

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022383Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of the Commissioner
Office of Good Clinical Practice
10903 New Hampshire Avenue, Bldg. 32, Rm. 5110
Silver Spring, MD 20993-0002

Tel 301-796-8342
FAX 301-847-8640

M E M O R A N D U M

Date: 6/6/11

From: Sara F. Goldkind, M.D., M.A., Senior Bioethicist
Office of Good Clinical Practice, OC

To: Sally Seymour, M.D., Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products, CDER

Through: Joanne R. Less, Ph.D., Director,
Office of Good Clinical Practice, OC

Re: **NDA 22-383, Arcapta Neoinhaler (indacaterol inhalation powder), at a dose of 75 or 150 mcg every day, for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema**

Materials Reviewed

Select review of:

- 1) Medical Officer Clinical Review: Anya C. Harry, 2/14/11
- 2) Cross-discipline Team Leader Review: Theresa M. Michele, 10/1/10
- 3) Division Director Memorandum for Members of Pulmonary-Allergy Drugs Advisory Committee: Badrul A. Chowdhury, 2/8/11
- 4) NDA submission: Submitted 9/28/10
- 5) Investigator's brochure: Edition 8, 7/21/08
- 6) Public Citizen's Letter to FDA
- 7) Public Citizen's Letter to OHRP
- 8) Albuterol drug label, revised 7/20/10
- 9) Formoterol drug label, Reference ID: 2906399

- 10) Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2010 (GOLD's 2010)¹ (Abbreviated for later use)
- 11) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease-2006 Update (GOLD's 2007)²
- 12) Standards for the diagnosis and treatment of patients with COPD: a summary of the American Thoracic Society (ATS)/European Respiratory Society (ERS) position paper³
- 13) Draft Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment, November 2007⁴

Background

Indacaterol, a new molecular entity, is a long-acting beta agonist (LABA) under review (NDA 22-383) for bronchodilation in patients with COPD. The original NDA was submitted to the FDA on December 15, 2008 for the use of indacaterol inhalation powder at a dose of 150 mcg or 300 mcg once-daily for the indication of long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. To support this application, Novartis submitted three studies:

1. B2335, An adaptive design, dose-ranging study in which four doses of indacaterol ranging between 75-600 mcg QD were studied in a 2-week initial run-in phase. Doses of 150 mcg and 300 mcg continued to be studied for 26 weeks in a randomized, placebo-controlled, add-on design in which subjects received either ICS + salbutamol/albuterol PRN, indacaterol 150 mcg, indacaterol 300 mcg or tiotropium 18 mcg BID. Endpoints were safety and efficacy FEV₁ trough at 24 hour and FEV₁ AUC₁₋₄ hour at week 2 and FEV₁ trough at 24 hour at week 12.
2. B2334, A 52-week safety and efficacy study with a randomized placebo-controlled, add-on design in which subjects received either ICS + salbutamol/albuterol PRN, indacaterol 300 mcg QD, indacaterol 600 mcg QD, or formoterol 12 mcg BID. Endpoints were safety and efficacy FEV₁ trough at 24 hour at week 12.
3. B2346, A 12-week safety and efficacy with a randomized placebo-controlled add-on design in which subjects received either ICS + salbutamol/albuterol PRN or indacaterol 150 mcg QD. Endpoints were safety and efficacy FEV₁ trough at 24 hour at week 12. (For further details see Appendix 1.)

FDA took a complete response action on this application on October 16, 2009. Key issues were:

¹ http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf

² Rabe, K.F., Hurd, S., Anzueto, A., et. al., American Journal of Respiratory and Critical Care Medicine, Vol. 176, No. 6, (September 2007): 532-55.

³ Celli, B.R., MacNee, W., and committee members, European Respiratory Journal 23 (2004): 932-948.

⁴ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071575.pdf>

1. *Unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD*
2. *Possible asthma-related deaths compared to salmeterol in patients with asthma*
3. *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.*

As a result, Division of Pulmonary, Allergy, and Rheumatology Products (DRARP) advised Novartis to explore efficacy and safety of lower doses and other dosing frequencies to both establish a minimum effective dose (MED) and to establish dose-response in terms of safety and efficacy.

To address these deficiencies, Novartis submitted a complete response on October 1, 2010, with results from six new pivotal studies in addition to ten phase 3 supportive studies. The proposed dose of indacaterol was lowered to 75 mcg or 150 mcg once daily based on data from the additional clinical studies. The key studies were:

1. B2336, A 26-week safety and efficacy study with a randomized placebo-controlled, add-on design in which subjects received either ICS + salbutamol/albuterol PRN, indacaterol 150 mcg QD, or salmeterol 50 mcg BID. Endpoints were safety and efficacy FEV₁ trough at 24 hour at week 12.
2. B2354, A 12-week safety and efficacy study with a randomized placebo-controlled add-on design in which subjects received either ICS + salbutamol/albuterol PRN or indacaterol 75 mcg QD. Endpoints were safety and efficacy FEV₁ trough at 24 hour at week 12.
3. B2355, A 12-week safety and efficacy study with a randomized placebo-controlled add-on design in which subjects received either ICS + salbutamol/albuterol PRN or indacaterol 75 mcg QD. Endpoints were safety and efficacy FEV₁ trough at 24 hour at week 12. (For further details see Appendix 1.)

On March 8, 2011 the DPARP presented the indacaterol development program to the Pulmonary-Allergy Drugs Advisory Committee (PADAC) for discussion of regulatory decision-making related to the approval of the drug product. Included in the issues for discussion were: 1) whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by the submitted data given that there were no studies directly comparing these proposed doses, and; 2) whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy and safety data.

PDAC top-line conclusions and recommendations from the 3/8/11 meeting⁵ included:

- The majority of committee members felt that there were strong efficacy data and adequate safety data for indacaterol 75 mcg QD.

⁵ <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM248744.pdf>

- The majority of the committee felt that the safety profile for indacaterol 150 mcg QD was adequate; however, they believed that there was only a small indication or no indication that there was improved efficacy with indacaterol 150 mcg QD.
- Head-to-head comparison, including severe COPD subgroups and broadened study groups (i.e., more heterogeneity) are needed.
- Post-marketing and long-term studies are needed

Public Citizen Health Research Group (Public Citizen) presented testimony at the March 8, 2011 meeting and followed up by submitting concerns to both FDA and the Office for Human Research Protections on 3/16/11. Specifically, Public Citizen contends:

- The lowest doses of Indacaterol that provides the desired efficacy has not been established;
- Long-term, placebo-controlled, phase 3 studies of Indacaterol in subjects with moderate to severe COPD are unethical as subjects would receive substandard care;
- FDA should not approve Indacaterol at any dose as it does not offer clinically significant advantages over other approved long-acting beta agonists (LABA's). Moreover, there is the concern that once approved Indacaterol will be used in asthmatics increasing their risk of serious adverse events, including death as has been shown in other LABA's.

DRARP plans to respond to Public Citizen on or around the PDUFA due date which is July 1, 2011 for this application. (Indacaterol is currently approved for COPD in over 30 countries worldwide including the European Union at doses of 150 and 300 mcg once daily.)

DRARP Questions

“1) Request review of informed consent +/- protocols in response to letter submitted by Public Citizen that raised concern regarding trials that were unethical and failed to minimize risks to subjects and satisfy the requirements in HHS regulations 45 CFR 46.111(a)(1) and 45 CFR 46.116(a)(1) and (2)⁶. Public Citizen submitted letters regarding concerns with the clinical program with indacaterol, including the use of placebo control in the clinical trials, failure to minimize risk to participants, and inadequate informed consent.

2) Please also comment on the adequacy of the description of the study procedures and risks and benefits and if the informed consent adequately protects research subjects.

3) We appreciate any other comments that you may have to aid in addressing the letter from Public Citizen, especially regarding the use of placebo control in trials in patients with COPD.”

Response to #1

⁶ The HHS regulations, 45 CFR 46, do not appear to be applicable to two of the studies conducted solely outside the US. It is possible that 45 CFR 46 applies to the remaining four studies. See Response Section, “Additional Concerns”. Corresponding FDA regulatory citations are: 21 CFR 56.111(a)(1) and 21 CFR 50.25(a)(1) and (2).

Use of placebo: My ethical analysis is done from a prospective perspective-as if at the time of initiation of the studies. That is, comparative safety and efficacy results from the individual studies will not be used to justify their merits nor will study interventions be assessed in relation to current 2011 guidelines for COPD medical management, but will be assessed in relation to treatment guidelines closer to the time when the studies' were designed and initiated. Both the GOLD's 2007 and the GOLD's 2010 state that "regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators." ["Evidence Category A: evidence is from endpoints of well-designed RCTs that provide a consistent pattern of finding in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants."]⁷ GOLD's 2010 additionally states that "regular use of a long-acting beta-agonist or a short or long-acting anticholinergic improves health status."⁸ Of particular note, the references associated with these statements do not include articles comparing SABA's and LABA's.

Although there are many aspects of placebo-controlled study designs that can be debated, there is general consensus that withholding a known effective and available treatment is unethical if increased risks of serious or irreversible harms are incurred.⁹ It should be clarified, that in the pivotal COPD studies under NDA 22-383, placebo is not equivalent to "no treatment"; these are add-on trials in which subjects in the control arm receive ICS + SABA PRN. Therefore, the ethical acceptability of these studies hinges upon whether the risks incurred by subjects randomized to the control arm are serious or irreversible. Pharmacotherapy for the treatment of COPD is for diminution of symptoms and complications but it is not disease-modifying as "none of the existing medications for COPD have been shown to modify the long-term decline in lung function."¹⁰ Therefore, the switch from LABA to ICS + SABA PRN is not expected to irreversibly affect pulmonary function. Affects on COPD exacerbations and death would constitute the serious or irreversible harms potentially associated with the change from the long-acting to short-acting formulations of beta agonists in these placebo-controlled add-on studies.

The seminal ethical questions are:

⁷ GOLD's 2007, p.540 and GOLD's 2010, p. 48.

⁸ GOLD's 2010, p. 52.

⁹ See: Declaration of Helsinki, 2008, Principle 32 at:

<http://www.wma.net/en/30publications/10policies/b3/17c.pdf>

Council for International Organizations of Medical Sciences in collaboration with World Health Organizations, 2002, Guideline 11 at:

http://www.cioms.ch/publications/layout_guide2002.pdf

ICH E-10, Choice of Control Group and Related Issues in Clinical Trials at:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf

¹⁰ GOLD's 2007, p.541 and GOLD's 2010, p. 48.

Diaz, P.T., Bruns, A.S., Ezzie, M.E., et. al., *Optimizing Bronchodilator therapy in Emphysema*, Proceeds American thoracic Society Vol. 5, (2008): 501-5.

Welte, T. *Optimizing treatment for COPD-new strategies for combination therapy*, International Journal of Clinical Practice Vol. 63, No. 8, (august 2009): 1136-49.

Montuschi, P., *Pharmacological treatment of chronic obstructive pulmonary disease*, International Journal of COPD Vol. 1, No. 4 (2006): 409-23.

- Are subjects placed at greater risk of serious or irreversible harms, i.e., COPD exacerbations and/or death, when assigned to ICS + SABA PRN instead of LABA, based upon an a priori available data?
- Are subjects placed at greater risk of COPD exacerbations and/or death when their stable COPD pharmacotherapy is discontinued and they are randomized to receive ICS + SABA PRN instead of LABA's, based upon an a priori analysis of available data?

Understanding the state-of-the-art clinical care of moderate to severe COPD patients, as well as an analysis of peer-reviewed literature and labeling information for SABA's and LABA's, contributes to the understanding of these important issues. A review of the literature in consultation with DRARP, however, reveals a paucity of meaningful data of direct comparisons of SABA's vs. LABA's at endpoints including serious and irreversible harm in the treatment of COPD (all degrees of severity). The GOLD's 2007 guidelines and the ATS recommendations of 2004 also do not reference head-to-head comparisons of SABA's and LABA's at endpoints that represent serious or irreversible harm. In fact, there are no data studies directly assessing LABA and SABA agents. It appears that convenience and anticipated compliance are the basis for recommending LABA rather than either SABA or LABA agents in the societal recommendations.¹¹

One large, long-term study, TORCH (Towards A Revolution in COPD Health),¹² was identified that provides insight into the question at hand. The TORCH Trial compares salmeterol vs. fluticasone propionate vs. combination therapy vs. placebo+ non LABA, non ICS background therapy, and provides important information in assessing the ethical use of ICS+ SABA PRN as a control arm for 12-52 weeks in the pivotal COPD studies NDA 22-383. In this study, the placebo arm essentially represents add-on therapy as subjects could continue other COPD pharmaceutical therapies. Since SABA are a key component of COPD management the assumption is made that the placebo-arm is reflective of background therapy that includes SABA.

The TORCH trial recruited 8,554 patients and randomized 6,184 patients. It is a three-year trial with a primary mortality endpoint. Based on post-bronchodilator FEV₁, subjects enrolled in the TORCH Trial had lung function at least as compromised as subjects in the pivotal COPD studies under NDA 22-383. Although the study failed its primary endpoint with a p-value of 0.052 for the endpoint of all-cause mortality (the authors posit the study lacked sufficient power to meet statistical significance for all-cause mortality), there were no trends to even suggest mortality differences across study arms out to 52 weeks, which is the duration of the longest pivotal COPD study submitted under NDA 22-383). (See curves, p.9).

¹¹ Diaz, P.T., Bruns, A.S., Ezzie, M.E., et. al., *Optimizing Bronchodilator Therapy in Emphysema*, Proceeds American Thoracic Society vol. 5, (2008): 501-5.

¹² Calverley, P.M.A., Anderson, J.A., Celli, B., et. al., *Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease*, NEJM Vol. 356, No. 8 (February 22, 2007): 775-89.

The next endpoint of relevance in considering the ethics of using ICS + SABA PRN as the control arm are serious events, e.g., COPD exacerbations. FDA's guidance on drug development for COPD treatment notes several different acceptable endpoints for COPD drugs, including modifying or preventing COPD exacerbations, although COPD exacerbations are not considered a surrogate for mortality.¹³

In the TORCH trial publication there are no Kaplan-Meier curves provided for this endpoint, although at 3 years there are statistically fewer COPD exacerbations in the LABA arm compared to the other arms with an annualized rate ratio of 0.85 (salmeterol group vs. placebo-which presumably includes SABA PRN). It is unknown at what point during the three year study these two arms begin to diverge.

In summary, upon review of the medical literature, there are little data that directly compare LABA's and SABA's and the only meaningful comparison appears to be in the TORCH trial discussed above. GOLD's 2007 do not reference this study. Moreover, the references cited to support their recommendation that LABA's should be used preferentially to SABA's are, interestingly, comparisons of LABA's and anticholinergic agents, not LABA's vs. SABA's. There does not appear to be compelling clinical or scientific evidence to suggest that ICS + SABA PRN is an unethical control arm in the indacaterol pivotal studies of 12-26 week duration. As there is some data, albeit limited and not statistically significant, that the annualized rate ratio of COPD exacerbations is increased, I hesitate without expert assessment of the TORCH data to comment on the 52-week safety and efficacy study, B2334.

The second key concern related to the ethics of the placebo-controlled add-on design is whether subjects are placed at greater risk of COPD exacerbations and/or death when their stable COPD pharmacotherapy is discontinued and they are randomized to receive ICS + SABA PRN instead of LABA's. Because the mechanisms of action of SABA's and LABA's are similar, and the main divergence between them is their duration of action, it would not a priori seem that discontinuation of a stable medical regimen including LABA's would place subjects at greater risk. Per clinical expertise in DRARP, SABA's and LABA's are frequently used interchangeably in medical practice with the predominant difference between them is their duration of action, and their safety profile for patients with asthma (or an asthmatic overlay to their COPD).¹⁴ For some homebound patients with severe COPD, SABA's may be used preferentially for increased symptoms and deterioration of pulmonary status, as the immediate response provided by SABA's is desirable. That having been said, SABA's are not routinely used in the setting where chronic therapy is needed as it is easier to comply with the less frequent dosage schedule afforded by LABA's. This convenience factor does not make SABA's less acceptable as a medical intervention in the control arm further supporting their administration in the control arm.

¹³ FDA Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment, November 2007.

¹⁴ Labels for LABA's contain a black box warning stating that LABA's may increase the risk of asthma-related death and that this is a class effect. All LABA's are contraindicated in patients with asthma without use of a long-term asthma control medication.

Minimization of risks to subjects: In general, strategies for minimizing risks typically include: selection of study population that would be least affected by the study-related risks (if possible), administration of rescue therapy, close monitoring, limiting the duration of placebo period to the least possible while still maintaining scientific rigor (particularly important if the placebo is synonymous with no treatment), and defining escape rules.

Subjects who are at increased risk of COPD exacerbations, serious risk from LABA therapy and death are excluded from the pivotal COPD studies under NDA 22-383 (i.e., subjects who were hospitalized for a COPD exacerbation within the past six weeks, require oxygen therapy, have concomitant pulmonary disease or have asthma). In addition, according to the review division, subjects are being assessed clinically more frequently (every 3-4 weeks) than they would be outside the research setting. In clinical practice, pulmonologists normally see a patient with stable COPD once every 3-6 months.

Subjects were afforded the ability to withdraw, and are provided rescue therapy as needed¹⁵. Per DRARP, SABA therapy is considered standard-of-care as a rescue medication in COPD. Moreover, DRARP explained that 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 therapies. DRARP states that this is also consistent with guidelines and standard-of-care for COPD. Also, emergency unblinding of treatment assignment was permitted when this knowledge was necessary to treat a study patient presenting with an emergency condition.

In addition to permitting subjects to discontinue from the study at any time for any reason, DRARP notes that the protocols state that, “study medication must be discontinued and the patient withdrawn from the study for . . . any significant risk to the patient’s safety. Furthermore, for the 52-week study B2335, patients were discontinued who experienced more than two COPD exacerbations in three month period or who were intubated for a COPD exacerbation”¹⁶

Based on the above information, appropriate measures were taken to minimize risks to subjects.

¹⁵ Per DRARP, “this is described in Section 6.6.5, p.37 of protocol B2335S but the other protocols have similar sections.”

¹⁶ Per DRARP, “this information is found in Section 3.2.3, p.10 of protocol B2335SE and in Section 6.6.6, p.38 of protocol B2335S. The 12-week protocols have similar sections without the last two criteria (re frequent exacerbations or intubations).”

COPYRIGHT PROTECTED



Response to #2

Inventory of informed consent documents:

- B2335-1
- B2346-1
- B2354-1
- B2354-3
 - original
 - protocol amendment
 - PK subgroup
- B2355-4
 - original
 - protocol amendment
 - serial spirometry group
 - PK

My review of the informed consent documents was restricted to the available informed consent templates for pivotal studies (B2335, B2346, B2354 and B2355) and not the IRB-approved documents nor the informed consent materials for the sub-studies. These informed consent documents are considered as a unit as the contents of the pertinent sections are largely similar for all of them.

I address each of the pertinent sections of the informed consent documents (“risks & inconveniences”, “benefits of treatment”, and “other treatments”) below.

“Description of risks & inconveniences”: The informed consent process should include a description of the risks of the study procedures as well as any foreseeable risks or discomforts. (21 CFR 50.25(a)(2)) That is, the risks or discomforts of tests, interventions and procedures required by the protocol, especially those that carry significant risk of morbidity or mortality must be explained. As such, this description should include the risks of: 1) receiving “placebo”, constituted by the risks, if any, of substituting ICS + SABA PRN for the subject’s routine medications; 2) the risks, if any, of discontinuing an established medical regimen for randomized treatment assignment; 3) the risks of COPD exacerbations (there are also significant discomforts associated with COPD exacerbations, but arguably subjects with moderate to severe COPD will already be aware of them)¹⁷; 4) the risks and discomforts of the study procedures, including venipuncture, and; 5) known serious or likely adverse reactions from LABA therapy or other agent administered in the study. As discussed above under “Use of placebos”, it is unclear that there are any additional risks associated with the substitution of LABA’s for ICS + SABA PRN, or the modification of stable pharmaceutical COPD management in favor of protocol-driven treatments. However, if DRARP believes, based on evidence to date, that these study interventions do confer potential risks then the informed consent documents should include a discussion of these risks.

¹⁷ Calverley, P.M.A., *COPD: what is the unmet need?* British Journal of Pharmacology 155 (2008): 487-93.

(They do describe the common and serious labeled risks of LABA and tiotropium.¹⁸)

“Description of benefits of treatment”: 21 CFR 50.25(a)(3) requires that a description of any benefits to the subjects or to others which may reasonably be expected from the research be included in the informed consent documents. This description should be balanced, not overstated or misleading. The informed consent documents are accurate in their descriptions of potential generalizable knowledge for others with COPD. However, they are misleading in describing benefits of the research to be receipt of medical care (the enrolled subjects were already receiving treatment in the clinical setting) and free study-related procedures, tests, examinations, and study drugs. These are not benefits of the study-intervention but a routine and expected part of the clinical research. Therefore, the description of benefits is inappropriate from both ethical and regulatory perspectives.

“Description of other procedures”: 21 CFR 50.25(a)(4) requires that informed consent documents disclose appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects. To enable an informed decision about taking part in a clinical investigation, subjects should be made aware of treatment options available to them. This section of the informed consent document is short and simply states, “There are medicines available to treat COPD. You should ask your doctor about other possible treatments.” In addition to not enrolling in the research, in this case, an important alternative would include a description of the nationally recognized current first-line care and the fact that the placebo-controlled add-on arm represents a deviation from this standard, even if the level of treatment provided in the study is not substandard.

Adequacy of protections afforded by the informed consent process: The informed consent process, even when well-executed, is insufficient to make an unethical study ethical. The ethics of a study are rooted in the scientific value and validity of the study objectives and other aspects of the study design. Furthermore, the informed consent process is limited in its ability to protect subjects if appropriate protections are not already inherent in the study design (e.g., minimization of risks, exclusion of subjects at greater risk of adverse reactions, escape rules, rescue therapies, close monitoring). That having been said, informed consent is an internationally established and valued principle for the protection of human subjects in clinical research. The “reasonable person” is a widely accepted standard for determining the adequacy of it. That is, “what would a reasonable person want/need to know in order to make a fully informed decision about participating in a study?”

The informed consent documents do not fully comply with the regulatory requirements for informed consent under 21 CFR 50.25 as discussed above. In addition, the discussion of benefits to research participation is potentially misleading. There are no substantive omissions in the discussion of risks and discomforts, absent additional risks as discussed above from study-related interventions. While the informed consent documents are not optimal, they are likely not so problematic as to undermine the ability of the average, rational individual to make an informed decision about enrolling in any of the pivotal COPD studies supporting the drug development program for indacaterol.

¹⁸ See, for example, salmeterol or formoterol labels and Spiriva label, respectively.

Response to #3

Assumption by Public Citizen that the safety and efficacy of the experimental therapy is acceptable: Public Citizen communications do not acknowledge an important point, that there is uncertainty related to both efficacy and safety associated with an experimental therapy, in this case, indacaterol. LABA's may be a drug class but each unapproved investigational agent in the class may have actions and adverse events that are unique, and hence there is a potential for approved SABA agents to have advantages over an unapproved therapy under study. The fact that there is a concern that higher doses of indacaterol studied in the initial NDA submission were associated with higher rates of cardiovascular and cerebrovascular events compared to SABA PRN + ICS arms in all three pivotal studies highlights this principal.

Standards of medical care of COPD: Since the initiation of the pivotal COPD studies under NDA 22-383 there do not appear to be any meaningful changes in the medical management of COPD (GOLD's of 2007 and 2010 are similar) to warrant stopping or modifying their study designs in a substantive manner in order to protect the subjects enrolled.

Application of federal human subject protection regulations: These six clinical investigations under discussion are clearly subject to FDA regulations, 21 CFR part 50 (informed consent) and 21 CFR part 56 (institutional review boards). HHS human subject protection regulations, 45 CFR 46, apply when a study is federally funded or conducted, or, when a US institution agrees to review all its research under HHS regulations, i.e., when it broadly applies its Federal Wide Assurance (FWA) to all clinical research conducted at that institution. All six of the studies are industry sponsored (Novartis), so HHS regulations would not be applicable by virtue of federal support or conduct. Therefore, the only mechanism for HHS regulations to apply would be through a US institution's voluntary agreement to conduct all its research under its FWA. Two of the six studies were conducted solely OUS (B2334 and B2336) so the HHS regulations could not apply to these studies. HHS regulations could potentially be applicable to the other four studies (B2335, B2346, B2354, B2355) if these studies were conducted at US institutions which apply their FWA broadly, as described above. If it is important to ascertain agency jurisdiction, the applicability of the FWA at US institutions (included in the submission) would have to be checked to see if it is restricted to federally funded/conducted research or is broadly applied to all clinical research conducted at the site(s).

Overall conclusion

A careful literature-based review, including references cited in ATS and GOLD's 2007 and 2010, together with discussions about acceptable clinical management of moderate to severe COPD with DRARP, leads me to conclude that 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. Given the non-statistically significant increase in the annualized rate ratio of COPD exacerbations for the placebo group in the TORCH trial vs. the salmeterol group, I hesitate without expert assessment of the TORCH data to comment on the 52-week safety and efficacy study, B2334.

The informed consent documents do not fully comply with the regulatory requirements for informed consent under 21 CFR 50.25 as they include potentially misleading information about benefits and omit relevant information about alternative procedures. Absent any additional risks associated with the study-interventions, there are no substantive omissions in the discussion of risks.

Recommendations for CDER

CDER's Manual of Policies and Procedures, MAPP 6030.2, INDs: Review of Informed Consent Documents¹⁹ states that the review of informed consent documents is at the discretion of the review division but, in most cases, should be reviewed as part of the review of IND submissions when the proposed investigational use raises a particular concern about the adequacy of informed consent. Deviation from standard-of-care is not listed as a circumstance in which informed consent document review is warranted. Consideration should be given to revising the MAPP such that deviation from standard-of-care is included as a circumstance in which FDA review of the informed consent document occurs. I am on CDER's Informed Consent Working Group and will bring this suggestion forward for consideration.

¹⁹ Effective Date: 11/13/02

Appendix 1. Pivotal placebo-controlled clinical studies with indacaterol maleate in moderate to severe COPD

ID Year	Study Type	Study duration	Patient Age range	Treatment groups	N	Primary efficacy Variable	Rescue/ Acceptable meds*	Country of study
Submitted with original NDA								
B2335 [2008]	Adaptive design, dose-ranging, safety, and efficacy	Initial 2-week run-in, continue for 26 weeks	40-88	Initial 2 wks. Indacaterol 75 mcg-600 mcg (4 diff. doses) Formoterol 12 mcg BID Tiotropium 18 mcg QD Placebo Cont'd 6 mos. Indacaterol 150 mcg 300mcg Tiotropium 18 mcg BID Placebo	424 112 112 104 416 416 415 418	FEV ₁ trough at 24 hr. at wk. 2 & wk. 12 FEV ₁ AUC _{1-4 hr} at wk. 2	ICS, salbutamol/ albuterol PRN, PO steroids	US, Canada, W & E Europe, India, S Korea, Argentina, Turkey, Taiwan
B2334 [2008]	Long-term efficacy and safety	52 weeks	40-90	Indacaterol 300 mcg 600 mcg Formoterol 12 mcg BID Placebo	437 425 434 432	FEV ₁ trough at 24 hr. at wk. 12	?	W & E Europe, Russia, C& S America, Mid East, S Korea
B2346 [2008]	Safety and efficacy	12 weeks	40-89	Indacaterol 150 mcg Placebo	211 205	FEV ₁ trough at 24 hr. at wk. 12	ICS, salbutamol/ albuterol PRN, PO steroids	US, Australia, Belgium, New Zealand

Submitted with complete response								
B2336 [2009]	Safety and efficacy	26 weeks	41-89	Indacaterol 150 mcg Salmeterol 50 mcg BID Placebo	330 333 335	FEV ₁ trough at 24 hr. at wk. 12	ICS, salbutamol/ albuterol PRN	W& E Europe, Russia, India, Peru, Taiwan, Canada, Columbia, Ireland (142 centers in 15 countries)
B2354 [2010]	Safety and efficacy	12 weeks	40-90	Indacaterol 75 mcg Placebo	163 160	FEV ₁ trough at 24 hr. at wk. 12	ICS, salbutamol/ albuterol PRN, PO or IV steroids	63 US centers
B2355 [2010]	Safety and efficacy	12 weeks	40-86	Indacaterol 75 mcg Placebo	159 159	FEV ₁ trough at 24 hr. at wk. 12	ICS, salbutamol/ albuterol PRN, PO or IV steroids	54 US centers

*The exclusion criteria for studies B2335, B2346, B2354 and B2355 include: subjects who had had a COPD exacerbation requiring hospitalization within the previous six weeks, a respiratory tract infection within six weeks, an oxygen requirement based on chronic hypoxemia, concomitant pulmonary disease, and a history of asthma. Subjects are scheduled for evaluation approximately every 3-4 weeks.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
06/27/2011
Entered for Dr. Goldkind

SARA F GOLDKIND
06/28/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 19, 2011

TO: Carol Hill
Regulatory Project Manager
Division of Pulmonary, Allergy and Rheumatology Products

FROM: Jose Javier Tavarez, M.S.
Human Subjects Protections Team
Division of Scientific Investigations

THROUGH: Kevin A. Prohaska, D.O., M.P.H.
Team Lead
Human Subjects Protections Team (HSP)
Division of Scientific Investigations (DSI)

SUBJECT: Request for Informed Consent Documents (ICD) Review for NDA 22-383

NDA: 22-383

Protocols: **CQAB149B2335S (Stage 1 and Stage 2)** entitled “A 26-week treatment, multicenter, randomized, double-blind, double dummy, placebo-controlled, adaptive, seamless, parallel-group study to assess the efficacy, safety and tolerability of two doses of indacaterol (selected from 75, 150, 300 & 600 µg o.d.) in patients with chronic obstructive pulmonary disease using blinded formoterol (12 µg b.i.d) and open label tiotropium (18 µg o.d.) as active controls”

CQAB149B2335SE entitled “A 26-week extension to a 26-week treatment, multicenter, randomized, double-blind, placebo-controlled, adaptive, seamless, parallel-group study to assess safety, tolerability and efficacy of two doses of indacaterol (150 and 300 µg o.d.) in patients with chronic obstructive pulmonary disease”

CQAB149B2346 entitled “A 12-week treatment, multi-center, randomized, double-blind, placebo controlled, parallel group study to assess the efficacy and safety of indacaterol (150 µg o.d.) in patients with chronic obstructive pulmonary disease”

QAB149B2354 entitled “A 12-week treatment, multi-center, randomized, double-blind, placebo-controlled, parallel-group study

to assess the efficacy and safety of once daily indacaterol in patients with chronic obstructive pulmonary disease.
CQAB149B2355 entitled “A 12-week treatment, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of once daily indacaterol in patients with chronic obstructive pulmonary disease.

Drug: Indacaterol
Sponsor: Novartis Pharmaceuticals Corporation

On May 9, 2011 the Human Subjects Protections Team (HSP) within the Division of Scientific Investigations (DSI) received a consultative request from Division of Pulmonary, Allergy and Rheumatology Products (DPARP). DPARP requests review of informed consent documents in response to letter submitted by Public Citizen that raised concern regarding trials using indacaterol that Public Citizen believes were unethical and failed to minimize risks to subjects and satisfy the requirements from federal regulations. The purpose of the request was for the DSI/HSP team to evaluate the informed consent documents for the above protocols for compliance with 21 CFR part 50. DPARP also requests comment on the adequacy of the description of the study procedures and risks and benefits.

Evaluation

As agreed to by the Review Division, DSI focused on the main Sponsor-provided templates for each of the above cited studies. DSI did not review the informed consent documents related to the substudies (e.g. spirometry substudy, pharmacogenetics substudy etc...) associated with the studies listed above. We have the following comments:

ICD for Protocol CQAB149B2335S (Stage 1 and Stage 2)

- 1) 21 CFR 50.25(a)(2) requires a description of any reasonably foreseeable risks or discomforts to the subject. The protocol states that “Patients taking fixed dose combination treatment with an inhaled corticosteroid plus a long acting β 2-agonist (LABA) must discontinue the combined medication and instead be prescribed an equivalent monotherapy inhaled corticosteroid (at an equivalent dose and dosing regimen) for the duration of the study, plus an inhaled short acting β 2-agonist (SABA) salbutamol/albuterol as needed.” However, the ICD does not describe any risks associated with being randomized to placebo treatment (i.e., subjects switched from LABA to SABA). All other cohorts either had LABA or anti-cholinergic. The question of whether there are risks associate with being switched from LABA to SABA is a clinical question that needs to be addressed by the Review Division. If there are substantive risks with such a change, the FDA would expect the informed consent document to describe these risks.
- 2) 21 CFR 50.25(a)(4) requires a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Page 7 of the ICD (under Other

Treatments section) states that “There are medicines available to patients to treat COPD. You should ask your doctor about other possible treatments.” However, the ICD does not disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject as required by 21 CFR 50.25(a)(4).

The FDA Information Sheet Guidance for Institutional Review Boards and Clinical Investigators (<http://www.fda.gov/oc/ohrt/irbs/default.htm>) contains the following statement that addresses the disclosure of alternative procedures or courses of treatment: “To enable a rational choice about participating in the research study, subjects should be aware of the full range of options available to them. Consent documents should briefly explain any pertinent alternatives to entering the study including, when appropriate, the alternative of supportive care with no additional disease-directed therapy. While this should be more than just a list of alternatives, a full risk/benefit explanation of alternatives may not be appropriate to include in the written document. The person(s) obtaining the subjects' consent, however, should be able to discuss available alternatives and answer questions that the subject may raise about them. As with other required elements, the consent document should contain sufficient information to ensure an informed decision.”

- 3) 21 CFR 50.25(a)(5) requires that the subject be provided with a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. The “Confidentiality” section of the ICD only refers to the Food and Drug Administration “sharing” medical information and does not specifically mention that the Food and Drug Administration may inspect the records.
- 4) For research involving more than minimal risk, 21 CFR 50.25(a)(6) requires an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Our review found that the ICD has what appear to be conflicting statements about what sort of compensation the subject may get if they are harmed during the study. Page 8 of the ICD (under Compensation For Subject Injury section) states that Novartis will pay for injuries related to the study drug, providing the study was done correctly but then states that Novartis will not pay for injuries resulting from the treatment of your disease. It is not clear whether the “treatment of your disease” is distinct from the care the subject receives “related to the study drug.”
- 5) The ICD does not contain an explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights as required by 21 CFR 50.25(a)(7).
- 6) The ICD does not contain a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled as required by 21 CFR 50.25(a)(8).

- 7) 21 CFR 50.20 requires, in part, that information given to the subject or the subject's representative be in a language understandable to the subject or the representative. Page 9 of the ICD states "If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study." This language may mislead subjects to believe that they will not get any care for their COPD.

ICD for Protocol CQAB149B2335SE

- 1) 21 CFR 50.25(a)(4) requires a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Page 5 of the ICD (under Other Treatments section) states that "There are medicines available to patients to treat COPD. You should ask your doctor about other possible treatments." However, the ICD does not disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject as required by 21 CFR 50.25(a)(4).
- 2) 21 CFR 50.25(a)(5) requires that the subject be provided with a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. The "Confidentiality" section of the ICD only refers to the Food and Drug Administration sharing medical information and does not specifically mention that the Food and Drug Administration may inspect the records.
- 3) For research involving more than minimal risk, 21 CFR 50.25(a)(6) requires an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Our review found that the ICD has what appear to be conflicting statements about what sort of compensation the subject may get if they are harmed during the study. Page 6 of the ICD (under Compensation For Subject Injury section) states that Novartis will pay for injuries related to the study drug, providing the study was done correctly but then states that Novartis will not pay for injuries resulting from the treatment of your disease. It is not clear whether the "treatment of your disease" is distinct from the care the subject receives "related to the study drug."
- 4) The ICD does not contain an explanation of whom to contact for answers to pertinent questions about the research and research subjects' as required by 21 CFR 50.25(a)(7).
- 5) The ICD does not contain a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled as required by 21 CFR 50.25(a)(8).

- 6) 21 CFR 50.20 requires, in part, that information given to the subject or the subject's representative be in a language understandable to the subject or the representative. Page 7 of the ICD states "If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study." This language may mislead subjects to believe that they will not get any care for their COPD.

ICD for Protocol CQAB149B2346

- 1) 21 CFR 50.25(a)(2) requires a description of any reasonably foreseeable risks or discomforts to the subject. The protocol states that "In cases where fixed-dose combination products or long acting β -agonists (LABA) are discontinued, regular dosage regimens of salbutamol/albuterol and/or use as rescue medication are permitted during the screening period. However, during the treatment period salbutamol/albuterol is only to be used for rescue ('when required') use." However, the ICD does not describe the risks associated with being randomized to placebo treatment (i.e., subjects taken off LABA and placed on rescue SABA). The question of whether there are risks associated with being switched from LABA to SABA is a clinical question that needs to be addressed by the Review Division. If there are substantive risks with such a change, the FDA would expect the informed consent document to describe these risks.
- 2) 21 CFR 50.25(a)(4) requires a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Page 1716 of the ICD (under Other Treatments section) states that "There are medicines available to patients to treat COPD. You should ask your doctor about other possible treatments." However, the ICD does not disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject as required by 21 CFR 50.25(a)(4).
- 3) 21 CFR 50.25(a)(5) requires that the subject be provided with a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. The "Confidentiality" section of the ICD only refers to the Food and Drug Administration sharing medical information and does not specifically mention that the Food and Drug Administration may inspect the records.
- 4) For research involving more than minimal risk, 21 CFR 50.25(a)(6) requires an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Our review found that the ICD has what appear to be conflicting statements about what sort of compensation the subject may get if they are harmed during the study. Page 1717 of the ICD (under Compensation For Subject Injury section) states that Novartis will pay for injuries related to the study drug, providing the study was done correctly but then states that Novartis will not pay for injuries resulting from the treatment of your disease.

It is not clear whether the “treatment of your disease” is distinct from the care the subject receives “related to the study drug.”

- 5) The ICD does not contain an explanation of whom to contact for answers to pertinent questions about the research and research subjects’ as required by 21 CFR 50.25(a)(7).
- 6) The ICD does not contain a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled as required by 21 CFR 50.25(a)(8).
- 7) 21 CFR 50.20 requires, in part, that information given to the subject or the subject’s representative be in a language understandable to the subject or the representative. Page 1718 of the ICD states “If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study.” This language may mislead subjects to believe that they will not get any care for their COPD.

In addition, when the ICD attempts to describe what a long acting beta agonist is they compare it to Serevent® and Foradil® using the trade names; however, when they talk about the serious risks of long acting beta agonist in asthma they use the generic name salmeterol and formoterol. This can be confusing to subjects and make it difficult to associate one idea with another.

ICD for Protocol QAB149B2354

- 1) 21 CFR 50.25(a)(2) requires a description of any reasonably foreseeable risks or discomforts to the subject. The protocol states that “During the treatment period salbutamol/albuterol is only to be used for rescue (‘when required’) use. No other rescue treatment is permitted.” However, the ICD does not describe the risks associated with being randomized to placebo treatment (i.e., subjects taken off LABA and placed on rescue SABA). The question of whether there are risks associate with being switched from LABA to SABA is a clinical question that needs to be addressed by the Review Division. If there are substantive risks with such a change, the FDA would expect the informed consent document to describe these risks.
- 2) 21 CFR 50.25(a)(4) requires a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Page 1601 of the ICD (under Other Treatments section) states that “There are other medicines available to patients to treat COPD. You should ask your doctor about other possible treatments.” However, the ICD does not disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject as required by 21 CFR 50.25(a)(4).

- 3) 21 CFR 50.25(a)(5) requires that the subject be provided with a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. The “Confidentiality” section of the ICD only refers to the Food and Drug Administration sharing medical information and does not specifically mention that the Food and Drug Administration may inspect the records.
- 4) For research involving more than minimal risk, 21 CFR 50.25(a)(6) requires an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Our review found that the ICD has what appear to be conflicting statements about what sort of compensation the subject may get if they are harmed during the study. Page 1601 of the ICD (under Compensation For Subject Injury section) states that Novartis will pay for injuries related to the study drug, providing the study was done correctly but then states that Novartis will not pay for injuries resulting from the treatment of your disease. It is not clear whether the “treatment of your disease” is distinct from the care the subject receives “related to the study drug.”
- 5) The ICD does not contain a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled as required by 21 CFR 50.25(a)(8).
- 6) 21 CFR 50.20 requires, in part, that information given to the subject or the subject’s representative be in a language understandable to the subject or the representative. Page 1602 of the ICD states “If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study.” This language may mislead subjects to believe that they will not get any care for their COPD.

In addition, when the ICD attempts to describe what a long acting beta agonist is they compare it to Serevent and Foradil using the trade names; however, when they talk about the serious risks of long acting beta agonist in asthma they use the generic name salmeterol and formoterol. This can be confusing to subjects and make it difficult to associate one idea with another.

ICD for Protocol CQAB149B2355

- 1) 21 CFR 50.25(a)(2) requires a description of any reasonably foreseeable risks or discomforts to the subject. The protocol states that “During the treatment period salbutamol/albuterol is only to be used for rescue (‘when required’) use. No other rescue treatment is permitted.” However, the ICD does not describe the risks associated with being randomized to placebo treatment (i.e., subjects taken off LABA and placed on rescue SABA). The question of

whether there are risks associate with being switched from LABA to SABA is a clinical question that needs to be addressed by the Review Division. If there are substantive risks with such a change, the FDA would expect the informed consent document to describe these risks.

- 2) 21 CFR 50.25(a)(4) requires a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Page 1538 of the ICD (under Other Treatments section) states that “There are other medicines available to patients to treat COPD. You should ask your doctor about other possible treatments.” However, the ICD does not disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject as required by 21 CFR 50.25(a)(4).
- 3) 21 CFR 50.25(a)(5) requires that the subject be provided with a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. The “Confidentiality” section of the ICD only refers to the Food and Drug Administration sharing medical information and does not specifically mention that the Food and Drug Administration may inspect the records.
- 4) For research involving more than minimal risk, 21 CFR 50.25(a)(6) requires an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Our review found that the ICD has what appear to be conflicting statements about what sort of compensation the subject may get if they are harmed during the study. Page 1539 of the ICD (under Compensation For Subject Injury section) states that Novartis will pay for injuries related to the study drug, providing the study was done correctly but then states that Novartis will not pay for injuries resulting from the treatment of your disease. It is not clear whether the “treatment of your disease” is distinct from the care the subject receives “related to the study drug.”
- 5) The ICD does not contain a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled as required by 21 CFR 50.25(a)(8).
- 6) 21 CFR 50.20 requires, in part, that information given to the subject or the subject’s representative be in a language understandable to the subject or the representative. Page 1539 of the ICD states “If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study.” This language may mislead subjects to believe that they will not get any care for their COPD.

In addition, when the ICD attempts to describe what a long acting beta agonist is they compare it to Serevent and Foradil using the trade names; however, when they talk about the serious risks of long acting beta agonist in asthma they use the generic name salmeterol and formoterol. This can be confusing to subjects and make it difficult to associate one idea with another.

Conclusion

From our review of the ICDs for the five indacaterol studies described above, we provide the following summary:

1. None of the ICDs, except for the extension study CQAB149B2335SE, discusses the risks associated with being randomized to placebo. The extension study ICD does not say much about placebo except that "your condition may worsen" and it does not attribute it to the change in medication. Although the FDA generally does not expect informed consent documents to describe risks associated with placebo, we note that all the studies involve the procedure of switching subjects from LABA to SABA in order to be included in the placebo cohort. As such, the FDA would expect any substantive risks associated with this procedure (if any) to be described in the informed consent document. The question of whether there are risks associate with being switched from LABA to SABA is a clinical question that needs to be addressed by the Review Division. We note the product label for Foradil (formoterol) and the treatment guidelines from Global Initiative for Chronic Obstructive Lung disease (GOLD) and the American Thoracic Society (ATS) do not describe risks associated with switching from LABA to SABA. However, both organizations (GOLD and ATS) do include LABA as their preferred treatment for COPD. Likewise, the GOLD recommendations, published in 2010, states, "*Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).*"¹ If this information is still considered clinically correct then there is a good argument that switching subjects from LABA to SABA may be suboptimal therapy for COPD associated with the risk of worsening of subjects COPD symptoms. As such, we would expect this risk to be described in all informed consent documents for studies in which subjects are taken off LABA and given SABA. We recommend the Review Division consider this point carefully.
2. Although all the other deficiencies in the informed consent document described above are important, we note that they are not directly relevant to the primary concerns raised by Public Citizen in their March 16, 2011 letter. Likewise, we would like to stress that sponsor templates were reviewed and not the actual final U.S. IRB-approved informed

¹ Global Initiative for Chronic Obstructive Lung Disease, "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease" Updated 2010, available at <http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=1116>, page 65

consent documents. The sponsor templates appear to be for an international audience and are in many ways very generic and not directly responsive to the requirements under 21 CFR 50.25.

Trends we noted in our review of these informed consent documents included the following:

- None of the informed consent documents elaborate on alternative therapies.
- None of the ICDs include an explicit statement that the FDA may inspect. Instead the ICDs states that the information may be "shared" with the FDA.
- Most of the ICDs have conflicting statements about what sort of compensation the subject may get if they are harmed during the study.
- All of the ICDs do not clearly states who to contact for answers to questions about the research and research subjects' rights.
- None of the ICDs have a specific statement about refusing to participate will not involve penalty or loss of benefits to which the subject is otherwise entitled. They do clearly say that subjects may leave at any time but they require the subjects to provide a written notification that they are leaving.
- Some of the overall language in the ICDs was concerning. For example, when the ICD attempts to describe what a long acting beta agonist is they compare it to Serevent and Foradil using the trade names however when they talk about the serious risks of long acting beta agonist in asthma they use the generic name salmeterol and formoterol. This can be confusing to subjects and make it difficult to associate one idea with another.

DSI would expect domestic IRBs to pick up on these deficiencies and make appropriate modifications to reflect the requirements of 21 CFR 50.25.

Additional guidance on 21 CFR 50.25 can be found at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>.

Please feel free to contact me at (301) 796-3376 should you have additional questions.

{See appended electronic signature page}

Jose Javier Tavarez, M.S.
Consumer Safety Officer

CONCURRENCE:

{See appended electronic signature page}

Kevin A. Prohaska, D.O., M.P.H.
Team Lead
Human Subjects Protections Team
Division of Scientific Investigations

O:\JJavierTavarez\IRBs\ICD Consults\NDA 22-383 (Indacaterol) ICD Consult_Final 5-19-11.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSE J TAVAREZ PAGAN
05/19/2011

KEVIN A PROHASKA
05/19/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 11, 2011

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matthew Falter, Regulatory Review Officer
Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robyn Tyler, Acting Direct-to-Consumer Group Leader
Olga Salis, Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022383
DDMAC labeling comments for Arcapta™ Neohaler™ (indacaterol
inhalation powder)

DDMAC has reviewed the proposed Prescribing Information (PI), Carton/Container Labeling, Medication Guide (Med Guide), and Patient Instructions for Use (PIU) for Arcapta™ Neohaler™ (indacaterol inhalation powder) submitted for consult on December 6, 2010.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "NDA 22383 SCPI Label.doc" that was sent via email from DPARP to DDMAC on April 27, 2011.

DDMAC's comments on the Med Guide and PIU are based on the proposed draft marked-up labeling titled, "11 0502 ARCAPTA DRISK MG (marked).doc" that was sent via email from DRISK to DDMAC on May 2, 2011. We agree with DRISK's comments and offer the following additional comments.

DDMAC's comments on the PI and Med Guide are provided directly in the marked-up document attached (see below).

DDMAC has reviewed the carton and container labels submitted by the applicant on February 9, 2011 available in the EDR at:



(b) (4)

- [\\cdsesub1\EVSPROD\NDA022383\0040\m1\us\arcapta-inhaler.pdf](#)
- [\\cdsesub1\EVSPROD\NDA022383\0040\m1\us\arcapta-75mcg-sample-carton-6s-\(b\)\(4\).pdf](#)
- [\\cdsesub1\EVSPROD\NDA022383\0040\m1\us\arcapta-75mcg-sampleblister-6s.pdf](#)
- [\\cdsesub1\EVSPROD\NDA022383\0040\m1\us\arcapta-75mcg-trade-carton-30s-\(b\)\(4\).pdf](#)
- [\\cdsesub1\EVSPROD\NDA022383\0040\m1\us\arcapta-75mcg-tradeblister-6s.pdf](#)

We offer the following comments on the proposed carton and container labeling:

1. We are concerned about the prominence of the trade name and established name throughout the carton and container labeling. We recommend that the proposed labeling be revised to present the established name in a font size that is at least half as large as that of the proprietary name and with a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI or carton/container labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions about the Med Guide or PIU, please contact Matt Falter at (301) 796- 2287 or matthew.falter@fda.hhs.gov.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERTA T SZYDLO
05/11/2011

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 22382

Name of Drug: Arcapta Neohaler (indacaterol maleate) Inhalation Powder – 75 and 150 mcg

Applicant: Novartis Pharmaceuticals Corporation

Labeling Reviewed

Submission Date: October 1 and December 15, 2010 and February 9, 2011

Receipt Date: October 1 and December 15, 2010 and February 9, 2011

Background and Summary Description:

On October 1, 2010, Novartis Pharmaceuticals Corporation resubmitted their New Drug Application (NDA) for Arcapta Neohaler (indacaterol maleate) in response to the Agency's Complete Response letter dated, October 16, 2009. The labeling in this submission includes package insert, medication guide, structured product labeling (SPL) and carton and container labeling. Prior to the issuance of the complete response letter of October 16, 2009, a discipline review letter dated, September 11, 2009 was sent informing Novartis that deficiencies were identified that precluded discussion of labeling during the first review cycle of the application. In a multi-discipline request for information letter dated, December 8, 2010, CMC requested revisions to the "HOW SUPPLIED" section of the package insert to more accurately describe the blister cards and the SPL style sheets for both strengths to list the lactose monohydrate as an inactive ingredient. Novartis responded to this request on December 15, 2010 and submitted revisions to the package insert and SPL labeling as requested. In response to comments received on September 9, 2010 from the Agency a May 10, 2010 submission to IND (b)(4), Novartis submitted on February 9, 2011, proposed labeling changes to differentiate features in the packaging (carton, blister and device). The Agency requested that Novartis choose a color that differs from the (b)(4), Foradil and Spiriva and to carry over the color linkage to the blister labeling and actual capsule color. Novartis proposed the use of a (b)(4) color on the following product components; the push buttons on the Concept 1 device, the blister sheet and the carton. Per the Agency's recommendations Novartis incorporated another differentiating feature, the use of a symbol to link components of the packaging. The symbol is included on the following: the Concept 1 device, the blister sheet, the capsule and the carton. In addition, a statement has been added to the inhaler "For use only with Arcapta capsules" to further minimize potential for device interchange.

Review

The proposed labeling dated, December 15, 2010 was reviewed using the SEALD Label Review Tool version, January 4, 2011. The labeling submitted on December 15, 2010 did not contain any deficiencies. The proposed changes in the February 9, 2011 submission were compared to the recommendations of the Agency dated, September 9, 2010 for IND (b) (4). The proposed changes did not deviate from the Agency's recommendations.

Recommendations

The labeling should be approved pending any recommendations from the review team.

Carol Hill	April 6, 2011
Regulatory Project Manager	Date
Sandy Barnes	May 5, 2011
Chief, Project Management Staff	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
05/05/2011

SANDRA L BARNES
05/05/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: May 2, 2011

To: Badrul Chowdhury, M.D., Director
**Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

Melissa Hulett, MSBA, RN, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Twanda Scales, RN, MSN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide
and Instructions for Use)

Drug Name: Arcapta Neohaler (indacaterol maleate inhalation
powder)

Dosage Form and
Route: Powder for inhalation

Application
Type/Number: NDA 22383

Applicant: Novartis Pharmaceutical Corporation

OSE RCM #: 2011-2224

1 INTRODUCTION

On December 15, 2008 Novartis Pharmaceuticals Corporation submitted a New Drug Application (NDA) for Arcapta Neohaler (indacaterol maleate inhalation powder). On October 16, 2009 a Complete Response letter was issued for clinical deficiencies. The purpose of the Applicant's September 28, 2010 submission was to respond to the October 16, 2009 Complete Response letter.

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Arcapta Neohaler (indacaterol maleate inhalation powder).

2 MATERIAL REVIEWED

- Draft Arcapta Neohaler (indacaterol maleate inhalation powder) Medication Guide (MG) and Instructions for Use (IFU) received on September 28, 2010.
- Draft Arcapta Neohaler (indacaterol maleate inhalation powder) Prescribing Information (PI) received September 28, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on April 27, 2010.
- Approved Foradil comparator labeling approved February 9, 2011, Brovana comparator labeling approved February 16, 2011, and Perforomist comparator labeling approved February 1, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable .

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG or the IFU.

Please let us know if you have any questions.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TWANDA D SCALES
05/02/2011

LASHAWN M GRIFFITHS
05/02/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 25, 2011

TO: Carol F. Hill, Regulatory Project Manager
Anya Harry, MD, Medical Officer
Theresa M. Michele, MD, Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPAAP)

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-383

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: indacaterol maleate inhalation powder (Arcapta™ Neohaler™)

THERAPEUTIC CLASSIFICATION/REVIEW: Priority Review

INDICATIONS: treatment of airflow obstruction (COPD)

CONSULTATION REQUEST DATE: November 16, 2010

DIVISION ACTION GOAL DATE: March 18, 2011

PDUFA DATE: April 1, 2011

I. BACKGROUND:

Novartis seeks indacaterol approval for the long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Indacaterol maleate is a novel long-acting inhaled beta2-adrenergic receptor agonist, proposed for once daily treatment in patients with COPD. (b) (4)

Novartis submitted an original application on December 15, 2008 for the use of indacaterol in patients with COPD. However, based on concerns with respect to safety and efficacy of the proposed doses, a CR letter was sent to the sponsor on 10/16/09, requesting that the sponsor conduct clinical studies to explore efficacy and establish the safety of lower doses than those proposed in the original application. Novartis submitted a Complete Response to provide additional clinical data with indacaterol in a relevant broncho-reactive population (patients with persistent asthma, in addition to COPD patients), to further characterize the dose response at the lower end of the indacaterol drug dose response curve not addressed by the sponsor in the previous NDA review cycle.

Per DPARP reviewers, Novartis is requesting drug “claims” in the clinical studies section of the COPD label for: (a) treatment of airflow obstruction, (b) onset of action within 5 minutes, (c) a higher dose for bronchodilation in severe patients, and (d) improved quality of life reflected by improvement in scores on the St. George’s Respiratory Questionnaire.

Results from three adequate and well-controlled studies were submitted in support of the application [COPD indication in adult patients (Studies B2354 and B2355) and asthma in adult patients (Study 2357)].

STUDY Protocols B2354/B2355

These studies were 12-week multicenter, randomized, double-blind, placebo-controlled, parallel-group trials to assess efficacy and safety of indacaterol 75 mcg dosed once daily in patients with COPD who had moderate to severe COPD [i.e., Forced Expiratory Volume at 1 second (FEV₁) was 80% or less and the predicted value was 30 percent or more]. For B2354, The number of patients randomized into the study was 323 (163 patients in the indacaterol 75 µg group and 160 patients in the placebo group). For B2355, a total of 318 patients were randomized equally to drug or placebo (i.e., 159 patients per group). The primary endpoint was the difference from placebo in the trough FEV₁ (24-hours post-dose) after 12 weeks treatment duration in the clinical study. A key secondary endpoint was the St. George’s Respiratory Questionnaire total score.

STUDY Protocol B2357

This study was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study to assess the efficacy and safety of various doses of indacaterol in adult patients with persistent asthma treated with inhaled corticosteroids, using salmeterol as an

active control. Study B2357 was a two-week dose finding study in patients with asthma who represented a more relevant and sensitive population to test the bronchodilatory action of indacaterol than the intended COPD population. Approximately 500 patients were randomized in 1:1:1:1:1 fashion to the following indacaterol dose groups: 18.75, 37.5, 75, 150 mcg daily, placebo, and salmeterol 59 mcg bid. The primary endpoint was trough FEV₁ on Day 15 of the clinical study.

Field inspections of the pivotal clinical studies for this drug, proposed as a new therapeutic option and new molecular entity for adults with COPD (airflow obstruction), were performed. The applicant was inspected to evaluate adherence to regulatory requirements as the product is a new molecular entity. All sites were chosen because of high enrollment of study subjects. While no specific outlier clinical sites were identified (per DPARP Medical and Biostatistics Teams), inspection of these sites, as well as the sponsor, is warranted in order to ensure that there are no data integrity concerns with the data submitted. This priority application (6-month clock) will go to a FDA Scientific Advisory Committee in early March 2011.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site	Insp. Date	EIR Received Date	Final Classification
James Meli, D.O.	Henderson, NV	Study Protocol B2354 Site #535	1/27-2/10, 2011	Pending	Pending (Preliminary: VAI)
James Pearle, M.D.	Fullerton, CA	Study Protocol B2355 Site #514	1/18-1/21, 2011	Pending	Pending (Preliminary: NAI)
Steven Weinstein, MD	Huntington Beach, CA	Study Protocol B2357 Site #521	1/10-1/13, 2011	NAI	NAI
Novartis Pharmaceuticals	East Hanover, New Jersey	SPONSOR	2/17-2/25, 2011	Pending	Pending (Preliminary: VAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. James Meli, D.O./Study Protocol B2354 Site #535

Clinical Research Advantage, Inc
6301 Mountain Vista St., Ste #109
Henderson, NV 89014

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from January 27-February 10, 2010.

A total of 17 subjects were screened, 17 enrolled and 11 patients completed the study. There was no under-reporting of deaths or SAEs. An audit of 5 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

No discrepancies were noted. In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a single-item Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for mainly isolated minor protocol deviations or regulatory deficiencies in recordkeeping.

Salient findings of the inspection included the following examples:

- (1) Subject #01's records did not list albuterol inhaler as a concomitant medication (6/2008 to 2/2010 inclusive)
- (2) Medical source records for the following subjects did not mention change in symptoms or medications, but diaries of these patients on specific isolated visits indicated a "yes" response to the question: "Did you have any new symptoms, change in symptoms, new medications, or adjustments to current medication today?"
 - a. Subject #1 [Visit #4 (3/16/2010)],
 - b. Subject #3 [Visit #8 (6/10/2010); Visit #4 (3/17/10), Visit #6 (4/15/2010)], Subject #7 [Visit #5 (3/23/2010)], and
 - c. Subject #15 [Visit #4 (4/14/2010); Visit #5 (4/15/2010); Visit #6 (5/13/2010); Visit #7 (6/9/2010)]
- (3) Patient #7's source document contained a response to the St. George's Respiratory Questionnaire Part 1 Question #3 (4/20/2010) as "few days a month," but the CRF response was recorded as "several days a week."

d. Data acceptability/reliability for consideration in the NDA review decision.

There were minor regulatory deficiencies observed that are considered isolated in nature, which are unlikely to significantly impact data reliability. The data in support of efficacy and safety from this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. James Pearle, M.D./Study Protocol B2355 Site #514

California Research Medical Group Inc.
2980 Terraza Pl.
Fullerton, CA 92835

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from January 18-21, 2011.

A total of 15 subjects were screened, and 11 subjects completed the study. There was no under-reporting of adverse events noted. An audit of 100% of enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Inspection revealed that the study was conducted adequately. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

3. Steven Weinstein, M.D./Study Protocol B2357 Site #521

Allergy and Asthma Specialists Medical
Group and Research Center
17742 Beach Boulevard, Ste # 310
Huntington Beach, CA 92647

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 10-13, 2010.

A total of 32 subjects were screened, 23 subjects were enrolled, randomized and completed the study. There was no under-reporting of adverse events noted. An audit of 23 of the enrolled study subjects was conducted and records were reviewed for informed consent and data verification of endpoints. There were 12 records reviewed for protocol compliance, eligibility and safety.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Inspection revealed that the study was conducted adequately. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

Reviewer's Note:

Although no Form FDA 483 was issued, isolated deficiencies with respect to drug accountability were noted. As reported in the drug accountability section of the Establishment Inspection Report (EIR) by the ORA field investigator, there were three patients who doubled their dose in the low dose group (18.75 microgram/day). Adequate patient instruction as per protocol was noted by the field investigator. No regulatory violations were derived at this site visit (Dr. Weinstein). Per Sponsor listing, "double dosing" was concentrated on the 18.75 unit dose in three patients, and that the dose was delivered once daily.

Per DPARP, EU has approved 150 and 300 unit doses, respectively, and Sponsor is seeking approval for the 75 and 150 unit doses, respectively at the Agency. DPARP asked the Sponsor to evaluate doses lower than 150 mcg as well as different regimens (e.g., twice daily dosing, every other day dosing in addition to once daily). Specifications for the exact doses or dosing regimens were left for Sponsor to propose for the COPD market use.

While patients #001, #003 and #005 doubled their 18.75 unit dose with no reported clinical consequence, this does not preclude potentially seeing more adverse events with indacaterol toxicity in the higher dose groups requested for approval, especially the 150 unit dose. As such, DSI brought this to DPARP's attention since this observation generated potential implications about drug use, drug device use, and medication error potential. DSI discussed with the Medical Team on January 14, 2011 the possibility that medication errors may be magnified if there are potential sources of errors in medication use in the following areas: (1) patient factors, with clear labeling and patient re-education and training issues for this specific product such as frequency of use, and (2) patient factors other than adequate labeling, because of a combination of drug and drug-device delivery systems (e.g., inhalation powder aerosol, nebulizer/puffer aerosol, tablet, capsule) as part of COPD or asthma disease management. If considered relevant, the DPARP may consider this as they proceed further in their NDA review.

d. Data acceptability/reliability for consideration in the NDA review decision.

Although isolated deficiencies were noted as per above, these are unlikely to impact data reliability from this site. The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

SPONSOR INSPECTION

4. Novartis Pharmaceuticals Corporation

One Health Plaza
East Hanover, New Jersey 07936-1080

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from February 14-25, 2011.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, communication with the Sponsor and drug accountability, staff training and site monitors.

b. Limitations of inspection

None.

c. General observations/commentary

Drug accountability and primary efficacy endpoints were verifiable, and no salient issues were identified. There was no evidence of under-reporting of adverse events.

Currently, as the inspection is still ongoing, and based on preliminary communication with the field investigator, at the end of the inspection, a Form FDA 483 (List of Inspectional Observations) will be issued for minor regulatory deficiencies related to the oversight observation described below.

Per communications with the field investigator on February 24, 2011, there was a minor regulatory deficiency noted, related to inadequate monitoring and record keeping of clinical investigative sites by Sponsor. For example, one site (Dr. Warren Pleskow Site #571, Study Protocol #B2357) did not obtain updated written informed consents for an additional “exploratory” study, on 7 patients who individually had undergone three sets of spirometry testing after initially providing verbal consent. All patients, however, signed the original versions 2 and 3 of the informed consent forms related to Study #B2357.

d. Data acceptability/reliability for consideration in the NDA review decision.

These observations appear to be isolated in nature. The data in support of efficacy and safety from this Sponsor oversight appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections three U.S. clinical investigator sites and Sponsor were inspected in support of this application, for Protocols B2354/Site 535, B2355/Site 552 and B2357/Site 521, respectively. Although regulatory violations were noted at Dr. Meli’s site as well as the sponsor’s site, the violations appear unlikely to significantly impact data reliability. The inspections documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

Note: Observations noted above, for the Drs. Meli and Pearle and Sponsor sites are based on the preliminary communications from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
02/28/2011

TEJASHRI S PUROHIT-SHETH
02/28/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 3, 2011

To: Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy and Rheumatology
Products

Through: Melina Griffis RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall Tobenkin, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Arcapta Neohaler (Indacaterol) Inhalation Powder

Application
Type/Number: NDA 022383

Applicant: Novartis

OSE RCM #: 2010-2234

1 INTRODUCTION

This review evaluates the proposed inhalation device, blister labels, carton and insert labeling for Arcapta Neohaler (NDA 022383) submitted by Novartis on October 1, 2010.

Post marketing surveillance with similar powder inhalation products previously conducted by DMEPA identified errors that involve swallowing the capsule, instead of inhaling the powder via the device. Because the proposed Arcapta Neohaler is of similar design to these currently marketed capsule/device formulations, DMEPA believes that similar misadministration errors will occur with the Arcapta Neohaler. The Division of Pulmonary, Allergy and Rheumatology (DPARP) also expressed concern with errors that could occur due to device and capsule interchangeability with another capsule/device product, i.e. Spiriva Handihaler®.

As a result of these concerns, DMEPA provides recommendations for all components of the Arcapta Neohaler product (including blister label, carton labeling, Neohaler device and capsule imprints) in an attempt to mitigate the misadministration and interchangeability errors.

2 PRODUCT INFORMATION

Arcapta Neohaler is indicated for the long term maintenance treatment of chronic obstructive pulmonary disease (COPD). Arcapta Neohaler is available as a capsule which must be inserted into the Neohaler device and then followed by inhalation of the powder, via the Neohaler. The usual dose is once capsule (75 mcg (b)(4)) inhaled (via the Neohaler) orally once daily. The proposed proprietary name, Arcapta Neohaler, is being reviewed under OSE review # 2010-2483.

3 METHODS AND MATERIAL REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels and labeling submitted on October 1, 2010 to identify vulnerabilities that may lead to medication errors. Additionally, DMEPA reviewed the November 23, 2010 proposal to include an imprint of a bird symbol on the capsule so that patients can correctly identify the capsule to be used with the Neohaler device.

See References for previous DMEPA reviews and Appendix A for samples of the draft container labels.

4 DISCUSSION

Arcapta Neohaler consists of capsules and an inhalation device which allows for oral inhalation of the powder. Arcapta Neohaler is indicated for COPD and is dosed once daily. Post-marketing surveillance of similarly designed capsule/device products has identified medication errors that involve swallowing the capsule, instead of inhaling the powder via the device. Based upon previous post-market reviews of similar products, DMEPA does not recommend this product design. A less error prone design would integrate the drug product in the device. However, as an alternative to this type of product redesign, we continue to recommend prominently displaying statements such as ‘do not swallow’ and ‘for use with Neohaler’ statements on both the blister label and carton

labeling. However we recognize that these statements will not completely prevent patients from the response prompted by capsule stimulus, which is to swallow.

Additionally, the Division of Pulmonary, Allergy and Rheumatology (DPARP) voiced additional concern related to the potential medication error that can occur if the Arcapta capsule or Neohaler device is interchanged with the Spiriva capsule or Handihaler device. Based on this concern, Novartis has proposed a usability study of capsule /device inhalation products to assess the color linkage approach to discourage device interchangeability. This ongoing study may reveal methods to help patients mitigate errors with inappropriate capsule and device interchangeability. However, until this usability study is completed and the results determine the most appropriate method of capsule/device recognition, DMEPA recommends that the capsules have the name 'Arcapta' imprinted on the capsule, rather than the bird symbol.

Our analysis of the blister labels and the carton labeling identified deficiencies including;

(b) (4)

(b) (4)

5 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified should be addressed prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors. We request the recommendations in Section 3.2 be communicated to Novartis prior to the approval of this NDA.

Please copy the Division of Medication Error Prevention and Analysis on any communication to (b) (4) with regard to this review. If you have further questions or need clarifications, please contact Carolyn Volpe, OSE Project Manager, at 301-796-5204.

5.1 COMMENTS TO THE DIVISION

A. General Comments

1. The Applicant is currently conducting a usability study of capsule/device inhalation products to assess effectiveness of the color linkage approach to discourage device interchangeability by COPD patients. DMEPA recommends the results of the ongoing usability study be available before making definitive recommendations because the results could alter our recommendations. However, if the application is to be approved prior to study

completion we recommend that the name ‘Arcapta’ appear on the capsule (rather than the proposed bird symbol) and Neohaler device.

B. Package Insert Comments

1. Revise the strength statements in the Highlights section so that all dose strengths are followed by the ‘mcg’ statement.
2. In the Dosage and Administration Section of the Highlights, the statement ‘75 mcg (b) (4) every day’, should include the verb ‘inhaled’ in order to emphasize the inhalation route of administration.
3. The Storage and Handling Section (16.2) recommends protecting the 75 mcg strength from light and moisture, (b) (4)

5.2 COMMENTS TO THE APPLICANT

A. General Comment

1. We note that the Applicant is currently conducting a usability study of capsule/device inhalation products to assess effectiveness of the color linkage approach to discourage device interchangeability by COPD patients. Our overall recommendations may be altered based on the results of the study.

2. (b) (4)

B. Capsules (75 mcg (b) (4))

1. DMEPA recommends the actual drug name ‘Arcapta’ be imprinted on the capsule rather than the proposed bird symbol. The name ‘Arcapta’ on the capsule will serve two purposes; it will communicate what drug product is contained in the capsule and it can also remind the patient to use this capsule with the Arcapta Neohaler because the Neohaler device will also have the name Arcapta displayed on front. This may also reduce the risk of using this capsule in another device.

C. Blister Labels (75 mcg (b) (4))

1. We are concerned that COPD patients who are on dual therapy with Spiriva Handihaler and Arcapta Neohaler could potentially confuse Spiriva capsules and Arcapta capsules. Both product capsules should be left in the blisters until immediately before use, therefore we recommend utilizing a different color, i.e. not (b) (4) and bolding ‘Arcapta Neohaler’ so that there is better visual differentiation between Arcapta Neohaler blister labels and Spiriva Neohaler blister labels and (See Appendices A and C).

2. As currently presented the Arcapta Neohaler blister labels are in (b) (4) [REDACTED] [REDACTED] Revise the blister labels so that they are presented in the same orientation for increased readability.
3. Include the statement ‘Do not swallow capsules’ on the blister label and relocate the ‘For use with Neohaler only’ so that these statements appear where the manufacture statement is located so that it is more prominent and is presented with the product information. Because similar statements appear on the Spiriva blister label in a box, these statements should be highlighted but not boxed.
4. Ensure that the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features pursuant to 21 CFR 201.10(g)(2).
5. Remove the NDC number from the sample blister label.

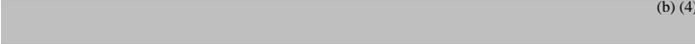
D. Carton Labeling (75 mcg (b) (4))

1. Utilize the same color and font for both ‘Arcapta’ and ‘Neohaler’ so that the practitioner and patient understand that Neohaler is appended to Arcapta and is a component of the proprietary name.
2. Revise the ‘Dosage’ statement to read, ‘Usual dosage: See Prescribing Information’.
3. The principal display panel displays the statement, ‘Each capsule contains...’, which can be relocated to the back panel in order to have the most important information prominently displayed on the principal panel.

C. Neohaler Dosing Device

1. Ensure that the Arcapta Neohaler has the statement, ‘Arcapta Neohaler’ and ‘For use only with Arcapta capsules’ on the device. The name, Arcapta Neohaler should appear on both the cap of the device and the device itself, so that if the cap is lost, the device can still be identified by the product name.

4 REFERENCES

1. OSE Review # 2009-265 and OSE Review # 2010-684, Foradil Aerolizer. Park, Judy. 2010.
2. OSE Review # 2010-1343,  (b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANNE CRANDALL
02/03/2011

MELINA N GRIFFIS
02/04/2011

CAROL A HOLQUIST
02/04/2011

DSI CONSULT: Request for Clinical Inspections

Date: November 16, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Joseph Salewski, Branch Chief (Acting), GCP2
Tejashri Purohith-Sheth, MD
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Anya Harry, MD, PhD Medical Officer, through
Theresa M. Michele, MD, Team Leader, through
Division of Pulmonary, Allergy and Rheumatology Products

From: Carol Hill, Pulmonary, Allergy and Rheumatology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22-383

Sponsor/Sponsor contact information (to include phone/email):

Ms. Ann Shea
Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
(tel) 862-778-4567
(fax) 973-781-2565
(e-mail) ann.shea@novartis.com

Drug: Trade Name (generic): Arcapta Neohaler (indacaterol maleate) inhalation powder

NME (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 18 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: 1) treatment of airflow obstruction, 2) onset of action within 5 minutes, 3) a higher dose for bronchodilation in severe patients, and 4) improved quality of life reflected by an improvement in St George's Respiratory Questionnaire, reduction in rescue medication use and improved percentage of days with no daytime symptoms/days able to perform normal daily activities

[note: the applicant is requesting claims #2-#4 in the clinical studies section of the label, not specific new indications]

DSI Consult

Reference ID: A665222

PDUFA: April 1, 2011

Action Goal Date: March 18, 2011

Inspection Summary Goal Date: March 1, 2011

II. Protocol/Site Identification

Novartis has submitted a Complete Response package for Arcapta Neohaler for the indications of: 1) treatment of airflow obstruction, 2) onset of action within 5 minutes, 3) a higher dose for bronchodilation in severe patients, and 4) improved quality of life reflected by an improvement in St George's Respiratory Questionnaire, reduction in rescue medication use and improved percentage of days with no daytime symptoms/days able to perform normal daily activities. The initial submission proposed doses of 150 mcg and 300 mcg once daily. It received a Complete Response Action on 10/16/09 due to several key deficiencies including: higher frequencies of cardiovascular and cerebrovascular serious adverse events in patients with chronic obstructive pulmonary disease and possible asthma-related deaths; lack of clinically meaningful efficacy difference between doses; the appropriate dosing frequency was not explored and no substantial evidence was provided in support of the use of two different doses in patients with COPD. In this resubmission, they have performed both dose finding and frequency studies as well as replicate 12 week confirmatory studies to address these deficiencies. Based on these studies, the sponsor is now proposing doses of 75 mcg and 150 mcg once daily. The initial submission included studies carried out at both domestic and international sites; the pivotal resubmission studies were conducted within the US.

Due to the approvability issues outlined above, a DSI audit was not requested during the initial submission. We now are requesting audits of 3 or 4 domestic sites for this application, focusing on the pivotal dose ranging and efficacy trials at the new lower dose.

Rationale for Choice of Sites

The medical officer reviewed sites for audit selection based on the following criteria: 1) enrollment, 2) death, and 3) financial disclosure. Enrollment was a primary criterion; only sites with 10 or more treated patients were included for consideration except for the sites selected due to the number of deaths. In addition to the criteria used by the medical officer for site selection, Dr. Dongmei Liu, FDA statistician for this application, reviewed sites for outliers based on efficacy; however, due to the low number of patients per center she was unable to detect any significant deviation in efficacy by statistical analysis. No particular outlier sites were identified. While there were some investigators from studies in the original submission that received significant payments, there were few patients per center and therefore we were unable to detect any significant deviation in efficacy by statistical analysis. These sites are not listed for inspection because the studies are no longer considered pivotal since they were conducted at a higher dose than is currently proposed. No investigator in the 5 new pivotal studies included in the Complete Response submission reported significant financial payments from the sponsor.

In order to provide flexibility for DSI inspections, we are listing 3 sites per pivotal trial with the anticipation that audits of 3 or 4 sites total would be conducted. The specific rationale for each site identified is given in Table 1.

Table 1: Domestic Sites for Inspection (choose 3-4)

Site (Name, Address, Phone number, email, fax#)	Study /Site #	Subjects Treated	Rationale for Selection
Talha Shamim Heartland Clinical Research, Inc 2201 North 90 th St., Ste#126 Omaha, NE 68134	B2354 502	10	-1 death -high enroller
James R. Taylor Multicare Pulmonary Specialists 2121 South 19 th St. Tacoma, WA 98405	B2354 521	10	-high enroller
James Meli Clinical Research Advantage, Inc 6301 Mountain Vista St., Ste #109 Henderson, NV 89014	B2354 535	11	-high enroller
Leonard Dunn Clinical Research of West Florida 2147 NE Coachman Road Clearwater, FL 33765	B2355 507	13	-high enroller
James Pearle California Research Medical Group, Inc. 2980 Terraza Pl. Fullerton, CA 92835	B2355 514	13	-high enroller
Charles Fogarty Spartanburg Medical Research 485 Simuel Road Spartanburg, SC 29303	B2355 552	13	-high enroller

Site (Name, Address, Phone number, email, fax#)	Site #	Subjects Treated	Rationale for Selection
Steven Weinstein Allergy and Asthma Specialists Medical Group and Research Center 17742 Beach Boulevard, Ste # 310 Huntington Beach, CA 92647	B2357 521	23	-high enroller
Jeremy Cole IPS Research Company 1111 N. Lee, Ste #400 Oklahoma City, OK 73103	B2357 538	16	-high enroller
Warren Pleskow 317 North El Camino Real, Ste #506 Encintas, CA 92024	B2357 571	20	-high enroller

III. Site Selection/Rationale

Study Summaries

Studies B2355/B2354 were 12 week multicenter, randomized, double-blind, placebo-controlled parallel group trials assessing the safety and efficacy of once daily indacaterol in patients with COPD. A total of 318 patients with moderate to severe COPD ($FEV_1 \leq 80\%$ and $\geq 30\%$ predicted) were randomized, 159 to Indacaterol 75 mcg and 159 to placebo. The primary endpoint was the difference from placebo in trough FEV1 after 12 weeks of treatment. Key secondary endpoints were the transition dyspnea index (TDI) focal score at week 12, spirometry measurements, rescue medication use, percentage of days with poor control, St George's Respiratory Questionnaire total score. Looking at changes from baseline in Study B2355, indacaterol treatment showed a statistically significant LS mean treatment difference of 0.14 (CI 0.10, 0.18) and in Study B2354, the LS mean difference was 0.12 (CI 0.08, 0.15), both meeting the predefined minimal clinical important difference. For key secondary endpoints, in Study B2355, the SGRQ total score at week 12 was statistically significantly better for indacaterol than placebo, but the difference (LS mean: -3.6) was less than the MCID (-4.0). The proportion of patients who achieved a decrease in SGRQ total score of 4.0 units at 12 weeks was statistically significantly greater for indacaterol 75 mcg (50.7%) than for placebo (37.2%), with an odds ratio of 1.71 (p=0.031).

Study 2357 was a two week dose ranging trial carried out in asthmatics who represent a more sensitive population in which to test the bronchodilatory action of β_2 agonists rather than the intended COPD population. The design was a randomized, double-blind, double-dummy, placebo controlled, parallel group study to assess the efficacy and safety of different doses of indacaterol in adult patients with persistent asthma, using salmeterol as an active control. All patients were required to use inhaled corticosteroids. A total of 502 patients were randomized 1:1:1:1:1 to 18.75 mcg indacaterol qd; 37.5 mcg indacaterol qd; 75 mcg indacaterol qd; 150 mcg indacaterol qd;

placebo qd and salmeterol 50 mcg bid. The primary endpoint was trough FEV1 on Day 15. The doses selected appear to demonstrate an increasing effect with the increasing dose and showed statistically significant differences vs. placebo, with the 75 mcg dose providing the largest LS mean difference of 0.17L while the active control, Salmeterol provided a 0.13L LS mean difference. However, none of the differences reached the predefined minimal clinical significant difference of 0.2L.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): deaths

In addition to standard audit procedures, please verify the following data points:

- deaths
 - during study
 - vital status (includes deaths for patients discontinuing prematurely)
 - investigator determined cause of death
 - adjudicated cause of death
- adverse events, with particular attention to cardiovascular events and stroke
- respiratory failure
- COPD exacerbations
- Forced expiratory volume (FEV1)—study primary endpoint
- St. George’s Respiratory Questionnaire (SGRQ)—key secondary endpoint (Studies B2355 and B2354 only)

Should you require any additional information, please contact Carol Hill at Ph: 301-796-1226 or Anya Harry, MD, PhD at Ph: 301-796-3954.

Concurrence: (as needed)

Anya Harry, MD, PhD, Medical Officer
Theresa Michele, MD, Medical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
11/17/2010

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-383 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Arcapta (b) (4)
Established Name: QAB149 (indacaterol maleate inhalation powder)
Strengths: 150/300 mcg

Applicant: Novartis Pharmaceuticals Corporation
Agent for Applicant (if applicable):

Date of Application: December 15, 2008
Date of Receipt: December 18, 2008
Date clock started after UN:
Date of Filing Meeting: February 2, 2009
Filing Date: February 16, 2009
Action Goal Date (optional):

User Fee Goal Date: October 18, 2009

Indication(s) requested: chronic obstructive pulmonary disease (COPD)

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.) NME

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

• Patent information submitted on form FDA 3542a? YES NO

• Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . .”

• Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or **request for deferral/partial waiver/full waiver of pediatric studies**) included? YES NO

• If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

• Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

• Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

• Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

• PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

• Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

• List referenced IND numbers: IND 48, 649 IND 66, 337 IND 69.754

• Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

• End-of-Phase 2 Meeting(s)? Date(s) October 10, 2006 NO
If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)? Date(s) April 7 and May 6, 2008 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NA NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

Not parenteral product.

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2FEB2009

NDA #: 22-383

DRUG NAMES: QAB149 (indacaterol maleate) -Arcapta

APPLICANT: Novartis

BACKGROUND:

New Drug Application submitted electronically on December 15, 2008. Tradename request submitted on December 16, 2008.

ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPAP
Anthony Durmowicz, M.D., Clinical Team Leader, DPAP
Lynne Wu, M.D., Clinical Reviewer, DPAP
Timothy Robison, Ph.D., Acting Nonclinical Supervisor, DPAP
Virgil Whitehurst, Ph.D., Nonclinical Reviewer, DPAP
Ali Al Hakim, Ph.D., Chief, Branch II, ONDQA
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Wei Qiu, Ph.D., Clinical Pharmacology Team Leader, OCP
Sandra Suarez., Ph.D., Clinical Pharmacology Reviewer, DPAP
Qian Li, Ph.D., Statistical Team Leader, OB
Dongmei Liu., Ph.D., Statistical Reviewer, OB
Sally Seymour, M.D., Deputy Director for Safety, DPAP
Leah Ripper, M.D., Associate Director for Regulatory Affairs, ODE II

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	Lynne Wu
Secondary Medical:	Tony Durmowicz
Statistical:	Dongmei Liu
Pharmacology:	Sandra Suarez
Statistical Pharmacology:	
Chemistry:	Prasad Peri
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Carol Hill
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain: **pending clinical request for consult**
- Advisory Committee Meeting needed? YES, date if known XX/XX/XX NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

Summary of meeting: Amend as you see fit

Clinical: fileable. There will be review issues and comments. There was discussion on whether the drug was more efficacious than formoterol because it is just a higher dose. There is concern that the dose is too high and potentially may have more adverse effects. Also, there was discussion that the sponsor did not show justification/comparison of QD and BID dosing. There are also safety concerns regarding the high dose.

Nonclinical: fileable

CMC: fileable. Badrul had comments on whether different capsules could be placed in the “^{(b)(4)}” device and potentially occur in “cross-use.” OSE will have to be involved. I have sent the MCR invite to Sean Bradley so that they can send to the OSE reviewer. Another discussion item was whether the drug is stable outside the blister because there has been a high incidence of patient cases where the drug is kept in a pill box rather than in the blisters. Another item discussed is how many pills ingested would equate to a safety risk. What is the potential generic landscape? Would the capsule be a generic looking ahead and then the device be approved with a 510K?

Statistics: fileable. There are review issues so there will be comments.

Other Discussion points:

1. Why are the drop out rates so high? Is this due to the safety issues?
2. Potential use in asthma through off label use. Sponsor needs to assess the efficacy/ dose in asthmatics before getting approved in COPD. Clinical will ask to submit studies in asthma.
3. Office (Curt and Leah) and OSE to be included in MCR and other discussions.
4. 74 day letter needs to be routed to Sally as well.

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS. 25Feb09
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74. 02Mar09

Eunice Haeyoon Chung, Pharm.D.
Regulatory Project Manager
Carol Hill, M.S.
Regulatory Health Project Manager

Drafted: Chung/10Feb09
 chill/25Feb09

Initialed: Barnes/September 29, 2009
Finalized: chill/October 16, 2009

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
10/16/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-383

Name of Drug: Arcapta (b) (4) (QAB149, indacaterol maleate inhalation powder)

Applicant: Novartis Pharmaceuticals

Material Reviewed:

Submission Date(s): December 15, 2008 and January 15, 2009

Receipt Date(s): December 18, 2008 and January 15, 2009

Submission Date of Structure Product Labeling (SPL): December 15, 2008

Type of Labeling Reviewed: WORD/SPL

Background and Summary

On December 15, 2008, Novartis Pharmaceuticals submitted PLR labeling in SPL format. The labeling submitted included the package insert (PI), medication guide (MedGuide) and carton and container labeling. At the request of the Agency, the word version of the PI and MedGuide was resubmitted on January 15, 2009 to provide a copy of the proposed labeling without track changes.

Review

The review of the labeling was compared to the SEALD Label Review Tool for the format of all sections of labeling. The following issues/deficiencies have been identified in the proposed labeling.

HIGHLIGHTS

1. In the Boxed Warning section, the verbatim statement “See full prescribing information for complete boxed warning” must be placed immediately following the heading of the boxed warning.

FULL PRESCRIBING INFORMATION

2. A Clinical Trials Experience subsection was not included in the ADVERSE REACTIONS section of the proposed label. However, clinical trials data is presented in the format suggested for this subsection. Preceding the presentation of adverse reactions from clinical trials, include the following statement (or appropriate modification):
“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
3. Potentially fatal adverse reactions described in the “Warnings and Precautions” section must be listed in the ADVERSE REACTIONS section.

Recommendations

Since a team labeling review was not performed and the regulatory action is a complete response during this review cycle, these minor deficiencies will be held until the next review cycle.

Carol Hill, MS
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: chill/February 29, 2009
Revised/Initialed: March 20, 2009
Finalized: chill/September 18, 2009
Filename: 29Feb09 CSO Labeling Review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
09/21/2009

SANDRA L BARNES
09/23/2009

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22-383
Brand Name	Arcapta™ (b) (4)™
Generic Name	Indacaterol maleate inhalation powder
Sponsor	Novartis
Indication	The long term, once-daily maintenance treatment in patients with chronic obstructive pulmonary disease (COPD)
Dosage Form	Dry powder for oral inhalation with (b) (4) inhaler
Drug Class	Beta ₂ -adrenergic agonist
Therapeutic Dosing Regimen	150 mcg or 300 mcg every day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not defined
Submission Number and Date	N000, 15 December 2008
Review Division	DPAP / HFD 570

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of indacaterol (150 mcg, 300 mcg and 600 mcg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between indacaterol (150 mcg, 300 mcg and 600 mcg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, blinded, five-arm parallel group study, 404 healthy subjects received indacaterol 150 mcg, indacaterol 300 mcg, indacaterol 600 mcg placebo, and a single oral dose of moxifloxacin 400 mg. The summary findings for the averaged baseline adjustment are presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for INDACATEROL (150 mcg, 300 mcg and 600 mcg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Indacaterol 150 mcg	2	2.7	(0.7, 4.6)
Indacaterol 300 mcg	2	2.9	(0.9, 4.9)
Indacaterol 600 mcg	6	2.7	(0.4, 5.1)
Moxifloxacin 400 mg*	2	14.0	(10.9, 17.0)

Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.8 ms.

The supratherapeutic dose (600 mcg QD) provided concentrations that were approximately 2-fold higher than those from the highest therapeutic doses of 300 mcg QD. Factors known to increase concentrations are metabolic inhibition with potent CYP3A4 inhibitor (30-40% increase in C_{max}) and genetic polymorphism for UGT1A1 (20% increase in exposure in healthy volunteers homozygous for the A (AT)7TAA variant). There were no relevant changes in C_{max} and AUC in patients with mild to moderate hepatic impairment compared to healthy volunteers.

1.1.1 Additional Reviewer’s Comments

For parallel studies, we recommend that time-matched baseline adjustment is used to address the diurnal patterns for each subject. The sponsor did not collect time-matched ECGs at baseline as we recommended during the review of the protocol. Instead, the sponsor used an averaged pre-dose QTc values as the baseline; this makes it hard to detect whether the on-treatment data has been adequately adjusted for diurnal variability. During our review, we performed a “no baseline-adjusted” analysis to assess whether larger variability in QTc measurements would change the overall results. We found that the overall conclusions are the same, thereby giving us confidence in the study results.

2 PROPOSED LABEL

The sponsor has proposed the following labeling statements describe the QTc effects in section 12.2 of the label. Our recommendations for labeling are shown using red strikethrough font for deleted text and blue underline text for insertions. We defer all final labeling decisions to the review division.

Healthy Subjects: Cardiovascular Effects

The effect of Arcapta ^{(b) (4)} on the QT interval was evaluated in a double-blind, placebo- and active (moxifloxacin)-controlled study following multiple doses of indacaterol 150 mcg, 300 mcg or 600 mcg once-daily for 2 weeks in 404 healthy volunteers. Fridericia’s method for heart rate correction was employed to derive the corrected QT interval (QTcF). Maximum mean prolongation of QTcF intervals were <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time-matched comparisons versus placebo. ^{(b) (4)}

(b) (4)

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Indacaterol maleate (R-enantiomer), QAB149, is a novel, long-acting inhaled β 2-adrenergic receptor agonist (LABA) intended for long-term, once daily (od), maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

(b) (4)

3.2 MARKET APPROVAL STATUS

Indacaterol is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From m4, NDA 22,383

“Initial application of 5 μ g/ml QAB149 decreased HERG tail current amplitude by approximately 33%. As an inhibition was observed with QAB149, concentrations of 0.5, 1 and 5 μ g/ml were investigated in order to determine the concentration-response relationship for the test item (n = 4 cells/concentration). QAB149 inhibited HERG tail current with a statistically significant inhibition observed at a concentration of 5 μ g/ml (P < 0.05 compared to vehicle using one-way ANOVA, followed by Dunnett's t-test); the decrease in HERG tail current amplitude was similar to that observed with the initial application of 5 μ g/ml QAB149. When the QAB149 and vehicle treated groups were compared 0.5 and 1 μ g/ml QAB149 had no statistically significant inhibitory effect on HERG tail current. QAB149 displayed no frequency-dependence of HERG current inhibition at the concentration and frequencies examined. When administered to 2 of the vehicle treated cells, the reference item, E-4031 (100 nM, approximately 15 min) inhibited HERG tail current by 86.1 %.

“The purpose of this study was to evaluate the pharmacological effects of a single inhalation dose of QVA149, NVA237 and QAB149 on hemodynamic and electrocardiographic parameters in the beagle dog via telemetry. NVA237 and QAB149 given as separate exposures at 0.149 and 0.349 mg/kg, respectively, also caused transient increases in heart rate. Following exposure to NVA237, at 0.149 mg/kg, heart rate increased by up to 82% during the exposure period, following which it gradually decreased and by 7 hours post dose was relative to baseline levels. QAB149, at 0.349 mg/kg, caused an increased heart rate of approximately 57% during the exposure period, heart rate continued to increase following

treatment and a maximum increase of approximately 110% was noted at 1 hour 30 minutes following start of inhalation exposure. Heart rate increases gradually diminished, although by 24 hours post start of exposure, there was still an approximate 25% increase relative to baseline. Increased heart rate, following both NVA237 and QAB149 exposures, was also associated with a shortening of the PR, P width and QT intervals. Whilst heart rate adjusted QT interval (QTc) decreased by up to approximately 30 and 20 ms, over the first 2 hours following dosing, relative to baseline, following exposure to NVA237 and QAB149 respectively. No biologically significant effect on systolic or diastolic pressures was noted following treatment with NVA237 and QAB149 individually. Ventricular arrhythmias were noted in one dog at 3 postdose intervals following dose 3 (0.146/0.376 mg/kg QVA149) that were likely due to a test article effect. A low frequency of ventricular premature complexes was noted in the same animal following dose 4 (0.149 mg/kg NVA237) and based on the low frequency of VPCs and presence at the predose interval as well as a single postdose interval, may represent a normal variant. There were no qualitative abnormalities due to the inhalation of 0.349 mg/kg QAB149 or 0.037/0.096 mg/kg QVA149.”

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety (Nov 26, 2008)

“**Standard 12-lead ECGs.** In the phase III, pivotal studies B2334, B2335S and B2346, ECGs were performed 25 min pre-dose, 30 min post-dose and 1 h post-dose at each visit as well as at screening and at the end of the study. ECGs were to include all 12 standard leads and a Lead II rhythm strip of at least 10-second duration. The original ECG tracings were sent electronically to the designated contract research organization (CRO: (b) (4)). Duplicate tracings were kept at the investigator site.

“**24 hour Holter monitoring.** Continuous 24 hour ECG recordings (Holter monitoring) were performed in a subset of patients in COPD study B2335S and asthma safety study B2338. The Holter monitoring data were read centrally by the designated CRO ((b) (4)). In COPD study B2335S, Holter monitoring was undertaken at screening and after 2, 12 and 26 weeks of treatment in a subset of patients randomized to one of two indacaterol dose groups or placebo. In total 522 randomized patients were to be included to ensure Holter monitoring data on at least 450 patients (150 patients in each group) were available for at least 12 weeks of treatment.

“In asthma safety study B2338, Holter monitoring was undertaken at screening and after 12 and 26 weeks of treatment in a subset of patients randomized to indacaterol 300 µg od, 600 µg od or salmeterol 50 µg bid. Approximately 330 patients were to undergo initial Holter monitoring at the screening visit to ensure that Holter monitoring data were collected in approximately 225 randomized patients (75 per treatment group).

“In the COPD safety population baseline PR intervals at corresponding time points were similar between treatment groups with mean values between 159.0 and 161.5 ms. Post-baseline there was an increase from baseline by approx. 1.5

ms over time irrespective of the dose. In addition there was a dose dependent decrease in the mean differences from baseline for several time points; e.g. at 6 months the differences were: +2.1 ms (150 µg), +1.0 ms (300 µg), and -1.8 ms (600 µg), vs. +0.3 ms on placebo (Table 4-8).

Table 4-8 Summary statistics of PR-interval (ms) by visit and time point in COPD safety population

Treatment	Visit	Time point	N	Baseline	Endpoint	Change from baseline	
				Mean (ms)	Mean (ms)	Mean (ms)	SD (ms)
Ind 150 µg	Day 1	30 min	400	160.8	161.2	0.4	8.53
		1 hour	611	161.9	162.6	0.8	9.77
	Week 2	1 hour	379	160.8	162.2	1.4	11.08
	Month 3	1 hour	524	161.6	163.0	1.4	11.46
	Month 6	1 hour	313	161.0	163.1	2.1	12.65
Ind 300 µg	Day 1	30 min	818	159.6	159.2	-0.5	8.62
		1 hour	816	159.6	159.8	0.1	9.57
	Week 2	1 hour	787	159.7	160.6	0.9	11.19
	Month 3	1 hour	725	159.9	160.3	0.4	11.50
	Month 6	1 hour	678	160.0	161.0	1.0	12.09
	Month 12	1 hour	312	159.0	160.2	1.3	13.03
Ind 600 µg	Day 1	30 min	521	161.5	160.6	-0.8	8.84
		1 hour	517	161.5	161.5	-0.0	8.57
	Week 2	1 hour	497	161.1	160.5	-0.6	11.20
	Month 3	1 hour	421	161.5	159.8	-1.7	11.75
	Month 6	1 hour	334	161.0	159.2	-1.8	11.32
	Month 12	1 hour	303	161.2	162.4	1.2	13.13
Placebo	Day 1	30 min	814	161.3	161.3	0.0	8.59
		1 hour	1014	161.4	161.9	0.5	9.14
	Week 2	1 hour	754	161.3	161.6	0.3	11.24
	Month 3	1 hour	828	161.2	161.6	0.4	11.98
	Month 6	1 hour	594	161.1	161.4	0.3	11.79
	Month 12	1 hour	271	159.1	160.8	1.7	11.97

Baseline defined as the averaged values at 25 min pre-dose of baseline visit
Source: [SCS-Appendix 1-Table 4.2-1]

“In the COPD safety population the duration of the baseline QRS interval at corresponding time points was similar between treatment groups with mean values between 90.6 and 91.9 ms. Post-baseline there was an increase over time irrespective of the dose. In addition there was a dose dependent increase in the mean differences for several time points; e.g. at 6 months the differences were: +1.4 ms (150 µg), +1.4 ms (300 µg), and +1.9 ms (600 µg), vs +1.1 ms on placebo. The maximum mean increase in the QRS duration was at month 12 on 600 µg with 2.8 ms (Table 4-9).

Table 4-9 Summary statistics of QRS-interval (ms) by visit and time point in COPD safety population

Treatment	Visit	Time point	N	Baseline	Endpoint	Change from baseline	
				Mean (ms)	Mean (ms)	Mean (ms)	SD (ms)
Ind 150 µg	Day 1	30 min	408	91.1	91.2	0.1	5.59
		1 hour	622	90.8	90.8	0	5.39
	Week 2	1 hour	387	90.9	90.9	0	6.75
		1 hour	533	90.7	92.0	1.3	6.45
	Month 6	1 hour	321	90.6	92.0	1.4	6.65
Ind 300 µg	Day 1	30 min	831	91.3	91.4	0.1	5.08
		1 hour	830	91.3	91.5	0.2	5.50
	Week 2	1 hour	800	91.4	91.6	0.3	6.56
		1 hour	736	91.3	92.1	0.8	6.68
	Month 6	1 hour	688	91.3	92.7	1.4	7.00
		1 hour	320	91.9	93.4	1.5	7.15
Ind 600 µg	Day 1	30 min	532	91.4	92.0	0.5	5.25
		1 hour	529	91.4	91.7	0.2	5.64
	Week 2	1 hour	508	91.3	91.7	0.3	6.71
		1 hour	434	90.7	91.9	1.2	7.28
	Month 6	1 hour	339	90.6	92.5	1.9	7.92
		1 hour	311	90.6	93.4	2.8	8.75
Placebo	Day 1	30 min	826	91.7	91.7	-0.1	5.05
		1 hour	1030	91.5	91.6	0.1	5.06
	Week 2	1 hour	764	91.5	91.5	0	6.30
		1 hour	838	91.3	91.9	0.7	6.60
	Month 6	1 hour	604	91.4	92.5	1.1	7.29
		1 hour	280	91.2	92.9	1.7	7.69

Baseline defined as the averaged values at 25 min pre-dose of baseline visit
Source: [SCS-Appendix 1-Table 4.2-1]

“Summaries of changes from pre-dose to post-dose values by ECG parameter, visit, and time point are provided in [SCS-Appendix 1-Table 4.2-3].

Note: only data from Day 1 are shown below, all visits showed same tendency

Table 4.2-3 (Page 26 of 35)
ECG intervals and heart rate: Summary of change from pre-dose to post-dose values by parameter, visit and time point
COPD safety population

Parameter: Frid. QTc

Visit/Time	Treatment	n	25-min pre-dose					post-dose					Change from pre-dose				
			Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Day 1 /30 min post-dose																	
	Ind 75ug (N=127)	126	406.81	19.93	405.67	366.50	456.33	407.31	20.88	404.50	360.00	463.50	0.50	10.05	0.83	-30.00	40.00
	Ind 150u (N=627)	408	406.05	19.29	406.17	354.67	515.33	406.93	19.65	406.00	358.50	515.50	0.88	9.92	1.17	-44.33	30.67
	Ind 300u (N=853)	831	406.69	18.12	405.67	359.33	485.00	407.99	18.92	407.00	359.00	473.00	1.30	10.36	1.00	-60.17	59.83
	Ind 600u (N=547)	531	405.13	18.48	404.00	357.00	470.00	407.58	19.86	406.00	344.00	498.00	2.45	10.20	2.50	-27.00	42.00
	For (N=556)	536	406.80	18.46	405.50	353.33	473.67	407.35	19.54	406.50	344.00	476.00	0.56	10.38	1.00	-51.50	30.67
	Tic (N=415)	408	406.32	19.99	405.67	355.33	507.00	405.82	21.00	403.50	351.00	523.50	-0.50	10.29	-0.25	-37.67	38.17
	Pbo (N=1055)	826	406.03	19.46	404.83	332.00	477.67	405.34	20.19	404.00	344.50	483.50	-0.69	10.17	-0.50	-49.83	47.33
Day 1 /1h post-dose																	
	Ind 75ug (N=127)	127	406.90	19.88	405.67	366.50	456.33	407.62	21.18	406.00	351.00	466.50	0.72	10.29	0.33	-32.67	29.00
	Ind 150u (N=627)	622	407.10	19.07	407.00	349.67	515.33	408.23	19.92	408.00	355.00	480.50	1.14	10.28	1.50	-42.33	34.33
	Ind 300u (N=853)	830	406.59	18.12	405.67	359.33	485.00	407.69	18.94	407.00	348.00	469.00	1.10	10.46	1.50	-61.67	32.83
	Ind 600u (N=547)	528	405.15	18.52	404.00	357.00	470.00	408.26	20.47	406.50	348.50	484.00	3.11	11.14	3.17	-35.50	46.00
	For (N=556)	538	406.84	18.53	405.50	353.33	473.67	407.45	19.92	405.25	355.50	485.50	0.61	11.43	1.67	-55.83	54.50
	Tic (N=415)	411	406.16	20.06	405.33	355.33	507.00	406.91	21.02	405.50	346.00	505.50	0.74	11.30	1.00	-38.00	56.00
	Pbo (N=1055)	1030	406.85	19.45	405.33	332.00	477.67	406.91	19.83	405.50	343.50	486.50	0.06	10.25	-0.17	-46.83	60.33

- Pre-dose is 25 min pre-dose at each respective visit.
- N = the number of patients in the analysis population
- n = number of patients with a value at both pre-dose and each respective post-dose time.
- Change from baseline = post-dose - pre-dose.
- Each patient has 3 consecutive ECGs at baseline (25 min before the first dose) and 2 consecutive ECGs at all subsequent scheduled time points. For each scheduled time point, the analysis is based on the averaged value.

report/pgm_saf/t_1_ecg_chpreds.sas@main/10 06NOV08:03:01 Final Version

“Three-months safety population: Events in the ischemic heart disease Standardized MeDRA Query (SMQ) occurred more frequently for indacaterol 150 µg (1.0%), indacaterol 300 µg (1.1%), and tiotropium (1.4%) than for indacaterol 75 µg (0), indacaterol 600 µg (0.4%), formoterol (0.2%) and placebo (0.5%). The incidence of myocardial infarction SMQ events was highest for tiotropium (1.0%) compared to rates ranging from 0 – 0.3% for the other groups. Torsades de pointes/ QT prolongation SMQ events occurred at the greatest frequency for indacaterol 75 µg (1.6%) and at the lowest frequency for indacaterol 300 µg (0.5%) and formoterol (0.5%); the frequencies for the remaining groups were comparable (0.9%-1.0%). Events in the cardiac failure SMQ only occurred

in the active treatment groups except for indacaterol 75 µg but at a very low frequency (0.1-0.5%).

“Six-months safety population. Events in the ischemic heart disease SMQ occurred more frequently for indacaterol 150 µg (1.4%), indacaterol 300 µg (1.4%), and tiotropium (1.7%) than for indacaterol 75 µg (0.8%), indacaterol 600 µg (0.9%), formoterol (0.7%) and placebo (0.7%). The incidence of myocardial infarction SMQ events was highest for tiotropium (1.2%) compared to rates ranging from 0 – 0.5% for the other groups. The frequency of Torsade de pointes/QT prolongation SMQ events was greatest for the indacaterol 150 µg group (2.2%), lowest for indacaterol 300 µg (0.6%) and formoterol (0.5%); frequencies for the other groups were indacaterol 75 µg (1.6%), tiotropium (1.4%), indacaterol 600 µg (0.9%) and placebo (1.2%). Events in the cardiac failure SMQ occurred with the highest frequency for formoterol (1.3%) and lowest frequency for placebo (0.1%) compared to rates of 0.5% - 0.8% for the remaining indacaterol groups and tiotropium.

“Four deaths on indacaterol were recorded in the clinical databases of the completed phase I, II and III clinical studies which constitute the All treated subjects population: 2 out of 3680 (0.05%) COPD patients on indacaterol (all doses and devices) in controlled studies, and 2 out of 1784 (0.11%) asthma patients on indacaterol (all doses and devices) in controlled studies. The two COPD patients were 1 on indacaterol 150 µg od in study B2335S (sudden death) and 1 on indacaterol 300 µg od in study B2334 (cardiac arrest), as summarized in Table 2-32. The 2 asthma patients were both on indacaterol 300 µg od in study B2338 (cardiac arrest and sudden death), as summarized in Table 2-34. In all the other studies, there were no deaths during indacaterol treatment recorded in the clinical databases.”

Reviewer’s comments: No clinically relevant ECG changes were reported in these studies. Some AEs of Torsades/QT prolongations SMQ events were reported in the COPD 3-, 6- and 12-months safety population analysis with frequencies slightly higher than in the placebo arm.

There was one sudden death and one cardiac arrest episode in the indacaterol arm ruled as linked (suspected) to study drug. The sudden death case was reported in an asthma patient and the cardiac arrest in a COPD patient. In both cases death was ruled as the result of complications because of preexisting pathology.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of indacaterol’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study.

The sponsor submitted the study protocol 3066K1-155-US for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, multiple-dose, placebo and positive-controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects

4.2.2 Protocol Number

CQAB149B2339

4.2.3 Study Dates

First subject enrolled: 04-Apr-2008 (first subject dosed)

Last subject completed: 14-Aug-2008 (end of study visit)

4.2.4 Objectives

Primary objective

- To determine the maximum change from baseline in QTcF following multiple dose treatment with indacaterol 150 µg, 300 µg and 600 µg qd for 14 days in healthy subjects, as compared to placebo.

Secondary objectives

- To evaluate the potential for effect of indacaterol 150 µg, 300 µg and 600 µg qd multiple-dose treatment for 14 days on uncorrected QT interval duration in healthy subjects.
- To evaluate the potential for effect of multiple dose treatment with indacaterol 150 µg, 300µg and 600 µg for 14 days on cardiovascular safety in healthy subjects.
- To determine the maximum change from baseline in QTcF following single dose treatment with oral moxifloxacin 400 mg in healthy subjects, as compared to placebo.
- To evaluate the pharmacokinetics and dose proportionality of indacaterol during 14 days of qd dosing with indacaterol 150 µg, 300 µg and 600 µg in healthy subjects.
- To evaluate the tolerability of indacaterol in comparison to placebo in healthy subjects. The main tolerability endpoint is cough.

Exploratory objective

- To evaluate the potential effect of indacaterol 150 µg, 300 µg and 600 µg multiple-dose treatment on cardiac conduction and repolarization as assessed by QTcI as an exploratory analysis.

4.2.5 Study Description

4.2.5.1 Design

This was a single center, randomized, multiple-dose, placebo and positive controlled, five-arm parallel group study in 404 healthy volunteers.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was double-blind with regard to the active drug, indacaterol and placebo. Subjects assigned to receive moxifloxacin were not aware of which treatment group they were in until Day 14, when they received the single moxifloxacin dose in an open-label manner.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Multiple-dose treatment with indacaterol 150 µg, 300 µg and 600 µg qd administered for 14 days; single dose of moxifloxacin administered to a subset of the placebo group on Day 14.

4.2.6.2 Sponsor's Justification for Doses

“The 150 µg and 300 µg doses selected for this study represent the two therapeutic doses evaluated in the Phase III clinical development program for indacaterol in COPD. The 600 µg dose represents a suprathreshold dose of indacaterol taking into consideration data on the influence of metabolism, genotype and drug-drug interaction at the time of study initiation. (b) (4)

4.2.6.3 Instructions with Regard to Meals

On the evenings of Days -2, -1, 13 and 14 all subjects were domiciled and remained at the clinic until 24 h after dosing. Subjects were to fast overnight on Day 13 (prior to Day 14 dosing). Breakfast was provided 30 minutes following dosing. Lunch and dinner were served at ~1300 and 1800 hours, respectively, and a large snack was served at 2000 hrs. No other food was consumed at any time during confinement. Subjects were to consume

the entire contents of the meal. Meals were similar in caloric content and distribution for all subjects. When meal and blood draw times coincide, blood was drawn BEFORE the meal was provided.

Reviewer's Comment: The formal food effect study was not conducted, as indacaterol is an inhaled drug. In the pivotal studies of the clinical development program indacaterol was administered as a morning dose regardless of the timing of food intake. Hence, the sponsor's food instruction was acceptable.

4.2.6.4 ECG and PK Assessments

A schedule of assessments is shown in Appendix 6.2.

At Baseline, a standard 12-lead ECG was performed using digital ECG equipment at 7:00-8:00 am (equivalent to pre-dose) and at 8:00-9:00 am (equivalent to 1 hour post-dose) and at 8:00-9:00 pm (equivalent to 12 hours post-dose). For evaluations on Days 1 and 14, a standard 12-lead ECG was performed using digital ECG equipment at each of the following time points: pre-dose, 10 min, 20 min, 40 min, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr, 12 hr, and 24 hr post-dose. The ECGs were recorded after the subject had rested in the supine position for 15 minutes (8 min for 10 min reading). Three ECGs were recorded within a range of 5 minutes at each time point. Only one ECG was collected at the end-of-study evaluation.

ECG recording preceded PK sampling, when sampling times coincided. The digital ECG equipment was provided to the study site by (b) (4), an external CRO and (b) (4) was used in this study for interpretation and analysis of ECGs. ECGs were also collected at screening and on Days 3, 5, 7, and 10 (Pre-dose and 1 hr post-dose) and were read locally by the investigator.

Reviewer's Comment: The sampling times are acceptable. ECGs measurements were collected frequently enough to monitor the effects of indacaterol. The mean T_{max} is approximately 15 min. The sponsor has collected ample ECG measurements before, around, and after the T_{max} .

4.2.6.5 Baseline

The sponsor used time-averaged baseline QT values on the Day -1.

4.2.7 ECG Collection

For specific QT interval determination, manual measurements of uncorrected QT interval (QTuncorr) and R-R intervals were performed on the 3 consecutive cycles from Lead II.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Four hundred and four healthy male and female subjects aged between 18 and 55 years of age (inclusive), in good health with a body mass index of between 18.5 – 32 kg/m² at screening and weighing at least 50 kg were enrolled and dosed; 389 subjects completed 14 days of dosing, 388 subjects completed the study

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the change from the time-averaged baseline adjusted mean differences between indacaterol (150 mcg, 300 mcg and 600 mcg) and placebo in QTcF (Δ QTcF) on Day 14. The sponsor used Linear Mixed Effect model including treatment, time and treatment and time point interaction and baseline QTcF as a covariate. The sponsor's analysis results of $\Delta\Delta$ QTcF for indacaterol 150 mcg, indacaterol 300 mcg, indacaterol 600 mcg, and moxifloxacin 400 mg are presented in Table 2. All the upper bounds of the 2-sided 90% CIs for the mean differences between indacaterol (150 mcg, 300 mcg and 600 mcg) and placebo at each time point were below 10 ms. For moxifloxacin treatment, the greatest mean difference from placebo in QTcF change from baseline was 13.9 ms at 2 hours post-dose and the lower bound was greater than 5 ms.

The sponsor concluded that no statistical evidence of a significant QT prolongation for any of the three indacaterol doses compared to placebo. All time points from 20 minutes until 24 hours post-dose following dosing with moxifloxacin demonstrated statistically significant QT prolongation compared to placebo, thus establishing the assay sensitivity of the trial.

Table 2: Sponsor's Mixed Model $\Delta\Delta$ QTcF for Indacaterol 150 mcg, Indacaterol 300 mcg, Indacaterol 600 mcg, and Moxifloxacin 400 mg

Hours post-dose	Indacaterol 150ug vs placebo	Indacaterol 300ug vs placebo	Indacaterol 600ug vs placebo	Placebo/moxifloxacin 400mg vs placebo
0.167	1.62 (-0.34, 3.57)	1.26 (-0.64, 3.16)	1.56 (-0.83, 3.94)	1.84 (-1.32, 5.01)
0.333	2.23 (0.34, 4.12)	2.24 (0.45, 4.03)	2.84 (0.72, 4.95)	3.74 (0.97, 6.51)
0.667	2.12 (0.21, 4.03)	1.54 (-0.41, 3.49)	1.40 (-0.96, 3.76)	8.25 (5.04,11.47)
1.000	0.89 (-1.12, 2.89)	1.05 (-0.99, 3.09)	0.70 (-1.72, 3.12)	10.76 (7.60,13.93)
2.000	2.66 (0.55, 4.77)	2.98 (1.02, 4.93)	2.18 (-0.25, 4.61)	13.90 (10.58,17.22)
3.000	0.48 (-1.53, 2.50)	1.06 (-0.91, 3.03)	2.14 (-0.19, 4.48)	11.12 (8.08,14.15)
4.000	0.36 (-1.82, 2.53)	0.29 (-1.76, 2.33)	1.17 (-1.26, 3.59)	11.91 (8.57,15.24)
6.000	0.46 (-1.70, 2.62)	1.21 (-0.64, 3.05)	3.34 (0.86, 5.82)	9.25 (5.93,12.57)
12.000	0.44 (-1.69, 2.57)	-1.24 (-3.26, 0.79)	-1.62 (-4.23, 0.98)	4.24 (0.82, 7.67)
24.000	1.88 (0.12, 3.64)	0.67 (-1.15, 2.49)	-0.08 (-2.27, 2.11)	7.77 (4.73,10.82)

Confidence intervals are based on a one-sided t-test at the 5% significance level using data from the respective timepoint and pair of treatment groups only.

Source: [Table 14.2-1.1](#)

Source: Sponsor's protocol CQAB149B2339 report: Table 1page 7 of the 14191

4.2.8.3 Safety Analysis

A total of 404 subjects were enrolled, randomized and dosed; 389 subjects completed 14 days of study treatment with 388 subjects completing the study. A total of 389 and 404 subjects were included in the QT analysis at Day 14 and Day 1, respectively.

Table 10-1 Subject disposition

	Indacaterol 150µg N=108	Indacaterol 300µg N=108	Indacaterol 600µg N=54	Placebo N=107	Placebo + Moxifloxacin 400mg N=27	All subjects N=404
Patients						
Randomized	108 (100%)	108 (100%)	54 (100%)	107 (100%)	27 (100%)	404 (100%)
Exposed to drug	108 (100%)	108 (100%)	54 (100%)	107 (100%)	27 (100%)	404 (100%)
Completed day 1	108 (100%)	108 (100%)	54 (100%)	107 (100%)	27 (100%)	404 (100%)
Completed day 14	102 (94.4%)	102 (94.4%)	53 (98.1%)	105 (98.1%)	27 (100%)	389 (96.3%)
Completed	102 (94.4%)	102 (94.4%)	53 (98.1%)	104 (97.2%)	27 (100%)	388 (96.0%)
Main cause of discontinuation						
Discontinued	6 (5.6%)	6 (5.6%)	1 (1.9%)	3 (2.8%)	0	16 (4.0%)
Adverse Event(s)	1 (0.9%)	1 (0.9%)	0	1 (0.9%)	0	3 (0.7%)
Abnormal laboratory value(s)	0	1 (0.9%)	0	0	0	1 (0.2%)
Subject withdrew consent	3 (2.8%)	1 (0.9%)	0	0	0	4 (1.0%)
Lost to follow-up	0	3 (2.8%)	1 (1.9%)	2 (1.9%)	0	6 (1.5%)
Protocol deviation	2 (1.9%)	0	0	0	0	2 (0.5%)

Source: Table 14.1-1.1

Fifteen (15) subjects did not complete 14 days of dosing. Three subjects discontinued due to AEs: Subject 1125 (receiving placebo) was withdrawn due to an episode of acute depression requiring hospitalization (hence, meeting the criteria for seriousness); Subject 1014 (receiving indacaterol 300 µg) was discontinued due to an AE described of chest pressure; Subject 1362 (receiving indacaterol 600 µg) was found to have an abnormal ECG on Day 1 at the 3 and 4 hour evaluations. The ECG tracings showed ventricular bigeminy.

The investigator felt that this anomaly would interfere with the evaluation of the QT interval and therefore, the subject was withdrawn from the study. The presence of ventricular bigeminy was confirmed by Holter monitoring 10 days after drug discontinuation.

Four cases of vasovagal syncope were reported, 3 in the indacaterol 300µg arm and one in the placebo arm.

The most common adverse event observed was contact dermatitis secondary to the repeated application of adhesive ECG electrodes. Post-inhalational (PI) cough occurring within 5 minutes of dosing was observed in between 62-82% of subjects across all indacaterol doses and days vs. 4-13% for placebo. There was no evidence of tolerance over time. The events were predominantly mild and moderate. PI cough did not lead to any subject discontinuing treatment.

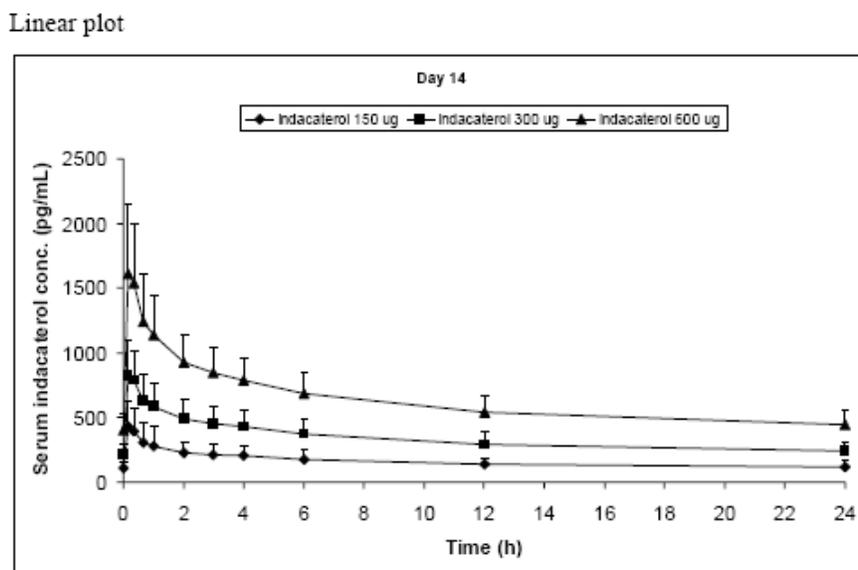
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The pharmacokinetics of indacaterol appears to be linear after 150 mcg and 600 mcg once daily dose. Mean plasma concentration-time profile of indacaterol is shown in Figure 1. Summary statistics of the pharmacokinetics of indacaterol are provided in Table

3The mean C_{max} and AUC_{∞} values after supratherapeutic dose (600 mcg qd) were 4 times higher, when compared to therapeutic dose (150 mcg qd).

Figure 1: Mean (SD) Indacaterol Concentration-time Profiles – Day 14



Source: A randomized, multiple-dose, placebo and positive controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects, Section 11.4, pg 65

Table 3: Summary Statistics of Indacaterol Pharmacokinetics Parameters in Healthy Volunteers at Day 14, from the Study of CQAB140B2339

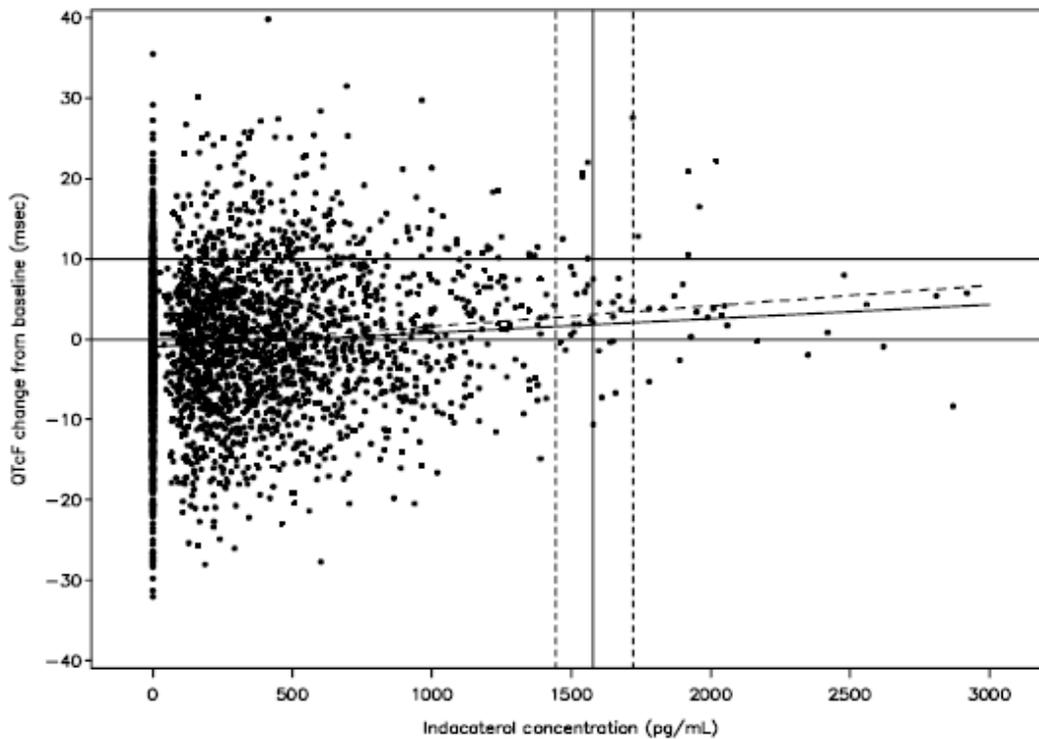
Dose (ug)	Statistic	t_{max} (h)	C_{avg} (pg/mL)	C_{min} (pg/mL)	C_{max} (pg/mL)	AUC_{0-24} (pg.h/mL)	CL_{ss}/F (L/h)
150	N	70	70	70	70	70	70
	Mean/median ¹	0.25	161.7	104.4	438.6	3882	45.1
	SD/range ¹	0.22-3.08	64.4	43.8	196.4	1545	24.2
	CV%	-	39.8	42	44.8	39.8	53.6
300	N	68	68	68	68	68	68
	Mean/median ¹	0.25	339.0	214.5	858.6	8137	40.1
	SD/range ¹	0.17-1.08	99.5	68.8	264.2	2388	12.0
	CV%	-	29.4	32.1	30.8	29.4	29.9
600	N	37	37	37	37	37	37
	Mean/median ¹	0.25	628.5	396.8	1656.6	15085	42.0
	SD/range ¹	0.25-0.42	142.8	121.4	540.8	3428	10.7
	CV%	-	22.7	30.6	32.6	22.7	25.4

Source: A randomized, multiple-dose, placebo and positive controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects, Section 11.4, pg 62

4.2.8.4.2 Exposure-Response Analysis

Figure 2 presents a scatter plot of the indacaterol concentration and corresponding change from baseline in QTcF for all indacaterol and placebo patients at all post-dose time-points on Day 14. The solid line shows the estimated regression of concentration against change from baseline in QTcF and the dashed line the corresponding 95% upper confidence band. The graph also shows two horizontal lines, at 0 and 10 ms QTcF change from baseline. At all concentrations up to 3000 pg/mL, the 95% confidence band of the regression line are below the line for 10 ms QTcF change from baseline.

Figure 2: Day 14 Indacaterol concentration and change from the baseline QTcF relationship following multiple dosing with Indacaterol 150, 300 or 600 mcg



For complete details of the sponsor’s exposure-response analysis, please refer to section 11.4 of the sponsor’s report: *A randomized, multiple-dose, placebo and positive controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects.*

Reviewer’s Comment: We do not recommend using ΔQTc as the dependent variable in the concentration- QTc analysis because it does not account for the placebo response. We performed an independent analysis using $\Delta\Delta QTcF$ as the dependent variable. The overall conclusions are the same as the sponsors. Our analysis is presented in section 5.2.

5 REVIEWERS' ASSESSMENT

5.1 QTC ANALYSIS

5.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect on Day 14. The model includes treatment, time and baseline values as a covariate. The analysis results are listed in Table 4. The largest upper bounds of the 2-sided 90% CI for the mean differences between indacaterol 150 mcg and placebo, between indacaterol 300 mcg and placebo, and between indacaterol 600 mcg and placebo are 4.6 ms, 4.9 ms, and 5.1 ms, respectively.

Table 4: Analysis Results of $\Delta\Delta$ QTcF for Indacaterol 150 mcg, Indacaterol 300 mcg, and Indacaterol 600 mcg, Day 14

	Placebo	Treatment Group								
		Indacaterol 150 mcg			Indacaterol 300 mcg			Indacaterol 600 mcg		
		Δ QTc	$\Delta\Delta$ QTc		Δ QTc	$\Delta\Delta$ QTc		Δ QTc	$\Delta\Delta$ QTc	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
10 min	1.8	3.5	1.6	(-0.3, 3.5)	3.1	1.2	(-0.7, 3.1)	3.2	1.3	(-1.0, 3.6)
20 min	0.9	3.1	2.3	(0.4, 4.1)	3.1	2.2	(0.4, 4.0)	3.5	2.6	(0.4, 4.8)
40 min	1.7	3.8	2.2	(0.2, 4.1)	3.2	1.6	(-0.4, 3.5)	2.9	1.3	(-1.1, 3.6)
1	1.8	2.7	0.9	(-1.1, 2.9)	2.8	1.0	(-1.0, 3.0)	2.2	0.5	(-1.9, 2.8)
2	-4.7	-2.0	2.7	(0.7, 4.6)	-1.8	2.9	(0.9, 4.9)	-2.9	1.8	(-0.6, 4.2)
3	-5.2	-4.7	0.5	(-1.4, 2.4)	-4.3	1.0	(-0.9, 2.9)	-3.5	1.7	(-0.6, 4.0)
4	-6.7	-6.3	0.4	(-1.6, 2.4)	-6.4	0.2	(-1.8, 2.3)	-5.9	0.8	(-1.7, 3.2)
6	-4.6	-4.1	0.5	(-1.5, 2.4)	-3.5	1.1	(-0.8, 3.0)	-1.8	2.7	(0.4, 5.1)
12	-0.0	0.4	0.5	(-1.5, 2.4)	-1.4	-1.3	(-3.3, 0.6)	-2.2	-2.2	(-4.6, 0.1)
24	-3.3	-1.4	1.9	(0.1, 3.7)	-2.7	0.6	(-1.2, 2.4)	-3.7	-0.4	(-2.7, 1.8)

5.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 5. The largest unadjusted lower bound of the 2-sided 90% CI for the mean differences between moxifloxacin and placebo is 10.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.8 ms, which indicates that an at least 5-ms QTcF effect due to moxifloxacin can be detected from the study.

Table 5: Analysis Results of $\Delta\Delta\text{QTcF}$ for Moxifloxacin 400 mg, Day 14

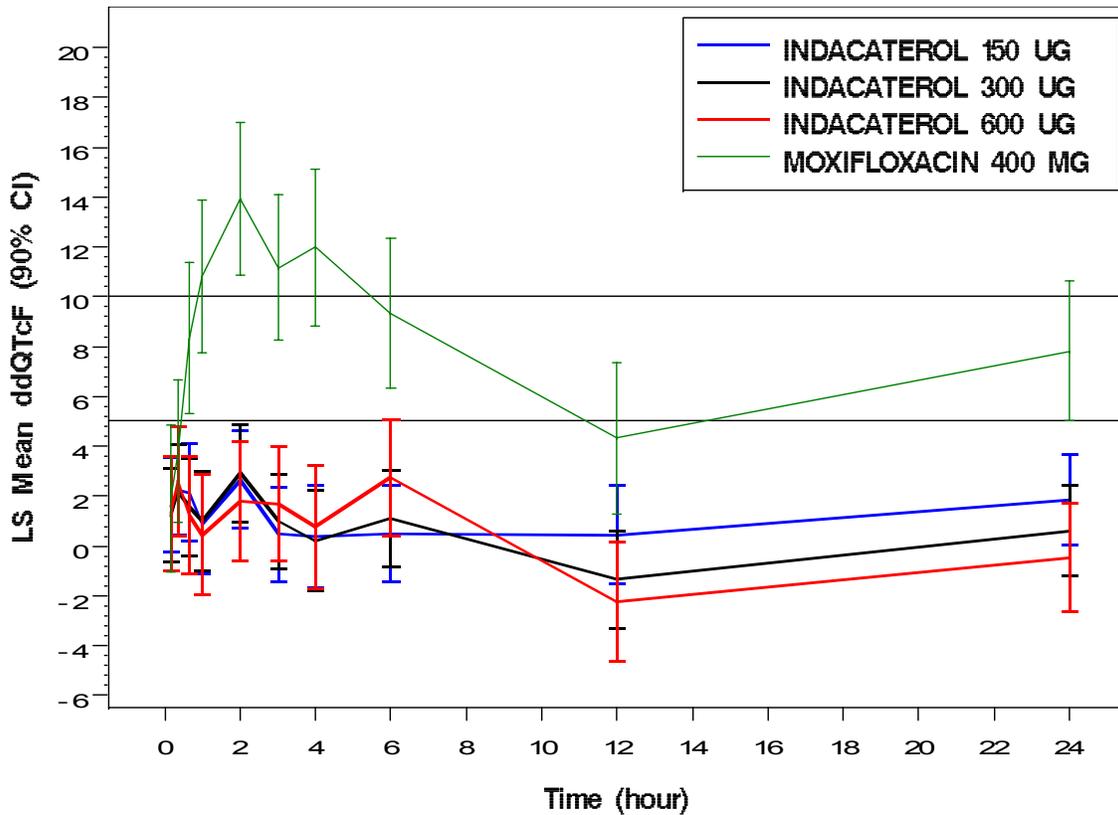
Time (hrs)	Placebo	Moxifloxacin 400 mg			
		ΔQTc	$\Delta\Delta\text{QTc}$		
		LS Mean	LS Mean Diff	90% CI	Adj 90% CI
10 min	1.8	3.7	1.9	(-1.1, 4.8)	(-2.1, 5.9)
20 min	0.9	4.7	3.8	(1.0, 6.6)	(-0.1, 7.7)
40 min	1.7	10.0	8.3	(5.3, 11.4)	(4.2, 12.5)
1	1.8	12.6	10.8	(7.7, 13.9)	(6.6, 15.0)
2	-4.7	9.3	14.0	(10.9, 17.0)	(9.8, 18.1)
3	-5.2	6.0	11.2	(8.2, 14.1)	(7.2, 15.2)
4	-6.7	5.3	12.0	(8.8, 15.1)	(7.7, 16.3)
6	-4.6	4.8	9.3	(6.4, 12.3)	(5.3, 13.4)
12	-0.0	4.3	4.3	(1.3, 7.4)	(0.2, 8.5)
24	-3.3	4.5	7.8	(5.0, 10.6)	(4.0, 11.7)

Bonferroni method was applied for multiple endpoint adjustment for 4 time points

5.1.2.1 Graph of $\Delta\Delta\text{QTcF}$ Over Time

Figure 3 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Time Course



(Note: CIs are all unadjusted including moxifloxacin)

5.1.2.2 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 6: Categorical Analysis for QTcF

Treatment	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
Indacaterol 150 mcg	108	107 (99.1%)	1 (0.9%)
Indacaterol 300 mcg	108	107 (99.1%)	1 (0.9%)
Indacaterol 600 mcg	54	54 (100%)	0 (0.0%)
Placebo	107	106 (99.1%)	1 (0.9%)
Moxifloxacin 400 mg	27	27 (100%)	0 (0.0%)

Table 7 lists the number of subjects as well as the number of observations whose change from baseline ≤ 30 ms, between 30 ms and 60 ms, and > 60 ms. One subject's change from baseline in placebo group was above 60 ms.

Table 7: Categorical Analysis of $\Delta QTcF$

Treatment	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms	Value>60 ms
Indacaterol 150 mcg	108	107 (99.1%)	1 (0.9%)	0 (0.0%)
Indacaterol 300 mcg	108	108 (100%)	0 (0.0%)	0 (0.0%)
Indacaterol 600 mcg	54	54 (100%)	0 (0.0%)	0 (0.0%)
Placebo	107	105 (98.1%)	1 (0.9%)	1 (0.9%)
Moxifloxacin 400 mg	27	26 (96.3%)	1 (3.7%)	0 (0.0%)

5.1.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean difference between indacaterol 150 mcg and placebo, between indacaterol 300 mcg and placebo, and between indacaterol 600 mcg and placebo are 2.0 ms, 2.0 ms and 0.9 ms, respectively. The outlier analysis results for PR interval greater than 200 ms are presented in Table 9.

Table 8: Analysis Results of $\Delta\Delta PR$ for Indacaterol 150 mcg, Indacaterol 300 mcg, and Indacaterol 600 mcg, Day 14

		Treatment Group								
		Indacaterol 150 mcg			Indacaterol 300 mcg			Indacaterol 600 mcg		
		ΔQTc	$\Delta\Delta QTc$		ΔQTc	$\Delta\Delta QTc$		ΔQTc	$\Delta\Delta QTc$	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.17	1.1	-0.3	-1.4	(-2.9, 0.1)	-0.9	-2.0	(-3.5, -0.5)	-2.1	-3.2	(-5.1, -1.4)
0.33	1.0	-0.1	-1.0	(-2.6, 0.5)	-1.0	-2.0	(-3.5, -0.5)	-3.1	-4.1	(-5.9, -2.2)
0.67	1.2	0.4	-0.8	(-2.3, 0.8)	-0.2	-1.4	(-3.0, 0.2)	-1.4	-2.6	(-4.5, -0.7)
1	1.5	0.1	-1.4	(-2.9, 0.1)	-0.4	-1.9	(-3.4, -0.3)	-2.4	-3.9	(-5.8, -2.1)
2	1.5	-0.2	-1.6	(-3.3, 0.1)	0.1	-1.3	(-3.0, 0.4)	-1.6	-3.1	(-5.1, -1.0)
3	0.0	-1.5	-1.4	(-3.1, 0.3)	-0.9	-0.9	(-2.6, 0.8)	-2.9	-2.9	(-5.0, -0.9)
4	-0.8	-2.0	-1.2	(-2.9, 0.5)	-1.9	-1.1	(-2.8, 0.6)	-2.3	-1.5	(-3.5, 0.6)
6	-4.7	-5.7	-1.0	(-2.7, 0.8)	-4.4	0.3	(-1.5, 2.0)	-5.9	-1.2	(-3.4, 0.9)
12	-3.3	-4.3	-1.0	(-2.7, 0.7)	-3.7	-0.4	(-2.1, 1.3)	-6.1	-2.8	(-4.8, -0.7)
24	-0.3	0.1	0.4	(-1.3, 2.0)	-0.1	0.2	(-1.5, 1.8)	-1.8	-1.6	(-3.6, 0.4)

Table 9: Categorical Analysis for PR Intervals

Treatment Group	Total N	PR < 200 ms	PR ≥200 ms
Indacaterol 150 mcg	108	101 (93.5%)	7 (6.5%)
Indacaterol 300 mcg	108	104 (96.3%)	4 (3.7%)
Indacaterol 600 mcg	54	52 (96.3%)	2 (3.7%)
Placebo	107	102 (95.3%)	5 (4.7%)
Moxifloxacin 400 mg	27	27 (100%)	0 (0.0%)

5.1.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean difference between indacaterol 150 mcg and placebo, between indacaterol 300 mcg and placebo and between indacaterol 600 mcg and placebo were 1.0 ms, 1.7 ms and 1sd.9 ms, respectively. There are no subjects who experienced QRS interval greater than 120 ms in indacaterol (150 mcg, 300 mcg and 600 mcg) groups.

Table 10: Analysis Results of $\Delta\Delta$ QRS for Indacaterol 150 mcg, Indacaterol 300 mcg, and Indacaterol 600 mcg, Day 14

		Treatment Group								
		Indacaterol 150 mcg			Indacaterol 300 mcg			Indacaterol 600 mcg		
		Placebo	Δ QTc		$\Delta\Delta$ QTc		Δ QTc		$\Delta\Delta$ QTc	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.17	-0.1	0.1	0.1	(-0.7, 1.0)	-0.2	-0.1	(-1.0, 0.7)	0.1	0.1	(-0.9, 1.2)
0.33	-0.1	-0.1	-0.0	(-0.9, 0.8)	0.0	0.1	(-0.8, 1.0)	0.7	0.8	(-0.3, 1.9)
0.67	0.7	0.6	-0.1	(-0.9, 0.6)	0.7	-0.0	(-0.8, 0.8)	0.7	0.0	(-1.0, 1.0)
1	0.4	0.0	-0.3	(-1.1, 0.5)	0.5	0.1	(-0.7, 0.9)	0.9	0.5	(-0.4, 1.5)
2	1.3	1.2	-0.1	(-1.0, 0.8)	2.1	0.8	(-0.0, 1.7)	1.4	0.1	(-1.0, 1.2)
3	1.0	0.3	-0.7	(-1.6, 0.1)	1.1	0.1	(-0.7, 1.0)	1.5	0.5	(-0.5, 1.5)
4	1.1	-0.0	-1.1	(-2.0, -0.2)	1.0	-0.1	(-1.0, 0.8)	0.9	-0.2	(-1.3, 0.9)
6	1.3	0.6	-0.7	(-1.6, 0.2)	1.1	-0.1	(-1.0, 0.7)	1.3	0.0	(-1.1, 1.1)
12	1.0	0.2	-0.8	(-1.7, 0.1)	0.8	-0.2	(-1.1, 0.7)	0.9	-0.1	(-1.2, 1.0)
24	0.7	0.4	-0.3	(-1.1, 0.4)	0.3	-0.4	(-1.2, 0.3)	0.8	0.1	(-0.8, 1.0)

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The plasma concentration and $\Delta\Delta$ QTcF data were analyzed using a linear mixed effects model. Two linear models were considered: model 1 is a linear model with an intercept and model 2 is a linear model with no intercept. Table 11 summarizes the results of the model and the relationship is shown in Figure 4.

The predicted change in $\Delta\Delta\text{QTcF}$ at peak concentrations for each dose group was computed from the slope and 90% confidence interval of the slope as shown in

Table 12. The slopes for both models are statistically significant but as shown in Figure 4, the predicted line is below 10 ms and the upper bound of 90% CI at C_{max} also is less than 10 ms. These results are consistent with the primary endpoint.

Table 11: Exposure-Response Analysis of Indacaterol associated $\Delta\Delta\text{QTcF}$ Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: $\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \text{Indacaterol Concentration}$		
Intercept (ms)	0.47 (-0.34; 1.29) 0.3403	5.25
Slope (ms per pg/mL)	0.00239 (0.00121; 0.00357) 0.0016	4.22
Residual Variability (ms)	5.93	--
Model 2: $\Delta\Delta\text{QTcF} = \text{slope} * \text{Indacaterol Concentration}$ (No Intercept)		
Slope (ms per pg/mL)	0.00466 (0.00222; 0.0071) 0.002	16.39
Residual Variability (ms)	6.48	--

Figure 4: $\Delta\Delta\text{QTcF}$ vs. Indacaterol concentration

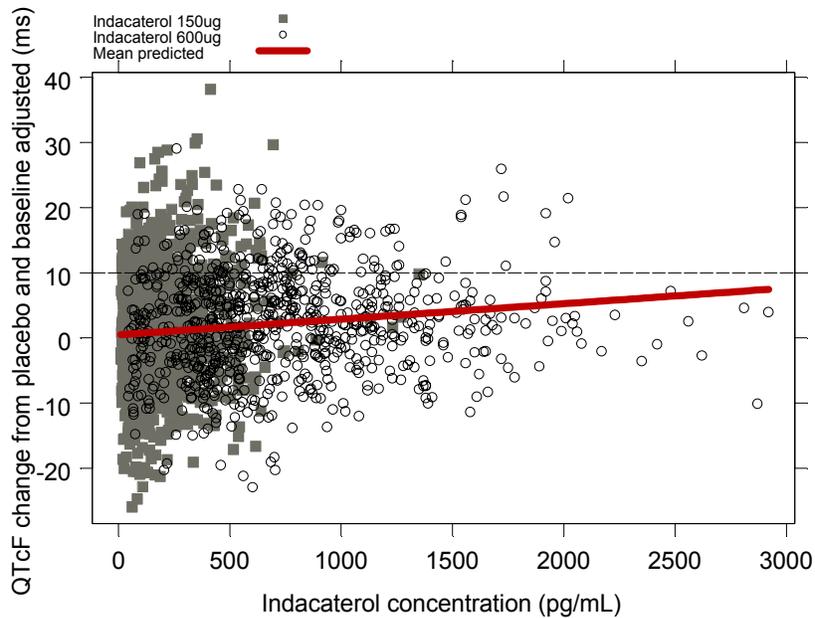


Table 12: Predicted Change of $\Delta\Delta$ QTcF Interval at Mean Peak Indacaterol Concentration using Model 1

Dose Group	Predicted change in $\Delta\Delta$ QTcF interval (ms)	
	Mean	90% Confidence Interval
Indacaterol 150 mcg		
Mean C_{max} (376 pg/mL)	1.37	(0.567; 2.17)
Indacaterol 600 mcg		
Mean C_{max} (1520 pg/mL)	4.11	(2.38; 5.85)

5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines, i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

Four cases of vasovagal syncope were reported, 3 in the indacaterol 300 μ g arm and one in the placebo arm.

5.3.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistic 93% of the ECGs were annotated in the primary lead II, with less than 0.05% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.3.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Absorption

The median time to reach peak serum concentrations of indacaterol was approximately 15 minutes after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 mcg to 600 mcg) in a dose proportional manner. Absolute bioavailability of indacaterol after an inhaled dose was on average 43%. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to (b) (4) days. The mean accumulation ratio of indacaterol, i.e. AUC over the 24-hour dosing interval on Day 14 compared to Day 1, was in the range of 2.9 to 3 (b) (4) for once-daily inhaled doses between (b) (4) mcg and 600 mcg.

Distribution

After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1-95.3% and 95.1-96.2%, respectively.

Metabolism

After oral administration of radiolabelled indacaterol in the human ADME study unchanged indacaterol was the main component in serum, accounting for about 1/3 of total drug-related AUC over 24 hour. A hydroxylated derivative was the most prominent metabolite in serum. (b) (4) phenolic O-glucuronide of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol.

In vitro investigations indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

Elimination

In clinical studies which included urine collection the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.2 L/h. When compared with the serum clearance of indacaterol of 23.3 L/h, it is evident that renal clearance plays a minor role (about 2 to (b) (4)% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with $\geq 90\%$ of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 5 (b) (4) hours which is consistent with the observed time-to-steady state of approximately 12- (b) (4) days.

Special Populations

A population pharmacokinetic analysis was performed for indacaterol utilizing data from 3 controlled clinical trials that included 1,844 patients with COPD aged 40 to 88 years who received treatment with Arcapta (b) (4)

A population analysis (b) (4) the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated (b) (4) did not suggest any difference between ethnic subgroups in this population.

Hepatic Impairment

Patients with mild and moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Renal Impairment

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

6.2 TABLE OF STUDY ASSESSMENTS

Assessment schedule

Study	Phase	Visits Numbers	Screen V 1	Baseline V 2	Treatment															Visit 777				
					V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	D 1	D 2	D 3	D 4	D 5	D 6		D 7	D 8	D 9	D 10
			Days - 21 to -2	Day -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	EOS				
Inclusion/Exclusion Criteria			X	X ²																				
Relevant Hx/Current Medical Conditions			X	X ²																				
Demography			X																					
Physical examination			X	X																X				
Alcohol test, Drug/Urine Cotinine screen			X	X																				
HIV, Hepatitis screen			X																					
Pregnancy test			X	X																X				
Practice using Inhaler				X																				
Drug administration (randomized Day -1)					←-----X-----→																			
Meal record				D -2, -1																X	X			
Study completion info																					X			
Comments			←-----As required-----→																					
Vital signs, body measurements																								
Body height			X																					
Body weight			X	X																	X			
Body temperature			X	X																	X			
Supine BP, Pulse rate			X ³	X ³	X ⁴	X ⁵	X ²					X ⁵					X ⁸	X	X					
ECG evaluation			X	X ^{7,8}	X ^{7,8}	X	X	X			X						X ^{7,8}	X ⁷	X					

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22383	ORIG 1	NOVARTIS PHARMACEUTICA LS CORP	INDACATEROL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOANNE ZHANG
08/19/2009

MOH JEE NG
08/20/2009

MONICA L FISZMAN
08/20/2009

JOO YEON LEE
08/20/2009

CHRISTINE E GARNETT
08/20/2009

NORMAN L STOCKBRIDGE
08/21/2009

Executive CAC**Date of Meeting:** August 4, 2009**Committee:** David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Todd Bourcier, Ph.D., DMEP, Alternate Member
Jean Wu, M.D., Ph.D., DPAP, Team Leader
Tim Robison, Ph.D., DPAP, Presenting Reviewer**Author of Draft:** Tim Robison, Ph.D., DPAP**The following information reflects a brief summary of the Committee discussion and its recommendations.****NDA #** 22-383**Drug Name:****Trade name:** Arcapta™ (b) (4)™**Generic name:** Indacaterol maleate inhalation powder**Code name:** QAB-149**Sponsor:** Novartis Pharmaceuticals Corporation**Background:**

QAB149 was not genotoxic as assessed by negative results in the *in vitro* assays, Ames and chromosomal aberration (Chinese hamster cells) and in the *in vivo* assay, bone marrow micronucleus (rat). The carcinogenic potential of QAB149 was assessed in a 24-month inhalation oncogenicity study in Sprague-Dawley rats and a 26-week oral (gavage) carcinogenicity study with CB6F1/TgrasH2 hemizygous mice.

Rat Carcinogenicity Study

Rats in the control-1, control-2, low dose, mid dose, and high dose groups were exposed to achieved inhalation doses of 0, 0, 0.21, 0.62, and 2.09 mg/kg/day, respectively. The route was the same as that used in the clinical setting. The duration of treatment was at least 104 weeks, which is acceptable.

There were no treatment-related effects on survival. Absolute body weights of males in the high dose group on days 546 and 728 were decreased to 88.26 and 86.15% of the pooled control, respectively. Decreased absolute body weight for males in the high dose group appears to indicate that a MTD was achieved for males.

Potential treatment-related non-neoplastic findings were observed in the heart, nasal cavity, lung, larynx, thymus, ovaries, testes, epididymides, pancreas, and eye. Non-neoplastic findings were also observed in the eye that might be attributed to animal housing conditions. Findings in the heart and ovaries appear to be characteristic of β_2 -adrenergic agonists. Findings in the testes and epididymides may also be characteristic of β_2 -adrenergic agonists. Findings in the nasal cavity,

larynx, and lung might be related to irritation associated with nose-only administration of QAB149.

Potential treatment-related neoplastic findings were evident in the pituitary gland and ovary.

In the pituitary gland, combined incidences of adenoma and carcinoma were increased for all male treatment groups and females in the high dose group. For males, the combined incidences of adenoma and carcinoma were statistically significant by pairwise comparison for the mid and high dose groups. For females, the combined incidence of adenoma and carcinoma was statistically significant by trend test and statistically significant by pairwise comparison for the high dose group. The historical control mean and range of pituitary adenoma in male and female Wistar rats were reported to 27.74% (18.0-58.3%) and 54.89% (42.0-68.0%), respectively (Fundamental and Applied Toxicology 22: 65-72, 1994). From (b) (4) (2003), the mean incidences of pituitary adenoma and carcinoma in male Wistar rats were 31.89% (21.82-50.91%) and 0.54% (0.00-3.63%), respectively. From (b) (4) (2003), the mean incidence of pituitary adenoma in female Wistar rats was 46.90% (1.67-61.82%). The findings in the present study appear to be within the published historical control range.

In the ovaries, leiomyoma was observed for 2 of 49 females in the high dose group. There were no findings in the low and mid dose groups. This tumor finding was statistically significant by trend test, but negative by pairwise comparison. It was noted that ovarian leiomyomas have been previously reported for other beta-adrenergic agonist drugs at much higher incidences, and are considered of limited relevance to human risk.

Tg.rasH2 Mouse Carcinogenicity Study

QAB149 was administered by oral gavage to male and female CB6F1/Jic-TgrasH2@Tac hemizygous mice at doses of 0, 100, 300 and 600 mg/kg/day of base and to male and female CB6F1 wild-type mice at doses of 0 and 600 mg/kg/day of base for at least 26 weeks. An additional group of CB6F1/Jic-TgrasH2@Tac hemizygous mice received 75 mg/kg N-methyl-N-nitrosourea, as an intraperitoneal injection on day 1 only, and served as a positive control. The sponsor used doses of QAB149 recommended by the ECAC (see meeting minutes dated December 17, 2003). The duration of treatment was at least 26 weeks, which is acceptable.

Deaths or moribund sacrifices of 1 transgenic female in the 300 mg/kg/day group and 1 transgenic male and 3 transgenic females in the 600 mg/kg/day group were potentially treatment-related. Moribund sacrifices of 1 wild-type male and 1 wild-type female in the 600 mg/kg/day group were potentially treatment-related. Other deaths and moribund sacrifices were attributed to oral gavage errors.

Based upon examination of body weight curves, body weight gains appeared to be lower for the three transgenic male QAB149 treatment groups; however, body weight gains were unaffected for the three transgenic female QAB149 treatment groups.

Deaths at 300 and 600 mg/kg/day as well as decreased body weights for males at all doses suggest that a MTD was achieved and possibly exceeded in the study.

QAB149 treatment-related histopathological findings were primarily evident in the stomach and kidneys.

Uterine endometrial stromal polyps were observed for 3 of 25 females in the 600 mg/kg/day group. This tumor finding was statistically significant by trend test, but negative by pairwise comparison. It was noted that in a 2-year carcinogenicity study with mice that received another β 2-adrenergic agonist, uterine endometrial stromal polyps were observed at a much higher incidence.

There were neoplastic findings for MNU-treated mice in several tissues.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was adequate, noting prior Exec CAC protocol concurrence.
- The Committee found that the study was negative for statistically significant increases in neoplasms, although there was an increased incidence of ovarian leiomyomas in high dose females. It was noted that this is a rare tumor in rats and has been found with other β 2-adrenergic agonists at much higher incidences (i.e., class effect), and is considered of limited relevance to human risk. The increased incidence of ovarian leiomyomas found in the present study did not reach the level of statistical significance.
- Pituitary tumors found in this study were statistically significant; however, the incidence was found to be within the historical control range and thus, considered to be unrelated to treatment.

Mouse:

- The Committee agreed that the study was adequate, noting prior Exec CAC protocol concurrence.
- The Committee found that the study was negative for statistically significant increases in neoplasms, although the study did show a positive trend in females for uterine endometrial stromal polyps. It was noted that this tumor has been observed before in mice treated with another β 2-adrenergic agonist.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/NDA 22-383Division File, DPAP

/JWu, DPAP

/VWhitehurst, DPAP

/TRobison, DPAP

/CHill, DPAP

/ASeifried, OND IO

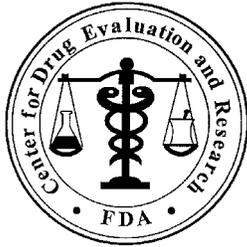
Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22383	----- ORIG 1	-----	----- INDACATEROL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADELE S SEIFRIED
08/05/2009

DAVID JACOBSON KRAM
08/05/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 18, 2009

To: Badrul Chowdhury, MD, Director
Division of Pulmonary and Allergy Products

Thru: Melina Griffis, R.Ph, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, R.Ph, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Arcapta TRADEMARK (Indacaterol Maleate Inhalation Powder)
150 mcg and 300 mcg

Application Type/Number: NDA # 22-383

Applicant/Applicant: Novartis Inc.

OSE RCM #: 2009-137

CONTENTS

EXECUTIVE SUMMARY	3
1 BACKGROUND.....	3
1.1 Introduction.....	3
1.2 Regulatory History	3
1.3 Product Information	3
2 METHODS AND MATERIALS	3
3 RESULTS.....	4
3.1 Do not Swallow statement	4
3.2 Lack of differentiation	4
3.3 Package Insert Labeling/Medication Guide.....	4
4 DISCUSSION	4
4.1 Presentation of “FOR ORAL INHALATION ONLY. Do not swallow capsule” Warning.....	4
4.2 Lack of Differentiation Between Product Strengths	5
4.3 Confusing Graphic	5
4.4 Extraneous Information.....	5
4.5 Medication Guide.....	5
5 CONCLUSIONS and RECOMMENDATIONS.....	6
5.1 Comments to the Division	6
5.2 Comments to the Applicant.....	6
APPENDICES	8

EXECUTIVE SUMMARY

Our evaluation of the Arcapta TRADEMARK labels and labeling noted areas of needed improvement that could be made to the blister label, carton labeling and package insert/Medication Guide labeling to minimize confusion and to increase readability of information presented on the label/labeling. Additionally, the term (b) (4) is not acceptable and should be removed from all labels and labeling in reference to the proprietary name. The revisions should be addressed prior to drug approval. The recommendations are provided in Section 5.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Applicant, Novartis, to review the container labels, carton and insert labeling/Medication Guide for NDA 22-383. DMEPA has conducted a review of the proposed name, Arcapta (b) (4) for this NDA under OSE review # 2008-2047, and found the (b) (4) component of the name unacceptable.

1.2 REGULATORY HISTORY

The NDA, along with the proposed proprietary name, label and labeling, were submitted December 15, 2008 to the Agency. The Applicant has three other INDs (48,649, 66,337, 69,754) in house currently under review for indications other than COPD.

1.3 PRODUCT INFORMATION

Arcapta TRADEMARK contains the active ingredient Indacaterol Maleate and the device/inhaler which allows for the oral inhalation of Indacaterol Maleate. Arcapta TRADEMARK is indicated for the long term maintenance treatment of chronic obstructive pulmonary disease. (b) (4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-

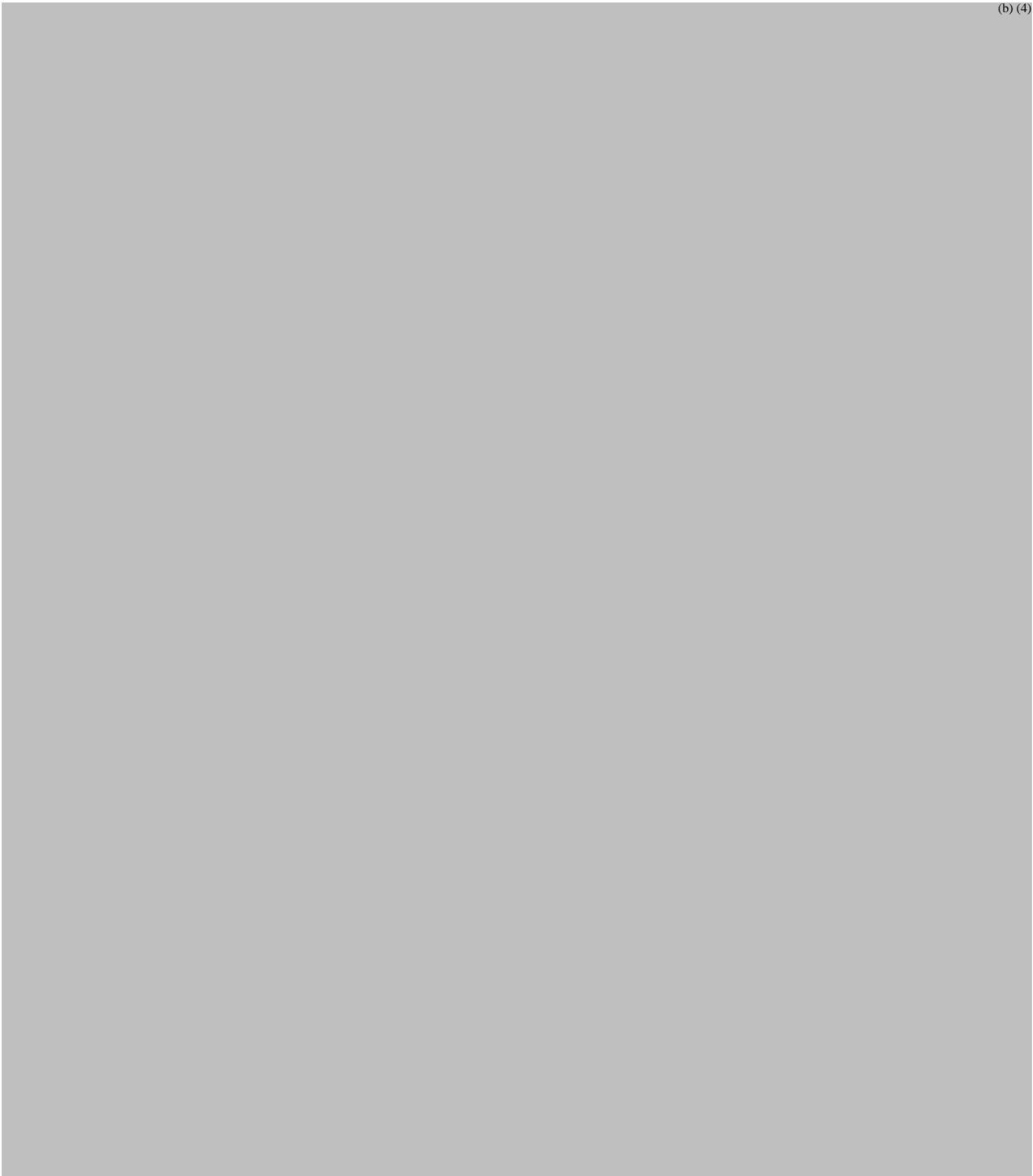
¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on December 15, 2008. See Appendices A through C for pictures of the labels and labeling.

(b) (4)



**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Anne Crandall
6/18/2009 02:52:55 PM
DRUG SAFETY OFFICE REVIEWER

Melina Griffis
6/18/2009 03:17:27 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/18/2009 04:04:04 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/18/2009 04:19:13 PM
DRUG SAFETY OFFICE REVIEWER