CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Addendum

Date	June 30, 2011
From	Theresa M. Michele, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-383, Complete Response Resubmission
Applicant	Novartis Pharmaceuticals
Date of Submission	October 1, 2010
PDUFA Goal Date	April 1, 2011 extended to July 1, 2011
Proprietary Name / Established (USAN) names	Arcapta Neohaler/ indacaterol maleate
Dosage forms / Strength	inhalation powder/ 75 and 150 mcg once daily
Proposed Indication(s)	Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
Recommended:	75 mcg dose: Approval 150 mcg dose: Complete Response

1. Introduction

This CDTL review addendum addresses issues raised in the open public hearing of the Pulmonary Allergy Drugs Advisory Committee (PADAC) Meeting for Arcapta Neohaler on March 8, 2011, and by the clinical reviewer, Dr. Anya Harry, in a review addendum dated April 5, 2011. In addition, this addendum addresses issues regarding dose selection and modeling raised by Novartis during labeling negotiations in a background package submitted to the NDA on May 18, 2011 and in a face-to-face meeting with FDA on May 31, 2011. All of these issues arose subsequent to the date of the CDTL review finalization (March 1, 2011). The primary points to be addressed are:

- Ethical issues related to use of placebo control arms in the indacaterol program
- Justification for approval of the 75 mcg dose versus a lower dose
- Novartis modeling analysis as support for 150 mcg dose
- Cardiovascular safety analysis

2. Regulatory history

Novartis submitted the initial 505(b)(1) new drug application (NDA 22-383) on December 15, 2008, for the use of Arcapta Neohaler (indacaterol maleate dry powder for inhalation) at doses of 150 and 300 mcg as a once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic

bronchitis and/or emphysema. FDA took a complete response action on this application on October 16, 2009. Key issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma-related deaths compared to salmeterol in patients with asthma. In addition, the dose and dosing frequency were not adequately explored, with no clinically meaningful difference between 75 mcg once daily and the proposed doses of 150 and 300 mcg. Novartis submitted a complete response on October 1, 2010. The proposed dose of indacaterol is lowered to 75 mcg or 150 mcg once daily based on data from additional clinical studies.

The PDUFA due date for this complete response application was extended from April 1, 2011 to July 1, 2011 in order to provide time for a full review of a solicited major amendment submitted February 8, 2011, within 3 months of the user fee goal date. The major amendment consisted of a blinded adjudicated meta-analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation. The Agency believed that such an analysis was necessary to provide balancing safety data to justify the proposed higher dose (150 mcg) of indacaterol and to attempt to evaluate whether a safety signal for asthma-related death might exist in COPD.

2. Ethical issues

In the open public forum of the PADAC meeting and again in letters to Dr. Woodcock, Director of the Center for Drug Evaluation and Research, FDA (March 16, 2011); Dr. Menikoff, Director of the Office for Human Research Protection (March 16, 2011); and Secretary Sebelius, Department of Health and Human Services (April 28, 2011), the consumer advocacy group Public Citizen raised the complaint that Novartis conducted a "series of unethical, placebo-controlled clinical trials testing the experimental drug indacaterol in human subjects with moderate to severe COPD that were conducted at multiple US institutions." The specific ethical concerns raised include the use of placebo control groups in the clinical trials, failure to minimize risk to participants, and inadequate informed consent.

The trials conducted in the United States identified by Public Citizen as having ethical issues are:

- Trial B2335
- Trial B2346
- Trial B2354
- Trial B2355

In addition, Public Citizen identified the following trials conducted in countries outside of the United States as having ethical issues:

- Trial B2334
- Trial B2336

For the purposes of this review, discussion of specific details will focus on the trials with US sites that were conducted under IND. However, Trials B2334 and B2336 had a similar design to the other trials, and the discussion generally applies.

2.1. Placebo control

There are a number of advantages of placebo controlled trials. As noted in the ICH E10 guidance, "*the placebo control design, by allowing blinding and randomization and including a group that receives an inert treatment, controls for all possible influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug. These influences include spontaneous change (natural history of the disease and regression to the mean), subject or investigator expectations, the effect of being in a trial, use of other therapy, and subjective elements of diagnosis or assessment."* These advantages apply both for efficacy as well as safety. Both the FDA and EMA guidances for COPD note that the most useful comparator in COPD trials is placebo.[1, 2, 3]

The ICH E10 guidance goes on to state: "*The use of a placebo control group does not imply that the control group is untreated. In many placebo-controlled trials, the new treatment and placebo are each added to a common standard therapy."* In the case of the indacaterol trials, patients were permitted to receive inhaled corticosteroids (ICS) and albuterol rescue medication (short-acting beta2-agonist; SABA) in place of an inhaled steroid, long-acting beta agonist (ICS/LABA) combination product. During exacerbations, investigators were allowed to prescribe whatever COPD medication they deemed appropriate for the patient.

In contrast to the benefits, the ICH E10 guidance also notes that placebo-controlled designs are inappropriate "*in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population*." For COPD, medications are approved primarily for symptomatic relief (i.e. bronchodilation), and no currently approved therapies prevent death or irreversible morbidity by influencing the course of disease (e.g. disease progression), suggesting that placebo-controlled trials may be ethical.

Another serious outcome in COPD is exacerbations. An argument could be made that medications known to prevent COPD exacerbations should be permitted as background therapy in all treatment groups because patients may potentially be harmed by having an exacerbation. Currently, there are three medications approved in the United States to reduce COPD exacerbations:

- Advair Diskus (fluticasone propionate and salmeterol xinafoate; a combination of an ICS and LABA), approved April 2008 for reducing exacerbations in patients with COPD
- Spiriva HandiHaler (tiotropium bromide, a long-acting anticholinergic), approved December 2009 for reducing COPD exacerbations
- Daliresp (roflumilast, a phosphodiesterase 4 inhibitor), approved February 2011 to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

1 FDA Draft Guidance: Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment, November 2007
2 EMA Draft Guidance: Guideline on clinical investigation of medicinal products in the treatment of Chronic Obstructive Pulmonary Disease (COPD), July 2010
3 EMA Points to Consider on Clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD), May 1999

There are a number of considerations regarding COPD exacerbations in clinical trials that impact the use of these medications in the indacaterol clinical trials. First, the time course of these trials in relationship to the approval of medications for COPD exacerbations is important. All of the trials in question were designed prior to the approval of tiotropium and roflumilast for COPD exacerbations. The roflumilast approval came after the NDA Complete Response for Arcapta Neohaler was submitted to FDA. In addition, Trials B2335 (52 week duration) and B2346 (12 week duration) were designed prior to approval of fluticasone/salmeterol. Of note, patients who were taking the combination product of fluticasone/salmeterol at the start of the trials were not taken off therapy, but were switched to the monocomponent (fluticasone) at an equivalent dose and a short-acting beta-agonist (SABA). The other ICS/LABA combination agent, Symbicort (budesonide/formoterol fumarate), is not approved for reduction in exacerbations.

Based on the data from the trials, a minority of patients were taking a LABA or tiotropium at the start of the trial. Baseline medications were comparable across treatment groups. See Table 1.

Table 1: Indacaterol trial baseline medications (placebo groups)

Trial number	Protocol finalization	N placebo	ICS n (%)	LABA n (%)	LABA/ICS combo n (%)	Advair n (%)	Spiriva n (%)
B2335	15-Dec 2006 14-Feb-2008 (extension)	418	165 (39.5)	21 (5.0)	104 (24.9)	87 (20.8)	80 (19.1)
B2346	17-Jan-2008	205	70 (34.1)	6 (2.9)	54 (26.3)	52 (24.9)	30 (14.6)
B2354	14-Dec-2009	160	76 (47.5)	10 (6.3)	51 (31.9)	45 (28.1)	62 (38.8)
B2355	10-Dec-2009	159	56 (35.2)	6 (3.8)	46 (28.9)	39 (24.5)	34 (23.3)

Because the number of exacerbations a patient has during a year is relatively small, it is anticipated that less than one exacerbation over a 3 to 12 month time course will be prevented with fluticasone/salmeterol, and the effect is likely contributable to both components.

- In two one year clinical trials, treatment with Advair Diskus 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% confidence interval (CI): 17.0, 41.8], p<0.001) in the first study and (30.4% reduction [95% confidence interval (CI): 16.9, 41.7]. p<0.001]) in the second study[4].

This translates to 1.06 moderate to severe exacerbations per patient year in the Advair Diskus group versus 1.53 for salmeterol in the first study and 1.10 versus 1.59 in the second study. These trials were enriched for patients who had a history of frequent exacerbations. In the long-term (3 year) TORCH trial conducted in an unenriched population, there was an annual

4 Advair product label.

rate of moderate-severe exacerbations of 0.85 in the Advair Diskus group, 0.97 in the salmeterol group, and 1.13 in the placebo group[5]. The annual rate of exacerbations requiring hospitalization was 0.16 in the Advair Diskus group, 0.16 in the salmeterol group, and 0.19 in the placebo group. These data suggest that changing an ICS/LABA to ICS and SABA (as needed) is unlikely to cause significant harm in the short term by precipitating frequent COPD exacerbations. In addition, large, long-term exposure trials were necessary to demonstrate effect of ICS/LABA on COPD exacerbations, suggesting that exposure to ICS and as needed SABA in a short-term trial does not put the individual patient at undue risk.

Although tiotropium was not approved for exacerbations until after finalization of all of the indacaterol protocols in question, similar arguments can be made for tiotropium as for ICS/LABA.

- Spriva HandiHaler significantly reduced the risk of exacerbation [in a 4 year 5992 patient trial] by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p<0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p<0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HandiHaler group[6]. [Placebo patients were permitted to take SABA, LABA, ICS, systemic steroids, and theophyllines.]

For tiotropium, these data translate to a rate of moderate to severe exacerbations of 0.73 per patient year in the Spiriva HandiHaler group versus 0.85 per patient year in the placebo group. The number of exacerbation-related hospitalizations per patient year was 0.15 in the Spiriva HandiHaler group compared to 0.16 in the placebo group.

The ethical issues raised by the Public Citizen group were also evaluated outside the Division, with a consult to Dr. Sara Goldkind, Senior Bioethicist, Office of Good Clinical Practice, Office of the Commissioner, Food and Drug Administration. Dr. Goldkind generally agreed with the conclusions of the Division regarding the ethical use of placebo in the indacaterol trials, stating:

"the study design, i.e., placebo-controlled "add-on" arms, involving ICS + SABA, as well as the risk minimization strategies employed in the pivotal COPD studies of 12-26 week duration submitted under NDA 22-383, are ethically acceptable."

2.2. Participant risk

All medical interventions, including clinical trials, carry some level of participant risk. Because the benefits may not be clearly defined, clinical trials carry design elements intended to minimize risk to participants. These design elements vary by individual trial, but in addition to Investigational Review Board (IRB) protocol review and oversight, may include Data Safety Monitoring Board (DSMB) oversight, escape rules, rescue medications/procedures, exclusion of patients who may be at greater risk for negative outcomes, minimizing time on placebo, and close monitoring of study subjects. The primary risks identified in these trials identified by Public Citizen are all related to inclusion of a "placebo" control group, which

5 Calverly PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New Eng J Med 356:775-89, 2007.
6 Spiriva HandiHaler product label.

may have put patients at greater risk of death or other serious COPD-related outcomes. Serious COPD-related outcomes are primarily exacerbations.

Because all of the trials in question (B2335, B2346, B2335, and B2355) employed standard designs for COPD trials that were not deemed to pose an unusual level of risk for study participants, none of the trials in question used a DSMB for safety evaluations. All four trials had similar escape rules, rescue medications/procedures, and exclusion criteria for patients who may be at greater risk of negative outcomes. Duration and monitoring frequency varied by trial. See Table 2.

Table 2: Trial design elements to minimize risk

Trial number	Protocol finalization	Escape	Rescue	Exclusions	Duration	Monitoring frequency
B2335	15-Dec 2006 14-Feb-2008 (extension)	Any reason, any time	SABA, any therapy for exacerbation	Very severe COPD, recent exacerbations	26 + 26 wks	1-8 wks
B2346	17-Jan-2008	Any reason, any time	SABA, any therapy for exacerbation	Very severe COPD, recent exacerbations	12 wks	4 wks
B2354	14-Dec-2009	Any reason, any time	SABA, any therapy for exacerbation	Very severe COPD, recent exacerbations	12 wks	4 wks
B2355	10-Dec-2009	Any reason, any time	SABA, any therapy for exacerbation	Very severe COPD, recent exacerbations	12 wks	4 wks

In all of the trials, patients were permitted to discontinue from the trial for any reason at any time. In addition, the protocols stated that "study medication must be discontinued and the patient withdrawn from the study for … any significant risk to the patient's safety." Also, in Trial B2335 (52 weeks duration) patients were discontinued who experienced more than two COPD exacerbations in a three month period or who were intubated for a COPD exacerbation.

With regard to rescue medication, all patients were issued albuterol inhalers as part of the study medication for as needed use. SABA therapy is considered standard of care as a rescue medication in COPD. During an exacerbation, investigators were permitted to use whatever medication they deemed necessary, although systemic corticosteroids (oral or IV) and antibiotics were suggested as first line therapy. This is also consistent with guidelines and standard of care for COPD. Patients were permitted to continue in the trial regardless of what therapies for exacerbation were used, with the exception of IM depot corticosteroids. IM depot corticosteroids are rarely, if ever, used to treat COPD in the US, and do not appear as a choice in the GOLD report 2009.[7]

A number of exclusion criteria were in place in these protocols to prevent patients who could be at greater risk of exacerbation from being enrolled. Most importantly, patients with an FEV1 of < 30% predicted, corresponding to GOLD stage IV (very severe) disease, were

7 The Global Strategy for Diagnosis, Management, and Prevention of COPD (updated 2009), www.goldcopd.org.

excluded from the trials. In addition, patients requiring oxygen therapy for chronic hypoxia, who had a COPD exacerbation within 6 weeks of screening, or who had an upper respiratory tract infection within 6 weeks of screening were also excluded. Finally, patients with other lung diseases, including COPD due to alpha-1-antitrypsin deficiency or with significant bronchiectasis, were excluded.

Most pulmonologists will give a COPD patient a trial of 2-3 months of therapy before determining whether or not the patient's symptoms have changed with that therapy. In addition, studies showing a benefit on COPD exacerbations have a minimum duration of 6 months, although most are of 12 months or longer. Given this, it seems unlikely that exposure to ICS and SABA (as needed) ("placebo") for a duration of 12 weeks could have a significant detrimental effect on patients. The trial that was of longer duration (B2335) had additional safeguards of discontinuing patients with frequent exacerbations or a very severe exacerbation.

While the frequency of visits for patients with COPD varies with the health care system, in the United States, most COPD patients are seen by their provider for this diagnosis alone (i.e. those seen by pulmonologists) every 3-12 months. Stable patients with moderate to severe disease, such as those enrolled in these trials, are generally monitored every 6-12 months, whereas patients with frequent exacerbations or very severe disease (excluded in these trials) are seen approximately every 3 months. Pulmonary function tests (PFTs), which can be used as a sign of deterioration or disease progression, are generally performed once a year. In these trials, patients were monitored much more frequently, PFTs were performed at every visit, and patients completed a daily symptom diary. Further, COPD exacerbations were considered an endpoint in the trials, with a specific definition and corresponding evaluation. In the 12 week trials (B2346, B2354, and B2355), clinic visits occurred every 4 weeks. In trial B2335, clinic visits occurred weekly for the first 3 weeks, biweekly for one visit, then every 4 weeks out to Week 26. Once patients entered the extension, they were monitored every 8 weeks for the remainder of the trial out to Week 52. Given this extremely frequent monitoring schedule, it seems unlikely that a patient with frequent exacerbations or other negative respiratory outcomes could go unnoticed.

2.3. Informed consent

The Division of Scientific Investigation was asked to review the informed consents for these trials to evaluate the validity of the Public Citizen claim that patients were not informed that they had a 25-50% chance of receiving placebo and were inadequately informed of the risks of being on placebo. As part of this review, the informed consent template was reviewed for each study. Because these were multicenter trials conducted under the auspices of multiple individual IRBs, it is expected that some modifications may have been made in the final informed consent documents used by individual study sites.

All of the informed consent documents informed patients that they had a chance of being assigned to a placebo treatment regimen during the trial, including exact numbers (i.e. 1 in 2 chance), and described what a placebo is ("an inhaler containing a dummy medicine with no active ingredients"). Likewise, all of the informed consents informed patients that "if you are now being treated with any medicines these may be stopped or changed." The FDA does not generally expect informed consent documents to describe risks associated with placebo, although if there were substantial risks associated with a switch from a LABA to a SABA this should be described. As noted in Sections 3.1. and 3.3., in the short term, it is unlikely that a

switch from LABA to SABA would result in substantial harm to the patient. The extension protocol B2335SE, which continued patients on randomized treatment out to 52 weeks, did have language in the informed consent that noted "your condition may worsen" while on placebo.

3. Dose selection

In the open public forum of the PADAC meeting and in a letter to Dr. Woodcock, the consumer advocacy group Public Citizen made the recommendation against approval of indacaterol (Arcapta Neohaler) at the proposed 75 mcg dose due to concerns that the appropriate lower dose has not been determined. In the letter to Dr. Woodcock, Public Citizen makes the following recommendations:

"In the interests of protecting the public health, the FDA should reject the recommendation of the PADAC to approve indacaterol at the 75 mcg dose and not approve indacaterol at any dose because:

(1) There is no evidence of any efficacy advantage of the 75 mcg dose over the 37.5 mcg dose, or any dose in between. Thus, the lowest effective dose of indacaterol in patients with moderate to severe COPD has not been established.

(2) The available data from the studies on indacaterol fail to provide sufficient information to determine whether indacaterol is safe in the intended COPD patient population, even for the 75 mcg dose. The dose versus toxicity-response curve for indacaterol is not yet well-defined, but from a public health standpoint, a 37.5 mcg dose will likely have a lower probability of serious toxicity than the 75 mcg dose.

(3) Indacaterol offers no clinically significant advantages over available FDA-approved long-acting bronchodilators.

(4) Once approved, the drug will certainly be used off-label in asthmatics, who would be placed at increased risk of serious adverse events, including death, from indacaterol as has been seen with other LABAs."

As part of the Complete Response for NDA 22-383, Novartis submitted an integrated analysis of bronchodilatory dose response based on a modeling approach of indacaterol in COPD. FDA concluded that there were inherent flaws in the analyses that limit the utility of the findings as presented at the PADAC meeting. During the labeling negotiations, Novartis provided an additional briefing document to address issues raised during the FDA review and further support their request for approval of a 150 mcg dose in patients with more severe disease. The additional briefing document was submitted on May 18, 2011 and was discussed on May 31, 2011, during a face-to-face meeting with FDA.

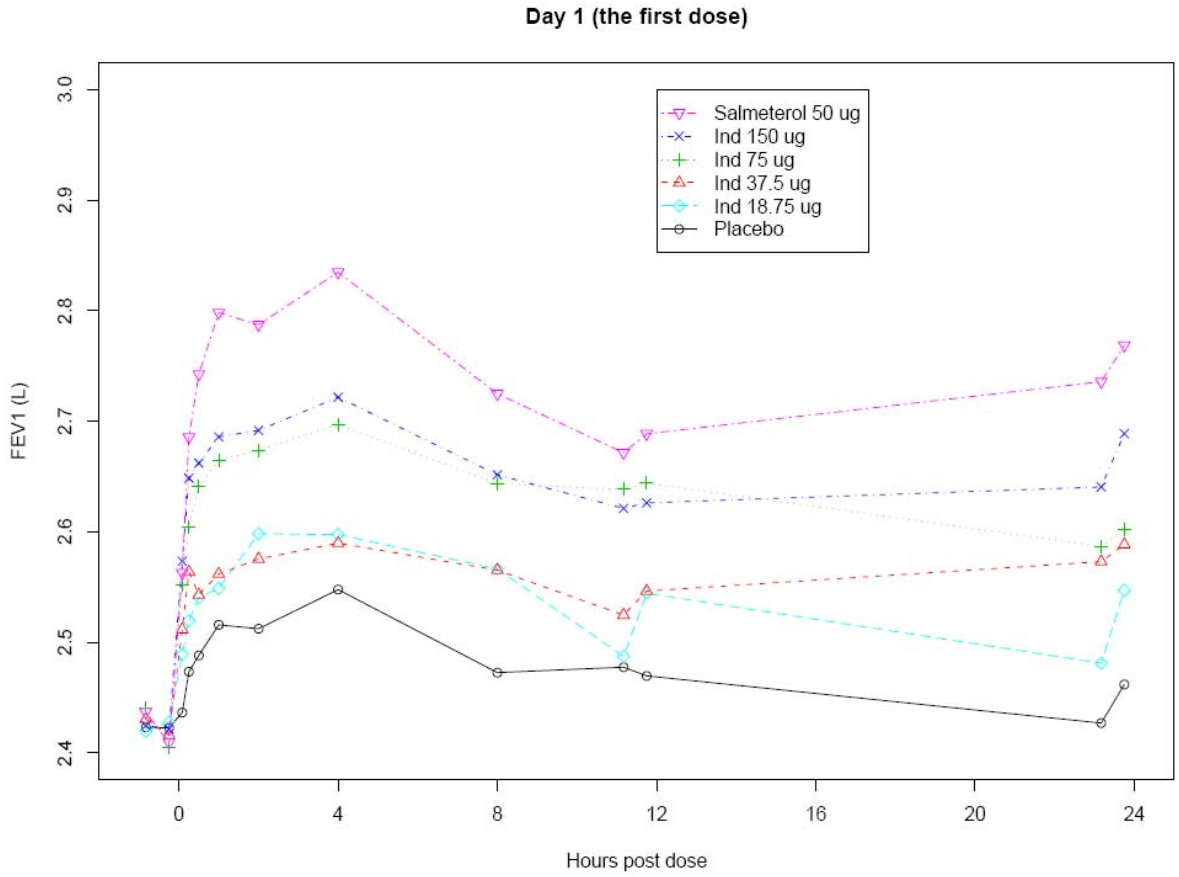
3.1. Dose selection efficacy

Dose selection for indacaterol has been extensively reviewed in both the original application and the complete response to NDA 22-383. It was also the primary topic for discussion at the PADAC meeting. At the request of FDA, Novartis conducted an additional dose ranging trial in asthma (B2357) as well as one in COPD (B2356). For a beta-agonist bronchodilator such as indacaterol, dose ranging in asthma patients, which by definition is the most bronchodilator

sensitive population, is particularly important to show differences in response. As such, the FDA focused on trial B2357 in asthma as the key dose ranging trial for the complete response.

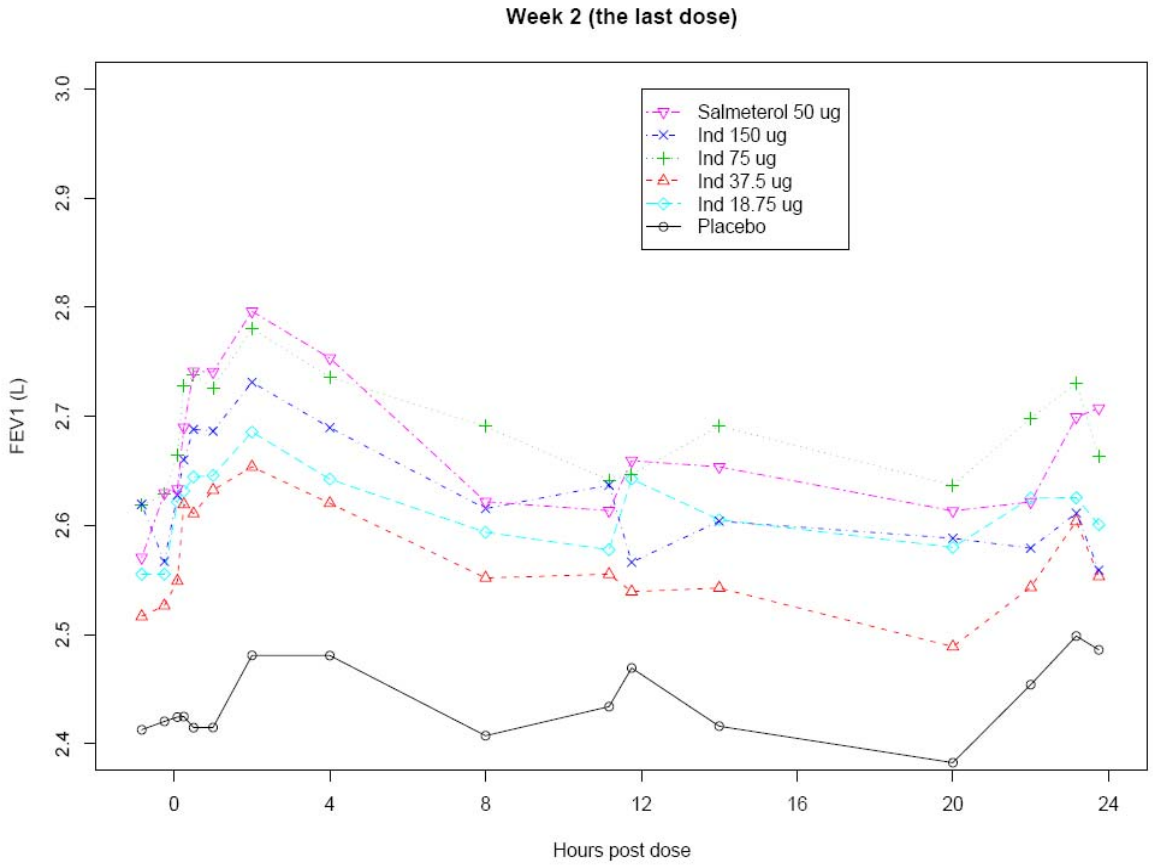
In trial B2357, a clear dose separation and ordering was observed after the first dose. See Figure 1.

Figure 1: Trial B2357 (asthma dose ranging) LS Mean FEV1 time profile curve over 24 hours after the first dose



As shown in Figure 1, both the 18.75 and 37.5 mcg doses show minimal benefit over placebo, which does not reach statistical significance at most timepoints. In contrast, both the 75 and 150 mcg doses both show statistically significant benefit over placebo at all timepoints on Day 1. There is a small benefit of the higher 150 mcg dose over the 75 mcg dose, which is lost by Day 15 as shown in Figure 2.

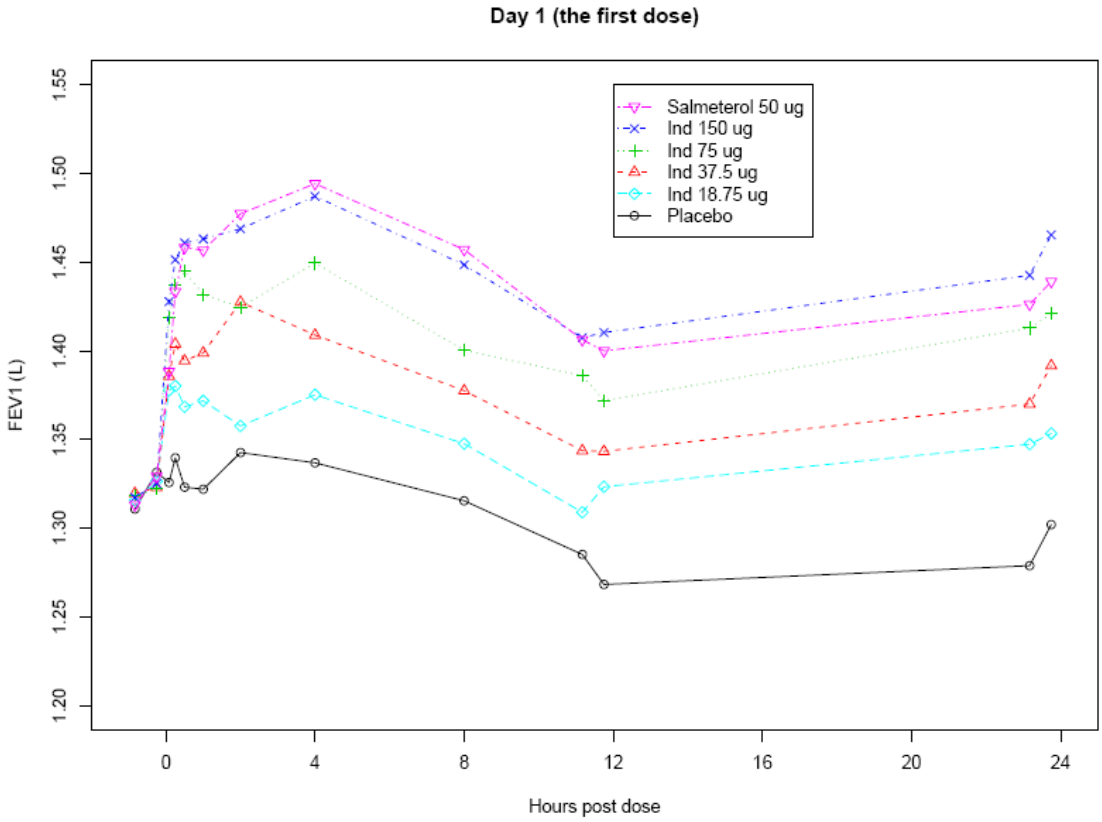
Figure 2: Trial B2357 (asthma dose ranging) LS Mean FEV1 time profile curve over 24 hours on Day 15



After two weeks of dosing, the 75 and 150 mcg doses showed statistically significant benefit over placebo; however, the 18.75 and 37.5 mcg doses still show less benefit, which does not reach statistical significance at all timepoints.

Although the benefit of the 75 mcg dose over the 37.5 mcg dose was less clear in the COPD population than in the asthma population, it is anticipated that dose separation would be more difficult to demonstrate in a population with some degree of fixed obstruction. Even in the COPD population, there is some advantage of the 75 mcg dose over the 37.5 mcg dose after the first dose. See Figure 3.

Figure 3: Trial B2356 (COPD dose ranging) LS mean FEV1 time profile curve over 24 hours after the first dose



3.2. Dose selection safety

There are two primary safety issues that were addressed related to dose selection as part of the indacaterol reviews, both in the initial application and in the complete response reviews. A further discussion of cardiovascular safety is discussed in Section 5 of this document. Respiratory safety, particularly as related to serious respiratory events, including asthma related death is summarized here.

In order to more completely address the issue of serious respiratory related events, the FDA requested that Novartis conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation. The All-treated COPD Safety Population from this analysis included a total of 11,755 patients in 23 studies. The majority of the studies were greater than 12 weeks in duration and were conducted with the to-be-marketed Concept1 (Neohaler®) device. Of the 11,755 COPD patients, 6863 were treated with indacaterol, 2482 with placebo, and 2408 with one of three active controls (formoterol n=556, tiotropium n = 842, and salmeterol n = 1010). In this analysis, there were 6/543 (1.1%) of patients with hospitalization due to pneumonia or COPD exacerbation in the 75 mcg dose group, 37/2743 (1.3%) in the 150 mcg dose group, and 47/2484 (1.9%) in the placebo group. Rates were also lower than or comparable to other LABA comparators (salmeterol and formoterol).

Based on these data, the 75 mcg dose appears to have demonstrated a reasonable safety profile with regard to respiratory-related events in COPD. In clinical trials with asthma, the two

respiratory-related deaths occurred at the 300 mcg indacaterol dose. Because the risk of serious asthma-related events has been shown to be dose related and it is unknown if such a risk may extend to COPD, caution in dose selection related to safety is warranted. However, choice of a subtherapeutic dose, even one that shows some efficacy, in order to obtain a theoretically better safety profile is not, when an efficacious dose has a risk not demonstrably greater than placebo or similar drugs in the class.

3.3. Advantage over available therapies

The FDA efficacy standard for approval as taken from 21 CFR 314.125 states that a product must demonstrate:

(b)(5) "…substantial evidence consisting of adequate and well-controlled investigations…that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

According to this standard, there is no requirement for approval stating that a product must demonstrate clinically significant advantages over available FDA-approved drugs in the same class. If approved, indacaterol will be the only once daily beta-agonist available in the United States, offering another option for patients with COPD.

3.4. Off-label use

If approved, indacaterol will carry the same class labeling as other LABAs, including a black box warning regarding asthma-related death. It will be clearly stated in the product label that indacaterol is not indicated for the treatment of asthma. Although indacaterol is not indicated for asthma, labeling will also include a description of available asthma safety data with indacaterol, including data from Trial B2338 (6 month asthma safety trial).

3.5. Modeling support for the 150 mcg dose

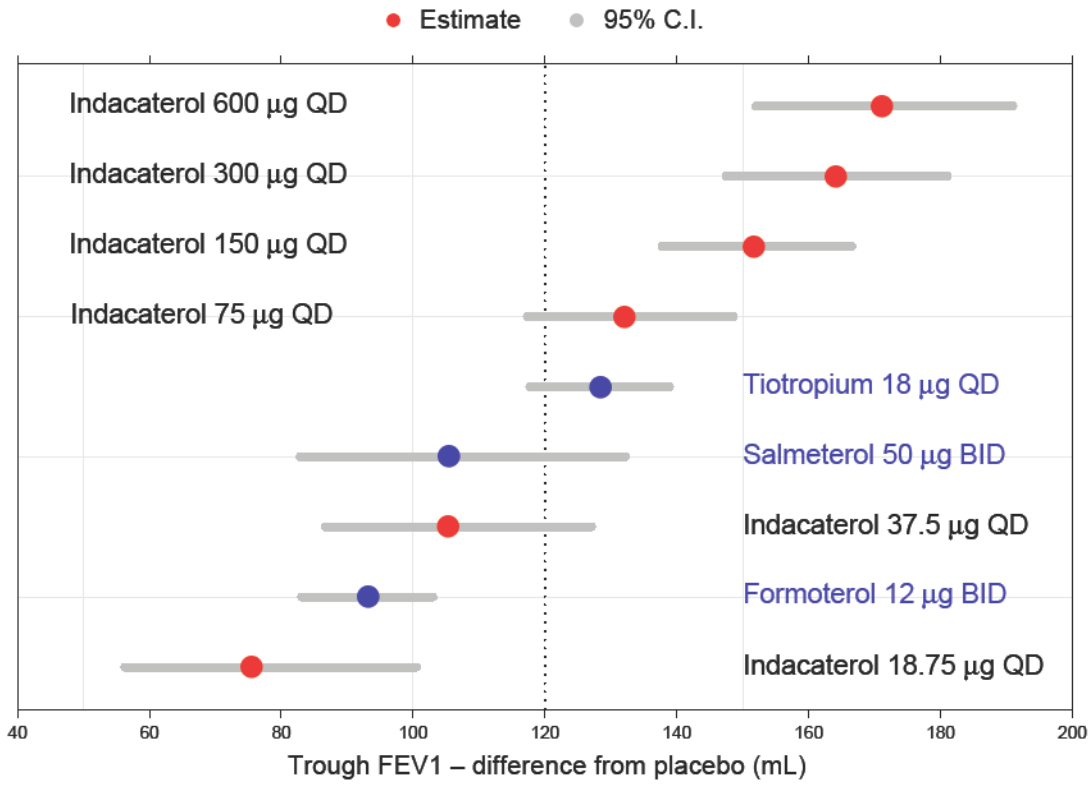
4.5.1. Novartis position

In the briefing document submitted on May 18, 2011, Novartis provided additional clarity regarding the integrated analyses of dose response in COPD patients that they performed and also provided an additional patient-level analysis including more data. There were three different analyses:

- A study-level analysis that predicted the dose response based on the pooled FEV1 results (least square mean values) reported for each of 12 studies , including 8111 patients total
- A patient-level analysis that predicted the dose response based on the individual trough FEV1 data collected on study days 14 and 15 from the two dose ranging trials (B2335S and B2356), including 1835 patients total
- Additional patient-level analysis including 5558 patients total

A summary of the study-level analysis is provided in Figure 4, taken from the May 18 briefing document.

Figure 4: Ranking of responses based on study-level analysis

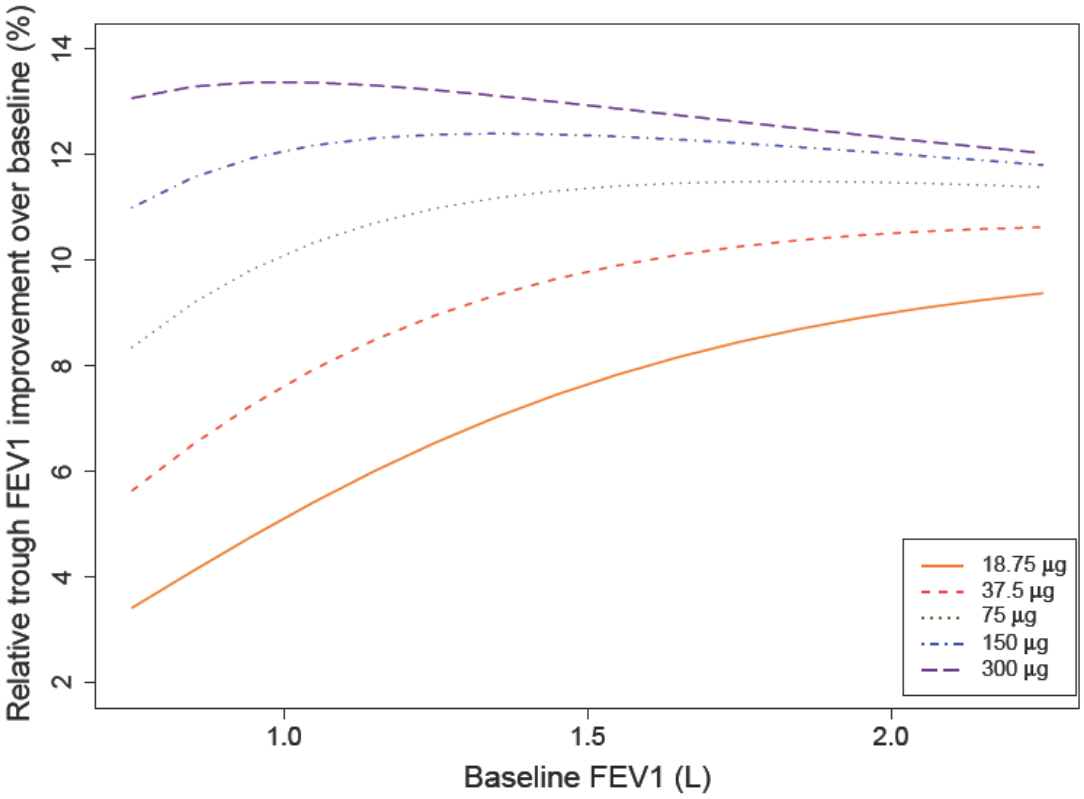


Based on this analysis, Novartis drew the following conclusions:

- *There is a 92 % probability that 37.5 mcg is less than the MCID of 120 mL.*
- *There is a 95 % probability that 75 mcg exceeds the MCID.*
- *150 mcg has an incremental benefit over 75 mcg and is the lowest indacaterol dose that exceeds the average bronchodilation observed for the comparators.*
- *150 mcg is located mid-way between the MCID and the maximum response.*
- *300 mcg intersects the maximum response.*

In the patient-level analysis, Novartis evaluated the dose response based on baseline FEV1 status. A summary of the patient-level analysis is provided in Figure 5, also taken from the May 18 briefing document. This analysis shows predicted values based on the model, not observed data.

Figure 5: Impact of baseline FEV1 on improvement in trough FEV1 relative to baseline



Based on this analysis, Novartis concluded:

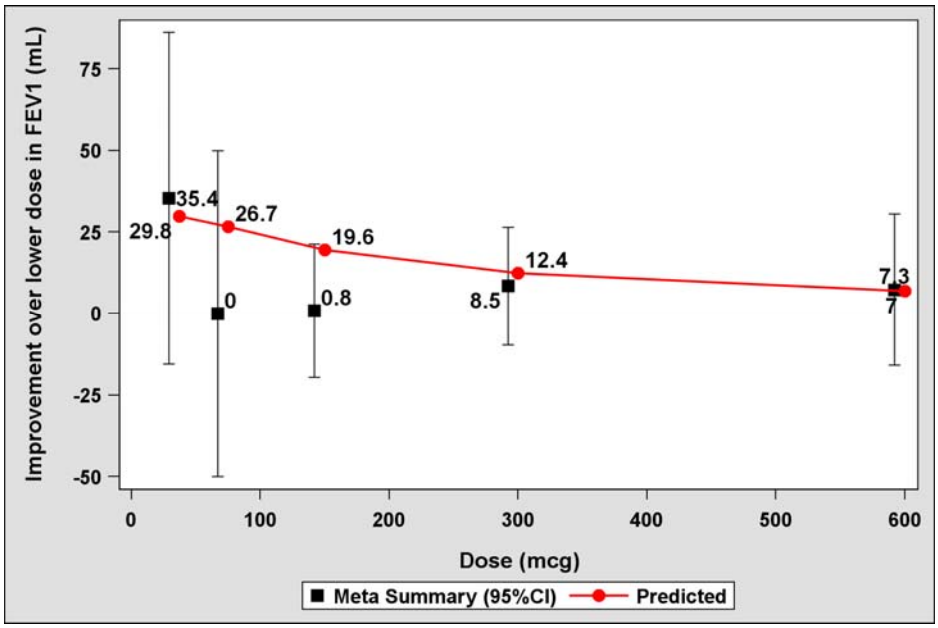
[The patient level analysis] "demonstrates that population heterogeneity in disease status is not adequately dealt with the 'one dose fits all' approach. It is for this reason that Novartis believes that while 75 mcg will provide minimum bronchodilation in most patients, 150 mcg provides incremental benefit in patients with severe COPD."

4.5.2. FDA position

As summarized in the meeting held on Tuesday, May 31, 2011, FDA disagrees with Novartis on both the methodology and conclusions from this analysis.

Dr. Yaning Wang re-analyzed the data from the Novartis modeling analysis and raised issues with regard to the claim of additional benefit of 150 mcg over 75 mcg for more severe patients. For the study level analysis, the model prediction overestimates the incremental difference between two adjacent doses, especially for 150 mcg versus 75 mcg and 75 mcg versus 37.5 mcg (see Figure 6). This may be due to: 1) data not supportive of a linear relationship between transformed dose and change in FEV1 variables presumed by the model, and 2) undersampling at lower doses.

Figure 6: Model prediction versus actual data for incremental difference between doses (study-level meta-analysis)



For the patient-level analysis, the model prediction is also not supported by the data (see Figure 7). Although the 95% confidence intervals for baseline FEV1 quartiles are wide, the point estimates based on the observed means or ANCOVA analysis of the true data (including day 14 and day 15 data from study B2335S and study B2356) do not support the model predicted trend. In addition, the FDA's sensitivity analysis based on the primary endpoint day 15 data demonstrates a flattened dose response in the more severe patients, suggesting that more severe patients will not have a greater response to doses above 75 mcg (see Figure 8), a conclusion that is opposite that from Novartis.

Figure 7: Model predictions versus actual data for FEV1 improvement of 150 mcg dose over 75 mcg dose

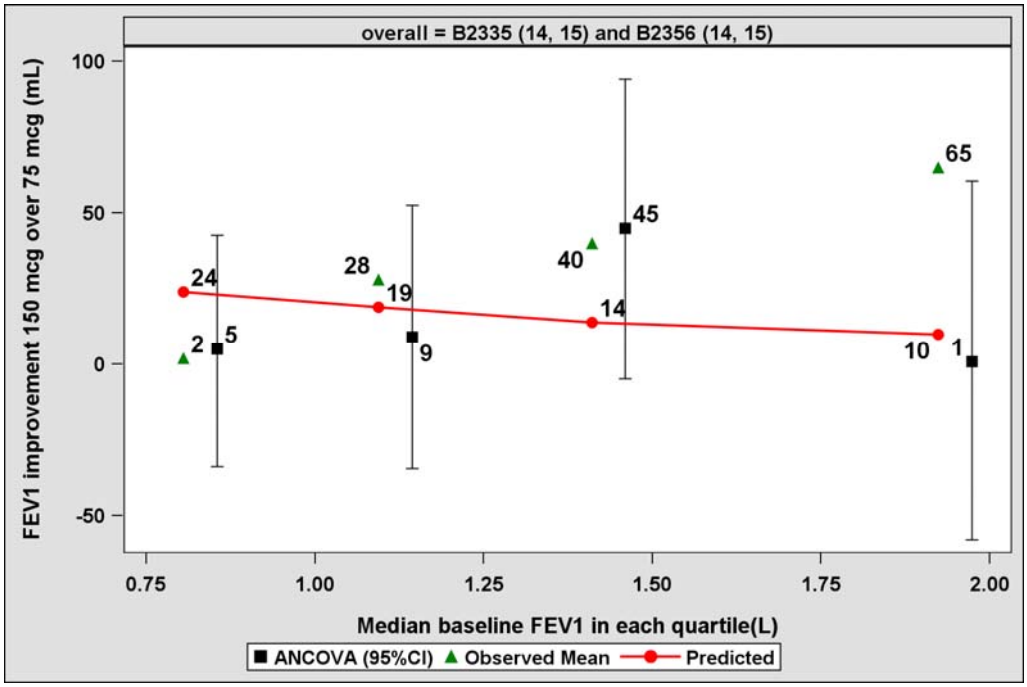
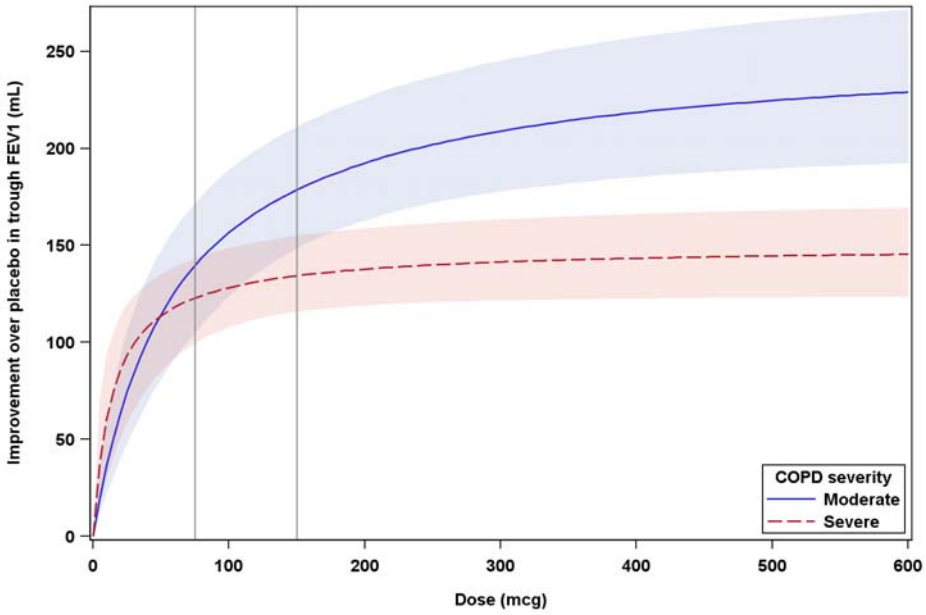


Figure 8: FDA sensitivity analysis of Novartis model



Ignoring these methodological issues and taking the Novartis analysis at face-value, a number of issues with the conclusions remain. Importantly, Novartis' conclusions are based on a minimal clinically important difference (MCID) of 120 ml for FEV1. As stated at the PADAC meeting, FDA has not determined an MCID for FEV1 for use in regulatory submissions. Most currently approved bronchodilators do not reach this level in the modeling analysis yet are clearly beneficial to patients. Benchmarking to marketed LABA products, salmeterol and

formoterol, Novartis' modeling analysis suggests that the 37.5 mcg dose of indacaterol would provide a similar level of bronchodilation as measured by trough FEV1 at steady state. However, the modeling analysis does not take into account bronchodilator effect at the first dose. As determined in the most sensitive population (asthma, Trial B2357), the 37.5 mcg dose does not provide an acceptable level of bronchodilation after the first dose, which is also important to patients. See Section 4.1.

4. Cardiovascular safety

On April 5, 2011, the primary clinical reviewer for the NDA 22-383 complete response, Dr. Anya Harry, filed a review addendum further evaluating her concern regarding cardiovascular safety which she first presented after all primary and secondary reviews were complete. Based on her re-analysis of data, Dr. Harry made the following recommendation:

"The safety profile of indacaterol 75 mcg is acceptable. Patients with increasing number of cardiovascular risk factors appear to have higher rates of cardiovascular disorder AEs. Therefore, a large simple trial of 12 months duration in patients with COPD to evaluate the cardiovascular AEs in patients with ≥1 cardiovascular risk factors is recommended by this reviewer as a post marketing commitment."

Cardiovascular safety was raised as an issue in the review of the initial submission of NDA 22-383. In the original submission, there were more cardiac or cerebrovascular AEs and serious adverse events (SAEs) in the indacaterol treatment groups compared to placebo (3.4% indacaterol 300 mcg versus 0.9% placebo SAEs) in the 12 month safety evaluation. Dr. Anthony Durmowitz, the CDTL for the initial indacaterol application drew the following conclusions:

"COPD patients that were treated with indacaterol at the 300 and 600 mcg doses for 12 months were noted to have higher rates of cardio- cerebrovascular (CCV) SAEs than either placebo or the formoterol active comparator. The rates for the indacaterol 300 and 600 mcg groups were approximately 3.5 and 2.5 times the rate observed in the placebo group and 2.5 and 2 times that observed for formoterol, respectively. The most frequent events in the indacaterol 300 mcg group were atrial fibrillation, heart failure and myocardial ischemia, and in the 600 mcg group these were coronary artery disease and myocardial infarction. In the placebo group there was no event reported in more than one single case."

As part of the complete response, Novartis was asked to provide balancing safety data to show no unacceptable safety disadvantage with the proposed doses. The 12 month safety data from the complete response, which includes data from the 26 week safety extension to the adaptive design study (Protocol B2335SE), shows that patients with SAEs in any organ system are balanced in the 150 mcg dose group compared to placebo (10.4% of patients in the indacaterol 150 mcg group compared to 11.0% in placebo). There were 0.69% of patients in the 150 mcg indacaterol group with cardiac or cerebrovascular SAEs compared to 1.4% in the placebo group. However, cardiac or cerebrovascular AEs occurred more frequently in the 150 mcg dose group compared to placebo (9.7% versus 5.4%). This was largely driven by an increase in ECG changes (QT prolongation, AV block, bundle branch block, sinus tachycardia, and repolarization abnormality). The database for 150 mcg is too small to draw more specific conclusions regarding these events. Because many of these events were ECG events detected

solely due to participation in a clinical trial and were not reflected in symptoms or serious events, the clinical significance is unclear.

In the Integrated Summary of Safety, Novartis also conducted an analysis of events by subgroup, including baseline cardiac risk factors. These included smoking, age, history of a CCV condition, history of diabetes mellitus, hyperlipidemia, and obesity. Use of ICS and COPD severity were also included. As expected, the number of serious cardiovascular events increased with an increasing number of cardiovascular risk factors. For the 12 month safety population, all serious adverse events in an indacaterol treatment group occurred in patients with at least one cardiac risk factor. See Table 1.

Table 3: Number and percentage of patients with cardio- or cerebrovascular SAEs by baseline CV risk factors in the COPD 12-month safety population

Number of CCV risk factors	Ind 150 mcg n/N (%)	Ind 300 mcg n/N (%)	Ind 600 mcg n/N (%)	Foradil n/N (%)	Placebo n/N (5)
0	0/13 (0)	0/46 (0)	0/26 (0)	1/38 (2.6)	0/40 (0)
≥ 1	1/144 (0.69)	18/583 (3.1)	11/425 (2.6)	6/434 (1.4)	8/556 (1.4)
1	1/34 (2.9)	3/140 (2.1)	3/119 (2.5)	0/104 (0)	0/149 (0)
2	0/38 (0)	6/168 (3.6)	7/116 (6.0)	1/123 (0.8)	2/148 (1.4)
≥ 3	0/59 (0)	9/229 (3.9)	1/164 (0.6)	4/169 (2.4)	6/219 (2.7)

Adapted from Table L-4.3-14, SCS Appendix 1 and Summary of Clinical Safety Table 2-86 NDA 22-383 complete response

The serious cardiovascular event in the indacaterol 150 mcg treatment group was an episode of atrial fibrillation. Evaluating groupings of SAEs by the Anti-Platelet Trialist Criteria (APTC) in the 12 month safety population does not reveal any significant safety issues as events occurred less frequently in all of the indacaterol arms compared to placebo. See Table 2.

Table 4: ATPC events by preferred term in COPD 12-month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with ≥1 APTC CCV AE	0	5 (0.86)	3 (0.71)	2 (0.46)	8 (1.44)
APTC CCV AEs:					
Myocardial infarction	0	2 (0.34)	2 (0.47)	1 (0.23)	3 (0.54)
Acute myocardial infarction	0	1 (0.17)	0	0	1 (0.18)
Cerebral infarction	0	1 (0.17)	0	0	0
Sudden death	0	1 (0.17)	0	0	3 (0.54)
Carotid artery occlusion	0	0	1 (0.24)	0	0
Cerebellar infarction	0	0	0	0	1 (0.18)
Cerebrovascular accident	0	0	1 (0.24)	1 (0.23)	0

Includes studies B2334 and B2335SE
Abbrev: Ind=indacaterol, For=formoterol, Pbo=placebo, APTC=antiplatelet trialists collaboration, CCV=cardiac and cerebrovascular
Events are sorted in descending order of frequency in the indacaterol 300 µg group. A patient with multiple AEs is counted only once in the total row.

Table 2-91 CTD 2.7.4. Summary of Clinical Safety, p. 249

Based on these data, it does not appear that a cardiovascular signal exists for the 150 mcg dose group of indacaterol. Since cardiovascular safety is expected to be a systemic rather than a

local effect of a beta-agonist drug, it is reasonable to assume that the lower proposed dose of indacaterol (75 mcg) would have a safety profile that is no worse than the 150 mcg dose. In addition, since patients with at least one cardiovascular risk factor were well-represented in the indacaterol clinical trial database, a dedicated clinical trial in patients with cardiovascular risk factors seems unlikely to add significantly to the overall safety profile of the product.

In meetings held June 1 and June 8, 2010, for Dr. Harry to discuss her findings regarding CV safety with the review team, the team raised a number of issues with Dr. Harry's review and conclusions. These issues included:

- There is an expected increase in numbers of CV events with increasing CV risk factors. A very large percentage of patients in the indacaterol database had one or more CV risk factors. It is unclear how Dr. Harry is drawing the conclusion that this translates into a need for additional studies of patients with CV risk factors.
- Many of the analyses were not exposure-adjusted.
- Grouping of AEs and SAEs together may not provide an accurate picture. Typically SAEs are of more interest due to the severity.
- It is unclear what the proportion (%) represents in Dr. Harry's analysis of MedDRA high level terms (HLT), high level group terms (HLGT), and preferred terms, as the numbers are not the percentage of patients with the event divided by the number of patients in the treatment group.
- Dr. Harry's conclusion that there may be a signal in the 150 mcg dose group is based primarily on the HLT of "coronary artery disorders NEC" for which there were 3 events in the 150 mcg dose group, 2 events in the 300 mcg dose group, and 1 event in the placebo group. When combined with the HLT "ischemic coronary artery disorders" for which there were a much larger number of events, into the HLGT "coronary artery disorders", the signal is not apparent.
- It is unclear why a dose response is not evident with higher dosing groups as the 600 mcg group appears to have fewer events. This may be due to random chance or artifacts induced by study level effects caused by pooling of data without correcting for exposure and trial.
- Point estimates may give an unreliable picture when confidence intervals are wide and overlapping as they are for these data.

After the meetings, Dr. Harry acknowledged the questions the review team had regarding her analysis and entered the following conclusion as a second addendum (June 8, 2011):

"The addition of this addendum to the clinical review of the data presented in NDA 22-383 continues to result in a recommendation of approval for indacaterol 75 mcg once daily dose in the maintenance treatment of COPD. An efficacy advantage of the higher 150 mcg dose in more severe patients with COPD was not demonstrated and my regulatory recommendation is a complete response for the 150 mcg once daily dose. Based on the evaluation of these additional data included in the addendum by the clinical and biostatistics review teams, I no longer recommend a post marketing commitment to evaluate the cardiovascular disorder adverse events in patients with ≥ 1 risk factors."

5. Conclusions and recommendation

A number of different issues that became apparent late in the review cycle are summarized in this CDTL review addendum. These issues cluster around two key topics, safety and efficacy issues related to dose selection and ethical concerns related to placebo controlled trials.

With regard to dose selection, the recommended regulatory action remains approval of the 75 mcg once daily dose without a requirement for a cardiovascular safety study and a complete response action for the 150 mcg dose. As determined in the most sensitive population (asthma, Trial B2357), the 37.5 mcg dose does not provide an acceptable level of bronchodilation after the first dose, which is also important to patients. The safety profile of the 75 mcg dose has demonstrated a reasonable safety profile with regard to respiratory-related events in COPD and cardiovascular events. A cardiovascular signal is not apparent for the 150 mcg dose in long-term studies, and patients with one or more cardiovascular risk factors were adequately represented in clinical trials.

Public Citizen raised the following specific ethical concerns for the indacaterol program: the use of placebo control groups in the clinical trials, failure to minimize risk to participants, and inadequate informed consent. The Division requested consults from the Office of Good Clinical Practice and the Division of Scientific Investigation at FDA to further evaluate the concerns. The question at the heart of these concerns is whether or not patients in the trials were put at risk from being on a placebo. Although containing a placebo medication, all patients in the trials were permitted to continue on inhaled corticosteroids and were given standard short-acting beta-agonist bronchodilator rescue medication. Thus, patients in the trials were not in a strictly “placebo” group, nor were they likely at risk of serious harm based on information available at the time the trials were conducted. All of the protocols contained design elements to minimize risk to participants, including escape rules, rescue medications, exclusion of patients at greater risk, minimizing time on placebo, and close monitoring. The informed consents for the trials all notified patients that they had a chance of receiving placebo, and that they may be required to switch from their currently prescribed COPD medications. Thus, the best evidence demonstrates that the trials were ethically conducted based on the information available at the time.

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/s/

THERESA M MICHELE
06/30/2011

Cross-Discipline Team Leader Review

Date	March 1, 2011
From	Theresa M. Michele, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-383, Complete Response Resubmission
Applicant	Novartis Pharmaceuticals
Date of Submission	October 1, 2010
PDUFA Goal Date	April 1, 2011
Proprietary Name / Established (USAN) names	Arcapta Neohaler/ indacaterol maleate
Dosage forms / Strength	inhalation powder/ 75 and 150 mcg once daily
Proposed Indication(s)	Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
Recommended:	75 mcg dose: Approval 150 mcg dose: Complete Response

1. Introduction

Novartis submitted the initial 505(b)(1) new drug application (NDA 22-383) on December 15, 2008, for the use of Arcapta Neohaler (indacaterol maleate dry powder for inhalation) as a once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed dose of 150 mcg had a qualifier that administration of a 300 mcg dose provided additional clinical benefit in some patients. To support this application, Novartis submitted three pivotal COPD studies: a 26-week adaptive design dose ranging study (with continuing doses of 150 and 300 mcg), a one-year efficacy and safety study (300 and 600 mcg), and a 12 week study (150 mcg).

FDA took a complete response action on this application on October 16, 2009. Key issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma related deaths compared to salmeterol in patients with asthma. In addition, the dose and dosing frequency were not adequately explored, with no clinically meaningful difference between 75 mcg once daily and the proposed doses of 150 and 300 mcg. Novartis was asked to explore efficacy and establish safety of lower doses and various dosing frequencies, to provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and to provide balancing safety data to show no unacceptable safety disadvantage with the higher dose.

Novartis submitted a complete response on October 1, 2010, with results from 6 new pivotal studies in addition to 10 Phase 3 supportive studies to address these deficiencies. The proposed dose of indacaterol is lowered to 75 mcg or 150 mcg once daily based on data from the additional clinical studies. Two doses are proposed with the reasoning that the higher dose will provide additional benefit in patients with more severe bronchial obstruction, the claimed advantage of 150 mcg dose over 75 mcg based on pharmacodynamic modeling analysis, and results of St George's Respiratory Questionnaire (SGRQ) results. The key pivotal studies include dose ranging and dose regimen studies in a bronchodilator-responsive asthma population, a dose ranging study in COPD, two replicative 12-week confirmatory studies in COPD with the 75 mcg dose, and one 26-week confirmatory study in COPD with the 150 mcg dose. Important long-term safety data for the 150 mcg dose comes from a 26-week extension to the adaptive design study, for a total duration of 1 year.

The PDUFA due date for this application is April 1, 2011. Indacaterol is approved for COPD in over 30 countries worldwide including the European Union at doses of 150 and 300 mcg once daily. This review will provide an overview of the complete response dossier, focusing on issues required to resolve the deficiencies from the initial application: dose and dose regimen selection, advantage of the proposed higher dose compared to the lower dose, and balancing safety data.

2. Background

2.1. Related drugs: issues with long-acting beta agonists (LABA)

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

As a result of the findings described above as well findings in smaller safety studies conducted with another LABA, formoterol, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting (PADAC). Based on this meeting and a follow up PADAC meeting on December 10, 2008, the existing product labels have been revised and now include a Boxed Warning and a Medication Guide for all marketed LABA products. In addition, the paradigm for asthma treatment with LABAs has now

changed, contraindicating the use of a LABA without a concomitant asthma controller medication, such as an inhaled corticosteroid (ICS)[1].

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

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

2.2. Regulatory history

Novartis studied three different inhalation indacaterol products. These were the single-dose dry powder inhaler (IND 48,649), an HFA propelled inhalation aerosol (IND 66,337), and a multi-dose dry powder inhaler using the Certihaler device (IND 69,754). IND 48,649 was submitted on February 13, 2004, and IND 69,754 was submitted on April 27, 2004, both to study persistent asthma. An end-of-phase 2 meeting was held on August 1, 2005, to discuss the development of indacaterol multi-dose dry powder product for asthma and COPD. Most of the questions and ensuing discussions were on the asthma program. Novartis later suspended the development of the HFA propelled inhalation aerosol product for technical reasons. The multi-dose dry powder inhaler using the Certihaler device was also suspended due to excessive delivery of dose because of a possible Certihaler device related problem. With the suspension of these delivery devices, which would provide for multiple dose products, the development of the single-dose dry powder product was continued. A second end-of-phase 2 meeting was held on October 10, 2006, to discuss the development of indacaterol single-dose dry powder product for COPD. There was some discussion on asthma, but most of the questions and ensuing discussions were regarding COPD. Novartis proposed a COPD study (Study 2335, discussed further below) with an adaptive design to build dose ranging assessment and determination into a pivotal efficacy and safety study. The Division cautioned that initiating such a phase 3 study was risky when using a single-dose dry powder product with limited prior information and Agency review of relevant data. On December 20, 2006, Novartis submitted the COPD study with adaptive design for Special Protocol Assessment (SPA). In a letter dated February 1, 2007, the Division expressed various concerns with the study, such as the role of the data monitoring committee (DMC), use of open-label tiotropium as an active comparator, selection of the non-inferiority margin to compare to tiotropium, definition of secondary endpoint of days of COPD exacerbation, and emphasis on trough FEV1 as dose selection criterion. While several discussions occurred between the Division and Novartis on the study, there were no formal SPA agreements. There were no agreements on dose selection criteria.

[1] Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Eng J Med 2010; 362:1169-71.

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

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

3. CMC/Device

3.1. General CMC information

The product Arcapta Neohaler contains Arcapta (indacaterol maleate inhalation powder) Capsules packaged in aluminum blister cards, and a Neohaler inhaler, also termed the "Concept 1" device during development. Arcapta Capsules are of two strengths, 75 mcg and 150 mcg. The capsules will be packaged as five blister cards with 6 capsules each in a box of 30. Each capsule contains a dry powder blend of either 75 mcg or 150 mcg of indacaterol maleate with approximately 25 mg of lactose monohydrate. The Neohaler inhaler is a plastic device to be used for inhaling Arcapta Capsules. The Neohaler inhaler consists of a white protective cap, a base with mouthpiece, capsule chamber, and two push buttons. To deliver a dose, the patient will place an Arcapta Capsule in the capsule chamber of the Neohaler inhaler, press the push buttons to pierce the capsule on each end, and breathe in rapidly and steadily through the mouthpiece.

The primary CMC reviews for both the initial and the complete response application were conducted by Craig Bertha, Ph.D. For the initial submission, his review concluded that from a CMC perspective, the application was approvable pending acceptable cGMP recommendation from the Office of Compliance, which has been obtained. All associated Drug Master Files were found acceptable or the pertinent information has been adequately provided in the application.

For the complete response, the CMC team initially recommended an approvable action. Dr. Bertha concludes that the applicant's proposed expiration dating period of (b) (4) months for the (b) (4) 12 months for the 75 mcg strength, are supported by the stability data provided. The recommended storage condition is room temperature although the labeling includes warnings about keeping the drug product in a dry place, which is typical for inhalation powder drug products.

On February 20, 2011, the Office of Compliance issued a WITHHOLD recommendation for this application. The Novartis site at Suffern, NY, which is a packaging site for the drug product, was issued an Official Action Indication alert. Additional information regarding the reasons for this action is pending at the time of this review. If the compliance issues cannot be resolved prior to the action date, then the CMC team recommends a complete response action.

3.2. Device interchangability

Because Arcapta Neohaler uses dry powder capsules that are separate from the device, the clinical team and OSE Division of Medication Error Prevention have raised concerns that patients might unintentionally attempt to use the indacaterol drug product capsules (Arcapta™) in other devices that are similar to the Concept1 or Neohaler™, even though misuse is prohibited by product labeling. Other similar devices that are already approved and marketed are the Aerolizer® device from the Foradil® Aerolizer® product that delivers formoterol fumarate, and the HandiHaler® device from the Spiriva® HandiHaler® drug product that delivers tiotropium bromide.

In the complete response application, the sponsor submitted a report that addressed this potential interchangeability from the *in vitro* performance testing perspective. The CMC team reviewed this report to gauge the characteristics and magnitude of any differences in the *in vitro* performance data. The applicant studied the effects of potential device interchanges on the pharmaceutical performance through the device-life of 30 days, for the 75 mcg strength Arcapta™ capsules. They assessed the key performance parameters of Aerodynamic particle size distribution (APSD) and delivered dose uniformity (DDU). In addition, the applicant provided comparative data in the first cycle, demonstrating the *in vitro* delivery performance (APSD and DDU) for 150 and 300 mcg Arcapta™ capsules with the Concept1 and the Aerolizer® devices (see chemistry review #2 dated 16-JUL-2009). In summary, the *in vitro* data for dose delivery and APSD were considered to be comparable, regardless of whether or not the Arcapta™ capsules were delivered from a Concept1 or an Aerolizer® device.

Dr. Bertha concluded that the DDU and APSD data observed for the 75 mcg Arcapta™ capsules with the Concept1 and Aerolizer® devices are comparable. This is consistent with the analogous data that were collected with the two higher strength capsules (150 and 300 mcg). Whereas there are no gross distinctions between the DDU and APSD behavior observed *in vitro* when the Arcapta™ capsules are used with the HandiHaler® versus the Concept1 device, there are some more subtle distinctions. Arcapta™ capsules used with the HandiHaler® delivered similar doses but the initial device drug hold-up that is observed with the Concept1 and Aerolizer devices was not seen. In addition, there was a drop in mean total mass of fine particles of drug below 5.0 mcm in size when the HandiHaler® device was used instead of the Concept1 device, i.e., a drop of about 15%.

The *in vitro* testing data are reassuring that medication errors related to switching of capsules in the device are unlikely to result in clinically significant dosing errors, although the exact correlation with the APSD data is unknown. This issue will be addressed in the patient Medication Guide labeling. (b) (4)

4. Nonclinical Pharmacology/Toxicology

A full nonclinical pharmacology/toxicology program was conducted for indacaterol. Dr. Virgil White conducted the primary toxicology review for both the initial and the complete response application. No new toxicology data were submitted in the complete response submission. Since the proposed doses are lower in the current submission than in the initial submission, no

new toxicology concerns are raised. The recommended action for both reviews is approval. The pharmacology/toxicology team does not recommend additional non clinical studies.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review for the original submission was conducted by Dr. Sandra Suarez. The primary Clinical Pharmacology reviewer for the complete response submission was Dr. Ying Fan, with support from the Pharmacometrics and Pharmacogenomics teams. Except where specifically noted, this summary includes only new data from the complete response.

The original application included 36 clinical studies that contain pharmacokinetic (PK) information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). In the current submission, the clinical pharmacology studies include 3 *in vitro* drug-drug interaction studies, 1 bioavailability study, 1 intrinsic factor PK study in healthy Chinese subjects, and 1 extrinsic factor PK study assessing the PK interaction of indacaterol with ritonavir in healthy adult subjects.

5.1. General considerations

Based on the current re-submission, the absolute bioavailability of indacaterol after an inhaled dose was on average 45%. Systemic exposure results from a composite of pulmonary and intestinal absorption.

5.2. Drug-drug interactions

Based on the *in vitro* investigations of enzyme and transporter induction, indacaterol has negligible potential to act as an inducer at clinically relevant serum levels. *In vitro* investigation indicated that indacaterol is unlikely to significantly inhibit transporter proteins such as P-glycoprotein (P-gp), multidrug resistance-associated protein 2 (MRP2), human breast cancer resistance protein (BCRP), the human organic cationic transporters hOCT1 and hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K, and that indacaterol has negligible potential to induce P-gp or MRP2.

Concomitant administration of indacaterol 300 μg with ritonavir 300 mcg b.i.d for 7.5 days resulted in a 1.7-fold increase in indacaterol AUC_{0-24} whereas indacaterol Cmax was unaffected. The magnitude of exposure increases does not raise safety concerns because Arcapta Neohaler has been evaluated in clinical trials of up to one year duration at doses up to 600 mcg once daily.

5.3. Intrinsic Factors

Information about the effect of covariates (such as age, gender, body weight, body mass index and race) on the PK of indacaterol was investigated using a population PK modeling approach with pooled pharmacokinetic data. In this submission, the sponsor updated the population PK report by adding new studies. The effects of weight, age and gender remained similar to the previous report; peak concentration (Cmax) increases with age, by 35% over the range of 49-78 years; Cmax in COPD patients decreases with body weight, by 28% over the range of 49-105kg; Cmax is an average of 7.6% greater in female COPD patients than in male patients. With these relatively small changes, no dose adjustments are required.

There were some observations of higher exposure in Asian subpopulations in the updated analysis; Cmax on average 17% and 25% higher in Korean and Japanese patients compared to the typical COPD patient. However, it is not conclusive whether there were true ethnic differences or whether the results were caused by inter-study variability in the population PK analyses. The PK characteristics of indacaterol in healthy Chinese subjects were evaluated in Study CQAB149B2101. The serum concentrations of indacaterol increased rapidly following drug inhalation and reached a maximal level approximately 15 minutes. At Day 1, following a 150 mcg dose, the systemic exposures are 0.974 ng.hr/mL for AUC0-24 h, and 0.206 ng/mL for Cmax, respectively. The systemic exposures are 2.43 ng.hr/mL for AUC0-24 h, and 0.518 ng/mL for Cmax following 300 mcg dose. Systemic exposure to indacaterol increased more than 2-fold between the 150 μg and 300 μg doses.

5.4. Special populations

No new data regarding special populations were evaluated as part of this review cycle.

5.5. QT assessment

As reviewed in the original application, the effect of indacaterol on the QT interval was evaluated in a double-blind, placebo controlled study following doses of indacaterol 150 mcg, 300 mcg or 600 mcg once-daily for 2 weeks, and a single oral dose of moxifloxacin 400 mg, in 404 healthy subjects (Study B2339). No significant QT prolongation effect of indacaterol (150 mcg, 300 mcg and 600 mcg) was detected in the QT study.

5.6. Dose selection and modeling

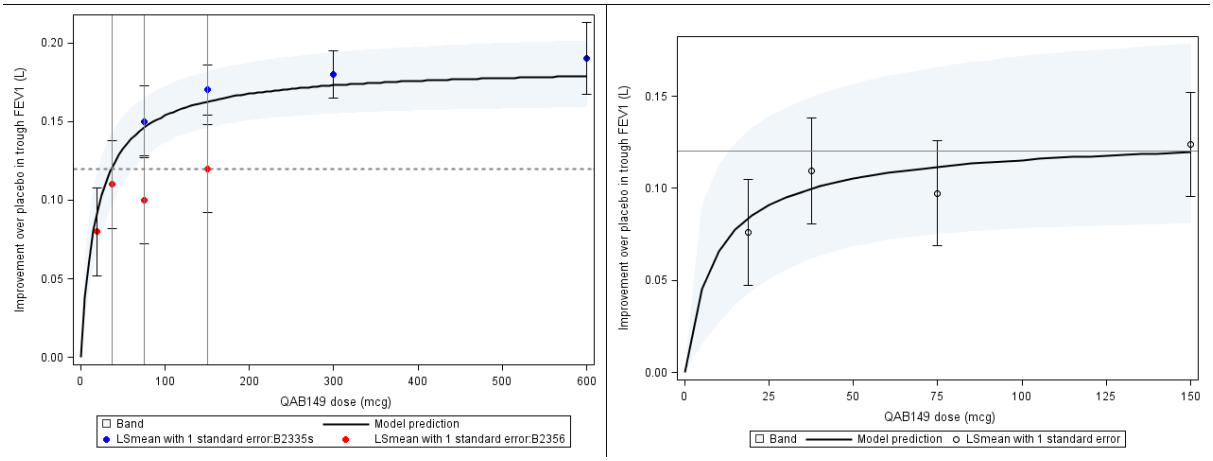
Novartis proposes a 150 mcg once daily dose "to provide additional benefit in patients with more severe bronchial obstruction." The sponsor is basing the claim for the higher 150 mcg dose on two points: modeling data from the dose ranging studies and the SGRQ. According to the sponsor, modeling data demonstrate an advantage of the 150 mcg dose, particularly in more severe patients. However, the sponsor also notes that the model does not match the data from the dose ranging trial in asthma (Protocol B2357), the study with the clearest dose response. In addition, when the modeling data were re-analyzed by the FDA clinical pharmacology reviewer, eliminating uncontrolled Day 14 data, this advantage was lost. Likewise, the clinical pharmacology team did not find that the modeling data support the sponsor's choice of 75 mcg as the lowest effective dose.

Two separate model-based methods were applied using Emax model: Bayesian meta-analysis and a non-linear mixed effect modeling (hereafter NLME). Least square mean (LSM) contrasts to placebo with standard error for three different endpoints (trough FEV1, observed peak, peak average response (AUC0-4)) at each visit up to 26 weeks from 13 studies were collected and used in the Bayesian meta-analysis. For NLME analysis trough FEV1 on day 14 and 15 from two dose-ranging studies (CQAB149B2335S, CQAB149B2356; hereafter B2335S and B2356) were pooled and analyzed. Both analyses produced similar results.

The sponsor's model predicted that 75 mcg just exceeds MCID of 0.12 L and 150 mcg is located mid-way between the MCID and the maximum response whereas 37.5 mcg is inferior to the MCID of 0.12 L, which resulted in 75 mcg as a minimum effective dose. However, as shown in Figure 1(left panel), there is little difference in LSM between 37.5 mcg (0.11 L) and

75 mcg (0.10 L) within study B2356 (please notice that B2356 is the only study which includes 18.75 mcg and 37.5 mcg in COPD patients). Noticeable differences were observed between the two dose-ranging studies for the common doses studied (75 mcg and 150 mcg). More importantly, the sponsor's prediction was mainly driven by study B2335S and the covariates identified in the model could not explain the difference between the two studies. The pharmacometrics reviewer reanalyzed the dose-response relationship with study B2356 only, and the result is shown in Figure 1(right panel). The reviewer's reassessment predicted that none of the doses (including 75 mcg and 150 mcg) in study B2356 could achieve FEV1 response above MCID of 0.12 L. Moreover, % maximum effect at both 37.5 mcg and 75 mcg are more than 80%, which are different from the sponsor's prediction (37.5 mcg: 66%, 75 mcg: 79%) based on the pooled analysis. The reviewer's analyses suggested that 37.5 mcg achieved comparable FEV1 response as 75 mcg within the same study. If 37.5 mcg were included in other studies where 75 mcg had larger effect size than that in study B2356, 37.5 mcg would be expected to have larger effect size as well.

Figure 1: Model-predicted dose-response (trough FEV1) relationship



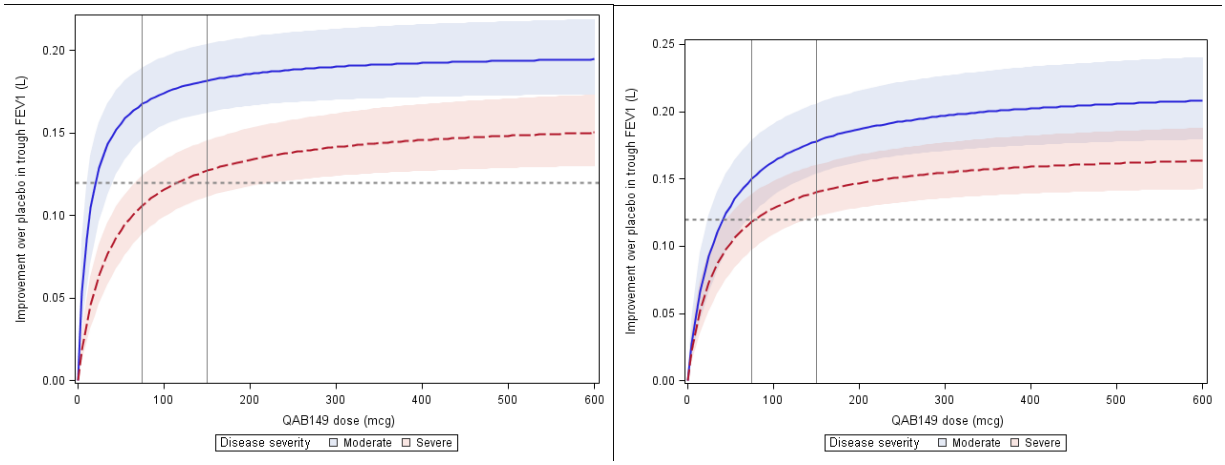
Left panel: the sponsor's analysis using pooled two studies with LSM with standard error for each study
Right panel: Dr. Joo Yeon Lee's analysis using study B2356 only

One of the sponsor's findings from NLME analysis is that baseline FEV1 was found to be a significant covariate for the maximum response and the dose that is required to achieve 50% of the maximum response. Figure 2 (left panel) shows the different predicted dose-response relationships between moderate and severe COPD patients from the sponsor's NLME analysis. The sponsor claimed that if 0.12 L is considered the MCID, 150 mcg is necessary to exceed this threshold in severe patients; therefore, 150 mcg provides additional benefit over 75 mcg in more severe patients.

However, the clinical pharmacology team determined that there is clear difference in observed dose-response profile between day 14 and 15. Since data from day 14 were not obtained under controlled condition, the reviewer excluded data on day 14 and fitted the same model as the sponsor's to the day 15 data only as a sensitivity analysis. Based on analysis using day 15 data only, baseline FEV1 was not found to be a significant covariate on ED50, which resulted in slightly different predicted lines by disease severity (Figure 2, right), and the dose of 75 mcg appears to meet the MCID criteria (0.12 L) for severe patients also. Hence, the sponsor's claim

of additional benefit with 150 mcg for severe patients based on MCID of 0.12L is sensitive to the data used for analysis so is not considered a robust finding.

Figure 2: Predicted dose-response relationship for trough FEV1 at steady state by COPD severity



Left panel: the sponsor's analysis using Day 14 and 15 data
Right panel: Dr. Joo Yeon Lee's analysis using Day 15 data only

5.7. Pharmacogenomics

The relationship between common single nucleotide polymorphisms in the β_2-adrenergic receptor gene (*ADRB2*; -47C/T Arg16Gly, Gln27Glu, Thr164Ile) and Arcapta Neohaler response was retrospectively analyzed in two of the controlled trials (n=626). Pooled analysis did not reveal any significant effect of *ADRB2* genotype on changes in FEV1 or other efficacy endpoints.

6. Clinical Microbiology

This section is not applicable.

7. Clinical/Statistical- Efficacy

7.1. Overview of the clinical program

To support the original application, Novartis submitted three pivotal COPD studies: a 26-week adaptive design dose ranging study (with continuing doses of 150 and 300 mcg), a one-year efficacy and safety study (300 and 600 mcg), and a 12 week study (150 mcg). In a complete response to regulatory action, Novartis now submits 6 new pivotal studies in addition to 10 Phase 3 supportive studies. The key pivotal studies include dose ranging and dose regimen studies in a bronchodilator-responsive asthma population, a dose ranging study in COPD, two replicative 12-week confirmatory studies in COPD with the 75 mcg dose, and one 26-week confirmatory study in COPD with the 150 mcg dose. Important long-term safety data for the 150 mcg dose comes from a 26-week extension to the adaptive design study, for a total duration of 1 year. Table 1, taken from Dr. Chowdhury's PADAC briefing document, contains a summary of pivotal trials. Table 2, taken from Dr. Anya Harry's clinical review of the complete response submission, contains a summary of newly submitted supportive trials.

Table 1: Key trials with indacaterol maleate

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups†	N (ITT)	Primary efficacy variable	Countries
Submitted with original NDA							
Dose- ranging studies in COPD patients							
B2201 [2004]	Parallel arm	4 weeks	40-75	IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	68 67 28	30 minutes post-dose FEV_1 on Day 1, 14, 28	Europe
B2205 [2004]	Parallel arm	1 week	38-75	IN MDDPI 50 mcg QD IN MDDPI 100 mcg QD IN MDDPI 200 mcg QD IN MDDPI 400 mcg QD IN SDDPI 400 mcg QD Tio 18 mcg BID Placebo	103 105 105 110 105 107	FEV_1 $AUC_{22\text{-}24\ hr}$ post-dose on Day 1	Europe, North America, South America
B2212 [2007]	Crossover	1 day treatment	43-73	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	51	FEV_1 trough at 24 hr	Belgium
1202 [2007]	Crossover	1 day treatment	40-75	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Placebo	50	FEV_1 $AUC_{22\text{-}24\ hr}$ post-dose	Japan
Pivotal COPD studies							
B2335 [2008]	Adaptive design, dose ranging, efficacy and safety	Initial 2 weeks, Continue for 26 weeks	40-88	*Initial 2 weeks:* IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Tio 18 mcg QD Placebo *Continue 6 months:* IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	 107 105 110 102 112 112 104 416 416 415 418	 FEV_1 trough at 24 hr at wk 2 FEV_1 $AUC_{1\text{-}4}$ hr at wk 2 FEV_1 trough at 24 hr at wk 12	USA, Canada, W Europe, India, S Korea, Argentina, Turkey, Taiwan
B2334 [2008]	Long-term Efficacy and safety	52 weeks	40-90	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	437 425 434 432	FEV_1 trough at 24 hr at wk 12	W and E Europe, Russia, C/S America, Mid East, S Korea
B2346 [2008]	Efficacy and safety	12 weeks	40-89	IN SDDPI 150 mcg QD Placebo	211 205	FEV_1 trough at 24 hr at wk 12	USA, NZ, Australia, Belgium
Short-time profiling studies in COPD patients							
B2340 [2008]	Crossover 24 hr FEV	2 weeks	≥ 40	IN SDDPI 300 mcg QD Sal 50 mcg BID Placebo	68	FEV_1 trough at 24 hr at day 15	USA, Belgium, Spain
B2331 [2008]	Crossover 24 hr FEV	2 weeks	≥ 40	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	169	FEV_1 trough at 24 hr at day 15	Europe, Australia, New Zealand, South Africa

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups†	N (ITT)	Primary efficacy variable	Countries
B2305 [2008]	Crossover Assess effect of dosing time	2 weeks	≥ 40	IN SDDPI 300 mcg QDAM IN SDDPI 300 mcg QDPM Sal 50 mcg BID Placebo	96	FEV_1 trough at 24 hr at day 15	France, Germany, Spain
B2307 [2008]	Crossover Onset of effect	Single dose	≥ 40	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Advair 50/500 mcg Albuterol 200 mcg Placebo	89	FEV_1 5 min post-dose on day 1	USA, Belgium, Germany, Hungary
Asthma studies							
A2210 [2004]	Safety	4 weeks	12-65	IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	59 59 26	None	Germany, Belgium, Canada, Czech R, Slovakia
B2338 [2008]	Safety with ICS	26 weeks	12-85	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Sal 50 mcg BID	268 268 269	None	USA, Canada, Europe, South America
Submitted with complete response							
Dose-ranging and dose-regimen studies in asthma and COPD patients							
B2357 [2010]	Dose ranging in asthma	2 weeks	18-82	IN SDDPI 18.75 mcg QD IN SDDPI 37.5 mcg QD IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	84 81 84 85 84 84	FEV_1 trough at 24 hr at day 15	US
B2356 [2010]	Dose ranging in COPD	2 weeks	40-87	IN SDDPI 18.75 mcg QD IN SDDPI 37.5 mcg QD IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	89 90 94 92 91 91	FEV_1 trough at 24 hr at day 15	US
B2223 [2010]	Dose regimen in asthma	2 weeks	18-80	IN SDDPI 37.5 mcg BID IN SDDPI 75 mcg QD IN SDDPI 150 mcg QOD Placebo	48 48 48 47	FEV_1 trough at 24 hr at wk 2 and FEV1 $AUC_{0\text{-}24hr}$	US, UK, France, Jordan, Germany, Netherlands
Pivotal COPD studies							
B2336 [2009]	Efficacy and safety	26 weeks	41-89	IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	330 333 335	FEV_1 trough at 24 hr at wk 12	W and E Europe, Russia, India, Peru, Taiwan, Canada, Columbia, Iceland
B2354 [2010]	Efficacy and safety	12 weeks	40-90	IN SDDPI 75 mcg QD Placebo	163 160	FEV_1 trough at 24 hr at wk 12	US
B2355 [2010]	Efficacy and safety	12 weeks	40-86	IN SDDPI 75 mcg QD Placebo	159 159	FEV_1 trough at 24 hr at wk 12	US

* Year study subject enrollment ended
† IN SDDPI = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); IN MDDPI = Indacaterol multiple dose dry powder inhaler; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva HandiHaler (tiotropium bromide inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)

Table 2: Supportive trials from complete response submission

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

Short-term profiling trials						
B2311	Exercise endurance in COPD	83	3 weeks (2 treatment periods separated by 2 weeks of wash out)	Indacaterol 300 mcg q.d. Placebo q.d.	Exercise endurance time (measured through constant-load cycle ergometry testing) after 3 weeks of treatment	AEs, SAEs, labs, VS, ECG, PE
B2331	24 h lung function profile in COPD	148	14 days (3 treatment periods separated by 2 weeks of wash out)	Indacaterol 150, 300 mcg q.d. Tiotropium 18 mcg q.d. Placebo q.d.	tFEV1 on Day 15	AEs (including COPD exacerbations),, SAEs, labs, VS, ECG, PE
Interim analysis for Japanese trial						
B1303	Efficacy/safety in COPD (Japan)	180	52 weeks (interim analysis at Week 24)	Indacaterol 300 mcg q.d. Salmeterol 50 mcg b.i.d.	tFEV1 on Day 169 (Week 24)	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events

Results from the previous submission are summarized in multiple documents including Dr. Chowdhury's PADAC briefing document (February 11, 2011), CDTL summary by Dr. Anthony Durmowicz, clinical review by Dr. Lynne Wu, and statistical review by Dr. Dongmei Liu. This document will focus on new data from the current complete response submission. Tables and text are adapted from Dr. Chowdhury's PADAC briefing document (February 11, 2011) and Dr. Dongmei Liu's statistical review (February 11, 2011). Results of the supportive trials submitted with the complete response are summarized by Dr. Anya Harry in her clinical review (February 14, 2011). Data from these trials are consistent with pivotal studies in the application for both safety and efficacy findings; thus, are not discussed further in this review.

7.2. Dose and dose regimen

A key deficiency from the previous submission was that the sponsor failed to adequately characterize the dose and dosing regimen for indacaterol. Dose ranging and regimen studies were conducted in an asthma population, per FDA's request, in order to evaluate the drug in the most bronchoresponsive population with the best opportunity to show dose-related differences. Based on the results of these studies, Novartis is now proposing to lower the dose of indacaterol from 150 and 300 mcg once daily to 75 and 150 mcg once daily.

Study B2357 was randomized, double blind, parallel group in design conducted in patients with persistent asthma 18 years of age and older. The study had a 14-day run-in period, followed by 2-week double blind treatment period. There were six treatment arms in this period as shown in Table 1. All enrolled patients were on inhaled corticosteroids (study requirement), had mean screening FEV1 ranging from 2.23 to 2.40 L in different treatment groups (study required FEV1 ≥50% and ≤90% of predicted normal), and mean screening

FEV1 reversibility ranging from 20.5% to 24.5% in different treatment groups (study required an increase of ≥12% and ≥200 mL in FEV1 over pre-bronchodilator value within 30 minutes after inhaling a total of 360 mcg of albuterol via an inhalation aerosol). The primary efficacy variable was 24-hour post-dose trough FEV1 on day 15. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. All patients had serial spirometry at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 11 hour 10 minutes, and 11 hour 45 minutes relative to study drug dosing on days 1 and 15. In a subset of patients (ranging from 44 to 49 patients in different treatment arms) additional time points were added at 14 hours, 20 hours, and 22 hours relative to dosing on day 15. The secondary efficacy variables were 24-hour post-dose trough FEV1 on day 1, peak FEV1 on day 1, FEV1 AUC on days 1 and 14, morning and evening PEFR over 14 days, and use of rescue medication. Safety assessments included adverse event recording including asthma exacerbation, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

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

Study B2223 was randomized, double blind, parallel group in design conducted in patients with persistent asthma 18 years of age and older. The design and conduct of this study was similar to study B2357, but with 3 treatments arms with different dose regimens of the same total daily dose of indacaterol 75 mcg as shown in Table 1. All enrolled patients were on inhaled corticosteroids (study requirement), had mean screening FEV1 ranging from 2.51 to 2.84 L in different treatment groups (which was higher than study B2357), and mean screening FEV1 reversibility ranging from 20.4% to 22.5% in different treatment groups (same as study B2357). Efficacy and safety assessments were the same as study B2357 with one difference of additional blood sampling on the first and last day of dosing for indacaterol pharmacokinetic analysis.

7.2.1. Primary dose selection

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

but after the last dose at week 2, indacaterol doses 37.5 mcg and above did not show clear separation (Figures 3 and 4). The FEV1 time profile curve for the indacaterol 150 mcg and 75 mcg once-daily doses were essentially superimposable after the first dose in patients with asthma (Figure 3). These FEV1-based data support the 75 mcg dose, but do not show clear efficacy advantage of the 150 mcg dose over the 75 mcg dose.

Table 3: Studies B2357, B2223, and B 2356, LS Mean for trough FEV1 (in L) at day 15 (primary efficacy time point)

Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2357 (asthma dose-ranging)			
IN 18.75 mcg	2.50	IN 18.75 - Placebo	0.09 (0.00, 0.17)
IN 37.5 mcg	2.52	IN 37.5 - Placebo	0.11 (0.02, 0.19)
IN 75 mcg	2.59	IN 75 - Placebo	0.17 (0.08, 0.26)
IN 150 mcg	2.54	IN 150 - Placebo	0.12 (0.04, 0.21)
Sal 50 mcg	2.54	Sal - Placebo	0.13 (0.04, 0.21)
Placebo	2.42		
Study B2356 (COPD dose-ranging)			
IN 18.75 mcg	1.35	IN 18.75 - Placebo	0.07 (0.02, 0.12)
IN 37.5 mcg	1.38	IN 37.5 - Placebo	0.10 (0.05, 0.16)
IN 75 mcg	1.38	IN 75 - Placebo	0.10 (0.04, 0.15)
IN 150 mcg	1.40	IN 150 - Placebo	0.12 (0.07, 0.17)
Sal 50 mcg	1.39	Sal - Placebo	0.10 (0.05, 0.16)
Placebo	1.28		
Study B2223 (asthma dose-regimen)			
IN 37.5 BID		IN 37.5 BID - Placebo	0.16 (0.08, 0.23)
IN 75 QD		IN 75 QD - Placebo	0.20 (0.12, 0.27)
IN 150 QOD		IN 150 QOD - Placebo	0.20 (0.12, 0.27)
Placebo			

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)

Figure 3: LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2357, asthma dose ranging)

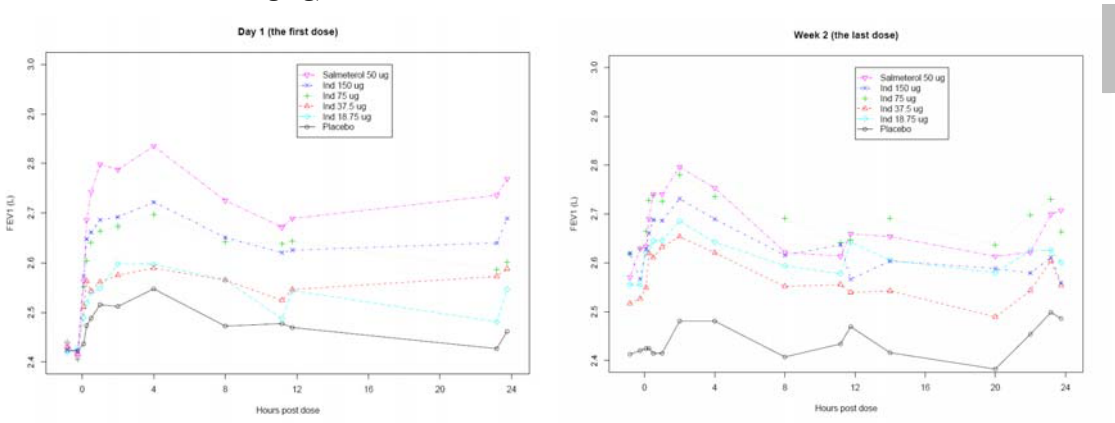
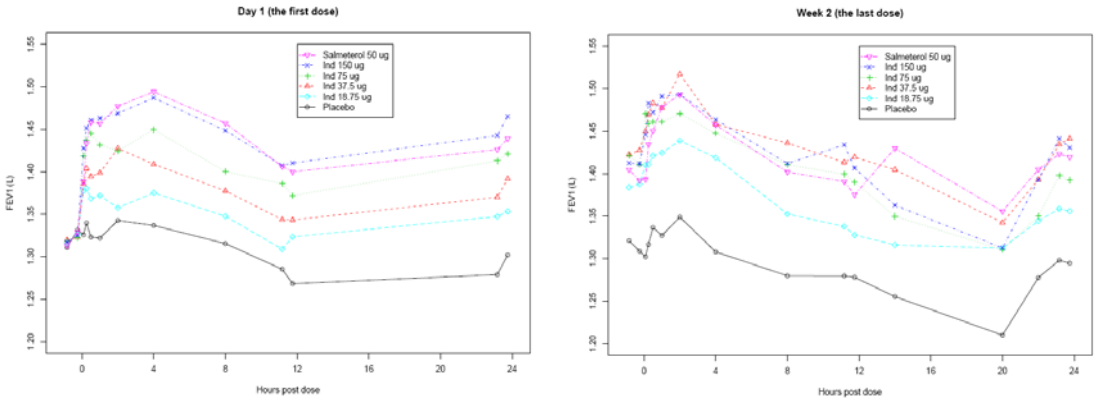


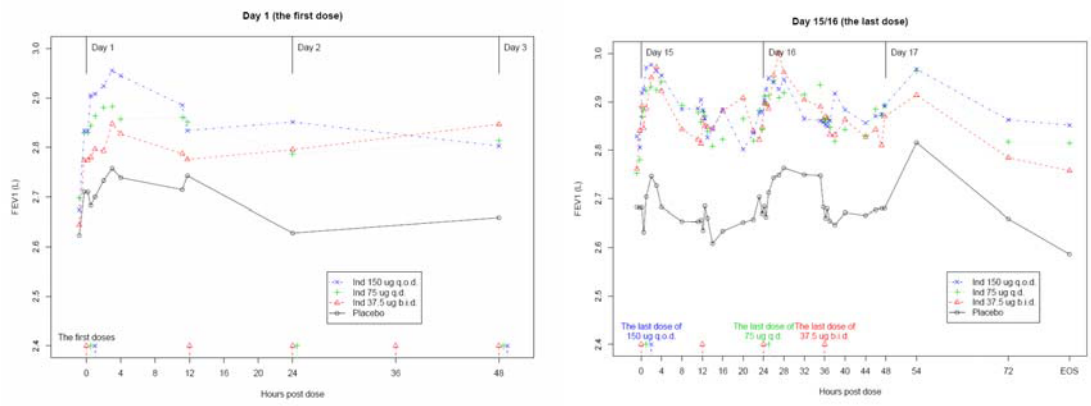
Figure 4: LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2356, COPD dose ranging)



7.2.2. Dose regimen

Results of study B2223, exploring three different dosing regimens of the same nominal dose are shown in Figure 4. Results of the study do not show clear separation of the different dosing regimens. One limitation of this study was that the screening baseline FEV1 was higher in this study compared to the asthma dose-ranging study (2.51 to 2.84 L in this study compared to 2.23 to 2.40 L in asthma dose ranging study B2357), which may make the study less sensitive to show differences among doses. Nevertheless, the three dosing regimens at day 1 showed some numerical separation (Figure 5) suggesting that even with higher baseline FEV1, the study was adequate to test different dosing regimens.

Figure 5: LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2223, asthma dose regimen)



7.3. Efficacy

Studies B2354 and B2355 were randomized, double blind, and parallel group in design. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, moderate-to-severe by GOLD guideline criteria, smoking history of at least 10 pack years, post-bronchodilator FEV1 <80% and ≥30% of predicted, and post-bronchodilator FEV1/FVC <70% (post-bronchodilator refers to 10-15 minutes post-inhalation of 400 mcg albuterol). Both studies had a 2-week run-in period, followed by 12-week double blind treatment with indacaterol 75 mcg QD or placebo (Table 1). The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. On the first day and last day of treatment, serial spirometry was done at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 23 hours 10 minutes, and 23 hours 45 minutes relative to study drug dosing. Other efficacy variables included additional spirometry measure at various time points, rescue medication use, nighttime awakenings, daytime symptoms, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score after 4 and 12 weeks of treatment, one month recall version SGRQ score at baseline, and after 4 and 12 weeks of treatment, and COPD exacerbation frequency. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. In a subset of patients blood samples were collected at the end of week 12 for indacaterol pharmacokinetic analysis.

7.3.1. Bronchodilator effects

Results of the pivotal efficacy study (Study B2336) that was started when the original NDA was submitted but completed later, and the two pivotal efficacy studies (Studies B2354 and B2355) in COPD patients with indacaterol 75 mcg once-daily dose are shown in Table 4. The results show statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at week 12 in the three studies (Table 4). Additional spirometry variables and other secondary measures went in a similar direction with trough FEV1 (data not shown in this document).

Table 4. Studies B2336, B2354, and B2355, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2336			
IN 150 mcg	1.45	IN 150 – Placebo	0.17 (0.13, 0.20)
		IN 150 – Sal 50	0.06 (0.02, 0.10)
Sal 50 mcg	1.39	Sal - Placebo	0.11 (0.07, 0.14)
Placebo	1.28		
Study B2354			
IN 75 mcg	1.38	IN 75 – Placebo	0.12 (0.08, 0.15)
Placebo	1.26		
Study B2355			
IN 75 mcg	1.49	IN 150 – Placebo	0.14 (0.10, 0.18)
Placebo	1.35		

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)

7.3.2. St. George Respiratory Questionnaire

Novartis is proposing the following labeling claim for SGRQ:

Arcapta Neohaler also significantly improved health-related quality of life (as measured using the St. George's Respiratory Questionnaire). 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: An improvement compared to placebo exceeding the minimal clinically important difference of 4 units was shown at 8 and 12 weeks in the 12-week study. In the other 26-week study, treatment with both Arcapta Neohaler 150 mcg resulted in a significantly lower (improved) mean SGRQ total scores compared to placebo with mean differences of 6.3 units ($p<0.001$) that exceeded the minimal clinically important difference of 4 units after 12 weeks and thus were also clinically relevant).

In addition to the modeling data presented in Section 5.6., the SGRQ forms the basis of Novartis' proposal for approval of the higher (150 mcg once daily) dose. Data supporting the SGRQ claim come from one study in the previous submission (B2336) and one study in the complete response (B2346). If approved, Arcapta Neohaler would become the only therapy with a claim for improvement in SGRQ in either COPD or asthma.

SGRQ was assessed in all pivotal COPD studies as either one of the key secondary efficacy variables (B2336) or as one of the many efficacy variables (B2335, B2334, B2346, B2354, and B2355). Results of analysis based on the difference in mean total SGRQ scores between active treatment and placebo are shown in Table 5, and based on the percentage of patients

with a minimally important difference (MID) of -4 units or more from baseline in SGRQ total score (defined as responder) are shown in Figure 6. The MID of -4 for SGRQ has support in the literature.[2, 3] Other than tiotropium, all active treatments, including indacaterol 75 mcg, 150 mcg, 300 mcg, and 600 mcg showed statistically significant separation from placebo. The difference in mean between indacaterol 150 mcg dose and placebo in studies B2336 and B2346 crossed the MID of -4, and the difference in mean between indacaterol 75 mcg dose and placebo did not cross the MID of -4 in studies B2354 and B2355 (Table 5). It is worth noting that the numerical difference for SGRQ scores between indacaterol 150 mcg dose and 75 mcg dose is small, and the difference in the mean score between indacaterol 300 mcg dose and placebo did not cross the MID of -4 in B2335 and B2334. Based on the analysis of COPD three-month efficacy population pooled data, comparing to placebo, the improvement of SGRQ total scores after 12 weeks treatment was -3.8 with a 95% CI of (-5.3, -2.3) for indacaterol 75 mcg, -4.6 with a 95% CI of (-5.5, -3.6) for indacaterol 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) for indacaterol 300 mcg. Confidence intervals for the three doses overlap considerably. The percentage of patients who had an improvement of SGRQ total score crossing the MID of -4 from baseline was 49% for indacaterol 75 mcg, 52% for indacaterol 150 mcg, 52% for indacaterol 300 mcg, and 40% in placebo (Figure 6). There was no statistically significant difference among different doses. Considering the evidence collectively, a labeling claim based on the improvement in SGRQ scores for the dose of 150 mcg seems is questionable.

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

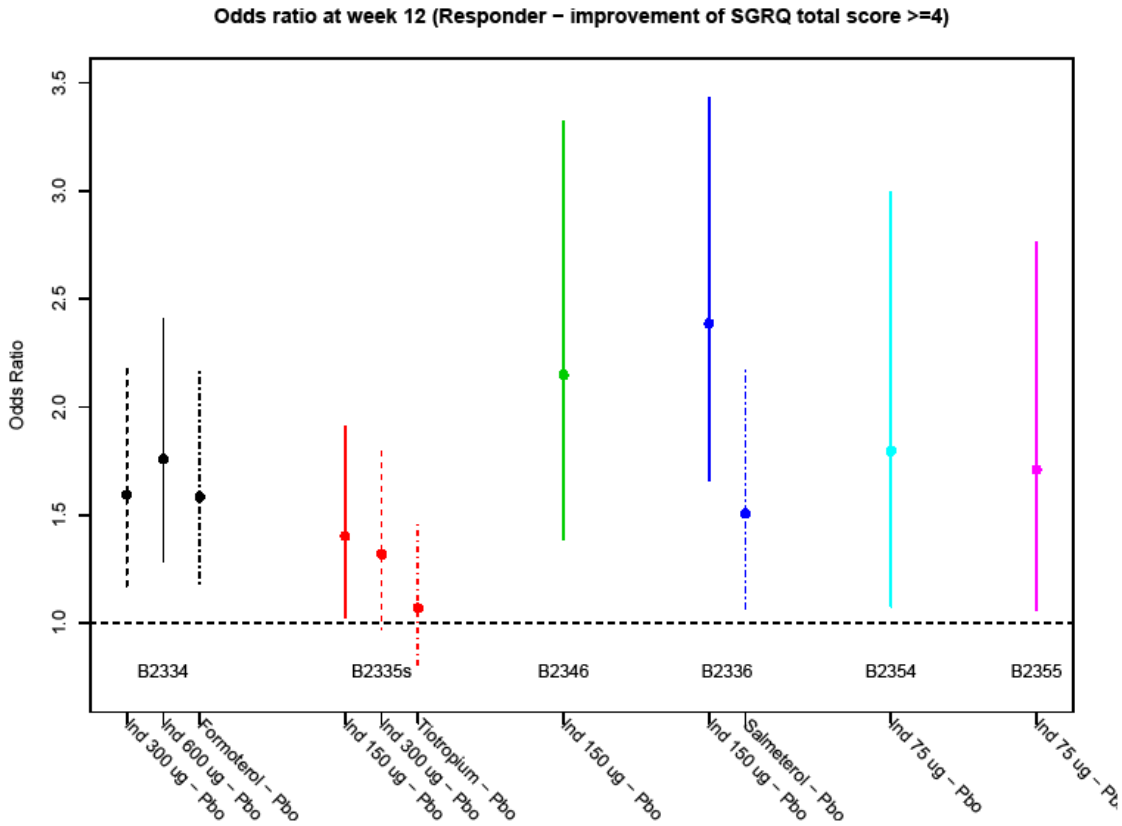
3 Jones PW. St. George's Respiratory Questionnaire: MCID. J of COPD 2005; 2:75-79.

Table 5: ANCOVA results of SGRQ total scores in various COPD studies

Treatment	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Change from Baseline (LS mean)	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2335					
IN 150 mcg	45.4	38.9	-5.6	IN 150 - Placebo	-2.8 (-4.5, -1.1)
IN 300 mcg	44.8	39.6	-5.2	IN 300 - Placebo	-2.5 (-4.2, -0.8)
Tio 18 mcg	44.6	41.0	-3.5	Tio - Placebo	-1.1 (-2.8, 0.6)
Placebo	45.7	42.7	-3.0		
Study B2334					
IN 300 mcg	44.4	38.6	-5.8	IN 300 - Placebo	-3.8 (-5.6, -2.1)
IN 600 mcg	44.4	38.3	-6.1	IN 600 - Placebo	-4.1 (-5.9, -2.3)
For 12 mcg	44.4	39.2	-5.2	For - Placebo	-3.2 (-5.0, -1.5)
Placebo	43.6	41.6	-2.1		
Study B2346					
IN 150 mcg	50.2	43.7	-6.5	IN 150 - Placebo	-4.8 (-7.2, -2.4)
Placebo	48.7	47.6	-1.1		
Study B 2336					
IN 150 mcg	43.6	35.9	-7.7	IN 150 - Placebo	-6.3 (-8.2, -4.3)
Sal 50 mcg	43.2	37.8	-5.4	Sal - Placebo	-4.2 (-6.1, -2.2)
Placebo	43.6	42.4	-1.2		
Study B2354					
IN 75 mcg	48.4	42.7	-5.8	IN 75 - Placebo	-3.8 (-6.2, -1.4)
Placebo	49.5	47.6	-2.0		
Study B2355					
IN 75 mcg	51.2	46.2	-4.9	IN 75 - Placebo	-3.6 (-6.4, -0.9)
Placebo	50.1	49.2	-0.9		

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder); Tio = Spiriva HandiHaler (tiotropium bromide inhalation powder)

Figure 6: Summary of SGRQ responder analysis in controlled COPD studies



7.4. Support for higher dose

Novartis proposes a 150 mcg once daily dose "to provide additional benefit in patients with more severe bronchial obstruction." The sponsor is basing the claim for the higher 150 mcg dose on two points: modeling data from the dose ranging studies and the SGRQ. Such a claim has no regulatory precedent, as all approved bronchodilators have only a single dose, generally for both asthma and COPD. This issue will be discussed further at the PADAC meeting March 8, 2011.

The 150 mcg once daily dose clearly demonstrates bronchodilator efficacy across a number of spirometric endpoints; however, there is no evidence that the 150 mcg dose produces better efficacy than the 75 mcg dose (Section 7.2.1). Further, the 75 mcg and 150 mcg doses have not been compared in primary efficacy trials, except for the 2-week dose ranging studies. Similarly, a comparison drawn from the pooled 3 month efficacy data from all double-blind, placebo and active controlled trials of at least 12 weeks duration, consisting of 10 trials, does not demonstrate a clinically meaningful benefit in the primary bronchodilator endpoint of tFEV1 at 12 weeks, with difference of only 10 ml between the two dose groups. A subgroup analysis of this data by Global initiative for chronic Obstructive Lung Disease (GOLD) stage likewise did not demonstrate a benefit of the 150 mcg dose over the 75 mcg dose for patients with severe disease. As noted by the clinical pharmacology team and discussed in Section 5.3., the sponsor's model is sensitive to the data used for analysis so is not considered a robust

finding. Although the SGRQ does meet the MCID of -4 in two different studies, it is unclear if it offers significant benefit over the 75 mcg dose (Section 7.3.2.). In addition, the 300 mcg dose does not meet the MCID of -4, calling into question the "dose response" of 150 mcg.

7.5. Efficacy conclusions

These conclusions represent the current thinking of the review team, but are subject to change pending discussion at the Advisory Committee meeting.

- Dose ranging and dose regimen trials support a once daily dose of 75 mcg.
- The proposed higher dose of 150 mcg once daily for more severe patients provides no additional efficacy benefit over the 75 mcg dose for bronchodilator effects or SGRQ. Likewise, pharmacokinetic modeling data do not support a higher dose.
- The claim for improvement in health related quality of life as measured by the SGRQ is not supported.

8. Safety

8.1. COPD population

The sponsor provided an integrated summary of safety including trials from both the original submission and the complete response. There were a total of 9441 patients in the 3 month COPD safety dataset, 4764 of whom received indacaterol in the following dose groups—75 mcg (N-449), 150 mcg (N=2611), 300 mcg (N=1157), and 600 mcg (N=547). Twelve month data is available for 2142 patients, 1152 of whom received indacaterol in the following dose groups—150 mcg (N=144), 300 mcg (N=583), and 600 mcg (N=425). Because only 3 month data exists for the 75 mcg dose, the sponsor intends to extrapolate long-term safety from the 150 mcg dose group.

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

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

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

8.2. Asthma population

Due to a safety concern regarding potential asthma related death, asthma safety was reviewed as part of this cycle. There were a total of 13 asthma studies conducted with indacaterol; however, the majority were either of short duration or conducted with another formulation of indacaterol. Results from the two key safety studies as discussed by Dr. Chowdhury in the PADAC briefing document are summarized.

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

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

These studies raise safety concerns for indacaterol as a bronchodilator because of findings of serious asthma events. There were 2 deaths seen in the asthma safety study B2338, both

occurring in patients treated with indacaterol 300 mcg once-daily while they were receiving concurrent ICS.

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

The second death occurred in a 75-year-old woman with a two-year history of asthma, allergic rhinitis, osteoporosis, and past history of respiratory arrest and anaphylactic reaction. On day 119 of treatment the patient experienced a cardiac arrest at home. The patient was resuscitated, intubated, and admitted to the hospital. On evaluation, significant findings were a small pneumothorax and pulmonary hyperinflation consistent with asthma. There were no findings consistent with myocardial infarction or other cardiovascular diseases. Life support was withdrawn on day 11 of hospitalization on family request and the patient expired. The patient was on inhaled mometasone 220 mcg once daily for the entire duration of the study.

SAEs related to asthma exacerbation or respiratory events seemed to be more common in patients treated with indacaterol in various asthma studies. In the asthma safety study B2338 (26-week study involving about 268 patients per treatment arm) where two deaths were seen (described above), SAEs related to asthma exacerbation were reported for 2 patients in the indacaterol 300 mcg group, 3 patients in indacaterol 600 mcg group, and for no patients in the salmeterol group. In the other asthma safety study (Study A2210, 4-week study involving 59 patients per active treatment arm) there were more respiratory-related SAEs in the indacaterol treated group compared to placebo (4 in indacaterol versus 0 in placebo). In addition, in the 2-week asthma dose regimen study (B2223, 2-week crossover study involving 48 patients; see Section 7.2.2.) there was one SAE of asthma exacerbation possibly due to viral influenza and pollen exposure reported in one patient while receiving indacaterol 150 mcg every other day.

8.3. Meta-analysis of respiratory-related events

On December 16, 2010, the Agency asked Novartis to conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation. The Agency believed that such an analysis was necessary to provide balancing safety data to justify the proposed higher dose (150 mcg) of indacaterol and to attempt to evaluate whether a safety signal for asthma-related death might exist in COPD. This meta-analysis was reviewed in detail by Dr. Banu Karimi-Shah (February 25, 2011), and the results of her review are summarized here.

The Agency requested that the Applicant conduct an analysis to evaluate the incidence of respiratory-related death, intubation, and hospitalization related to asthma, COPD, or pneumonia in indacaterol-treated patients compared to control. The Agency requested that the Applicant implement an adjudication committee to provide an independent assessment of all serious adverse events (SAEs) occurring during the development of indacaterol, in both COPD and asthma. The committee was charged with categorizing which deaths, hospitalizations, and intubations were respiratory-related. They were further asked to classify events according to

whether they were asthma-, COPD-, or pneumonia-related. Only events that occurred on-treatment were to be included in the meta-analysis. Per FDA request, the Applicant included all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration in patients with both asthma and COPD, in which indacaterol maleate was delivered using the single dose dry powder inhaler Concept 1 (or similar) device, whether or not the trials were submitted as part of the NDA. The Applicant analyzed the data in six defined populations based on whether the studies included were in asthma or COPD patients, and whether they were active- or placebo-controlled.

The All-treated COPD Safety Population included a total of 11,755 patients in 23 studies. The majority of the studies were greater than 12 weeks in duration and were conducted with the to-be-marketed Concept1 (Neohaler®) device. Of the 11,755 COPD patients, 6863 were treated with indacaterol, 2482 with placebo, and 2408 with one of three active controls (formoterol n=556, tiotropium n = 842, and salmeterol n = 1010).

In the All-treated COPD-safety population I, a total of 239 of 11,755 patients were identified as having had a respiratory-related event. Of these 239 patients, there were 219 patients who had an acute respiratory-related hospitalization or intubation. There were no acute respiratory-related deaths in this population. The incidence of total and acute respiratory-related events is depicted in Table 6. “Total” refers to any respiratory related event (e.g. pulmonary embolus, lung cancer), while “acute” includes only those respiratory-related deaths which were adjudicated to be asthma-, COPD-, or pneumonia-related.

Table 6: Total and acute respiratory-related events: all-treated COPD safety population I

	Indacaterol Treatment Groups (mcg)[a]						Active Comparators			
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL[b] n=6863	For n=556	Tio n=842	Sal n=1010	PBO n=2484
Composite, n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	54 (3.8)	15 (2.6)	134 (2.0)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Hospitalizations, n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	53 (3.7)	15 (2.6)	133 (1.9)	32 (5.8)	7 (0.8)	14 (1.4)	50 (2.0)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	47 (1.9)
Intubations, n(%)										
Total	0	1 (<0.1)	1 (<0.1)	2 (0.1)	0	4 (0.1)	3 (0.5)	0	1 (<0.1)	1 (<0.1)
Acute	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)

a. Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table [e.g. 18.75 mcg (n=173), 37.5 mcg QD/BID (n=219), 150 mcg QOD (n= 48), 400 mcg QD (n=7)]; all dosing regimens are QD unless otherwise noted
b. Includes patients that used other similar delivery device in addition to those patients who used the Concept1 device
Total: Includes those patients who had any respiratory related event
Acute: Includes those events that were deemed COPD/pneumonia related;
For: formoterol; Tio: tiotropium; Sal: salmeterol
Hospitalizations: admission or emergency room visit > 24 hours in duration (± corticosteroid treatment)
Intubations: endotracheal intubation for mechanical ventilation for the treatment of acute hypoxemic or hypercapneic respiratory failure
Source table: re2.1c1 pages 478-483

Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, particularly those that were adjudicated as having been COPD-related (Table 6) as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase in the composite endpoint is driven primarily by an increase in acute-respiratory related hospitalizations related to COPD, with no dose-related increase in pneumonia hospitalizations. Exposure adjusted data shows a similar picture, although the data are not as clear due to the small exposure history in some dose groups. When patients were

analyzed by reversibility to bronchodilator (12% and 200 mL; yes or no) and duration on treatment (> 12 weeks or <12 weeks), the trend appeared consistent across these subgroups. In the All-Treated COPD Safety Population II, which excluded any studies that were not placebo-controlled, a similar numerical trend towards a dose-related safety signal was observed.

The meta-analysis included far fewer patients with asthma when compared with the COPD patient population. The All-treated Asthma Safety Population I included a total of 1914 patients in 7 studies. Of the 1914 asthma patients, 1307 were treated with indacaterol, 254 with placebo, and 353 with a salmeterol active control. It is notable, however, that even in this relatively small cohort of asthma patients, asthma-related serious adverse events occurred at a relatively high frequency. There was 1 death and 1 intubation in the 300 mcg indacaterol group (study B2338, n~268/arm, total n=805) versus none in the placebo group. Additionally, there were 3 hospitalizations each in the indacaterol 300 mcg and 600 mcg groups versus none in the placebo group, in patients who were taking concomitant ICS per protocol. The second potential asthma-related death noted in Study B 2338 (see Section 7.2) was not included in this meta-analysis because the patient was taken off study drug when she entered the hospital for an acute-respiratory related event and was therefore counted as off-treatment. It is notable, however, that this patient, though enrolled in an asthma-clinical trial, was adjudicated as having had a COPD-related death and intubation. Although the Applicant is not proposing to market indacaterol for an asthma indication, the adjudication of this death in an asthma patient as being COPD-related illustrates the clinical overlap that exists between these two disease entities and the possible safety implications that arise when considering the doses that are proposed for registration.

8.4. Post-marketing safety

On January 24, 2011, Novartis submitted a summary of fatal cases from a branded patient support program ongoing in Mexico. Novartis began a branded patient support program on September 26, 2010, with the last of 1316 patients enrolling in the 30 day program on January 4, 2011. Based on a survey of participating physicians, the sponsor suggests that the majority of patients enrolled in the program had severe or very severe COPD. As of January 19, Novartis reports a total of 16 deaths (1.2%) in the Mexican patient support registry. The most common cause of death was respiratory (3 pneumonia, 1 respiratory insufficiency, 1 COPD, and 1 PE), followed by cardiac (1 CHF, 2 cardiac arrest) and cancer (breast, lymphoma, GI). There were also 2 deaths of unknown cause, one GI bleed and one due to progression of Wegener's disease. Of the 16 patients who died, 11 were aged 75 years or older. The three patients who died of cardiac causes reportedly had pre-existing cardiac disease. While these deaths represent a much larger number than the rest of the post-marketing deaths from over 50 countries put together, it is difficult to determine the clinical meaningfulness of these events in the context of post-marketing reporting. The events in the Mexican patient support program were solicited as opposed to spontaneous reports in the rest of the database, which traditionally results in significant underreporting. The causes of death do not appear to be particularly unusual for a severe COPD patient population.

Novartis states that the estimated patient exposure to indacaterol based on worldwide sales is approximately 57,000 patient years. Excluding the deaths reported in the Mexican patient support program, there are 10 other fatal cases in post-marketing reports. These cases ranged in age from 44 to 96 years. The most common cause of death was respiratory: COPD

exacerbation, status asthmaticus, respiratory failure, and pulmonary embolis. Three patients died of unknown causes, one of which was reported as sudden death. The other three patients died of circulatory collapse following diuresis, sepsis, and myocardial infarction.

In light of the known risk of asthma-related death with LABAs, the one concerning event is the patient who died of status asthmaticus. This was a 44 year old female with a history of asthma and COPD. Approximately 6 weeks prior to the fatal event, she developed a series of exacerbations requiring systemic corticosteroids. In addition, her maintenance regimen was changed from fluticasone plus tiotropium to indacaterol (unknown dose) plus tiotropium. An autopsy was not performed. While all of the details surrounding the case are unavailable, the single report of death from status asthmaticus raises the concern of LABA-related death. Unfortunately, it is not known whether the patient received a 150 mcg or 300 mcg indacaterol dose. Although her ICS was stopped, the patient was reportedly receiving concomitant oral corticosteroids.

8.5. Safety conclusions

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

The potential dose related increase in COPD-related events raises questions regarding safety of the 150 mcg dose. This issue will be discussed at the PADAC meeting, including whether balancing safety data exits to support the two proposed doses of indacaterol.

9. Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee Meeting is being held for Arcapta Neohaler on March 8, 2011, after the date of this review. The major issues for discussion at the PADAC meeting are: a) whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data, b) whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data, c) whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses, and finally, d) the safety of the proposed dose and dosing regimen of indacaterol.

10. Pediatrics

Novartis is requesting a claim for Arcapta Neohaler for COPD only and is not requesting a claim for asthma. Since COPD is a disease that occurs only in adults, FDA granted a pediatric waiver for this application. The product label will clearly state that indacaterol is not indicated for children.

(b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

11.1. Ethics and data integrity

For the pivotal studies submitted in this complete response application, there were a total of 5 investigators who reported payments in excess of $25,000. In the original submission, three investigators enrolled patients in Protocol B2335S (adaptive design dose ranging) and one in Protocol B2338 (asthma safety). Neither of these trials is considered pivotal for the current application. For all of these trials, no investigator enrolled a significantly high proportion of patients such that any change to the data in these double-blind trials would be likely to influence the outcome of the study.

Because of the complete response action, no clinical site audits were conducted in the previous cycle. For the complete response action, the Division of Scientific Investigations (DSI) was consulted to conduct site inspections for three key pivotal trials, B2354 (75 mcg COPD), B2355 (75 mcg COPD), and B2357 (asthma dose ranging). These studies were all conducted solely in the US. DSI audited one site from each study: Drs. Steven Weinstein (B2354), James Pearle (B2355) and James Meli (B2357). The auditor did not identify any significant GCP or scientific integrity issues at these sites.

11.2. Risk Evaluation and Mitigation Strategy (REMS)

Novartis submitted a Risk Evaluation and Mitigation Strategy (REMS) for Arcapta Neohaler consisting of a Medication Guide and a communication plan regarding LABA safety (asthma related death). The communication plan includes a Dear Health Care Professional Letter, information posted on a website, and letters of notification to professional societies. The professional societies include the American Thoracic Society, American College of Chest Physicians, American College of Physicians, National Medical Association, and American Academy of Nurse Practitioners. The Division of Risk Management (OSE-DRISK) reviewed the REMS and found it to be generally consistent with existing REMS for other LABAs. Final edits based on FDA comments are ongoing at the time of this review.

12. Labeling

Due to the 6 month review clock for this application and Advisory Committee meeting late in the cycle, many issues regarding approvability (e.g. dose) that directly impact labeling are pending at the time of this review. Therefore, the Division has adopted an alternative approach to labeling discussions. For the purposes of labeling, the Division is assuming that only the 75 mcg dose will be approved. This assumption allows the majority of label sections to proceed, with only the clinical sections (Highlights, Section 6 Adverse Events, Section 14 Clinical Trials, and Medication Guide) pending input from the AC. At the time of this review, labeling comments on the non-clinical sections have been sent to the sponsor. A labeling teleconference was held on February 23, 2011 in which a few relatively minor sponsor comments were addressed.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name. DMEPA found the proposed proprietary name, Arcapta Neohaler, acceptable for this product based on the product characteristics and safety profile.

13. Recommendations/Risk Benefit Assessment

13.1. Recommended regulatory action

The recommended regulatory action for this application is: 1) approval of the 75 mcg once daily dose for a bronchodilator indication without granting a claim for SGRQ, and 2) a complete response action for the 150 mcg dose. This recommendation is provisional, assuming that the manufacturing compliance issues can be resolved satisfactorily prior to the April 1, 2011 action date. In addition, this recommendation is subject to modification based on the results of the PADAC meeting on March 8, 2011.

13.2. Risk benefit assessment

Replicate findings of statistically significant differences between indacaterol 75 mcg or 150 mcg once-daily and placebo were shown in COPD patients for the primary efficacy endpoint of 24-hour post-dose trough FEV1 after 12 weeks of treatment, and for various secondary measures of efficacy, including for total SGRQ at 12 weeks. There were no major identified safety concerns with COPD patients; however, there were two asthma related deaths in a relatively small asthma safety study (26-week safety involving about 268 patients per treatment arm) in patients treated with indacaterol 300 mcg once-daily while they were receiving a background of concurrent ICS treatment. SAEs related to asthma exacerbation or respiratory events seemed to be more common in patients treated with indacaterol in various asthma studies. In addition, in the respiratory safety meta-analysis there was a numerical trend of increasing incidence of acute respiratory-related events as the dose of indacaterol rises from 75 mcg to 300 mcg. There was also a post-marketing safety report of an asthma-related death in a 44 year old woman who also had COPD (indacaterol dose unknown, either 150 or 300 mcg). The major safety concern with indacaterol is linked to selection of appropriate dose, because bronchodilators, particularly at high doses, have safety concern of severe asthma exacerbations and asthma related deaths in patients who use these drugs to treat asthma. Based on lack of significant efficacy advantage and potential asthma-related safety concerns, approval of the higher 150 mcg dose is not recommended.

13.3. Recommendation for postmarketing Risk Evaluation and Management Strategies

Arcapta Neohaler will carry standard class labeling for LABA agents in addition to having a REMS consisting of a Medication Guide and communication plan.

13.4. Recommendation for other postmarketing requirements and commitments

There are no recommendations for further postmarketing requirements and commitments at the time of this review. However, the issue will be discussed at the PADAC meeting, and will be revisited based on the committee's recommendations.

13.5. Recommended comments to applicant

Comments to the applicant will be finalized after the PADAC meeting. Preliminary comments are as follows:

- The submitted data do not provide substantial evidence to support use of two different doses of Arcapta Neohaler in patients with COPD. The data submitted did not show a clinically meaningful advantage of the 150 mcg dose over the 75 mcg dose, especially in regards to potential safety disadvantages associated with administration of a higher dose.
- To support approval of the 150 mcg dose conduct clinical studies to establish a clinically meaningful efficacy advantage over the 75 mcg dose and provide balancing safety data.

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/s/

THERESA M MICHELE
03/01/2011