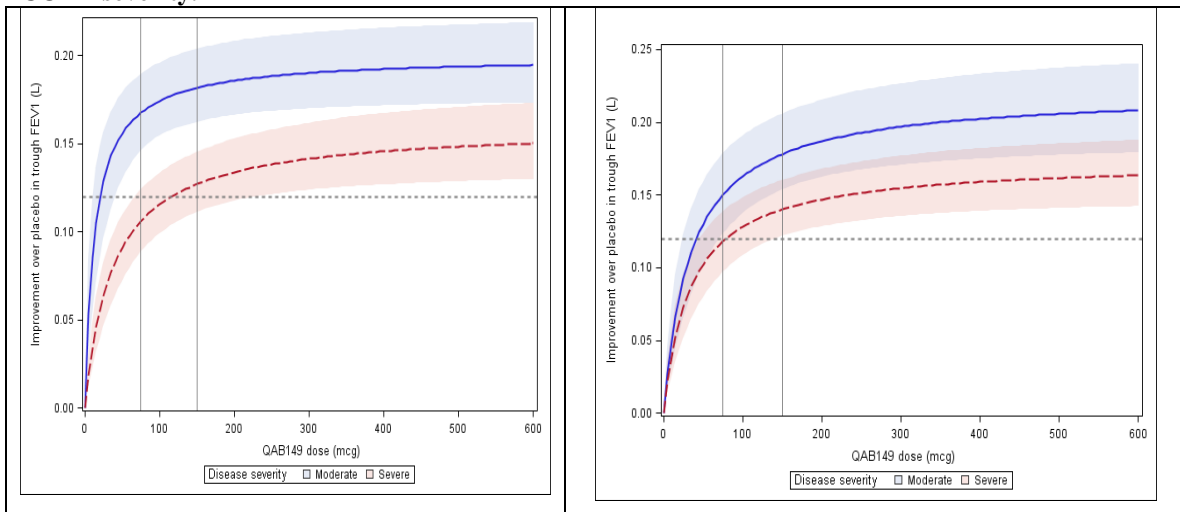


*Is the sponsor's claim of additional benefit with 150 mcg over 75 mcg for more severe patients appropriate?*

One of the sponsor's findings from NLME analysis is that baseline FEV1 was found to be a significant covariate for the maximum response and the dose that is required to achieve 50% of the maximum response. Figure 2 (left panel) shows the different predicted dose-response relationships between moderate and severe COPD patients from the sponsor's NLME analysis. The sponsor claimed that if 0.12 L is considered the MCID, 150 mcg is necessary to exceed this threshold in severe patients, and therefore 150 mcg provides additional benefit over 75 mcg in more severe patients.

However, the reviewer observed that there is clear difference in observed dose-response profile between day 14 and 15. Since data from day 14 were not obtained under controlled condition, the reviewer excluded data on day 14 and fitted the same model as the sponsor's to the day 15 data only as a sensitivity analysis. Based on analysis using day 15 data only, baseline FEV1 was not found to be a significant covariate on ED50, which resulted in slightly different predicted lines by disease severity (Figure 2, right), and the dose of 75 mcg appears to meet the MCID criteria (0.12 L) for severe patients also. Hence, the sponsor's claim of additional benefit with 150 mcg for severe patients based on MCID of 0.12L is sensitive to the data used for analysis. It is not considered a robust finding by the reviewer.

**Figure 2. Predicted dose-response relationship for trough FEV1 at steady state for typical patient by COPD severity.**



# FORADIL<sup>®</sup> AEROLIZER<sup>®</sup>

(formoterol fumarate inhalation powder)

For Oral Inhalation Only

Rx only

## Prescribing Information

### **WARNING: ASTHMA RELATED DEATH**

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol (see WARNINGS). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

### ***Pediatric and Adolescent Patients***

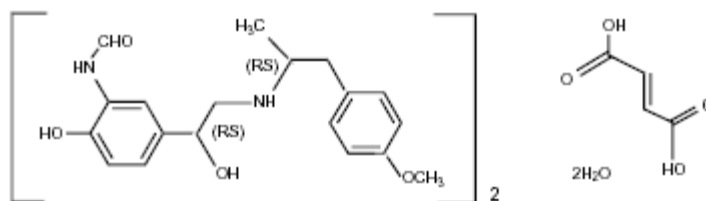
Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

## DESCRIPTION

FORADIL<sup>®</sup> AEROLIZER<sup>®</sup> consists of a capsule dosage form containing a dry powder formulation of FORADIL (formoterol fumarate) intended for oral inhalation only with the AEROLIZER Inhaler.

Each clear, hard gelatin capsule contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose (which contains trace levels of milk proteins) as a carrier.

The active component of FORADIL is formoterol fumarate, a racemate. Formoterol fumarate is a selective beta<sub>2</sub>-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate; its structural formula is



Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is (C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>)<sub>2</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>•2H<sub>2</sub>O. Formoterol fumarate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

The AEROLIZER Inhaler is a plastic device used for inhaling FORADIL. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the AEROLIZER Inhaler delivered 10 mcg of formoterol fumarate from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the AEROLIZER Inhaler were evaluated in 33 adult and adolescent patients and 32 pediatric patients with mild-to-moderate asthma. Mean PIFR was 117.82 L/min (range 34-188 L/min) for adult and adolescent patients, and

99.66 L/min (range 43-187 L/min) for pediatric patients. Approximately ninety percent of each population studied generated a PIFR through the device exceeding 60 L/min.

To use the delivery system, a FORADIL capsule is placed in the well of the AEROLIZER Inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Formoterol fumarate is a long-acting selective beta<sub>2</sub>-adrenergic receptor agonist (beta<sub>2</sub>-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at beta<sub>2</sub>-receptors than at beta<sub>1</sub>-receptors. Although beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, there are also beta<sub>2</sub>-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists may have cardiac effects.

The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-

responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

## **Animal Pharmacology**

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

## **Pharmacokinetics**

Information on the pharmacokinetics of formoterol in plasma has been obtained in healthy subjects by oral inhalation of doses higher than the recommended range and in Chronic Obstructive Pulmonary Disease (COPD) patients after oral inhalation of doses at and above the therapeutic dose. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

## ***Absorption***

Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively, at 10 min, 2 h and 6 h post inhalation.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 4 weeks or 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol ranged from 1.63 to 2.08 in

comparison with the first dose. For COPD patients, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19 - 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

### ***Distribution***

The binding of formoterol to human plasma proteins in vitro was 61%-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin in vitro was 31%-38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

### ***Metabolism***

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

### ***Excretion***

Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from

blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of 12 mcg or 24 mcg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

### ***Special Populations***

*Gender:* After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

*Geriatric and Pediatric:* The pharmacokinetics of formoterol have not been studied in the elderly population, and limited data are available in pediatric patients.

In a study of children with asthma who were 5 to 12 years of age, when formoterol fumarate 12 or 24 mcg was given twice daily by oral inhalation for 12 weeks, the accumulation index ranged from 1.18 to 1.84 based on urinary excretion of unchanged formoterol. Hence, the accumulation in children did not exceed that in adults, where the accumulation index ranged from 1.63 to 2.08 (see above). Approximately 6% and 6.5% to 9% of the dose was recovered in the urine of the children as unchanged and conjugated formoterol, respectively.



*Hepatic/Renal Impairment:* The pharmacokinetics of formoterol have not been studied in subjects with hepatic or renal impairment.

## **Pharmacodynamics**

### ***Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships***

The major adverse effects of inhaled beta<sub>2</sub>-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults and adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between heart rate, ECG parameters, and serum potassium levels and the urinary excretion of formoterol were evaluated in 10 healthy male volunteers (25 to 45 years of age) following inhalation of single doses containing 12, 24, 48, or 96 mcg of formoterol fumarate. There was a linear relationship between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate.

In a second study, PK/PD relationships between plasma formoterol levels and pulse rate, ECG parameters, and plasma potassium levels were evaluated in 12 healthy volunteers following inhalation of a single 120 mcg dose of formoterol fumarate (10 times the recommended clinical dose). Reductions of plasma potassium concentration were observed in all subjects. Maximum reductions from baseline ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly correlated with the reduction in plasma potassium concentration. Generally, the maximum effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm was observed 6 hours post dose. The maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fridericia's correction. The QTc returned to baseline within 12-24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on plasma potassium, pulse rate, and QTc interval are known pharmacological effects of this class of study drug and were not

unexpected at the very high formoterol dose (120 mcg single dose, 10 times the recommended single dose) tested in this study. These effects were well-tolerated by the healthy volunteers.

The electrocardiographic and cardiovascular effects of FORADIL AEROLIZER were compared with those of albuterol and placebo in two pivotal 12-week double-blind studies of patients with asthma. A subset of patients underwent continuous electrocardiographic monitoring during three 24-hour periods. No important differences in ventricular or supraventricular ectopy between treatment groups were observed. In these two studies, the total number of patients with asthma exposed to any dose of FORADIL AEROLIZER who had continuous electrocardiographic monitoring was about 200.

Continuous electrocardiographic monitoring was not included in the clinical studies of FORADIL AEROLIZER that were performed in COPD patients. The electrocardiographic effects of FORADIL AEROLIZER were evaluated versus placebo in a 12-month pivotal double-blind study of patients with COPD. An analysis of ECG intervals was performed for patients who participated at study sites in the United States, including 46 patients treated with FORADIL AEROLIZER 12 mcg twice daily, and 50 patients treated with FORADIL AEROLIZER 24 mcg twice daily. ECGs were performed predose, and at 5-15 minutes and 2 hours post-dose at study baseline and after 3, 6 and 12 months of treatment. The results showed that there was no clinically meaningful acute or chronic effect on ECG intervals, including QTc, resulting from treatment with FORADIL AEROLIZER.

### ***Tachyphylaxis/Tolerance***

In a clinical study in 19 adult patients with mild asthma, the bronchoprotective effect of formoterol, as assessed by methacholine challenge, was studied following an initial dose of 24 mcg (twice the recommended dose) and after 2 weeks of 24 mcg twice daily. Tolerance to the bronchoprotective effects of formoterol was observed as evidenced by a diminished bronchoprotective effect on FEV<sub>1</sub> after 2 weeks of dosing, with loss of protection at the end of the 12 hour dosing period.

Rebound bronchial hyper-responsiveness after cessation of chronic formoterol therapy has not been observed.

In three large clinical trials in patients with asthma, while efficacy of formoterol versus placebo was maintained, a slightly reduced bronchodilatory response (as measured by 12-hour FEV<sub>1</sub> AUC) was observed within the formoterol arms over time, particularly with the 24 mcg twice daily dose (twice the daily recommended dose). A similarly reduced FEV<sub>1</sub> AUC over time was also noted in the albuterol treatment arms (180 mcg four times daily by metered-dose inhaler).

## **CLINICAL TRIALS**

### **Adolescent and Adult Asthma Trials**

In a placebo-controlled, single-dose clinical trial, the onset of bronchodilation (defined as a 15% or greater increase from baseline in FEV<sub>1</sub>) was similar for FORADIL AEROLIZER and albuterol 180 mcg by metered-dose inhaler.

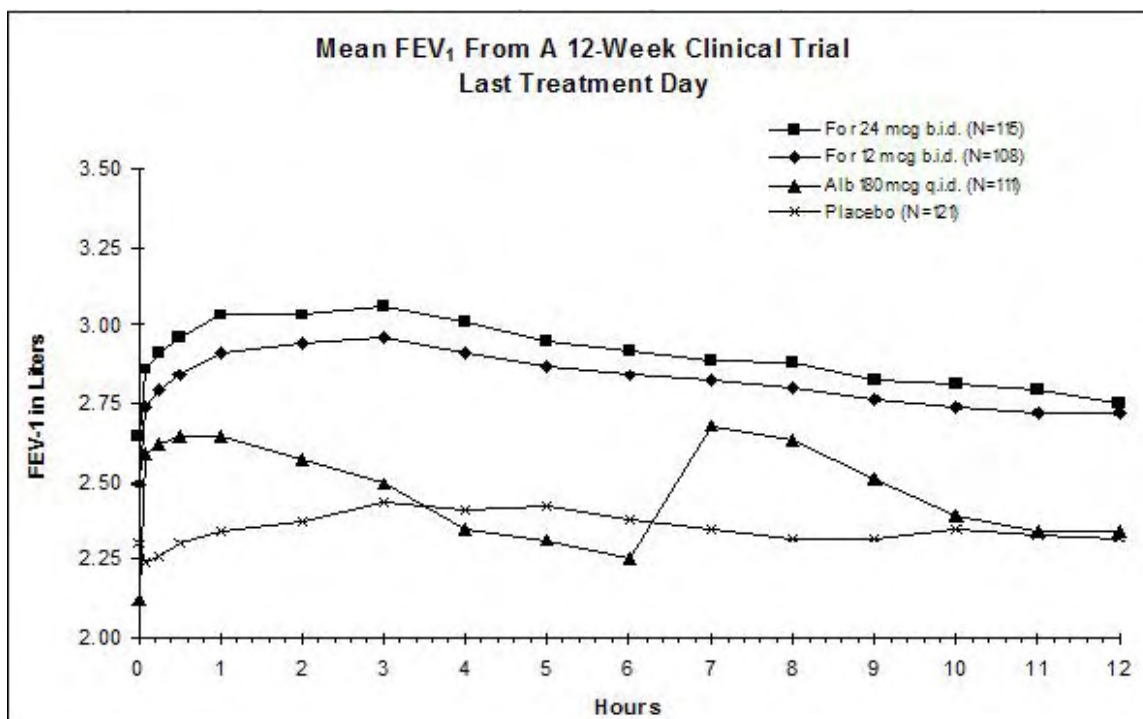
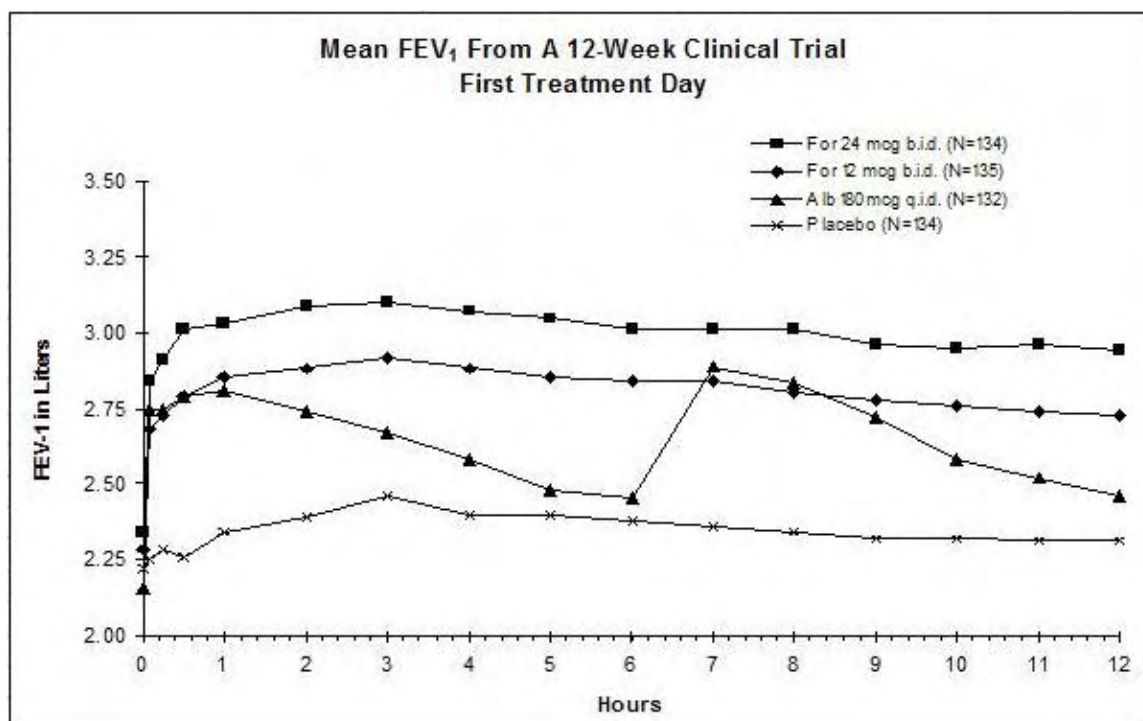
In single-dose and multiple-dose clinical trials, the maximum improvement in FEV<sub>1</sub> for FORADIL AEROLIZER 12 mcg generally occurred within 1 to 3 hours, and an increase in FEV<sub>1</sub> above baseline was observed for 12 hours in most patients.

FORADIL AEROLIZER 12 mcg twice daily was compared to FORADIL AEROLIZER 24 mcg twice daily, albuterol 180 mcg four times daily by metered-dose inhaler, and placebo in a total of 1095 adult and adolescent patients 12 years of age and above with mild-to-moderate asthma (defined as FEV<sub>1</sub> 40%-80% of the patient's predicted normal value) who participated in two pivotal, 12-week, multi-center, randomized, double-blind, parallel group studies.

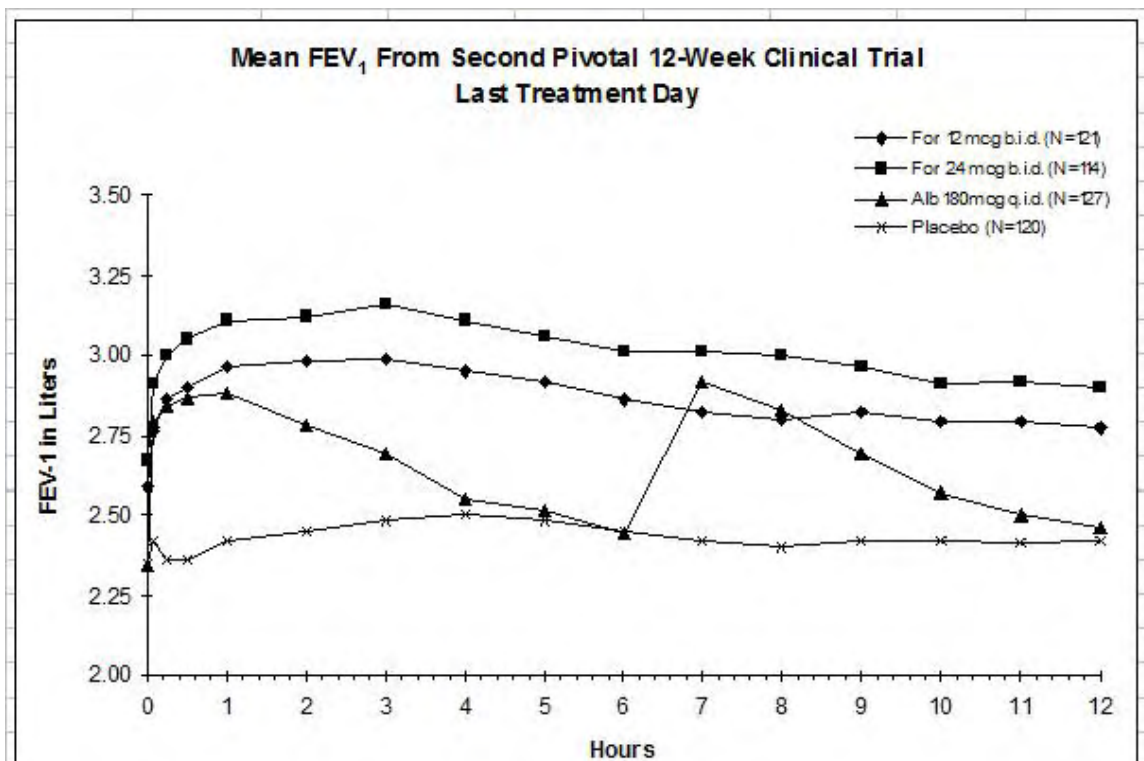
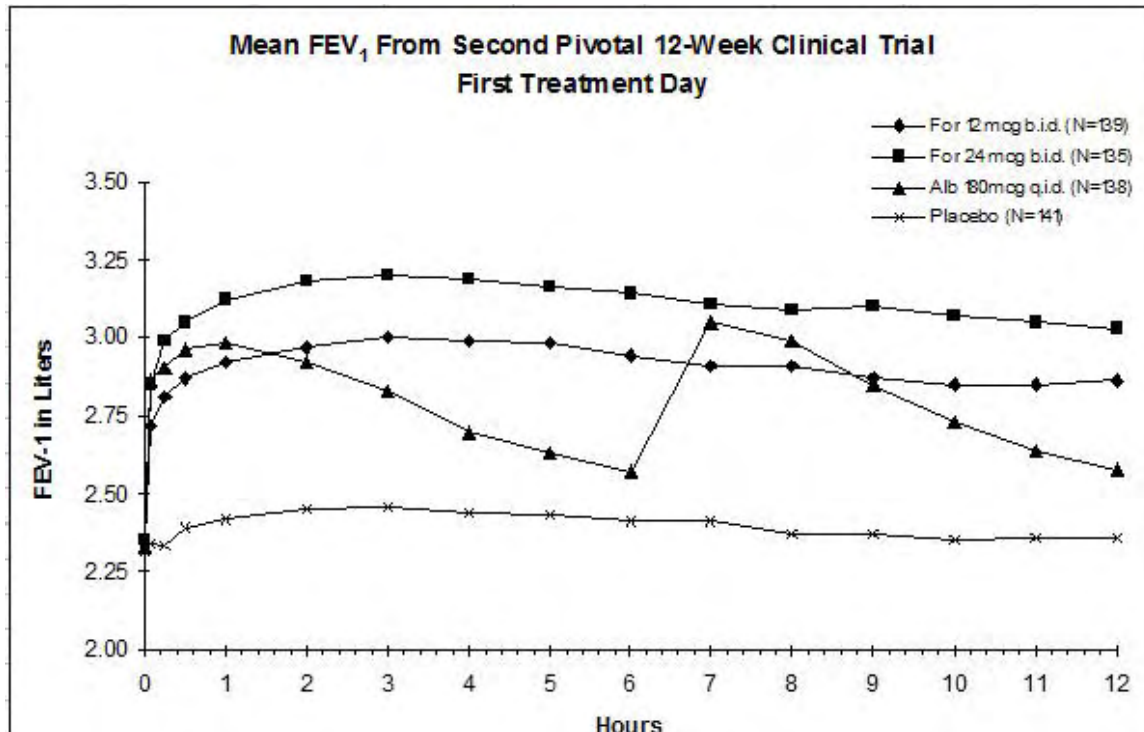
The results of both studies showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV<sub>1</sub> for 12 hours post-dose) throughout the 12-week treatment period. There was no significant difference in post-dose bronchodilation between FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily, but serious asthma exacerbations occurred more commonly in the higher dose group (see WARNINGS and ADVERSE REACTIONS). Mean FEV<sub>1</sub> measurements from

both studies are shown below for the first and last treatment days (see Figures 1 and 2).

Figures 1a and 1b: Mean FEV<sub>1</sub> from Clinical Trial A



Figures 2a and 2b: Mean FEV<sub>1</sub> from Clinical Trial B



Compared with placebo and albuterol, patients treated with FORADIL AEROLIZER 12 mcg demonstrated improvement in many secondary efficacy endpoints, including improved combined and nocturnal asthma symptom scores,

fewer nighttime awakenings, fewer nights in which patients used rescue medication, and higher morning and evening peak flow rates. FORADIL AEROLIZER 24 mcg twice daily did not provide any additional improvements in these secondary endpoints compared to FORADIL AEROLIZER 12 mcg twice daily.

A 16-week, randomized, multi-center, double-blind, parallel-group study enrolled 1568 patients 12 years of age and older with mild-to-moderate asthma (defined as FEV<sub>1</sub> ≥40% of the patient's predicted normal value) in three treatment groups: FORADIL AEROLIZER 12 mcg twice daily, FORADIL AEROLIZER 24 mcg twice daily, and placebo. The study's primary endpoint was the incidence of serious asthma-related adverse events. Serious asthma exacerbations occurred in 3 (0.6%) patients who received FORADIL AEROLIZER 12 mcg twice daily, 2 (0.4%) patients who received FORADIL AEROLIZER 24 mcg twice daily, and 1 (0.2%) patient who received placebo. The size of this study was not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups. All serious asthma exacerbations resulted in hospitalizations. While there were no deaths in the study, the duration and size of this study were not adequate to quantify the rate of asthma-related death. See WARNINGS for information about a study which compared another long-acting beta<sub>2</sub>-adrenergic agonist to placebo.

### **Pediatric Asthma Trial**

A 12-month, multi-center, randomized, double-blind, parallel-group, study compared FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily to placebo in a total of 518 children with asthma (ages 5-12 years) who required daily bronchodilators and anti-inflammatory treatment. Efficacy was evaluated on the first day of treatment, at Week 12, and at the end of treatment.

FORADIL AEROLIZER 12 mcg twice daily demonstrated a greater 12-hour FEV<sub>1</sub> AUC compared to placebo on the first day of treatment, after twelve weeks of treatment, and after one year of treatment. FORADIL AEROLIZER 24 mcg twice daily did not result in any additional improvement in 12-hour FEV<sub>1</sub> AUC compared to FORADIL AEROLIZER 12 mcg twice daily.

## **Exercise-Induced Bronchospasm Trials**

The effect of FORADIL AEROLIZER on exercise-induced bronchospasm (defined as >20% fall in FEV<sub>1</sub>) was examined in four randomized, single-dose, double-blind, crossover studies in a total of 77 patients 4 to 41 years of age with exercise-induced bronchospasm. Exercise challenge testing was conducted 15 minutes, and 4, 8, and 12 hours following administration of a single dose of study drug (FORADIL AEROLIZER 12 mcg, albuterol 180 mcg by metered-dose inhaler, or placebo) on separate test days. FORADIL AEROLIZER 12 mcg and albuterol 180 mcg were each superior to placebo for FEV<sub>1</sub> measurements obtained 15 minutes after study drug administration. FORADIL AEROLIZER 12 mcg maintained superiority over placebo at 4, 8, and 12 hours after administration. Most subjects were protected from exercise-induced bronchospasm for up to 12 hours following administration of FORADIL AEROLIZER; however, some were not. The efficacy of FORADIL AEROLIZER in the prevention of exercise-induced bronchospasm when dosed on a regular twice daily regimen has not been studied.

## **Adult COPD Trials**

In multiple-dose clinical trials in patients with COPD, FORADIL AEROLIZER 12 mcg was shown to provide onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV<sub>1</sub>) within 5 minutes of oral inhalation after the first dose. Bronchodilation was maintained for at least 12 hours.

FORADIL AEROLIZER was studied in two pivotal, double-blind, placebo-controlled, randomized, multi-center, parallel-group trials in a total of 1634 adult patients (age range: 34-88 years; mean age: 63 years) with COPD who had a mean FEV<sub>1</sub> that was 46% of predicted. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (greater than 10 pack-years), age (at least 40 years), spirometry results (prebronchodilator baseline FEV<sub>1</sub> less than 70% of the predicted value, and at least 0.75 liters, with the FEV<sub>1</sub>/VC being less than 88% for men and less than 89% for women), and symptom score (greater than zero on at least four of the seven days prior to randomization). These studies included approximately equal numbers of patients with and without baseline bronchodilator reversibility, defined as a 15% or greater increase FEV<sub>1</sub> after inhalation of 200 mcg of

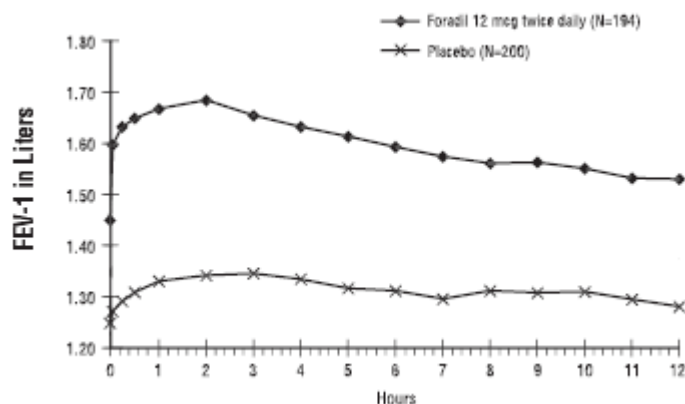


albuterol sulfate. A total of 405 patients received FORADIL AEROLIZER 12 mcg, administered twice daily. Each trial compared FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily with placebo and an active control drug. The active control drug was ipratropium bromide in COPD Trial A, and slow-release theophylline in COPD Trial B (the theophylline arm in this study was open-label). The treatment period was 12 weeks in COPD Trial A, and 12 months in COPD Trial B.

The results showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV<sub>1</sub> for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated after 12 weeks of treatment in both trials, and after 12 months of treatment in the 12-month trial (COPD Trial B). Compared to FORADIL AEROLIZER 12 mcg twice daily, FORADIL AEROLIZER 24 mcg twice daily did not provide any additional benefit on a variety of endpoints including FEV<sub>1</sub>.

Mean FEV<sub>1</sub> measurements after 12 weeks of treatment for one of the two major efficacy studies are shown in the figure below.

**Figure 3**  
**Mean FEV<sub>1</sub> after 12 Weeks of treatment from COPD Trial A**



FORADIL AEROLIZER 12 mcg twice daily was statistically superior to placebo at all post-dose timepoints tested (from 5 minutes to 12 hours post-dose) throughout the 12-week (COPD Trial A) and 12-month (COPD Trial B) treatment periods.

In both pivotal trials compared with placebo, patients treated with FORADIL AEROLIZER 12 mcg demonstrated improved morning pre-medication peak expiratory flow rates and took fewer puffs of rescue albuterol.

## INDICATIONS AND USAGE

### Asthma

FORADIL AEROLIZER is indicated for the treatment of asthma and in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid, in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma. Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as formoterol, the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death (see WARNINGS). Use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained,

assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

### **Pediatric and Adolescent Patients**

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS). For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

### **Exercise-Induced Bronchospasm**

FORADIL AEROLIZER is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 5 years of age and older, when administered on an occasional, as-needed basis. Use of FORADIL AEROLIZER as a single agent for the prevention of exercise induced bronchospasm may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of FORADIL AEROLIZER for the prevention of exercise induced bronchospasm may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid.

### **Chronic Obstructive Pulmonary Disease**

FORADIL AEROLIZER is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

## **CONTRAINDICATIONS**

Because of the risk of asthma-related death and hospitalization, use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (see Warnings – Asthma Related Death).

FORADIL (formoterol fumarate) is contraindicated in patients with a history of hypersensitivity to formoterol fumarate or to any components of this product.

## **WARNINGS**

### **ASTHMA RELATED DEATH**

Long-acting beta<sub>2</sub>-adrenergic agonists, such as formoterol, the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

### ***Pediatric and Adolescent Patients***

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both

**an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.**

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of the long-acting beta<sub>2</sub>-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with FORADIL AEROLIZER has been conducted.

Clinical studies with FORADIL AEROLIZER suggested a higher incidence of serious asthma exacerbations in patients who received FORADIL AEROLIZER than in those who received placebo (See ADVERSE REACTIONS). The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

**The studies described above enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by long-acting beta<sub>2</sub>-adrenergic agonists.**

- **FORADIL AEROLIZER should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. The use of FORADIL AEROLIZER in this setting is inappropriate.**
- **FORADIL AEROLIZER should not be used in conjunction with an inhaled, long-acting beta<sub>2</sub>-agonist. FORADIL AEROLIZER should not be used with other medications containing long-acting beta<sub>2</sub>-agonists.**

- **FORADIL AEROLIZER is not a substitute for inhaled or oral corticosteroids. Corticosteroids should not be stopped or reduced at the time FORADIL AEROLIZER is initiated.**
- **When beginning treatment with FORADIL AEROLIZER, patients who have been taking inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma symptoms.**
- **See PRECAUTIONS, Information for Patients and the accompanying Medication Guide.**

### **Paradoxical Bronchospasm**

As with other inhaled beta<sub>2</sub>-agonists, formoterol can produce paradoxical bronchospasm, that may be life-threatening. If paradoxical bronchospasm occurs, FORADIL AEROLIZER should be discontinued immediately and alternative therapy instituted.

### **Deterioration of Asthma**

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting beta<sub>2</sub>-adrenergic agonists or a significant decrease in peak expiratory flow (PEF) or lung function. Such findings require immediate evaluation. Patients should be advised to seek immediate attention should their condition deteriorate. Increasing the daily dosage of FORADIL AEROLIZER beyond the recommended dose in this situation is not appropriate. FORADIL AEROLIZER should not be used more frequently than twice daily (morning and evening) at the recommended dose.

### **Use of Anti-inflammatory Agents**

There are no data demonstrating that FORADIL has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating

FORADIL AEROLIZER. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for Patients).

### **Cardiovascular Effects**

Formoterol fumarate, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of FORADIL AEROLIZER at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS, General).

### **Immediate Hypersensitivity Reactions**

Immediate hypersensitivity reactions may occur after administration of FORADIL AEROLIZER, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

### **Do Not Exceed Recommended Dose**

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In addition, data from clinical trials with FORADIL AEROLIZER suggest that the use of doses higher than recommended is associated with an increased risk of serious asthma exacerbations (see ADVERSE REACTIONS).

## **PRECAUTIONS**

### **General**

FORADIL AEROLIZER should not be used to treat acute symptoms of asthma. FORADIL AEROLIZER has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing FORADIL AEROLIZER, the physician should also provide the patient with an inhaled, short-acting beta<sub>2</sub>-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of FORADIL AEROLIZER. Patients should also be cautioned that increasing inhaled beta<sub>2</sub>-agonist use is a signal of deteriorating asthma. (See Information for Patients and the accompanying Medication Guide.)

Formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with formoterol. Doses of the related beta<sub>2</sub>-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of FORADIL AEROLIZER at the recommended dose.

FORADIL AEROLIZER contains lactose, which contains trace levels of milk proteins. Allergic reactions to products containing milk proteins may occur in patients with severe milk protein allergy.



FORADIL capsules should ONLY be used with the AEROLIZER Inhaler and SHOULD NOT be taken orally.

FORADIL capsules should always be stored in the blister, and only removed IMMEDIATELY before use.

### **Information for Patients**

**Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.** Patients should be given the following information:

- 1. Patients should be informed that long-acting beta<sub>2</sub>-adrenergic agonists (LABA), including formoterol, the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Patients should be informed that FORADIL AEROLIZER should not be the only therapy for the treatment of asthma and must only be used as additional therapy when a long-term asthma control medication (e.g., inhaled corticosteroids) do not adequately control asthma symptoms. Patients should be informed that when FORADIL AEROLIZER is added to their treatment regimen they must continue to use their long-term asthma control medication.**
- 2. FORADIL AEROLIZER is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta<sub>2</sub>-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if FORADIL AEROLIZER treatment becomes less effective, or if they need more inhalations of a short-acting beta<sub>2</sub>-agonist than usual. Patients**

should not inhale more than the contents of one capsule at any one time. The daily dosage of FORADIL AEROLIZER should not exceed one capsule twice daily (24 mcg total daily dose).

3. FORADIL AEROLIZER should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with FORADIL AEROLIZER.
4. The active ingredient of FORADIL (formoterol fumarate) is a long-acting, bronchodilator used for the treatment of asthma, including nocturnal asthma, and for the prevention of exercise-induced bronchospasm. FORADIL AEROLIZER provides bronchodilation for up to 12 hours. Patients should be advised not to increase the dose or frequency of FORADIL AEROLIZER without consulting the prescribing physician. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice.
5. When FORADIL AEROLIZER is used for the prevention of EIB, the contents of one capsule should be taken at least 15 minutes prior to exercise. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic FORADIL AEROLIZER administration twice daily and these patients should not use additional FORADIL AEROLIZER for prevention of EIB.
6. Patients should be informed that treatment with beta<sub>2</sub>-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness.
7. Patients should be informed never to use FORADIL AEROLIZER with a spacer and never to exhale into the device.
8. Patients should avoid exposing the FORADIL capsules to moisture and should handle the capsules with dry hands. The AEROLIZER Inhaler should never be washed and should be kept dry. The patient should always use the new AEROLIZER Inhaler that comes with each refill.

9. Women should be advised to contact their physician if they become pregnant or if they are nursing.
10. Patients should be told that in rare cases, the gelatin capsule might break into small pieces. These pieces should be retained by the screen built into the AEROLIZER Inhaler. However, it remains possible that rarely, tiny pieces of gelatin might reach the mouth or throat after inhalation. The capsule is less likely to shatter when pierced if: storage conditions are strictly followed, capsules are removed from the blister immediately before use, and the capsules are only pierced once.
11. It is important that patients understand how to use the AEROLIZER Inhaler appropriately and how it should be used in relation to other asthma medications they are taking (see the accompanying Medication Guide).

## **Drug Interactions**

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonist with non-potassium sparing diuretics.

Formoterol, as with other beta<sub>2</sub>-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these

agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta<sub>2</sub>-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 45 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 590 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 60 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2

mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 25 times human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis).

### **Pregnancy, Teratogenic Effects, Pregnancy Category C**

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Formoterol fumarate did not cause malformations in rats or rabbits following oral administration. Because there are no adequate and well-controlled studies in pregnant women, FORADIL AEROLIZER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **Use in Labor and Delivery**

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis) and above in rats receiving the drug for several days at the end of pregnancy. These effects were not produced at a dose of

0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis). There are no adequate and well-controlled human studies that have investigated the effects of FORADIL AEROLIZER during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, FORADIL AEROLIZER should be used during labor only if the potential benefit justifies the potential risk.

## **Nursing Mothers**

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if FORADIL AEROLIZER is administered to nursing women. There are no well-controlled human studies of the use of FORADIL AEROLIZER in nursing mothers.

## **Pediatric Use**

### ***Asthma***

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs (see INDICATIONS AND USAGE and WARNINGS).

A total of 776 children 5 years of age and older with asthma were studied in three multiple-dose controlled clinical trials. Of the 512 children who received formoterol, 508 were 5-12 years of age, and approximately one third were 5-8 years of age.

### ***Exercise-Induced Bronchospasm***

A total of 25 pediatric patients, 4-11 years of age, were studied in two well-controlled single-dose clinical trials.

The safety and effectiveness of FORADIL AEROLIZER in pediatric patients below 5 years of age has not been established. (See CLINICAL TRIALS, Pediatric

Asthma Trial, and ADVERSE REACTIONS, Experience in Pediatric, Adolescent and Adult Patients.)

### **Geriatric Use**

Of the total number of patients who received FORADIL AEROLIZER in adolescent and adult chronic dosing asthma clinical trials, 318 were 65 years of age or older and 39 were 75 years of age and older. Of the 811 patients who received FORADIL AEROLIZER in two pivotal multiple-dose controlled clinical studies in patients with COPD, 395 (48.7%) were 65 years of age or older while 62 (7.6%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. A slightly higher frequency of chest infection was reported in the 39 asthma patients 75 years of age and older, although a causal relationship with FORADIL has not been established. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. (See PRECAUTIONS, Drug Interactions.)

## **ADVERSE REACTIONS**

**Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), including formoterol, the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Clinical trials with FORADIL AEROLIZER suggested a higher incidence of serious asthma exacerbations in patients who received FORADIL AEROLIZER than in those who received placebo. (See WARNINGS)**

### **Experience in Pediatric, Adolescent and Adult Patients with Asthma**

Of the 5,824 patients in multiple-dose controlled clinical trials, 1,985 were treated with FORADIL AEROLIZER at the recommended dose of 12 mcg twice daily. The following table shows adverse events where the frequency was greater than or equal to 1% in the FORADIL twice daily group and where the rates in the FORADIL group exceeded placebo. Three adverse events showed dose ordering among tested doses of 6, 12 and 24 mcg administered twice daily; tremor, dizziness and dysphonia.

**NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN PATIENTS 5 YEARS OF AGE AND OLDER FROM MULTIPLE-DOSE CONTROLLED CLINICAL TRIALS**

Adverse Event	FORADIL AEROLIZER 12 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total Patients	1985	(100)	969	(100)
Infection viral	341	(17.2)	166	(17.1)
Bronchitis	92	(4.6)	42	(4.3)
Chest infection	54	(2.7)	4	(0.4)
Dyspnea	42	(2.1)	16	(1.7)
Chest pain	37	(1.9)	13	(1.3)
Tremor	37	(1.9)	4	(0.4)
Dizziness	31	(1.6)	15	(1.5)
Insomnia	29	(1.5)	8	(0.8)
Tonsillitis	23	(1.2)	7	(0.7)
Rash	22	(1.1)	7	(0.7)
Dysphonia	19	(1.0)	9	(0.9)

In two 12-week controlled trials with combined enrollment of 1095 patients 12 years of age and older, FORADIL AEROLIZER 12 mcg twice daily was compared to FORADIL AEROLIZER 24 mcg twice daily, albuterol 180 mcg four times daily, and placebo. Serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with FORADIL AEROLIZER 24 mcg twice daily than with the recommended dose of FORADIL AEROLIZER 12 mcg twice daily, albuterol, or placebo. The results are shown in the following table.



**NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN  
PATIENTS 12 YEARS OF AGE AND OLDER FROM TWO 12-WEEK  
CONTROLLED CLINICAL TRIALS**

	<b>Foradil 12 mcg twice daily</b>	<b>Foradil 24 mcg twice daily</b>	<b>Albuterol 180 mcg four times daily</b>	<b>Placebo</b>
	<b>Trial #1</b>			
<b>Serious asthma exacerbations</b>	0/136 (0)	4/135 (3.0%) <sup>1</sup>	2/134 (1.5%)	0/136 (0)
	<b>Trial #2</b>			
<b>Serious asthma exacerbations</b>	1/139 (0.7%)	5/136 (3.7%) <sup>2</sup>	0/138 (0)	2/141 (1.4%)

<sup>1</sup> 1 patient required intubation

<sup>2</sup> 2 patients had respiratory arrest; 1 of the patients died

In a 16-week, randomized, multi-center, double-blind, parallel-group trial, patients who received either 24 mcg twice daily or 12 mcg twice daily doses of FORADIL AEROLIZER experienced more serious asthma exacerbations than patients who received placebo (see CLINICAL TRIALS). The results are shown in the following table.

**NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN  
PATIENTS 12 YEARS OF AGE AND OLDER FROM A 16-WEEK  
TRIAL**

	<b>Foradil 12 mcg twice daily</b>	<b>Foradil 24 mcg twice daily</b>	<b>Placebo</b>
<b>Serious asthma exacerbations</b>	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

### **Experience in Children with Asthma**

The safety of FORADIL AEROLIZER 12 mcg twice daily compared to FORADIL AEROLIZER 24 mcg twice daily and placebo was investigated in one large, multicenter, randomized, double-blind, 52-week clinical trial in 518 children with

asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. More children who received FORADIL AEROLIZER 24 mcg twice daily than children who received FORADIL AEROLIZER 12 mcg twice daily or placebo experienced serious asthma exacerbations, as shown in the next table.

**NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 5-12 YEARS OF AGE FROM A 52-WEEK TRIAL**

	<b>Foradil 12 mcg twice daily</b>	<b>Foradil 24 mcg twice daily</b>	<b>Placebo</b>
<b>Serious asthma exacerbations</b>	8/171 (4.7%)	11/171 (6.4%)	0/176 (0)

The numbers and percent of patients who reported adverse events were comparable in the 12 mcg twice daily and placebo groups. In general, the pattern of the adverse events observed in children differed from the usual pattern seen in adults. The adverse events that were more frequent in the formoterol group than in the placebo group reflected infection/inflammation (viral infection, rhinitis, tonsillitis, gastroenteritis) or abdominal complaints (abdominal pain, nausea, dyspepsia).

### **Experience in Adult Patients with COPD**

Of the 1634 patients in two pivotal multiple-dose Chronic Obstructive Pulmonary Disease (COPD) controlled trials, 405 were treated with FORADIL AEROLIZER 12 mcg twice daily. The numbers and percent of patients who reported adverse events were comparable in the 12 mcg twice daily and placebo groups. Adverse events (AE's) experienced were similar to those seen in asthmatic patients, but with a higher incidence of COPD-related AE's in both placebo and formoterol treated patients.

The following table shows adverse events where the frequency was greater than or equal to 1% in the FORADIL AEROLIZER group and where the rates in the FORADIL AEROLIZER group exceeded placebo. The two clinical trials included doses of 12 mcg and 24 mcg, administered twice daily. Seven adverse events showed dose ordering among tested doses of 12 and 24 mcg administered twice daily; pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor.

**NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN  
ADULT COPD PATIENTS TREATED IN MULTIPLE-DOSE  
CONTROLLED CLINICAL TRIALS**

Adverse Event	FORADIL AEROLIZER 12 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total patients	405	(100)	420	(100)
Upper respiratory tract infection	30	(7.4)	24	(5.7)
Pain back	17	(4.2)	17	(4.0)
Pharyngitis	14	(3.5)	10	(2.4)
Pain chest	13	(3.2)	9	(2.1)
Sinusitis	11	(2.7)	7	(1.7)
Fever	9	(2.2)	6	(1.4)
Cramps leg	7	(1.7)	2	(0.5)
Cramps muscle	7	(1.7)	0	
Anxiety	6	(1.5)	5	(1.2)
Pruritis	6	(1.5)	4	(1.0)
Sputum increased	6	(1.5)	5	(1.2)
Mouth dry	5	(1.2)	4	(1.0)

Overall, the frequency of all cardiovascular adverse events in the two pivotal studies was low and comparable to placebo (6.4% for FORADIL AEROLIZER 12 mcg twice daily, and 6.0% for placebo). There were no frequently-occurring specific cardiovascular adverse events for FORADIL AEROLIZER (frequency greater than or equal to 1% and greater than placebo).

Other adverse reactions to FORADIL AEROLIZER are similar in nature to other selective beta<sub>2</sub>-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

### **Post Marketing Experience**

In extensive worldwide marketing experience with FORADIL, serious exacerbations of asthma, including some that have been fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma (see

WARNINGS), a few have occurred in patients with less severe asthma. It is not possible to determine from these individual case reports whether FORADIL AEROLIZER contributed to the events.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of formoterol fumarate inhalation powder.

## **DRUG ABUSE AND DEPENDENCE**

There was no evidence in clinical trials of drug dependence with the use of FORADIL.

## **OVERDOSAGE**

The expected signs and symptoms with overdosage of FORADIL AEROLIZER are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of FORADIL AEROLIZER.

Treatment of overdosage consists of discontinuation of FORADIL AEROLIZER together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of FORADIL AEROLIZER. Cardiac monitoring is recommended in cases of overdosage.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 53,000 and 25,000 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m<sup>2</sup> basis). The median

lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

## **DOSAGE AND ADMINISTRATION**

FORADIL capsules should be administered only by the oral inhalation route and only using the AEROLIZER Inhaler (see the accompanying Medication Guide). **FORADIL capsules should not be ingested (i.e., swallowed) orally.** FORADIL capsules should always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

### **Treatment of Asthma**

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as formoterol, the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death (see Warnings). **Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated.** Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

### **Pediatric and Adolescent Patients**

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be

taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

For adults and children 5 years of age and older, the usual dosage is the inhalation of the contents of one 12-mcg FORADIL capsule every 12 hours using the AEROLIZER Inhaler. The patient must not exhale into the device. The total daily dose of FORADIL should not exceed one capsule twice daily (24 mcg total daily dose). More frequent administration or administration of a larger number of inhalations is not recommended. If symptoms arise between doses, an inhaled short-acting beta<sub>2</sub>-agonist should be taken for immediate relief.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be re-evaluated.

### **For Prevention of Exercise-Induced Bronchospasm (EIB)**

Use of FORADIL AEROLIZER as a single agent for the prevention of exercise induced bronchospasm may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of FORADIL AEROLIZER for the prevention of exercise induced bronchospasm may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid. For adults and children 5 years of age or older, the usual dosage is the inhalation of the contents of one 12-mcg FORADIL capsule at least 15 minutes before exercise administered on an occasional as needed basis. When used intermittently as needed for prevention, protection may last up to 12 hours.

Additional doses of FORADIL AEROLIZER should not be used for 12 hours after the administration of this drug. Regular, twice-daily dosing has not been studied in preventing EIB. Patients who are receiving FORADIL AEROLIZER twice daily for treatment of their asthma should not use additional doses for prevention of EIB and may require a short-acting bronchodilator.

## **For Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)**

The usual dosage is the inhalation of the contents of one 12 mcg FORADIL capsule every 12 hours using the AEROLIZER inhaler.

A total daily dose of greater than 24 mcg is not recommended.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

### **HOW SUPPLIED**

FORADIL AEROLIZER contains: aluminum blister-packaged 12-mcg FORADIL (formoterol fumarate) clear gelatin capsules with "CG" printed on one end and "FXF" printed on the opposite end; one AEROLIZER Inhaler; and Medication Guide.

Unit Dose (blister pack)

Box of 12 (strips of 6). . . . . NDC 0085-1402-01

Unit Dose (blister pack)

Box of 60 (strips of 6). . . . . NDC 0085-1401-01

FORADIL capsules should be used with the AEROLIZER Inhaler only. The AEROLIZER Inhaler should not be used with any other capsules.

**Prior to dispensing:** Store in a refrigerator, 2°C-8°C (36°F-46°F)

**After dispensing to patient:** Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Always discard the FORADIL capsules and AEROLIZER Inhaler by the "Use by" date and always use the new AEROLIZER Inhaler provided with each new prescription.

Keep out of the reach of children.

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SCHERING CORPORATION

Manufactured by:

Novartis Pharma AG, Basle, Switzerland

for

Schering Corporation, Kenilworth, NJ 07033

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## Medication Guide

**Foradil® [FOR-a-dil] Aerolizer®**  
(formoterol fumarate inhalation powder)

**Important: Do not swallow FORADIL capsules. FORADIL capsules are used only with the Aerolizer inhaler that comes with FORADIL AEROLIZER. Never place a capsule in the mouthpiece of the AEROLIZER Inhaler.**

Read the Medication Guide that comes with FORADIL AEROLIZER before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your health care provider about your medical condition or treatment.

### **What is the most important information I should know about FORADIL AEROLIZER?**

**FORADIL AEROLIZER can cause serious side effects, including:**

**1. People with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines, such as formoterol fumarate inhalation powder (FORADIL AEROLIZER), have an increased risk of death from asthma problems.**

- Call your healthcare provider if breathing problems worsen over time while using FORADIL AEROLIZER. You may need a different treatment.
- Get emergency medical care if:
  - breathing problems worsen quickly, and
  - you use your rescue inhaler medicine, but it does not relieve your breathing problems.

**2. Do not use FORADIL AEROLIZER as your only asthma medicine. FORADIL AEROLIZER must only be used with a long-term asthma control medicine, such as an inhaled corticosteroid.**

3. When your asthma is well controlled, your healthcare provider may tell you to stop taking FORADIL AEROLIZER. Your healthcare provider will decide if you can stop FORADIL AEROLIZER without loss of asthma control. You will continue taking your long-term asthma control medicine, such as an inhaled corticosteroid.

4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

## **What is FORADIL AEROLIZER?**

FORADIL AEROLIZER is a long-acting beta<sub>2</sub>-agonist (LABA). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

FORADIL AEROLIZER is used for asthma, exercise-induced bronchospasm (EIB) and chronic obstructive pulmonary disease (COPD) as follows:

### **Asthma**

FORADIL AEROLIZER is used with a long-term asthma control medicine, such as an inhaled corticosteroid, in adults and children ages 5 and older:

- to control symptoms of asthma, and
- to prevent symptoms such as wheezing

LABA medicines, such as FORADIL AEROLIZER, increase the risk of death from asthma problems. FORADIL AEROLIZER is not for adults and children with asthma who are well controlled with long-term asthma control medicine, such as low to medium dose of an inhaled corticosteroid medicine.

### **Exercise-Induced Bronchospasm (EIB)**

FORADIL AEROLIZER is used to prevent wheezing caused by exercise in adults and children 5 years of age and older.

- If you have EIB only, your healthcare provider may prescribe only FORADIL AEROLIZER for your condition
- If you have EIB and asthma, your healthcare provider should also prescribe a long-term asthma control medicine, such as an inhaled corticosteroid.

### **Chronic Obstructive Pulmonary Disease (COPD)**

FORADIL AEROLIZER is used long-term, 2 times each day (morning and evening), to control symptoms of COPD and prevent wheezing in adults with COPD.

### **Who should not use FORADIL AEROLIZER?**

- Do not take FORADIL AEROLIZER to treat your asthma without a long-term asthma control medicine, such as an inhaled corticosteroid.
- If you are allergic to formoterol fumarate or any of the ingredients in FORADIL AEROLIZER. Ask your healthcare provider if you are not sure. See the end of this Medication Guide for a complete list of ingredients in FORADIL AEROLIZER.

### **What should I tell my healthcare provider before using FORADIL AEROLIZER?**

**Tell your healthcare provider about all of your health conditions, including if you:**

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- are pregnant or planning to become pregnant. It is not known if FORADIL AEROLIZER may harm your unborn baby.
- are breastfeeding. It is not known if FORADIL AEROLIZER passes into your milk and if it can harm your baby.
- are allergic to FORADIL AEROLIZER, any other medicines, or food products.

FORADIL AEROLIZER contains lactose (milk sugar) and a small amount of milk proteins. It is possible that allergic reactions may happen in patients who have a severe milk protein allergy.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. FORADIL AEROLIZER and certain other medicines may interact with each other. This may cause serious side effects.

Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

### **How do I use FORADIL capsules with the Aerolizer inhaler?**

**See the step-by-step instructions for using FORADIL Capsules with the Aerolizer inhaler at the end of this Medication Guide.** Do not use FORADIL unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Children should use FORADIL AEROLIZER with an adult's help, as instructed by the child's healthcare provider.
- Use FORADIL AEROLIZER exactly as prescribed. **Do not use FORADIL AEROLIZER more often than prescribed.**
- For asthma and COPD, the usual dose is 1 FORADIL capsule inhaled through the AEROLIZER inhaler 2 times each day (morning and evening). The 2 doses should be about 12 hours apart.
- For preventing exercise-induced bronchospasm, the usual dose is 1 FORADIL capsule inhaled through the AEROLIZER inhaler at least 15 minutes before exercise, as needed. Do not use FORADIL AEROLIZER more often than every 12 hours. Do not use extra FORADIL AEROLIZER before exercise if you already use it 2 times each day.
- If you miss a dose of FORADIL AEROLIZER, just skip that dose. Take your next dose at your usual time. Never take 2 doses at one time.
- Do not use a spacer device with FORADIL AEROLIZER.

- Do not breathe into FORADIL AEROLIZER.
- While you are using FORADIL AEROLIZER 2 times each day, do not use other medicines that contain a long-acting beta<sub>2</sub>-agonist (LABA) for any reason. Ask your healthcare provider or pharmacist for a list of these medicines.
- Do not stop using FORADIL AEROLIZER or any of your asthma medicines unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- FORADIL AEROLIZER does not relieve sudden symptoms. Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.
- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with FORADIL AEROLIZER
  - you need to use your rescue inhaler medicine more often than usual
  - your rescue inhaler medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days in a row
  - you use 1 whole canister of your rescue inhaler medicine in 8 weeks time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using FORADIL AEROLIZER regularly for 1 week.

### **What are the possible side effects with FORADIL AEROLIZER?**

**FORADIL AEROLIZER may cause serious side effects, including:**

- **See “What is the most important information I should know about FORADIL AEROLIZER?”**
- **Bronchospasm with wheezing or coughing and difficulty breathing**
- **Low blood potassium** (which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm)
- **Fast or irregular heart beat** (palpitations)
- **Serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.

**Other possible side effects with FORADIL AEROLIZER include:**

- chest pain

- increased blood pressure
- nervousness
- dry mouth
- muscle cramps
- nausea
- dizziness
- tiredness
- high blood sugar
- high blood acid
- trouble sleeping

**Common side effects with FORADIL AEROLIZER include:**

- headache
- tremor

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with FORADIL AEROLIZER. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How do I store FORADIL AEROLIZER?**

- Store FORADIL AEROLIZER at room temperature between 68°F and 77°F (20°C to 25°C). Protect FORADIL AEROLIZER from heat and moisture. Do not remove FORADIL capsules from their foil package until just before use.
- Always discard the old AEROLIZER inhaler by the “Use by” date and use the new one provided with each new prescription.
- Safely discard FORADIL capsules and the Aerolizer inhaler if no longer needed or is out-of-date.
- **Keep FORADIL AEROLIZER and all medicines out of the reach of children.**

**General Information about FORADIL AEROLIZER**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FORADIL AEROLIZER for a condition for which it was not prescribed. Do not give FORADIL AEROLIZER to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about FORADIL AEROLIZER. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for

information about FORADIL AEROLIZER that was written for healthcare professionals. If you have any questions about the use of FORADIL AEROLIZER, call (toll-free) 1-800-526-4099 or go to [www.foradil.us](http://www.foradil.us).

### **What are the ingredients in FORADIL AEROLIZER?**

Active ingredient: formoterol fumarate

Inactive ingredients: lactose (contains milk proteins), gelatin (capsule shell)

### **Instructions for Using FORADIL AEROLIZER**

**Do not swallow FORADIL capsules.**

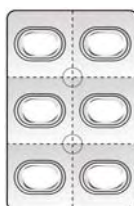
Follow the instructions below for using your FORADIL AEROLIZER. **You will breathe-in (inhale) the medicine in the FORADIL capsules from the FORADIL AEROLIZER.** If you have any questions, ask your healthcare provider or pharmacist.

#### **FORADIL AEROLIZER**

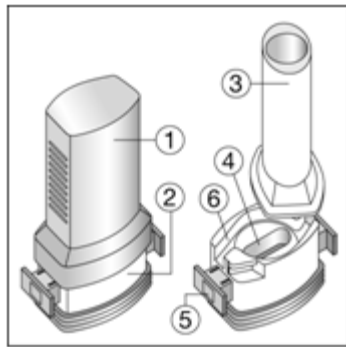
- **FORADIL AEROLIZER consists of FORADIL capsules and a AEROLIZER Inhaler.**
- **FORADIL capsules come on blister cards and are wrapped in foil pouches. Do not open a foil pouch until you are ready to use FORADIL AEROLIZER.**
- **Keep your FORADIL and AEROLIZER Inhaler dry. Handle with DRY hands.**



Aluminum pouch covering the foil blister cards



Foil blister card



The Aerolizer consists of the following parts:

1. A cap to protect the mouthpiece of the base
2. A base that allows the proper release of medicine from the capsule. The base consists of:
  3. A mouth piece
  4. A capsule chamber
  5. A button with "winglets" (projecting side pieces) and pins on each side
  6. An air inlet channel.

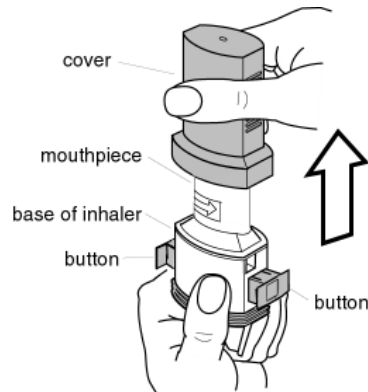
With each new prescription of FORADIL AEROLIZER or refill, your pharmacist should have written the "Use by" date on the sticker on the outside of the FORADIL AEROLIZER box. Remove the "Use by" sticker on the box and place it on the AEROLIZER Inhaler cover that comes with FORADIL. If the sticker is blank, count 4 months from the date you got your FORADIL AEROLIZER from the pharmacy and write this date on the sticker. Also, check the expiration date stamped on the box. If this date is less than 4 months from your purchase date, write this date on the sticker.

Do not use FORADIL capsules with any other capsule inhaler, and do not use the AEROLIZER inhaler to take any other capsule medicine.

**Taking a dose of FORADIL AEROLIZER requires the following steps:**

1. Open the foil pouch containing a blister card of FORADIL capsules. Do not remove a FORADIL capsule until you are ready for a dose.
2. Pull off the AEROLIZER Inhaler cover. (Figure 1)

Figure 1



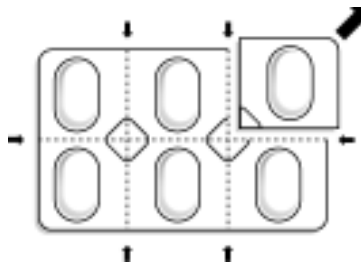
3. Hold the base of the AEROLIZER Inhaler firmly and twist the mouthpiece in the direction of the arrow to open. (Figure 2) Push the buttons in on each side to make sure that you can see 4 pins in the capsule well of the AEROLIZER Inhaler.

Figure 2



4. Separate one FORADIL capsule blister by tearing at the pre-cut lines. (Figure 3)

Figure 3



5. Peel the paper backing that covers one FORADIL capsule on the blister card. Push the FORADIL capsule through the foil. (Figure 4)

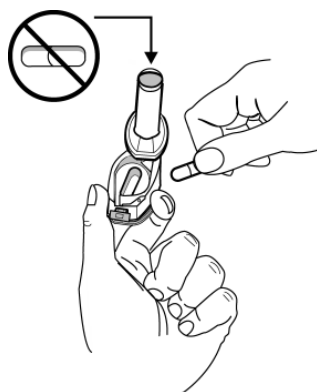
Figure 4





6. Place the FORADIL capsule in the capsule-chamber in the base of the AEROLIZER Inhaler. **Never place a capsule directly into the mouthpiece.** (Figure 5)

Figure 5



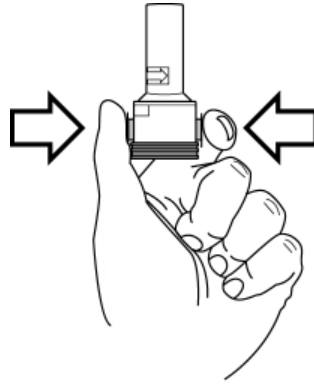
7. Twist the mouthpiece back to the closed position. (Figure 6)

Figure 6



8. Hold the mouthpiece of the AEROLIZER Inhaler upright and press both buttons **ONCE**. You should hear a click as the FORADIL capsule is being pierced. (Figure 7)

Figure 7



9. Release the buttons. If the buttons stay stuck, grasp the wings on the buttons and pull them out of the stuck position before the next step. Do not push the buttons a second time. This may cause the FORADIL capsule to break into small pieces. There is a screen built into the AEROLIZER Inhaler to hold these small pieces. It is possible that tiny pieces of a FORADIL capsule might reach your mouth or throat when you inhale the medicine. This will not harm you, but to avoid this, only pierce the capsule once. The FORADIL capsules are also less likely to break into small pieces if you store them the right way (See “How do I store FORADIL AEROLIZER?”).

10. Breathe out (exhale) fully. **Do not exhale into the AEROLIZER mouthpiece.** (Figure 8)

Figure 8

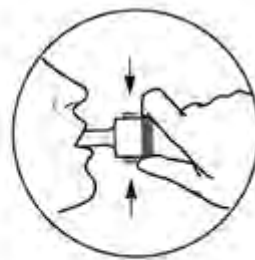


11. Tilt your head back slightly. Keep the AEROLIZER Inhaler level, with the blue buttons to the left and right (**not up and down**). Place the mouthpiece in your mouth and close your lips around the mouthpiece. (Figures 9 and 10)



**CORRECT**

Figure 9



**INCORRECT**

Figure 10

12. Breathe in quickly and deeply (Figure 11). This will cause the FORADIL capsule to spin around in the chamber and deliver your dose of medicine. You should hear a whirring noise and experience a sweet taste in your mouth. If you do not hear the whirring noise, the capsule may be stuck. If this occurs, open the AEROLIZER Inhaler and loosen the capsule allowing it to spin freely. **Do not try to loosen the capsule by pressing the buttons again.** (You will have to repeat steps 10 to 12 again to get your dose.)

Figure 11



13. Remove the AEROLIZER Inhaler from your mouth. Continue to hold your breath as long as you can and then exhale.

14. Open the AEROLIZER Inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 10 to 13. Most people are able to empty the capsule in one or two inhalations.

15. After use, open the AEROLIZER Inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.

16. Close the mouthpiece and replace the cover.

**Remember:**

- Never breathe into the AEROLIZER Inhaler.

- Never take the AEROLIZER Inhaler apart.
- Never place a FORADIL capsule directly into the mouthpiece of the AEROLIZER Inhaler.
- Never leave a used FORADIL capsule in the AEROLIZER Inhaler chamber.
- Always use the AEROLIZER Inhaler in a level position.
- Never wash the AEROLIZER Inhaler. **Keep it dry.**
- Always keep the AEROLIZER Inhaler and FORADIL capsules in a dry place.
- Always use the new AEROLIZER Inhaler that comes with your refill.

**Rx only**



SCHERING CORPORATION

Manufactured by:

Novartis Pharma AG, Basle, Switzerland

for

Schering Corporation, Kenilworth, NJ 07033

FORADIL is a registered trademark of Astellas Pharma Inc.

AEROLIZER is a registered trademark of Novartis AG.

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May 2010

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**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

## PRINCIPAL DISPLAY PANEL

Package Label – 12 mcg per capsule

Rx Only                      NDC 0085-1401-01

Foradil® Aerolizer®

(formoterol fumarate inhalation powder)

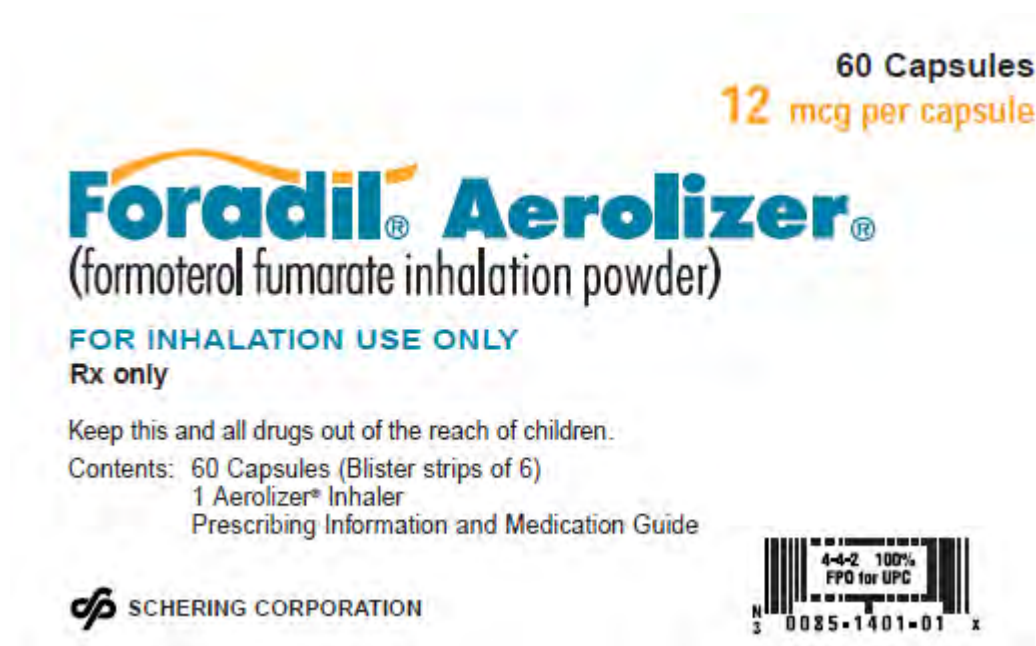
FOR INHALATION USE ONLY

Keep this and all drugs out of the reach of children.

Contents:    60 Capsules (Blister strips of 6)

1 Aerolizer® Inhaler

Prescribing Information and Medication Guide



## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEREVENT DISKUS safely and effectively. See full prescribing information for SEREVENT DISKUS.

### SEREVENT DISKUS (salmeterol xinafoate inhalation powder) FOR ORAL INHALATION

Initial U.S. Approval: 1994

#### **WARNING: ASTHMA-RELATED DEATH**

*See full prescribing information for complete boxed warning.*

- Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. (5.1)
- Prescribe SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1.1, 5.1)
- Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)

#### **RECENT MAJOR CHANGES**

Boxed Warning	November 2010
Indications and Usage (1.1, 1.2)	November 2010
Dosage and Administration (2.1, 2.2)	November 2010
Warnings and Precautions, Asthma-Related Death (5.1)	November 2010

#### **INDICATIONS AND USAGE**

SEREVENT DISKUS is a LABA indicated for:

- Treatment of asthma in patients aged 4 years and older. (1.1)
- Prevention of exercise-induced bronchospasm (EIB) in patients aged 4 years and older. (1.2)
- Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). (1.3)

Important limitation:

- Not indicated for the relief of acute bronchospasm. (1.1, 1.3)

#### **DOSAGE AND ADMINISTRATION**

For oral inhalation only.

- Treatment of asthma in patients ≥4 years: 1 inhalation twice daily in addition to concomitant treatment with an inhaled corticosteroid. (2.1)
- EIB: One inhalation at least 30 minutes before exercise
- Maintenance treatment of bronchospasm associated with COPD: 1 inhalation twice daily. (2.3)

#### **DOSAGE FORMS AND STRENGTHS**

DISKUS device containing salmeterol (50 mcg) as an oral inhalation powder. (3)

#### **CONTRAINDICATIONS**

- Asthma: Without concomitant use of a long-term asthma control medication such as an inhaled corticosteroid.
- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

#### **WARNINGS AND PRECAUTIONS**

- Asthma-related death and asthma-related hospitalizations: Long-acting beta<sub>2</sub>-adrenergic agonists increase the risk. Prescribe for asthma only as concomitant therapy with an inhaled corticosteroid. (5.1)
- Deterioration of disease and acute episodes: Do not initiate during rapidly deteriorating asthma. Do not use to treat acute symptoms. (5.2)
- Corticosteroids: Not a substitute for corticosteroids. Patients with asthma must take a concomitant inhaled corticosteroid. (5.3)
- Use with additional long-acting beta<sub>2</sub>-agonist: Do not use in combination because of risk of overdose (5.4)
- Paradoxical bronchospasm: Discontinue SEREVENT DISKUS and institute alternative therapy if paradoxical bronchospasm occurs. (5.5)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.6)
- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Risk of cardiovascular effects. Use not recommended with SEREVENT DISKUS. (5.8)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.9)
- Metabolic effects: Be alert to hypokalemia and hyperglycemia. (5.10)

#### **ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥5%) are:

- Asthma: Headache, influenza, nasal/sinus congestion, pharyngitis, rhinitis tracheitis/bronchitis. (6.1)
- COPD: Cough, headache, musculoskeletal pain, throat irritation, viral respiratory infection. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### **DRUG INTERACTIONS**

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use not recommended. May increase risk of cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

#### **USE IN SPECIFIC POPULATIONS**

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved MEDICATION GUIDE.

Revised: 12/2010

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### WARNING: ASTHMA-RELATED DEATH

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT<sup>®</sup> DISKUS<sup>®</sup>, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT<sup>®</sup> Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

**Pediatric and Adolescent Patients:** Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

## 1 INDICATIONS AND USAGE

### 1.1 Treatment of Asthma

SEREVENT DISKUS is indicated for the treatment of asthma and in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid, in patients aged 4 years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. LABA, such as salmeterol, the



active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death [see *Warnings and Precautions (5.1)*]. Use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated [see *Contraindications (4)*]. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

**Pediatric and Adolescent Patients:** Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

**Important Limitation of Use:** SEREVENT DISKUS is NOT indicated for the relief of acute bronchospasm.

## **1.2 Prevention of Exercise-Induced Bronchospasm**

SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm (EIB) in patients aged 4 years and older. Use of SEREVENT DISKUS as a single agent for the prevention of EIB may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of SEREVENT DISKUS for the prevention of EIB may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid.

## **1.3 Maintenance Treatment of Chronic Obstructive Pulmonary Disease**

SEREVENT DISKUS is indicated for the long-term twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis).

**Important Limitation of Use:** SEREVENT DISKUS is NOT indicated for the relief of acute bronchospasm.

## **2 DOSAGE AND ADMINISTRATION**

SEREVENT DISKUS should be administered by the orally inhaled route only.

For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations

(more than 1 inhalation twice daily) is not recommended. Patients using SEREVENT DISKUS should not use additional LABA for any reason. [See Warnings and Precautions (5.4, 5.6).]

## **2.1 Asthma**

LABA, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death [see Warnings and Precautions (5.1)].

**Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid is contraindicated.** Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

**Pediatric and Adolescent Patients:** Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

For bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children aged 4 years and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should be taken for immediate relief.

## **2.2 Exercise-Induced Bronchospasm**

Use of SEREVENT DISKUS as a single agent for the prevention of EIB may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of SEREVENT DISKUS for the prevention of EIB may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid. One inhalation of SEREVENT DISKUS at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients aged 4 to 11 years. Additional doses of SEREVENT should not be used for 12

hours after the administration of this drug. Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

### **2.3 Chronic Obstructive Pulmonary Disease**

For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart).

## **3 DOSAGE FORMS AND STRENGTHS**

Disposable teal green device with 60 blisters containing salmeterol (50 mcg) as an oral inhalation powder formulation. An institutional pack containing 28 blisters is also available.

## **4 CONTRAINDICATIONS**

**Because of the risk of asthma-related death and hospitalization, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated [see Warnings and Precautions (5.1)].**

SEREVENT DISKUS is contraindicated as primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required [see Warnings and Precautions (5.2)].

SEREVENT DISKUS is contraindicated in patients with severe hypersensitivity to milk proteins [see Warnings and Precautions (5.7), Adverse Reactions (6.3), Description (11)].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Asthma-Related Death**

**LABA, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**

**Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.**

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require

**addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.**

The Salmeterol Multi-center Asthma Research Trial (SMART) was a large 28-week placebo-controlled US study comparing the safety of salmeterol (SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy, that showed an increase in asthma-related deaths in patients receiving salmeterol [*see Clinical Studies (14.1)*]. Given the similar basic mechanisms of action of beta<sub>2</sub>-agonists, the findings seen in the SMART study are considered a class effect.

A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

**The SNS and SMART studies enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by LABA.**

## **5.2 Deterioration of Disease and Acute Episodes**

SEREVENT DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SEREVENT DISKUS has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SEREVENT DISKUS in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for adding additional inhaled

corticosteroid or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of SEREVENT DISKUS.

SEREVENT DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta<sub>2</sub>-agonist, not SEREVENT DISKUS, should be used to relieve acute symptoms such as shortness of breath. When prescribing SEREVENT DISKUS, the physician must also provide the patient with an inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of acute symptoms.

When beginning treatment with SEREVENT DISKUS, patients who have been taking oral or inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

### **5.3 SEREVENT DISKUS is Not a Substitute for Corticosteroids**

There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect such as that associated with corticosteroids. When initiating and throughout treatment with SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma, patients must continue taking a suitable dosage of corticosteroids to maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

### **5.4 Excessive Use of SEREVENT DISKUS and Use With Other Long-Acting Beta<sub>2</sub>-Agonists**

As with other inhaled beta<sub>2</sub>-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SEREVENT DISKUS should not use an additional LABA (e.g., formoterol fumarate, arformoterol tartrate) for any reason.

### **5.5 Paradoxical Bronchospasm and Upper Airway Symptoms**

As with other inhaled medications, SEREVENT DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SEREVENT DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator; SEREVENT DISKUS should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

### **5.6 Cardiovascular and Central Nervous System Effects**

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see *Overdosage (10)*]. Therefore, SEREVENT DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

## **5.7 Immediate Hypersensitivity Reactions**

Immediate hypersensitivity reactions may occur after administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm. There have been reports of anaphylactic reactions in patients with severe milk protein allergy; therefore, patients with severe milk protein allergy should not take SEREVENT DISKUS [*see Contraindications (4)*].

## **5.8 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors**

Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of SEREVENT DISKUS with strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended [*see Drug Interactions (7.1)*].

## **5.9 Coexisting Conditions**

SEREVENT DISKUS, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

## **5.10 Hypokalemia and Hyperglycemia**

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [*see Clinical Pharmacology (12.2)*]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant and dose-related changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SEREVENT DISKUS at recommended doses.

# **6 ADVERSE REACTIONS**

**LABA, including salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Data from a large 28-week placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving**

salmeterol. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients [see Warnings and Precautions (5.1), Clinical Studies (14.1)].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

## 6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Patients Aged 12 Years and Older: Two multicenter, 12-week, controlled studies evaluated twice-daily doses of SEREVENT DISKUS in patients aged 12 years and older with asthma. Table 1 reports the incidence of adverse reactions in these 2 studies.

**Table 1. Adverse Reaction Incidence in Two 12-Week Clinical Trials in Adult and Adolescent Patients With Asthma**

Adverse Event	Percent of Patients		
	Placebo (N = 152)	SEREVENT DISKUS 50 mcg Twice Daily (N = 149)	Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 150)
Ear, nose, and throat			
Nasal/sinus congestion, pallor	6	9	8
Rhinitis	4	5	4
Neurological			
Headache	9	13	12
Respiratory			
Asthma	1	3	<1
Tracheitis/bronchitis	4	7	3
Influenza	2	5	5

Table 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Pharyngitis, sinusitis, upper respiratory tract infection, and cough occurred at  $\geq 3\%$  but were more common in the placebo group. However, throat irritation has been described at rates exceeding that of placebo in other controlled clinical trials.

**Additional Adverse Reactions:** Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with SEREVENT DISKUS compared with patients treated with placebo include the following: contact dermatitis, eczema, localized aches and pains, nausea, oral

mucosal abnormality, pain in joint, paresthesia, pyrexia of unknown origin, sinus headache, and sleep disturbance.

**Pediatric Patients Aged 4 to 11 Years:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 2 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

**Table 2. Adverse Reaction Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma**

Adverse Event	Percent of Patients		
	Placebo (N = 215)	SEREVENT DISKUS 50 mcg Twice Daily (N = 211)	Albuterol Inhalation Aerosol 200 mcg 4 Times Daily (N = 115)
Ear, nose, and throat			
Ear signs and symptoms	3	4	9
Pharyngitis	3	6	3
Neurological			
Headache	14	17	20
Respiratory			
Asthma	2	4	<1
Skin			
Skin rashes	3	4	2
Urticaria	0	3	2

The following events were reported at an incidence of >1% in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or with events that would be expected with the use of inhaled corticosteroids.

**Laboratory Test Abnormalities:** Elevation of hepatic enzymes was reported in ≥1% of patients in clinical trials. The elevations were transient and did not lead to discontinuation from the studies. In addition, there were no clinically relevant changes noted in glucose or potassium.

## **6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease**

Two multicenter, 24-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For presentation (Table 3), the placebo data from



a third trial, identical in design, patient entrance criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

**Table 3. Adverse Reactions With  $\geq 3\%$  Incidence in US Controlled Clinical Trials With SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease<sup>a</sup>**

Adverse Event	Percent of Patients	
	Placebo (N = 576)	SEREVENT DISKUS 50 mcg Twice Daily (N = 341)
Cardiovascular		
Hypertension	2	4
Ear, nose, and throat		
Throat irritation	6	7
Nasal congestion/blockage	3	4
Sinusitis	2	4
Ear signs and symptoms	1	3
Gastrointestinal		
Nausea and vomiting	3	3
Lower respiratory		
Cough	4	5
Rhinitis	2	4
Viral respiratory infection	4	5
Musculoskeletal		
Musculoskeletal pain	10	12
Muscle cramps and spasms	1	3
Neurological		
Headache	11	14
Dizziness	2	4
Average duration of exposure (days)	128.9	138.5

<sup>a</sup> Table 3 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common in the group receiving SEREVENT DISKUS than in the placebo group.

**Additional Adverse Reactions:** Other events occurring in the group receiving SEREVENT DISKUS that occurred at a frequency of  $\geq 1\%$  and were more common than in the placebo group were as follows: anxiety; arthralgia and articular rheumatism; bone and skeletal pain; candidiasis mouth/throat; dental discomfort and pain; dyspeptic symptoms; edema and

swelling; gastrointestinal infections; hyperglycemia; hyposalivation; keratitis and conjunctivitis; lower respiratory signs and symptoms; migraines; muscle pain; muscle stiffness, tightness, and rigidity; musculoskeletal inflammation; pain; and skin rashes.

Adverse reactions to salmeterol are similar in nature to those seen with other selective beta<sub>2</sub>-adrenoceptor agonists, e.g., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm; headache; tremor; nervousness; and paradoxical bronchospasm.

**Laboratory Abnormalities:** There were no clinically relevant changes in these trials. Specifically, no changes in potassium were noted.

### **6.3 Postmarketing Experience**

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of salmeterol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating [*see Warnings and Precautions (5.2)*], but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

**Cardiovascular:** Arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), and anaphylaxis.

**Non-Site Specific:** Very rare anaphylactic reaction in patients with severe milk protein allergy.

**Respiratory:** Reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking; oropharyngeal irritation.

## **7 DRUG INTERACTIONS**

### **7.1 Inhibitors of Cytochrome P450 3A4**

In a drug interaction study in 20 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C<sub>max</sub> increased 1.4-fold). Three (3) subjects were withdrawn due to beta<sub>2</sub>-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong

CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

## **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

SEREVENT DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

## **7.3 Beta-Adrenergic Receptor Blocking Agents**

Beta-blockers not only block the pulmonary effect of beta-agonists, such as SEREVENT DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

## **7.4 Diuretics**

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the coadministration of SEREVENT DISKUS with nonpotassium-sparing diuretics.

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No teratogenic effects occurred in rats at oral doses approximately 160 times the maximum recommended daily inhalation dose (MRHD) on an mg/m<sup>2</sup> basis. In pregnant Dutch rabbits administered oral doses approximately 50 times the MRHD based on comparison of the AUCs, salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose approximately 20 times the MRHD based on comparison of the AUCs.

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at an oral dose approximately 1,600 times the MRHD on an mg/m<sup>2</sup> basis. Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

## **8.2 Labor and Delivery**

There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with

uterine contractility, use of SEREVENT DISKUS during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

### 8.3 Nursing Mothers

Plasma levels of salmeterol, [a component of SEREVENT DISKUS](#), after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. Since there are no data from controlled trials on the use of salmeterol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SEREVENT DISKUS, taking into account the importance of SEREVENT DISKUS to the mother. Caution should be exercised when SEREVENT DISKUS is administered to a nursing woman.

### 8.4 Pediatric Use

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs [*see Indications and Usage (1.1), Warnings and Precautions (5.1)*].

The safety and efficacy of SEREVENT DISKUS in adolescents (aged 12 years and older) has been established based on adequate and well-controlled trials conducted in adults and adolescents [*see Clinical Studies (14.1)*]. A large 28-week placebo-controlled US study comparing salmeterol (SEREVENT Inhalation Aerosol) and placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol [*see Clinical Studies (14.1)*]. Post-hoc analyses in pediatric patients aged 12 to 18 years were also performed. Pediatric patients accounted for approximately 12% of patients in each treatment arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12% [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

The safety and efficacy of SEREVENT DISKUS have been evaluated in over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS in pediatric patients is warranted for either asthma or EIB.

In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week treatment period with respect to peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV<sub>1</sub>). SEREVENT DISKUS was effective in demographic subgroups (gender and age) of the population.

In 2 randomized studies in children aged 4 to 11 years with asthma and EIB, a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

## 8.5 Geriatric Use

Of the total number of adolescent and adult patients with asthma who received SEREVENT DISKUS in chronic dosing clinical trials, 209 were aged 65 years or older. Of the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing clinical trials, 167 were aged 65 years or older and 45 were aged 75 years or older. No apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta<sub>2</sub>-agonists, however, special caution should be observed when using SEREVENT DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Data from the trials in patients with COPD suggested a greater effect on FEV<sub>1</sub> of SEREVENT DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However, based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is warranted.

## 8.6 Hepatic Impairment

The pharmacokinetics of salmeterol base has not been studied in patients with hepatic impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

## 10 OVERDOSAGE

The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following: seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia. Overdosage with SEREVENT DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of SEREVENT DISKUS.

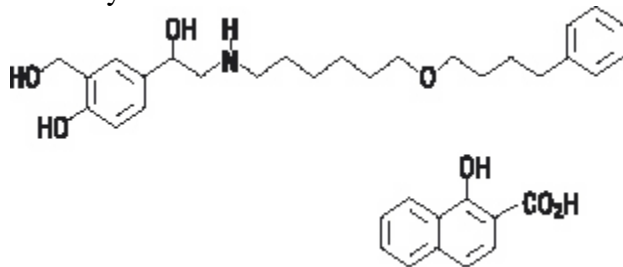
Treatment consists of discontinuation of SEREVENT DISKUS together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of SEREVENT DISKUS. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 240 and 110 times the MRHD for adults and children, respectively, on an mg/m<sup>2</sup> basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times the MRHD for adults and children, respectively, on an mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times the MRHD for adults and

children, respectively, on an mg/m<sup>2</sup> basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times the MRHD for adults and children, respectively, on an mg/m<sup>2</sup> basis).

## 11 DESCRIPTION

SEREVENT DISKUS contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a selective beta<sub>2</sub>-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy- $\alpha$ <sup>1</sup>-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>•C<sub>11</sub>H<sub>8</sub>O<sub>3</sub>. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

SEREVENT DISKUS is a specially designed plastic device containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50 mcg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean FEV<sub>1</sub> 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS<sup>®</sup> inhalation device was 82.4 L/min (range: 46.1 to 115.3 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although beta<sub>2</sub>-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-adrenoceptors are the predominant receptors in the heart, there are also beta<sub>2</sub>-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors

has not been established, but their presence raises the possibility that even highly selective beta<sub>2</sub>-agonists may have cardiac effects.

The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D<sub>2</sub>, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

## **12.2 Pharmacodynamics**

Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [*see Warnings and Precautions (5.6, 5.10)*]. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients receiving 50-mcg doses of salmeterol inhalation powder (N = 67) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 3 months of therapy, and no clinically significant dysrhythmias were noted.

In 24-week clinical studies in patients with COPD, the incidence of clinically significant abnormalities on the predose electrocardiograms (ECGs) at Weeks 12 and 24 in patients who received salmeterol 50 mcg was not different compared with placebo.

No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 91) and after 12 weeks of therapy (N = 74). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo [*see Adverse Reactions (6.1)*].

**Concomitant Use of SEREVENT DISKUS With Other Respiratory Medications:**  
***Short-Acting Beta<sub>2</sub>-Agonists:*** In two 12-week repetitive-dose adolescent and adult clinical

565 trials in patients with asthma (N = 149), the mean daily need for additional beta<sub>2</sub>-agonist in  
566 patients using SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six percent  
567 (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-  
568 agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged  
569 over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of  
570 cardiovascular events was observed among the 3 patients who averaged 8 to 11 inhalations/day;  
571 however, the safety of concomitant use of more than 8 inhalations/day of short-acting beta<sub>2</sub>-  
572 agonist with SEREVENT DISKUS has not been established. In 29 patients who experienced  
573 worsening of asthma while receiving SEREVENT DISKUS during these trials, albuterol therapy  
574 administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement  
575 in FEV<sub>1</sub> and no increase in occurrence of cardiovascular adverse events.

576 In 2 clinical trials in patients with COPD, the mean daily need for additional beta<sub>2</sub>-  
577 agonist for patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-  
578 four percent (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more  
579 inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of  
580 cardiovascular adverse reactions was observed among patients who averaged 6 or more  
581 inhalations per day.

582 *Methylxanthines:* The concurrent use of intravenously or orally administered  
583 methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been  
584 completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation  
585 Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates  
586 similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline.  
587 Resting heart rates were slightly higher in the patients on theophylline but were little affected by  
588 therapy with SEREVENT Inhalation Aerosol.

589 In 2 clinical trials in patients with COPD, 39 patients receiving SEREVENT DISKUS  
590 concurrently with a theophylline product had adverse event rates similar to those in 302 patients  
591 receiving SEREVENT DISKUS without theophylline. Based on the available data, the  
592 concomitant administration of methylxanthines with SEREVENT DISKUS did not alter the  
593 observed adverse event profile.

594 *Cromoglycate:* In clinical trials, inhaled cromolyn sodium did not alter the safety  
595 profile of salmeterol when administered concurrently.

### 596 **12.3 Pharmacokinetics**

597 Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-  
598 hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and  
599 eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not  
600 predict therapeutic effect.

601 Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low  
602 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder  
603 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
604 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in



7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

**Distribution:** The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

**Metabolism:** Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to  $\alpha$ -hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of  $\alpha$ -hydroxysalmeterol in vitro.

**Elimination:** In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

**Drug Interactions: Inhibitors of Cytochrome P450 3A4: Ketoconazole:** In a placebo-controlled crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

**Erythromycin:** In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol  $C_{max}$  at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03],  $p = 0.12$ ), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03],  $p < 0.04$ ), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77],  $p = 0.34$ ), and no change in plasma potassium.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHD for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHD for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHD for adults and children, respectively, on an mg/m<sup>2</sup> basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHD for adults and children, respectively, on an mg/m<sup>2</sup> basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the MRHD for adults on an mg/m<sup>2</sup> basis).

### **13.2 Animal Toxicology and/or Pharmacology**

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

Reproductive Toxicology Studies: No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the MRHD on an mg/m<sup>2</sup> basis).

In Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times and above the MRHD based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the MRHD based on comparison of the AUCs). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the MRHD on an mg/m<sup>2</sup> basis).

Salmeterol crossed the placenta following oral administration to mice and rats.

## **14 CLINICAL STUDIES**

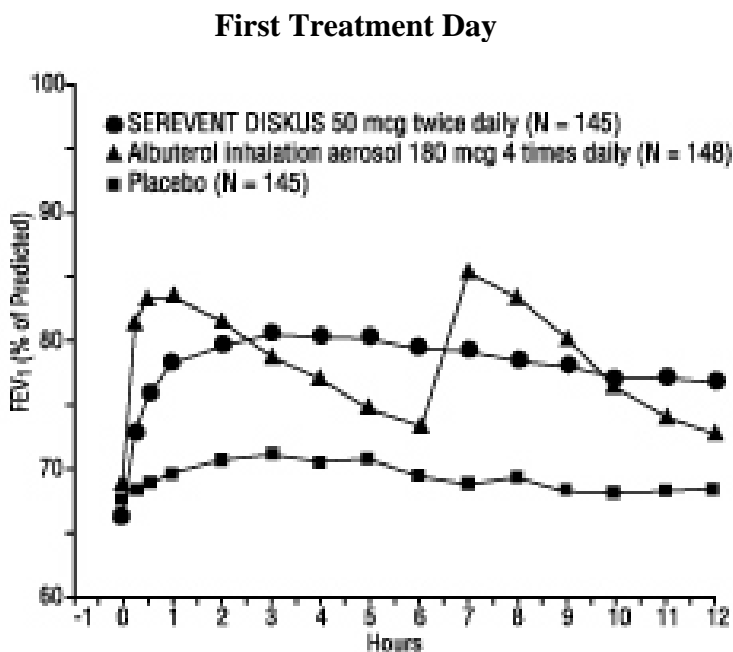
### **14.1 Asthma**

The initial studies supporting the approval of SEREVENT DISKUS for the treatment of asthma did not require the regular use of inhaled corticosteroids. However, for the treatment of

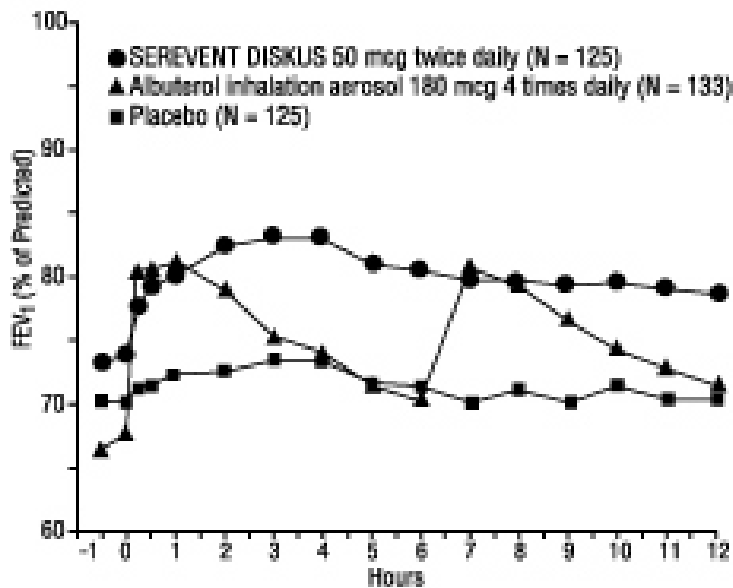
asthma, SEREVENT DISKUS is currently indicated only as concomitant therapy with an inhaled corticosteroid [see *Indications and Usage (1.1)*].

**Adult and Adolescent Patients Aged 12 Years and Older:** In 2 randomized double-blind studies, SEREVENT DISKUS was compared with albuterol inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma (protocol defined as 50% to 80% predicted FEV<sub>1</sub>, actual mean of 67.7% at baseline), including patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week period with no change in effectiveness over this time period (see Figure 1). There were no gender- or age-related differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect was noted in these studies. FEV<sub>1</sub> measurements (mean change from baseline) from these two 12-week studies are shown in Figure 1 for both the first and last treatment days.

**Figure 1. Serial 12-Hour FEV<sub>1</sub> From Two 12-Week Clinical Trials in Patients With Asthma**



700 Last Treatment Day (Week 12)



701 Table 4 shows the treatment effects seen during daily treatment with SEREVENT  
702 DISKUS for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.  
703  
704

705 **Table 4. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)**

Parameter	Time	Placebo	SEREVENT DISKUS	Albuterol Inhalation Aerosol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow (L/min)	Baseline 12 weeks	394 396	395 427 <sup>a</sup>	394 394
Mean % days with no asthma symptoms	Baseline 12 weeks	14 20	13 33	12 21
Mean % nights with no awakenings	Baseline 12 weeks	70 73	63 85 <sup>a</sup>	68 71
Rescue medications (mean no. of inhalations per day)	Baseline 12 weeks	4.2 3.3	4.3 1.6 <sup>b</sup>	4.3 2.2
Asthma exacerbations (%)		14	15	16

706 <sup>a</sup>Statistically superior to placebo and albuterol (p<0.001).

707 <sup>b</sup>Statistically superior to placebo (p<0.001).

708  
709 Maintenance of efficacy for periods up to 1 year has been documented.  
710 SEREVENT DISKUS and SEREVENT Inhalation Aerosol were compared with placebo  
711 in 2 additional randomized double-blind clinical trials in adolescent and adult patients with mild-

to-moderate asthma. SEREVENT DISKUS 50 mcg and SEREVENT Inhalation Aerosol 42 mcg, both administered twice daily, produced significant improvements in pulmonary function compared with placebo over the 12-week period. While no statistically significant differences were observed between the active treatments for any of the efficacy assessments or safety evaluations performed, there were some efficacy measures on which the metered-dose inhaler appeared to provide better results. Similar findings were noted in 2 randomized, single-dose, crossover comparisons of SEREVENT DISKUS and SEREVENT Inhalation Aerosol for the prevention of EIB. Therefore, while SEREVENT DISKUS was comparable to SEREVENT Inhalation Aerosol in clinical trials in mild-to-moderate patients with asthma, it should not be assumed that they will produce clinically equivalent outcomes in all patients.

*Patients on Concomitant Inhaled Corticosteroids:* In 4 clinical trials in adult and adolescent patients with asthma (N = 1,922), the effect of adding SEREVENT Inhalation Aerosol to inhaled corticosteroid therapy was evaluated over a 24-week treatment period. The studies compared the addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid dose.

Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled patients (aged 18 to 82 years) with persistent asthma who were previously maintained but not adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all patients were switched to beclomethasone dipropionate (BDP) 168 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of BDP to 336 mcg twice daily. As compared with the doubled dose of BDP, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reduction in supplemental albuterol use. The percent of patients who experienced asthma exacerbations overall was not different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol versus 17.9% in the higher-dose beclomethasone dipropionate group).

Two randomized, double-blind, controlled, parallel-group clinical trials (N = 925) enrolled patients (aged 12 to 78 years) with persistent asthma who were previously maintained but not adequately controlled on prior asthma therapy. During the 2- to 4-week run-in period, all patients were switched to fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of fluticasone propionate to 220 mcg twice daily. As compared with the increased (2.5 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reductions in supplemental albuterol use. Fewer patients receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those receiving the higher dose of fluticasone propionate (8.8% versus 13.8%).

Table 5 shows the treatment effects seen during daily treatment with SEREVENT Inhalation Aerosol for 24 weeks in adolescent and adult patients with mild-to-moderate asthma.

**Onset of Action:** During the initial treatment day in several multiple-dose clinical trials with SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) ranged from 30 to 48 minutes after a 50-mcg dose.

One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had  $\geq 15\%$  improvement in FEV<sub>1</sub>. Maximum improvement in FEV<sub>1</sub> generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

**Pediatric Patients:** In a randomized, double-blind, controlled study (N = 449), 50 mcg of SEREVENT DISKUS was administered twice daily to pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was demonstrated over the 12-week treatment period with respect to periodic serial PEF (36% to 39% postdose increase from baseline) and FEV<sub>1</sub> (32% to 33% postdose increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and age) and was effective when coadministered with other inhaled asthma medications such as short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind, placebo-controlled study (N = 207) with 50 mcg of salmeterol inhalation powder via an alternate device supported the findings of the trial with the DISKUS.

**Salmeterol Multi-center Asthma Research Trial:** The SMART study was a randomized double-blind study that enrolled LABA-naïve patients with asthma (average age of 39 years; 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared with placebo when added to usual asthma therapy.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 5 and Figure 2). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% versus 0.02%, relative risk: 4.37 [95% CI: 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% versus 0.01%, relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% versus 0.04%, relative risk: 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 5).

Post-hoc analyses in pediatric patients aged 12 to 18 years were also performed. Pediatric patients accounted for approximately 12% of patients in each treatment arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12%

[2/1,653]) and the placebo group (0.12% [2/1,622]); relative risk: 1.0 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control therapy mitigates the risk of asthma-related death.

**Table 5: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)**

	Salmeterol n (% <sup>a</sup> )	Placebo n (% <sup>a</sup> )	Relative Risk <sup>b</sup> (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients <sup>c</sup> (95% Confidence Interval)
<b>Total Population<sup>d</sup></b> Salmeterol: N = 13,176 Placebo: N = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
<b>Caucasian</b> Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
<b>African American</b> Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

<sup>a</sup> Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

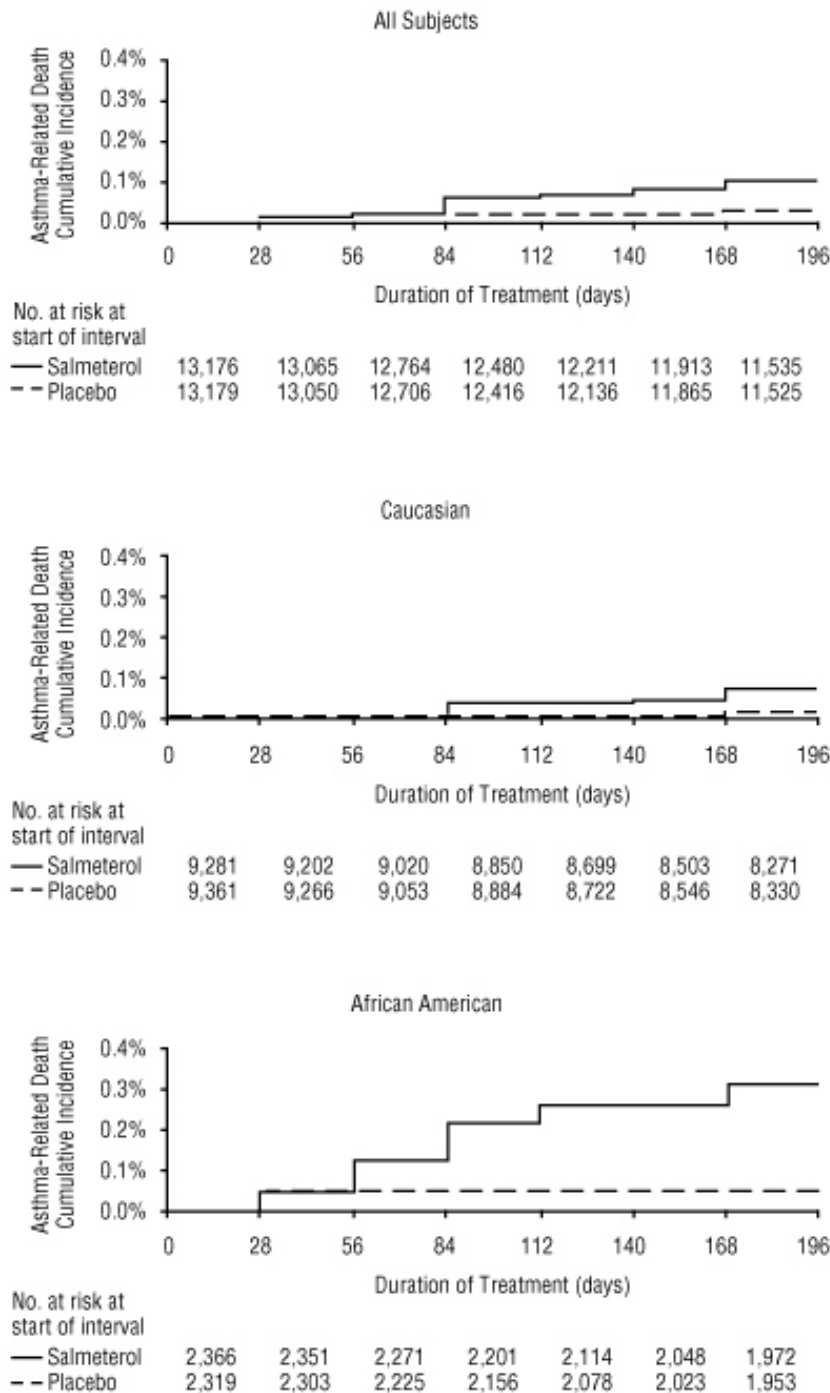
<sup>b</sup> Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

<sup>c</sup> Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

<sup>d</sup> The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death

occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

**Figure 2. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment**





## 14.2 Exercise-Induced Bronchospasm

In 2 randomized, single-dose, crossover studies in adolescents and adults with EIB (N = 52), 50 mcg of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise. For some patients, this protective effect against EIB was still apparent up to 8.5 hours following a single dose (see Table 6).

**Table 6. Results of 2 Exercise-Induced Bronchospasm Studies in Adolescents and Adults**

	Placebo (N = 52)		SEREVENT DISKUS (N = 52)	
	n	% Total	n	% Total
0.5-Hour postdose exercise challenge	<u>% Fall in FEV<sub>1</sub></u>			
	<10%			
	15	29	31	60
	≥10%, <20%			
	3	6	11	21
	≥20%			
	34	65	10	19
Mean maximal % fall in FEV <sub>1</sub> (SE)	-25% (1.8)		-11% (1.9)	
8.5-Hour postdose exercise challenge	<u>% Fall in FEV<sub>1</sub></u>			
	<10%			
	12	23	26	50
	≥10%, <20%			
	7	13	12	23
	≥20%			
	33	63	14	27
Mean maximal % fall in FEV <sub>1</sub> (SE)	-27% (1.5)		-16% (2.0)	

In 2 randomized studies in children aged 4 to 11 years with asthma and EIB (N = 50), a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

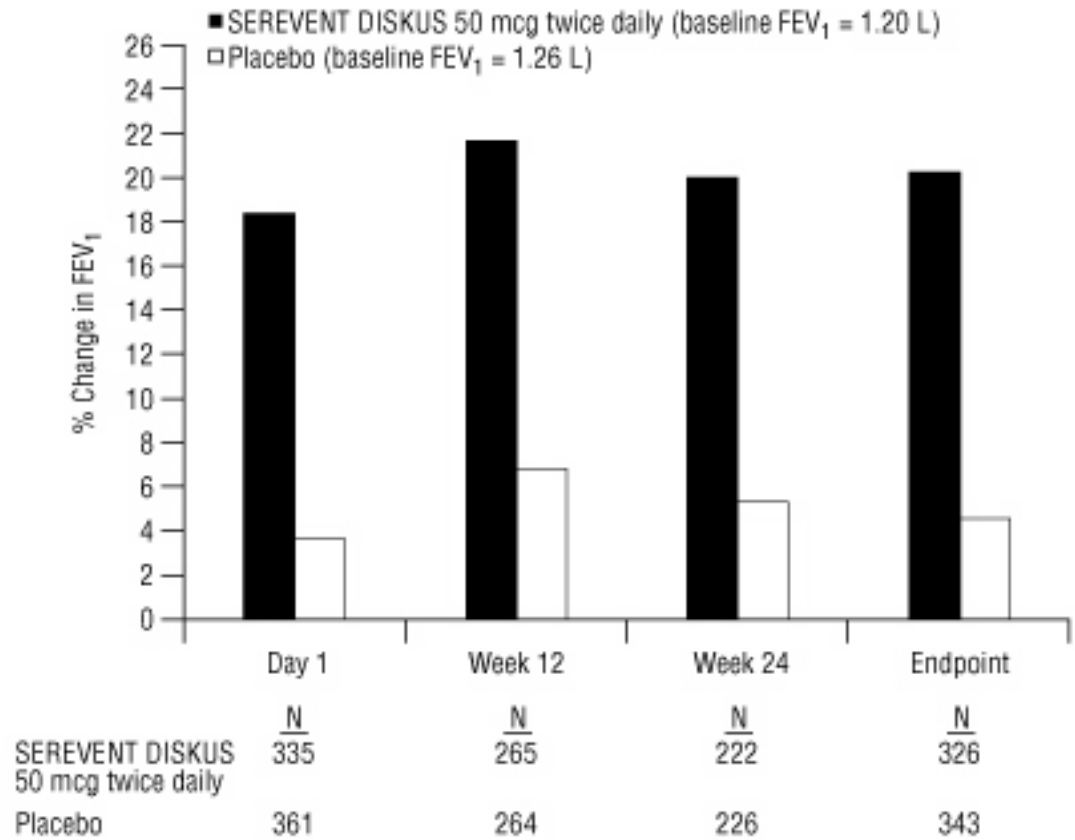
## 14.3 Chronic Obstructive Pulmonary Disease

In 2 clinical trials evaluating twice-daily treatment with SEREVENT DISKUS 50 mcg (N = 336) compared with placebo (N = 366) in patients with chronic bronchitis with airflow limitation, with or without emphysema, improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with placebo. Treatment with SEREVENT DISKUS did not result in significant improvements in secondary endpoints assessing COPD symptoms in either clinical trial. Both trials were randomized, double-blind, parallel-group studies of 24 weeks' duration and were identical in design, patient entrance criteria, and overall conduct.

Figure 3 displays the integrated 2-hour postdose FEV<sub>1</sub> results from the 2 clinical trials. The percent change in FEV<sub>1</sub> refers to the change from baseline, defined as the predose value on Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable FEV<sub>1</sub>) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly greater improvements in 2-hour postdose FEV<sub>1</sub> at Endpoint (216 mL, 20%) compared with

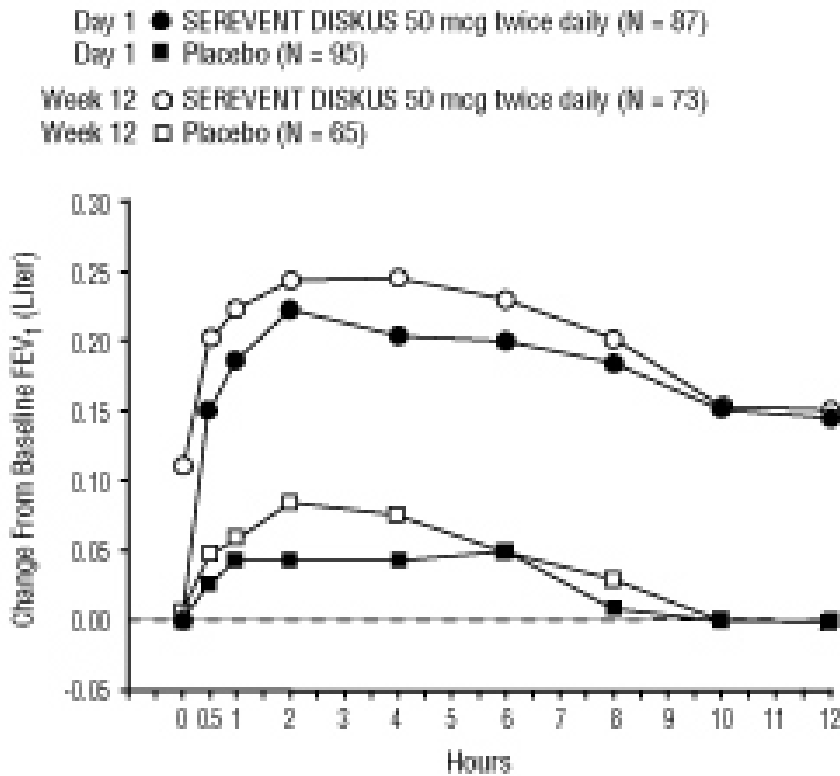
placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

**Figure 3. Mean Percent Change From Baseline in Postdose FEV<sub>1</sub> Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation**



Onset of Action and Duration of Effect: The onset of action and duration of effect of SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean FEV<sub>1</sub> increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the bronchodilating effect after 12 weeks of treatment was similar to that observed after the first dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

**Figure 4. Serial 12-Hour FEV<sub>1</sub> on the First Day and at Week 12 of Treatment**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

SEREVENT DISKUS is supplied as a disposable teal green device containing 60 blisters. The DISKUS inhalation device is packaged within a plastic-coated, moisture-protective foil pouch (NDC 0173-0521-00).

SEREVENT DISKUS is also supplied in an institutional pack of 1 disposable teal green unit containing 28 blisters. The drug product is packaged within a plastic-coated, moisture-protective foil pouch (NDC 0173-0520-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 6 weeks after removal from the moisture-protective foil pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. Do not attempt to take the DISKUS apart.

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved Medication Guide.*

### 17.1 Asthma-Related Death

**Patients should be informed that salmeterol increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and**

adolescent patients. Patients should be informed that SEREVENT DISKUS should not be the only therapy for the treatment of asthma and must only be used as additional therapy when long-term asthma control medications (e.g., inhaled corticosteroids) do not adequately control asthma symptoms. They should also be informed that currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Patients should be informed that when SEREVENT DISKUS is added to their treatment regimen they must continue to use their long-term asthma control medication.

## **17.2 Not for Acute Symptoms**

SEREVENT DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist such as albuterol. The physician should provide the patient with such medication and instruct the patient in how it should be used.

Patients should be instructed to notify their physicians immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists
- Need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with SEREVENT DISKUS without physician/provider guidance since symptoms may recur after discontinuation.

## **17.3 SEREVENT DISKUS is Not a Substitute for Corticosteroids**

All patients with asthma should be advised that they must also continue regular maintenance treatment with an inhaled corticosteroid if they are taking SEREVENT DISKUS.

SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT DISKUS.

## **17.4 Do Not Use Additional Long-Acting Beta<sub>2</sub>-Agonists**

When patients are prescribed SEREVENT DISKUS, other LABA should not be used.

## **17.5 Risks Associated With Beta-Agonist Therapy**

Patients should be informed of adverse effects associated with beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

## **17.6 Treatment of Exercised-Induced Bronchospasm**

When used for the treatment of EIB, additional doses of SEREVENT should not be used for 12 hours. Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

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Research Triangle Park, NC 27709

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Month Year

SRD:XPI

## MEDICATION GUIDE

### **SEREVENT<sup>®</sup> [*ser' uh-vent*] DISKUS<sup>®</sup>** **(salmeterol xinafoate inhalation powder)**

Read the Medication Guide that comes with SEREVENT DISKUS before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

#### **What is the most important information I should know about SEREVENT DISKUS?**

**SEREVENT DISKUS can cause serious side effects, including:**

- 1. People with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines such as salmeterol (SEREVENT DISKUS), have an increased risk of death from asthma problems.**
  - Call your healthcare provider if breathing problems worsen over time while using SEREVENT DISKUS. You may need a different treatment.
  - Get emergency medical care if:
    - breathing problems worsen quickly, and
    - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- 2. Do not use SEREVENT DISKUS as your only asthma medicine. SEREVENT DISKUS must only be used with a long-term asthma-control medicine, such as an inhaled corticosteroid.**
- 3. When your asthma is well controlled, your healthcare provider may tell you to stop taking SEREVENT DISKUS. Your healthcare provider will decide if you can stop SEREVENT DISKUS without loss of asthma control. You will continue taking your long-term asthma-control medicine, such as an inhaled corticosteroid.**

4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

### **What is SEREVENT DISKUS?**

- SEREVENT DISKUS is a LABA medicine. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD) as follows:

#### **Asthma:**

SEREVENT DISKUS is used in adults and children aged 4 years and older, with a long-term asthma control medicine, such as an inhaled corticosteroid:

- to control symptoms of asthma, and
- to prevent symptoms such as wheezing.

LABA medicines, such as SEREVENT DISKUS, increase the risk of death from asthma problems. SEREVENT DISKUS is not for adults and children with asthma who are well controlled with a long-term asthma-control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.

#### **Exercise-Induced Bronchospasm:**

SEREVENT DISKUS is used to prevent wheezing caused by exercise in adults and children aged 4 years and older.

- If you have EIB only, your healthcare provider may prescribe only SEREVENT DISKUS for your condition.
- If you have EIB and asthma, your healthcare provider should also prescribe an asthma control medicine, such as an inhaled corticosteroid.

#### **Chronic Obstructive Pulmonary Disease:**

SEREVENT DISKUS is used long term, 2 times each day (morning and evening) to control symptoms of COPD and prevent wheezing in adults with COPD.

### **Who should not use SEREVENT DISKUS?**

#### **Do not take SEREVENT DISKUS:**

- to treat your asthma without an asthma medicine known as an inhaled corticosteroid
- if you are allergic to salmeterol or any of the ingredients in SEREVENT DISKUS. Ask your healthcare provider if you are not sure. See the end of this Medication Guide for a complete

997 list of ingredients in SEREVENT DISKUS.

998

999 **What should I tell my healthcare provider before using SEREVENT DISKUS?**

1000 Tell your healthcare provider about all of your health conditions, including if you:

1001 • have heart problems

1002 • have high blood pressure

1003 • have seizures

1004 • have thyroid problems

1005 • have diabetes

1006 • have liver problems

1007 • are pregnant or planning to become pregnant. It is not known if SEREVENT DISKUS may  
1008 harm your unborn baby.

1009 • are breastfeeding. It is not known if SEREVENT DISKUS passes into your milk and if it can  
1010 harm your baby.

1011 • are allergic to SEREVENT DISKUS, any other medicines, or food products. See the end of  
1012 this Medication Guide for a complete list of ingredients in SEREVENT DISKUS.

1013 Tell your healthcare provider about all the medicines you take including prescription and non-  
1014 prescription medicines, vitamins, and herbal supplements. SEREVENT DISKUS and certain  
1015 other medicines, especially those used to treat infections, may interact with each other. This may  
1016 cause serious side effects.

1017 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist  
1018 each time you get a new medicine.

1019

1020 **How do I use SEREVENT DISKUS?**

1021 See the step-by-step instructions for using the SEREVENT DISKUS at the end of this  
1022 Medication Guide. Do not use SEREVENT DISKUS unless your healthcare provider has taught  
1023 you and you understand everything. Ask your healthcare provider or pharmacist if you have any  
1024 questions.

1025 • Children should use SEREVENT DISKUS with an adult's help, as instructed by the child's  
1026 healthcare provider.

1027 • Use SEREVENT DISKUS exactly as prescribed. Do not use SEREVENT DISKUS more  
1028 often than prescribed.

1029 • For asthma and COPD, the usual dose is 1 inhalation 2 times each day (morning and  
1030 evening). The 2 doses should be about 12 hours apart.

1031 • For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before  
1032 exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra  
1033 SEREVENT DISKUS before exercise if you already use it 2 times each day.

- 1034 • If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your  
1035 usual time. Do not take 2 doses at one time.
- 1036 • Do not use a spacer device with SEREVENT DISKUS.
- 1037 • Do not breathe into SEREVENT DISKUS.
- 1038 • While you are using SEREVENT DISKUS 2 times each day, do not use other medicines that  
1039 contain a long-acting beta<sub>2</sub>-agonist or LABA for any reason. Ask your healthcare provider or  
1040 pharmacist for a list of these medicines.
- 1041 • Do not stop using SEREVENT DISKUS or any of your asthma medicines unless told to do  
1042 so by your healthcare provider because your symptoms might get worse. Your healthcare  
1043 provider will change your medicines as needed.
- 1044 • SEREVENT DISKUS does not relieve sudden symptoms. Always have a rescue inhaler  
1045 medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting  
1046 bronchodilator, contact your healthcare provider to have one prescribed for you.
- 1047 • Call your healthcare provider or get medical care right away if:
  - 1048 • your breathing problems worsen with SEREVENT DISKUS
  - 1049 • you need to use your rescue inhaler medicine more often than usual
  - 1050 • your rescue inhaler medicine does not work as well for you at relieving symptoms
  - 1051 • you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days  
1052 in a row
  - 1053 • you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
  - 1054 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers  
1055 that are right for you.
  - 1056 • you have asthma and your symptoms do not improve after using SEREVENT DISKUS  
1057 regularly for 1 week.
  - 1058 • after a change in your asthma medicines you have any worsening of your asthma  
1059 symptoms or an increase in the need for your rescue inhaler medicine.

1060

1061 **What are the possible side effects with SEREVENT DISKUS?**

1062 **SEREVENT DISKUS can cause serious side effects, including:**

- 1063 • **See “What is the most important information I should know about SEREVENT**  
1064 **DISKUS?”**
- 1065 • **serious allergic reactions.** Call your healthcare provider or get emergency medical care if  
1066 you get any of the following symptoms of a serious allergic reaction:
  - 1067 • rash
  - 1068 • hives
  - 1069 • swelling of the face, mouth, and tongue
  - 1070 • breathing problems.



1071 • **sudden breathing problems immediately after inhaling your medicine**

1072 • **effects on heart**

1073 • increased blood pressure

1074 • a fast and irregular heartbeat

1075 • chest pain

1076 • **effects on nervous system**

1077 • tremor

1078 • nervousness

1079 • **changes in blood (sugar, potassium)**

1080

1081 **Common side effects of SEREVENT DISKUS include:**

1082 **Asthma in adults and children:**

1083 • headache

1084 • nasal congestion

1085 • bronchitis

1086 • throat irritation

1087 • runny nose

1088 • flu

1089 **Chronic obstructive pulmonary disease:**

1090 • headache

1091 • musculoskeletal pain

1092 • throat irritation

1093 • cough

1094 • respiratory infection

1095 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1096 These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or  
1097 pharmacist for more information.

1098 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
1099 800-FDA-1088.

1100

1101 **How do I store SEREVENT DISKUS?**

1102 • Store SEREVENT DISKUS at room temperature between 68°F to 77°F (20°C to 25°C).  
1103 Keep in a dry place away from heat and sunlight.

1104 • Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or  
1105 after the dose indicator reads “0”, whichever comes first.

1106 • Keep SEREVENT DISKUS and all medicines out of the reach of children.

1107

1108 **General Information about SEREVENT DISKUS**

1109 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not  
1110 use SEREVENT DISKUS for a condition for which it was not prescribed. Do not give your  
1111 SEREVENT DISKUS to other people, even if they have the same condition that you have. It  
1112 may harm them.

1113 This Medication Guide summarizes the most important information about SEREVENT  
1114 DISKUS. If you would like more information, talk with your healthcare provider or pharmacist.  
1115 You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS  
1116 that was written for healthcare professionals. You can also contact the company that makes  
1117 SEREVENT DISKUS (toll free) at 1-888-825-5249 or at [www.serevent.com](http://www.serevent.com).

1118  
1119 **What are the ingredients in SEREVENT DISKUS?**

1120 Active ingredient: salmeterol xinafoate

1121 Inactive ingredient: lactose (contains milk proteins)

1122

1123 **Instructions for Using SEREVENT DISKUS**

1124 Follow the instructions below for using your SEREVENT DISKUS. **You will breathe in**  
1125 **(inhale) the medicine from the DISKUS.** If you have any questions, ask your healthcare  
1126 provider or pharmacist.



1127  
1128 Take the SEREVENT DISKUS out of the box and foil pouch. Write the **“Pouch opened”** and  
1129 **“Use by”** dates on the label on top of the DISKUS. **The “Use by” date is 6 weeks from date of**  
1130 **opening the pouch.**

1131

- The DISKUS will be in the closed position when the pouch is opened.

1133

- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*).



Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

## 1. OPEN

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (*see Figure 2*).



Figure 2

## 2. CLICK

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to use.



Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

### 3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out into the DISKUS mouthpiece.**



Figure 4

Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.



Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you

to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

**Remember:**

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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Research Triangle Park, NC 27709

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1219 SRD:4MG

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROAIR HFA safely and effectively. See full prescribing information for PROAIR HFA Inhalation Aerosol.

### PROAIR HFA (albuterol sulfate) INHALATION AEROSOL

Initial U.S. Approval: 1981

#### RECENT MAJOR CHANGES

Dosage and Administration

07/2010

#### INDICATIONS AND USAGE

PROAIR HFA Inhalation Aerosol is a beta<sub>2</sub>-adrenergic agonist indicated for:

- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. (1.1)
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

#### DOSAGE AND ADMINISTRATION

For oral inhalation only

- Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, one inhalation every 4 hours may be sufficient. (2.1)
- Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise. (2.2)
- Priming information: Prime PROAIR HFA before using for the first time, or when the inhaler has not been used for more than 2 weeks. To prime PROAIR HFA, release 3 sprays into the air away from the face. Shake well before each spray. (2.3)
- Cleaning information: At least once a week, wash the actuator with warm water, shake off excess, and air dry thoroughly. (2.3)

#### DOSAGE FORMS AND STRENGTHS

Inhalation Aerosol: Each actuation delivers 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base). Supplied in 8.5-g canister containing 200 actuations. (3)

#### CONTRAINDICATIONS

Hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol Components. (4)

#### WARNINGS AND PRECAUTIONS

- Life-threatening paradoxical bronchospasm may occur. Discontinue PROAIR HFA immediately and treat with alternative therapy. (5.1)
- Need for more doses of PROAIR HFA than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- PROAIR HFA is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular or convulsive disorders. (5.4, 5.7)
- Excessive use may be fatal. Do not exceed recommended dose. (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue PROAIR HFA immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

#### ADVERSE REACTIONS

Most common adverse reactions ( $\geq 3.0\%$  and  $>$ placebo) are headache, tachycardia, pain, dizziness, pharyngitis, and rhinitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-482-9522 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7)
- Beta-blockers: May decrease effectiveness of PROAIR HFA and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- Diuretics, or non-potassium sparing diuretics: May potentiate hypokalemia or ECG changes. Consider monitoring potassium levels. (7.2)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2010

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\*Sections or subsections omitted from the full prescribing information are not listed.



## 1 INDICATIONS AND USAGE

### 1.1 Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

### 1.2 Exercise-Induced Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Bronchospasm

For treatment of acute episodes of bronchospasm or prevention of symptoms associated with bronchospasm, the usual dosage for adults and children 4 years and older is two inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient.

### 2.2 Exercise-Induced Bronchospasm

The usual dosage for adults and children 4 years of age or older is two inhalations 15 to 30 minutes before exercise.

### 2.3 Administration Information

Administer PROAIR HFA by oral inhalation only. Shake well before each spray. To maintain proper use of this product and to prevent medication build-up and blockage, it is important to follow the cleaning directions carefully.

**Priming:** Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

**Cleaning:** As with all HFA-containing albuterol inhalers, to maintain proper use of this product and to prevent medication build-up and blockage, it is important to clean the plastic mouthpiece regularly. The inhaler may cease to deliver medication if the plastic actuator mouthpiece is not properly cleaned and dried. To clean: Wash the plastic mouthpiece with warm running water for 30 seconds, shake off excess water, and air dry thoroughly at least once a week. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage. If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, spray twice into the air away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly. [see *Patient Counseling Information* (17.8)].

## 3 DOSAGE FORMS & STRENGTHS

PROAIR HFA is an inhalation aerosol. PROAIR HFA is supplied as an 8.5 g/200 actuations pressurized aluminum canister with a red plastic actuator and white dust cap each in boxes of one. Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

## 4 CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate [see *Warnings and Precautions* (5.6)].

## **5 WARNINGS & PRECAUTIONS**

### **5.1 Paradoxical Bronchospasm**

PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

### **5.2 Deterioration of Asthma**

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

### **5.3 Use of Anti-inflammatory Agents**

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

### **5.4 Cardiovascular Effects**

PROAIR HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

### **5.5 Do Not Exceed Recommended Dose**

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

### **5.6 Immediate Hypersensitivity Reactions**

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR HFA Inhalation Aerosol.

### **5.7 Coexisting Conditions**

PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

### **5.8 Hypokalemia**

As with other beta-agonists, PROAIR HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to

produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

## 6 ADVERSE REACTIONS

Use of PROAIR HFA may be associated with the following:

- Paradoxical bronchospasm [see *Warnings and Precautions* (5.1)]
- Cardiovascular Effects [see *Warnings and Precautions* (5.4)]
- Immediate hypersensitivity reactions [see *Warnings and Precautions* (5.6)]
- Hypokalemia [see *Warnings and Precautions* (5.8)]

### 6.1 Clinical Trials Experience

A total of 1090 subjects were treated with PROAIR HFA Inhalation Aerosol, or with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol, during the worldwide clinical development program.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adult and Adolescents 12 Years of Age and Older:** The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*				
Body System/ Adverse Event (as Preferred Term)		PROAIR HFA Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2
* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.				

Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation

Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

**Pediatric Patients 4 to 11 Years of Age:** Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily) to a matching placebo HFA inhalation aerosol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

### **6.2 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of PROAIR HFA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

The following adverse events have been observed in postapproval use of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

## **7 DRUG INTERACTIONS**

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with PROAIR HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

### **7.1 Beta-Blockers**

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

### **7.2 Diuretics**

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

### **7.3 Digoxin**

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is

unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR HFA Inhalation Aerosol.

#### **7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants**

PROAIR HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

### **8 USE IN SPECIFIC POPULATIONS**

#### **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies of PROAIR HFA Inhalation Aerosol or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m<sup>2</sup> basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD.

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD [see *Nonclinical Toxicology* (13.2)].

#### **8.2 Labor and Delivery**

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta<sub>2</sub>-agonists, including albuterol.

#### **8.3 Nursing Mothers**

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR HFA Inhalation Aerosol are excreted in human milk.

Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### **8.4 Pediatric Use**

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for the treatment or prevention of bronchospasm in children 12 years of age and older with reversible obstructive airway disease is based on one 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, and one single-dose crossover study comparing doses of 90, 180, and 270 mcg with placebo in 58 patients [see *Clinical Studies (14.1)*]. The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 24 adults and adolescents with exercise-induced bronchospasm comparing doses of 180 mcg with placebo [see *Clinical Studies (14.2)*].

The safety of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is based on one 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo. The effectiveness of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR HFA 90 mcg and 180 mcg with placebo in 55 patients with asthma and a 3-week clinical trial using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol in 95 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol four times daily with placebo [see *Clinical Studies (14.1)*].

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

#### **8.5 Geriatric Use**

Clinical studies of PROAIR HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Warnings and Precautions (5.4, 5.7)*].

All beta<sub>2</sub>-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

### **10 OVERDOSAGE**

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR HFA Inhalation Aerosol.

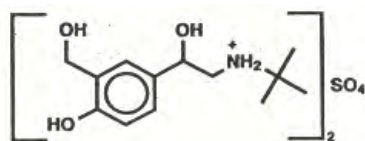
Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 3,200 times the maximum recommended daily inhalation dose

for children on a mg/m<sup>2</sup> basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). The inhalation median lethal dose has not been determined in animals.

## 11 DESCRIPTION

The active ingredient of PROAIR HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, a racemic salt, of albuterol. Albuterol sulfate has the chemical name  $\alpha^1$ -[(*tert*-butylamino) methyl]-4-hydroxy-*m*-xylene- $\alpha,\alpha'$ -diol sulfate (2:1) (salt), and has the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is (C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub>. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is the official generic name in the United States, and salbutamol sulfate is the World Health Organization recommended generic name. PROAIR HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane) and ethanol.

Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face. After priming, each actuation delivers 108 mcg albuterol sulfate, from the actuator mouthpiece (equivalent to 90 mcg of albuterol base). Each canister provides 200 actuations (inhalations).

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Albuterol sulfate is a beta<sub>2</sub>-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta<sub>2</sub>-adrenergic receptors on airway smooth muscle. Activation of beta<sub>2</sub>-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta<sub>2</sub>-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta<sub>2</sub>-adrenergic receptors. The precise function of these receptors has not been established [see *Warnings and Precautions* (5.4)].

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at

comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [see *Warnings and Precautions* (5.4)].

## 12.2 Pharmacokinetics

The systemic levels of albuterol are low after inhalation of recommended doses. In a crossover study conducted in healthy male and female volunteers, high cumulative doses of PROAIR HFA Inhalation Aerosol (1,080 mcg of albuterol base administered over one hour) yielded mean peak plasma concentrations ( $C_{max}$ ) and systemic exposure ( $AUC_{inf}$ ) of approximately 4,100 pg/mL and 28,426 pg/mL\*hr, respectively compared to approximately 3,900 pg/mL and 28,395 pg/mL\*hr, respectively following the same dose of an active HFA-134a albuterol inhaler comparator. The terminal plasma half-life of albuterol delivered by PROAIR HFA Inhalation Aerosol was approximately 6 hours. Comparison of the pharmacokinetic parameters demonstrated no differences between the products.

The pharmacokinetic profile of PROAIR HFA Inhalation Aerosol was evaluated in a two-way cross-over study in 11 healthy pediatric volunteers, 4 to 11 years of age. A single dose administration of PROAIR HFA Inhalation Aerosol (180 mcg albuterol base) yielded a least square mean (SE)  $C_{max}$  and  $AUC_{0-\infty}$  of 1,100 (1.18) pg/mL and 5,120 (1.15) pg/mL\*hr, respectively. The least square mean (SE) terminal plasma half-life of albuterol delivered by PROAIR HFA Inhalation Aerosol was 166 (7.8) minutes.

**Metabolism and Elimination:** Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULT1A3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULT1A3.

The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

**Geriatric, Pediatric, Hepatic/Renal Impairment:** No pharmacokinetic studies for PROAIR HFA Inhalation Aerosol have been conducted in neonates or elderly subjects.

The effect of hepatic impairment on the pharmacokinetics of PROAIR HFA Inhalation Aerosol has not been evaluated.

The effect of renal impairment on the pharmacokinetics of albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in albuterol clearance. Caution should be used when administering high doses of PROAIR HFA Inhalation Aerosol to patients with renal impairment [see *Use in Specific Populations* (8.5)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In another study this effect was blocked by the coadministration



of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 740 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 210 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 100 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

### **13.2 Animal Toxicology and/or Pharmacology**

**Preclinical:** Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when  $\beta$ -agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 - 1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 - 27 minutes in animals and 5 - 7 minutes in humans. Time to maximum plasma concentration ( $T_{max}$ ) and mean residence time are both extremely short leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

**Reproductive Toxicology Studies:** A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 fetuses (37%) when albuterol sulfate was administered orally at 50 mg/kg (approximately 630 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

In an inhalation reproduction study in Sprague-Dawley rats, the albuterol sulfate/HFA-134a did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

## 14 CLINICAL STUDIES

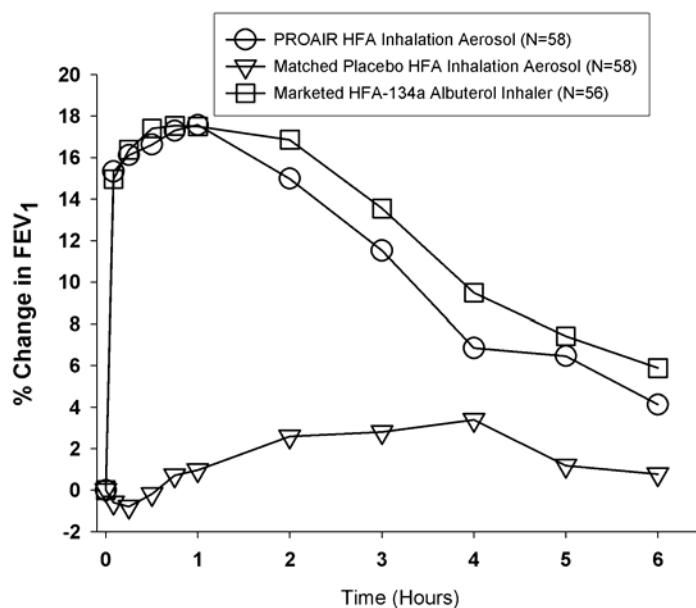
### 14.1 Bronchospasm Associated with Asthma

**Adult and Adolescent Patients 12 Years of Age and Older:** In a 6-week, randomized, double-blind, placebo-controlled trial, PROAIR HFA Inhalation Aerosol (58 patients) was compared to a matched placebo HFA inhalation aerosol (58 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. An evaluator-blind marketed active comparator HFA-134a albuterol inhaler arm (56 patients) was included.

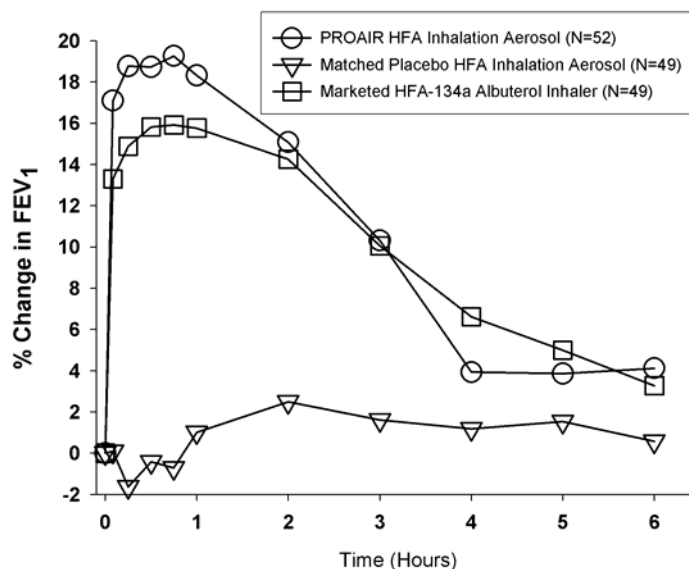
Serial FEV<sub>1</sub> measurements, shown below as percent change from test-day baseline at Day 1 and at Day 43, demonstrated that two inhalations of PROAIR HFA Inhalation Aerosol produced significantly greater improvement in FEV<sub>1</sub> over the pre-treatment value than the matched placebo, as well as a comparable bronchodilator effect to the marketed active comparator HFA-134a albuterol inhaler.

#### FEV<sub>1</sub> as Mean Percent Change from Test-Day Pre-Dose in a 6-Week Clinical Trial

Day 1



Day 43



In this study, 31 of 58 patients treated with PROAIR HFA Inhalation Aerosol achieved a 15% increase in FEV<sub>1</sub> within 30 minutes post-dose on Day 1. In these patients, the median time to onset, median time to peak effect, and median duration of effect were 8.2 minutes, 47 minutes, and approximately 3 hours, respectively. In some patients, the duration of effect was as long as 6 hours.

In a placebo-controlled, single-dose, crossover study, PROAIR HFA Inhalation Aerosol, administered at albuterol doses of 90, 180 and 270 mcg, produced bronchodilator responses significantly greater than those observed with a matched placebo HFA inhalation aerosol and comparable to a marketed active comparator HFA-134a albuterol inhaler.

**Pediatric Patients 4 to 11 Years of Age:** In a 3-week, randomized, double-blind, placebo-controlled trial, the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (50 patients) was compared to a matched placebo HFA inhalation aerosol (45 patients) in asthmatic children 4 to 11 years of age at a dose of 180 mcg albuterol four times daily. Serial FEV<sub>1</sub> measurements, expressed as the maximum percent change from test-day baseline in percent predicted FEV<sub>1</sub> at Day 1 and at Day 22 observed within two hours post-dose, demonstrated that two inhalations of HFA albuterol sulfate produced significantly greater improvement in FEV<sub>1</sub> over the pre-treatment value than the matched placebo.

In this study, 21 of 50 pediatric patients treated with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol achieved a 15% increase in FEV<sub>1</sub> within 30 minutes post-dose on Day 1. In these patients, the median time to onset, median time to peak effect and median duration of effect were 10 minutes, 31 minutes, and approximately 4 hours, respectively. In some pediatric patients, the duration of effect was as long as 6 hours.

In a placebo-controlled, single-dose, crossover study in 55 pediatric patients 4 to 11 years of age, PROAIR HFA Inhalation Aerosol, administered at albuterol doses of 90 and 180 mcg, was compared with a matched placebo HFA inhalation aerosol. Serial FEV<sub>1</sub> measurements, expressed as the baseline-adjusted percent predicted FEV<sub>1</sub> observed over 6 hours post-dose, demonstrated that one and two inhalations of PROAIR HFA Inhalation Aerosol produced significantly greater bronchodilator responses than the matched placebo.

#### **14.2 Exercise-Induced Bronchospasm**

In a randomized, single-dose, crossover study in 24 adults and adolescents with exercise-induced bronchospasm (EIB), two inhalations of PROAIR HFA taken 30 minutes

before exercise prevented EIB for the hour following exercise (defined as maintenance of FEV<sub>1</sub> within 80% of post-dose, pre-exercise baseline values) in 83% (20 of 24) of patients as compared to 25% (6 of 24) of patients when they received placebo.

Some patients who participated in these clinical trials were using concomitant steroid therapy.

## **16 HOW SUPPLIED/STORAGE & HANDLING**

PROAIR HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister with a red plastic actuator and white dust cap each in boxes of one. Each canister contains 8.5 g of the formulation and provides 200 actuations (NDC 59310-579-20). Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

**SHAKE WELL BEFORE USE.** Store between 15° and 25°C (59° and 77°F). Contents under pressure. Do not puncture or incinerate. Protect from freezing temperatures and prolonged exposure to direct sunlight. Exposure to temperatures above 120°F may cause bursting. For best results, canister should be at room temperature before use. Avoid spraying in eyes. Keep out of reach of children.

See FDA-Approved Patient Labeling (17.8) for priming and cleaning instructions.

The red actuator supplied with PROAIR HFA Inhalation Aerosol should not be used with the canister from any other inhalation aerosol products. The PROAIR HFA Inhalation Aerosol canister should not be used with the actuator from any other inhalation aerosol products.

The labeled amount of medication in each actuation cannot be assured after 200 actuations, even though the canister may not be completely empty. Discard the inhaler (canister plus actuator) after 200 actuations have been used. Never immerse the canister into water to determine how full the canister is ("float test").

PROAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

## **17 PATIENT COUNSELING INFORMATION**

See FDA-Approved Patient Labeling (17.8)

Patients should be given the following information:

### **17.1 Frequency of Use**

The action of PROAIR HFA Inhalation Aerosol should last for 4 to 6 hours. Do not use PROAIR HFA Inhalation Aerosol more frequently than recommended. Instruct patients to not increase the dose or frequency of doses of PROAIR HFA Inhalation Aerosol without consulting the physician. If patients find that treatment with PROAIR HFA Inhalation Aerosol becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual, they should seek medical attention immediately.

### **17.2 Priming and Cleaning**

**Priming:** Priming is essential to ensure appropriate albuterol content in each actuation. Instruct patients to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

**Cleaning:** To ensure proper dosing and prevent actuator orifice blockage, instruct patients to wash the red plastic actuator mouthpiece and dry thoroughly at least once a week. Detailed cleaning instructions are included in the illustrated Information for the Patient leaflet.

### **17.3 Paradoxical Bronchospasm**

Inform patients that PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm. Instruct patients to discontinue PROAIR HFA Inhalation Aerosol if paradoxical bronchospasm occurs.

### **17.4 Concomitant Drug Use**

While patients are taking PROAIR HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by a physician.

#### **17.5 Common Adverse Events**

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

#### **17.6 Pregnancy**

Patients who are pregnant or nursing should contact their physician about the use of PROAIR HFA Inhalation Aerosol.

#### **17.7 General Information on Use**

Effective and safe use of PROAIR HFA Inhalation Aerosol includes an understanding of the way that it should be administered.

Shake well before each spray.

Use PROAIR HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been used. Never immerse the canister in water to determine how full the canister is ("float test").

In general, the technique for administering PROAIR HFA Inhalation Aerosol to children is similar to that for adults. Children should use PROAIR HFA Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

#### **17.8 FDA-Approved Patient Labeling**

See tear-off illustrated Information for the Patient leaflet below.

U.S. Patent Nos. 5605674, 5695743, 7105152, 7566445

Mktd by: Teva Respiratory, LLC  
Horsham, PA 19044

Mfd by: IVAX Pharmaceuticals Ireland  
Waterford, Ireland

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| Manufactured In Ireland

PE XXXX Rev. 07/10

Attention Pharmacist:  
Detach Patient's Instructions for use from package insert and dispense with the product.

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### Information for the Patient

## **PROAIR<sup>®</sup> HFA (albuterol sulfate) Inhalation Aerosol**

Read this leaflet carefully before you start to use PROAIR HFA.

Keep this leaflet because it has important summary information about PROAIR HFA. Your healthcare provider has more information or advice.

Read the new leaflet that comes with each refill of your prescription because there may be new information.

### **What is PROAIR HFA?**

PROAIR HFA is a kind of medicine called a fast-acting bronchodilator. Fast-acting bronchodilators help to quickly open the airways in your lungs so that you can breathe more easily.

Each dose of PROAIR HFA should last up to 4 to 6 hours.

Take PROAIR HFA as directed by your doctor. Do not take extra doses or take more often without asking your doctor.

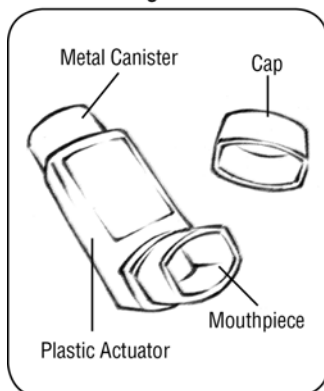
Get medical help right away if PROAIR HFA no longer helps your symptoms. Also get medical help if your symptoms get worse or if you need to use your inhaler more often.

While you are using PROAIR HFA, use other inhaled medicines and asthma medicines only as directed by your doctor. Tell your doctor if you are pregnant or nursing, and ask about the use of PROAIR HFA.

Possible side effects of taking PROAIR HFA include fast or irregular heartbeat, chest pain, shakiness, and nervousness. With the first use of a new canister, worsening of wheezing may occur.

### **The parts of your PROAIR HFA inhaler:**

**Figure 1**



There are 2 main parts to your PROAIR HFA inhaler—the metal canister that holds the medicine and the red plastic actuator that sprays the medicine from the canister (see Figure 1).

The inhaler also has a cap that covers the mouthpiece of the actuator.

**Do not use the PROAIR HFA actuator with a canister of medicine from any other inhaler. And do not use a PROAIR HFA canister with an actuator from any other inhaler.**

### How to Use Your PROAIR HFA

#### Before using your PROAIR HFA:

If a child needs help using the inhaler, an adult should help the child use the inhaler. An adult should watch a child use the inhaler to be sure it is used correctly.

The inhaler should be at room temperature before you use it.

Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the mouthpiece to make sure there are no foreign objects there, especially if the cap is not being used to cover the mouthpiece.

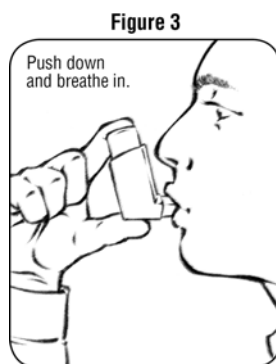
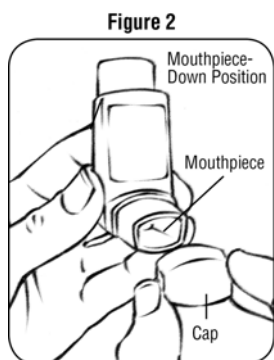
#### Priming your PROAIR HFA:

You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time or if you have not used it for more than 14 days. To prime the inhaler, take the cap off the mouthpiece of the actuator. Then shake the inhaler well, and spray it into the air away from your face. Shake and spray the inhaler like this 2 more times to finish priming it.

#### Instructions for taking a dose from your PROAIR HFA:

Read through the 6 steps below before using PROAIR HFA. If you have any questions, ask your doctor or pharmacist.

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** before each spray.
2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.
3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.



4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.
5. If your doctor has prescribed more sprays, wait 1 minute and **shake** the inhaler again. Repeat steps 2 through 4.

6. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

### When to Replace Your PROAIR HFA

- **Before you reach 200 sprays**, you should refill your prescription or ask your doctor if you need another prescription for PROAIR HFA.
- **Throw the inhaler away** when you have used 200 sprays. You should not keep using the inhaler after 200 sprays even though the canister may not be completely empty because you cannot be sure you will receive any medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

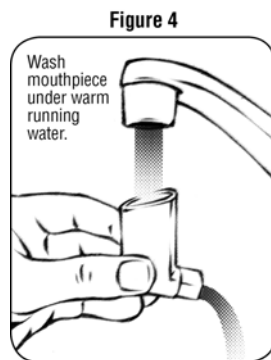
### How to Clean Your PROAIR HFA

**It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. Do not try to clean the metal canister or let it get wet.** The inhaler may stop spraying if it is not cleaned correctly.

Wash the actuator at least once a week.

#### Cleaning instructions:

- Take the canister out of the actuator, and take the cap off the mouthpiece.
- Wash the actuator through the top with warm running water for 30 seconds (see Figure 4). Then wash the actuator again through the mouthpiece (see Figure 5).



- Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat steps in Figures 4 and 5.
- Let the actuator air-dry completely, such as overnight (see Figure 6).

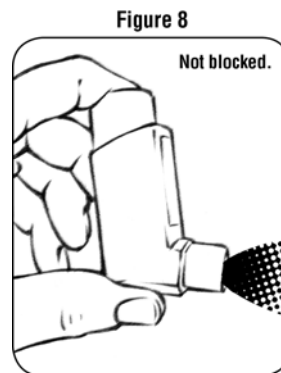
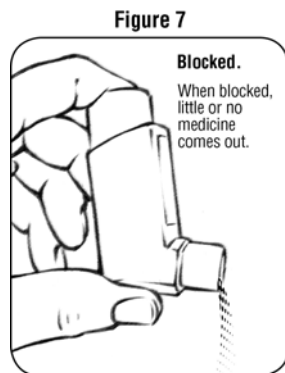




- When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it twice into the air away from your face. Put the cap back on the mouthpiece.

#### **If your actuator becomes blocked:**

Blockage from medicine build-up is more likely to happen if you do not let the actuator air-dry completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece (see Figures 7 and 8), wash the actuator as described in the “Cleaning Instructions” section above.



**However, if you need to use your inhaler before the actuator is completely dry, shake as much water off the actuator as you can.** Put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it twice into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

#### **Storing Your PROAIR HFA**

Store between 15° and 25° C (59° and 77° F). Avoid exposure to extreme heat and cold. For best results, canister should be at room temperature.

**Shake well before use.**

**Contents Under Pressure.** Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

Avoid spraying in eyes. Keep out of reach of children.

For questions related to proper use and maintenance of your PROAIR HFA inhaler, please call Teva Respiratory customer service at 1-888-482-9522.

Mktd by: Teva Respiratory, LLC  
Horsham, PA 19044

Mfd by: IVAX Pharmaceuticals Ireland  
Waterford, Ireland

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| Manufactured In Ireland

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# Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment

## ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Dr. Badrul A. Chowdhury at 301-827-1050.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**November 2007  
Clinical/Medical**

# **Guidance for Industry**

## **Chronic Obstructive Pulmonary**

### **Disease: Developing Drugs**

### **for Treatment**

*Additional copies are available from:*

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**November 2007  
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**Guidance for Industry<sup>1</sup>**  
**Chronic Obstructive Pulmonary Disease:**  
**Developing Drugs for Treatment**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This guidance is intended to assist the pharmaceutical industry in designing a clinical development program for new drug products<sup>2</sup> for the treatment of chronic obstructive pulmonary disease (COPD). The emphasis of this guidance is on the assessment of efficacy of a new molecular entity (NME) in phase 3 clinical studies of COPD.

Development of NMEs for COPD poses challenges and opportunities. This guidance outlines the Food and Drug Administration's (FDA's) current thinking on the development of various types of drugs for COPD. Not all drugs developed for COPD will fit into the types described, and the efficacy endpoints discussed in this guidance may not fit the need for all drugs. The FDA encourages pharmaceutical sponsors to develop clinical programs that fit their particular needs and to discuss their planned approach with the Division of Pulmonary and Allergy Products. For novel approaches, where warranted, outside expertise can be sought, including consultation with the Pulmonary-Allergy Drugs Advisory Committee.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.<sup>3</sup> This

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<sup>1</sup> This guidance has been prepared by the Division of Pulmonary and Allergy Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> In this guidance, the word *drug* includes all types of therapeutic agents, such as small and large molecule drugs, and therapeutic biological products, regulated within CDER.

<sup>3</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

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guidance focuses on specific drug development and trial design issues that are unique to the study of COPD.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

COPD is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma, and is usually associated with tobacco smoking or prolonged exposure to other noxious particles and gasses. The disease is characterized by progressive airflow obstruction that is sometimes partially reversible with the administration of a bronchodilator. There is heterogeneity in disease activity and in the nature of symptomatic impairment experienced by patients. The typical symptoms are cough, excess sputum production, and dyspnea. The term COPD encompasses a spectrum of pulmonary processes, with chronic bronchitis and emphysema as two clearly defined entities within that spectrum. Various consensus panels and position papers have defined and described COPD (see References).

There is pressing need to develop new drugs for COPD because the global prevalence of COPD is rising, the disease is associated with significant morbidity and mortality, and current treatment options are limited. The currently available drugs for COPD are mostly for symptomatic treatment and have not been conclusively shown to alter the underlying inflammation or to alter disease progression. The principles of development applied to COPD drugs have been generally derived from those used to develop drugs for asthma, with the primary focus aimed at demonstrating improvements in airway obstruction. With improved understanding of the pathophysiology and clinical manifestations of COPD, and the awareness of the importance of inflammation in COPD and how this inflammation differs from that occurring in asthma, this is an appropriate time to define characteristics of specific drug development programs for COPD.

## **III. DEVELOPMENT PROGRAM**

### **A. Overall Considerations**

#### ***1. Disease Target and Indication***

The clinical development program should define whether the target of the program is the whole spectrum of COPD patients or patients with only one of its clearly defined entities, such as chronic bronchitis or emphysema. Since chronic bronchitis and emphysema are histologically and clinically distinct entities, we recognize that a drug may be effective for one and not the

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other. Therefore, it is helpful to define early in the development program the specific indicated population the clinical development program is proposed to support.

### ***2. Types of Drugs for COPD***

There are several types of drugs that can be developed for COPD based on whether the drug is intended to improve airflow obstruction, provide symptom relief, modify or prevent exacerbations, or alter the natural progression of the disease. It is possible that a drug may affect only one aspect of the disease or that it may act on many. It is also possible that a drug may benefit COPD patients in other meaningful ways beyond these areas cited. Therefore, whereas this guidance focuses on established areas of research or intervention, the division welcomes other proposals. Novel proposals, in particular, can benefit from early discussions with the division, such as in a pre-investigational new drug application meeting.

Each of the following targets in COPD therapy can involve different endpoints, study designs, and study duration, and can likely lead to differing explicit indications. Therefore, it is important for sponsors to develop their drugs with the appropriate drug action or actions in mind.

#### ***a. Improving airflow obstruction***

Improvement in airflow obstruction historically has been the main therapeutic strategy in COPD drug development. These drugs provide benefit through relief of reversible airflow obstruction that is an important, though not universal, feature of COPD. Improvement in airflow obstruction can result from direct relaxation of the airway smooth muscles, or by other mechanisms such as reduction of airway inflammation or improved clearance of mucous in chronic bronchitis.

#### ***b. Providing symptom relief***

Drugs that reduce chronic cough, excess sputum production, dyspnea, or other debilitating symptoms of COPD may provide meaningful benefit to patients. Drugs may provide symptom relief either by acting centrally or by acting within the lung. Drugs that relieve dyspnea usually accomplish this by improving airflow obstruction. It is also possible that drugs may target the sensation of dyspnea independent of effects on airflow obstruction. The division has concerns about granting a specific COPD claim for drugs that relieve dyspnea without otherwise benefiting the lung process. For instance, systemic opiates or benzodiazepines may reduce the sensation of dyspnea, but would not otherwise specifically benefit a COPD patient and, therefore, would not be appropriate drugs for granting a specific claim of treating COPD.

#### ***c. Modifying or preventing exacerbations***

COPD exacerbations can be life-threatening and have been linked to comorbid conditions. In addition, exacerbations are believed to potentially contribute to further permanent decrements in lung function. Therapeutic drugs that modify the severity or duration of COPD exacerbations or that prevent COPD exacerbations will provide meaningful benefit to patients.



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### d. Altering disease progression

There is ongoing research to identify therapies that modify the inflammatory processes of COPD and thereby may alter disease progression. Drugs aimed at attenuating ongoing lung damage in COPD may not yield direct discernable symptomatic benefit to patients, at least in the course of clinical studies, nor short-term improvement in lung function, but would, if effective, have longer term tangible benefits by delaying the development of COPD-related disability or death. Such drugs will provide meaningful benefit to patients with COPD.

### e. Modifying lung structure

Damage of lung structure is a known feature of COPD progression. At present there are no clear strategies that can modify or regenerate damaged lung tissue, but some drugs have shown promise in animal studies. Drugs that can modify damaged lung structure and generate functional lung tissues will be of benefit to patients with COPD.

## 3. *Drug Development Population*

Because COPD represents a spectrum of pathology and manifestations, a therapy can target COPD broadly (e.g., as defined by American Thoracic Society criteria or other expert consensus statement) or specifically target subsets of the disease, such as emphysema or chronic bronchitis. This depends to a large extent on the mechanism of action of the drug being proposed. If a sponsor chooses to study a restricted subset of COPD either by specific intent or by the choice of entry criteria used, the indication would be appropriately restricted to the subset as well. Because emphysema and chronic bronchitis frequently coexist, it may be difficult to define clinical entry criteria sufficient to enroll patients with only one of these COPD subsets. Sponsors who intend to develop a drug for one subset should adequately address this issue.

## 4. *Dose Selection*

The dose or doses of drugs for definitive phase 3 efficacy and safety studies should be selected based on pharmacokinetic considerations and from earlier phase dose-ranging studies using a pharmacodynamic (PD) or clinical efficacy endpoint that is consistent with the expected benefit to be derived from the drug. The dose or doses selected for phase 3 studies should be based on benefit to risk assessment. If more than one dose is ultimately intended to be marketed, the clinical program design should produce data that allow for a comparative assessment of efficacy and safety between the doses in addition to the usual comparison of the doses of the new drug to placebo. In circumstances where PD measures are used in phase 2 for dose identification, there is merit in considering including more than one dose level in at least one phase 3 study, even if the goal is to market a single dose. This is because even a well-validated PD endpoint may not fully predict efficacy as assessed by a clinical outcome endpoint in larger, longer term phase 3 studies, and usually will not be predictive of safety. Finally, with some treatment targets, there may be no known short-term PD or clinical endpoint that can be identified for dose-selection. This may be true, for instance, in disease modification therapies that do not affect short-term symptoms or lung function testing. In such cases, use of a range of doses in phase 3 studies is strongly encouraged.

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### 5. *Efficacy Assessment*

The selection of efficacy endpoints for phase 3 studies depends on the drug's putative mechanism of action and the type of therapeutic claim sought. In the following sections, some efficacy endpoints that can be used in COPD studies are briefly discussed and grouped into broad categories of objective physiological assessments, patient- or evaluator-reported outcome measures, and biomarkers and surrogate endpoints. We recognize that not all efficacy endpoints will be appropriate for all drugs and other efficacy endpoints not discussed may be more appropriate for an NME.

#### a. Objective physiological assessments

The following objective physiological assessments should be considered.

- **Pulmonary function tests.** Pulmonary function testing by spirometry can be a useful way to assess airflow obstruction and, therefore, can be a useful tool to assess efficacy of a COPD treatment. Forced expiratory volume in one second (FEV1) obtained from typical spirometry is commonly used as an efficacy endpoint because FEV1 is a reflection of the extent of airway obstruction. Spirometry is also well standardized, easy to perform, and when conducted appropriately gives consistent, reproducible results across different pulmonary function laboratories. Air-trapping and hyperinflation are common features in COPD, particularly in the emphysematous-type, and are reflected in parameters of lung function testing, such as an elevation in the residual volume to total lung capacity ratio (RV/TLC). Hyperinflation is believed to be responsible, at least in part, for the sensation of dyspnea. The division does not have a great deal of regulatory experience in the use of parameters of lung function other than spirometric measures in therapeutic approvals, but is open to considering alternative assessments. These alternatives should be discussed with the division early in drug development.
- **Exercise capacity.** Reduced capacity for exercise is a typical consequence of airflow obstruction in COPD patients, particularly because of dynamic hyperinflation occurring during exercise. Assessment of exercise capacity by treadmill or cycle ergometry combined with lung volume assessment potentially can be a tool to assess efficacy of a drug. Alternate assessments of exercise capacity, such as the Six Minute Walk or Shuttle Walk, also can be used. However, all these assessments have limitations. For instance, the Six Minute Walk test reflects not only physiological capacity for exercise, but also psychological motivation. Some of these assessments are not rigorously precise and may prove difficult in standardizing and garnering consistent results over time. These factors may limit the sensitivity of these measures and, therefore, limit their utility as efficacy endpoints, since true, but small, clinical benefits may be obscured by measurement *noise*.

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### b. Patient- or evaluator-reported outcome measures

The following outcome measures should be considered.

- **Symptom scores.** Symptom scores determined by asking patients to evaluate specific symptoms on a categorical, visual, or numerical scale can be a simple way to assess efficacy of a drug based on the patient's own assessment of health status. Symptom scores can be valuable for assessing efficacy of a drug specifically aimed at relieving a symptom. In clinical programs aimed at other aspects of COPD, patient-reported symptom scores can be useful in assessing secondary effects of the therapy and may provide important additional evidence of efficacy. Symptom scores as the sole measure or primary measure of efficacy in COPD are discouraged because of their subjective nature, precision issues, and lack of standardization. If a symptom score is used, particularly a novel scoring, the issue of validation of the scoring should be addressed.
- **Activity scales.** Activity scales such as the Medical Research Council dyspnea score, the Borg Scale, and the Mahler Baseline Dyspnea Index/Transitional Dyspnea Index can be used as supportive of efficacy. These scales are relatively simple to administer, but they have limitations that make them unsuitable for use as the sole or primary evidence of efficacy and for supporting specific labeling claims. These scales were not specifically developed for use in clinical studies of drugs and their attributes in longitudinal interventional settings may not be fully elucidated. Also, the results can be difficult to interpret in terms of levels of clinical significance, because for some of these scales the minimal important difference has not been identified and validated. Scales that are third-party rated (e.g., Mahler's dyspnea indices) may prove less compelling than validated patient-rated instruments, as third-party assessments have been shown in some circumstances to be less reflective of patient status than first-party assessments. In addition, scales that require patients to recall prior symptoms (e.g., how do you feel now compared to baseline?) are problematic, because patients' memory may fade over time, particularly in studies lasting several months.
- **Health-related quality-of-life instruments.** Health-related quality-of-life instruments, such as the St. George's Respiratory Questionnaire and the Chronic Respiratory Questionnaire, are designed to systematically assess many different aspects of the effect of COPD on a patient's life. These instruments can be used to assess efficacy of a drug, but they have some limitations. These instruments are multidimensional and assess various effects of the disease on a patient's life and health status. Therefore, these instruments may be insufficient to determine a treatment effect in cases of a drug narrowly targeted to a specific, but clinically meaningful aspect, of COPD. When they are used to assess efficacy in the setting of multinational trials, the instruments should be validated for all languages and cultures in which the studies are conducted.

### c. Biomarkers and surrogate endpoints

With the exception of lung function tests, there are no well-validated biomarkers or surrogate endpoints that can be used to establish efficacy of a drug for COPD. For a nonbronchodilator

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drug, the use of lung function test parameters, such as FEV<sub>1</sub>, as a marker of disease status has become *validated* as a surrogate endpoint through years of clinical and regulatory experience, and is commonly used and accepted as an endpoint to support efficacy.

There are many biomarkers that can be considered for use in clinical studies. Some of these biomarkers include sensitive radiological evaluation of lung tissue structure (such as high-resolution chest computed tomography (CT)), concentration of certain gases in exhaled air or breath condensate, inflammatory mediators or cells in relevant biological fluids, and sensitive measures of airflow based on imaging of radiolabeled gases. With the possible exception of the high-resolution CT, none of these biomarkers are sufficiently validated to date for use as the primary evidence of efficacy or for supporting specific labeling claims. Some of the biomarkers may be technically challenging to perform or present important additional considerations (e.g., total X-ray dose exposure in patients subjected to multiple serial CT scans). These biomarkers and surrogates can be considered as supportive of the drug's putative mechanism of action. If proposed as primary assessments of efficacy, discussions with the division early on in development would be useful to allow for earlier phase studies to not only test the drug, but help establish validity of the measure itself. A single study should not be used to establish both the validity of a novel primary endpoint and the efficacy of the drug in question.

### *6. Recommended Primary and Secondary Efficacy Endpoints*

For phase 3 studies, the primary and secondary efficacy endpoints should be chosen based on the drug's putative mechanism of action and the proposed indication. It is not possible to categorically state in all cases what the primary and secondary efficacy endpoints should be. Some common efficacy endpoints that may be suitable for use in the clinical studies of different types of drugs for COPD are mentioned in the following sections.

#### *a. Primary efficacy endpoints*

The following primary efficacy endpoints should be considered for the respective indications.

- **Improving airflow obstruction.** The primary efficacy endpoint should be change in post-dose FEV<sub>1</sub> for a bronchodilator (e.g., a new beta-adrenergic agent or a new anticholinergic agent) and change in pre-dose FEV<sub>1</sub> for a nonbronchodilator. A bronchodilator drug may improve the FEV<sub>1</sub> from a direct effect on the airway smooth muscle, and a nonbronchodilator drug may improve the FEV<sub>1</sub> by other mechanisms such as reduction of airway inflammation. For a bronchodilator drug, serial post-dose FEV<sub>1</sub> assessments should be performed to characterize a time profile curve that will help in the estimation of time to effect and duration of effect. Assessments of post-dose FEV<sub>1</sub> for a bronchodilator drug and pre-dose FEV<sub>1</sub> for a nonbronchodilator drug should be performed periodically over the duration of the study to ensure that the beneficial effect is sustained over time.
- **Providing symptom relief.** The primary efficacy endpoint should reflect the claimed clinical benefit (e.g., a drug intended to reduce cough should show that effect through assessments of coughing, subjectively and/or objectively measured). The selected

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primary efficacy endpoint should be clinically meaningful, and the magnitude of improvement that is proposed to be shown should be clinically relevant. In addition, if the action of the drug targets the underlying process, but manifests as symptom relief, secondary endpoints should assess other aspects of the drug's effects (e.g., measures of lung function, airflow, sputum production).

- **Modifying or preventing exacerbations.** The primary efficacy endpoint should be a clinically meaningful measure of exacerbations. Such measures can include the duration of exacerbations, severity of exacerbations, delay in the occurrence of an exacerbation, or reduction in the frequency of exacerbations. If one of these measures is chosen as the primary efficacy endpoint, the others also should be assessed to ensure that some other measure has not worsened. For instance, a delay in occurrence of a first exacerbation would not be clinically meaningful if the end result were more frequent exacerbations over a longer period of assessment. The protocol should define exacerbations in a way that is clinically meaningful, and specify criteria to determine when worsening of symptoms become an exacerbation. Criteria to consider in defining exacerbation include worsening of shortness of breath, increased sputum volume, increased purulence of sputum, worsening in symptoms requiring changes in treatment, or worsening of symptoms requiring urgent treatment or hospitalization. Since exacerbations are often associated with precipitous falls in airflow, the rapidity of recovery of a pulmonary function measure, such as FEV1, following an exacerbation to pre-exacerbation status also can be considered a reasonable primary efficacy endpoint.
- **Altering disease progression.** A preferred primary efficacy endpoint is the serial measurement of FEV1 over time, with the expectation that the FEV1 decline slopes will diverge in favor of active treatment (i.e., airflow is preserved relative to the comparator). When the claim is alteration of disease progression, such divergence should exclude the possibility of parallel declines in FEV1 with the active treatment offset by an initial and sustained bronchodilator effect. This latter circumstance may still be one in which a drug approval is possible (e.g., for a bronchodilation claim), but would not be appropriate for supporting a claim of altering disease progression.
- **Modifying lung structure.** The primary efficacy endpoint can be a sensitive radiological assessment of lung structure with supportive evidence that the regenerated lung tissue is functional and that the treatment provides clinically meaningful benefit to patients.

### b. Secondary efficacy endpoints

Secondary efficacy endpoints can provide useful information on the effect of the treatment and should be carefully selected to provide support to the primary efficacy endpoint. Secondary efficacy endpoints also can explore other effects of the drug on the disease. Commonly used secondary efficacy endpoints include various measures of lung function, exercise capacity, symptom scores, activity scales, and health-related quality-of-life instruments. Biomarkers can, in some cases, also provide support of efficacy. For some efficacy measures, such as symptom scores, activity scales, and disease-specific, health-related quality-of-life instruments, the

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threshold that defines a clinically meaningful improvement may not be well defined for use in clinical studies that test new drugs. Having such a *benchmark* of effect would be important in interpreting the meaning of differences shown in the clinical trials. Therefore, the study protocol should define minimal clinically important difference with appropriate reasoning and justification. Consideration also should be given to the added complexity of the use of these measures in clinical studies for drugs, such as comparisons to baseline, comparisons to placebo, multiplicity, missing data, and the effect of study duration (e.g., recall of baseline status over time).

In studies where an objective measure is used as an endpoint, such as FEV<sub>1</sub>, use of subjective measures as important secondary assessments may be particularly useful in judging the value of mean changes in the primary endpoint. Similarly, in treatments intended to affect subjective perceptions of the disease through an effect on the underlying pathophysiology of COPD, secondary objective measures also can provide useful additional assessments to support the efficacy of the drug.

### 7. Study Duration

The duration of active treatment in the phase 3 studies that will support efficacy depends on the type of drug being developed, because different types of drugs will need different periods to show clinically meaningful effect. Differing claims also will demand differing durations of assessments.

- **Improving airflow obstruction:** the duration of treatment should be at least 3 months for a bronchodilator drug and at least 6 months for a nonbronchodilator drug. This is both to establish durable efficacy and to assess safety.
- **Symptom relief:** the duration of treatment should be at least 6 months.
- **Modifying or preventing exacerbations:** the duration of treatment may need to be at least 1 year. In studies for this type of claim, the timing of study treatment may prove important (e.g., capturing winter *cold* season in the majority of patients).
- **Altering disease progression:** the duration of treatment normally should be at least 3 years.
- **Modifying lung structure:** the duration of treatment will vary depending on the expected magnitude of clinically meaningful benefit, but likely will be several years in duration.

The durations of treatment described here refer to the portion of the clinical study intended to support efficacy. Longer durations of treatment may be needed to adequately assess safety.

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### **8. *Number of Studies***

The number of studies that will support efficacy depends on the type of drug that is being developed. Generally, two confirmatory phase 3 studies should be conducted to establish efficacy for a drug being developed to improve airflow obstruction, provide symptom relief, or modify or prevent exacerbations. The two studies should provide replicated evidence of efficacy, but need not be identical in design. For a drug being developed to alter disease progression or modify lung structure, a single confirmatory study may be appropriate, provided the study is reasonably large, the endpoint is well validated, the findings are robust and clinically persuasive, and there is sufficient weight of evidence from prior data to suggest a clear benefit of the treatment.

### **9. *Considerations Regarding Demonstration of Efficacy***

For most drugs, phase 3 studies that use a single primary efficacy endpoint with supportive secondary efficacy endpoints will be adequate to establish efficacy, provided the efficacy findings are robust and clinically meaningful. Such a program should support an indication derived from the effect assessed by the primary efficacy endpoint used and the drug type.

It is possible that some drugs may have relatively small, but statistically significant, effects on a single measure of the disease that is made more clinically convincing through corroboration in other areas of the disease. This may be because of the mechanism of action of the drug or the inherent complexity and heterogeneity of COPD. In such a situation, two efficacy endpoints may need to be declared as primary endpoints in phase 3 studies to support efficacy. An example of using two primary efficacy endpoints would be measurement of lung function, such as FEV1, plus a measure of a patient-reported outcome, such as a validated symptom score, activity scale, or disease-specific, health-related quality-of-life instrument. The indication granted would reflect this broader assessment. In choosing multiple variables as primary endpoints, careful consideration should be given to issues of effect size and of multiplicity.

### **10. *Considerations Regarding Demonstration of Safety***

Treatment of COPD is usually prolonged; therefore, long-term data on safety evaluation should be collected. The extent of the safety database should be consistent with the ICH guideline for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. Consideration should be given to whether the drug is designed for intermittent or continuous use. Consideration also should be given to other concomitant diseases that COPD patients are likely to have and other concomitant drugs that these patients are likely to take. Finally, the intended use (i.e., treatment versus preventive) may further inform the size and duration of safety assessments. In cases where efficacy studies are substantially less than 1 year, or if the drug is to be chronically administered, separate long-term safety studies should be conducted. Since the goal should be to rule out long-term effects on the disease characteristics, consideration should be given to including a control arm and assessing efficacy over time as well. In some cases, specific safety hypotheses should be tested, depending on if safety signals are identified during nonclinical studies or early clinical studies.

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### **B. Specific Efficacy Study Considerations**

#### *1. Study Design*

The nature and design of phase 3 studies depends on the type of drug that is being studied and the clinical benefit to be demonstrated. In general, studies should be placebo-controlled, double-blinded, randomized, and parallel-group in design. Use of an active comparator in addition to a placebo is, while encouraged, not necessary, unless comparative efficacy or safety claims are desired, or when there is uncertainty about a novel efficacy assessment methodology and a validation of the methodology is desired. The use of a placebo control does not necessarily preclude *usual care* treatment in patients randomized to placebo (see section III.B.3., Concomitant Treatments). The appropriateness of a placebo control may change in the future when drugs become available such that use of placebo control raises ethical issues (i.e., if a drug is shown to be convincingly effective in disease modification or changes mortality). This may be more relevant for certain types of studies, such as studies for drugs that alter disease progression. However, active-controlled studies can be a viable alternative to placebo controls when the intent of the study is to show superiority.

When there is a desire to show noninferiority to an active comparator and no placebo is planned, many important design issues are raised, including assay sensitivity, the noninferiority margin, and knowledge of how the chosen endpoint performs in historical studies with the active comparator. To propose a noninferiority design at all is dependent on there being a well-defined, reproducible treatment effect for the established comparator such that the effect of that treatment in further studies can be inferred. Any such proposal should be carefully considered and discussed in depth with the division before starting clinical studies using this design.

#### *2. Study Populations*

In general, it is desirable to include patients broadly representative of the spectrum of the COPD population. Patients should be diagnosed for inclusion in the study based on accepted clinical practice parameters and criteria set by consensus panels (see References). Asthma and COPD can coexist and asthma is, in many senses, a more remediable disease. Therefore, in specific COPD drug development programs, patients whose primary disease is asthma should be carefully excluded using existing guidelines for its diagnosis supported by assessment of FEV1 reversibility with a predefined criterion of reversibility that would classify a patient as asthmatic. For drugs designed to improve airflow obstruction, FEV1 reversibility should be determined using a beta-adrenergic agonist and/or an anticholinergic agent in all patients to serve as a basis for characterizing the patient population being studied, but not necessarily as a strict entry criterion. For drugs designed to provide symptom relief, enrollment of patients with consistent clinical evidence of the symptoms being investigated during a baseline period should be included in the study.



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### **3. Concomitant Treatments**

Patients enrolled in the study should be permitted to use concomitant treatments as needed to manage disease symptoms. Use of concomitant treatments should be recorded for each patient throughout the study. An appropriate analysis plan should be defined in the protocol to account for possible imbalance of concomitant treatment use between treatment groups. For some treatments, consideration should be given in the design, conduct, and interpretation of the study to the need for any *rescue* medications for acute symptoms (e.g., corticosteroids in exacerbations).

### **4. Handling of Tobacco Smoking**

Given the etiology of COPD, a large proportion of patients enrolled in the studies will be current or past tobacco smokers, and change of smoking status during the study may influence the outcome of a patient's response to the drug. The study protocol should define how smoking status will be handled, including the way in which it will be monitored throughout the study, and how patients who change their smoking status during the study will be handled and accounted for in the analyses. It may be reasonable to stratify patients according to current and previous smoking status and conduct secondary analyses to determine the potential effect of smoking status on the investigational treatment. To assess the effect of change in smoking status during the study, it may be reasonable to conduct secondary analyses excluding patients who significantly change their smoking status during the study.

To maintain appropriate standard of care of patients enrolled in the studies, active smokers should be encouraged to discontinue tobacco smoking and provided appropriate counseling and help. This is particularly important for long-term studies, such as studies lasting for more than 3 months.

Another consideration with regard to smoking is that there are emerging data suggesting that in asthma, inhaled corticosteroids have less efficacy in smokers than in nonsmokers. It is possible that for certain therapies in the future, the indication of medicines for smoking-related pulmonary diseases may have specific wording regarding patient smoking status (e.g., drug X is indicated for active smokers with COPD). Although it is premature to make a definitive statement in this regard, sponsors should keep in mind that if they do not wish to contemplate such a restricted indication, clinical studies may need to include active smokers, ex-smokers and, where applicable, nonsmokers.

## **C. Other Considerations**

### **1. Drugs Administered by Inhaled Route**

For drugs delivered by the orally inhaled route, the delivery systems, comprising the formulation and the device, may affect safety and efficacy. The development of the delivery system should take into consideration the characteristics of the COPD patient population. For breath-actuated devices, the inspiratory flow-rate that will be necessary to activate the device should be such that a COPD patient can easily generate that level of flow. The device should have a dose indicator

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or counter that informs patients of the number of doses remaining. The device should be durable and the dexterity required to use the device should be within the capability of COPD patients who may often be elderly and may have co-existent arthritides. Phase 3 studies should assess device durability in patients' hands and assess whether patients can follow the instructions to use the device effectively.

It is likely that early phase clinical studies will be conducted using a prototype device and the device may undergo design changes as more information about it is gathered from in vitro studies and from early clinical studies. Depending on the design changes, in vitro and clinical data may be necessary to link the various versions of the device. Changes in the formulation, excipients, drug flow path, or device components that affect the drug delivery characteristics are critical and will likely affect the clinical performance of the drug product. Since most inhaled drugs do not have short-term PD endpoints suitable for establishing relative bioavailability (i.e., delivery to the site of action in the lungs, not systemic exposure), clinical studies may be needed to demonstrate clinical acceptability of such changes. To avoid having to conduct clinical bridging studies, critical clinical studies, such as definitive dose-finding studies and phase 3 efficacy and safety studies, should be conducted with the to-be-marketed formulation and device whenever possible.

### ***2. Combination Drug Products***

Given the complexity of COPD, it is possible that a single new drug may not possess all necessary pharmacological activity to result in a desired therapeutic effect. Therefore, a new drug product can be a combination of two more individual drugs. A combination drug product also can be for convenience where more than one singly active drug is formulated as one product. In most situations, the individual drugs are likely to have been previously evaluated and approved for use in humans. It is possible that one or more of the individual drugs may not be previously evaluated and approved for use in humans.

Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosing of each component is such that the combination is safe and effective for a significant patient population (21 CFR 300.50, Combination Rule). A reasonable way to support the efficacy of a combination drug product would be to compare the combination drug product to each of its constituents in the same clinical study to demonstrate that the combination drug product provides clinical benefit that is superior to each of its constituents. Since the pharmacological action of the two components may be disparate, the efficacy endpoint selected to show superiority of the combination drug product to one component may be different than the efficacy endpoint selected to show superiority to another component (i.e., two primary endpoints may be assessed, one for drug A versus combination drug AB and another for drug B versus combination drug AB). In these cases, the study should show separate superiority on both endpoints to meet the Combination Rule.

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