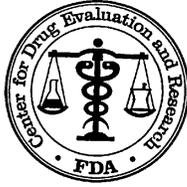


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



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.

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1 EXECUTIVE SUMMARY

1.1 *Conclusions and Recommendations*

Novartis proposes indacaterol maleate, a long-acting beta₂-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 FEV₁ 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 regimen 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 FEV₁ 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 FEV₁ 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 FEV₁, peak FEV₁, FEV₁ AUC_(0-12h/0-24h/0-48h), were similar in the three arms both in day 1 and after two weeks of treatment. There was no separation among the 48-hour FEV₁ 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 FEV₁ 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 clinically 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 FEV₁

The primary efficacy endpoint in the key controlled efficacy studies was the 24-hour post-dose trough FEV₁ after 12 weeks treatment.

In Study B2336, the treatment effect of indacaterol 150 mcg once daily measured by the 24-hour post-dose trough FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 beta₂-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 beta₂-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.

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)
B2223 (Mar. 2010 – Jul 2010)	USA Europe Jordan	Dosing regimen trial in asthma patients, 16 days, Parallel-arm, Placebo controlled	48	Ind 37.5 mcg (b.i.d)
			48	Ind 75 mcg (q.d.)
			48	Ind 150 mcg (q.o.d.)
			47	placebo
B2357 (Feb. 2010 – Jul. 2010)	USA	Dose ranging trial in asthma patients, 2 weeks, Parallel-arm, Placebo and active controlled	85	Ind 18.75 mcg (q.d.)
			85	Ind 37.5 mcg (q.d.)
			84	Ind 75 mcg (q.d.)
			86	Ind 150 mcg (q.d.)
			86	Sal 50 mcg (b.i.d)
			85	Placebo (double dummy)
B2356 (Mar. 2010 – Jul. 2010)	USA	Dose ranging trial in COPD patients, 2 weeks, Parallel-arm, Placebo and active controlled	92	Ind 18.75 mcg (q.d.)
			91	Ind 37.5 mcg (q.d.)
			94	Ind 75 mcg (q.d.)
			92	Ind 150 mcg (q.d.)
			92	Sal 50 mcg (b.i.d)
			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)
B2334 (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)
B2335s (Apr. 2007 - Aug. 2008)	USA, Canada, South America, West Europe, Asia	1 st stage – 2 weeks, (dose selection) 2 nd 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)
B2346 (Feb. 2008 - Jul. 2008)	USA, Belgium, New Zealand	12 weeks, Parallel-arm, Placebo controlled	211 205	Ind 150 mcg Placebo
B2336 (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)
B2354 (Jan. 2010 – Jul. 2010)	USA	12 weeks, Parallel- arm, Placebo controlled	163 160	Ind 75 mcg Placebo
B2355 (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 FEV₁ after 2 weeks treatment. The 24-hour post-dose trough FEV₁ was defined as the average of two FEV₁ 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 FEV₁, weighted mean FEV₁ over 0-4 hours post-dose, weighted mean FEV₁ over 0-12 hours post-dose, etc. Weighted mean FEV₁ over 0-4 hours was defined as standardized AUC for FEV₁ 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 FEV₁ after 12 weeks treatment. The secondary efficacy endpoints include peak FEV₁, 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 FEV₁, 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 FEV₁ 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 FEV₁ 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	
	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 FEV₁ < 80% and ≥30% of the predicted normal value; post-bronchodilator FEV₁/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 N (%)	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)
	≥ 65 yrs	149 (45)	155 (47)	155 (46)	78 (48)	76 (47)	63 (40)	65 (41)
Sex N (%)	Male	238 (72)	249 (75)	258 (77)	89 (55)	87 (54)	83 (52)	89 (56)
	Female	92 (28)	84 (25)	77 (23)	74 (45)	73 (46)	76 (48)	70 (44)
Race N (%)	Caucasian	250 (76)	258 (78)	251 (75)	145 (89)	146 (91)	151 (95)	147 (93)
	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 N (%)	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
	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 N (%)	No	181 (55)	181 (54)	200 (60)	70 (43)	76 (47)	96 (60)	103 (65)
	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 FEV₁ 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, FEV₁ prior and post to inhalation of salbutamol/albuterol (components of SABA reversibility), FEV₁ 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 FEV₁ 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 FEV₁ was regarded as missing. A missing trough FEV₁ value at week 12 was replaced by carrying forward trough FEV₁ from the last evaluable visit as long as the visit was not prior to Day 29. The primary analysis on trough FEV₁ 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 FEV₁ time serial profile for dosing regimen selection. Figure 2 and Figure 3 give the FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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, FEV₁ 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 FEV₁ scores in the two asthma studies (Studies B2223 and B2357) were not comparable. As shown in Figure 6, baseline FEV₁ in Study B2223 was around 0.26 to 0.27 L, but the baseline FEV₁ in Study B2357 was around 0.24 L. Patients in Study B2223 reached about 0.3 to 0.35 L improvement in FEV₁ 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 FEV₁. The 18.75 mcg dose was clearly not as effective as the higher doses. In terms of FEV₁ AUC_(0-12h/0-24h/12-24h), 37.5 mcg was better than all other doses.

Looking at the FEV₁ time serial profile (Figure 8), in day 1, there was a clear dose response, the higher the dose was, the greater the FEV₁ 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.

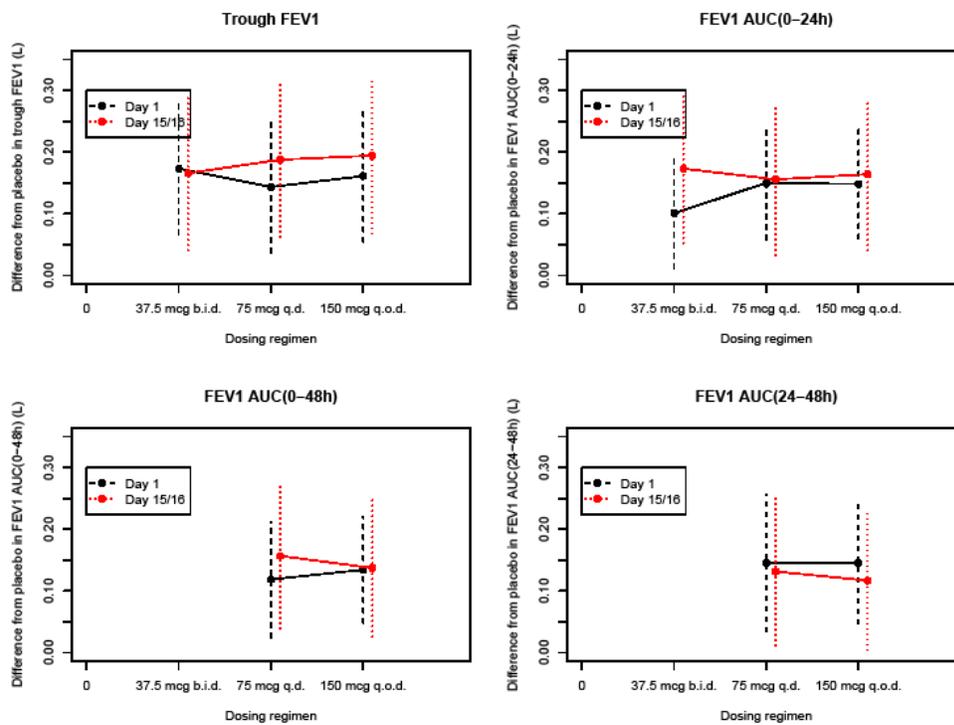


Figure 1 Study B2223 summary of spirometric parameters at day 1 and after 2 weeks treatment.

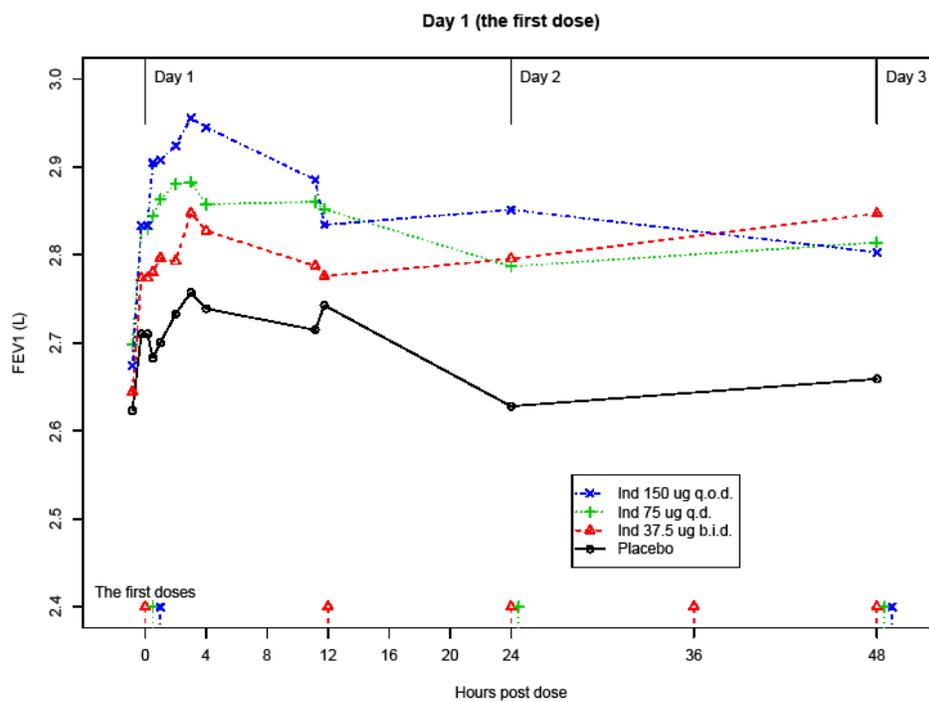


Figure 2 Study B2223 48-hour FEV₁ profile after the first dose.

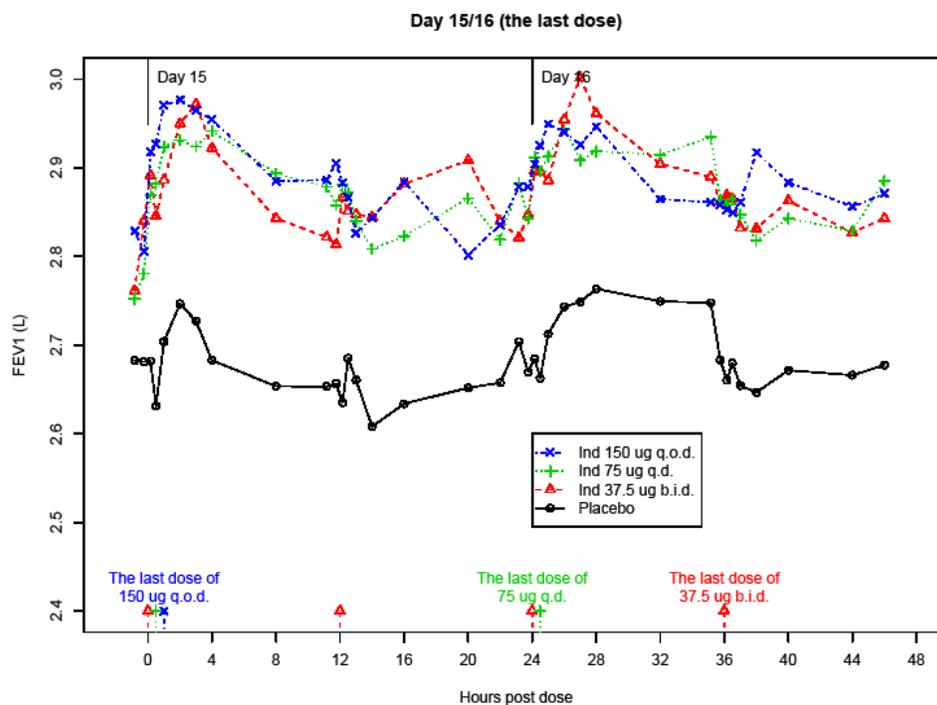


Figure 3 Study B2223 48-hour FEV₁ profile after the last dose.

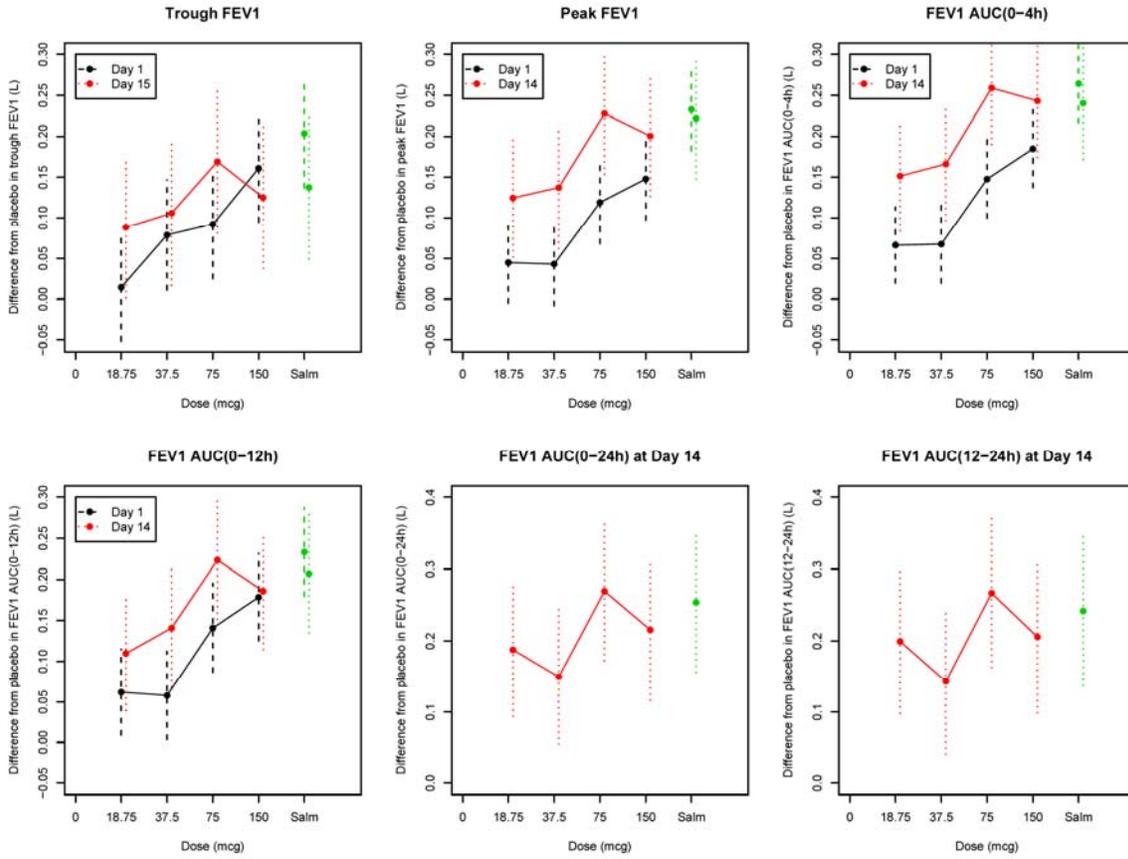


Figure 4 Study B2357 Summary of spirometric parameters at Day 1 and after 2 weeks treatment.

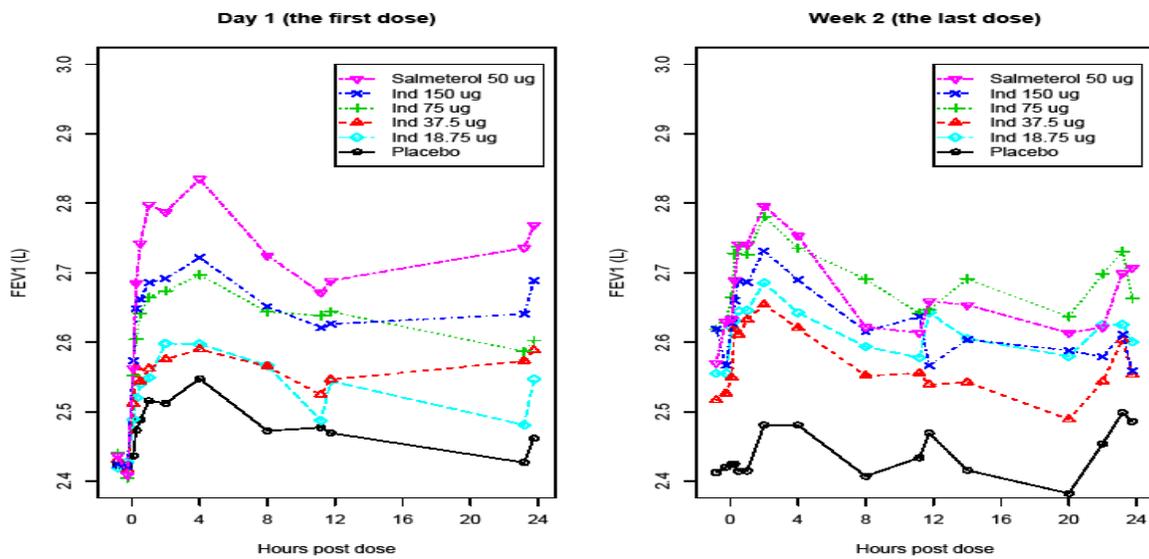


Figure 5 Study B2357 24-hour FEV₁ profile after the first and last doses.

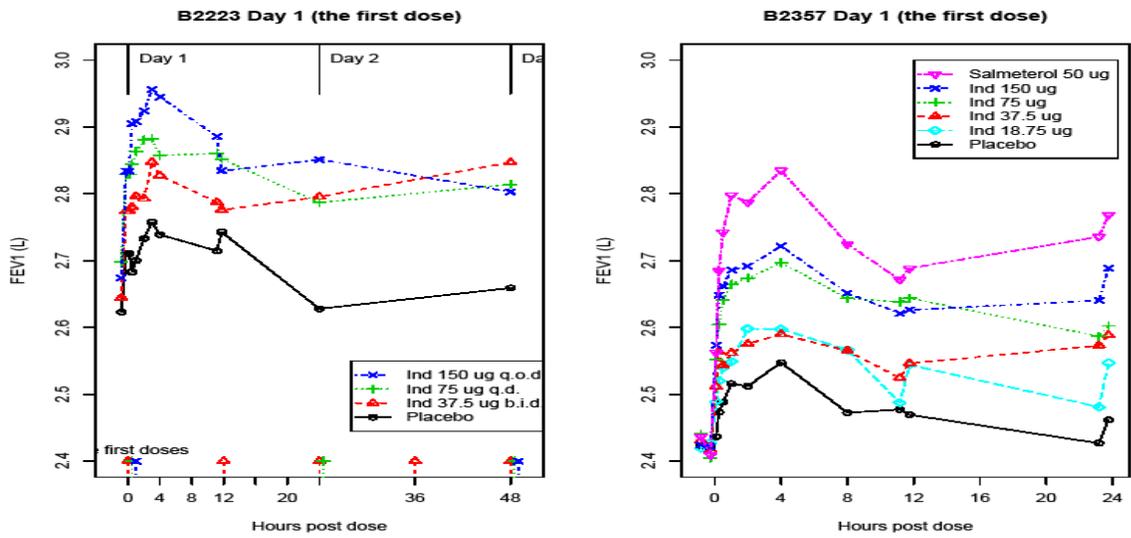


Figure 6 Comparison of baseline FEV₁ in Studies B2223 and B2357.

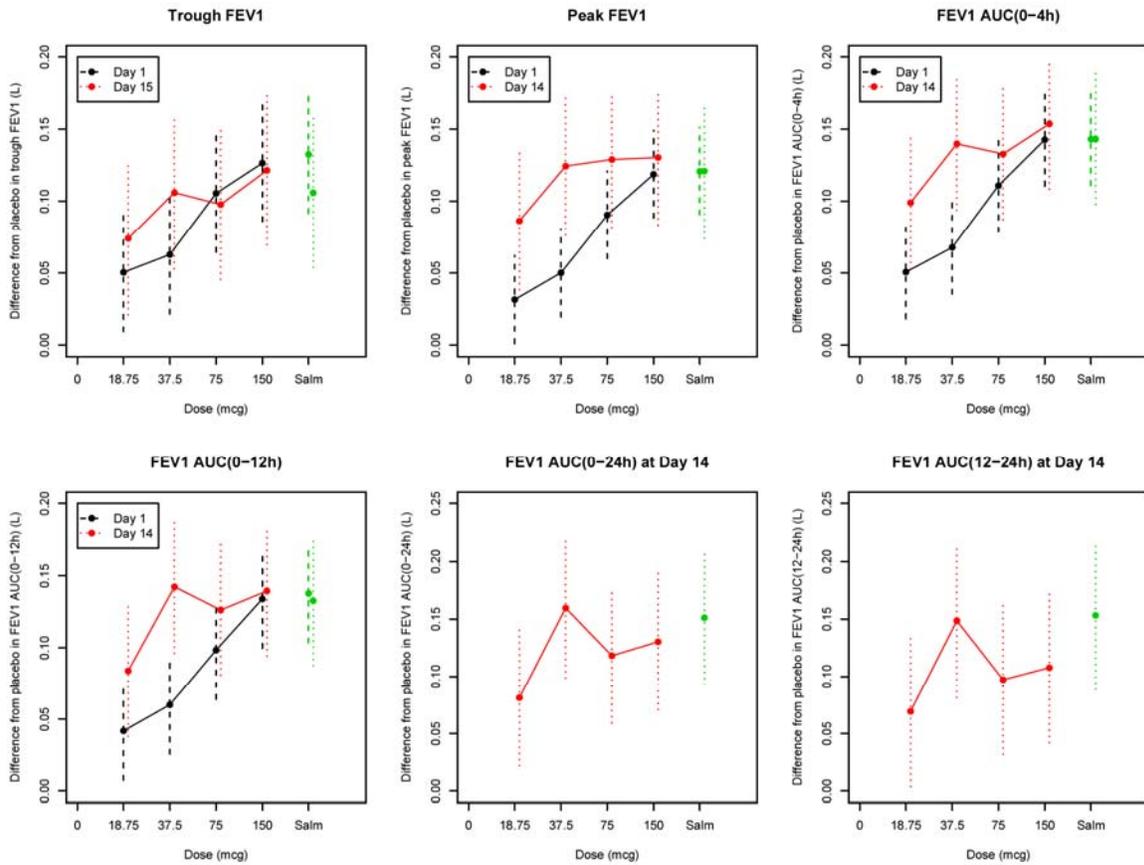


Figure 7 Study B2356 summary of spirometric parameters at Day 1 and after 2 weeks treatment.

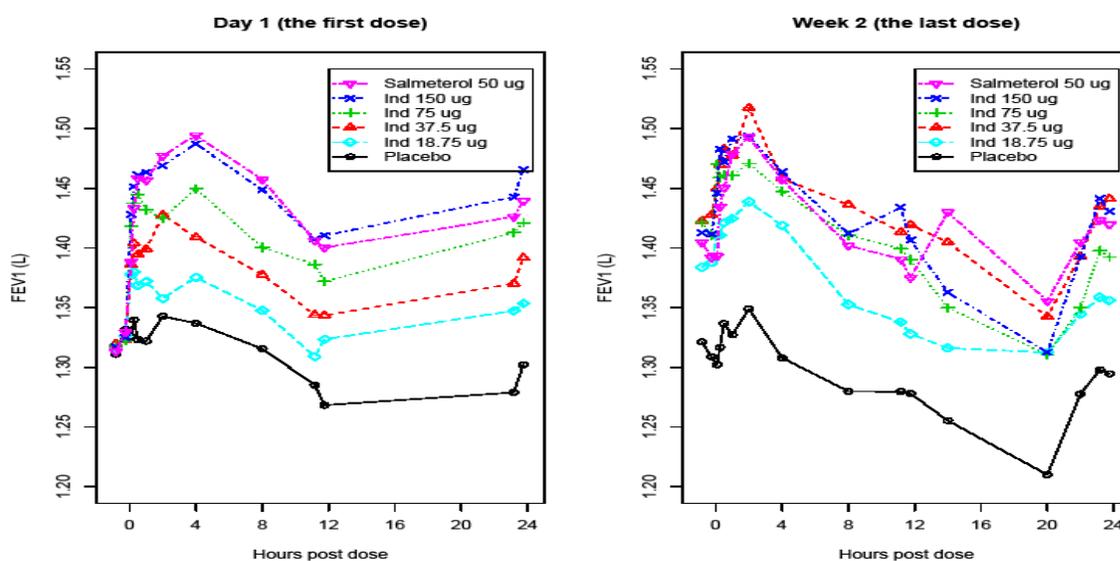


Figure 8 Study B2356 24-hour FEV₁ profile after the first and last doses.

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 FEV₁ 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 FEV₁ 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.

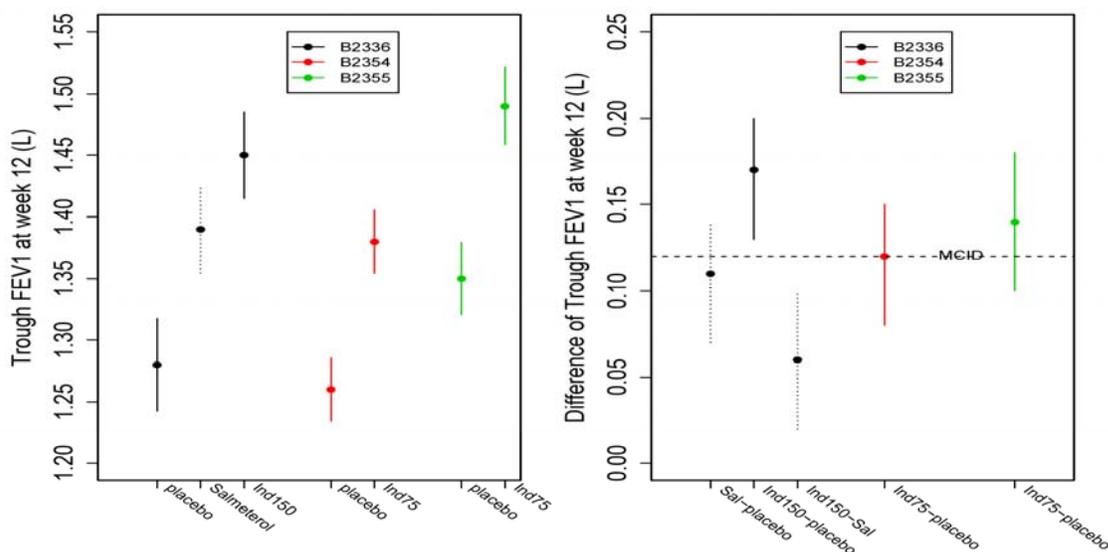


Figure 9 Summary of the primary efficacy endpoint (trough FEV₁ at week 12 imputed with LOCF) in the three new key controlled efficacy studies.

Table 5 Summary of the primary efficacy endpoint (trough FEV₁ 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	---	---	---	---	---

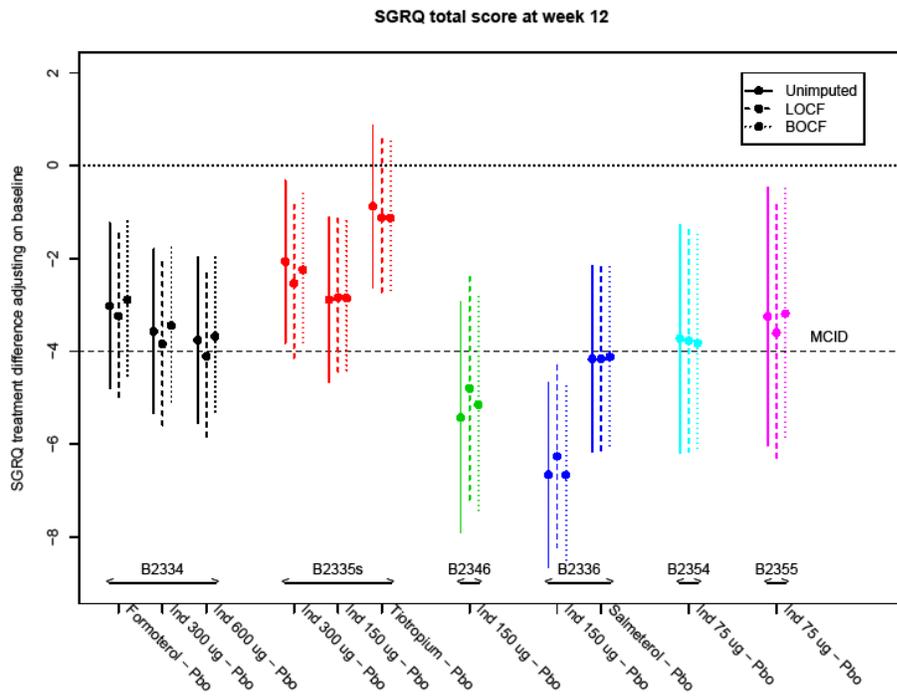


Figure 10 ANCOVA results of SGRQ total scores (imputed with LOCF) in the key controlled efficacy studies.

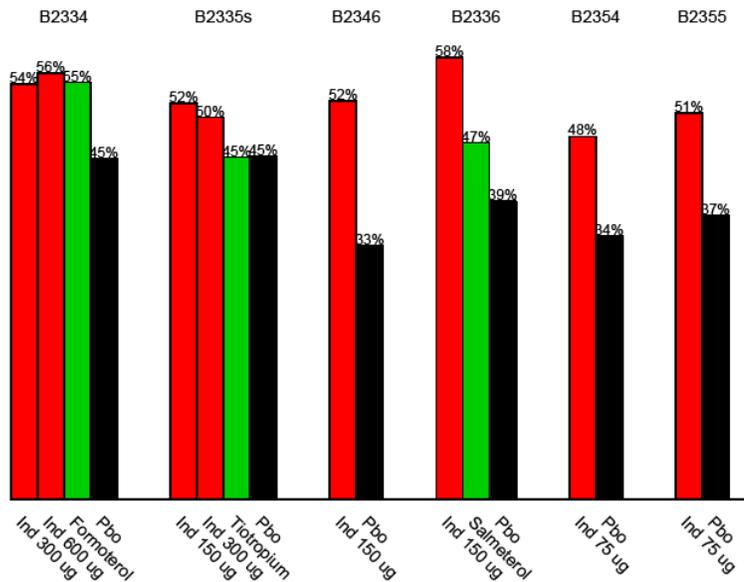


Figure 11 Summary of proportion of SGRQ (imputed with LOCF) responders in key controlled efficacy studies.

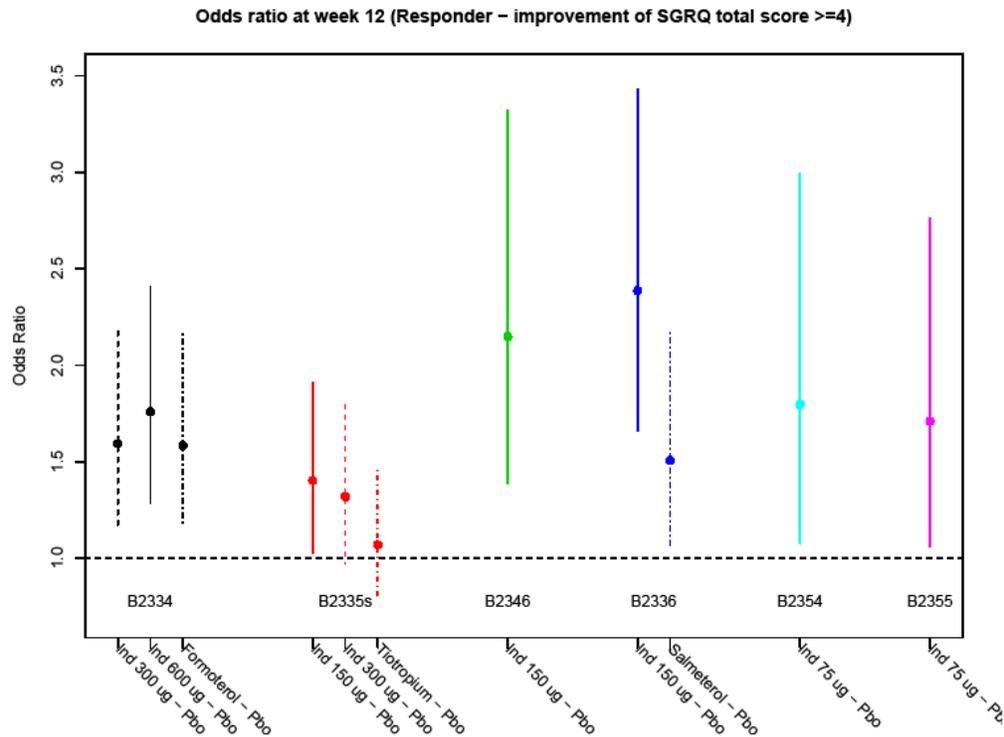


Figure 12 Summary of SGRQ (imputed with LOCF) responder analysis results in key controlled efficacy studies.

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 ≥ 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 ≥ 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 ≥ 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)
B2334 (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
B2335s (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
B2346 (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
B2336 (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
B2354 (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
B2355 (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.

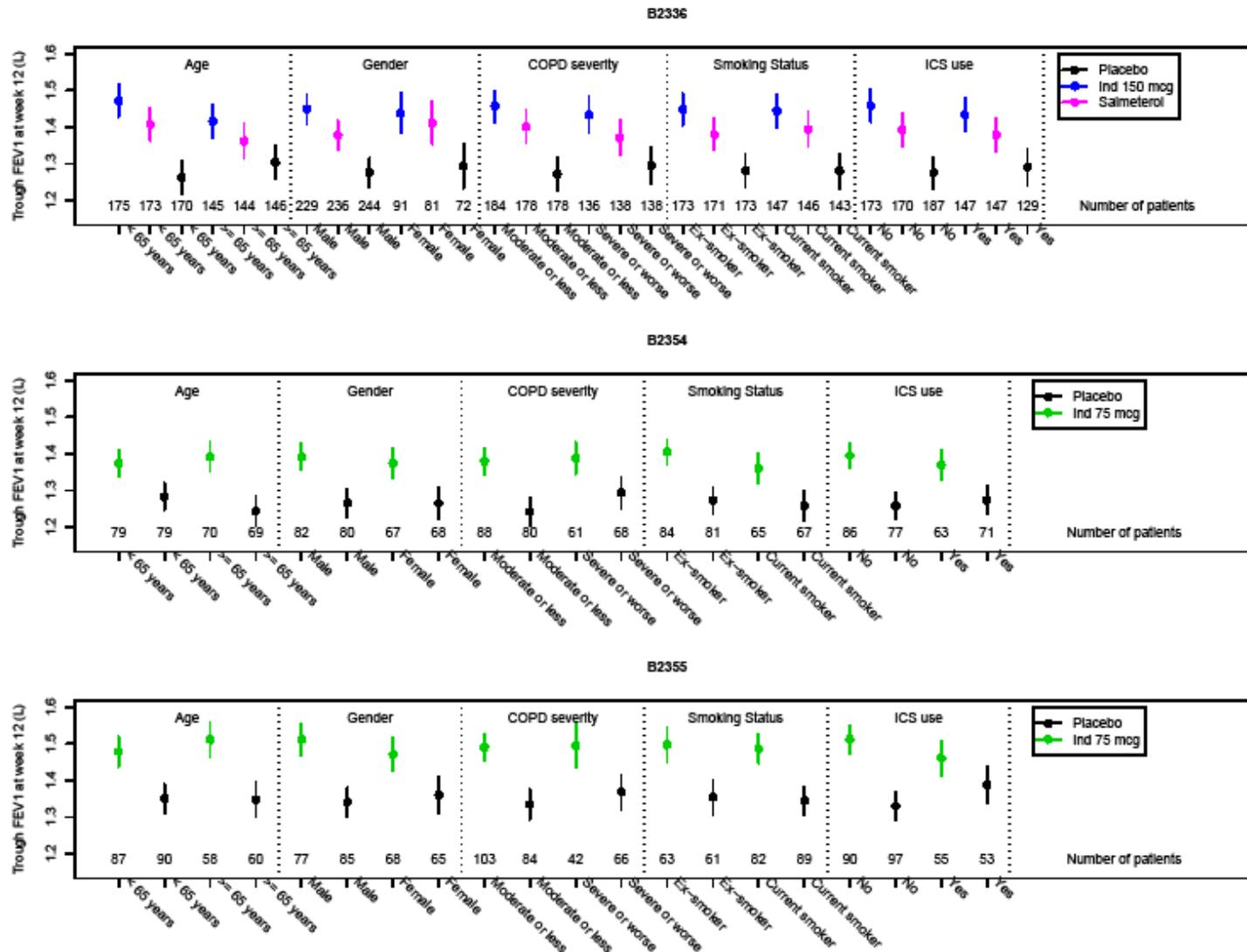


Figure 13 Summary of subgroup analysis on the primary efficacy endpoint in the three new key controlled efficacy studies.

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	75 µg q.d	150 µg q.o.d		
	N=48	N=48	N=48		
	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%)
Main cause of discontinuation					
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			Placebo
		37.5 µg b.i.d	75 µg q.d	150 µg q.o.d	
		N=48	N=47	N=48	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 ₁ (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 ₁ (%)	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
Patients							
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)
Primary reason for premature discontinuation							
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
Age (years)	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
Age group - n (%)	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)
Sex - n (%)	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)
Race - n (%)	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 (GOLD 2008) n (%)	Mild	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
Patients							
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)
Primary reason for premature discontinuation							
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
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)

- Quoted from the submitted study report.

Table 19 Summary of baseline disease characteristics of patients in 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
Duration of Asthma (years)	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
Duration of Asthma (years) – n (%)	< 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)
Severity of Asthma – n (%)	Mild persistent	19 (22.6)	20 (24.7)	22 (26.2)	21 (24.7)	21 (25.0)	20 (23.8)	123 (24.5)
	Moderate persistent	59 (70.2)	55 (67.9)	56 (66.7)	58 (68.2)	57 (67.9)	58 (69.0)	343 (68.3)
	Severe persistent	6 (7.1)	6 (7.4)	6 (7.1)	6 (7.1)	6 (7.1)	6 (7.1)	36 (7.2)
	ICS use – n (%)	Yes	84 (100.0)	81 (100.0)	84 (100.0)	85 (100.0)	84 (100.0)	84 (100.0)
Smoking history – n (%)	Never Smoker	63 (75.0)	70 (86.4)	67 (79.8)	68 (80.0)	67 (79.8)	65 (77.4)	400 (79.7)
	Ex-smoker	19 (22.6)	8 (9.9)	15 (17.9)	17 (20.0)	13 (15.5)	17 (20.2)	89 (17.7)
	Current Smoker	2 (2.4)	3 (3.7)	2 (2.4)	0 (0.0)	4 (4.8)	2 (2.4)	13 (2.6)

- Quoted from the submitted study report.

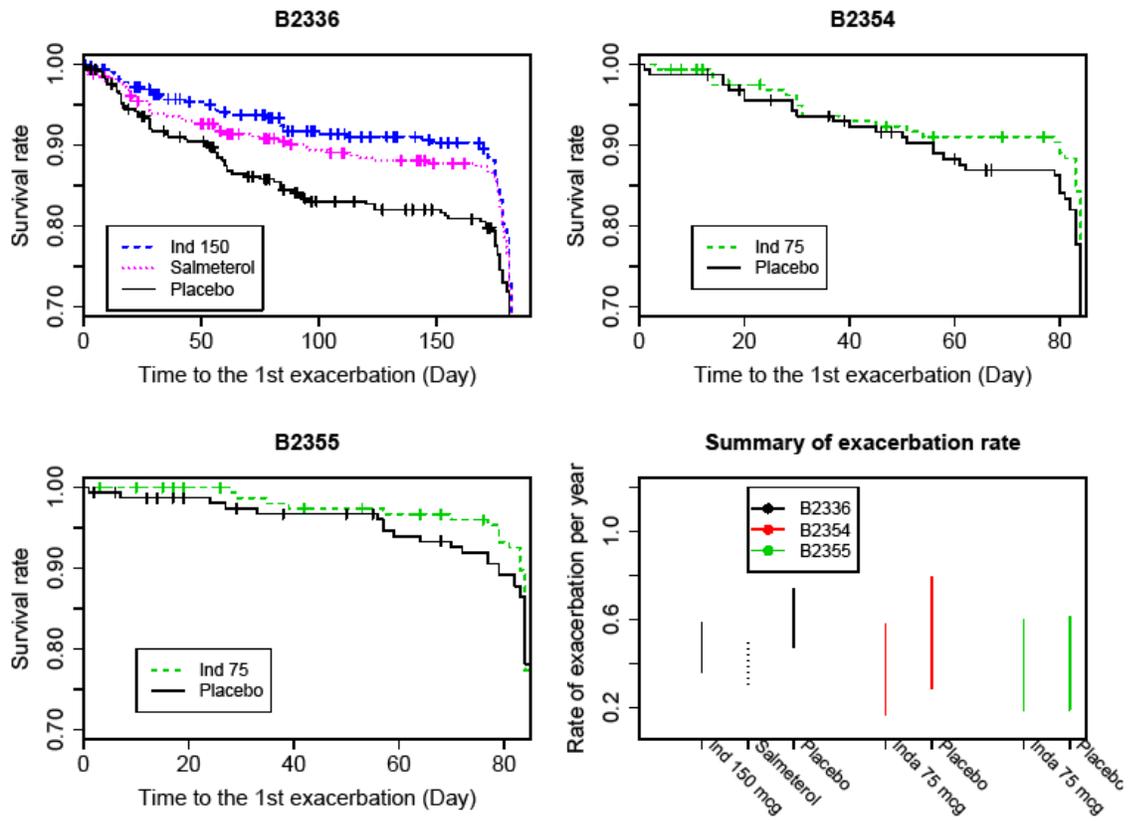


Figure 14 Summary of COPD exacerbations (without imputation) in the three new key controlled efficacy studies.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dongmei Liu, Ph.D.
Date: February 8, 2011

Statistical Team Leader: Joan Buenconsejo, Ph.D.

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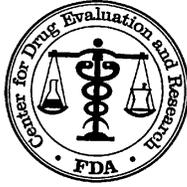
/s/

DONGMEI LIU
02/11/2011

JOAN K BUENCONSEJO
02/11/2011

I concur with Dr. Dongmei Liu's statistical review of NDA22-383 serial no. 0027 (Arcapta Neohaler) for the treatment of chronic obstructive pulmonary disease.

THOMAS J PERMUTT
02/11/2011
concur



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

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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 beta₂-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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ at 24 hour post-dose and weighted mean FEV₁ 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 beta₂-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 beta₂-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 FEV₁ (forced expiratory volume in one second) alone was not adequate dose-selection criteria, other variables such as peak FEV₁ and

FEV₁ AUC (area under the curve) would be considered in the review of dose selection. While the applicant may base dose selection on trough FEV₁ 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)
B2334 (Oct. 2006 - Jul. 2008)	West Europe,	52 weeks,	405	Inda 300 mcg
	East Europe,	Parallel-arm,	396	Inda 600 mcg
	South and Central America, Asia	Placebo and active controlled	399	Placebo (double dummy) For 12 mcg (b.i.d)
			400	
B2335s (Apr. 2007 - Aug. 2008)	USA,	26 weeks,	107	Inda 75 mcg
	Canada,	Parallel arm,	105 / 325 †	Inda 150 mcg *
	South America,	Placebo and active controlled	110 / 341 †	Inda 300 mcg *
	West Europe, Asia		102	Inda 600 mcg
			104 / 294 †	Placebo (double dummy) * For 12 mcg (b.i.d)
		112	Tio 18 mcg * (open-label)	
		112 / 331 †		
B2346 (Feb. 2008 - Jul. 2008)	USA,	12 weeks,	211	Inda 150 mcg
	Belgium,	Parallel-arm,	205	Placebo
	New Zealand	Placebo controlled		

- * 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.

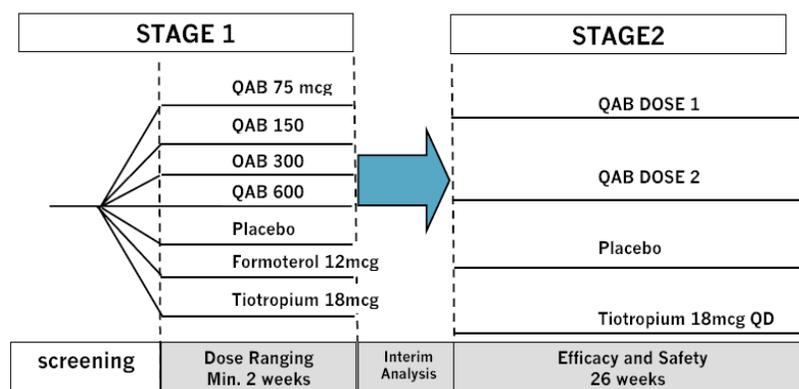


Figure 1 Study design of B2335s (quoted from the clinical study report).

3.1.2 Efficacy Endpoints and Assessment Schedule

The primary efficacy endpoints in all three pivotal studies were 24-hour post-dose trough FEV₁ after 12 weeks treatment. The 24-hour post-dose trough FEV₁ was defined as the average of two FEV₁ 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 ≥ 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 FEV₁, 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 FEV₁ and weighted mean FEV₁ over 1-4 hours after 2 weeks of treatment. Weighted mean FEV₁ over 1-4 hours was defined as standardized AUC for FEV₁ 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 FEV₁ 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 FEV₁ over 1-4 hours.

In B2334, 24-hour post-dose trough FEV₁ 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 FEV₁ 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 FEV₁ < 80% and ≥30% of the predicted normal value; post-bronchodilator FEV₁/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 FEV₁/FVC and FEV₁ 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 FEV₁ 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 FEV₁ measurement, FEV₁ prior to inhalation of salbutamol/albuterol, FEV₁ 30 minute post inhalation of salbutamol/albuterol (components of SABA reversibility), FEV₁ prior to inhalation of ipratropium, and FEV₁ 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 FEV₁ 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 FEV₁ was regarded as missing. A missing trough FEV₁ value at week 12 was replaced by carrying forward trough FEV₁ 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 FEV₁ and numerically higher than tiotropium and formoterol.*
- *The selected dose needed to be numerically higher than tiotropium and formoterol in terms of weighted mean FEV₁ over 1-4 hours.*

The summary of interim analysis results is given in Table 3.

Based on analysis of weighted mean FEV₁ 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	N	Treatment		Comparison	Treatment difference		
		LS mean	SE		LS mean	SE	95% CI
Trough FEV₁ (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	0.14	0.028	(0.08, 0.19)
Placebo	104	1.31	0.024				
AUC 1h-4h FEV₁ (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	0.22	0.032	(0.16, 0.28)
Tio	99	1.49	0.034	Tio - Placebo	0.19	0.031	(0.13, 0.25)
Placebo	90	1.30	0.033				

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 FEV₁ and weighted mean FEV₁ 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.

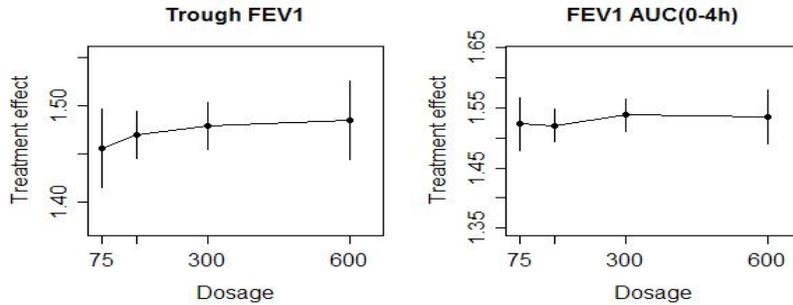


Figure 2 Dose responses by trough FEV₁ and weighted mean FEV₁ over 0-4 hours at Day 15 in B2335s.

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 FEV₁ 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.

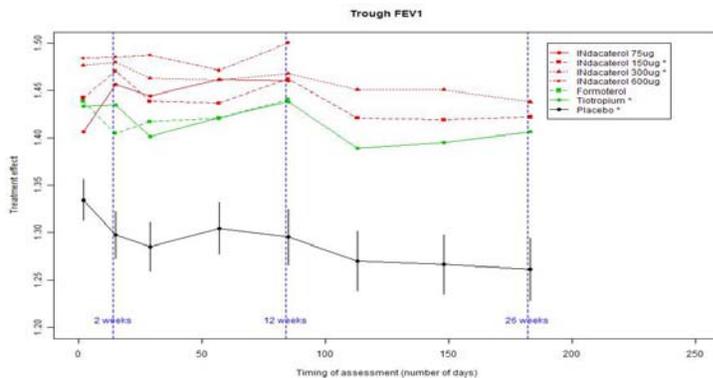


Figure 3 Summary of trough FEV₁ by treatment arms in B2335s at different assessment time.

This reviewer also checked the distribution of change from baseline in trough FEV₁ 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 FEV₁ 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 (FEV₁ and FVC up to 60 minutes post-dose), 75 mcg was even numerically higher than 150 mcg.

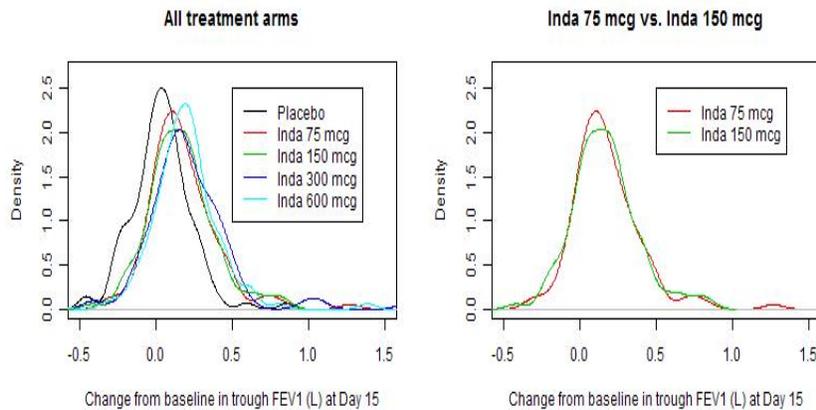


Figure 4 Distribution of change from baseline in trough FEV₁ at Day 15 in study B2335s.

The applicant's dose selection rationale 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 FEV₁ 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 FEV₁ 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 collectively evaluating multiple doses. For these reasons, no multiplicity adjustment is applied in reporting the study results.

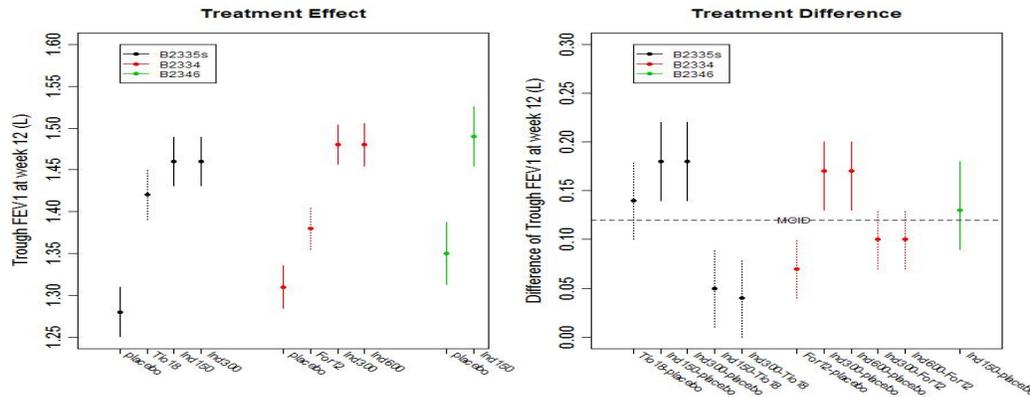


Figure 5 Summary of the primary efficacy endpoint (trough FEV₁ at week 12) in pivotal studies.

Table 4 Summary of the primary efficacy endpoint (trough FEV₁ 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.

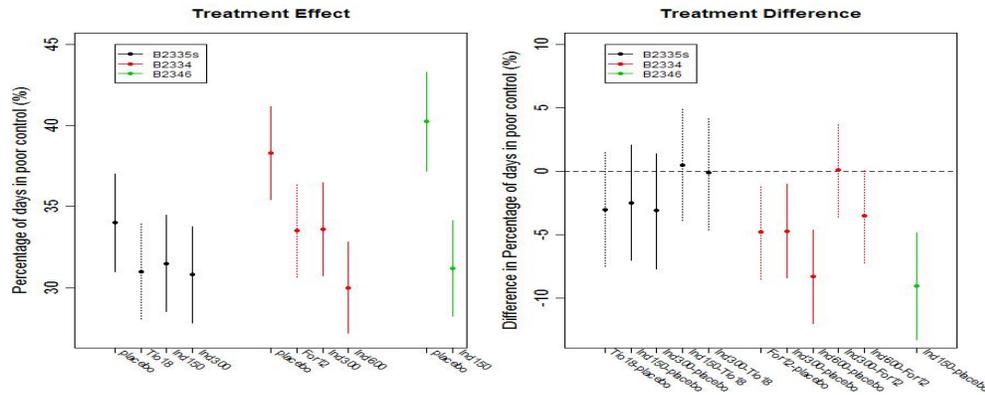


Figure 6 Summary of the key secondary efficacy endpoint (DOPC) in pivotal studies.

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.

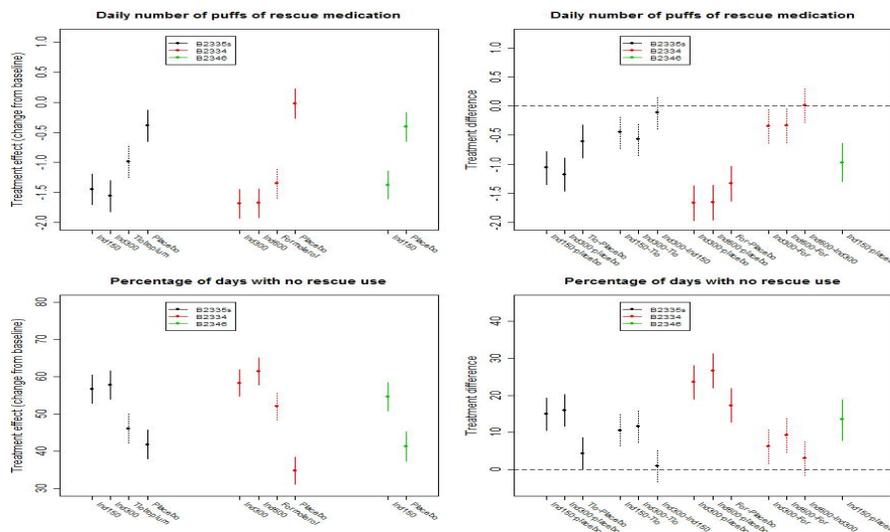


Figure 7 Summary of rescue medication use in pivotal studies.

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 FEV₁ 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.

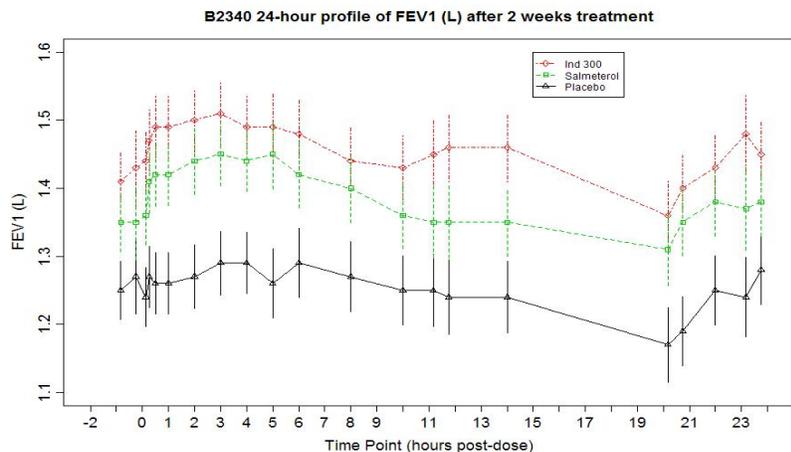


Figure 8 24-hour FEV₁ profile after two weeks treatment in study B2340.

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 FEV₁ 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 FEV₁ relative to placebo. The evening and morning indacaterol doses were associated with a similar increase in trough FEV₁.

The efficacy results in study B2307 show that FEV₁ 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.

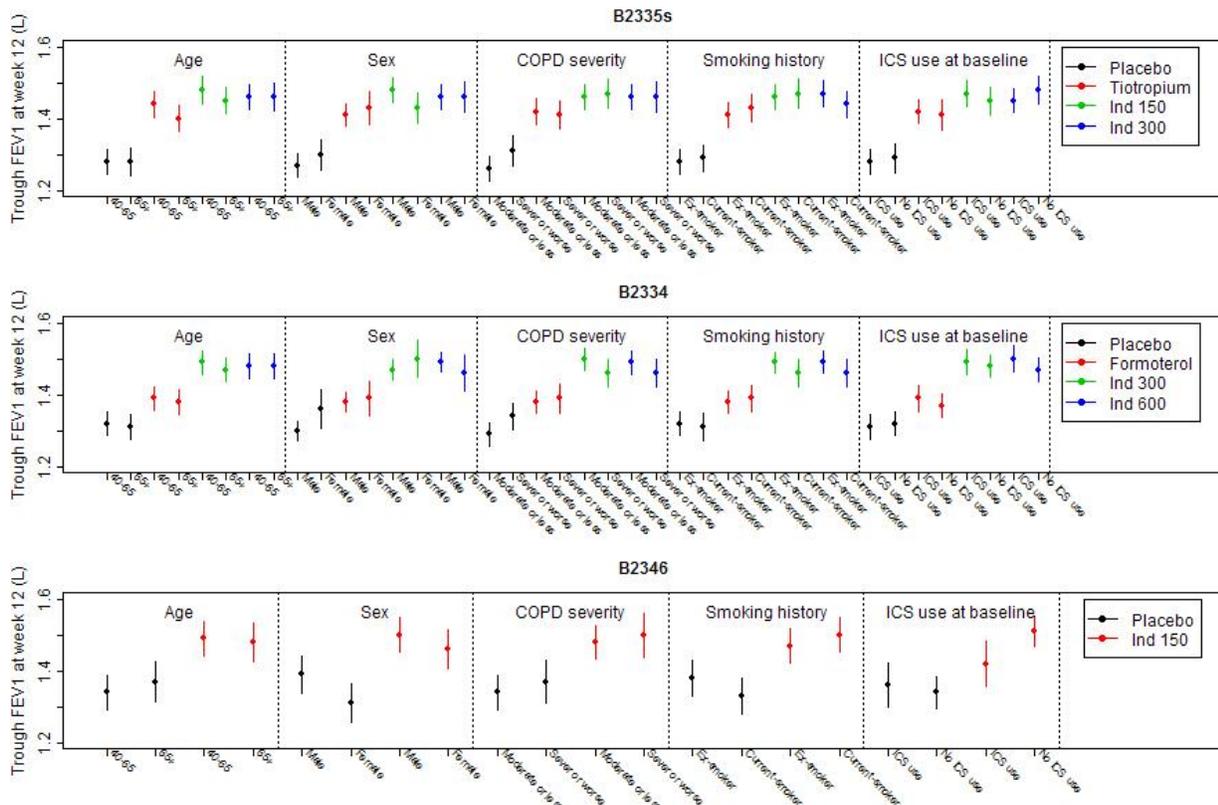


Figure 9 Summary of subgroup analysis (a) in pivotal studies.

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.

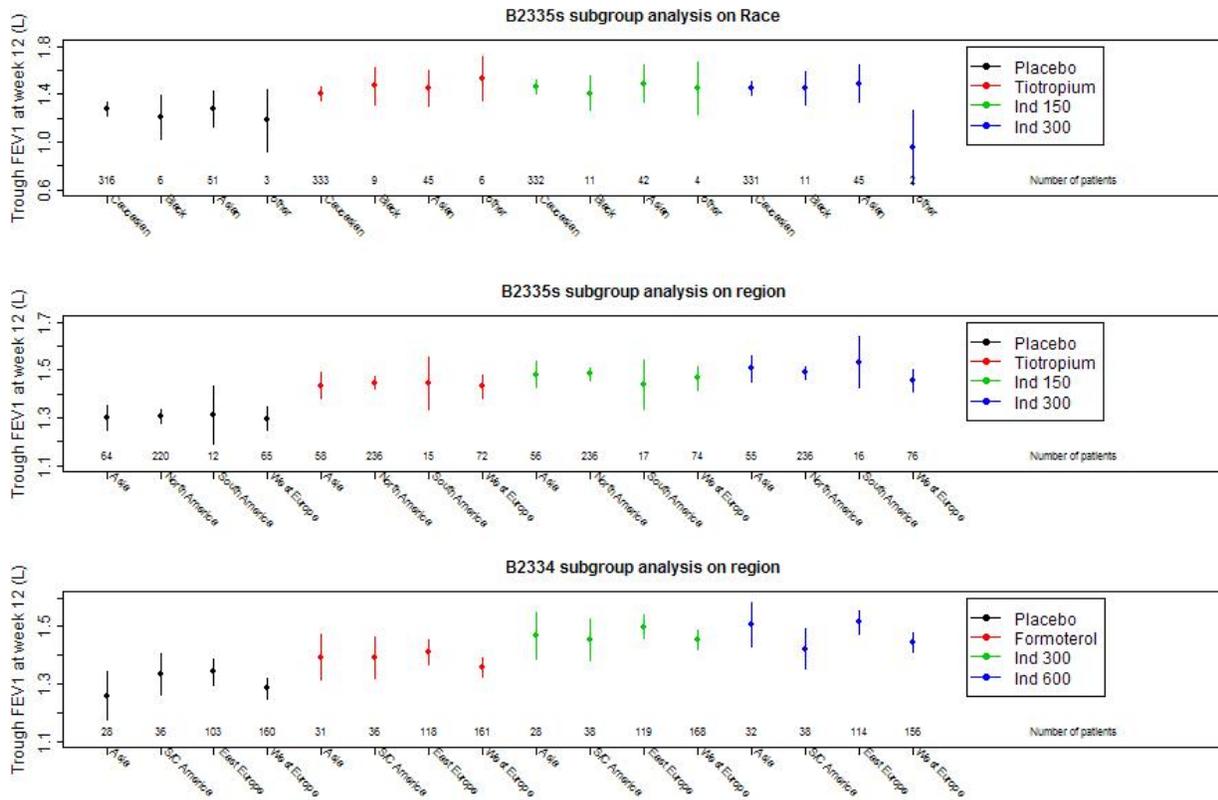


Figure 10 Summary of subgroup analysis (b) in pivotal studies.

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)
B2201 (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)
B2205 (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)
B2212 (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.)
B1202 (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
B2340 (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 ₁ profile
B2305 (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
B2307 (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
Pre-bronchodilator (SABA) FEV1 at Visit 1 (L)	n	416	416	415	414	1661
	Mean	1.34	1.36	1.28	1.33	1.33
	SD	0.485	0.509	0.494	0.471	0.490
	Median	1.31	1.26	1.20	1.27	1.25
	Min - Max	0.53-3.19	0.43-2.95	0.41-2.94	0.44-2.90	0.41-3.19
Post bronchodilator (SABA) FEV1 at Visit 1 (L)	n	416	416	415	418	1665
	Mean	1.52	1.53	1.45	1.51	1.50
	SD	0.497	0.521	0.505	0.490	0.504
	Median	1.48	1.44	1.38	1.43	1.43
	Min - Max	0.62-3.45	0.57-3.14	0.48-3.00	0.53-2.98	0.48-3.45
Post bronchodilator (SABA) FEV1 at Visit 1 (% predicted)	n	416	416	415	418	1665
	Mean	56.1	56.3	53.9	56.1	55.6
	SD	14.47	14.50	15.56	14.27	14.73
	Median	56.0	55.5	52.9	55.1	54.7
	Min - Max	29.3-116.6	21.3-90.0	23.6-132.3	28.4-95.1	21.3-132.3
Post bronchodilator (SABA) FEV1/FVC at Visit 1 (%)	n	416	416	415	418	1665
	Mean	53.0	52.6	52.7	53.4	52.9
	SD	9.97	10.07	10.14	10.11	10.07
	Median	53.9	53.1	53.0	53.6	53.3
	Min - Max	24.4-69.7	25.7-69.5	24.7-72.6	24.0-69.9	24.0-72.6
FEV1 reversibility after SABA at Visit 1 (% increase)	n	416	416	415	414	1661
	Mean	15.6	15.2	15.6	15.5	15.5
	SD	15.43	15.44	17.64	18.03	16.66
	Median	13.2	13.3	12.8	12.8	13.0
	Min - Max	-22.5-88.2	-45.2-89.3	-35.4-81.1	-32.4-222.7	-45.2-222.7
FEV1 reversibility after anti-cholinergic at Visit 2 (% increase)	n	415	412	414	417	1658
	Mean	15.3	15.9	14.8	15.9	15.5
	SD	15.37	21.85	16.05	18.28	18.05
	Median	14.0	13.5	12.5	13.2	13.2
	Min - Max	-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
Pre bronchodilator (SABA)	n	437	425	434	432	1728
FEV₁ at Visit 1 (L)	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
Post bronchodilator (SABA)	n	437	425	434	432	1728
FEV₁ at Visit 1 (L)	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
Post bronchodilator (SABA)	n	436	424	432	431	1723
FEV₁ at Visit 1 (% predicted)	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
Post bronchodilator (SABA)	n	437	425	434	432	1728
FEV₁/FVC at Visit 1 (%)	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
FEV₁ reversibility after SABA at Visit 1 (% increase)	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	
FEV₁ reversibility after anti-cholinergic at Visit 2 (% increase)	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).

		Ind 150 µg N = 211	Pbo N = 205	Total N = 416
Pre-bronchodilator (SABA)	n	211	205	416
FEV₁ at Visit 1 (L)	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
Post-bronchodilator (SABA)	n	211	205	416
FEV₁ at Visit 1 (L)	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
Post-bronchodilator (SABA)	n	211	205	416
FEV₁ at Visit 1 (% predicted)	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
Post-bronchodilator (SABA)	n	211	205	416
FEV₁/FVC at Visit 1 (%)	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
FEV₁ reversibility after SABA at Visit 1 (% increase)	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
FEV₁ reversibility after anti-cholinergic at Visit 2 (% increase)	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

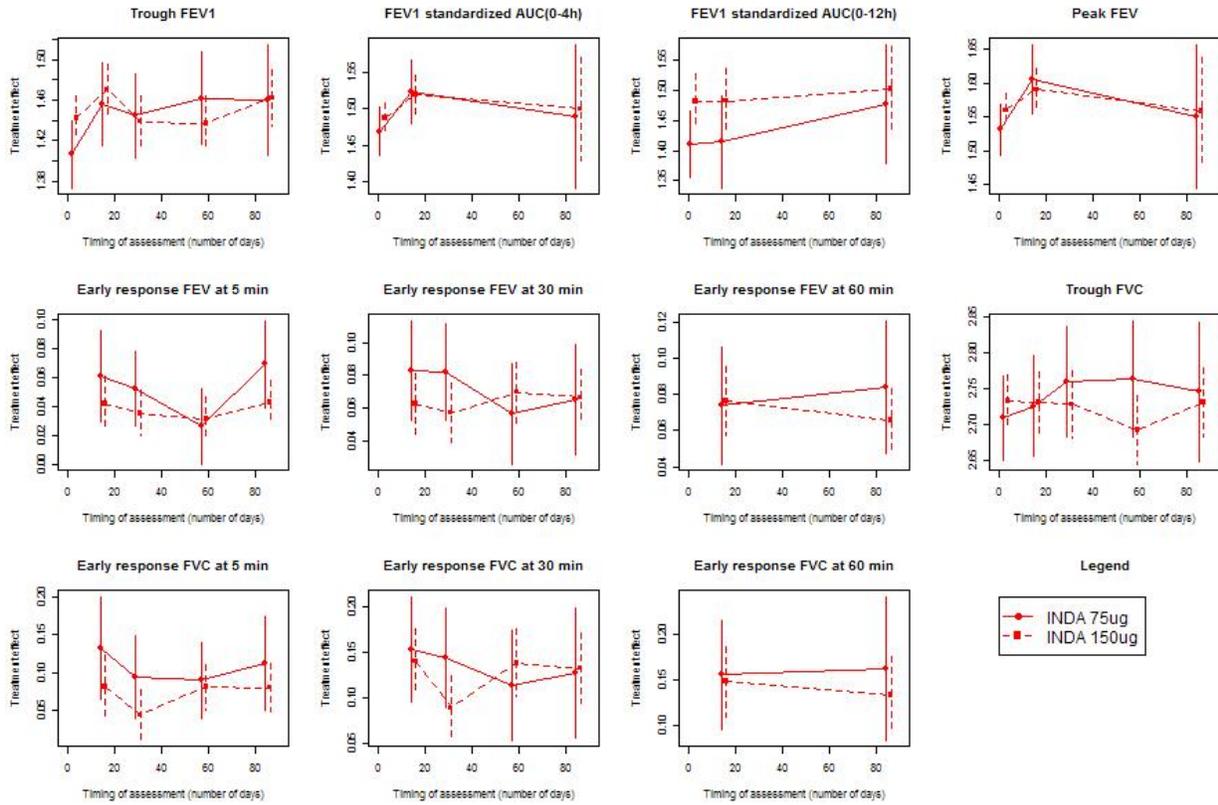


Figure 11 Comparison of spirometry measurements between Indacaterol 75 mcg and 150 mcg at different assessment times in B2335s.

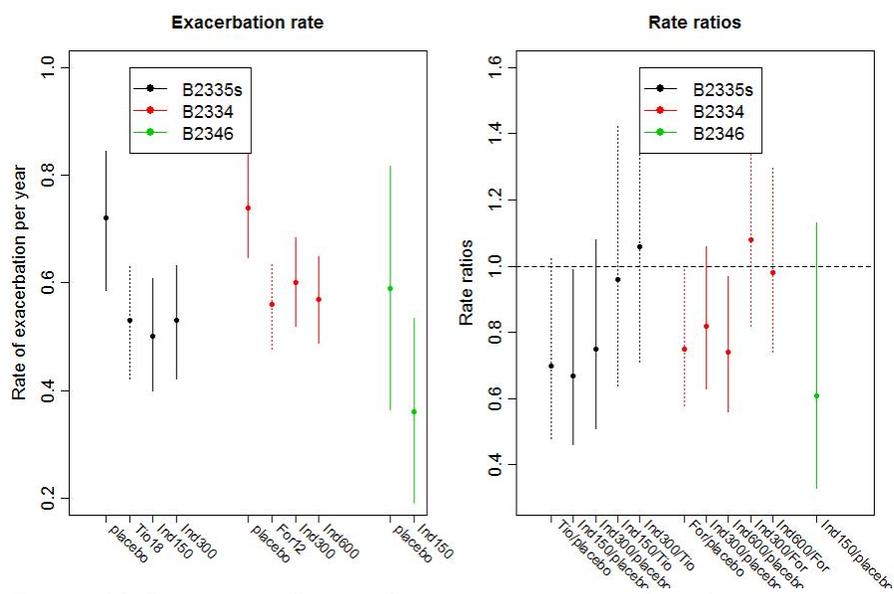


Figure 12 Summary of exacerbation rate in pivotal studies.

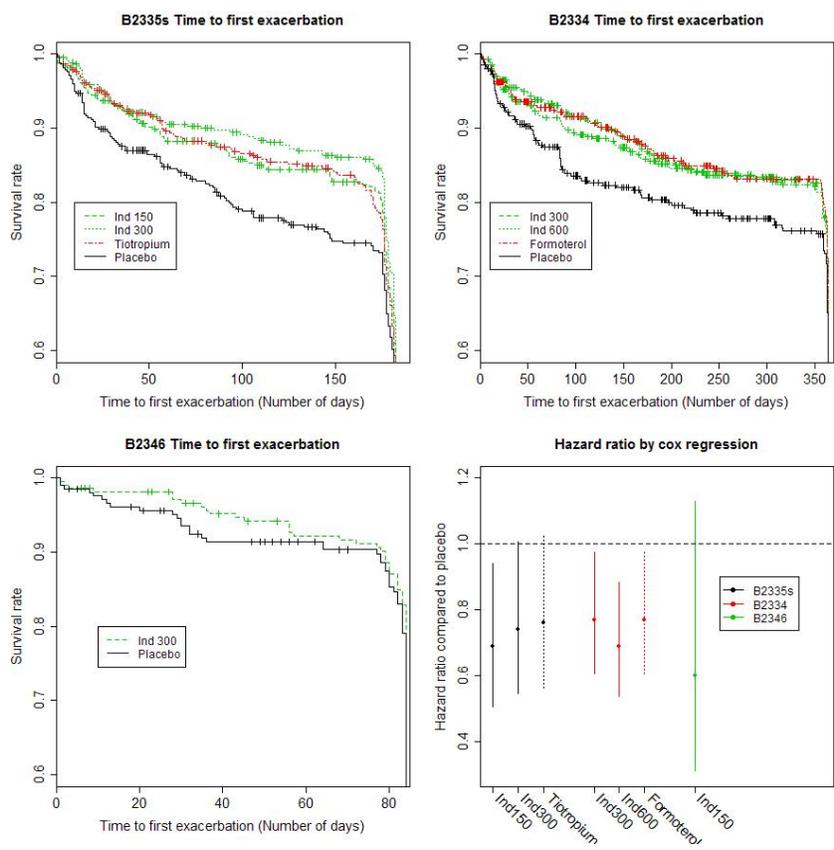


Figure 13 Summary of time to the first exacerbations in pivotal studies.

SIGNATURES/DISTRIBUTION LIST

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	INDACATEROL

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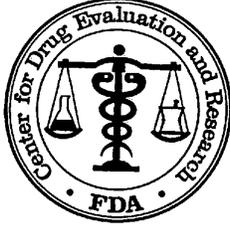
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Drug
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: NDA 22-383

Drug Name: QAB-149 (Trade name: Arcapta™ (b) (4))

Indication(s): 104 weeks regular rat and 26 weeks transgenic mice carcinogenicity studies

Applicant: Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936-1080

Testing Facilities:
Rat: (b) (4)
Mouse: Novartis Pharmaceuticals Corporation, East Hanover, NJ

Documents Reviewed: Submission and data: Rat: Dec 15, 2008
Mouse: June 26, 2009

Review Priority: Standard

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Keywords: Carcinogenicity, Dose-Response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of QAB-149 when administered at appropriate drug levels via inhalation once daily using a snout in rats for about 104 weeks, and orally via gavage in mice for 26 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Robison.

104 Week regular rat study

1.1. Design

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated groups (Groups 3, 4, and 5) and two control groups (Groups 1, and 2). Two hundred and fifty Han Wister Crl:WI (Glx/BRL/Han) IGS BR rats of each sex were randomly allocated to treated and control groups in equal size of 50 animals. The study drug was administered via inhalation once daily using a snout. The targeted dose levels were as follows:

Targeted Aerosol Concentrations and Dose Levels for Rat Study

Dose Group/ Treatment	Target Aerosol Concentration ¹ (mg QAB149/L)	Target Dose ¹ (mg QAB149/kg/day)	Animal Numbers ^{2,3}	
			Males	Females
1 - Air Control	0	0	100-119, 602, 121-149	150-195, 620, 197-199
2 - Air Control*	0	0	200-217, 601, 219-249	250-265, 615, 267-271, 616, 617, 274-299
3 - Low Dose	0.1	0.2	300-349	350-391, 618, 393-399
4 - Intermediate Dose	0.1	0.6	400-422, 603, 424-439, 604, 441-449	450-499
5 - High Dose	0.1	2.0	500-549	550-556, 619, 614, 559-599

The two control groups were identical except Group 2 was housed and dosed in a separate room to allow the animals being housed and dosed in a fully controlled and clean environment for comparison.

Mortality checks were performed twice a day (am and pm) during all phases of the study. Any animals showing signs of severe debility or intoxication and determined to be moribund or suffering excessively were killed. All animals were examined for reaction to treatment daily during the course of the study. Animals were observed pre-dose, intermittently during the inhalation exposure, immediately on completion of exposure and at approximately 1 h after exposure; a further observation was made if the animal had clinical signs after exposure. The onset, intensity and duration of any signs observed were recorded and reported per individual animal. Once each week all animals received a detailed clinical examination and palpation including appearance, movement and behaviour patterns, skin and hair condition, eyes and mucous membranes, respiration and excreta. The size, appearance, position and duration of any masses detected were recorded. Body weights were recorded once weekly commencing one week before the start of treatment until the end of the first 13 weeks of the study. After this, body weights were recorded once every 4 weeks until Week 77 and then once every 2 weeks until the end of the study. Animals showing weight loss or deterioration in condition were weighed more frequently as necessary.

1.2. Sponsor's analyses

1.2.1. Survival analysis

Mortality data is presented graphically using Kaplan-Meier survival curves and pairwise comparisons against Group 1 were made using Wilcoxon rank sum tests modified for censored survival data.

1.2.1.1. Sponsor's findings

The sponsor's analysis showed that there were 12/50 premature deaths in males from Group 5, compared with 8/50, 5/50, 15/50 and 15/50 in Groups 1-4 respectively. Female premature decedents numbered 16/50, 15/50, 16/50, 14/50 and 12/50 in Groups 1-5 respectively. The sponsor considered the differences in mortality between different groups as incidental and not statistically significant. The sponsor stated that the Longevity of all of the groups was similar to the background data of rats of this strain on this kind of study at (b) (4).

1.2.2. Tumor data analysis

Pairwise comparisons of the incidence of tumor and histological lesions were made using the Fisher's exact test. Further analyses were performed using Peto's time adjusted methods. For non-palpable tumors, the Study Pathologist classified each of the tumors as fatal, probably fatal, probably incidental or incidental. For the purposes of statistical analysis, tumors classified as either fatal or probably fatal were considered fatal and those tumors classified as probably incidental or incidental were considered incidental. All tumors detected in animals that died in a planned sacrifice were automatically classified as incidental. For the purposes of statistical analysis, all palpable tumors were considered to be fatal and the time of first detection was used in the age-adjusted analysis. For palpable tumors not detected in-life, the time to death was used in the analysis as time of detection.

Methods used for the age-adjusted analysis of fatal and incidental tumors were based on the IARC guidelines (Peto R *et al*, 1980; Hoel DG and Walburg HE, 1972 and Fairweather WR *et al*, 1998). All age-adjusted analyses of tumor data were performed at the 5% significance level using one sided tests. The analysis of incidental tumors was conducted by dividing the experimental period into the following fixed time intervals: 1-52 weeks, 53-78 weeks, 79-92 weeks, over 92 weeks and a single interval for the terminal sacrifice.

Two separate data sets were used for the statistical analysis of tumor findings (1) Groups 1, 3, 4 and 5 only and (2) Groups 2, 3, 4 and 5 only. For each considered dataset, the significance of a linear dose-related increase in tumor incidence was evaluated using a one-sided trend test. For the purposes of the trend tests, the values 0, 2, 6 and 20 were used as scores. Furthermore, Peto's one-tailed test was also used to test whether or not the tumor incidence in each treated group was significantly higher than Group 1. In addition, Peto analysis was undertaken for anterior pituitary between Groups 1 and 4 and Groups 2 and 4. For each statistical test performed on a dataset containing 10 or less tumors, the discrete permutation distribution was used to calculate the corresponding P-value.

1.2.2.1. Sponsor's findings

Sponsor's evaluation of palpable mass data showed that there were no intergroup differences in the number of animals bearing palpable masses or in the mean time to the onset of palpable masses and no significant

trend in the type of masses observed which could be attributed to treatment with QAB149. The sponsor stated that the palpable swellings recorded were typical of those normally seen in aging rats.

Sponsor's Peto analysis indicated a significant dose-related increase in ovarian leiomyoma when the incidence was compared with either Group 1 or Group 2, although none of the pairwise comparisons of control with treated groups were statistically significant in either case. The sponsor commented that this tumor is an expected finding with this class of compound, and is therefore considered to be related to administration of QAB149. The increased incidence of the related hyperplastic change, focal hyperplasia of ovarian smooth muscle, noted in Group 5 females is also considered to be related to treatment with QAB149. The incidence of anterior lobe pituitary adenomas was increased in Group 4 and 5 males and in Group 5 females, which resulted in an increase in the incidences of combined tumors (adenomas plus carcinomas).

In sponsor's analysis the Peto trend test indicated an increase in the incidence of combined tumors of the anterior lobe of the pituitary gland in both males and females when compared with Control Group 1 ($p=0.017$, $p=0.004$ for males and females respectively) and Control Group 2 ($p=0.028$, $p=0.030$ for males and females respectively). Sponsor's further analysis by excluding group 5 from the analysis, the trend tests were significant for males only compared with Control Group 1 and Control Group 2 ($p=0.020$, $p=0.041$ respectively). The sponsor's pairwise comparisons with Control Group 1, the incidence of this tumor was statistically increased in males from Groups 4 ($p=0.015$) and 5 ($p=0.005$) and in females from Group 5 ($p=0.005$). When these incidences were compared with Control Group 2, statistical significance was achieved only in males in Groups 4 ($p=0.029$) and 5 ($p=0.012$). However, when the p-values are interpreted according to the current FDA guidance (Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, 2001), the suggested threshold for significance for common tumors using pairwise comparison ($p<0.01$) or Peto trend test ($p<0.005$) was not achieved when any treated group was compared with Control Group 2. Based on the lack of a treatment-related effect relative to Control Group 2, the sponsor concluded that the evidence for the apparent increase in comparison with Control Group 1 being related to administration of QAB149 is not convincing.

Sponsor's pairwise comparisons further showed statistically significant increased incidence of mammary gland fibroadenoma in Group 4 females. However, the sponsor considered this incidence to be due to chance, since the incidence in Group 5 females was not increased compared with Group 1; nor was there any evidence of a dose-related increase with Peto analysis when incidences were compared with either Group 1 or Group 2. The sponsor concluded that the increased incidence of mammary fibroadenoma is not related to administration of QAB149.

1.3. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

In this review, the reviewer analyzed the survival and the tumor data. As mentioned before, in this study there were two identical control groups. The first control group was housed in the same room along with the other treated groups, while the second control group was housed and dosed in a separate room to allow the animals being housed and dosed in a fully controlled environment for comparison. Other than this difference the two control groups were identical in every other respect. Also there was no statistically significant difference in survival between these two control groups. Therefore, for both the survival and tumor data analyses this reviewer pooled these two control groups and performed all tests against this pooled control. This way we increase the power of the test (by increasing the group size).

1.3.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the likelihood ratio test and log-rank test, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

1.3.1.1. Reviewer's findings

Reviewer's analysis showed the end of the study mortality rates of 16%, 10%, 30%, 26%, and 24% for male rats in control 1, control 2, low, medium, and high dose groups, respectively, and 30%, 30%, 30%, 28%, and 24% for female rats in control 1, control 2, low, medium, and high dose groups, respectively.

The tests showed no statistically significant dose response relationship in mortality among the treatment groups in either sex. Pairwise comparisons showed statistically significant increased mortality in the low and medium dose groups in male rats.

Reviewer's comment: There were some discrepancies between the sponsor's and this reviewer's calculations of mortalities in male rat medium dose group, and female rat control 1, and low dose groups. These discrepancies are due to the fact that there were two male rats in medium dose group (Animal #426 and #444), one female rat in control 1 (Animal #620) and one female rat in low dose group (Animal #391) that died naturally during the sacrifice period (after week 104). The sponsor considered them as dead, (and counted them among naturally dead animals), while this reviewer considered them as survivors (and counted them among the terminally sacrificed animals).

1.3.2. Tumor data analysis

The tumor data were analyzed for dose response relationship and pairwise comparisons of combined control group with treated groups. The analysis of the tumor data was performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

Multiple testing adjustment: Adjustment for the multiple testing of dose response relationships and pairwise comparisons in the statistical review of carcinogenicity studies from this Division is generally done using the methods stated in the current FDA guidance (2001). This method recommends the use a significance level $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors for a submission with two studies in two species, and a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for a submission with one study in one species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons the guidance recommends to use a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

However, it should be noted that the adjustment methods in the FDA guidance were recommended for long term studies (two year study). The recommendations were based on anticipated number of tumor incidences and therefore number of tests to be performed per study. The present submission consists of one long term study in rats and one short term study in mouse. It is speculated that the short term studies may produce fewer number of tumors compared to long term studies. It is therefore suspected that the recommend test levels in the FDA guidance may not be applicable in this case. The most appropriate solution for this case is not known to this reviewer. To be conservative, this reviewer used the test with significance level of $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for both studies.

1.3.2.1.Reviewer’s findings

Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups (full table in the appendix).

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Sex	Organ Name	Tumor Name	Cont N=100	Low N=50	Med N=50	Hi gh N=50	P_Val ue			
							Dose Resp C vs. L	C vs. M	C vs. H	
Mal e	PI TUI TARY GLAND	ADENOMA, ANTERI OR LO	7	7	11	11	0.0096*	0.1195	0.0094*	0.0071*
		ADENOMA+CARCINOMA*	8	9	12	12	0.0110	0.0516	0.0079*	0.0058*
Femal e	MAMMARY GLAND	FIBROADENOMA [B]	4	4	8	1	0.7099	0.2585	0.0152	0.5366
	OVARY	LEI OMYOMA [B]	0	0	0	2	0.0386*	.	.	0.1078
	PI TUI TARY GLAND	ADENOMA, ANTERI OR LO	31	16	18	28	0.0011*	0.5054	0.3450	0.0027*
		ADENOMA+CARCINOMA*	34	17	19	28	0.0031*	0.5359	0.3776	0.0070*
UTERUS	ADENOCARCINOMA [M]	9	11	7	2	0.9318	0.0340	0.2510	0.7661	

* adenoma+carcinoma= anterior lobe adenoma + intermediate lobe [b] adenoma + anterior lobe carcinoma

Based on the multiple testing adjustment criteria discussed above, the incidences of pituitary gland/adenoma, anterior lobe in male rats, and ovary/leiomyoma [b], pituitary gland/adenoma anterior lobe and combined incidence of pituitary gland adenoma and carcinoma were considered to have statistically significant positive dose response relationship. The pairwise comparisons marked by asterisk were considered to be statistically significant for the increased incidences in the treated groups compared to the combined control.

26 Week Tg.rasH2 Transgenic Mouse study

1.4. Design

Two separate experiments, one in males and one in females were conducted. There were seven treatment groups. One hundred and twenty five CB6F1/Tg.rasH2 hemizygous mice of each sex were randomly allocated to the first five groups (vehicle control, low, medium, high, and positive control groups) in equal size of 25 animals, and fifty CB6F1 wild type mice of each sex were randomly allocated to the last two groups (vehicle control and high dose groups) in equal size of 25 animals. The study drug was administered orally via gavage once daily. The treatment group size and dose levels were as follows:

Group Size and Dose Levels for Tg.rassH2 Mouse Study

Table 3-1 Study design, animal allocation and test article doses (0470002) CB6F1/TgrasH2 (hemizygous mice)					
Group	Number/sex	Animal numbers		Dose Base/Salt* (mg/kg/day)	Conc. Salt* (mg/ml)
		Males	Females		
1	25	1001-25	1501-25	0	0
Control	2 toxicokinetic	1026-27	1526-27		
2	25	2001-25	2501-25	100/129.6	12.96
Low	10 toxicokinetic	2026-35	2526-35		
3	25	3001-25	3501-25	300/388.8	38.88
Mid	10 toxicokinetic	3026-35	3526-35		
4	25	4001-25	4501-25	600/777.6	77.76
High	10 toxicokinetic	4026-35	4526-35		
5	25	5001-25	5501-25	75	7.5
MNU (Positive control)				(dosed IP on day 1 only)	

*Salt/base ratio for QAB149 is 1.296.

Table 3-2 Study design, animal allocation and test article doses (0470002w) CB6F1/TgrasH2 (wild-type mice)					
Group	Number/sex	Animal numbers		Dose Base/Salt* (mg/kg/day)	Conc. Salt* (mg/ml)
		Males	Females		
6	25	6001-25	6501-25	0	0
Control	2 toxicokinetic	6026-27	6526-27		
7	25	7001-25	7501-25	600/777.6	77.76
High	10 toxicokinetic	7026-35	7526-35		

*Salt/base ratio for QAB149 is 1.296.

In order to facilitate on-line data collection, CB6F1/TgrasH2 hemizygous mice were assigned to (b) (4) study number 0470002 and wild-type mice were assigned to the (b) (4) study number 0470002w.

The positive control group received N-methyl-N-nitrosourea (MNU) and the vehicle control received 0.5% (w/v) hydroxypropylcellulose (grade HF), NF (Klucel), aqueous solution.

Each animal was observed twice daily (a.m. and p.m.) and at least once daily on week ends and holidays for mortality. Clinical signs were observed at least once daily. Body weight was observed once on all animals during pretest, and once weekly on all animals during the dosing period. After at least 26 weeks of treatment, all surviving animals were anesthetized with CO₂/O₂ inhalation, exsanguinated, and necropsied. Terminal body weights were also recorded.

Palpable mass examinations were conducted on all animals beginning of Week 2 and every two weeks thereafter. Due to the development of multinodular masses in the perivaginal or scrotal areas of the group 5 positive control animals, only the onset of the first palpable nodule in these areas was recorded a single mass, beginning approximately 16-Jul-2004. When additional apparently associated nodules in these areas were noted, it was described in the palpable mass data as multi-nodular. The onset day was designated as the date of the appearance of the first nodule (mass). Palpable mass data previously recorded as multiple masses was reported by Pathology as a single mass with the earliest onset date.

1.5. Sponsor's analyses

1.5.1. Survival analysis

In this submitted report the sponsor did not mention of any statistical methodologies used for mortality and tumor data analyses. Some summary tables were presented.

1.5.2. Sponsor's Findings

The sponsor's analysis showed the following survival rates male and female mice:

Group Dose (mg/kg/day)	Survival (%)	
	Males	Females
1 (0)	25/25 (100%)	23/23 (100%)*
2 (100)	25/25 (100%)	25/25 (100%)
3 (300)	24/24 (100%)*	24/25 (96%)
4 (600)	23/24 (96%)*	21/24 (88%)*
5 (MNU @75)	6/25 (24%)	8/25 (32%)
6 (0 wild -type)	25/25 (100%)	25/25 (100%)
7 (600 wild-type)	24/25 (96%)	22/23 (96%)*

*= survival adjusted to exclude early sacrifices/deaths attributable to gavage accidents.

The sponsor concluded that there were no QAB149-related effects on mortality/moribundity during the study. There was significant MNU-related mortality/moribundity in the positive control group.

1.5.3. Tumor data analysis

In this submitted report the sponsor also did not mention of any statistical methodologies used for tumor data analyses. Some summary tables were presented.

1.5.4. Sponsor's Findings

The sponsor concluded that there were no QAB149-related effects on the incidence of palpable masses or QAB149-related neoplastic findings observed during the in-life phase of the study.

1.6. Reviewer's analysis

Similar to the rat study, to verify sponsor's findings and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

1.6.1. Survival analysis

The survival data were analyzed using similar statistical methodologies as this reviewer used to analyze the survival data of rat study. The intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 2A and 2B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

1.6.1.1. Reviewer's findings

Reviewer's analysis showed the end of the study mortality rates of 0%, 0%, 0% and 8% for male mice in control, low, medium, and high dose groups, respectively, and 8%, 0%, 0% and 12% for female mice in control, low, medium, and high dose groups, respectively.

The tests showed no statistically significant dose response relationship in mortality among the treatment groups

in either sex. Pairwise comparisons did not show statistically significant increased incidence of mortality in any of the treated groups compared to the control in either sex of mice.

Reviewer’s comment: There were some discrepancies between the sponsor’s and this reviewer’s calculations of mortalities in female mice high dose group. This discrepancy is due to the fact that there was a female mouse in high dose group (Animal #4511) that died naturally during the sacrifice period (after week26). The sponsor considered it as dead, (and counted it among naturally dead animals), while this reviewer considered it as survivors (and counted it among the terminally sacrificed animals).

1.6.2. Tumor data analysis

The tumor data were also analyzed using similar statistical methodologies this reviewer used to analyze the tumor data or rat study.

1.6.2.1. Reviewer’s findings

Following tumor type showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups (full table in the appendix).

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Sex	Organ Name	Tumor Name	Cont	Low	Med	High	P_Val ue		
			N=25	N=25	N=25	N=25	Dose Resp C vs. L	C vs. M	C vs. H
Female	UTERUS	POLYP ENDOMETRIAL ST	0	0	0	3	0.0124*	.	0.1092

Based on the multiple testing adjustment criteria discussed above, the incidence of uterus/endometrial stromal polyp was considered to have statistically significant positive dose response relationship. None of the pairwise comparisons of treated groups with the control for any of the tested tumor types was considered to be statistically significant.

2. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of QAB-149 when administered at appropriate drug levels via inhalation once daily using a snout in rats for about 104 weeks, and orally via gavage in mice for 26 weeks.

In this review, the phrase "dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

2.1. Rat study

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated groups (Groups 3, 4, and 5) and two identical control groups (Group 1, and 2). Two hundred and fifty Han Wister Cr:WI (Glx/BRL/Han) IGS BR rats of each sex were randomly allocated to treated and control groups in equal size of 50 animals. The study drug was administered via inhalation once daily using a snout. The dose levels for treated groups were 0.2, 0.6, and 2.0 mg/kg/day. The controls remained untreated.

The tests showed no statistically significant dose response relationship in mortality among the treatment groups in either sex. Pairwise comparisons showed statistically significant increased mortality in the low and medium dose groups in male rats.

The tests showed statistically significant positive dose response relationships in the incidences of pituitary gland/anterior lobe adenoma in male rats, and ovary/leiomyoma [b], pituitary gland/anterior lobe adenoma and combined incidence of pituitary gland adenoma and carcinoma in female rats. The pairwise comparisons in male rats showed statistically significant increased incidence of pituitary gland anterior lobe adenoma, and combined incidence of pituitary adenoma and carcinoma in medium and high dose groups compared to the combined control. Also the pairwise comparisons in female rats showed statistically significant increased incidence of pituitary gland anterior lobe adenoma, and combined incidence of pituitary adenoma and carcinoma in high dose group compared to the combined control.

2.2. Tg.rassH2 mouse study

Two separate experiments, one in males and one in females were conducted. There were seven treatment groups. One hundred and twenty five CB6F1/Tg.rassH2 hemizygous mice of each sex were randomly allocated to the first five groups (vehicle control, low, medium, high, and positive control groups) in equal size of 25 animals, and fifty CB6F1 wild type mice of each sex were randomly allocated to the last two groups (vehicle control and high dose groups) in equal size of 25 animals. In this review data from the first five groups of CB6F1/Tg.rassH2 hemizygous mice were used. The study drug was administered orally via gavage once daily. The dose levels for treated groups were 100, 300, and 600 mg/kg/day.

The tests showed no statistically significant dose response relationship in mortality among the treatment groups in either sex. Pairwise comparisons did not show statistically significant increased incidence of mortality in any of the treated groups compared to the control in either sex of mice.

The tests showed statistically significant positive dose response relationships in the incidences of uterus/endometrial stromal polyp. None of the pairwise comparisons of treated groups with the control for any of the tested tumor types was considered to be statistically significant.

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3. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	Control 1		Control 2		0.2 mg kg day		0.6 mg kg day		2.0 mg kg day	
	No. of Death	Cum. %								
0 - 52	3	6.00	1	2.00	2	4.00	1	2.00	2	4.00
53 - 78	1	8.00	2	6.00	2	8.00	2	6.00	2	8.00
79 - 91	1	10.00	1	8.00	5	18.00	3	12.00	4	16.00
92 - 104	3	16.00	1	10.00	6	30.00	7	26.00	4	24.00
Ter. Sac.	42	84.00	45	90.00	35	70.00	37	74.00	38	76.00

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Week	Control 1		Control 2		0.2 mg kg day		0.6 mg kg day		2.0 mg kg day	
	No. of Death	Cum. %								
0 - 52	1	2.00	.	.	1	2.00	2	4.00	2	4.00
53 - 78	4	10.00	1	2.00	1	4.00	1	6.00	1	6.00
79 - 91	4	18.00	4	10.00	2	8.00	3	12.00	4	14.00
92 - 104	6	30.00	10	30.00	11	30.00	8	28.00	5	24.00
Ter. Sac.	35	70.00	35	70.00	35	70.00	36	72.00	38	76.00

**Table 2A: Intercurrent Mortality Comparison*
Male Rats**

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.9226
Homogeneity	Log-Rank	0.0517

*Tests were performed using combined control

**Table 2B: Intercurrent Mortality Comparison*
Female Rats**

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.2626
Homogeneity	Log-Rank	0.8561

*Tests were performed using combined control

**Table 3A: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Male Rats**

Organ Name	Tumor Name	0 mg	0.2 mg	0.6 mg	2.0 mg	P_Val ue	P_Val ue C vs. L	P_Val ue C vs. M	P_Val ue C vs. H
		Cont N=100	Low N=50	Med N=50	Hi gh N=50	Dos Resp			
ABDOMI NAL CAV	FI BROSARCOMA [M]	0	0	1	0	0.3973	.	0.3285	.
	MESOTHELI OMA [M]	0	1	0	0	0.3956	0.3235	.	.
ADRENAL GLAND	CORTI CAL ADENOMA [B]	2	0	0	0	0.8324	0.5372	0.5507	0.5440
	PHAECHROMOCYTOMA [B]	0	0	2	0	0.3946	.	0.1063	.
BRAI N	GRANULAR CELL TUMOR	0	0	0	1	0.1964	.	.	0.3235
EAR	FI BROMA [B]	0	0	1	0	0.4000	.	0.3333	.
EPI DI DYMI S	LI POSARCOMA [M]	0	1	0	0	0.3956	0.3235	.	.
	MESOTHELI OMA [M]	0	0	1	0	0.3973	.	0.3285	.
FEMUR	OSTEOSARCOMA [M]	0	0	1	1	0.1172	.	0.3285	0.3235
HARDERIAN GLAND	ADENOMA [B]	1	0	0	0	0.5867	0.3162	0.3261	0.3212
HEART	MALI GNANT SCHWANNOMA	1	0	0	0	0.5893	0.3185	0.3285	0.3235
	MYXOMA [B]	0	1	0	0	0.3973	0.3185	.	.
	PARAGANGLI OMA [B]	1	0	0	0	0.5893	0.3185	0.3285	0.3235
HEMOPOI ETIC SYS	HI STIOCYTI C SARCOMA	1	0	0	0	0.5867	0.3162	0.3261	0.3212
	LYMPHOMA [M]	1	0	1	0	0.4731	0.3185	0.5572	0.3235
LI VER	HAEMANGI OSARCOMA [M]	1	0	0	0	0.5893	0.3185	0.3285	0.3235
	HEPATOCELLULAR ADENO	1	0	0	0	0.5893	0.3185	0.3285	0.3235
	HEPATOCELLULAR CARCI	1	0	0	0	0.5867	0.3162	0.3261	0.3212
MAMMARY GLAND	FI BROMA [B]	0	1	0	0	0.3973	0.3185	.	.
MESENTERI C LN	HAEMANGI OMA [B]	4	0	0	0	0.9726	0.7888	0.8010	0.7951
	HAEMANGI OSARCOMA [M]	2	1	0	0	0.8347	0.6868	0.5507	0.5440
	LYMPHANGI OMA [B]	0	1	0	0	0.3973	0.3185	.	.
ORAL CAVI TY	SQUAMOUS-CELL CARCIN	0	1	0	0	0.3956	0.3235	.	.
PI TUITARY GLAND	ADENOMA, ANTERI OR LO	7	7	11	11	0.0096*	0.1195	0.0094*	0.0071*
	ADENOMA, I NTERMEDI AT	1	2	1	0	0.6991	0.2380	0.5507	0.3235
	CARCI NOMA, ANTERI OR	0	0	0	1	0.1964	.	.	0.3235
	ADENOMA+CARCI NOMA	8	9	12	12	0.0110	0.0516	0.0079*	0.0058*
SKELETAL MUSCLE	FI BROSARCOMA [M]	1	0	0	0	0.5893	0.3185	0.3285	0.3235
SKI N AND SUBCUT	BASAL CELL ADENOMA [0	1	0	0	0.3956	0.3235	.	.
	FI BROLI POMA [B]	1	0	0	0	0.5893	0.3185	0.3285	0.3235
	FI BROMA [B]	0	0	1	1	0.1172	.	0.3285	0.3235
	FI BROSARCOMA [M]	0	0	2	0	0.3946	.	0.1063	.
	KERATOACANTHOMA [B]	2	3	4	4	0.0907	0.1917	0.0906	0.0906
	PAPI LLOMA [B]	1	0	0	0	0.5893	0.3185	0.3285	0.3235

**Table 3B: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Female Rats**

Organ Name	Tumor Name	0 mg	0.2 mg	0.6 mg	20 mg	P_Val ue	P_Val ue C vs. L	P_Val ue C vs. M	P_Val ue C vs. H
		Cont N=100	Low N=50	Med N=50	Hi gh N=50	Dos Resp			
ADRENAL GLAND	CORTI CAL ADENOMA [B]	1	1	1	0	0.5883	0.5605	0.5539	0.3308
	PHAECHROMOCYTOMA [B]	1	0	0	0	0.5991	0.3358	0.3308	0.3308
BRAI N	GRANULAR CELL TUMOR	0	0	0	1	0.1982	.	.	0.3308
CAECUM	LEI OMYOSARCOMA [M]	1	0	0	0	0.5991	0.3358	0.3308	0.3308
CERVIX	ADENOCARCI NOMA [M]	0	0	1	0	0.3964	.	0.3308	.
	STROMAL POLYP [B]	1	1	0	0	0.6771	0.5605	0.3308	0.3308
	STROMAL SARCOMA [M]	1	0	0	0	0.5991	0.3358	0.3308	0.3308
DUODENUM	LEI OMYOSARCOMA [M]	1	0	0	0	0.5991	0.3358	0.3308	0.3308
HEART	MALI GNANT SCHWANNOMA	0	0	1	0	0.3964	.	0.3308	.
	PARAGANGLI OMA [B]	0	0	0	1	0.1982	.	.	0.3308
HEMOPOI ETIC SYS	LYMPHOMA [M]	2	1	0	1	0.4584	0.7070	0.5506	0.7004
LIV ER	HEPATOCELLULAR ADENO	0	0	1	0	0.3964	.	0.3308	.
MAMMARY GLAND	ADENOCARCI NOMA [M]	1	1	0	0	0.6771	0.5605	0.3308	0.3308
	ADENOMA [B]	0	1	0	0	0.3964	0.3358	.	.
	FI BROADENOMA [B]	4	4	8	1	0.7099	0.2585	0.0152	0.5366
MESENTERI C LN	HAEMANGI OMA [B]	1	0	0	0	0.5991	0.3358	0.3308	0.3308
	LYMPHANGI OMA [B]	1	0	0	0	0.5991	0.3358	0.3308	0.3308
ORAL CAVI TY	SQUAMOUS-CELL CARCI N	1	0	0	1	0.3636	0.3358	0.3308	0.5605
OVARY	CYSTADENOMA [B]	0	0	1	0	0.3991	.	0.3358	.
	GRANULOSA CELL TUMOU	4	1	1	3	0.2262	0.5466	0.5366	0.4234
	LEI OMYOMA [B]	0	0	0	2	0.0386*	.	.	0.1078
	LUTEOMA [B]	0	1	0	0	0.3964	0.3358	.	.
	SERTOLI CELL TUMOR	0	1	0	0	0.3964	0.3358	.	.
TUBULOSTROMAL ADENOM	0	1	0	0	0.3964	0.3358	.	.	
PANCREAS	ISLET CELL ADENOMA [1	0	0	0	0.5991	0.3358	0.3308	0.3308
PARATHYROID GLN	ADENOMA [B]	0	1	0	0	0.3964	0.3358	.	.
PHARYNX	SQUAMOUS-CELL CARCI N	0	1	0	0	0.3964	0.3358	.	.
PI TUITARY GLAND	ADENOMA, ANTERI OR LO	31	16	18	28	0.0011*	0.5054	0.3450	0.0027*
	ADENOMA, I NTERMEDI AT	2	0	1	0	0.6863	0.5605	0.7037	0.5539
	CARCI NOMA, ANTERI OR	1	1	0	0	0.6771	0.5605	0.3308	0.3308
	ADENOMA+CARCI NOMA	34	17	19	28	0.0031*	0.5359	0.3776	0.0070*
SALV GLND PAROT	ADENOMA [B]	0	0	1	0	0.3964	.	0.3308	.

**Table 4A: Intercurrent Mortality Rate
Male Mice**

Week	0 mg kg day		100 mg kg day		300 mg kg day		600 mg kg day	
	No. of Death	Cum. %						
0 - 10	1	4.00	.	.
11 - 15	1	4.00
21 - 26	1	8.00
Ter. Sac.	25	100.00	25	100.00	24	96.00	23	92.00

**Table 4B: Intercurrent Mortality Rate
Female Mice**

Week	0 mg kg day		100 mg kg day		300 mg kg day		600 mg kg day	
	No. of Death	Cum. %						
0 - 10	1	4.00
16 - 20	1	4.00	.	.
21 - 26	2	8.00	2	12.00
Ter. Sac.	23	92.00	25	100.00	24	96.00	22	88.00

**Table 5A: Intercurrent Mortality Comparison*
Male Mice**

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.7404
Homogeneity	Log-Rank	0.2947

**Table 5B: Intercurrent Mortality Comparison*
Female Mice**

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.8211
Homogeneity	Log-Rank	0.1555

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

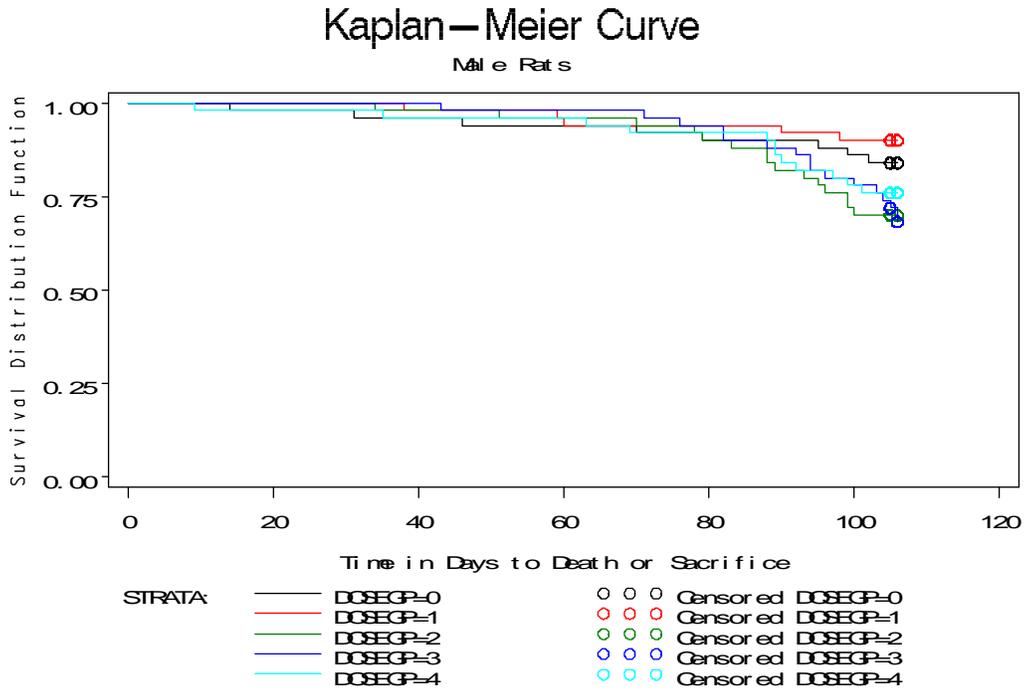


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

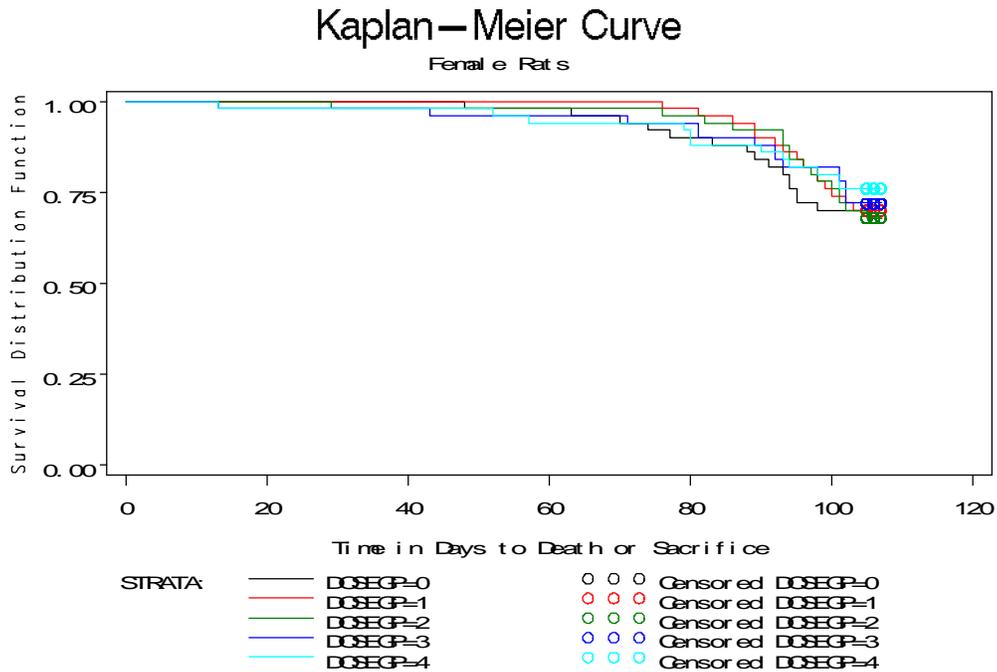


Figure 2.1A: Kaplan-Meier Curve for Time to First Actual Papillomas Male Mice

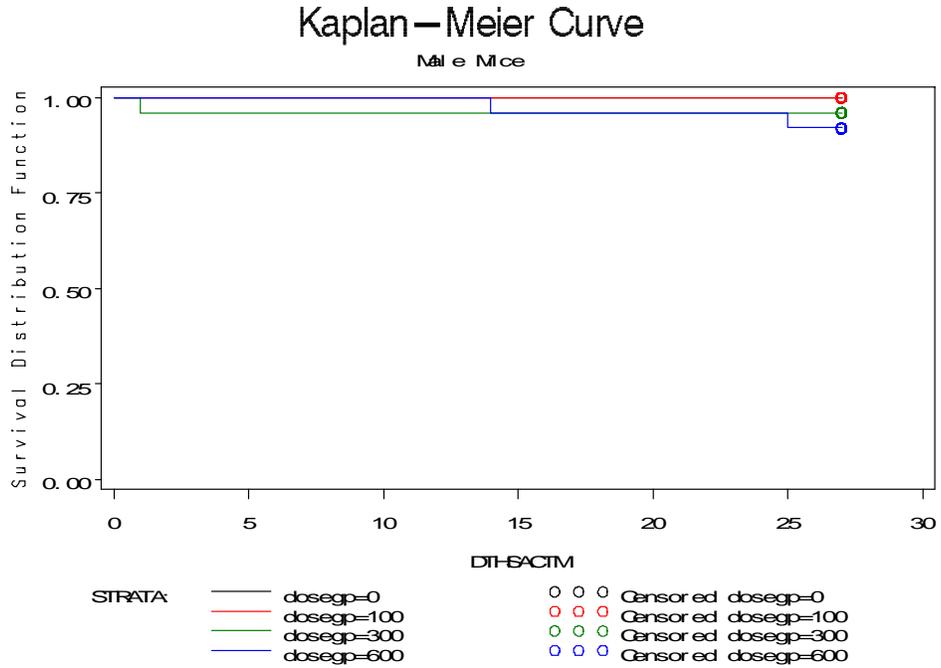
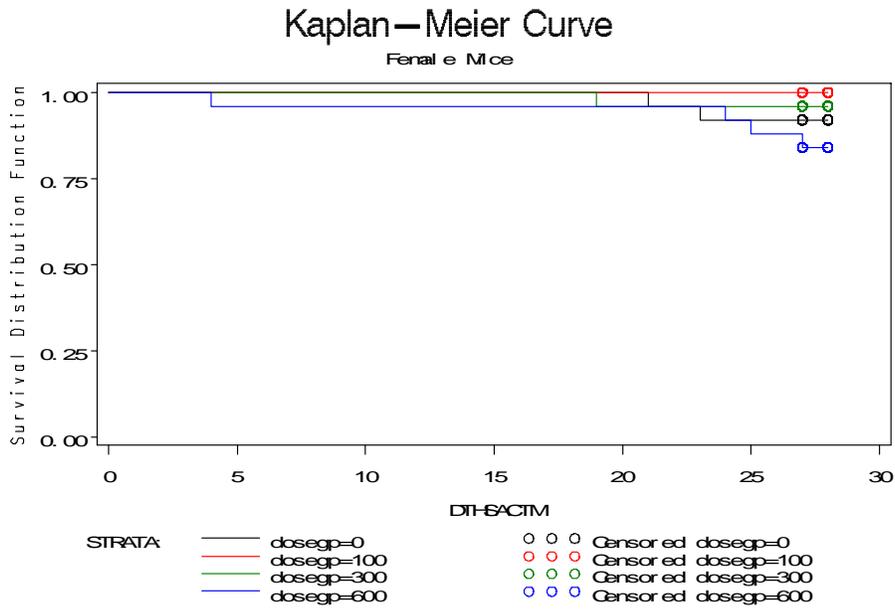


Figure 2.1A: Kaplan-Meier Curve for Time to First Actual Papillomas Female Mice



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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22383	ORIG 1		INDACATEROL
NDA 22383	ORIG 1		INDACATEROL

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/s/

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Concur with review