CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22383 SUPPL # HFD #

Trade Name Arcapta Neohaler

Generic Name indacataerol maleate

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known July 1, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Carol Hill, M.S.
Title: Regulatory Health Project Manager, Division of Pullmonary, Allergy, and Rheumatolog Products
Date: July 1, 2011

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Director, Division of Pulmonary, Allergy, and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
07/01/2011

BADRUL A CHOWDHURY
07/01/2011

NDA 22-383

Indacaterol Maleate (QAB149)

Debarment Certification

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Ting Chen, MS, Director
Drug Regulatory Affairs

12/3/08
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22383 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Arcapta Neohaler Established/Proper Name: indacaterol maleate Dosage Form: inhalation powder		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):
RPM: Carol F. Hill		Division: Pulmonary, Allergy, and Rheumatology Products

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions • Proposed action • User Fee Goal Date is July 1, 2011	☒ AP ☐ TA ☒ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR October 16, 2009
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☒ Communication Plan ☐ ETASU ☐ REMS not required Comments:	
❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	July 5, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP July 1, 2011 75 mcg CR July 1, 2011 150 mcg CR October 16, 2009 150/300 mcg
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	July 1, 2011
• Original applicant-proposed labeling	RS October 1, 2010 Ori December 15, 2008
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	July 1, 2011
• Original applicant-proposed labeling	RS October 1, 2010 Ori December 18, 2009
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	June 24, 2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	AP February 15, 2011 AP July 23, 2009 NAP March 18, 2009 Reviews April 14, 2011 February 4, 2011 July 9, 2009 March 11, 2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM May 5, 2011, September 23, 2009 ☒ DMEPA February 4, 2011, June 18, 2009 ☒ DRISK May 2, 2011, August 6, 2009 ☒ DDMAC May 11, 2011 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	February 2, 2009 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC August 26, 2011 If PeRC review not necessary, explain: Indication is COPD • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	June 30, 29, 23, 21, 16, 8 and 7, May 23, April 25, March 29 and 22, February 24, 18 and 16, and January 12, 2011; December 28, 20, 16 and 8, November 5, October 7, September 1, February 3 and 2, 2010; December 24, November 23, October 30, September 11, July 31, May 29, April 24, 11 and 2, March 23, 13 and 11, February 27, and January 8, 2009
❖ Internal memoranda, telecons, etc.	June 27, 2011
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg November 24, 2009
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg May 6, 2008 April 7, 2008
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg October 10, 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	CAC August 4, 2009
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	March 8, 2011
• 48-hour alert or minutes, if available *(do not include transcript)*	Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None July 1, 2011 Octobe 16, 2009
Division Director Summary Review *(indicate date for each review)*	☐ None July 1, 2011 October 16, 2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None June 30, 2011 March 1, 2011 September 29, 2009
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	June 8, 2011 April 12, and 4, 2011 February 15, 2011

[5] Filing reviews should be filed with the discipline reviews.

	September 25, 2009 (S/U) August 25, 2009 February 27, 2009 F/P
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	thics & Good Clinical Practices fo Clin. Rev. February 15, 2011 and August 25, 2009
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Ethics June 28, 2011 DSI Human Subjects Protection Team May 19, 2011 QT IRT August 21, 2011
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	REMS Doc/Supporting Statement June 23, 2011 (Amendment) June 10, 2011 (Amendment) April 22, 2011 (Amendment) October 1, 2010 (Resubmission) December 15, 2008 (Original) REMS MEMOS July 1, 2011 October 15, 2009 ☐ None July 1, 2011 June 16, 2011 March 18, 2011 August 6, 2009
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested June 7, 2011 April 8 and 5, February 28 and 16, 2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None September 8, 2009
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None September 4, 2009
Statistical Review(s) *(indicate date for each review)*	☐ None February 11, 2011 September 4, 2009

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None September 9, 2009
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None June 15, 2011 February 15, 2011 August 25 and February 20, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None February 28, 2011 October 16, 2009 September 9, 2009
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None February 16, 2011 August 25, 2009 August 12, 2009 March 19, 2009 February 12, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None CMC January 15 ,2009
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc August 5, 2009
❖ ECAC/CAC report/memo of meeting	☐ None August 5, 2009 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None September 3, 2009
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None March 15, 2011 February 23, 2011 January 14, 2011 December 20, 2010 November 18, 2010 October 14, 2009 July 17, 2009 March 8, 2009 February 17, 2009
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None PT March 19, 2009

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	July 19, 2009
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: March 14, 2011 October 13, 2009 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

CAROL F HILL
07/05/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: Jun. 30, 11

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Revisions VII

Total no. of pages including cover: 20

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 24, 2011, submission and the June 28, 2011 teleconference. We also refer to the June 28, 29, and 30 emails and our teleconference on June 30, 2011. We have included track changes in the attached physician insert. Insertions are underlined and deletions are strike-outs. Submit revised labeling on June 30, 2011.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

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

Drafted by: CHill/June 30, 2011
Clearance: Barnes/June 30, 2011
Michele/June 30, 2011
Finalized: CHill/June 30, 2011

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/s/

CAROL F HILL
06/30/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Additional Labeling Comments and Revisions VI

Total no. of pages including cover: 20

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 24, 2011, submission and the June 28, 2011 teleconference. In the attached package insert, we have additional edits to sections 12.2 and 14. To distinguish these revisions, we have highlighted the changes made. We ask that you submit these changes along with your final labeling changes by 12:00 pm on June 30, 2011.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

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

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Finalized: CHill/June 29, 2011

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/s/

CAROL F HILL
06/29/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Comments and Revisions VI

Total no. of pages including cover: 29

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 24, 2011, submission and the June 28, 2011 teleconference. We have included track changes in the attached physician insert and the medication guide. The insertions are underlined and the deletions are marked-up. Additionally, we request that you update page one of your REMS document to include the following information to be listed below the established name of the drug: class of product per label and the applicant's name and address. Be advised that additional labeling comments and revisions may be forthcoming. Submit revised labeling by 12:00 pm on June 30, 2011.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

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

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Finalized: CHill/June 29, 2011

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/s/

CAROL F HILL
06/29/2011

MEMORANDUM

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

DATE: June 27, 2011

TO: Ann Shea, Director, Drug Regulatory Affairs, Novartis Pharmaceuticals Corporation

FROM: Carol F. Hill, M.S., Senior Regulatory Health Project Manager, Division of Pulmonary, Allergy, and Rheumatology Products

SUBJECT: Applicant's Request for Information

APPLICATION/DRUG: NDA 22383/Arcapta Neohaler

On June 14 2011, Novatis requested that the FDA Pharmacometrics Team provide the code and data used for their presentation at the May 31, 2011 meeting. In response to their request, we provided on June 27, 2011, via email, 3 SAS files which includes the data requested.

Attachment:
Email Correspondence

From: Wang, Yaning
Sent: Wednesday, June 22, 2011 4:03 PM
To: Hill, Carol; Gobburu, Jogarao V
Cc: Michele, Theresa; Lee, Joo-Yeon (CDER)
Subject: RE: Pharmacometrics Request

Attachments: metaArchival.sas; quartileAnalysisArchival.sas; simulationDay15.sas; Readme.pdf

Carol:
Attached is the requested information by the sponsor.
Thanks
Yaning

Yaning Wang, Ph.D.
Associate Director for Science
Division of Pharmacometrics
Office of Clinical Pharmacology
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 301-796-1624
Email: yaning.wang@fda.hhs.gov

From: Hill, Carol
Sent: Wednesday, June 15, 2011 7:09 AM
To: Gobburu, Jogarao V; Wang, Yaning
Cc: Michele, Theresa
Subject: FW: Pharmacometrics Request

Good Morning:

Please see the attached email. Novartis has requested the code and data used by Pharmacometrics for the May 31, 2011, presentation.

^j^*Carol*

From: ann.shea@novartis.com [mailto:ann.shea@novartis.com]
Sent: Tuesday, June 14, 2011 5:01 PM
To: Hill, Carol
Subject: Pharmacometrics Request

Hi Carol,

We would like to request the code and data used by the FDA Pharmacometrics group for the analysis presented at the meeting on May 31, 2011, as we would like to understand the FDA's analysis and approach to help us with future projects.

Best regards,

Ann Shea
Novartis Pharmaceuticals Corporation
PH, DRA-RTM
USEH, 405-3071
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA
Phone: +1 862 778-4567
Email : ann.shea@novartis.com

Drafted by: CHill/June 24, 2011
Clearance: Barnes/June 27, 2011
Wang/June 24, 2011
Finalized: CHill/June 27, 2011

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/s/

CAROL F HILL
06/27/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 23, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – Carton/container Labeling Comments and Revisions

Total no. of pages including cover: 3

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 21, 2011, submission regarding carton and container labels.

We have the following labeling comments:

1. We recommend that you put an imprint of the product name or number on the capsule in addition to the logo to address both concerns for safety and linkage to the device. Based on the usability study results, the product name would be the best linkage for correct capsule and device identification; however, we agree that if the font size cannot be large enough to read, the product name on the capsule is of little use to the patient. However, we would like to point out that the imprint on the capsule serves more than linkage purposes. According to 21 CFR 206.10, inclusion of a letter or number in the imprint, while not required, is encouraged as a more effective means of identification than a symbol or logo by itself. In the case of accidental ingestion, an imprint which includes numbers and letters can help rapidly identify the product, which is helpful in determining the proper response.

2. Present the words ‘Arcapta’ and ‘Neohaler’ in the same (b) (4) color. We do not agree that Arcapta and Neohaler should be presented in two different colors. We consider presenting both components of the name in the same color and font as one way to communicate that both 'Arcapta' and 'Neohaler' represent the whole product and therefore should be used together. By presenting Arcapta and Neohaler in two different colors, practitioners and patients may assume that 'Neohaler' is not part of the name and drop the 'Neohaler' component during prescribing of the drug product or consultation about the product. Additionally, presenting the product and device in the same color mimics other currently marketed products with similar configurations, such as Foradil Aerolizer.

Provide revised carton and container labeling by COB on, June 24, 2011. If you have any questions, please call Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.

Drafted: Michele/June 22, 2011

Clearance: Barnes/June 23, 2011

Finalized; CHill/June 23, 2011

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/s/

CAROL F HILL
06/23/2011

Food and Drug Administration
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FACSIMILE TRANSMITTAL SHEET

DATE: June 21, 2011

To: Ann Shea Sr. Assoc. Dir., Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – Labeling Comments and Revisions IV

Total no. of pages including cover: 33

Comments: Please confirm receipt.

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010, submissions, and have taken into account your comments in the June 14, 2011, teleconference and June 15, 2011, submission. Track changes from the previous version of the label (PI) faxed, on June 7, 2011 and the Medication Guide faxed, on June 8, 2011 are included. Insertions are underlined and deletions are marked-up. We ask that you respond to all revisions noted in this version of each.

In addition, we have the following labeling comments:

- We have taken into consideration your comments regarding off-label use in asthma and have made revisions to the Boxed Warning and Contraindications. Submit an updated REMS document to reflect these changes.

- Because the meta-analysis for respiratory-related events was conducted post-hoc and there are inherent complexities and assumptions related to its conduct and statistical analysis, it is used primarily for exploratory purposes. As such, we have removed the meta-analysis from the PI.

Provide revised labeling by COB on June 23, 2011. If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

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

Drafted by: Michele/June 20, 2011
Clearance: Barnes/June 21, 2011
Finalized: EChung-Davies for CHill/June 21, 2011

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/s/

EUNICE H CHUNG-DAVIES
06/21/2011
on behalf of Carol Hill

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 16, 2011

To: Ann Shea, Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Comments and Revisions III

Total no. of pages including cover: 26

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010, submissions. We are also reviewing the proposed labeling submitted on June 9, 2011, in response to our June 7 and 8 labeling comments. We have the following comments pertaining to the carton and container labeling and dosing device. We have included revisions to the enclosed package insert and medication guide, insertions are underlined and deletions are in strike-out. Please provide revised labeling incorporating the comments and revisions listed below by COB on Monday, June 20, 2011.

Carton and container labeling comments

A. General Comment

1. We note that you are 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.

B. Capsules

2. Imprint the actual drug name 'Arcapta' 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 reduce the risk of using this capsule in another device.

C. Blister Labels

3. We recommend utilizing the same color for the blister label as your proposed device and bolding 'Arcapta Neohaler' so that there is better visual differentiation between Arcapta Neohaler blister labels and blister labels from other marketed products.
4. As currently presented the Arcapta Neohaler blister labels are in two different orientations and must be flipped in order to read the labels. Revise the blister labels so that they are presented in the same orientation for increased readability.
5. 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. These statements should be highlighted but not boxed.

6. 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).
7. Remove the NDC number from the sample blister label.

D. Carton Labeling

8. 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.
9. Revise the 'Dosage' statement to read, 'Usual dosage: See Prescribing Information".
10. Relocate the statement, 'Each capsule contains…', from the principal display panel displays to the back panel in order to have the most important information prominently displayed on the principal panel.

E. Neohaler Dosing Device

11. 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.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

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

Drafted by: CHill/June 16, 2011
Clearance History: Barnes/June 16, 2011
Michele/June 15, 2011
Finalized: CHill/June 16, 2011

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/s/

CAROL F HILL
06/16/2011

Food and Drug Administration
Center for Drug Evaluation and Research
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FACSIMILE TRANSMITTAL SHEET

DATE: June 8, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 - REMS II and Labeling Revisions and Comments: Medication Guide

Total no. of pages including cover: 13

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

In our correspondence dated, June 7, 2011, we note that one of the labeling pieces, the medication guide was not attached to the document as stated. Please see the attached medication guide.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Enclosure:
Medication Guide

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CAROL F HILL
06/08/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 7, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 301-862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383- REMS II and Labeling Comments and Revisions

Total no. of pages including cover: 42

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

We are reviewing the label in your October 1 and December 15, 2010, submissions. We are also reviewing the proposed REMS submitted on May 18, 201, in response to our April 25, 2011 REMS comments and revisions. We have the following comments and revisions to the attached package insert, medication guide and REMS. Insertions are underlined and deletions are in strike-out. Only the changes included since our April 25, 2011 correspondence are tracked. Please provide revised labeling incorporating the revisions and comments listed below by COB on Thursday, June 9, 2011.

Comments pertaining to the Package Insert

1. Modify cross reference fonts/styles such that they are consistent throughout the label. Avoid all capital letters if possible.

2. Modify the font and font size consistent throughout the document.

Comments pertaining to the REMS

1. Please see our track changes to the REMS document, the DHCPL, the Dear Medical Society Letter, and the Web-based materials.

2. Your proposed goals are acceptable.

3. Addition of the COPD Foundation to the list of professional societies is acceptable.

4. Ensure that the boxed warning and the prescribing guidelines are not only consistent with the Arcapta label but are also consistent with the approved Brovana and Perforomist labels.

5. Make sure that your supporting document is updated to be consistent with the REMS document and the appended materials.

6. Deletion of the following prescribing guideline from the REMS document and the DHCPL is not acceptable:

   "All LABA, inlcuding Arcapta Neohaler, are contraindicated in patients with asthma without use of a long-term asthma control."

   This prescribing guideline must be included to be consistent with the Class labeling change for the LABAs.

7. We note that you omitted the following subsections from the section on Patient Counseling (page 16) in the web-based materials (also see our track changes):

- Information for Patients
- Asthma-Related Death
- Acute Exacerbations or Deteriorations
- Appropriate Dosing
- Concomitant Therapy
- Common Adverse Reactions with Beta2-agonists
- Instructions for Administration

Provide language for these sections. We refer you to the Brovana and the Perforomist web-based materials.

8. Your REMS language in the REMS document needs to be consistent with the Class LABA REMS language. Delete the following: (b) (4) and replace with: "from approval of the REMS." See track changes.

9. General Comments: Resubmission Requirements and Instructions:

   - Submit the revised proposed REMS for Arcapta Neohaler with attached materials and the REMS Supporting Document. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

10. Make boxed warning language consistent with the language for the boxed warning in the attached label.

If you have any questions, please contact Carol Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Enclosures:
Package Insert
Medication Guide
REMS

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Drafted by: CHill/June 6, 2011
Clearance History: Barnes/June 7, 2011
Michele/June 6, 2011
Finalized: CHill/June 7, 2011

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/s/

CAROL F HILL
06/07/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments: Please acknowledge receipt and provide your response by COB on May 27, 2011

Document to be mailed: **YES** **xNO**

Your submission dated, May 18, 2011, to NDA 22383, is currently under review. We have the following comments or request(s) for information:

1. Provide all datasets, programs and outputs for your re-analysis which was stated on page 16 of your recent report: "Novartis comments on the FDA review of the integrated dose response analysis".

2. Use the following instructions when submitting the requested information.

    a. Submit all datasets used for model development and validation as SAS transport files (*.xpt).

    b. Provide a description of each data item in a Define.pdf file.

    c. Submit model codes or control streams and output listings as ASCII text files with the (*.txt) file extension.

Provide your response to this request no later than COB on May 27, 2011. If you have any questions, please contact Carol F. Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: CHill/May 23, 2011
Clearance: Lee/May 23, 2011
Wang/May 23, 2011
Gobburu/May 23, 2011
Raggio for Barnes/May 23, 2011
Finalized: CHill/May 23, 2011

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
05/23/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol F. Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Clinical Information Request

Total no. of pages including cover: 4

Comments: Please acknowledge receipt and submit your response by COB on May 26, 2011.

Document to be mailed: YES xNO

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

Please refer to your September 28, 2010, submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009; our labeling fax dated April 25, 2011; and your response to that fax dated May 18, 2011.

Provide the following information previously requested in the April 25, 2011, labeling fax by, Thursday, May 26, 2011.

The Arcapta Neohaler safety database reflects exposure of (b) (4) patients to Arcapta Neohaler at doses of 75 mcg or greater for at least 12 weeks in six confirmatory clinical trials (See Section 14). In these trials, 449 patients were exposed to the recommended dose of 75 mcg for 3 months, and 144 and 583 COPD patients were exposed to a dose of 150 and 300 mcg for one year, respectively. Overall, patients had a mean prebronchodilator forced expiratory volume in one second (FEV1) percent predicted of XXX. The mean age of patients was 64 years, with (b) (4) of patients aged 65 years or older, and the majority (b) (4) was Caucasian. In these six confirmatory clinical trials, XX% of patients treated with any dose of Arcapta Neohaler reported an adverse reaction compared with XX% of patients treated with placebo. The proportion of patients who discontinued treatment due to adverse reaction was XX% for Arcapta Neohaler-treated patients and XX% for placebo-treated patients. The most common adverse reactions that lead to discontinuation of Arcapta Neohaler were COPD and dyspnea.

The most common serious adverse reactions were COPD exacerbation, pneumonia, angina pectoris, and atrial fibrillation, which occurred at similar rates across treatment groups. **[FDA Comment: Fill in the XXX fields in the highlighted sections to reflect trials B2335S, B2354, B2355, B2336, B2346, and B2334.]**

Table 1 displays adverse drug reactions reported by at least 2% of patients (and higher than placebo) during a 3 month exposure at the recommended 75 mcg once daily dose. Adverse drug reactions are listed according to MedDRA (version 13.0) system organ class and sorted in descending order of frequency.

Table 1 Number and frequency of adverse drug reactions greater than 2% (and higher than placebo) in COPD patients exposed to Arcapta Neohaler 75 mcg for 3 months in multiple dose, controlled trials
[FDA Comment: Provide this information in table format for trials B2354 and B2355.]

Additional adverse drug reactions reported in >1% (and higher than placebo) in patients dosed with 150 or 300 mcg for 12 months were as follows: **[FDA Comment: Provide this information from trials B2334 and B2335S/SE.]**

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

If you have any questions, call Carol Hill, Senior Regulatory Health Project Manager, at (301) 796-1226.

Drafted: Michele/May 23, 2011

Clearance: Raggio for Barnes/May 23/2011

Finalized: CHill/May 23/2011

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
05/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR ETHICS CONSULTATION
Adults and Pediatrics

Sara F. Goldkind, MD, MA
Senior Bioethicist, Office of Good Clinical Practice Program,
10903 New Hampshire Avenue, WO32-5110
Silver Spring, MD 20993-0002
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FROM: Sally Seymour, Deputy Director for Safety
Center: CDER
Division: DPARP
Requesting Reviewer Name/Email: Sally Seymour, sally.seymour@fda.hhs.gov
RPM/CSO Name/Email: Carol Hill, carol.hill@fda.hhs.gov

DATE	IND/BLA/IDE NO.	NDA//510(K)/PMA NO.
May 9, 2011		22383

PRODUCT NAME:	PRIORITY CONSIDERATION	PRODUCT CLASSIFICATION	DESIRED COMPLETION DATE
Indacaterol	Yes	LABA	May 19, 2011

SPONSOR: Novartis Pharmaceuticals Corporation

PHASE OF PRODUCT DEVELOPMENT

☐ NONCLINICAL ☐ CLINICAL PHASE: ☐ 1 ☐ 2 ☒ 3 ☐ 4 | POPULATION: ☐ PEDIATRICS ☒ ADULTS

REASON FOR REQUEST

☐ NEW PROTOCOL
☐ NEW CORRESPONDENCE
☐ CLINICAL HOLD
☐ RESUBMISSION
☐ SAFETY/EFFICACY(please explain below)

☒ MEETING
☐ PreIND
☐ End of Phase II
☐ Internal
☐ Sponsor
☐ AC Planning

☐ RESPONSE TO DEFICIENCY LETTER
☐ LABELING REVISION
☐ GUIDANCE DEVELOPMENT
☐ INSPECTION REPORT
☐ SUBJECT OF ADVISORY COMMITTEE MEETING
x OTHER (SPECIFY BELOW):

SUPPORTING INFORMATION FOR CONSULT
(please provide electronic copy if possible)

X PROTOCOL
☐ MEDICAL OFFICIER'S REVIEW(S)
x INFORMED CONSENT DOCUMENTS
☐ MEETING PACKAGE

☐ INVESTIGATOR'S BROCHURE
☐ SUPERVISOR'S REVIEW
☐ OTHER CONSULTATIONS
☐ PEER REVIEW ARTICLES

SPECIFIC ETHICAL QUESTION(S) TO BE ADDRESSED

1. Please comment on the assertion that the trials failed to minimize risks to subjects
2. Please comment on the assertion of inadequate informed consents of subjects
3. Please comment on the use of placebo control in patients with chronic obstructive pulmonary disease (COPD)
4. We also welcome any other comments you may have to aid in responding to the letter from Public Citizen.
5.

COMMENTS/SPECIAL INSTRUCTIONS: Indacaterol is a long-acting beta agonist (LABA) under review (NDA 22383) for bronchodilation in patients with COPD. The PDUFA date is July 1, 2011. 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 (see attached letters).

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 DHHS regulations 45 CFR 46.111(a)(1) and 45 CFR46.116(a)(1) and (2). Please see attached protocols with informed consents. DSI is also reviewing the informed consents for compliance with 21 CFR 50.25. 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. 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.

Please contact us if you have any questions.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sally Seymour	☒ EMAIL ☐ INTER-OFFICE
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
	Carol Hill

11-2517

Jackson, Valerie

From: O'Grady, Jordana
Sent: Thursday, March 17, 2011 3:46 PM
To: Jackson, Valerie
Subject: FW: Letter Regarding Indacaterol
Attachments: 110316_Follow-up letter to FDA on Indacaterol_FINAL.pdf

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From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Wednesday, March 16, 2011 10:05 AM
To: Chowdhury, Badrul A; Woodcock, Janet; Commissioner FDA
Subject: Letter Regarding Indacaterol

Dear Drs. Woodcock, Hamburg, and Chowdhury:

Attached please find a letter regarding the drug indacaterol. Original hardcopies will follow by regular mail. Thank you.

Sincerely,

Michael A. Carome, M.D.
Deputy Director, Health Research Group
Public Citizen
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PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 16, 2011

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Woodcock:

These comments from the Public Citizen Health Research Group are being submitted in follow-up to our testimony presented at the March 8, 2011 meeting of the Food and Drug Administration (FDA) Pulmonary-Allergy Drugs Advisory Committee (PADAC) regarding the drug indacaterol maleate (Arcapta™ Neohaler™).

(1) We urge FDA to (a) reject the March 8 PADAC recommendation to approve indacaterol at a dose of 75 mcg daily, and (b) not approve the New Drug Application for indacaterol – even at the 75 mcg dose – because the lowest dose that provides the desired efficacy at the lowest possible risk in the chronic obstructive pulmonary disease (COPD) population has not been determined.

(2) Further long-term, placebo-controlled, phase 3 studies of indacaterol, in which placebo-control subjects with moderate to severe COPD are randomized to groups that receives substandard (placebo) care for prolonged periods of time, must not be conducted.

FDA Should not Approve Indacaterol, Even at the 75 mcg Dose

Prior FDA Review of Indacaterol

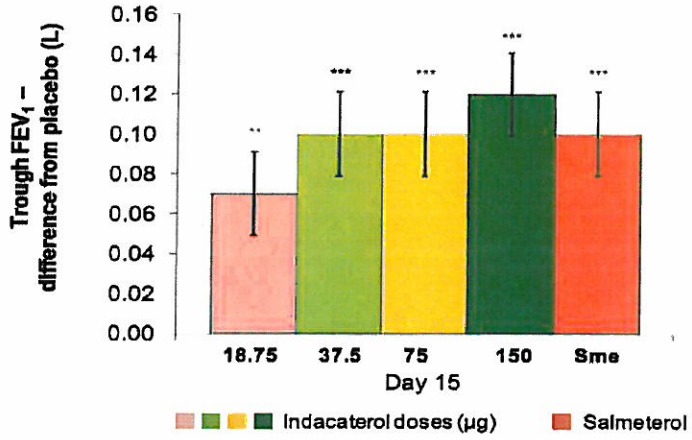
The FDA did not approve Novartis's original application for use of indacaterol at doses of 150 and 300 mcg for COPD because of clinical deficiencies. In particular, the agency concluded that the data submitted did not show meaningful efficacy differences between the proposed doses and a lower dose of 75 mcg, and was concerned about higher frequencies of serious adverse events compared to control subjects in COPD and asthma subjects treated with indacaterol.[1]

The new data submitted by the sponsor and discussed at the March 8 PADAC meeting document the same concerns regarding a possible unfavorable risk:benefit relationship of indacaterol, even at the proposed 75 mcg dose.

Benefit Assessment

For study B2356, a key short-term dose-ranging study in subjects with moderate to severe COPD, the trough FEV1-difference from placebo was identical at the 37.5 and 75 mcg doses (see figure 5-11 below excerpted from Novartis briefing document).[2]

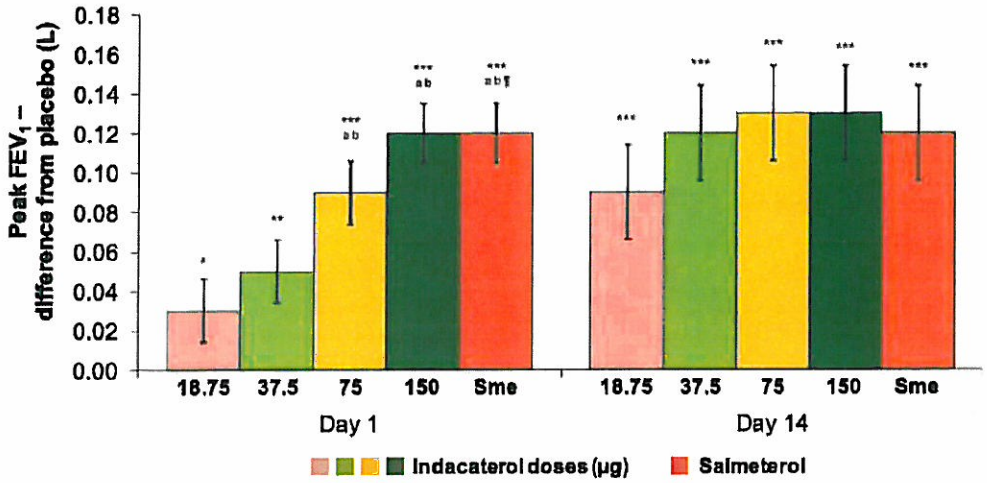
Figure 5-11 Trough FEV_1 (L) at Day 15, B2356, dose-ranging in COPD



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

Also, peak FEV1-difference from placebo in the first 4 hours post the morning dose on day 14 in study B2356 showed no statistically significant differences between the 37.5 and 75 mcg doses (see figure 5-13 below excerpted from Novartis briefing document).[3]

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



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

The FDA review noted the following regarding the comparison of the 75 and 150 mcg doses of indacaterol:

> On cross study comparison, which has limitations, the bronchodilatory effect sizes do not show a clear efficacy advantage of the 150 mcg dose over the 75 mcg dose.[4]

The FDA statistical reviewer also noted the following regarding data comparing different doses of indacaterol in COPD patients:

> [In] study B2356....The dose of 150 mcg appeared to achieve its maximum bronchodilation effect more rapidly than the other doses, but lost its advantage after two weeks of treatment. Considering indacaterol is proposed to be used as a long term maintenance bronchodilator treatment, the 150 mcg dose's rapid effect in day 1 may not be important, especially balancing with safety concerns on higher dose. **From the week 2 data, it appears indacaterol 37.5 mcg, 75 mcg, and 150 mcg once daily worked equally well in terms of bronchodilatory effect.**[5] [emphasis added]

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

Risk Assessment

The phase 3 COPD studies testing indacaterol were not sufficiently powered to detect serious adverse events that may have major adverse public health consequences if the drug is prescribed to millions of COPD patients over many years. Therefore, significant

weight must be given to any signal suggesting safety concerns, particularly since indacaterol is not a breakthrough drug and offers no clinically significant advantages over available FDA-approved long-acting bronchodilators.

Such an adverse safety signal has been identified in the FDA's analysis of data from the sponsor's blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation in all blinded, randomized, controlled trials of 7 or more days of treatment in both asthma and COPD subjects. The FDA medical officer noted the following regarding this data:

> Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, **particularly those that were adjudicated as having been COPD-related,** as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase...is driven primarily by an increase in acute-respiratory related hospitalizations....The possibility that such a signal may exist in COPD rather than asthma **further underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator.**[6] [emphasis added]

The dose versus toxicity-response curve for indacaterol is not yet well-defined, but from a public health standpoint, it is reasonable to assume a 37.5 mcg dose will have a lower probability of serious toxicity than a 75 mcg dose.

One supplementary trial submitted to FDA (study B2341) also revealed concerning adverse safety signals. This study, which randomized 1134 subjects with moderate to severe COPD to indacaterol plus tiotropium or placebo plus tiotropium (an ethically designed study), revealed the following:

> The most frequent adverse event was cough, which occurred more frequently in the combination group (10.4% versus 3.7%)...Likewise, discontinuations due to AEs occurred more frequently in the combination group, with 21 (3.7%) versus 9 (1.6%). There were two on-treatment deaths in the trial, both in the combination group. Cause of death was anaphylaxis 30 minutes after receiving ceftriaxone for a COPD exacerbation and myocardial infarction.[7]

This data is consistent with results of a prior meta-analysis by Salpeter et al which showed that inhaled anticholinergics significantly reduced severe exacerbations and respiratory deaths in patients with COPD, whereas β-agonists were associated with increased risk of respiratory deaths.[8]

Concerns about Indacaterol Use in Patients with Asthma

As the FDA is well aware, once approved for the proposed use in COPD patients, indacaterol will be used off-label in asthmatics. Inhaled long-acting β-agonists (LABAs) have been linked to severe asthma exacerbations and asthma-related deaths.[9] In discussing the safety concerns identified in studies of indacaterol in asthmatic patients, the FDA review noted that:

> The two deaths in patients with asthma while receiving indacaterol with background of concurrent ICS treatment is concerning. The deaths are reminiscent of asthma-related deaths seen with other LABAs.... The possible imbalance of SAEs related to asthma exacerbation further supports the safety concerns for indacaterol.[10]

Recommendations

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

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

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

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

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

Further Long-Term, Placebo-Controlled Trials Testing Indacaterol Must not be Permitted

Standard Treatment for Moderate to Severe COPD

Moderate to severe COPD is a serious, life-threatening illness for which regular use of one or more bronchodilators has been the mainstay of treatment. Since at least 2005, the Global Initiative for Chronic Obstructive Lung Disease, a well-recognized authoritative source for COPD management, has had guidelines stating that "regular treatment with one or more long-acting bronchodilators," supplemented with a short-acting β-agonists when needed for acute symptoms and daily inhaled corticosteroids for patients who have frequent exacerbations, should be used to treat moderate to severe COPD.[11]

Six Unethical Studies in Which Placebo-Control Subjects Received Prolonged Substandard Care

Despite sponsor and investigator awareness of these standard COPD treatment guidelines,[12,13] Novartis conducted at least 6 pivotal long-term phase 3, placebo-controlled studies (B2335[14], B2334[15], B2346[16], B2336[17], B2354[18], and B2355[19]) in subjects with moderate to very severe COPD, apparently with the endorsement of the FDA.

These studies were unethical primarily because a total of more than 1700 subjects with a serious, life-threatening disease were assigned to placebo groups that received substandard care for prolonged periods of time ranging from 3 to 12 months. In particular, while placebo subjects were permitted to use daily inhaled steroids and short-acting β-agonists for rescue use, they were not permitted to use any LABAs or short- or long-acting inhaled anticholinergics.

Furthermore, based on available data at the time of study initiation, there appeared to be no reasonable state of uncertainty on the part of the investigators regarding the comparative merits of the indacaterol – or the active FDA-approved long-acting bronchodilators used in three of the long term trials – and placebo. As a result, these studies, particularly the most recent ones and the three that used FDA-approved active comparators, lacked equipoise and were therefore unethical.[20]

As the sponsor stated in its briefing document, "[o]ptimizing bronchodilation is **essential** to the management of COPD"[21] [emphasis added]. Not surprisingly, administration of placebo in place of long-acting bronchodilators clearly did not optimize bronchodilation.

Predictably, in all 6 studies, placebo subjects had worse COPD management based on multiple outcome measures than indacaterol subjects or subjects treated with an FDA-approved active comparator. In addition, an analysis of these studies reveals a trend toward an increased death rate in the placebo subjects (0.64%) versus subjects in all active treatment groups combined (0.21%). An analysis by Novartis of subject deaths for the entire COPD safety population and related control subjects showed a similar trend toward an increased death rate in placebo subjects.[22] Among the causes of the 14 placebo-subject deaths noted by Novartis were cardiac arrest, cardio-respiratory arrest, COPD, multiorgan failure, and myocardial infarction. It is highly plausible that substandard care leading to respiratory failure, hypoxemia, and/or respiratory acidosis contributed to the death of some placebo subjects.

The scientific question of whether indacaterol was better than placebo for treating moderate to severe COPD was not an important or clinically useful question, given the existing state of knowledge about COPD treatment at the time these studies were conducted. Rather, the important question is whether indacaterol is at least as good as currently available bronchodilator therapy.

Recommendations

Further long-term placebo-controlled trials, involving the withholding of standard bronchodilator therapy, must not be conducted in subjects with moderate to severe COPD. Any ongoing such studies should be terminated immediately.

Thank you for taking our comments into account.

Sincerely,

Michael A. Carome, M.D.
Deputy Director

Sidney M. Wolfe, M.D.
Director
Health Research Group

cc: Dr. Margaret A. Hamburg, Commissioner, FDA
Dr. Badrul A. Chowdhury, Director, Division of Pulmonary, Allergy, and Rheumatology Products, Center for Drug Research and Development, FDA

---

[1] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 3. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[2] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 46. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

[3] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 48. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

[4] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 23. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[5] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 262. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[6] Food and Drug Administration. Addendum to the Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 8. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245638.pdf. Accessed March 4, 2011.

[7] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 168.
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[8] Salpeter SR, Buckley NS, and Salpeter EE. Meta-analysis: anticholinergics, but not β-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006;21:1011-1019.
[9] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 5.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[10] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 27.
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[12] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 112.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[13] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[14] Donohue JF, Fogarty C, Lötvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182(2):155-62.
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[16] Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med. 2010;10:11.
[17] Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol *versus* twice daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011; 37:273-279.
[18] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 130-141.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[19] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 111-129.
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[21] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 14.
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[22] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 82.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 16, 2011

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

Kristina Borror, Ph.D.
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

Dear Drs. Menikoff and Borror:

We hereby request that the Office for Human Research Protections (OHRP) conduct a compliance oversight evaluation of the following research studies for any U.S. institution that was engaged in the research and held an applicable Federalwide Assurance at the time the research was conducted:

(1) 26 week efficacy, safety and tolerability study of indacaterol in patients with chronic obstructive pulmonary disease (COPD); sponsor: Novartis; ClinicalTrials.gov identifier: NCT00463567; Novartis study number: B2335;[1,2]

(2) Efficacy and safety of indacaterol in patients with COPD; sponsor: Novartis; ClinicalTrials.gov identifier: NCT00624286; Novartis study number: B2346;[3,4]

(3) 12-week efficacy of indacaterol; sponsor: Novartis; ClinicalTrials.gov identifier NCT01072448; Novartis study number: B2354;[5] and

(4) Comparison of efficacy of indacaterol versus placebo over 12 weeks; sponsor; Novartis; ClinicalTrials.gov identifier: NCT01068600; Novartis study number: B2355.[6]

We allege that each of the above-referenced studies, as conducted, was unethical and failed to satisfy the following requirements of the Department of Health and Human Services regulations at 45 CFR part 46:

(1) 45 CFR 46.111(a)(1): The research as conducted failed to minimize risks to subjects because study design was unsound and unnecessarily exposed subjects to risk. In particular, in each study large numbers of placebo-control subjects with moderate to severe COPD were randomized to a study group that received substandard (placebo) care for up to 3 to 6 months.

(2) 45 CFR 46.116(a)(1) and (2): It is likely that the IRB-approved informed consent process and document failed to adequately describe the procedures involved in the research and reasonably foreseeable risks and discomforts to the subjects with respect to the placebo-control group subjects.

The following discussion provides a detailed overview of the rationale for our allegations.

Failure to Minimize Risks to Subjects

Standard Treatment for Moderate to Severe COPD

Moderate to severe COPD is a serious, life-threatening illness for which regular treatment with one or more long-acting bronchodilators, such as long-acting β-adrenergic agonists (LABAs)(e.g., salmeterol and formoterol) or long-acting anticholinergic agents (e.g., tiotropium), has been the mainstay of treatment for many years. Since at least 2005, the Global Initiative for Chronic Obstructive Lung Disease, a well-recognized authoritative source for COPD management, has had guidelines stating that "regular treatment with one or more long-acting bronchodilators," supplemented with a short-acting β-agonists when needed for acute symptoms and daily inhaled corticosteroids for patients who have frequent exacerbations, should be used to treat moderate to severe COPD.[7]

Six Unethical Studies in Which Placebo-Control Subjects Received Prolonged Substandard Care

Despite sponsor and investigator awareness of these standard COPD treatment guidelines and the importance of optimizing bronchodilation in moderate to severe COPD[8,9], the 6 pivotal, long-term, phase 3, placebo-controlled studies listed in the Table below were conducted in subjects with moderate to very severe COPD, apparently with the endorsement of the FDA (studies B2334 and B2336 were conducted entirely outside the U.S.).

These studies were unethical primarily because a total of more than 1700 subjects with a serious, life-threatening disease were assigned to placebo groups that received substandard care for prolonged periods of time ranging from 3 to 12 months. In particular, while placebo subjects were permitted to use daily inhaled steroids (if already on such steroids at a stable dose at the time of study enrollment) and short-acting β-agonists for rescue use, they were not permitted to use any LABAs or short- or long-acting inhaled anticholinergics or to start inhaled corticosteroids.

Furthermore, based on available data at the time of study initiation, there appeared to be no reasonable state of uncertainty on the part of the investigators regarding the comparative merits of the indacaterol – or the active FDA-approved long-acting bronchodilators used in three of the long term trials – and placebo. As a result, these studies, particularly the most recent ones and the three that used FDA-approved active comparators, lacked equipoise and were therefore unethical.[10]

As the sponsor stated in a briefing document recently submitted to the FDA, "[o]ptimizing bronchodilation is **essential** to the management of COPD" [11] [emphasis added]. Not surprisingly, administration of placebo in place of long-acting bronchodilators clearly did not optimize bronchodilation.

TABLE: Description of Long-Term Randomized, Placebo-Controlled Studies Testing Indacaterol

Study #	Dates of Enrollment	Active Treatment Intervention	# of Placebo Subjects	Duration
B2335[12]	April 07-August 08	Indacaterol 150 mcg (N=416) Indacaterol 300 mcg (N=416) Tiotropium 18 mcg (N=415)	418	6 months
B2334[13]	?-2008	Indacaterol 300 mcg (N=437) Indacaterol 600 mcg (N=425) Formoterol 12 mcg bid (N=434)	432	12 months
B2346[14]	?-2008	Indacaterol 150 mcg (N=211)	205	3 months
B2336[15]	Nov 2007-Jan 2009	Indacaterol 150 mcg (N=330) Salmeterol 50 mcg (N=333)	335	6 months
B2354[16]	?-2010	Indacaterol 75 mcg (N=163	160	3 months
B2355[17]	?-2010	Indacaterol 75 mcg (N-159)	159	3 months

Predictably, in all 6 studies, placebo subjects had worse COPD management based on multiple outcome measures than indacaterol subjects or subjects treated with an FDA-approved active comparator. In addition, an analysis of these studies reveals a trend toward an increased death rate in the placebo subjects (0.64%) versus subjects in all active treatment groups combined (0.21%). An analysis by Novartis of subject deaths for the entire COPD safety population and related control subjects showed a similar trend toward an increased death rate in placebo subjects.[18] Among the causes of the 14 placebo-subject deaths noted by Novartis were cardiac arrest, cardio-respiratory arrest, COPD, multiorgan failure, and myocardial infarction. It is highly plausible that substandard care leading to respiratory failure, hypoxemia, and/or respiratory acidosis contributed to the death of some placebo subjects.

The scientific question of whether indacaterol was better than placebo for treating moderate to severe COPD was not an important or clinically useful question, given the existing state of knowledge about COPD treatment at the time these studies were conducted. Rather, the important question is whether indacaterol is at least as good as currently available bronchodilator therapy.

Inadequate Informed Consent of Subjects

While adequate informed consent would not have been sufficient to make these studies ethical, it is likely that subjects were not informed that they had a 25 to 50% chance of being assigned a substandard treatment regimen for 3 or 6, and that they were almost certainly likely to experience more shortness of breath, more dyspnea on exertion, decreased exercise tolerance, more frequent COPD exacerbations, and an increased risk of death since they would not be receiving the usual standard medical care with regular use of long-acting bronchodilators.

FDA Involvement

It is our understanding that OHRP routinely refers complaints about industry-sponsored clinical trials to FDA for review and action. In this case, it is clear that FDA has a conflict of interest and should not be asked to investigate our allegations because Novartis conducted these placebo-controlled trials with the full knowledge and endorsement of the FDA. Therefore, since FDA is complicit in this unethical research, we urge OHRP to take the lead in investigating our allegations. We acknowledge that OHRP may need FDA's assistance in identifying the U.S. institutions that were engaged in each of the above-referenced studies since, except for study B2335, the citations on ClinicalTrials.gov do not provide the specific names of the research institutions enrolling subjects for each study.

Please note that OHRP may share our complaint letter with identifiers with anyone. We will be posting a copy on our website as well.

We look forward to OHRP's thorough and careful investigation of our allegations. Please contact us if you have any questions or need additional information.

Sincerely,

Michael A. Carome, M.D.
Deputy Director

Sidney M. Wolfe, M.D.
Director
Health Research Group

Enclosures:
(1) ClinicalTrial.gov citations for studies NCT00463567, NCT00624286, NCT01072448, and NCT01068600.
(2) Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182:155-162.
(3) Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomized, 12-week study. BMC Pulm Med. 2010;10:11.

cc: Honorable Kathleen Sebelius, Secretary of Health and Human Services

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[1] ClinicalTrials.gov citation for NCT00463567. http://clinicaltrials.gov/ct2/show/study/NCT00463567?term=b2335&rank=2&show_locs=Y#locn. Accessed March 14, 2011.
[2] Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182:155-162.
[3] ClinicalTrials.gov citation for NCT00463567. http://clinicaltrials.gov/ct2/show/study/NCT00463567?term=b2335&rank=2&show_locs=Y#locn. Accessed March 14, 2011.
[4] Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomized, 12-week study. BMC Pulm Med. 2010;10:11.
[5] ClinicalTrials.gov citation for NCT01072448. http://clinicaltrials.gov/ct2/show/study/NCT01072448?term=b2354&rank=1&show_locs=Y#locn. Accessed March 14, 2011.
[6] ClinicalTrials.gov citation for NCT01068600. http://clinicaltrials.gov/ct2/show/study/NCT01068600?term=b2355&rank=1&show_locs=Y#locn. Accessed March 14, 2011.
[7] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2005-2010 updates. Available at http://www.goldcopd.com/. Accessed March 4, 2011.
[8] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 112. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[9] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[10] Freedman B. Equipoise and the ethics of clinical research. NEJM. 1987;317:141-145.
[11] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 14. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[12] Donohue JF, Fogarty C, Lötvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182(2):155-62.
[13] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β_2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[14] Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med. 2010;10:11.
[15] Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol *versus* twice daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011; 37:273-279.
[16] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 130-141. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[17] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 111-129. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[18] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 82. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

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/s/

CAROL F HILL
05/09/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 25, 2011

To: Ann Shea Sr. Assoc. Dir., Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 301-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Comments and Revisions II

Total no. of pages including cover: 25

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

We are reviewing the label in your October 1 and December 15, 2010 submissions. Additional labeling comments will be forthcoming as we continue to review the labeling. Insertions are underlined and deletions are marked-up. Please note that sections 6 and 14 have been completely rewritten, so track changes are not included. We ask that you respond to all revision noted in this version.

If you have any questions, please contact Carol Hill, Senior Regulatory Project Manager, at 301-796-1226.

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

Drafted by: CHill/April 25, 2011
Clearance: Barnes/April 25, 2011
Buenconsejo/April 18, 2011
Michele/April 18, 2011
Seymour/April 19, 2011
Chowdhury/April 19 & 22, 2011
Finalized: CHill/April 25, 2011

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/s/

CAROL F HILL
04/25/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: March 29, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager carol.hill@fda.hhs.gov
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – REMS Comments and Information Request

Total no. of pages including cover: 16

Comments: Please acknowledge receipt.

Document to be mailed: YES ☑NO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Your resubmitted NDA dated, October 1, 2010, for Arcapta Neohaler is currently under review. The enclosed Risk Evaluation and Mitigation Strategy (REMS) document contains clarification comments for some of the changes made to the proposed REMS. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all inclusive and we may have additional comments as we continue our review. Submit a revised REMS to include the recommendations listed below and incorporate the changes shown in the attached marked up REMS.

If you have any questions, please contact Carol Hill, Regulatory Project Health Manager, at 301-796-1226.

Enclosure: Recommendations to the REMS

1. Goals:

Revise the goals as follows:

- To inform healthcare providers and prescribers of the increased risk of asthma related death and serious outcomes with the long-acting beta-2-adrenergic agonists (LABAs) including Arcapta Neohaler.
- To inform healthcare providers and prescribers of the appropriate use of long acting $beta_2$-adrenergic agonists (LABAs) including Arcapta Neohaler.
- To inform patients that people with asthma who take long-acting $beta_2$-adrenergic agonist (LABA) medicines, such as indacaterol, the active moiety in Arcapta Neohaler, have been associated with an increased risk of death from asthma related events.
- To inform patients of other serious risks associated with Arcapta Neohaler.

2. Medication Guide (MG)

According to the Draft Guidance for Industry titled Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), the Agency has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS, and may decide the Medication Guide should be required as labeling but not part of a REMS. We have determined that a Medication Guide is not required as part of your proposed REMS; therefore, we have removed the MG language (including patient surveys) from the REMS document/DHCPL. Comments on your proposed Medication Guide will be sent separately.

Make sure that that this change is reflected in your Dear Medical Society letter, printed/web materials and the supporting document.

3. Communication Plan

a. Your plan to distribute the DHCPL within 60 days of REMS approval is acceptable.

b. The DHCPL must include the new safety information and the new prescribing guidelines for LABAs; (b) (4)

c. Submit the letter directed to the leadership of the professional societies for review. In addition to the letter, your communication to the professional societies must include a link to the Arcapta Neohaler website. Your distribution plan for this letter is acceptable.

d. Submit the printed or web-based educational materials for review. These materials will be required to be available on the Arcapta Neohaler website within 30 days of REMS approval and remain on the website for 3 years. **We refer you to the recently approved BROVANA and PERFOROMIST REMS communication plan posted on the FDA website to use as an example when drafting these letters/web-based materials.** The content of the print or web-based material for must include at a minimum the following:

- Information about the risk
- Key data regarding the risk (e.g. SMART, SNS)
- New prescribing guidelines
- Currently available LABAs and approved uses
- Prescribing information for Arcapta Neohaler
- Patient Counseling Information
- Questions and Answers
- DHCP Letter (for a period of 1 year)

Some optional pieces could include:

- Resource list of future meetings and peer reviewed journal articles related to LABAs
- Links to FDA Alert(s) for the LABAs

e. Expand your proposed list of the professional societies to include the following:

- The American Academy of Allergy, Asthma & Immunology (AAAAI)
- The American College of Allergy, Asthma & Immunology (ACAAI)
- The American Academy of Family Physicians (AAFP)
- The American Academy of Physician Assistants (AAPA)

f. Include nurse practitioners and physician assistants to your list of targeted healthcare providers.

g. We acknowledge that the October 16, 2009, CR letter specified the REMS assessments at 18 months, 3 years and at 7th year from the REMS approval. The REMS for the class of long-acting beta$_2$-adrenergic agonists (LABAs) requires annual REMS assessments. Therefore, you must submit your revised timetable for submission of assessments no less than annually.

h. Update your REMS supporting document to be consistent with the REMS document and the educational materials.

i. You must include the date of the REMS approval in the REMS document; the date (mm/yyyy) must appear in a header on the top left-hand corner of the first page of the REMS document. For example: Initial REMS Approval: 02/2011

4. Information Needed for Assessment

a. Revise your list of information needed for assessments as follows:

1. An evaluation of the prescriber understanding of the increased risk of asthma related deaths and the safe use of LABAs.
2. A description of specific measures that would be taken to increase awareness if the assessment of the prescribers indicates that the prescribers' awareness is not adequate.
3. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.
4. An annual assessment and conclusions regarding the success of the REMS in meeting the stated goals.
5. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)
6. An assessment of the communication plan including:
   i. The date of launch of the communication plan (DHCPL, website, and communication to professional societies)
   ii. The number of recipients of the DCHP letter distribution
   iii. Date(s) of distribution of the DHCP letter
   iv. A copy of all documents included in each distribution
   v. The professional societies that you communicated with
   vi. The information that the professional societies disseminated to their members and the timing of the dissemination

b. The following comments are on the proposed methodology for the assessment:

We acknowledge that you provided a brief description of the survey methodology and instruments to assess the REMS. We will defer our comment until the full methodology is submitted, but offer the following guidance as you develop your proposal.

Submit for review the detailed plan you propose to use to evaluate prescribers' understanding about the safe use of Arcapta Neohaler at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Arcapta Neohaler.

1. Recruit respondents using a multi-modal approach.
   Explain how often you perform non-respondent follow-up or reminders.
   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.
   Explain how you select recruitment sites.
   Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
3. Define the expected number of prescribers to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
4. Ensure the sample is demographically representative of the population who prescribe the drug, regardless of the condition for which they prescribe it.
5. List the inclusion criteria for prescribers. For example, eligible respondents might be:
   - Has prescribed Arcapta Neohaler at least one time in the past 3 months
   - Not currently participating in a clinical trial involving Arcapta Neohaler

   Submit any screener instruments, and describe any quotas of sub-populations (different medical specialties) used.
6. Explain how you administer surveys and the intended frequency.
   Offer respondents multiple options for completing the survey. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person. Explain how you train surveyors.
7. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
8. Submit for review the introductory text used to inform respondents about the purpose of the survey.
   Tell potential respondents that their answers will not affect their ability to prescribe the drug, and that their answers and personal information will be kept confidential and anonymous.
9. Clarify in your methodology that respondents are eligible for one wave of the survey only.
10. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
    You may stratify the data by any relevant demographic variable, in addition to the presentation in aggregate. Submit with your assessments all methodology and instruments utilized.
11. The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating healthcare providers' knowledge of:
    - the serious risks associated with use of Arcapta Neohaler,
    - how to properly prescribe Arcapta Neohaler,
    - how to properly monitor for the serious risks associated with the use of Arcapta Neohaler;

    The assessment does not assess healthcare providers' comprehension of the educational materials.
    Do not offer respondents an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.
12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

13. Ensure the healthcare provider knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials.
    Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure each question has an "I don't know" answer option.
    Randomize the order of the multiple choice responses on each survey.

14. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions.
    Do not allow respondents the opportunity or ability to go back to previous questions in the survey.
    Explain if and when any education will be offered for incorrect responses.

15. Use the following (or similar) questions to assess receipt and use of the educational materials.

    - Prior to today, which of the following were you aware of or received with regard to Arcapta Neohaler? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	☐	☐
Medication Guide	☐	☐
Dear Healthcare Provider Letter	☐	☐
Something else - please explain:	☐	☐
None of the above	☐	☐

    - Did you read the Full Prescribing Information?
      a) All,
      b) Most,
      c) Some,
      d) None
      e) I did not receive the Arcapta Neohaler Full Prescribing Information
    - Did you read the Medication Guide?
      a) All,
      b) Most,
      c) Some,
      d) None
      e) I did not receive the Arcapta Neohaler Medication Guide
    - Did you read the Dear Healthcare Provider Letter?
      a) All,
      b) Most,
      c) Some,
      d) None
      e) I did not receive the Arcapta Neohaler Dear Healthcare Provider Letter

- Do you have any questions about any of the educational materials related to Arcapta Neohaler? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

C. **General Comments**

Resubmission Requirements and Instructions:

- Submit the revised proposed REMS for Arcapta Neohaler with attached materials and the REMS Supporting Document. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

- Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

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/s/

CAROL F HILL
03/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383

REVIEW EXTENSION – MAJOR AMENDMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey

Attention: Ann Shea
Director, Regulatory Affairs

Dear Ms Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate inhalation powder), 150/300 mcg per capsule.

On February 8, 2011, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 1, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 14, 2011.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CAROL F HILL
03/22/2011
Signed for Sandy Barnes

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 24, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22-383 – Clinical Information Request

Total no. of pages including cover: 3

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals, Corporation
Arcapta Neohaler

Your submission dated February 8, 2011, to NDA 22-383 is currently under review. We have the following requests for information:

The following table provides incidences of total respiratory- and acute-respiratory related events as a composite, and is divided by hospitalizations and intubations in the All-treated COPD Safety Population I.

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

1. Provide exposure-adjusted incidences for each of the values listed in the table.

2. Similarly, provide exposure-adjusted incidences for the All-treated and All-treated Asthma Safety Populations as well.

We request your reply by COB, Monday, February 28, 2011. If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: Karimi-Shah/February 23, 2011
Clearance History: Michele/February 23, 2011
Barnes/February 24, 2011
Finalized: chill/February 24 2011

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/s/

CAROL F HILL
02/24/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary and Allergy Products

Memorandum of Facsimile Correspondence

Date: February 18, 2011
To: Ann Shea, Senior Associate Director, Drug Regulatory Affairs
Company: Novartis Pharmaceutical Corporation
Email Address: ann.shea@novartis.com
Phone: 867-778-4567
From: Carol Hill, MS
Regulatory Health Project Manager
Division of Pulmonary, Allergy and Rheumatology Products

Subject: NDA 22383 – Labeling Comments and Revisions I
# of Pages: 24

Thank you.
carol.hill@fda.hhs.gov

NDA 22383
Novartis Pharmaceutical Corporation
Arcapta Neohaler

We have begun our review of the label in your October 1 and December 15, 2010 submissions. Be advised that additional labeling comments will be forthcoming as we continue to review the labeling. Also be advised that the comments provided are not final and no decision on approvability, dose, dose regimen, indication or other claims has been made.

Note that we have not provided comments on the following sections: Highlights, Section 6 (Adverse events), Section 14 (Clinical Trials), and Section 17.5 (Medication Guide). Since we will be providing our revisions and comments to specific sections of the labeling, we do not expect you to provide revised labeling at present. However, if you have questions regarding any of the revised sections, we request that you forward your comments so that we may address any issues you may have. In the attached revised package insert labeling, insertions are underlined and deletions are strike-out.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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

Drafted by: Chill/February 17, 2011
Clearance: Barnes/February 17, 2011
Fan/February 17, 2011
Xu/February 17, 2011
Michele/February 17, 2011
Finalized: Chill/February 18, 2011

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/s/

CAROL F HILL
02/18/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 16, 2011

To: Ann Shea Senior Associate Director, Drug Regulatory Affairs	**From: Carol Hill, M. S.** **Regulatory Health Project Manager**
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-8565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22-383 (indacaterol) – Clinical Information Request

Total no. of pages including cover: 2

Comments: Please acknowledge receipt.

Document to be mailed: **YES** **xNO**

Your submission dated February 8, 2011, to NDA 22-383 is currently under review. We have the following comments or request(s) for information:

1. Provide a listing of deaths from the safety database that were not included in this analysis and the reason for exclusion.

2. Provide the narratives and adjudication listing for all events included in the analysis.

3. In reference to Table 7-2: Provide an explanation as to why the number of non-respiratory events together with the respiratory events is lower than the total number of patients with adjudicated narratives.

4. In reference to Table 7-2: Provide a further breakdown of the numbers of deaths, hospitalizations, and intubations under the subdivisions of asthma-, COPD-, and pneumonia-related.

5. It appears that the events in the IND OTH (other device) category are not included in the IND ALL category. Provide the indacaterol dose group for those events which occurred in the IND OTH category.

We request your reply by COB, Thursday, February 17, 2011. If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: Karimi-Shah/February 15, 2011
Clearance History: Michele/February 15, 2011
Barnes/February 16, 2011
Finalized: chill/February 16, 2011

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/s/

CAROL F HILL
02/16/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022383

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

ATTENTION: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) dated October 1, 2010, received October 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol Maleate Inhalation Powder, 75 mcg and 150 mcg.

We also refer to your November 19, 2010, correspondence, received November 19, 2010, requesting review of your proposed proprietary name, Arcapta Neohaler. We have completed our review of the proposed proprietary name, Arcapta Neohaler and have concluded that it is acceptable. The proposed proprietary name will be re-reviewed 90 days before approval of the NDA. If we find the name unacceptable following re-review, we will notify you.

We also refer to your November 19, 2010 request to receive confirmation that the proposed proprietary name Arcapta Neohaler would also be acceptable if the product were to have only a single strength of either 75 mcg or 150 mcg. At this time our assessment of the proposed proprietary name Arcapta Neohaler can only consider the proposed product characteristics as listed in the November 19, 2010 submission, therefore if **any** of the proposed product characteristics as stated in this submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Carol Hill, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/15/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 12, 2011

To: **Ann Shea** **Director, Drug Regulatory Affairs**	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 –Statistical Response to Submission dated, December 24, 2010

Total no. of pages including cover: 3

Comments: Please acknowledge Receipt

Document to be mailed: **YES** **xNO**

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Your submission dated December 24, 2010, in response to our December 16, 2010 Clinical Information Request, is currently under review. We have the following comments or requests for information regarding the statistical analysis plan.

1. In Section 2.1, add the following analysis sets: a) placebo-controlled COPD studies and b) placebo-controlled asthma studies.

2. In Section 2.6.2.1, clarify what is meant by "If a patient experiences multiple events only first event of a particular type will be considered." Does this mean that for each type of event listed in Section 2.6.2.2, a separate analysis will be conducted and multiple events refer only to the event being analyzed?

3. In Section 2.6.2.2, perform additional Cox models regressions stratified only by study.

4. In Section 3.1, use 4 decimal places in reporting events per year.

If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: CHill/January 11, 2011
Clearance History: Barnes/January 11, 2011
Levenson/January 11, 2011
Liu/January 11, 2011
Buenconsejo/January 11, 2011
Michele/January 11, 2011
Seymour/January 11, 2011
Finalized: CHill/January 12, 2011

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/s/

CAROL F HILL
01/12/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 28, 2010

To: **Ann Shea** **Director, Drug Regulatory Affairs**	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp	Division of Pulmonary, Allergy, Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Clinical Response to Submission dated, December 24, 2010

Total no. of pages including cover: 3

Comments: Please acknowledge Receipt

Document to be mailed: **YES** **xNO**

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Your submission dated December 24, 2010, in response to our December 16, 2010 Clinical Information Request, is currently under review. We have the following comments or requests for information. Please note that additional comments regarding the statistical analysis plan will be provided soon.

1. As soon as possible, submit a table of the studies with indacaterol that you plan to exclude in the analysis and the reason that each study is excluded.

2. For cause of death, all non-respiratory related events will be listed as "non-respiratory". Specific cause of death should be determined by the committee even if non-respiratory. Categories such as MI, sudden death, stroke, etc. are encouraged rather than preferred terms. Include a comparison with the preferred term cause of death as determined by the investigator.

3. The Adjudication Committee Charter notes that AC members may ask for additional information only in the event of a disagreement between members, [Step 4, p.15]. There should be some mechanism by which members may ask for additional information earlier in the process.

4. Include subgroup analysis for trials of 7 days treatment duration and less vs. trials longer than 7 days treatment duration for both asthma and COPD.

If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: Seymour/12-27-10
Clearance History: Chowdhury/12-27-10
Barnes/12-28-10
Finalized: CHill/12-28-10

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/s/

CAROL F HILL
12/28/2010

Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: December 20, 2010

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Email address: **ann.shea@novartis.com**	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – Statistical Information Request

Total no. of pages including cover: **5**

Comments: Please acknowledge your receipt.

Document to be mailed: YES XNO

Your submission dated, September 28, 2010, received, October 1, 2010 for NDA 22383 is currently under review. We have the following comments or request for information.

1. In your submitted dataset “qab149b2336\analysis\aspider.xpt”, the SGRQ score imputed with LOCF (param_1a=”TOT_L”) is identical to the unimputed SGRQ score (param_1a=”TOT”). Please explain why the two sets of scores are identical. Submit your dataset with unimputed SGRQ (the total score and three components) by visit, including a column that flags whether the patient discontinued or not, a column with reasons for discontinuation, a column indicating at which visit the patient discontinued. Add visit 999 with imputed SGRQ scores by LOCF. The dataset should also include all the variables that are included in the ANCOVA model. We have the same request for studies B2335s, B2334, B2346, B2354 and B2355.

2. On page 108 of your clinical study report of CQAB149B2336, you reported the ANCOVA result on SGRQ total score in table 11-7. The snapshot of the table is shown below for your reference. In dataset “qab149b2336\analysis\aspider.xpt”, the number of subjects with imputed SGRQ total score at week 12 (param_1a=”TOT_L” & visnam1a=”Day 84”) are 302 for Indacaterol 150 mcg, 293 for Salmeterol, and 274 for placebo. Please explain the discrepancy between the dataset and your result. We found similar discrepancy for studies B2334, B2346, B2335s, B2354 and B2355. Provide explanation for those studies as well.

Table 11-7 SGRQ total score at Week 12: treatment comparisons (ITT population)

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Ind 150 µg	309	36.4	1.04	Ind 150 µg - Pbo	-6.3	0.99	(-8.2,-4.3)	<.001*
				Ind 150 µg - Salm	-2.1	0.99	(-4.0,-0.2)	0.033
Salm	301	38.5	1.04	Salm - Pbo	-4.2	1.01	(-6.1,-2.2)	<.001
Pbo	294	42.6	1.05					

3. Fill out the following two table shells based on both imputed and unimputed SGRQ scores. Provide similar summaries for studies B2334, B2346, B2335s, B2354 and B2355, i.e. the same table header with proper treatment arms in each study.

Study ID	SGRQ Score	Treatment	Number of subjects in ITT	Number of patients with non missing data	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Changing from baseline at week 12 (arithmetic mean)
B2336	Total	Ind 150 mcg					
		Salmeterol					
		Placebo					
	Activity	Ind 150 mcg					
		Salmeterol					
		Placebo					
	Impact	Ind 150 mcg					
		Salmeterol					
		Placebo					
	Symptom	Ind 150 mcg					
		Salmeterol					
		Placebo					

Study ID	SGRQ Score	Treatment	Number of subjects in ITT	Number of patients with non missing data	Number of subjects included in ANCOVA	LS mean of treatment effect at week 12	SE	Comparison	LS mean	SE	95% CI	P
B2336	Total	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				
	Activity	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				
	Impact	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				
	Symptom	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				

Please respond to our request by COB on December 27, 2010 with a formal submission to the application. If you have any questions, call Carol Hill, Regulatory Health Project Manager at 301-796-1226.

Drafted by: liu/12-20-10
Clearance: Barnes/12-20-10
Buenconsejo/12-20-10
Finalized: chill/12-20-10

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/s/

CAROL F HILL
12/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383 **INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We also refer to your September 28, 2010 submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009.

In our action letter for your original submission, we stated the following:

> *To support approval of two doses of indacaterol in COPD patients, provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose.*

In addition to the risk benefit assessment of indacaterol in COPD patients, another important potential safety issue noted in the action letter is possible asthma-related death. Additional information is required to address these issues. To facilitate our safety review of your product, we have the following request for information.

Conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control. Use the following criteria to provide guidance in formulating your analysis.

1. <u>Study inclusion criteria</u>
   a. Include all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration that were conducted with indacaterol maleate delivered using the single dose dry powder inhaler Concept 1 device (to-be-marketed indacaterol product) for the treatment of COPD or asthma, whether or not the trials were submitted as part of the NDA.

b. Include trials in which the to-be-marketed indacaterol product was administered as randomized treatment, either with or without a concomitant inhaled corticosteroid (ICS) or other adjunctive therapy. Include trials conducted with indacaterol combination products that have a treatment arm(s) using the to-be-marketed indacaterol product.

c. Include trials with any dose of the to-be-marketed indacaterol product.

d. Include both placebo- and active-controlled trials.

e. Include trials in which there was a randomized blinded phase followed by an open label extension phase. However, include only the blinded phase of the trial in your analysis.

f. Include randomized, double-blind crossover design trials. However, include only the first cross-over period of the trial.

g. Do not include trials in healthy volunteers, indications other than asthma or COPD, uncontrolled trials, or trials designed primarily to obtain clinical pharmacology data (e.g., Phase I trials).

h. Do not include trials in children less than 12 years of age.

i. Do not include trials conducted solely with devices other than the Concept 1 device or with other formulations of indacaterol, such as alternative salts.

2. <u>Identification and adjudication of events</u>
   a. Adverse events of interest to include:

      1. all-cause death,

      2. asthma-related death,

      3. asthma-related intubation,

      4. asthma-related hospitalization,

      5. COPD-related death,

      6. COPD-related intubation,

      7. COPD-related hospitalization,

      8. pneumonia-related death,

      9. pneumonia-related intubation, and

10. pneumonia-related hospitalization.

b. Review all serious adverse events reported in the trials, in a manner blind to treatment, to determine whether the event involved death, hospitalization, or intubation. For events involving one or more of these outcomes, determine whether the event occurred in the setting of an acute respiratory event or was otherwise respiratory-related. Base the determination of respiratory-relatedness on the clinical judgment of an independent adjudication committee. Do not rely upon the coded adverse event term to determine respiratory-relatedness, as the reliability and validity of the specific terms may be variable.

c. For the analysis of individual events, a patient may have more than one respiratory event related to a single experience. For example, a patient who had an asthma-related hospitalization, followed by an asthma-related intubation and died of an asthma-related cause should be considered as having each of four events. All four events are to be counted in the analysis, not just the most critical.

d. Count on-treatment events, not events that occurred after treatment. Include events regardless of determination of drug-relationship.

e. For each patient who died during the trial, provide cause of death as determined by an independent adjudication committee. Compare the adjudicated cause to the adverse event resulting in death as determined by the investigator.

f. Provide narrative summaries for each patient with an adverse event of interest.

3. <u>Statistical methods</u>

a. Analyze event rates based on exposure. Include time to event analyses and hazard ratios compared to placebo. Consider methods with statistical properties suited for the known incidence rates.

b. Consider composite endpoints of all COPD-related events, all asthma-related events, and all respiratory-related events. For composite endpoints, count only the first event if more than one event occurred for a single patient.

c. Include all available blinded, controlled data for a trial. Do not truncate based on an arbitrary cut off date.

d. Include at least the following analysis sets:

1. all included studies conducted using the to-be-marketed product,

2. placebo-controlled studies,

3. COPD only studies,

4. asthma only studies, and

5. COPD only studies greater than 7 days duration.

b. Complete the analyses for each individual indicaterol dose. Also do an analysis with all indacaterol dosage groups combined.

c. For COPD only studies, conduct a subgroup analysis of patients with baseline bronchodilator responsiveness compared to non-bronchodilator responsive patients. Define bronchodilator responsiveness according to the American Thoracic Society criteria of FEV1 change of >200 ml and >12%. [Pellegrino R, Viegi G, Brusasco RO, et al. Interpretive strategies for lung function testing. *Eur Respir J* 2005; 26:948-68.]

d. Summarize non-completers by treatment group. Include reasons for non-completion, follow-up time after dropout, AEs of interest before dropout, and any known AEs of interest after dropout.

Please provide your proposed analysis plan and timeline for analysis completion by COB on January 2. Also provide in your timeline the planned date of submission of your Adjudication Committee charter. Include a detailed description of the procedures for adjudicating serious adverse events and cause of death in your Adjudication Committee charter.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
12/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383 **INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We also refer to your September 28, 2010 submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009.

During our preliminary review of your complete response, we identified the following potential review issues:

1. No regulatory paradigm exists for the use of two doses of a long acting beta agonist (LABA) for bronchodilatory effect. It is unclear whether the role for two doses is supported or, specifically, adequate data has been submitted to support a clinically meaningful efficacy or safety advantage of a higher dose over a lower dose.

2. You have requested a claim that Arcapta Neohaler improves the St. George's Respiratory Questionnaire score: *"Arcapta Neohaler 150 mcg resulted in a significantly lower (improved) mean SGRQ total score compared to placebo."* The data submitted in support of this claim, adequacy of the duration of the trials and the variability that exists amongst the key efficacy trials will be review issues.

3. You have requested an onset of action claim: "*onset of action within 5 minutes*." The definition of onset of action and data in support of this claim will be review issues.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are

preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

To facilitate our review, we have the following requests for information.

Clinical Pharmacology

4. Submit SAS transport files, containing identification, treatment, dose, individual concentrations, and individual pharmacokinetic (PK) parameters for the PK study: CQAB1492101.

Statistical

5. On page 61 of the clinical study report CQAB149B2223, Table 11-3 and Table 11-4, summarize the statistical analysis of trough FEV1 and time-standardized AUCs on days 15/16 (PD analysis set). The tables are provided below for your reference. Provide the programs used to generate the tables and include the input datasets.

Table 11-3 Summary of the statistical analysis of change from baseline in trough FEV_1 and time-standardized AUCs on days 15/16 (PD analysis set)

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

Source: PT-Table 14.2-2.1

A secondary analysis was performed on these PD variables providing all two-way contrasts between the treatments (PT-Table 14.2-2.4). The contrasts with placebo on day 15/16 are shown in Table 11-4.

Table 11-4 Summary of the statistical analysis of contrasts with placebo for change from baseline in trough FEV_1 and time-standardized AUCs on days 15/16 (PD analysis set)

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

Source: PT-Table 14.2-2.4

Chemistry, Manufacturing and Controls

6. Agree to reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once a sufficient number of batches (e.g., ≥ten) are tested using the new reporting limit of (b) (4). Propose acceptance criteria that are reflective of the data obtained. The limited data for three batches of lactose provided thus far do not support the permissive limit of up to (b) (4) total impurities in lactose, with all having less than (b) (4) totals.

7. Revise the HOW SUPPLIED section of the package insert to more accurately describe the blister cards, e.g., "Box of 30 (5 blister cards with 6 capsules each)."

8. Revise the SPL style sheets for both strengths to list the lactose monohydrate as an inactive ingredient.

9. (b) (4) the drug product, when exposed to the ICH Q1B photostability stress conditions, which is also reflected in the STORAGE AND HANDLING section of the package insert.

Please provide your response to our request for information by COB on December 15, 2010. If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CAROL F HILL
12/08/2010

BADRUL A CHOWDHURY
12/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Carol RPM/ODE II/DPARP 301-796-1226	
DATE December 6, 2010	IND NO.	NDA NO. 22383	TYPE OF DOCUMENT NDA Resubmission	DATE OF DOCUMENT October 1, 2010
NAME OF DRUG Arcapta Neohaler (indacaterol maleate)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Beta 2 Agonist	DESIRED COMPLETION DATE February 11, 2010

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: We request a review of the carton and container, package insert, medication guide, patient instructions for use, and proposed REMS included in the 9/28/10 submission in the EDR.

Mid-Cycle Meeting: [1/11/11]

Labeling Meetings: [1/11/11]

Wrap-Up Meeting: [1/28/11]

SIGNATURE OF REQUESTER Carol Hill	METHOD OF DELIVERY (Check one) ☑MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

CAROL F HILL
12/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Carol Hill/RPM, ODE II/DPARP 301-796-1226

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
December 6, 2010		22383	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Arcapta Neohaler	Standard	Beta2-Agonist	February 11, 2011

NAME OF FIRM:	
Novartis	PDUFA Date: April 1, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☑ PACKAGE INSERT (PI)
☑ PATIENT PACKAGE INSERT (PPI)
☑CARTON/CONTAINER LABELING
☑ MEDICATION GUIDE
☑INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☑ORIGINAL NDA/BLA (RESUBMISSION)
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☑ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\cdsesub1\EVSPROD\NDA022383\\0027\m1\us\proposed.pdf
Submission is dated September 28, 2010 in the EDR.

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: We request a review of the carton and container, package insert, medication guide, patient instructions for use, and proposed REMS included in the 9/28/10 submission in the EDR.

Mid-Cycle Meeting: [1/11/11]

Labeling Meetings: [1/11/11]

Wrap-Up Meeting: [1/28/11]

SIGNATURE OF REQUESTER
Carol Hill

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☑eMAIL ☐ HAND

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/s/

CAROL F HILL
12/06/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 5, 2010

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 - Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate) Inhalation Powder.

We also refer to your September 28, 2010, submission, containing your response to our October 16, 2009, Complete Response action letter.

We are reviewing your submission and have the following requests for information.

1. Provide all datasets, programs and outputs for the dose-response analyses modeling report "Update of the bronchodilatory dose-response analysis of indacaterol in COPD".

2. Use the following instructions when submitting the requested information.

    a. Submit all datasets used for model development and validation as SAS transport files (*.xpt).

    b. Provide a description of each data item in a Define.pdf file.

    c. Submit model codes or control streams and output listings as ASCII text files with the (*.txt) file extension.

Provide your response to this request no later than COB on November 12, 2010. If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Drafted: chill/November 1, 2010
Clearance History: Barnes/November 4, 2010
Lee/November 5, 2010
Wang/November 5, 2010
Finalized: chill/November 5, 2010

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/s/

CAROL F HILL
11/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022383 **ACKNOWLEDGE CLASS 2 RESPONSE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

We acknowledge receipt on October 1, 2010 of your, September 28, 2010, resubmission to your new drug application for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We consider this a complete, class 2 response to our, October 16, 2009, action letter. Therefore, the user fee goal date is April 1, 2010.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CAROL F HILL
10/07/2010
Signed for Sandy Barnes

10/7/10

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in DARRTS for this cancellation.

Complete the information below and check form into DARRTS.

Application Type	☐ P-IND ☐ IND ☑NDA/sNDA ☐BLA/sBLA
Application Number	NDA 22383
DATE Meeting Cancelled (per communication with requester)	September 15, 2010
Scheduled Meeting Date	November 29, 2010
Reason for Cancellation	Due to the date of the scheduled meeting with respect to the timing of their planned resubmission of NDA 22383, Novartis decided to cancel the meeting.
Project Manager	Carol Hill, MS

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/s/

CAROL F HILL
10/07/2010

9/1/10

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022383

MEETING REQUEST GRANTED

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07963-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate inhalation powder).

We also refer to your August 16, 2010, correspondence requesting a meeting to discuss your planned approach to respond to the Agency's Complete Response Letter dated October 16, 2009. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: November 29, 2010
Time: 12:00 PM to 1:30 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

CDER Participants: (Tentative)
Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP
Kimberly Witzmann, M.D., Clinical Reviewer, DPARP
Joan Buenconsejo, Ph.D., Acting Statistical Team Leader, Division of Biometrics II
Dongmei Liu, Ph.D., Statistical Reviewer, DOBII
Jogarao V. Gobburu, Ph.D., Director, Office of Clinical Pharmacology
Carol Hill, M.S., Regulatory Health Project Manager, DPARP

Please e-mail me any updates to your attendees at carol.hill@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency

issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Carol Hill, extension 61226.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 10 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by November 1, 2010, we may cancel or reschedule the meeting.

Submit the 10 desk copies to the following address:

Carol Hill
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3333
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Hill, M.S.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	November 29, 2010 at 12:00 PM
MEETING ENDING DATE AND TIME	November 29, 2010 at 1:30 PM
PURPOSE OF MEETING	Industry
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building 22, Conference Room: 1419
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Carol Hill, Regulatory Health Project Manager White Oak Building, Room 3333, 301-796-1226
ESCORT INFORMATION (If different from Hosting Official)	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	GI-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CAROL F HILL
09/01/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 2, 2010

To: Ann Shea Director, Reg. Affairs	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-8565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383 – Comments regarding Clarification of December 24, 2009 Meeting Minutes**

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

We have the following response to the questions in your January 15, 2010, request for clarification on the meeting minutes dated December 24, 2009:

1. With regard to the potential need to address safety of indacaterol in asthma, it is Novartis' understanding that the Agency was open to considering the data from ongoing QMF149 (fixed dose combination product of indacaterol and mometasone furoate) Study A2210 (asthma safety study).

DPAP response: Safety of long acting beta-agonists in asthma patients for an asthma indication is currently undergoing active discussion at the agency. However, it is not necessary to demonstrate the long-term safety of indacaterol in asthma patients for a COPD indication.

2. Further to the meeting, Novartis provided proposed study synopses for the Agency's review. These proposals address the Agency's request to assess the dose selection and dosing regimen for indacaterol in patients with asthma to support the dose and dosing regimen for COPD. It is Novartis' understanding that the dose and dosing regimen selected from these two studies in asthma could apply directly to COPD, and that full development in asthma is not a prerequisite to move ahead and gain approval in COPD.

DPAP response: Yes, the results from dose ranging and dosing regimen studies performed in asthma patients can apply to COPD and a full development program in asthma is not needed to gain approval for COPD.

3. It is Novartis' understanding that the additional data (further evaluation of CCV events in studies already submitted, as well as an evaluation from two recently completed studies; 12-month Study B2335SE and 6-month Study B2336) provided in the Briefing document may provide adequate support for the safety of the 150 mcg dose (or lower if determined from the proposed dose-ranging study) and may address the Agency's concern about the imbalance in the CCV events in Study B2334.

DPAP response: As we have stated previously "long term safety of a lower dose may be supported by the safety profile of the 12 month safety data obtained for the 150 mcg dose." Whether the data from the 12 month study B2335SE and 6 month study B2336 provide safety support for the daily dose of 150 mcg or lower will be a review issue.

If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: Wu/January 28, 2010
Clearance: Barnes/January 29, 2010
Wu/January 28, 2010
Durmowicz/January 28, 2010
Finalized: chill/February 2, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	GI-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CAROL F HILL
02/02/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 3, 2010

To: Ann Shea Director, Drug Reg. Affairs	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22-383 – Response to Protocol Synopsis Questions

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES xNO

We have the following response to the questions in your "request for comment on protocol Synopses CQAB149B2357 and CQAB149B2223" dated, December 11 and 15, 2009:

Dose-ranging study

1. All subjects need to be on a stable dose of inhaled corticosteroids (ICS) four weeks prior to entry into the study. They will be maintained on this dose and brand throughout the study. Does the Agency agree that subjects on different maintenance doses (and brands) of ICS are comparable and that this is acceptable in the study design?

DPAP response: Yes, it is acceptable.

2. The duration of dosing in the dose-ranging study is two weeks. Novartis believes that the program has already demonstrated pharmacodynamic steady state at two weeks.
Does the Agency agree that a two week study is sufficient for the purposes of dose ranging?

DPAP response: Yes, we agree.

3. Please note that in the dose-ranging study there will be no pharmacokinetic (PK) assessments, as Novartis feels that the dose proportionality of PK of once daily indacaterol has been adequately described previously. Does the Agency agree with this proposal?

DPAP response: We agree that PK assessment is not necessary in this dose-ranging study. However, additional PK assessments may be needed in future studies, depending on the final dosing regimen selected.

4. Does the Agency have any other comments on the design, population or size of this study?

DPAP response: We recommend that you collect spirometry time points over the entire 24 hour dosing interval. Specifically, we recommend that you include more time points during the second half of the dosing interval. The evaluation of additional time points can be performed on a subset of patients.

Dosing regimen study

5. Does the Agency agree that the selection of 75 mcg as the total daily dose for the dosing regimen study is acceptable to draw conclusions about the differences between different regimens and will lead to selection of a dosing regimen that best serves patients' needs? Does the Agency agree that the outcome of the dosing regimen study will be applicable to other doses in the event that a dose other than 75 mcg is selected from the dose-ranging study?

DPAP response: It is premature to comment with certainty on the acceptability of the specific doses for the dosing regimen study as the doses selected may be influenced by the findings from the dose ranging study. For example, if the dose chosen in the dose ranging study is

lower than 75 mcg once daily (e.g. 37.5 mcg), you may need to study a dose of 18.75 mcg twice daily in the dosing regimen study. While you may be able to conduct both studies concurrently, doing so adds an element of risk in the dosing regimen study.

6. The primary endpoint in the dosing regimen study will be trough value at the end of the last 48 hour dosing period; that is 48 hours after the QOD dose, 24 hours after the last QD dose and 12 hours after the last BID dose. Does the Agency agree that this is the appropriate measure for the primary comparisons of the regimen?

DPAP response: While trough FEV1 is an important endpoint, as we have advised you previously at an EOP2 meeting in 2006, in addition to trough FEV1, other measures such as total FEV1 curve, peak FEV1 and FEV1 AUC are also important variables to consider for evaluation of dose regimen.

7. Does the Agency agree with the spirometry time points that were selected to characterize the bronchodilator response of the three dosing regimens?

DPAP response: We recommend more frequent spirometry time points toward the end of the dosing interval (e.g., 22 hr) in order to better characterize the FEV1 curve, peak FEV1 and AUC FEV1.

8. In the dosing regimen study, PK and PD will be followed for 72 hours after the steady state assessment, when no further doses will be given. Does the Agency agree that this approach is appropriate?

DPAP response: Yes, we agree.

9. Does the Agency have any other comments on the design, population or size of this study?

DPAP response: One way of assessing a dosing frequency of greater than once daily would be to serially follow the FEV1 curve up to 48 hours after the last dose administered (that is, last dose administered on day 14) in the dose ranging study (study B2357).

<u>Overall question</u>

10. Does the Agency agree that the selection of the dose and dosing regimen in asthma from the proposed studies, CQAB149B2357 and CQAB149B2223, will serve as the basis for dose selection in COPD and that further dose-ranging in COPD is not required?

DPAP response: Yes, in general, selection of the dose and dosing regimen in asthma patients can serve as the basis for dose selection in COPD and that further dose-ranging in COPD is not required. See comments above for recommendations regarding the conduct and timing of studies CQAB149B2357 and CQAB149B2223.

If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: wu/January 28, 2010
Clearance: Barnes/February 2, 2010
Fan/January 28, 2010
Xu/January 28, 2010
Durmowicz/January 28, 2010
Finalized: chill/February 3, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	GI-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CAROL F HILL
02/03/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: November 23, 2009

To: Ann Shea Sr. Assoc. Dir. Regulatory Affairs	From: Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565 Email: ann.shea@novartis.com	Fax number: 301-796-9728
Phone number: 862-778-4567 Cell number: 862-902-9169	Phone number: 301-796-1226

Subject: NDA 22-383 – Preliminary Comments for November 24, 2009 Meeting

Total no. of pages including cover: 6

Comments: Please acknowledge receipt.

Document to be mailed: YES XNO

NDA 22-383
Arcapta Neohaler
Novartis Pharmaceuticals

Attached are the FDA responses to your questions (in bold italics) in your November 5, 2009, meeting package regarding Arcapta Neohaler. You have the option of canceling our meeting of November 24, 2009, if these answers are clear to you. If you choose to have the meeting, notify the Division of the specific questions for discussion and we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request.

Please notify the Division as soon as possible if you would like to cancel the meeting or change it to a teleconference.

INTRODUCTORY COMMENT

We acknowledge your proposals in your submission dated November 5, 2009, to further support the safety of indacaterol maleate for use as a long-acting bronchodilator (LABA) in patients with chronic obstructive pulmonary disease (COPD). While your proposals may add some additional safety information for the 150 mcg dose of indacaterol in patients with COPD, they are not adequate to support the dose, dosing frequency, or the safety of the dose ultimately selected for approval. The dose and dosing frequency of indacaterol have been inadequately explored which has lead to what we feel is potentially too high a proposed dose. In addition, the long half life of indacaterol (approximately 49 hrs) that results in a 5 times increase in trough and a 3 times increase in AUC_{0-24} levels at steady-state lead us to be concerned that the dose accumulation with once daily dosing may also be a safety issue. These potentially excessive doses may be responsible for the unacceptable safety profile of indacaterol as evidenced by an increase in combined cerebrovascular and cardiac (CCV) serious adverse events in patients with COPD and, most notably, in the finding of two asthma deaths in patients receiving the 300 mcg dose of indacaterol along with inhaled corticosteroids in a relatively short asthma study of six months duration.

We consider LABAs as medications which have a narrow therapeutic index and which require careful and precise dose selection in order to balance the risk to benefit ratio of their use both in patients with COPD and asthma. Since asthma patients by definition possess significant bronchoreactivity to beta-2 agonists and are more sensitive to the severe adverse events that have been linked to the use of beta-2 agonists in asthma patients (death, intubations), our thinking has evolved such that we believe that the safety and efficacy of LABAs and other beta-2 agonists are best characterized first in asthma patients, and then in COPD patients. Moving forward, we feel that characterizing the

dose, dosing frequency, and safety of indacaterol in the patient population most sensitive to both the bronchodilator and adverse event effects of LABAs will provide for selection of the safest while still effective dose in patients with asthma and COPD both. Thus, prior to further development of indacaterol for patients with COPD we recommend that you:

- *Assess the dose and dosing frequency fully in patients with asthma (including doses less than 150 mcg and at dosing intervals both less than and greater than once daily)*

- *Assess the long-term safety of a dose or doses of indacaterol in patients with asthma.*

Once a relatively safe but effective dose and dosing frequency of indacaterol has been determined in patients with asthma, development should then proceed in patients with COPD.

Question #1

Regarding safety, Novartis has undertaken additional analyses of existing data and completed analyses of new data. Additional six-month and 1-year safety data of indacaterol 150 µg (Study B2335SE and Study B2336), as well as additional one-year safety data of indacaterol 300 µg (Study B2335SE) have become available since submission of the NDA and the 120-day Safety Update and lend further support to the safety of indacaterol 150 µg and 300 µg doses with regard to combined cardiac and/or cerebrovascular serious adverse events, compared to placebo and active comparators.

Novartis would like to obtain feedback from the Agency on whether these further analyses of the existing data in the NDA and the additional long-term safety data address the Agency's concern and provide substantial evidence of safety to support the use of Arcapta Neohaler in patients with COPD?

Response:

While the data may provide some safety support for the 150 mcg dose, the additional data will not fully address our concerns over the safety, dose selection, or dosing frequency of indacaterol.

Question #2

Notwithstanding the additional safety data presented above with respect to CCV SAEs to support the efficacy and safety of indacaterol, Novartis proposes to conduct, post-approval, a dose-ranging study to evaluate and determine whether there is a dose below 150 µg that is a more appropriate therapeutic once daily dose of indacaterol in patients with COPD. A model based approach focused on the maximal effect (Emax) for

bronchodilation is proposed in preference to traditional pairwise comparisons to placebo for a range of doses, using statistical analysis of covariance (ANCOVA) to identify the therapeutic dose.

Does the Agency agree that the proposed modeling methodology is appropriate to sufficiently determine the therapeutically optimal once-daily dose of Arcapta Neohaler? Does the Agency agree that this study can be conducted post-approval?

Response:

We do not agree. Both dose selection and dosing frequency need to be established prior to marketing approval. Additionally, dose selection should be determined by conducting an appropriately designed conventional dose-ranging study which should include lower doses of indacaterol in order to be able to assess the pulmonary response at lower dose ranges.

Question #3

If a dose below 150 µg from the aforementioned dose-ranging study is selected, would a single, adequately-powered, 12-week efficacy study be sufficient for registration, along with the additional safety data from Studies B2335SE and B2336 as described above?

Response:

No, the dose and dosing frequency will require replicate, adequately designed efficacy studies. The long-term safety of a lower dose may be supported by the safety profile of the 12 month safety data obtained for the 150 mcg dose.

Question #4

Novartis would like to understand if the Agency's request to explore dosing frequency is to determine whether a twice daily regimen may provide more benefit to the patient than a reduction in the once daily dose of indacaterol?

Response:

We are interested in determining the lowest dose of indacaterol that is efficacious that has a tolerable safety profile in patients with COPD. A lower total daily dose of indacaterol administered more frequently may achieve that goal. As patients with asthma may be more sensitive to the adverse effects of LABAs, you should consider determination of dose and dosing frequency in patients with asthma prior to conducting further clinical trials in patients with COPD.

Question #5

In addition to the supplementary safety data to support the 150 and 300 µg doses, we have undertaken further efficacy analysis which show that the higher proposed dose of 300 µg compared to 150 µg has incremental improvements in efficacy in some aspects

of bronchodilation (e.g. more effective bronchodilation on first dose to encourage good compliance) and symptom control (e.g. dyspnea as measured by BDI/TDI, as well as numerical advantage with regard to mean daily use of rescue therapy and percentage of days with no rescue therapy).

Would such additional data suffice to support the use of these two doses in patients with COPD?

Response:

No, these data would not support the use of a higher dose in patients with COPD. In order to do so, you will need to demonstrate that patients who do not adequately respond to a lower dose of indacaterol achieve a meaningful benefit in pulmonary function from the higher proposed dose. This was not addressed in your COPD clinical program.

Question #6

Novartis plans to include safety data for all studies completed after NDA submission, and blinded safety data for ongoing studies, in a future resubmission, but does not plan to integrate these studies with those submitted in the NDA. The data from these studies will, however, be integrated with those submitted in the NDA (B2346, B2335S, B2334) with respect to CCV events. The cut-off date will be two months prior to the resubmission and it will follow the format of the Summary of Clinical Safety and 120-Day Safety Update.

Is the proposed plan acceptable to the Agency?

Response:

No, we do not agree. All safety data from controlled clinical trails in patients with COPD should be integrated based on dose and length of dosing. In addition, any new safety data from trials conducted in patients with asthma should also be submitted.

If you have any questions, you may contact Ms. Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: chill/November 23, 2009
Clearance History: Barnes/November 23, 2009
Durmowicz/November 23, 2009
Chowdhury/November 23, 2009
Finalized: chill/November 23, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	GI-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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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
11/23/2009

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type C
Meeting Category:	End of Review Conference
Meeting Date and Time:	November 24, 2009, 1-2:30 pm
Meeting Location:	White Oak, Bldg. 21, Rm 1417
Application Number:	NDA 22-383
Product Name:	Arcapta Neohaler
Received Briefing Package	November 5, 2009
Sponsor Name:	Novartis Pharmaceuticals Corporation
Meeting Requestor:	Ann Shea, Director, Drug Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder:	Carol Hill, M.S.
Meeting Attendees:	

FDA Attendees

Curtis Rosebraugh, M.D., Director, Office of Drug Evaluation II
Leah Ripper, ADRA
Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products
Lydia I. Gilbert-McClain, M.D., Deputy Director
Anthony Durmowicz, M.D., Clinical Team Leader
Susan Limb, M.D., Clinical Team Leader
Lynne Wu, M.D., Clinical Reviewer
Luqi Pei, Ph.D., Supervisory Pharmacology/Toxicology
Virgil E. Whitehurst, Ph.D., Pharmacology/Toxicology Reviewer
Jean Wu, M.D., Ph.D., Pharmacology/Toxicology Reviewer
Philantha Bowen, M.P.H., R.N., Senior Regulatory Management Officer
Eunice Chung, Pharm.D., Senior Regulatory Management Officer
Michelle Y. Jordan-Garner, M.S., OTR/L, Senior Regulatory Management Officer

Carol Hill, M.S., Regulatory Health Project Manager

Prasad Peri, Ph.D., Acting Chief, Branch 2, Office of New Drug Quality Assessment

Craig Bertha, Ph.D., CMC Reviewer

Chandrahas G. Sahajwalla, Ph.D., Director, Clinical Pharmacology, Office of Biostatics II

Partha Roy, Ph.D., Acting Team Leader, Clinical Pharmacology

Yaning Wang, Ph.D., Pharmacometric Team Leader

Joo-Yeon Lee, Ph.D., Pharmacometric Reviewer

Atul Bhattaram, Ph.D., Pharmacometric Reviewer

Novartis Pharmaceuticals Corporation Attendees

Eric Coutour, Ph.D., Drug Regulatory Affairs, Global Head, Respiratory

Rob Kowalski, Pharm.D., Drug Regulatory Affairs, Global Head

Steve Pascoe, M.D., Clinical Development, Global Head, Respiratory

Lorraine Murphy, Ph.D., Respiratory Development, Global Project Head

Steffen Roellinger, Ph.D., Respiratory Development, Global Head

Trevor Mundel, M.D., Development, Global Head

James Donohue, M.D., Professor and Chief of Pulmonary Diseases and Critical Care Medicine, University of North Carolina, Chapel Hill

Jonca Bull, Ph.D., Drug Regulatory Affairs, FDA Liaison Office

1.0 BACKGROUND

After review of an action taken on NDA 22383, a post-action meeting was scheduled for November 12, 2009 with Novartis Pharmaceuticals Corporation to discuss lessons learned during the review cycle. This meeting was later combined with the End of Review Conference meeting requested on October 29, 2009, as a response to the Complete Response action letter dated, October 16, 2009. The Agency's comments to the questions in the November 5, 2009 meeting package were emailed to the applicant on November 23, 2009. On November 24, 2009, Novartis notified the Agency of its intent to attend the meeting and requested to focus the discussion on the introductory comments included in the Agency's responses.

2.0 DISCUSSION

Any discussion that took place at the meeting is captured in section 2.0 including any changes in our original position. Novartis' questions are in *bold italics* and FDA's response is in *italics;* the discussion is in normal font.

INTRODUCTORY COMMENT

We acknowledge your proposals in your submission dated November 5, 2009, to further support the safety of indacaterol maleate for use as a long-acting bronchodilator (LABA) in patients with chronic obstructive pulmonary disease (COPD). While your proposals may add some additional safety information for the 150 mcg dose of indacaterol in patients with COPD, they are not adequate to support the dose, dosing frequency, or the safety of the dose ultimately selected for approval. The dose and dosing frequency of indacaterol have been inadequately explored which has lead to what we feel is potentially too high a proposed dose. In addition, the long half life of indacaterol (approximately 49 hrs) that results in a 5 times increase in trough and a 3 times increase in AUC_{0-24} levels at steady-state lead us to be concerned that the dose accumulation with once daily dosing may also be a safety issue. These potentially excessive doses may be responsible for the unacceptable safety profile of indacaterol as evidenced by an increase in combined cerebrovascular and cardiac (CCV) serious adverse events in patients with COPD and, most notably, in the finding of two asthma deaths in patients receiving the 300 mcg dose of indacaterol along with inhaled corticosteroids in a relatively short asthma study of six months duration.

We consider LABAs as medications which have a narrow therapeutic index and which require careful and precise dose selection in order to balance the risk to benefit ratio of their use both in patients with COPD and asthma. Since asthma patients by definition possess significant airway reactivity to beta-2 agonists and are more sensitive to the severe adverse events that have been linked to the use of beta-2 agonists in asthma patients (death, intubations), our thinking has evolved such that we believe that the safety and efficacy of LABAs and other beta-2 agonists are best characterized first in asthma patients, and then in COPD patients. Moving forward, we feel that characterizing the

dose, dosing frequency, and safety of indacaterol in the patient population most sensitive to both the bronchodilator and adverse event effects of LABAs will provide for selection of the safest while still effective dose in patients with asthma and COPD both. Thus, prior to further development of indacaterol for patients with COPD we recommend that you:

- *Assess the dose and dosing frequency fully in patients with asthma (including doses less than 150 mcg and at dosing intervals both less than and greater than once daily)*

- *Assess the long-term safety of a dose or doses of indacaterol in patients with asthma.*

Once a relatively safe but effective dose and dosing frequency of indacaterol has been determined in patients with asthma, development should then proceed in patients with COPD.

DISCUSSION:

Novartis opened the meeting by stating that the discussion would be focused to gain feedback regarding the Agency's response in the November 23, 2009, correspondence, the Complete Response action letter dated October 16, 2009, and a path forward for the NDA that would be approved by the Agency. Novartis stated that the Agency's recommendation to characterize the safety and efficacy of long acting beta agonists (LABAs) and other beta-2 agonists first in asthma patients and then in COPD represents a fundamental shift and asked if the Agency would provide feedback as to how this new way of thinking evolved. The Agency stated that its thinking regarding LABAs and in effect, all beta agonists has evolved over time as additional safety data has been obtained, especially over the past several years. Historically, beta agonists were first developed in asthma patients who had considerable airway reactivity which is useful for assessing the bronchodilatory effect of beta agonists then the dose arrived at was carried over to the COPD population in which the response to beta agonists is much more heterogeneous. The more recent safety concerns over the use of LABAs in the asthma population has resulted in companies shifting away from first developing beta agonists in asthma to now their development in COPD first. While this is understandable, we believe the COPD population is not necessarily the best population in which to define an appropriate dose of a beta agonist since the overall population may lack the degree of airway reactivity needed to define the lowest effective dose of a particular beta agonist. The asthma population which, by definition, possesses a significant degree of airway reactivity is felt to be the more appropriate population to study in order to define the dose response of beta agonists and arrive at the lowest effective dose. The issue of finding the lowest dose that is effective with a tolerable safety profile is important because we believe that LABAs are drugs with a narrow therapeutic index which require careful dose-ranging to arrive at

a the correct dose. The narrow therapeutic index was demonstrated in your formoterol program when the higher dose just twice that of the approved dose was not approved for asthma in the United States because of safety concerns of intubations in asthma patients receiving the higher dose. In the same light we have concerns over dose selection for your indacaterol program where 2 patients with asthma (both on ICS) receiving 300 mcg died. It is very concerning finding that with indacaterol there were two deaths in patients with asthma who were on ICS. The Agency stated that the comparative assessment in Study 2335-S, in which the doses selected for continued development must have been demonstrated to be more effective that both formoterol and tiotropium, likely contributed to the selection of higher doses of indacaterol for the pivotal trials. In summary, we believe that patients with demonstrated airway reactivity to beta agonists, as asthma patients have, are the most appropriate population to select the best dose of beta agonists. Since the drugs act as bronchodilators, there is no reason the selected dose(s) would not also be effective in the subpopulation of COPD patients with airway reactivity.

Novartis questioned whether asthma patients are reflective of COPD patients since the asthma population is relatively young compared to the COPD population and COPD patients have more co-morbid conditions. The Agency commented that Novartis's concerns were understood but that a bronchodilator therapy is a bronchodilator whether for asthma or COPD patients with bronchoreactivity. With regard to co-morbidities, it is somewhat reassuring that the safety signal of LABAs seen with asthma patients was not detected in the TORCH trial in COPD patients. Novartis stated that with the known issues around the safety of LABAs in asthma, the clear direction was not to go forward to an asthma indication with a monotherapy but to develop combination therapies (with mometasone and an anti-muscarinic) for COPD.

Novartis asked is there a way to move forward with the COPD program instead of stopping the COPD program for 2-3 years to work on the asthma program to develop the correct dose and collect additional safety data. The Agency inquired how the dose would be defined for COPD development. Novartis proposed conducting studies in asthma and correlate to COPD to demonstrate that the dose selected is efficacious and safe in COPD. The Agency stated that we are looking for a dose selection and subsequent determination of efficacy with a tolerable safety profile. With regards to dose selection, doses less than and equal to 75 mcg of indacaterol should be studied to define a full dose response curve including a less than clinically effective dose. Dose frequencies both less than and greater than once daily should also be explored. These assessments can be performed in asthma patients in trials of relatively short duration. For example, for albuterol, a good dose response profile was provided with a short term single dose study, confirmed by studies lasting up to 12 weeks. The selected dose(s) and dosing regimen could then be carried over to the COPD population.

Novartis stated that within the next 6 to 9 months a package will be provided that may possibly generate data around the 75 mcg dose of indacaterol. The Agency recommended performing additional dose ranging/dose interval assessments as described above. Novartis asked would a single dose study with good separation mitigate the Agency's concerns over dose selection. The Agency stated that demonstrating good separation in a single dose study would be reassuring but given the long half life of indacaterol, data would also be needed to assess for dose accumulation for whatever

dosing interval attained. Novartis stated that a single dose study can be conducted and questioned that if there is an issue with accumulation effects would this require another study. The Agency stated that both could be done in one study as long as FEV1 and PK are included. The Agency recommended to first conduct the bronchodilator responsiveness assessment and added that the phase 3 study may include more than 1 dose. Novartis ask for advice regarding phase 3 multiple dose studies. The Agency encouraged Novartis to submit a protocol for review.

Novartis commented that in reference to the development of the combination program would it be appropriate to study 2 doses in the asthma population. The Agency stated that historically for asthma and COPD only one dose of LABA is selected, but it will depend whether the data showed a benefit of the higher dose over the lower dose. For a bronchodilator, a different dose for asthma and COPD has not been demonstrated. Novartis commented that the protocols will be provided.

Question #1

Regarding safety, Novartis has undertaken additional analyses of existing data and completed analyses of new data. Additional six-month and 1-year safety data of indacaterol 150 µg (Study B2335SE and Study B2336), as well as additional one-year safety data of indacaterol 300 µg (Study B2335SE) have become available since submission of the NDA and the 120-day Safety Update and lend further support to the safety of indacaterol 150 µg and 300 µg doses with regard to combined cardiac and/or cerebrovascular serious adverse events, compared to placebo and active comparators.

Novartis would like to obtain feedback from the Agency on whether these further analyses of the existing data in the NDA and the additional long-term safety data address the Agency's concern and provide substantial evidence of safety to support the use of Arcapta Neohaler in patients with COPD?

Response:

While the data may provide some safety support for the 150 mcg dose, the additional data will not fully address our concerns over the safety, dose selection, or dosing frequency of indacaterol.

Question #2

Notwithstanding the additional safety data presented above with respect to CCV SAEs to support the efficacy and safety of indacaterol, Novartis proposes to conduct, post-approval, a dose-ranging study to evaluate and determine whether there is a dose below 150 µg that is a more appropriate therapeutic once daily dose of indacaterol in patients with COPD. A model based approach focused on the maximal effect (Emax) for bronchodilation is proposed in preference to traditional pairwise comparisons to

placebo for a range of doses, using statistical analysis of covariance (ANCOV A) to identify the therapeutic dose.

Does the Agency agree that the proposed modeling methodology is appropriate to sufficiently determine the therapeutically optimal once-daily dose of Arcapta Neohaler? Does the Agency agree that this study can be conducted post-approval?

Response:

We do not agree. Both dose selection and dosing frequency need to be established prior to marketing approval. Additionally, dose selection should be determined by conducting an appropriately designed conventional dose-ranging study which should include lower doses of indacaterol in order to be able to assess the pulmonary response at lower dose ranges.

Question #3

If a dose below 150 µg from the aforementioned dose-ranging study is selected, would a single, adequately-powered, 12-week efficacy study be sufficient for registration, along with the additional safety data from Studies B2335SE and B2336 as described above?

Response:

No, the dose and dosing frequency will require replicate, adequately designed efficacy studies. The long-term safety of a lower dose may be supported by the safety profile of the 12 month safety data obtained for the 150 mcg dose.

Question #4

Novartis would like to understand if the Agency's request to explore dosing frequency is to determine whether a twice daily regimen may provide more benefit to the patient than a reduction in the once daily dose of indacaterol?

Response:

We are interested in determining the lowest dose of indacaterol that is efficacious that has a tolerable safety profile in patients with COPD. A lower total daily dose of indacaterol administered more frequently may achieve that goal. As patients with asthma may be more sensitive to the adverse effects of LABAs, you should consider determination of dose and dosing frequency in patients with asthma prior to conducting further clinical trials in patients with COPD.

Question #5

In addition to the supplementary safety data to support the 150 and 300 µg doses, we

have undertaken further efficacy analysis which show that the higher proposed dose of 300 µg compared to 150 µg has incremental improvements in efficacy in some aspects of bronchodilation (e.g. more effective bronchodilation on first dose to encourage good compliance) and symptom control (e.g. dyspnea as measured by BDI/TDI, as well as numerical advantage with regard to mean daily use of rescue therapy and percentage of days with no rescue therapy).

Would such additional data suffice to support the use of these two doses in patients with COPD?

Response:

No, these data would not support the use of a higher dose in patients with COPD. In order to do so, you will need to demonstrate that patients who do not adequately respond to a lower dose of indacaterol achieve a meaningful benefit in pulmonary function from the higher proposed dose. This was not addressed in your COPD clinical program.

Question #6

Novartis plans to include safety data for all studies completed after NDA submission, and blinded safety data for ongoing studies, in a future resubmission, but does not plan to integrate these studies with those submitted in the NDA. The data from these studies will, however, be integrated with those submitted in the NDA (B2346, B2335S, B2334) with respect to CCV events. The cut-off date will be two months prior to the resubmission and it will follow the format of the Summary of Clinical Safety and 120-Day Safety Update.

Is the proposed plan acceptable to the Agency?

Response:

No, we do not agree. All safety data from controlled clinical trails in patients with COPD should be integrated based on dose and length of dosing. In addition, any new safety data from trials conducted in patients with asthma should also be submitted.

Drafted: chill/December 4, 2009

Clearance History: Durmowicz/December 24, 2009

Chowdhury/December 24, 2009

Finalized: chill/December 24, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	GI-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CAROL F HILL
12/24/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

10/30/09

Food and Drug Administration
Silver Spring MD 20993

NDA 022383

MEETING GRANTED

Novartis
One Health Plaza
East Hanover, NJ 07963-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler.

We also refer to your October 29, 2009, correspondence requesting a meeting to discuss the Complete Response letter dated, October 16, 2009 and what steps should be taken before the application can be approved. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date:	November 24, 2009
Time:	1:00 – 2:30 PM
Location:	Food and Drug Administration Division of Pulmonary and Allergy Products White Oak, Building 22 10903 New Hampshire Avenue Silver Spring, MD 20993-0002

CDER Participants (tentative list):
Curtis Rosebraugh, M.D., Director, ODE II
Leah W. Ripper, ADRA, ODE II
Badrul A. Chowdhury, M.D., Ph.D., Director, DPAP
Anthony Durmowicz, M.D., Clinical Team Leader, DPAP
Lynne Wu, M.D., Clinical Team Leader, DPAP
Luqi Pei, Ph.D., Acting Supervisory, Pharmacology/Toxicology, DPAP
Jean Wu, M.D., Ph.D., Pharmacology/Toxicology Reviewer, DPAP
Virgil E. Whitehurst, Ph.D., Pharmacology/Toxicology Reviewer, DPAP
Prasad Peri, Ph.D., Acting Chief, Branch 2, DPA I, ONDQA
Craig M. Bertha, Ph.D., CMC Reviewer, Branch 2, DPA I, ONDQA
Chandrahas G. Sahajwalla, Ph.D., Director, DCP 2, OCP
Partha Roy, Ph.D., Acting Clinical Pharmacology Team Leader, DCP2, OCP

Sandra Suarez, Ph.D., Clinical Pharmacology Reviewer, DCP2, OCP
Qian H. Li, Sc.D., Statistical Team Leader, DOB II, OB
Dongmei Liu, Ph.D., Statistical Reviewer, DOB II, OB
Yaning Wang, Ph.D., Pharmacometrics Reviewer, OCP, PS
Joo-Yeon Lee, Ph.D., Pharmacometrics Reviewer, OCP, PS
Venkatesh A. Bhattaram, Ph.D., Pharmacometrics Reviewer, OCP, PS
Carol Hill, M.S., Regulatory Health Project Manager, DPAP

If any of your attendees are visitors from outside of the U.S., have them complete the enclosed Foreign Visitor Data Request Form and return it as soon as possible. Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail any updates to your attendees at carol.hill@fda.hhs.gov so that our security staff has sufficient time to prepare temporary visitor badges. Upon arrival at FDA, give the guards the following number to request an escort to the conference room: Carol Hill, extension 61226

Provide the background information for the meeting (three copies to the application and 20 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by November 6, 2009, we may cancel or reschedule the meeting.

If you have any questions, call Carol Hill, Regulatory Health Project Manager/me at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Novartis Pharmaceutical Corporation
MEETING START DATE AND TIME	November 24, 2009 1:00 pm
MEETING ENDING DATE AND TIME	November 24, 2009 2:30 pm
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building 22, Room 1417
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	NO
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Carol Hill, MS Regulatory Health Project Manager Division of Pulmonary & Allergy Products Office of Drug Evaluation II Office of New Drugs Center for Drug Evaluation and Research 10993 New Hampshire Avenue, Building 22, Room 3333 Silver Spring, MD, 20993 (301) 796-1226
ESCORT INFORMATION (If different from Hosting Official)	

Foreign Visitor: Any Foreign National who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge/Card is considered to be a Foreign Visitor.

Foreign National: An individual who is not a U.S. citizen is considered to be a Foreign National. Resident aliens are not U.S. citizens; therefore, they are also considered to be Foreign Nationals. If an individual has dual citizenship (U.S. and another country), the individual is not considered to be a Foreign National.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	GI-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CAROL F HILL
10/30/2009
Signed for Sandy Barnes

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-383 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Arcapta Neohaler Established/Proper Name: indacaterol maleate Dosage Form: inhalation powder		Applicant: Norvartis Pharmaceutical Corporation Agent for Applicant (if applicable):
RPM: Carol Hill		Division: Pulmonary and Allergy Drug Products

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	October 18, 2009 October 16, 2009
❖ Actions	
• Proposed action	☐ AP ☐ TA ☐ AE ☐ NA ☒ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain:	August 26, 2009
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

➢ Exclusivity	
• Is approval of this application blocked by any type of exclusivity? See if the drug is listed in the orange book.	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes,**" skip to question (4) below. If "**No,**" continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No,**" continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No,**" the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No,**" continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	October 16, 2009
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included NA
Documentation of consent/non-consent by officers/employees	☐ Included NA
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR October 16, 2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	December 15, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	December 15, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	December 15, 2008
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM September 22, 2009 ☒ DMEDP June 18, 2009 ☒ DRISK August 6, 2009 ☒ DDMAC June 16, 2009 ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 July 9 and March 11, 2009 July 29, and March 18, 2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	September 23, 2009
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included NA
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	September 11, July 31, May 29, April 24, 11, and 2, March 23 and 11, February 27, and January 8, 2009
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable August 26, 2009
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg May 6, 2008 April 7, 2008
• EOP2 meeting *(indicate date)*	☐ No mtg October 10, 2006
• Other (e.g., EOP2a, CMC pilot programs) Exec CAC	August 4, 2009
❖ Advisory Committee Meeting(s)	☐ AC mtg Scheduled but canceled
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None October 16, 2009
Division Director Summary Review *(indicate date for each review)*	☐ None October 16, 2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Clinical September 29, 2009
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	August 25 and February 27, 2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	9/25/09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Ethics & Good Clinical Practices of Clin. Rev. dated August 25, 2009
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None QT IRT August 21, 2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

• REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None September 8, 2009
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None September 4, 2009
Statistical Review(s) *(indicate date for each review)*	☐ None September 4, 2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None October 16, 2009
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None September 9, 2009
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None August 25 and February 20, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None September 9, 2009
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None August 25 and February 12, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc August 10, 2009
❖ ECAC/CAC report/memo of meeting	☐ None August 5, 2009 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None September 3, 2009
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None March 8, July 17, February 17, and October 13, 2009
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each*	☒ Not needed

review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None PT March 19, 2009
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	7/19/09
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection One site still pending.	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: October 13, 2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	 Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

From: Greeley, George
Sent: Monday, October 05, 2009 11:01 AM
To: Hill, Carol
Cc: Stowe, Ginneh D.
Subject: NDA 22-383 Arcapta Neohaler

Importance: High

Hi Carol,

The Arcapta Neohaler (indacaterol maleate) full waiver was reviewed by the PeRC PREA Subcommittee on August 26, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children.

The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383 **DISCIPLINE REVIEW LETTER**

Novartis Pharmaceuticals, Inc.
One Health Plaza
East Hanover, NJ 07936

Attention: Ann Shea
Senior Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate) inhalation powder, 150 and 300 mcg.

This letter is to notify you that we are cancelling the labeling teleconference scheduled for September 14, 2009, from 1:30-2:30 pm. During the ongoing review of the indacaterol application for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) we have identified certain deficiencies and determined that the deficiencies preclude discussion of labeling at this time. Those deficiencies include:

1. You have not adequately demonstrated a dose or doses of indacaterol that is both safe and efficacious for the treatment of bronchospasm associated with COPD. Data from study B2335s suggest that indacaterol at doses of 75-300 µg once daily elicit a similar FEV1 response compared to placebo. However, the long-term safety of indacaterol at the proposed doses of 150 and 300 µg has not been determined. In the 12 month safety study (B2334), COPD patients who received indacaterol at doses of 300 µg and 600 µg once daily had more combined cardiac and/or cerebrovascular (CCV) serious adverse events than those who received placebo or the marketed long-acting beta-2 agonist, formoterol (3.4%, 2.6%, 1.4%, and 0.9% for indacaterol 300 µg, 600 µg, formoterol and placebo, respectively). The long-term safety of indacaterol at doses less than 300 µg has not been evaluated.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

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/s/

SANDRA L BARNES
09/11/2009

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 [redacted] (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 [redacted] (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 β2-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 β2-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 β2-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

MEMORANDUM

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

DATE: July 31, 2009

TO: Ann Shea of Novartis

THROUGH : Carol Hill/email

FROM: Timothy Robison, PhD, DABT

SUBJECT: Non-clinical Information Request

APPLICATION/DRUG: NDA 22-383/Arcapta Neohaler (indacaterol)

Content of the Email dated, July 31, 2009

For the 26-week carcinogenicity study with TgrasH2 mice, uterine endometrial stromal polyps were observed for 3 of 25 female TgrasH2 mice in the 600 mg/kg/day group. Provide the background incidence of uterine endometrial stromal polyps in female TgrasH2 mice. Please provide your response by email or fax by COB EST on Monday, August 3, 2009 or at the latest by 9:00am on Tuesday, August 4, 2009. Also formally submit your response to the application.

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

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/s/

CAROL F HILL
07/31/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-383

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) dated December 18, 2008, received December 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol Maleate Inhalation Powder, 150 mg and 300 mg.

We also refer to your April 28, 2009, correspondence, received April 28, 2009, requesting review of your proposed proprietary name, Arcapta Neohaler. We have completed our review of the proposed proprietary name, Arcapta Neohaler, and have concluded that it is acceptable.

The proposed proprietary name, Arcapta Neohaler, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 28, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, Regulatory Safety Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact OND Regulatory Project Manager in the Division of Pulmonary and Allergy Products.

Sincerely,

{See appended electronic signature page}

Carol Holquist, R.Ph.
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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 /s/
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Carol Holquist
7/23/2009 12:15:42 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Division of Cardiovascular and Renal Products-QT IRT Team	Carol Hill, PM, x1226 Division of Pulmonary and Pulmonary Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 21, 2009		22-383		December 15, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Arcapta Neohaler (indacaterol)		LABA	August 28, 2009

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- × OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a request for review of the QT study contained in the NDA submission dated December 15, 2008. This submission is electronic and may be found in the EDR under the same date.

PDUFA Due Date: October 18, 2009

SIGNATURE OF REQUESTER Carol Hill	METHOD OF DELIVERY (Check one) × MAIL ☐ HAND
SIGNATURE OF RECEIVER Devi Kozeli	SIGNATURE OF DELIVERER See electronic signature

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/s/

Carol F. Hill
7/21/2009 06:43:46 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **May 29, 2009**

To: **Ann Shea** **Sr. Assoc. Dir., Drug Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals Corp.**	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383: Revised Clinical Pharmacology Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-383
Novartis Pharmaceuticals Corporation
Indacaterol

We are in the process of reviewing your new drug application (NDA) dated, December 15, 2008, and have the following requests regarding the datasets of the bronchodilatory dose-response and frequency of dosing for indacaterol in the Modeling Report (release date: 24-Apr-2009).

1. Provide all datasets which were used for the Bayesian meta-analysis

2. Provide all datasets which were used for the peak-to-trough ratio analysis.

3. Provide full program (S-plus) which was used for NLME analysis.

Please disregard the information request sent today by email on May 29, 2009 at 3:47 pm. If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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/s/

Carol F. Hill
5/29/2009 05:22:19 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **May 29, 2009**

To: **Ann Shea** **Sr. Assoc. Dir., Drug Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals Corp.**	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383: Clinical Pharmacology Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-383
Novartis Pharmaceuticals Corporation
Indacaterol

We are in the process of reviewing your new drug application (NDA) dated, December 15, 2008, and have the following requests regarding the datasets for the report in Appendix-2-dose-response-and-regimen-modeling.

1. Provide all datasets which were used for the Bayesian meta-analysis

2. Provide all datasets which were used for the peak-to-trough ratio analysis.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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/s/

Carol F. Hill
5/29/2009 03:43:10 PM
CSO

4/24/09

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-383

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea, Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your Investigational New Drug Application (IND)/New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for indacaterol maleate, inhalation powder, 150 and 300 mcg for the treatment of chronic obstructive pulmonary disease (COPD).

We also refer to your April 15, 2009, correspondence, received April 17, 2009, requesting a Type A meeting to discuss the potential review issue comment number 1 listed in the Agency's Filing communication Letter dated, February 27, 2009. We have considered your request and concluded that the proposed discussion is premature. In addition, your request does not qualify as a Type A meeting request.

Our expectation is that your response will address all deficiencies listed in the February 27, 2009 correspondence.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
4/24/2009 10:51:25 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **April 11, 2009**

To: **Fernando Marcella, M.S.** **Drug Regulatory Affairs-GR CMC**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals Corp.**	Division of Pulmonary and Allergy Products
Fax number: 973-781-3320	**Fax number:** 301-796-9728
Phone number: 862-778-5062	**Phone number:** 301-796-1226

Subject: **NDA 22-383 – CMC Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-383
Novartis Pharmaceuticals Corporation
Arcapta (b) (4)

We are in the process of reviewing your amendment dated, March 31, 2008 and we have the following preliminary comments and requests.

1. Provide report IDD00483A which provides details of the investigation of how non-optimal capsule piercing affects the pharmaceutical performance of the drug product. Without this information it is not possible for us to completely gauge the results of the study of the 21 complaint devices returned from the trials.

(b) (4)

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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/s/

Carol F. Hill
4/11/2009 11:41:10 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **April 2, 2009**

To: **Ann Shea, Sr. Assoc. Dir. Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals**	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383 – Statistical Information Request**

Total no. of pages including cover: **1**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-383
Novartis Pharmaceuticals
Indacaterol

Please refer to your submission dated, December 20, 2006 for IND 48,649. In our February 1, 2007, response, to your request for a special clinical protocol assessment for study QAB149B2335s, additional comment (b) specifically stated:

> *Some subjects will be treated with study medication for longer than two weeks prior to making the decision regarding dose selection for stage two. Additional safety and efficacy information will be obtained on these subjects during that time period. Following dose selection, subjects participating in the two dose groups that are not carried forward will be discontinued from further participation in the study. Assure that your study report includes a summary of the additional efficacy and safety data (beyond the two week time point) for these subjects who are discontinued.*

You responded, February 21, 2007 with the following comment:

> *Novartis agrees to include a summary in the study report of the additional efficacy and safety data (beyond the two week time point) for these subjects who are discontinued.*

We were unable to locate this summary in the clinical study report, for QAB149B2335s, included in your NDA submission. If it is included in the NDA submission, indicate the specific section and page number for this summary; if it is not included, provide this report. Summarize the data at the following time points: Day 2, Day 15, Day 29, Day 57, Day 85, Day 113, Day 148, and Day 182. Also include a summary of trough FEV_1 and FEV_1 $AUC_{(1\text{-}4h)}$. A similar output as the one in your response submitted on March 16, 2009 would be appropriate.

Please submit your response by COB on April 6, 2009 via email to carol.hill@fda.hhs.gov or fax at 301-796-9728. If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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/s/

Carol F. Hill
4/2/2009 02:15:26 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: March 23, 2009

To: Ann Shea

Company: Novartis Pharmaceuticals Corporation

Fax: TBD

Phone: 862-778-4567

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-383; Response to Clarifying Questions

# of pages: 3

Thank you.

NDA 22-383
Indacaterol
Novartis

Please see the response below to your March 9, 2009, email request for clarification to the February 27, 2009, FDA filing communication sent on March 2, 2009:

Sponsor Question:

Novartis only seeks the approval of QAB for COPD indication. All the asthma studies that were conducted with QAB in the early drug development were submitted to the NDA 22-383. Could you please clarify this request?

Does the Agency want the SAS transport files or CRTs or neither of these for the relevant asthma studies?

FDA Response:

While we acknowledge that Novartis is seeking approval of QAB at this time for a COPD indication only, we believe for a beta agonist that will likely be used in patients with asthma as well as COPD, it is important to look at available dose response and dosing interval data that is available for asthma patients as well. Submission of summary data for QAB from the asthma clinical trials (rather than looking at each asthma trial individually) by Novartis would facilitate the review process significantly.

We do not need SAS files or CRTs at this time

If you have any questions, please contact Carol Hill at 301-796-1226.

_____
Eunice H. Chung, Pharm.D.
Regulatory Project Manager

NDA 22-383
Indacaterol
Novartis

Drafted: EChung/9MAR2009
Initialed: SBarnes/20MAR2009
LWu/23MAR2009
ADurmowicz/23MAR2009

Finalized: EChung/23MAR2009

Cc: Carol Hill

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/s/

Eunice Chung
3/23/2009 04:04:39 PM
CSO
on behalf of Carol Hill

Eunice Chung
3/23/2009 04:05:03 PM
CSO
on behalf of Carol Hill

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: March 23, 2009

To: Ann Shea

Company: Novartis Pharmaceuticals Corporation

Fax: TBD

Phone: 862-778-4567

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-383; Statistical Information request #2

# of pages: 3

Thank you.

NDA 22-383
Indacaterol
Novartis

We are currently reviewing your December 15, 2009, New Drug Application 22-383 and have the following requests:

1. On page 54, section 2.7.3 Summary of clinical efficacy, you presented table 3-21 (attached below). The second part of the table provides only the summary of FEV_1 $AUC_{(1\text{-}4h)}$, submit an expansion of that information.

    a. Provide summaries for all study arms at all time points when FEV_1 $AUC_{(1\text{-}4h)}$ is available, including comparisons between all possible pairs of treatment arms in a similar format as the results you presented in the March 16, 2009, response submitted on to our March 9, 2009, statistical information request.

2. Indicate which data set was used to generate the table. We were only able to find "AUC_0_4" evaluated at time points: "Week 1 Day 1", "Week 2 Day 14", "Week 12 Day 84", and "Week 26 Day 182" in data set "B2335s\a_spider.xpt".

Table 3-21 Study B2335S Key interim analysis results at Day 15 (imputed with LOCF): treatment comparisons (interim ITT population)

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

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center(country), with center(country) as a random effect.
Bold LS mean differences were those identified as reference values by dose selection criteria, * = selected doses
Source: [Study B2335S-Table 11-5]

NDA 22-383
Indacaterol
Novartis

Please submit your response by March 27, 2009 COB via email to Carol.hill@fda.hhs.gov or via fax at 301 796-9718. If you have any questions, please contact Carol Hill at 301-796-1226.

_____
Eunice H. Chung, Pharm.D.
Regulatory Project Manager

NDA 22-383
Indacaterol
Novartis

Drafted: EChung/18MAR2009
Initialed: SBarnes/20MAR2009
DLiu/23MAR2009
QLi/23MAR2009

Finalized: EChung/23MAR2009

Cc: Carol Hill

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/s/

Eunice Chung
3/23/2009 03:50:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-383

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ting Chen, MS
Director, Drug Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 18, 2008, received December 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for indacaterol maleate inhalation powder, QAB149.

We also refer to your December 19, 2008, correspondence, received December 19, 2008, requesting review of your proposed proprietary name, Arcapta (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reason.

(b) (4)

Additionally, during our evaluation of the proposed proprietary name, Arcapta (b) (4), we evaluated the root name, Arcapta. Our findings indicate that the name Arcapta, without the term (b) (4) did not appear to be vulnerable to name confusion that could lead to medication errors. Thus, we propose you consider the use of the name Arcapta without "(b) (4)" for this product.

If you choose to use the proposed proprietary name, Arcapta, please re-submit a name request for this proposed name. However, if you intend to use an alternative proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, Regulatory Safety Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact Carol Hill, Regulatory Project Manager in the Division of Pulmonary and Allergy Products.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
3/18/2009 03:57:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-383 **DISCIPLINE REVIEW LETTER**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07636-1080

Attention: Ting Chen, M.S.
Director, Regulatory Affairs

Dear Ms. Chen:

Please refer to your December 15, 2008, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta (b) (4) (Indacaterol Maleate Inhalation Powder).

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

The following comments pertain to the drug substance.

1. With respect to the (b) (4) at Novartis Pharma AG site:

   a. Provide an explanation for its use.

   b. Provide the amount used.

   c. Provide the identity of this material, or provide a letter of authorization to allow our reference to a master file containing this pertinent information.

2. Provide the micronization parameters that are used for (b) (4) the drug substance.

3. Provide, or give reference to the pertinent section of the application that includes, the acceptance criteria that are applied to recovered (b) (4) of the drug substance (S.2.2.4.3.9). These could not be located in S.2.3.

4. Revise the description of the drug substance manufacturing process so that all points at which recovered (b) (4) are used, are identified.

5. Provide a representative certificate of analysis for the (b) (4) final indacaterol maleate.

6. As the purification of (b) (4)

7. Provide a brief description of how the single (b) (4) .

8. Revise the method 10331.01 *Particle size by laser light diffraction* to indicate the equipment (measuring and dispersing devices) that will be used for the routine collection of data. Due to the importance of the method, it is not acceptable to merely give examples of these items, which are often unique and which produce particle size distribution data distinct from that obtained with alternate equipment. Switching reagents and equipment would require a study of comparability or might necessitate a change of the acceptance criteria.

9. For method 10331.01, clarify whether or not the [redacted] (b) (4) the validation study. If not, provide data demonstrating how the use of this agent impacts the PSD results obtained with the method.

10. Modify the method 20901.01 *Identity by X-ray Diffraction* such that it specifies that a [redacted] (b) (4) will be used, as per the statements made in the introduction of the method validation report VR20901A. Alternately, specify another [redacted] (b) (4) identity testing.

11. Revise the method 32001.01 *Enantiomer by HPLC* used for the determination of the enantiomer [redacted] (b) (4) content in the drug substance to include the shelf lives of the various solutions and standards, consistent with what was found in the validation studies.

12. Revise the method 35601.01 [redacted] (b) (4) in the drug substance to include the shelf lives of the various solutions and standards, consistent with what was found in the validation studies.

13. Revise the system suitability criteria for the method 35601.01 such that the requirements are a more reasonable reflection of the capability demonstrated by the data in the validation report VR35601B.

14. Revise the method 35602.01 [redacted] (b) (4) in the drug substance to include the shelf lives of the various solutions and standards, consistent with what was found in the validation studies.

15. Revise the system suitability criteria for the method 35602.01 such that the requirements are a more reasonable reflection of the capability demonstrated by the data in the validation report VR35611C.

16. For the method 36911.01 *Heavy metals by ICP-OES*:

    a. Revise the system suitability criteria for precision (not more than [redacted] (b) (4) of the analyte measurements for the calibration check solution to reflect the precision that is demonstrated in the validation report VR36911B.

    [redacted] (b) (4)

17. Additional comments regarding the acceptance criteria and reporting limit for [redacted] (b) (4) may be forthcoming pending review by the pharmacology/toxicology team.

18. For the drug substance method 54001.01 *Impurities and assay by HPLC* [redacted] relative standard deviation (RSD) for the replicate injections (n = 6) of reference solution 2, considering the repeatability data in the validation report VR30001C.

19. For method 54001.01, include the use of the response factor for the potential impurity (b) (4) or unspecified impurities.

20. Revise method 54001.01 to include direction regarding the sample and reference solution shelf-lives.

21. (b) (4) Provide an agreement to revisit this acceptance criterion and revise it appropriately once a sufficient number of batches of drug substance are prepared with the commercial process on production equipment.

22. Based on the data provided for the batches of drug substance prepared with the (b) (4) process on production equipment (July-August 2008 batches), the acceptance criteria for related substances are considered to be too permissive. However, since the number of these batches is limited, provide an agreement to revisit these acceptance criteria and revise as appropriate once a sufficient number of batches of drug substance are prepared with the commercial process on production equipment.

23. Set acceptance criteria for (b) (4) in the drug substance that are more closely reflective of what your production process routinely achieves, as there is no therapeutic benefit to the patient from (b) (4), nor has it been shown that (b) (4) levels approaching your proposed acceptance criteria do not impact drug substance stability or drug product performance or stability.

The following comments pertain to the drug product.

24. DMF (b) (4) was reviewed and was found to be inadequate to support your application. A deficiency letter was forwarded to the holder.

25. Provide an agreement to revisit and revise, if appropriate, the device extractables acceptance criteria for the (b) (4) release agent once you have collected data from multiple commercial scale device batches.

26. Provide the report on the complaint investigations for the phase III drug product as indicated in section P.2.4.3.7.

27. Revise the reporting limit for related substances in the lactose to more closely reflect the true limit of quantitation. The data in the validation report are supportive of a limit of quantitation that is much lower than the 0.3% limit currently in use.

28. Provide data and rationale for your justification of the reporting limit of (b) (4) for the three unknown impurities in the lactose excipient (b) (4)).

29. Propose an acceptance criterion for the total impurities allowed in lactose and base it on data from batches that have been used in preparing the phase 3 clinical material and registration stability batches. Provide these data along with the revised impurities acceptance criteria.

30. Provide the numerical impurities data in tabular format for the seventeen batches of lactose that were said to be used to set the acceptance criteria for impurities and related substances and indicate what these batches of lactose were used for in the development program (e.g., preparation of phase 3 clinical batches, preparation of phase 1 clinical batches, preparation of registration stability batches).

31. (b) (4) the acceptance criteria for the particle size by laser diffraction for the lactose excipient. Based on the representative data provided (n = 5 batches) in the justification of specifications section, the limits for (b) (4), and the span are excessive. Provide the particle size laser diffraction data for

the lactose used to prepare the clinical and registration stability batches along with the revised acceptance criteria.

32. Provide performance data (dose delivery and APSD) for batches of drug product prepared with lactose having (b) (4) content up to (b) (4), the maximum amount said to have been observed in the seventeen representative lactose batches used to set the (b) (4) content limit of NMT (b) (4). Without such data it is unknown whether or not there are any consequences in terms of the drug product performance. Alternately, lower the acceptance criteria to the quantitation limit (i.e., not more than (b) (4)), as most of the batches were not observed to have detectable (b) (4) lactose.

33. Based on the representative data provided in the section on justification of lactose specifications, (b) (4) the acceptance criterion for protein content to not more than (b) (4)).

34. The validation report VR32001K for method 32001.01 *Enantiomer by HPLC* for the drug product did not address the potential for interference from the three specified drug substance impurities, (b) (4). Provide data demonstrating the specificity of the method and the ability to assess the amount of (b) (4) in the presence of any of these drug substance impurities.

35. Comments regarding the acceptance criteria for foreign particulates in the drug product determined by method 37321.01 *Light obscuration particle count* may be forthcoming, depending on the evaluation of our pharmacology/toxicology team.

36. Provide the results of specificity studies for the method 59701.01 *Assay and uniformity of dosage units by content uniformity by HPLC* to demonstrate the discrimination of the analyte in the presence of impurities (degradants, by-products).

37. Revise the method 50211.01 *Delivered-Dose Uniformity by HPLC* to remove the allowance of a (b) (4) excessive with respect to the typical volume of air withdrawn through such products by patients during use.

38. The validation report VR50211D *Content uniformity of delivered dose by HPLC* contains data showing both strengths delivering well below the target deliveries of (b) (4). In fact, with a mean delivery of (b) (4) observed for the (b) (4) strength, the proposed acceptance criterion of (b) (4) of the target is not achieved. Provide an explanation or reference the part of the application containing an explanation for this observed low emitted dose delivery, when compared to other batch analyses data provided (e.g., in P.5.4).

39. For the method 10351.01 *Aerodynamic particle size distribution by Andersen Cascade Impactor*, clarify how results would be assessed relative to the specification acceptance criteria if mass balance requirements were not met for any individual test and repeat tests (up to two) were performed. This was not clear from the "material balancing, averaging and reporting or results" section of the method.

40. Revise the method 10351.01 to remove the allowance of a second (b) (4) is excessive with respect to the typical volume of air withdrawn through such products by patients during use.

41. DMF (b) (4) for the information supporting the manufacture of the Concept1 device was reviewed and was found to be inadequate. A deficiency letter was forwarded to the holder.

42. Provide justification for the allowance of up to (b) (4) of force to open and close the mouthpiece, with consideration given to the ranges that were measured with device samples from batch B1320 presented in the application.

43. Provide conformation that the photostability studies performed on the drug product dosage form used a light source that was consistent with the recommendations of ICH Q1B. Provide justification if the source deviated from those recommendations.

44. Provide data for more than one batch of devices (b) (4)

45. Revise the method validation package to include a list of samples that includes the impurity (b) (4) since it is needed for the assurance of sufficient resolution for both the drug substance and drug product impurities methods. Samples of (b) (4) should be provided if a request for samples is made by Agency laboratories.

46. Specify the type of lactose used to prepare the placebo capsules and provide the specification to which it is tested.

47. If revisions are made to various sections of the application in response to the comments above, include these revised sections in appendices to the response with flags identifying the changes made.

48. We have the following preliminary labeling comments.

a. Revise the DESCRIPTION section of the labeling as follows: Each clear, hard gelatin capsule contains a dry powder blend of (b) (4) indacaterol (b) (4) with approximately 25 mg of lactose monohydrate (which contains trace levels of milk proteins) as the carrier.

b. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a brief description of the appearance of the device.

c. Revise the section of the med-guide entitled "How do I store Arcapta (b) (4)?" to specifically state that both the inhaler and the blister-packaged capsules should be protected from moisture and heat and be stored at room temperature.

d. Revise the section of the med-guide entitled "(b) (4)" such that it is clear that the "Arcapta (b) (4)" refers to the complete drug product, i.e., the inhaler and the blister-packaged capsules.

e. Revise the med-guide section to include a clear, separate, and specific warning to patients to only open the blister packaging immediately before they are to administer a capsule for inhalation. The current statements under the "Remove an Arcapta capsule" do not emphasize this point in a strong enough manner. Also, revise the "Remember:" section adding a statement to the same effect, e.g. "CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER, AND ONLY REMOVED IMMEDIATELY BEFORE USE."

f. The established name and the product strength must match. Therefore, you have the following two options:

i. Change the established name of the drug product to indacaterol inhalation powder while retaining the strength (b) (4) and include footnotes stating, respectively, (b) (4) or

ii. Change the (b) (4) while retaining the established name as indacaterol maleate inhalation powder, in which case no additional statement is needed.

g. (b) (4)

h. Revise the dosage form in the SPL style sheets to "powder, metered" from "inhalant."

i. Revise the SPL style sheet for the (b) (4) strength such that the amount of lactose per capsule is 25 mg.

49. Provide the expected introduction concentration (EIC) of the active moiety entering the aquatic environment from patient use. If the calculation of the EIC differs from that recommended in the Agency guidance entitled *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications*, provide the calculations for our review and evaluation.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Eunice Chung, Project Management Staff, at (301) 796-4006.

Sincerely,

Ali Al-Hakim, Ph.D.
Chief, Branch II
Division of Premarketing I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ali Al-Hakim
3/11/2009 02:31:58 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: March 9, 2009

To: Ting Chen, MS
Director
Drug Regulatory Affairs

Company: Novartis

Fax: 973-781-2565

Phone: 862-778-1530

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-383; Statistical Information Request

# of pages: 3

Thank you.

NDA 22-383
Indacaterol
Novartis

We are currently reviewing your December 15, 2008, New Drug Application (NDA) and have the following request:

> In the table attached from section 2.7.3 Summary of clinical efficacy you commented:
>
> > *At 14 days, the pharmacodynamic effect is stable, with no evidence of an improved effect with longer dosing periods, as shown in table 3-24 from study B2335s. Thus the data at 14 days are a reliable basis for dose selection.*
>
> We would like to see an expanded table with information on all study arms, i.e. Ind 75µg, Ind 150µg, Ind 300µg, Ind 600µg, Formoterol, Tiotropium, and placebo at 4 time points: day 2, day 15, week 12, and week 26. Please use trough FEV_1 with imputation and without imputation (using available FEV1 only). Other than the number of patients (N) you already included in the table with the LOCF imputation approach, please add one more column to indicate the number of patients without imputation.

Please submit your response to my attention via facsimile to 301-796-9718 or via email to Eunice.Chung@fda.hhs.gov by COB on March 16, 2009. Your response will need to be submitted officially to the NDA as well.

Table 3-24 Study B2335S Trough FEV_1 (L) at Day 2, Day 15, and Week 26 (imputed with LOCF): treatment comparisons (ITT population)

	Treatment				Treatment difference			
Treatment	**N**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**	**p-value**
Day 2								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	400	1.44	0.011	Ind 150 µg - Placebo	0.11	0.012	(0.08, 0.13)	<.001
Ind 300 µg	396	1.48	0.011	Ind 300 µg - Placebo	0.14	0.012	(0.12, 0.16)	<.001
Tio	395	1.43	0.011	Tio - Placebo	0.10	0.012	(0.07, 0.12)	<.001
Placebo	391	1.34	0.011					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.01	0.012	(-0.01, 0.03)	<.001
				Ind 300 µg - Tio	0.04	0.012	(0.02, 0.07)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.03	0.012	(0.01, 0.06)	0.006
Day 15 (imputed with LOCF)								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	389	1.47	0.013	Ind 150 µg - Placebo	0.17	0.015	(0.14, 0.20)	<.001
Ind 300 µg	391	1.48	0.013	Ind 300 µg - Placebo	0.18	0.015	(0.15, 0.21)	<.001
Tio	393	1.43	0.013	Tio - Placebo	0.14	0.015	(0.11, 0.17)	<.001
Placebo	377	1.29	0.013					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.03	0.015	(0.01, 0.06)	<.001
				Ind 300 µg - Tio	0.04	0.015	(0.02, 0.07)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.01	0.015	(-0.02, 0.04)	0.461
Week 26 (imputed with LOCF)								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	349	1.41	0.017	Ind 150 µg - Placebo	0.16	0.019	(0.12, 0.19)	<.001
Ind 300 µg	361	1.44	0.017	Ind 300 µg - Placebo	0.18	0.018	(0.14, 0.22)	<.001
Tio	356	1.40	0.017	Tio - Placebo	0.14	0.018	(0.10, 0.18)	<.001
Placebo	317	1.26	0.017					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.02	0.018	(-0.02, 0.05)	<.001
				Ind 300 µg - Tio	0.04	0.018	(0.00, 0.07)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.02	0.018	(-0.01, 0.06)	0.204

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country), with center(country) as a random effect.
Superiority to placebo means that the two-sided $p < 0.05$ and the 95% CI is entirely higher than 0 L.
Non-inferiority to tiotropium means that the one-sided $p < 0.025$ and the 95% CI is entirely higher than -0.055 L.
-15 min time point is equal to 23h 45min as measured at Visit 14 after 26 weeks treatment prior to final dose.
Source: [Study B2335S-Table 11-9]

If you have any questions, please contact Eunice H. Chung at 301-796-4006.

Eunice H. Chung, Pharm.D.
Regulatory Project Manager

NDA 22-383
Indacaterol
Novartis

Drafted: EChung/March 9, 2009
Initialed: SBarnes/March 9, 2009
DLiu/ March 10, 2009
QLi/March 10, 2009

Finalized: Robinson for EChung/March 11, 2009

Cc: Carol Hill

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/s/

Angela Robinson
3/13/2009 08:35:07 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-383

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ting Chen, MS
Director, Drug Regulatory Affairs

Dear Ms. Chen:

Please refer to your new drug application (NDA) date December 15, 2008, received December 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Arcapta (b) (4) (proposed) (indacaterol maleate inhalation powder, QAB149). We also refer to your submissions dated, December 19, 2008 and January 15, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is October 18, 2009

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 14, 2009.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. After preliminary assessment of the dose-ranging and dosing interval data submitted it is unclear whether the appropriate dose and dosing interval of indacaterol for the treatment of bronchospasm associated with chronic obstructive lung disease have been chosen.

2. We are concerned that the name "Arcapt [redacted] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Clinical:

1. Submit summary dose response and dosing frequency data for indacaterol that you have collected from studies conducted to support its clinical development for patients with asthma. Include trough FEV_1, 12 and 24 hour FEV_1 time curves, data on once and twice daily dosing of indacaterol (if assessed), and data for active comparators that were given concurrently in clinical trials.

Clinical Pharmacology:

2. Submit information on the potential of indacaterol/major metabolites to induce the major CYP P450 enzymes.

3. Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PK Parameters, and other relevant study information for the following PK studies:

   a. CQAB149A2106, CQAB149A2311, CQAB149B2216, CQAB149B2220, CQAB149A2215, CQAB149B2202, CQAB149A2211, CQAB149A2221, CQAB149B2201, CQAB149A2307, CQAB149B2103, CQAB149A2212

4. Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PD Parameters, and other relevant study information for the following PD studies:

   a. CQAB149B2202, CQAB149B2201, CQAB149B2217

Chemistry, Manufacturing and Controls:

5. Provide a reference to 21CFR regulations for food contact materials or results from suitability tests for the [redacted] (b) (4) used to store the drug substance.

6. Provide 100% size mock ups of carton and container label.

7. Provide samples of the drug product.

8. Update the drug substance specification to include a test for [redacted] (b) (4).

9. We note that the capsule sizes for the approved Foradil Aerolizer and your proposed Arcapta [redacted] (b) (4) are the same. Provide available in vitro performance data for the indacaterol capsules being delivered by the Aerolizer device and formoterol capsule delivered by the [redacted] (b) (4) device to see if interchanging the devices and capsules provides comparable in vitro performance results. Address the possibility that patients might interchange the devices and capsules since the capsule sizes are identical and could potentially be interchanged.

10. Provide available stability and in vitro performance information for your drug product when the capsules are stored outside of the blister (as is usual for patients to put them in pill boxes) for a period of seven days.

11. Provide certifications from the excipient manufacturers that their products conform to USP OVI limits.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
2/27/2009 03:48:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Office of Surveillance and Epidemiology

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Carol Hill, Project Manager, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/16/09		22-383	N	December 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
indacaterol maleate	Standard	LABA	May 8, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
This is a request for review of the REMS which may be obtained from the EDR in the submission dated, December 15, 2008.

Mid-Cycle Review: May 12, 2009
Wrap Up: August 18, 2009
Division Goal: October 16, 2009
PDUFA Date: October 18, 2009

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER
Sean Bradley

PRINTED NAME AND SIGNATURE OF DELIVERER
Carol Hill

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 /s/
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Carol F. Hill
1/16/2009 11:05:47 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Office of Surveillance and Epidemiology

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Carol Hill, Project Manager, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/16/09		22-383	N	December 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
indacaterol maleate	Standard	LABA	July 31, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
This is a request for review of the label (proposed Trade name Arcapta [redacted] (b) (4)). The draft package insert, medication guide and carton and container labels may be found in the EDR submission dated, December 18, 2008 and January 15, 2009.
Mid-Cycle Review: May 12, 2009
Labeling Meeting: August 11, 2009
Division Goal Date: October 16, 2009
PDUFA Date: October 18, 2009

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER
Sean Bradley

PRINTED NAME AND SIGNATURE OF DELIVERER
Carol Hill

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/s/

Carol F. Hill
1/16/2009 10:58:11 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Drug, Marketing, Advertising and Communications (DDMAC) WO 22 RM 1400

FROM (*Name, Office/Division, and Phone Number of Requestor*):
Carol Hill, Project Manager, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/16/09		22-383	N	December 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
indacaterol maleate	Standard	LABA	July 31, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
This request is for review of the label (proposed trade name Arcapta [redacted] (b) (4)). The draft package insert, medication guide and carton and container labels may be found in the EDR submission dated, December 15, 2009 and January 15, 2009.
Mid-Cycle Review: May 12, 2009
Labeling Meeting: August 11, 2009
Division Goal Date: October 16, 2009
PDUFA Date: October 18, 2009

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER
Wayne Amchin

PRINTED NAME AND SIGNATURE OF DELIVERER
Carol Hill

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/s/

Carol F. Hill
1/16/2009 10:49:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION				REQUEST FOR CONSULTATION
TO: *(Division/Office)* Tim Robison, Ph.D., Acting Pharm/Tox Team Leader			FROM: Craig M. Bertha, Ph.D., ONDQA, Div I	
DATE 15-JAN-2009	IND NO. IND 48,649	NDA NO. N22-383	TYPE OF DOCUMENT Original NDA [505(b)(1)]	DATES OF DOCUMENTS 17-DEC-2008
NAME OF DRUG Arcapta (b) (4) (indacaterol maleate) inhalation powder		PRIORITY CONSIDERATION 1	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE by 15-MAR-2008 if possible
NAME OF FIRM: Novartis Pharmaceuticals Corporation				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY	PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW X OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER	CHEMISTRY PHARMACOLOGY BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

DISSOLUTION BIOAVAILABLITY STUDIES PHASE IV STUDIES	DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS *(List below)* COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL
COMMENTS/SPECIAL INSTRUCTIONS: Please see attached. cc: Orig. NDA # 22-383 ONDQA/DIV I/CBertha ONDQA/DIV I/AAI-Hakim OND/DPAP/CHill OND/DPAP/TRobison OND/ONDQA/DIV I/PPeri	
SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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1/15/2009 03:34:51 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-383

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07963-1080

Attention: Ting Chen, M.S.
Director, Regulatory Affairs

Dear Ms. Chen:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Arcapta [redacted] (b) (4) (proposed)
QAB149 (Indacaterol Maleate Inhalation Powder)

Date of Application: December 15, 2008

Date of Receipt: December 18, 2008

Our Reference Number: NDA 22-383

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Hill, M.S.
Regulatory Health Project Manager
Division of Pulmonary and Allergy Product
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Carol F. Hill
1/8/2009 10:41:57 AM

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B
Meeting Category:	CMC Pre-NDA
Meeting Date and Time:	May 6, 2008 @ 13:30 pm
Meeting Location:	White Oak, Building 22
Application Number:	IND 48,649
Product Name:	QAB149 Inhalation Powder Hard Capsules
Received Briefing Package	April 4, 2008
Sponsor Name:	Novartis Pharmaceuticals Corporation
Meeting Requestor:	Fred Marcella
Meeting Chair:	Prasad Peri
Meeting Recorder:	Carol Hill
Meeting Attendees:	

FDA Attendees

Badrul A. Chowdhury, MD., PhD, Director, DPAP, ODE II
Sally Seymour, MD, Clinical Team Leader, DPAP, ODE II
Banu Karimi-Shah, MD, Clinical Reviewer, DPAP, ODE II
Ali H. Al Hakim, PhD, Chief, Branch 2, DPA I, ONDQA, OPS
Prasad Peri, PhD, Pharmaceutical Assessment Lead, Branch 2, DPA I, ONDQA, OPS
Craig Bertha, PhD, CMC Reviewer
Angela Robinson, LCDR, RN, MSN, Sr. Regulatory Project Manager
Carol Hill, MS, Regulatory Project Manager

Sponsor Attendees

Ting Chen, MS, Drug Regulatory Affairs
Mukul Dalvi, PhD, Inhalation and Device Development

Juergen Dedrichs, PhD, Technical Research and Development

Thomas Faller, PhD, Chemical and Analytical Development

Peter Fernandes, PharmD, Drug Regulatory Affairs

Benjamin Kramer, MD, Clinical Leader

Fred Marcella, MS, Drug Regulatory Affairs, CMC

Soraya Madani, Drug Regulatory Affairs

1.0 BACKGROUND

Novartis Pharmaceutical Corporation submitted a meeting request dated, February 28, 2008 received February 29, 2008. The meeting was requested to address chemistry, manufacturing, and controls questions regarding the sponsor's proposed information on the drug substance, drug product, and device to be provided in their upcoming NDA submission. The briefing document dated April 3, 2008 was received on April 4, 2008. An update to Appendix 3 of the briefing document was forwarded on April 21, 2008. This update included a copy of the FDA response dated, July 31, 2008 to the stability protocol assessment request dated, May 21, 2007.

2.0 DISCUSSION

The sponsor's questions appear in bold italic below, the FDA responses to the questions are in italics and the discussion appears in normal font.

Question 1

Novartis seeks FDA agreement on the designation of compounds (b) (4) as regulatory starting materials. As such, we would not be required to provide information regarding the manufacture of these compounds in the NDA.

Does the Agency agree?

FDA Response to Question 1

No, we do not agree.

It is indicated in section 2.1.2 of the briefing document that for both (b) (4), you may use "starting material from a new commercial source or by a different manufacturing process.". The information you have provided on the possible impurities/by-products that may be present in the proposed starting materials (b) (4) (table 2-2) and (b) (4) (table 2-4), is dependent on the syntheses routes and processes that you have outlined in figures 2-2 and 2-4, respectively. Without inclusion of these routes in the NDA, there will be no assurance that you will have a reproducible and well-characterized impurity profile in the drug substance synthesized from these proposed starting materials. This is particularly relevant for the (b) (4) intermediate, as there are (b) (4) (section 3.1.2).

Discussion:

Novartis addressed the Agency's concern regarding the proposal to employ a new commercial source or a different manufacturing process for starting materials (b) (4) by assuring complete assessment of any changes to the synthetic route. Novartis added that complete documentation of the synthesis-related impurity profiles will be provided by the implementation of a comparability protocol compiled to the Agency standards.

Novartis inquired if their plan would address the Agency's concerns. The Agency stated that without actual data, our comments are necessarily reserved, however; the approach should be simple and straight forward. The concern is whether the contractors will be committed to maintain the synthetic route included in the NDA. Also, at issue will be the ability of the impurities method to adequately detect any new impurities as a result of alteration of the processes precipitated by changes in suppliers. Novartis understood the Agency's concern and stated that the NDA will, in addition to the inclusion of the synthetic routes to (b) (4), include a commitment to these synthetic processes. However they indicated that no drug master files (DMFs) will be available from the suppliers of (b) (4) The Agency also noted that changes to the synthesis may involve routes that include intermediates or impurities that may be structural alerts that would have to be identified and qualified. With regard to compounds (b) (4), Novartis inquired whether the Agency would prefer DMFs from the suppliers, or the inclusion of the synthetic processes for these in the NDA and the contractors' commitments to implement the process as submitted. The Agency did not have a particular preference, as long as there was a commitment made that the processes would not change, and if they did, that the appropriate steps would be taken to assure the safety of the purity profile of the resultant drug substance made from the compounds (b) (4) The Agency stated that depending on the synthetic route, the compounds (b) (4) (b) (4) may have impurities that may be of toxicological concern (b) (4). The presence of such impurities would then require appropriate controls and qualification. Novartis commented that they have evaluated potential genotoxic substances from the currently used synthetic process. All intermediates have been screened and controlled via the Ames test. Novartis acknowledged their understanding that changes in the synthetic processes for the proposed starting materials (b) (4) should be addressed by appropriate submission to the NDA or, alternatively, in DMFs for the synthetic processes for which the Agency is given letters of authorization (LOA). Such DMFs would contain commitments to maintain the manufacturing process as described therein.

Question 2:

Two tests are applied to characterize the physical parameters of the drug substance, namely particle size by laser light diffraction and amorphous content determination by microcalorimetry. Novartis is considering those two tests as sufficient for adequate control of the physical characteristics of the drug substance.

Does the FDA agree that these two tests are sufficient for quality control of physical parameters?

FDA Response to Question 2

Yes we agree, based on the following:

1. *The crystalline form of the drug substance is routinely confirmed as is stated 2.2.1 (X-ray powder diffraction and FT-IR spectroscopy.*
2. *The laser diffraction and microcalorimetry methods are suitably validated and the associated acceptance criteria are appropriate, i.e., are based on data collected for the batches of drug substance used to prepare the batches of drug product that support the NDA (clinical, stability).*

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 3

Indacaterol inhalation powder hard capsules are [redacted] (b) (4) after manufacture. During this time there is [redacted] (b) (4) [redacted] (b) (4) Based on results of thorough investigations, Novartis plans to implement an [redacted] (b) (4) step as part of the drug product manufacturing process. Novartis considers that the performed investigations are sufficient to define the [redacted] (b) (4) conditions with adequate process controls.

Does the Agency agree that provided data package is sufficient to justify proposed [redacted] (b) (4) conditions? Is the approach acceptable?

FDA Response to Question 3

The use of [redacted] (b) (4) step as part of the manufacturing process for the drug product is not prohibited in and by itself. This assumes that it can be shown that the product found to be safe and efficacious in the clinical trials is sufficiently reproducible in exhibiting limited trending of the important in vitro performance test results during the proposed shelf life under recommended storage conditions and those conditions likely to be encountered through patient use. However, we encourage your efforts aimed at understanding and mitigating the cause of the observed phenomenon and the presentation of the summary of such studies in the upcoming application. We recommend that you also address this phenomenon and the potential consequences for your other dry powder inhaler products containing QAB149 (i.e., INDs 76,377 and 69,754).

Discussion:

Novartis acknowledged the Agency's comments and stated that they will implement the [redacted] (b) (4) program as part of the drug manufacturing process for their other INDs containing QAB149. Novartis mentioned that the [redacted] (b) (4) [redacted]. Novartis also commented that they plan to demonstrate batch-to-batch consistency of the drug product manufactured with the [redacted] (b) (4) step in place and

inquired if this would be acceptable. The Agency (as already stated in our response) stated that the proposal would be acceptable and recommended that any additional data from their ongoing study of the [redacted] (b) (4) be included in the NDA. The Agency asked if capsules other than gelatin capsules have been used for the drug product. Novartis commented that the drug substance is hydrophobic [redacted] (b) (4) [redacted] (b) (4) The Agency inquired if [redacted] (b) (4) [redacted] (b) (4) Novartis answered yes and noted that more details and data will be provided in the NDA submission.

Question 4

Novartis plans to test aerodynamic particle size distribution (APSD) by using an Andersen Cascade Impactor (ACI) procedure, which varies from the USP procedure (USP <601>). Novartis considers the proposed validated ACI testing method to be robust and suitable for quality control testing.

Does the Agency agree?

FDA Response to Question 4

The use of a testing flow rate of [redacted] (b) (4) *for APSD testing is acceptable for routine quality control purposes in conjunction with a one-time characterization of the dependency of the APSD on the flow rate. APSD data presentations should account for the variable cut-offs of the cascade impactor at different flow rates. The validation data supporting the suitability and the robustness of the APSD method will be evaluated during the review of the NDA.*

Discussion:

Novartis requested clarification for APSD determinations based on comment number 3 in the Agency's July 3, 2007 response to the request for special protocol assessment dated, May 21, 2007. Novartis commented that the current routine APSD testing is conducted as [redacted] (b) (4) per time point. Per the Agency's recommendation, for the registration stability batches (6 months onward), [redacted] (b) (4) will be evaluated per time point with each determination using a new device. Novartis added that device-to-device variability will be assessed in the device scale-up data package. The Agency noted that in the response to the Agency responses, Novartis failed to include the commitment to also use [redacted] (b) (4) for the APSD testing of future commercial supplies that had been stated in the original meeting package on p. 31. Novartis agreed to the use of [redacted] (b) (4) for the testing of future commercial supplies for the APSD parameter.

Question 5

Novartis seeks agreement for the strategy for the Dose content uniformity tests and specifications.

In the FDA's 03-Jul-2007 response to our request for Special Protocol Assessment of the registration stability protocol [Appendix 3], the Agency recommended that Novartis considers Parametric Tolerance Interval Testing (PTIT) as an alternate approach to controlling the uniformity of the delivered dose. Novartis proposes to maintain the current approach to controlling the uniformity of the delivered dose.

Novartis proposes to maintain the current approach, which is based on the FDA Draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products, 1998 for determining the acceptance criteria for uniformity of the delivered dose for the registration stability batches and for subsequent batches until a sufficient database is available to take a decision on the future approach.

Does the Agency agree?

FDA Response to Question 5

Although recommended, there is no requirement that you apply a Parametric Tolerance Interval Test (PTIT) approach for the testing of dose content uniformity. Therefore, you may maintain your current use of the zero tolerance approach. Specific comments on the acceptance criteria proposed, regardless of the approach, will be provided, if necessary, upon a review of the data supporting the application.

Discussion:

Novartis stated that the specifications in the briefing document are the same as those used in the development of the drug. Novartis proposes a specification for dose content uniformity (DCU) of [redacted] (b) (4) for individuals and [redacted] (b) (4) for the mean. Incoming data will continue to be accessed until NDA submission. The Agency stated that they agreed with the proposal and inquired why the volume to be drawn through the device is [redacted] (b) (4) instead of [redacted] (b) (4) The Agency advised that comparison testing should be done to determine if there is any difference in the doses delivered with the two distinct volumes [redacted] (b) (4) and that this data should be included in the NDA. If there is no difference in the two volumes then the use of [redacted] (b) (4) would be considered acceptable.

Question 6

Novartis intends to test Concept1 SDDPI (Singe dose dry powder inhaler) devices after patient use in clinical phase III studies. Testing will be conducted on regular return and any complaint devices for pharmaceutical performance parameters and physical attributes. Novartis considers this approach to be sufficient to adequately characterize the handling related properties of the device for inclusion in the NDA.

Does the Agency agree with this approach and is the testing protocol acceptable?

FDA Response to Question 6

Yes, we agree with the proposed protocol.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 7

For all characterization studies phase III devices will be used. Phase III devices have been produced using (b) (4) ***. For commercial supplies tools with*** (b) (4) ***In order to demonstrate that there is no impact on the product performance characteristics and to demonstrate equivalence Novartis will conduct in vitro studies, APSD (aerodynamic particle size distribution) and DCU (dose content uniformity) on three batches of each device.***

Does the Agency agree with this approach?

FDA Response to Question 7

Yes we agree with the approach and the plan to base the determination of pharmaceutical performance on the acceptance criteria of the proposed specification. However, fine particle fraction (FPF) values (as stated on p. 37) alone will not suffice in defining the acceptance criteria for the APSD parameter. The NDA should contain data for APSD on a stage-by-stage basis. Acceptance criteria should be proposed in terms of 3-4 groupings of stages that account for the complete particle size profile of the emitted drug.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 8

According to the Draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products, Control Extraction Studies have to be performed on "critical components" (Section G.2.b). The primary closure system for the inhalation hard capsule consists of a blister with a lidding foil. Both the blister material and lidding foil comply with the indirect Food Additive requirements. Novartis considers this kind of packaging material not critical and therefore does not envisage to perform extraction studies.

Does the Agency agree?

FDA Response to Question 8

Yes, we agree, with the understanding that if the blister and lidding material are "critical" for the stability of the drug product, this can be assessed via the performance testing data generated from your stability protocol.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

3.0 ATTACHMENTS AND HANDOUTS

- ❑ Novartis' Response to the FDA Pre-Meeting Comments dated 29April08
- ❑ QAB149 – Pre-NDA CMC Meeting Handouts dated 06May08

Drafted by: chill/May 22, 2008

Initialed by: Bertha/May 22, 2008

Peri/May 22, 2008

Al Hakim/May 22, 2008

Finalized by: chill/May 28, 2008

Drug Regulatory Affairs

IND 48,649

QAB149 Pre-NDA FDA Meeting 6 May 2008

Response to FDA Pre-meeting comments dated 29 April 2008

Authors: Ting Chen

Release date: May 1, 2008

Table of contents

1 Question 1

Novartis seeks FDA agreement on the designation of compounds [redacted] (b) (4) as regulatory starting materials. As such, we would not be required to provide information regarding the manufacture of these compounds in the NDA.

Does the Agency agree?

FDA Response
No, we do not agree.

It is indicated in section 2.1.2 of the briefing document that for both [redacted] (b) (4) you may use "starting material from a new commercial source or by a different manufacturing process." The information you have provided on the possible impurities/by-products that may be present in the proposed starting materials [redacted] (b) (4) (table 2-2) and [redacted] (b) (4) (table 2-4), is dependent on the syntheses routes and processes that you have outlined in figures 2-2 and 2-4, respectively. Without inclusion of these routes in the NDA, there will be no assurance that you will have a reproducible and well-characterized impurity profile in the drug substance synthesized from these proposed starting materials. This is particularly relevant for the [redacted] (b) (4) intermediate, as there are [redacted] (b) (4) (section 3.1.2).

Novartis Response:

Novartis acknowledges the Agency's concern about assurance of a reproducible and well-characterized impurity profile from a new source or by a different manufacturing process. Novartis agrees to provide an overview of the proposed synthetic scheme for each of the starting materials in the Original NDA. Any change in source or manufacturing process would be tracked via an established change control system. Additionally, Novartis will provide a comparability protocol detailing the parameters that will be evaluated (e.g., impurities, residual solvents, stability) in the event that any changes are made to the synthetic route of these starting materials which may impact the quality and impurity profile of these starting materials and may eventually impact the drug substance quality.

Under the prerequisites above, does the Agency concur with declaration of [redacted] (b) (4) as regulatory starting materials?

2 Question 2

Two tests are applied to characterize the physical parameters of the drug substance, namely particle size by laser light diffraction and amorphous content determination by microcalorimetry. Novartis is considering those two tests as sufficient for adequate control of the physical characteristics of the drug substance.

Does the FDA agree that these two tests are sufficient for quality control of physical parameters?

FDA Response
Yes, we agree, based on the following:

1. *The crystalline form of the drug substance is routinely confirmed as is stated 2.2.1 (X-ray powder diffraction and FT-IR spectroscopy).*
2. *The laser diffraction and microcalorimetry methods are suitably validated and the associated acceptance criteria are appropriate, i.e., are based on data collected for the batches of drug substance used to prepare the batches of drug product that support the NDA (clinical, stability).*

Novartis Response

We acknowledge FDA comments. No further discussion is needed.

3 Question 3

Indacaterol inhalation powder hard capsules are [redacted] (b) (4) after manufacture. During this time there is [redacted] (b) (4) Based on results of thorough investigations, Novartis plans to implement an [redacted] (b) (4) step as part of the drug product manufacturing process. Novartis considers that the performed investigations are sufficient to define the [redacted] (b) (4) conditions with adequate process controls.

Does the Agency agree that provided data package is sufficient to justify proposed [redacted] (b) (4) conditions? Is the approach acceptable?

FDA Response
The use of [redacted] (b) (4) step as part of the manufacturing process for the drug product is not prohibited in and by itself. This assumes that it can be shown that the product found to be safe and efficacious in the clinical trails is sufficiently reproducible in exhibiting limited trending of the important in vitro performance test results during the proposed shelf life under recommended storage conditions and those conditions likely to be encountered through patient use. However, we encourage your efforts aimed at understanding and mitigating the cause of the observed phenomenon and the presentation of the summary of such studies in the upcoming application. We recommend that you also address this phenomenon and the potential consequences for your other dry powder inhaler products containing QAB149 (i.e., INDs 76,377 and 69,754).

Novartis response:

We acknowledge FDA's comments and we will also address this phenomenon and the potential consequences for our other dry powder inhaler products containing QAB149.

Novartis will submit data from multiple drug product batches, manufactured at commercial scale, to demonstrate reproducible drug product performance and limited trending over shelf life for the important *in vitro* performance tests (Andersen Cascade Impactor test). Batch to

batch consistency will be achieved by [redacted] (b) (4), as described in the briefing book.

We will also submit data on additional commercial scale batches [redacted] (b) (4) under these conditions to demonstrate reproducible performance during and after [redacted] (b) (4).

As described in the briefing book extensive studies were conducted to understand the cause of the observed phenomenon. These studies identified [redacted] (b) (4) Studies designed to confirm our understanding of the [redacted] (b) (4) phenomenon are on-going. Data from these studies will also be included in the NDA.

Does the Agency agree that the above described NDA data package is sufficient for the demonstration of reproducible drug product performance and a thorough understanding of the cause of the observed phenomenon?

4 Question 4

Novartis plans to test aerodynamic particle size distribution (APSD) by using an Andersen Cascade Impactor (ACI) procedure, which varies from the USP procedure (USP <601>). Novartis considers the proposed validated ACI testing method to be robust and suitable for quality control testing.

Does the Agency agree?

FDA Response
The use of a testing flow rate of [redacted] (b) (4) *for APSD testing is acceptable for routine quality control purposes in conjunction with a one-time characterization of the dependency of the APSD on the flow rate. APSD data presentations should account for the variable cut-offs of the cascade impactor at different flow rates. The validation data supporting the suitability and the robustness of the APSD method will be evaluated during the review of the NDA.*

Novartis Response:

We acknowledge FDA comments.

Novartis would like further clarification/discussion at the scheduled meeting this Tuesday, May 6th for point #3, the Division's Response to our Request for Special Protocol Assessment dated 3 July 2007:

> *"For APSD measurement, we recommend that you test 5 capsules from 5 devices and report the results for each test to evaluate device variability. Evaluate mass balance results from these tests as well."*

Routine APSD measurements are conducted as [redacted] (b) (4) per time point. Each determination uses a new device and is evaluated for mass balance results. The 0.3 mg and the 0.15 mg products use [redacted] (b) (4) per determination, respectively.

Registration stability samples are treated in the same manner except that [redacted] (b) (4) per time point are being performed for the 25°C/60%RH storage condition starting from the 6 months time point onwards.

An evaluation of device and single capsule variability is being conducted as a one-off characterization study. This study will use fresh and aged drug product and multiple device lots. APSD profiles will also be generated for individual capsules. The results from this study will be summarized in the NDA.

Does the Agency agree that Novartis has satisfactorily addressed the point #3, the Division's Response to our Request for Special Protocol Assessment dated 3 July 2007?

5 Question 5

Novartis seeks agreement for the strategy for the Dose content uniformity tests and specifications.

In the FDA's 03-Jul-2007 response to our request for Special Protocol Assessment of the registration stability protocol [Appendix 3], the Agency recommended that Novartis considers Parametric Tolerance Interval Testing (PTIT) as an alternate approach to controlling the uniformity of the delivered dose. Novartis proposes to maintain the current approach to controlling the uniformity of the delivered dose.

Novartis proposes to maintain the current approach, which is based on the FDA Draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products, 1998 for determining the acceptance criteria for uniformity of the delivered dose for the registration stability batches and for subsequent batches until a sufficient database is available to take a decision on the future approach.

Does the Agency agree?

FDA Response
Although recommended, there is no requirement that you apply a Parametric Tolerance Interval Test (PTIT) approach for the testing of dose content uniformity. Therefore, you may maintain your current use of the zero tolerance approach. Specific comments on the acceptance criteria proposed, regardless of the approach, will be provided. If necessary, upon a review of the data supporting the application.

Novartis Response:

We acknowledge FDA comments. Novartis would like further clarification/discussion at the scheduled meeting this Tuesday, May 6th:

The current specifications are for development only. Novartis intends to propose a specification for DCU of [redacted] (b) (4) and [redacted] (b) (4), for individuals, and [redacted] (b) (4) of target delivered dose for the mean for the release of drug product. These will be consistent with the MDI/DPI Guidance "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation". However, we will conduct a

statistical evaluation of the extensive data base generated on stability for DCU and will propose appropriate data driven stability specifications.

Novartis would also like to clarify the testing procedure for DCU. The current procedure requires a volume of (b) (4) to be drawn through the device at a flow rate of (b) (4) We will include in the NDA one time characterization studies that compare volumes of (b) (4) and (b) (4) and assess flow rates from (b) (4).

Does the Agency agree with the specification approach and the testing procedure?

6 Question 6

Novartis intends to test Concept1 SDDPI (Singe dose dry powder inhaler) devices after patient use in clinical phase III studies. Testing will be conducted on regular return and any complaint devices for pharmaceutical performance parameters and physical attributes. Novartis considers this approach to be sufficient to adequately characterize the handling related properties of the device for inclusion in the NDA.

Does the Agency agree with this approach and is the testing protocol acceptable?

FDA Response
Yes, we agree with the proposed protocol.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

7 Question 7

For all characterization studies phase III devices will be used. Phase III devices have been produced using (b) (4) ***For commercial supplies tools with*** (b) (4) ***In order to demonstrate that there is no impact on the product performance characteristics and to demonstrate equivalence Novartis will conduct in vitro studies, APSD (aerodynamic particle size distribution) and DCU (dose content uniformity) on three batches of each device.***

Does the Agency agree with this approach?

FDA Response
Yes, we agree with the approach and the plan to have the determination of pharmaceutical performance on the acceptance criteria of the proposed specification. However, fine particle fraction (FPF) values (as stated on p. 37) alone will not suffice in defining the acceptance criteria for the APSD parameter. The NDA should contain data for APSD on a stage-by-stage basis. Acceptance criteria should be proposed in terms of 3-4 groupings of stages that account for the complete particle size profile of the emitted drug.

Novartis Response:

We acknowledge FDA comments. No further discussion is needed.

8 Question 8

According to the Draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products, Control Extraction Studies have to be performed on "critical components" (Section G.2.b). The primary closure system for the inhalation hard capsule consists of a blister with a lidding foil. Both the blister material and lidding foil comply with the indirect Food Additive requirements. Novartis considers this kind of packaging material not critical and therefore does not envisage to perform extraction studies.

Does the Agency agree?

FDA Response
Yes, we agree, with the understanding that if the blister and lidding material are "critical" for the stability of the drug product, this can be assessed via the performance testing data generated from your stability protocol.

Novartis Response:

We acknowledge FDA comments. No further discussion is needed.

9 Seeking Additional Comment from the Division:

Novartis would like further clarification/discussion at the scheduled meeting this Tuesday, May 6th.

The briefing package submitted for the April 7 Pre-NDA meeting (Pg 11 of the Briefing Book), we sought the Agency agreement on content and format for the proposed NDA. Novartis included a proposal to include 9 months drug product stability data at time of submission, with a commitment to update with 12 month data within 3 months following submission. The calculation of the shelf-life will be based on the 12-months stability dataset.

Does the Agency confirm that you agreed with this approach?

5 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name
IND 48649	NOVARTIS PHARMACEUTICALS CORP	QAB 149 (INHALATION POWDER HARD CAPS)

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
05/29/2008

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 7, 2008, 11:00 am-12:00 pm
Meeting Location:	Food and Drug Administration White Oak Campus, Building 22 10903 New Hampshire Avenue Silver Spring, MD 20993-0002
Application Number:	IND 48,649
Product Name:	QAB149
Received Briefing Package	March 7, 2008
Sponsor Name:	Novartis
Meeting Requestor:	Ting Chen, MS Senior Associate Director Drug Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D., Division Director
Meeting Recorder:	Lori Garcia, R.Ph., Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, MD, PhD, Division Director, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II
Sally Seymour, MD, Clinical Team Leader, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II
Banu Karimi-Shah, MD, Clinical Reviewer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Ted Guo, PhD, Statistical Reviewer, Division of Biometrics II, Office of Biostatistics
Qian Li, PhD, Statistical Team Leader, Division of Biometrics II, Office of Biostatistics
Lori Cantin, RPh, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II
Partha Roy, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology 2
Craig Bertha, PhD, Quality Reviewer, Division of Pre-Marketing Assessment I, Office of New Drug Quality Assessment
Virgil Whitehurst, PhD, Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II
Tim McGovern, PhD, Pharmacology/Toxicology Team Leader, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II
Angela Robinson, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Sponsor Attendees

Ting Chen, M.S., Drug Regulatory Affairs
Hans-Juergen Fuelle, M.D., Ph.D., Drug Regulatory Affairs
Peter Fernandes, Pharm.D., Drug Regulatory Affairs
Eric Couture, Ph.D., Drug Regulatory Affairs
Benjamin Kramer, M.D., Clinical Research
Roger Owen, Ph.D., Biostatistics
BeateElisabeth Vogel, Ph.D., Pre-clinical Safety
Lorraine Murphy, Ph.D., Global Program Director
Soraya Madani, Ph.D., Drug Regulatory Affairs

1.0 BACKGROUND

Novartis submitted a meeting request dated February 4, 2008, for a Type B meeting to discuss the proposed content and format for the NDA to support the registration of QAB149 Inhalation Powder hard capsules for patients with COPD.

A briefing package for this meeting was submitted on March 7, 2008. Upon review of the briefing package, the Division responded to Novartis's questions via fax on April 3, 2008. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Novartis's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2.0 DISCUSSION

2.1 QUESTION 1

Novartis believes that the proposed content and format of this NDA as described will be adequate for filing. A full table of contents is found in Appendix 1. In addition, the safety information planned to be included in the 120-Day Safety Update is outlined. Does the Agency agree with the content and format proposals?

FDA Response

In general the proposed content and format for NDA submission appear reasonable; however, clarify the location of the ISE and ISS. Refer to the "Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" for information (http://www.fda.gov/cder/guidance/7621dft.pdf).

We remind you that your NDA should be complete with all the information you deem necessary to support approval at the time of NDA submission. We expect Study B2339 (QTc study) to be submitted in the original NDA submission.

2.2 QUESTION 2

Novartis requests a waiver for conducting trials in pediatrics as COPD does not occur in this population. Does the Agency agree to grant a waiver for QAB149 from the requirements of the Pediatric Research Equity Act for patients under 18 years of age?

FDA Response

Although COPD is not a disease of the pediatric population, as a once-daily beta-agonist, QAB149 has potential for off-label use in asthma patients, including pediatric patients. Due to the potential for off-label use in asthma, we expect studies to be conducted in patients with asthma, including pediatric patients.

Discussion

Novartis requested clarification regarding the acceptability of submitting a request for a pediatric waiver in the future NDA submission. The Division stated that it could not guarantee that a waiver would be granted at this point in time, as this would ultimately be a review issue. As an example, the Division noted that pediatric studies had been required of two long-acting beta-agonists recently approved for COPD, due to their potential off-label use in asthma patients. Novartis proposed to address the potential for off-label use by developing a risk management program, using strict, robust, and clear language in the labeling, and providing an educational program. Novartis also proposed a plan to proactively monitor for off-label use in order to correct the problem if it occurs. The Division stated that its concerns may not be alleviated by these measures, but that Novartis could submit this information as part of their justification for a waiver. The Division noted that labeling reflecting the fact that the drug has not been studied in children may not be enough to prevent off-label use for asthma in pediatric patients. The

Division also noted that any pediatric studies performed would likely be included in the product label.

2.3 QUESTION 3

Pooled efficacy data of indacaterol will be summarised and pooled for all long-term (at least 50 days in length) COPD studies: B2334, B2335S and B2346. In addition, subgroup analyses will be presented for key endpoints as indicated below.
Does the Agency agree?

FDA Response

Your pooling strategy for the SCE appears reasonable.

2.4 QUESTION 4

All indacaterol studies of adults (See Appendix 3: studies listed in Tables 1-1, 1-2a, 1-2b and 1-2d, but excluding the pediatric study C2101) will be pooled for a summary of exposure to the drug. The summaries will be broken down as follows:
All the studies including an indacaterol mono-therapy arm:

1. ***Exposure for all indacaterol devices as well as a breakdown into exposure for 75, 150, 300 and 600 mcg inhaled through the Concept 1 device or any dose through all 'other' devices will be summarised. In addition, exposure will be summarised for the comparator treatment categories including placebo and the fixed dose combinations QMF and QVA. The information will be presented by subject type (healthy volunteer, COPD patients and asthma patients).***
2. ***Data from all long-term (at least 50 days in length) COPD studies: B2334, B2335S and B2346.***
3. ***Data from all short term studies (less than 50 days in length) (see Appendix 3: studies listed in Tables 1-1, 1-2a, 1-2b and 1-2d, but excluding B2334, B2335S, B2346, A2222 and C2101). The information will be presented by subject type (healthy volunteer, COPD patients and asthma patients).***

Does the Agency agree?

FDA Response

Your pooling strategy appears reasonable. Clarify where in the SCS you plan to include the discussion regarding the Holter monitoring data.

Discussion

Novartis indicated that Holter data from a subset of patients (n≈450) from the phase 3 study (B2335S) will be provided in the clinical study report and in the CTD section 2.7.4.4: Vital Signs, physical findings, and other observations related to safety. The

proposed analysis is to include 24-hour daily mean heart rate, hourly mean heart rate, frequency of arrhythmias, ventricular arrhythmias, and supraventricular events, and will be summarized by treatment for each visit separately. The Division stated that Novartis' plan appeared reasonable, but noted that patients with significant changes (e.g. heart rate or arrhythmias) should also be identified (outliers).

2.5 QUESTION 5

Adverse events will be summarised for all studies and all treatment groups. The summaries will be broken down as follows:

1. ***Pooling of 3 month COPD data from COPD stuides: study B2346 and the first 3 months of studies B2334 and B2335S***
2. ***Pooling of 6 month data from COPD studies: study B2335S and the first 6 months of study B2334***
3. ***12 month COPD data: study B2334***
4. ***Pooling of data from all short term studies (less than 50 days in length) (see Appendix 3: studies listed in Tables 1-1, 1-2a, 1-2b and 1-2d, but excluding studies B2334, B2335S, B2346, A2222 and C2101).***

In addition, deaths or SAEs will be summarized for all the studies including the indacaterol mono-therapy arm.

Does the Agency agree?

FDA Response

We agree.

2.6 QUESTION 6

In alignment with the request at the end of phase 2 meeting to fully characterize the post-inhalation cough (PI cough), the following measures were put in place in the pivotal trials to assess the occurrence of cough. There is a specific eCRF page (Appendix 4) to capture post-inhalation events and their time of onset and duration. An assessment will be made of possible evidence for an association between PI cough and each of the following: decreases in FEV_1 within 30 minutes of dosing, bronchospasm reported as an AE, FEV_1 across time, exacerbations, AE leading to discontinuation and patient disposition.

Does the Agency agree with the proposals to address potential concerns regarding PI cough?

FDA Response

Your proposal appears reasonable.

2.7 QUESTION 7

Further to previous discussions with the Agency regarding non-clinical study results of glycogen deposition, Novartis is monitoring serum glucose in the Phase 3 trials and will report the results in the NDA as described.

Does the Agency agree with the proposal?

FDA Response
We remain concerned regarding the periportal hepatocellular vacuolation/ glycogen deposition that was seen in dog toxicity studies as this toxicity is not easily monitored in humans. The results of the serum glucose monitoring in your Phase 3 program and the issue of glycogen deposition will be a review issue.

Discussion

Novartis response to the FDA response provided above, is as follows:

- Glycogen deposition/hepatic vacuolation in dogs is observed on dosing with QAB149 as is the case with marketed inhaled beta2 agonists and inhaled corticosteroids. This finding is not associated with any other liver findings nor with any liver enzyme elevations. The severity does not increase over time and is fully reversible within 4 weeks of discontinuation of dosing.

- Literature references indicate that the presence of increased levels of glycogen in the liver probably reflects a minor alteration in glucose utilization or production due to the pharmacological activity of the drug.

- The clinical experience with LABAs and inhaled corticosteroids, to the best of our knowledge, has not provided any evidence of a similar finding in man.

- Following previous Agency interactions that monitoring of glucose is reasonable, Novartis is evaluating serum glucose as a marker for glycogen metabolism in clinical studies up to one year. In addition, Novartis is providing supportive data on liver function tests in the phase 3 program.

Novartis requested that the Division further elaborate on its concerns regarding glycogen deposition. The Division stated they were in agreement with Novartis from a non-clinical perspective. From a clinical perspective, the Division did not feel that Novartis' approach to monitoring serum glucose was unreasonable; however, the Division did not necessarily agree that there was a correlation between serum glucose and hepatic glycogen deposition. The Division acknowledged that there are other drugs which have shown similar findings.

2.8 QUESTION 8

Novartis proposes to submit CRFs and SAE narratives from studies of indacaterol in patients with COPD (i.e., the proposed indication) and asthma for all formulations studied for patients experiencing death or SAEs.

Does the Agency agree with this proposal?

FDA Response

We agree.

2.9 QUESTION 9

a) ***Non-PK data for all completed Phase 3 studies (studies B2334, B2335S, B2346, B2305, B2307, B2340, and B2339) will be submitted to the Agency as both raw and derived data sets. Pooled SCS and SCE derived data sets will also be submitted. For other studies data sets will be available on request. Additionally, for the long-term studies (studies B2334, B2335S, and B2346) and for study B2339, we propose to submit mapped SDTM data sets in addition to the raw and derived data.***

   Does the Agency agree?

FDA Response

We agree.

b) ***PK source data will be provided from studies B1202, B2212, B2334, and B2335S in Novartis format as SAS V5 transport files and as a merged NONMEM dataset including dosing and covariate information. For other studies PK source datasets will be available on request.***

Does the Agency agree?

FDA Response

We recommend that you submit datasets from study B2339 (QTc study) in addition to the studies mentioned above.

2.10 QUESTION 10

Clinical Study Reports (CSRs) for all Phase 1 studies and all Phase 2 studies will be submitted and the corresponding datasets will be made available on request.

Does the Agency agree?

FDA Response

We agree.

2.11 QUESTION 11

Programs for the analysis of the primary efficacy variable will be available on request. Is this acceptable to the Agency?

FDA Response

No, this is not acceptable. The programs for the analysis of the primary efficacy variable should be included in the NDA submission.

2.12 QUESTION 12

Novartis seeks the Agency's concurrence on the following proposals for providing the data:

a. ***Novartis proposes annotating the CRFs in NovDD (Novartis Data Dictionary) and providing documentation detailing the conversion from NovDD to SDTM. Is this acceptable?***

FDA Response

Yes, this is acceptable. It is helpful to provide the translation between the Annotation of CRF and NovDD and that of SDTM.

b. ***Novartis proposes naming the supplemental qualifiers using the convention "Supplemental Qualifiers for <domain name>" since multiple physical data sets of supplemental qualifiers will be submitted, rather than one physical file. Is this acceptable?***

FDA Response

Yes, this approach is acceptable, and necessary to accommodate multiple data files.

c. ***Some data sets will exceed 100MB. Novartis proposes not splitting such data sets. Is this acceptable?***

FDA Response

*Yes, this is acceptable. Do not split the data set regardless of size. We encourage you to make every effort to reduce the size of the data set by eliminating redundant, irrelevant, or unimportant variables. Examples of such variables include: variables with all values missing, variables such as PAGE_*

SIZE which may be useful only for the sponsor's computer system.

d. Since the data were not collected in SDTM, Novartis proposes that the data will use the controlled terminology available in our legacy systems. Is this acceptable?

FDA Response

Yes, it is acceptable to adopt your existing data standard. SDTM is not required by the Agency.

2.13 ADDITIONAL COMMENTS-CLINICAL

We note that there are few results reported from your clinical development program in this pre-NDA meeting package. Without results from your Phase 3 program, we are unable to provide general comments on the adequacy of your program to support the proposed indication(s) or labeling claims.

Although you have not provided draft labeling in your meeting package, we remind you that your label should include the class labeling (including boxed warning) regarding asthma-related deaths which is present in the label of all LABA-containing drug products.

Your NDA should include a discussion of device durability/performance from the clinical development program and in vitro testing for durability/ruggedness. Include a summary of patient reports of problems with the device and the in vitro testing of any returned problem devices. Clearly identify the location of this information in your NDA.

Your NDA should address the issues regarding dose selection in Study B2335S that were raised in the October 10, 2006, EOP-2 Meeting, including issues with the DMC, confidentiality agreements, monitoring process, and compliance.

We remind you that you will need to provide justification for your proposed once daily dosing frequency. In addition to the 24-hour FEV_1 response curve and trough FEV_1, we will also consider the efficacy results for QAB149 in comparison to the twice-daily active comparators, salmeterol and formoterol.

Discussion

Novartis requested clarification regarding the Division's request for justification of the once daily dosing frequency of QAB149. Novartis summarized the endpoints that will be reported, including trough FEV1 as the primary endpoint and 24-hour FEV1 profiling in two studies. Novartis also provided a table that summarized all the studies which included twice-daily beta agonists as active comparators to their product. Novartis requested the Division's input regarding additional information required to justify the dosing frequency. The Division stated that the intent of this comment was not to imply

that additional studies should be conducted. Rather, the Division wanted to remind Novartis that there are a number of ways to justify dosing frequency. Since Novartis has not compared multiple dosing regimens of QAB149 within their clinical development program, the Division emphasized that, in addition to the endpoints mentioned, it will also use the comparison with the twice-daily LABAs to further evaluate the dosing frequency. The Division reminded Novartis that statistical significance in the pre-specified endpoints (e.g. trough FEV1) versus placebo would not necessarily be enough to justify the dosing interval. Other supportive information will be taken into account. With regard to supportive information, however, the Division cautioned that we are not necessarily willing to conclude that information such as nighttime awakenings and use of rescue medication would be enough to support once-daily dosing for a bronchodilatory drug.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that required further discussion.

4.0 ACTION ITEMS

No action items were identified during the meeting.

5.0 ATTACHMENTS

5.1 ATTACHMENT 1

NOVARTIS'S 4.4.08 RESPONSE TO 4.3.08 FDA FAX
(Response to FDA_7Apr08.pdf-provided via email on 4.4.08).

NOVARTIS

Drug Regulatory Affairs

IND 48,649, QAB149

Pre-NDA FDA Meeting 7 April 2008

Response to FDA Pre-meeting comments dated 3 April 2008

Authors:

Release date:

Table of contents

1 Regulatory Questions

1.1 Question 1

Novartis believes that the proposed content and format of this NDA as described will be adequate for filing. A full table of contents is found in Appendix 1. In addition, the safety information planned to be included in the 120-Day Safety Update is outlined. Does the Agency agree with the content and format proposals?

FDA Response
In general the proposed content and format for NDA submission appear reasonable; however, clarify the location of the ISE and ISS. Refer to the "Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" for information (http://www.fda.gov/cder/guidance/7621dft.pdf).

We remind you that your NDA should be complete with all the information you deem necessary to support approval at the time of NDA submission. We expect Study B2339 (QTc study) to be submitted in the original NDA submission.

Novartis Response:

Novartis will follow and comply with the guidance for the NDA submission and will submit Study B2339 (QTc study) in the original NDA submission.

1.2 Question 2

Novartis requests a waiver for conducting trials in pediatrics as COPD does not occur in this population. Does the Agency agree to grant a waiver for QAB149 from the requirements of the Pediatric Research Equity Act for patients under 18 years of age?

FDA Response
Although COPD is not a disease of the pediatric population, as a once-daily betaagonist, QAB149 has potential for off-label use in asthma patients, including pediatric patients. Due to the potential for off-label use in asthma, we expect studies to be conducted in patients with asthma, including pediatric patients.

Novartis Response:

Novartis is conducting a safety study B2338 to provide 6 month safety data in adult and adolescent asthmatic patients following previous discussions with the Agency regarding potential off label use of QAB149 in asthma. The study has enrolled 805 patients of which approximately 50 are pediatric patients between 12-18 years old.

On this basis, Novartis would request a pediatric waiver in the NDA.

Novartis would like further clarification/discussion at the scheduled meeting this Monday, April 7th.

2 Content and Format of SCE

2.1 Question 3

Pooled efficacy data of indacaterol will be summarised and pooled for all long-term (at least 50 days in length) COPD studies: B2334, B2335S and B2346. In addition, subgroup analyses will be presented for key endpoints as indicated below.

Does the Agency agree?

FDA Response
Your pooling strategy for the SCE appears reasonable.

Novartis response:

We acknowledge FDA's comment. No further discussion is needed.

3 Content and Format of SCS

3.1 Question 4

All indacaterol studies of adults (See Appendix 3: studies listed in Tables 1-1, 1-2a, 1-2b and 1-2d, but excluding the pediatric study C2101) will be pooled for a summary of exposure to the drug. The summaries will be broken down as follows:

All the studies including an indacaterol mono-therapy arm:

1. ***Exposure for all indacaterol devices as well as a breakdown into exposure for 75, 150, 300 and 600 mcg inhaled through the Concept 1 device or any dose through all 'other' devices will be summarised. In addition, exposure will be summarised for the comparator treatment categories including placebo and the fixed dose combinations QMF and QVA. The information will be presented by subject type (healthy volunteer, COPD patients and asthma patients).***
2. ***Data from all long-term (at least 50 days in length) COPD studies: B2334, B2335S and B2346.***
3. ***Data from all short term studies (less than 50 days in length) (see Appendix 3: studies listed in Tables 1-1, 1-2a, 1-2b and 1-2d, but excluding B2334, B2335S, B2346, A2222 and C2101). The information will be presented by subject type (healthy volunteer, COPD patients and asthma patients).***

Does the Agency agree?

FDA Response
Your pooling strategy appears reasonable. Clarify where in the SCS you plan to include the discussion regarding the Holter monitoring data.

Novartis Response:

Holter data will be derived from a subset of patients in study B2335S (approximately n = 450), and will be presented within the relevant Clinical Study Report, and discussed within the SCS.

The analysis plan includes presentation of data on 24 h daily mean heart rate, hourly mean heart rate and frequency of arrhythmia, ventricular arrhythmia and supraventricular events. These will be summarized by treatment for each visit separately. Holter monitor data recorded at Visit 1 will be used as the baseline measurement. The 24 h daily mean and hourly mean heart rates at all visits will be analyzed using a similar mixed model as for the primary analysis.

Novartis seeks further clarification regarding the Agency preference for the discussion of Holter monitoring data within the SCS.

3.2 Question 5

Adverse events will be summarised for all studies and all treatment groups. The summaries will be broken down as follows:

1. ***Pooling of 3 month COPD data from COPD stuides: study B2346 and the first 3 months of studies B2334 and B2335S***
2. ***Pooling of 6 month data from COPD studies: study B2335S and the first 6 months of study B2334***
3. ***12 month COPD data: study B2334***
4. ***Pooling of data from all short term studies (less than 50 days in length) (see Appendix 3: studies listed in Tables 1-1, 1-2a, 1-2b and 1-2d, but excluding studies B2334, B2335S, B2346, A2222 and C2101).***

In addition, deaths or SAEs will be summarized for all the studies including the indacaterol mono-therapy arm.

Does the Agency agree?

FDA Response
We agree.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

3.3 Question 6

In alignment with the request at the end of phase 2 meeting to fully characterize the post-inhalation cough (PI cough), the following measures were put in place in the pivotal trials to assess the occurrence of cough. There is a specific eCRF page (Appendix 4) to capture post-inhalation events and their time of onset and duration. An assessment will be made of possible evidence for an association between PI cough and each of the following: decreases in FEV_1 within 30 minutes of dosing, bronchospasm reported as an AE, FEV_1 across time, exacerbations, AE leading to discontinuation and patient disposition.

Does the Agency agree with the proposals to address potential concerns regarding PI cough?

FDA Response
Your proposal appears reasonable.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

3.4 Question 7

Further to previous discussions with the Agency regarding non-clinical study results of glycogen deposition, Novartis is monitoring serum glucose in the Phase 3 trials and will report the results in the NDA as described.

Does the Agency agree with the proposal?

FDA Response
We remain concerned regarding the periportal hepatocellular vacuolation/glycogen deposition that was seen in dog toxicity studies as this toxicity is not easily monitored in humans. The results of the serum glucose monitoring in your Phase 3 program and the issue of glycogen deposition will be a review issue.

Novartis Response:

Glycogen deposition/hepatic vacuolation in dogs is observed on dosing with QAB149 as is the case with marketed inhaled beta2 agonists and inhaled corticosteroids. This finding is not associated with any other liver findings nor with any liver enzyme elevations. The severity does not increase over time and is fully reversible within 4 weeks of discontinuation of dosing.

Literature references indicate that the presence of increased levels of glycogen in the liver probably reflects a minor alteration in glucose utilization or production due to the pharmacological activity of the drug.

The clinical experience with LABAs and inhaled corticosteroids, to the best of our knowledge, has not provided any evidence of a similar finding in man.

Following previous Agency interactions that monitoring of glucose is reasonable, Novartis is evaluating serum glucose as a marker for glycogen metabolism in clinical studies up to one year. In addition, Novartis is providing supportive data on liver function tests in the PhIII program.

Novartis would like further clarification/discussion with FDA about their concerns at the scheduled meeting this Monday, April 7th.

4 Patient Narratives, Case report forms (CRFs)

4.1 Question 8

Novartis proposes to submit CRFs and SAE narratives from studies of indacaterol in patients with COPD (i.e., the proposed indication) and asthma for all formulations studied for patients experiencing death or SAEs.

Does the Agency agree with this proposal?

FDA Response
We agree.

Novartis Response:

We acknowledge FDA's comments. No further discussion is needed.

5 Availability of datasets

5.1 Question 9

a) ***Non-PK data for all completed Phase 3 studies (studies B2334, B2335S, B2346, B2305, B2307, B2340, and B2339) will be submitted to the Agency as both raw and derived data sets. Pooled SCS and SCE derived data sets will also be submitted. For other studies data sets will be available on request. Additionally, for the long-term studies (studies B2334, B2335S, and B2346) and for study B2339, we propose to submit mapped SDTM data sets in addition to the raw and derived data. Does the Agency agree?***

FDA Response
We agree.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

b) ***PK source data will be provided from studies B1202, B2212, B2334, and B2335S in Novartis format as SAS V5 transport files and as a merged NONMEM dataset including dosing and covariate information. For other studies PK source datasets will be available on request. Does the Agency agree?***

FDA Response
We recommend that you submit datasets from study B2339 (QTc study) in addition to the studies mentioned above.

Novartis Response:

We acknowledge FDA's comment. We will provide the PK dataset from study B2339 (QTc study). No further discussion is needed.

5.2 Question 10

Clinical Study Reports (CSRs) for all Phase 1 studies and all Phase 2 studies will be submitted and the corresponding datasets will be made available on request. Does the Agency agree?

FDA Response
We agree.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

5.3 Question 11

Programs for the analysis of the primary efficacy variable will be available on request. Is this acceptable to the Agency?

FDA Response
No, this is not acceptable. The programs for the analysis of the primary efficacy variable should be included in the NDA submission.

Novartis Response:

We acknowledge FDA's comment. We will provide the requested information. No further discussion is needed.

6 Format of datasets (CDISC)

6.1 Question 12

Novartis seeks the Agency's concurrence on the following proposals for providing the data:

a. Novartis proposes annotating the CRFs in NovDD (Novartis Data Dictionary) and providing documentation detailing the conversion from NovDD to SDTM. Is this acceptable?

FDA Response
Yes, this is acceptable. It is helpful to provide the translation between the Annotation of CRF and NovDD and that of SDTM.

Novartis Response:

We acknowledge FDA's comment. We will provide the requested information. No further discussion is needed.

b. ***Novartis proposes naming the supplemental qualifiers using the convention "Supplemental Qualifiers for <domain name>" since multiple physical data sets of supplemental qualifiers will be submitted, rather than one physical file. Is this acceptable?***

FDA Response
Yes, this approach is acceptable, and necessary to accommodate multiple data files.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

c. ***Some data sets will exceed 100MB. Novartis proposes not splitting such data sets. Is this acceptable?***

FDA Response
Yes, this is acceptable. Do not split the data set regardless of size. We encourage you to make every effort to reduce the size of the data set by eliminating redundant, irrelevant, or unimportant variables. Examples of such variables include: variables with all values missing, variables such as PAGE_SIZE which may be useful only for the sponsor's computer system.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

d. ***Since the data were not collected in SDTM, Novartis proposes that the data will use the controlled terminology available in our legacy systems. Is this acceptable?***

FDA Response
Yes, it is acceptable to adopt your existing data standard. SDTM is not required by the Agency.

Novartis Response:

We acknowledge FDA's comment. No further discussion is needed.

7 Additional Clinical Comments from the Division:

We note that there are few results reported from your clinical development program in this pre-NDA meeting package. Without results from your Phase 3 program, we are unable to provide general comments on the adequacy of your program to support the proposed indication(s) or labeling claims. Although you have not provided draft labeling in your meeting package, we remind you that your label should include the class labeling (including boxed warning) regarding asthma-related deaths which is present in the label of all LABAcontaining drug products.

Your NDA should include a discussion of device durability/performance from the clinical development program and in vitro testing for durability/ruggedness. Include a summary of

patient reports of problems with the device and the in vitro testing of any returned problem devices. Clearly identify the location of this information in your NDA.

Your NDA should address the issues regarding dose selection in Study B2335S that were raised in the October 10, 2006, EOP-2 Meeting, including issues with the DMC, confidentiality agreements, monitoring process, and compliance.

We remind you that you will need to provide justification for your proposed once daily dosing frequency. In addition to the 24-hour FEV_1 response curve and trough FEV_1, we will also consider the efficacy results for QAB149 in comparison to the twice-daily active comparators, salmeterol and formoterol.

Novartis Response:

We acknowledge FDA's comments.

A CMC meeting is to be held with the Agency on the 6th May, which will include device related matters.

Trough FEV_1 is the primary endpoint in our pivotal studies. The 24-hour FEV_1 response curve is being evaluated in 2 different studies, one with Salmeterol and one with open label tiotropium.

With regard to comparisons with twice daily treatment LABAs, our intention is to provide the Agency with a number of studies in the original NDA (the details of which are included in the Table 7-1, below).

We would like to further understand the Agency's perspective on comparison of QAB149 vs. Salmeterol and Formoterol.

Table 7-1 QAB149 comparison studies with other LABAs to be provided in the original NDA

	Studies with Formoterol comparisons		Studies with Salmeterol comparisons	
	B2334	**B2335S**	**B2340**	**B2305**
Protocol Design/Duration	multi center, double blind, double dummy, parallel group design, 1 year	multi center, double blind for formoterol, adaptive seamless parallel group design, 6month	randomized, double-blind, placebo controlled, multicenter, 3-period, 14-day dosing crossover	This study is a multi center, double blind, double dummy, 4 treatments, 3 period incomplete cross-over design.
Treatment	QAB 300 µg q d, QAB 600 µg q d Formoterol 12.5 µg b.i.d , placebo ratio = 1:1:1:1	Stage 1: QAB 75, 150, 300, 600 µg qd, Formoterol 12.5 µg b.i.d , OL tiotropium 18 µg qd ratio = 1:1 for all 7 arms for at least 2 weeks treatment	QAB 300 µg q d, Salmeterol 50 µg bid, patients will be randomized to one of three treatment sequences using an allocation ratio of 1:1:1	QAB 300 µg q d, (am and pm). Salmeterol (50 µg), placebo: pts will be randomized to receive 3 of the 4 possible treatments in approximately equal numbers
Total Sample size	1733 subjects	2059 subjects	Approximately 54 subjects	Approximately 78 subjects
Primary Endpoint	To assess indacaterol (300 & 600 µg o.d. via SDDPI) superiority in patients with COPD as compared to placebo with respect to 24 h post dose (trough) FEV1 after 12 weeks of treatment	To demonstrate superiority of at least one dose of indacaterol (selected at study Stage 1 from 75, 150, 300 or 600 µg o.d. via SDDPI) versus placebo with respect to 24 h post dose (trough) FEV_1 after 12 weeks of treatment in patients with COPD	To demonstrate the superiority of indacaterol (300 µg o.d.) over placebo in terms of 24-h trough FEV_1 on Day 14 of treatment. The 24-h trough FEV_1 is defined as the mean of FEV_1measurements at 23 h 10 min and 23 h 45 min post-dose.	To assess the efficacy of indacaterol 300 µg o.d. when dosed in the evening compared to pbo in patients with mod. to sev. COPD, as assessed by trough FEV_1 at 23 h 10 min and 23 h 45 min post dose taken on Day 14.
Secondary or Exploratory Endpoints	To evaluate the effect of indacaterol (300 & 600 µg o.d.) on the percentage of 'days of poor control' reported over the 52 week randomized treatment period, as compared to placebo. Study B2334 compares once daily dosing of QAB149 vs twice daily dosing of formoterol 12 µg and provides data on trough FEV_1 and symptom control across 52 weeks, and further supported by data collected for each 12 h period of the day/night in relation of symptoms and rescue medication. Also in a subgroup of 440 patients, it provides 0-12h FEV_1 curves (AUC and individual timepoint comparisons)	Study B2335S includes comparisons to formoterol 12 µg b.i.d. in stage 1 (805 subjects) of the adaptive design (for at least 2 weeks and some patients for periods in excess of 12 weeks) in relation to FEV_1 0-4h, and trough FEV_1. It also includes in Stage 2 (in a subgroup of 432 subjects) comparison to pbo and open label tiotropium for 0-12h FEV_1 curves (AUC and individual timepoint comparisons) during the study and 24h FEV_1 profiling at the end of 6m treatment in a sub-group (at time points 6,12,16, 22 and 24 h post dose). This is supported by data collected for all subjects for each 12 h period of the day/night in relation of symptoms and rescue medication.	To evaluate the FEV_1 area under the time curves from 0-24 h and 0-12 h of indacaterol versus placebo on Days 1 and 14 of treatment. Study B2340 provides FEV_1 comparisons between QAB149 300 µg and open label salmeterol 50 µg b.i.d. at regular intervals out to 12h and then at 14, 20h and trough.	Comparisons versus placebo of trough FEV_1 (at 23 h 10 min and 23 h 45 min post dose) of indacaterol 300 µg o.d. (evening dosing), indacaterol 300 µg o.d. (morning dosing), and FEV1 of salmeterol 50 µg b.i.d. (as assessed at 11 h 10 min and 11 h 45 min post dose) after 14 days of treatment.

Drafted by: LCantin/April 8, 2008

Initialed: VWhitehurst/4.10.08
TMcGovern/4.10.08
Karimi-Shah/4.10.08
SSeymour/4.10.08
Chowdhury/4.10.08

Finalized: LCantin/

Linked Applications	Sponsor Name	Drug Name
IND 48649	NOVARTIS PHARMACEUTICALS CORP	QAB 149 (INHALATION POWDER HARD CAPS)

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

/s/

LORI A Garcia
04/10/2008

MEETING MINUTES

APPLICATION: IND 48,649
SPONSOR: Novartis Pharmaceuticals Corp.
DRUG NAME: QAB149 (indacaterol)
DATE: October 10, 2006

Novartis's Representatives:
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Ruthie Davi, M.S., Statistical Team Leader
Carol Hill, M.S., Regulatory Project Manager

Reference is made to the end of phase 2 meeting held between representatives of Novartis Pharmaceuticals Corp and the Division of Pulmonary and Allergy Products on October 10, 2006. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 796-1226.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: October 27, 2006

To: Ann Shea Associate Director, Regulatory Affairs	From: Carol Hill, M.S. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	Fax number: 301-796-9715 or -9718
Phone number: 862-778-4567	Phone number: 301-796-1226

Subject: IND 48,649 – October 10, 2006 EOP2 Meeting Minutes

Total no. of pages including cover: 13

Comments:

Document to be mailed: YES XNO

Background:

Novartis submitted a type B meeting request dated July 5, 2006, to discuss the acceptability of the phase 3 program to support registration of QAB149 (indacaterol) Inhalation Powder Hard Capsules in a single-dose dry powder inhaler (concept 1) for patients with COPD. Novartis also submitted a briefing package dated September 5, 2006, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to Novartis's questions via fax on October 6, 2006. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Novartis's questions and comments are in bold italics; FDA's response is in italics; discussion is in normal font.

Question #1

Does the Agency agree that the proposed QT study (Study A2318) is appropriate to sufficiently quantify the degree of any potential QT prolongation?

Response:

We agree with the general design of the study. However, we have questions about the sample size and statistical hypothesis for the supra-therapeutic dose (b) (4) *as well as your choice of the dose.*

To test if the investigational drug produces potential QT prolongation, you propose the following statistical hypotheses:

(b) (4)

Here Δ(t) denotes the mean difference between the QTcF for the two treatments at time t. We agree with this statistical hypothesis for the therapeutic dose. However, you assumed that the true mean difference for the (b) (4) *dose is 13 msec which is outside the boundary of the alternative hypothesis. The conventional statistical hypothesis cannot be applied here.*

If the goal of the (b) (4) *dose is to assess QT/QTc prolongation risk at high concentrations of indacaterol, then we recommend that you modify the alternative hypothesis and recalculate sample size for that arm.*

We recommend selecting the supratherapeutic dose for the study based on clinical situations of maximum drug exposure. Prior to designing a thorough QT study, you should have a good understanding of factors that will increase exposure of indacaterol (such as possible increased exposure in UGT1A1 deficient population and/or in presence of a strong CYP3A inhibitor, etc); if you have not explored these factors, then we recommend that you hold off on designing the thorough QT study until such an exploration is completed. Therefore, based on the NDA data submission, the acceptability of (b) (4) *dose as the supra-therapeutic dose in this protocol will be a review issue.*

Comment:
Novartis acknowledges that the protocol will be clarified to specify that the statistical hypothesis should refer to an upper limit of 20 msec for the highest dose. Please note that the sample size for the highest dose remains as initially calculated.

Novartis acknowledges the Agency's comment and will re-examine the highest dose to be studied. Novartis would like to clarify if the Agency's comment refers to the supratherapeutic dose as the exposure to the highest dose to be given in the clinical program, taking into account populations who may have poor metabolism (i.e. the highest exposure of the selected therapeutic dose).

Discussion:
Novartis asked the Division to clarify its definition of supratherapeutic dose. The Division defined the supratherapeutic dose as the dose to achieve the highest exposure expected based upon factors, such as metabolism, genotype, and drug-drug interactions. All factors including safety that are associated with the exposure to the patient should be considered before deciding on a supratherapeutic dose. The potential metabolism of the drug and the genotype affecting drug-drug interactions at this stage of development is not known. The Division recommended further exploration of the metabolic profile prior to determining the supratherapeutic dose for the thorough QT study. Novartis stated that they have ongoing studies to examine metabolic and polymorphic disposition of the drug and that the results of these studies will be taken into consideration in determining the supratherapeutic dose for the QT study.

Additional Comments regarding QT study (A2318):

1. *Due to large variability of T_{max} values observed in previous studies, we recommend adding at least two more post-dose time points around the T_{max} on Day 14. Collect ECG and PK samples at times that cover the C_{max} of parent and metabolites as well as for demonstrating an increase and decrease in QT with drug exposure. We also recommend time-matched ECG as well as PK collections at baseline (Day-1). Therefore, based on the information provided, the suggested time points for ECG and PK sampling on Days 1 and 14 would be pre-dose (0), 10 min, 20 min, 40 min, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr, 12 hr, and 24 hr post-dose.*

Comment:
Novartis acknowledges the Agency's comments.

2. *Multiple dose studies up to 28 days suggested that steady state was reached at 2 to 3 weeks following once daily dosing. Consider extending the study from 2 to 3 weeks duration to allow subjects to reach steady-state.*

Comment:

Novartis agrees that the study will be at steady-state.

3. *We understand that you plan to evaluate the pharmacogenetics of UGT1A1 in Study A2318 and Study A2221. Consider exploring UGT1A1 polymorphisms and their effects on QTcF interval changes. Depending on the data from the ongoing study (A2221), if subject safety is viewed to be compromised at the supra-therapeutic dose in UGT1A1*

deficient population, you may also want to consider UGT1A1 poor metabolizer phenotype as an exclusion entry criterion for the QT study to ensure subject safety.

Comment:
Novartis agrees with the Agency. The higher dose would not be given to patients who may experience exposure above the exposure anticipated from the higher dose to be studied. Novartis is in the process of looking at the exposure of indacaterol in patients with UGT1A1 deficiency.

4. *We are interested in understanding the relationship between drug exposure and effect on QTc interval. In addition to the primary statistical analysis of the data as defined by the ICH E14 guidance, we plan to use a linear mixed effects modeling approach to estimate the population slope (β) and standard error of slope (SE_β) of the plasma concentration and $\Delta\Delta$QTc (placebo- and baseline- adjusted QTc) interval for each analyte (e.g. parent, any metabolite[s]). Note that in addition to fitting a linear model to the data, the need for a model relating delays in maximum concentration and maximum response will be evaluated. Additionally, the need for an Emax model relating concentration to response will be considered. If you choose to perform these analyses, submit the results, along with accompanying analysis datasets.*

Comment:
Novartis acknowledges the Agency's comments.

5. *Phlebotomy has the potential to affect the QT interval. In order to provide a more meaningful comparison of QTc between time points, consider including blood draws during baseline ECG sampling on Day-1.*

Comment:
Novartis acknowledges the Agency's comments.

6. *Specify in the protocol the specific lead(s) to be used for QT measurement.*

Comment:
Novartis agrees.

7. *Limit the number of skilled readers in the central ECG laboratory to control variability in interpretation.*

Comment:
Novartis agrees.

8. *Blind ECG readers to subject identifiers, treatment, time, and day (i.e., Day -1; Day 1).*

Comment:
Novartis acknowledges the Agency's comments.

9. *Designate a single reader to read all ECGs from a particular subject.*

Comment:
Novartis acknowledges the Agency's comments.

10. Assess inter- and intra-reader variability through re-read of a subset of tracings.

Comment:
Novartis acknowledges the Agency's comments.

11. As evidence of assay sensitivity, the mean difference between moxifloxacin and placebo should be greater than 5 msec at a minimum of one time point. Collect the ECG data for moxifloxacin at the same time points as the drug and placebo to facilitate comparison; however, you can pre-specify the number of time points for the assay sensitivity analysis.

Comment:
Novartis agrees.

12. Submit the data in CDISC format. If you are unable to submit the data in CDISC format, contact the project manager to discuss an alternative format and content of datasets.

Comment:
Novartis agrees.

13. Submit all ECG waveforms collected to the FDA's ECG warehouse.

Comment:
Novartis agrees.

General Clinical Pharmacology Comments:

14. Analyze PK blood samples for both parent drug and any active/major metabolite(s) in studies A2318 and B2335S.

Comment:
Novartis is planning to have PK samples collected in the studies mentioned. Novartis does not intend to analyse any metabolite because there is no evidence that any active metabolite would contribute to a great extent to the overall activity at the beta$_2$ receptor.

15. CYP3A mediated oxidative metabolism may constitute a significant elimination pathway for indacaterol. Conduct a drug interaction study with a known CYP3A inhibitor, such as ketoconazole, to evaluate the extent of inhibition and potential increase in indacaterol exposure levels. The representative supra-therapeutic dose in your QT interval study (A2318) should also take into account such potential drug interactions.

Comment:
Novartis is conducting a study on the influence of ketoconazole on the PK of indacaterol at present. As indacaterol appears to be metabolized by UGT1A1 as well as by CYP3A4, the hypothesis is that inhibition of one pathway alone will not have impact on the overall clearance of indacaterol. Hence the expected outcome of the study is to confirm that a prototypical CYP3A4 inhibitor has no clinically relevant impact on the systemic PK of indacaterol.

16. *Address the issue of whether QAB149 (indacaterol) is a substrate of p-glycoproteins and the implication for inhibition or induction of p-glycoproteins on the PK of QAB149 (indacaterol).*

Comment:

Novartis acknowledges that recent data indicate that indacaterol may be a substrate of the p-glycoproteins efflux transporter. Novartis will perform further investigation with the aim to clarify whether this property will have impact on the clinical pharmacokinetics of of indacaterol. At this point, the evidence that two independent metabolic pathways contribute to the systemic clearance of indacaterol make it unlikely that efflux via p-glycoproteins provides an additional significant contribution to the pharmacokinetics of indacaterol.

Question #2

Novartis plans to conduct a pivotal safety and efficacy COPD study (Study B2335S) which incorporates an interim analysis based on 2 weeks treatment to select and determine safe and effective doses to be studied until final database lock. Is this trial design considered to be acceptable and adequate to support approval?

Response:

In general, the study design is acceptable; however, see our responses to the questions 2a, 2b, 2c, and 2d.

Question #2a

Are the proposed process for interim analysis and dose selection rules adequate and acceptable to support approval of indacaterol?

Response:

If the following comments are satisfied, the interim analysis and dose selection rules are adequate and acceptable to support demonstration of the efficacy of indacaterol.

17. *The Data Monitoring Committee (DMC) roles and decision rules should be pre-specified and eliminate interpretation of efficacy results.*

Comment:

The roles and decision rules are pre-specified in the DMC Charter (see Attachment 5 of the Briefing Book). Novartis seeks clarification of the Agency's statement regarding eliminating interpretation of efficacy results by the DMC.

Discussion:

The Division indicated that they had reviewed Attachment 5 of the submission including the roles and decision rules in the DMC charter and that their concern arose from the statement that the DMC would have discretion to deviate appropriately from the decision criteria in the case of unexpected results. Novartis responded that they believed giving the DMC no discretion to respond would not be appropriate especially if an unusual response in the efficacy data is

observed. The Division indicated that the decisions the DMC makes (if they deviate from the pre-specified decision rules) could impact the type I error. Novartis noted that the type I error is controlled by a very conservative approach (i.e., by dividing alpha by four, the original number of doses of the new treatment) and that they believed this would be adequate regardless of what action was taken by the DMC. The Division acknowledged these comments and stated that this would become a review issue if the DMC takes an action other than that indicated by the decision rules.

18. *Although the proposed primary efficacy endpoint for this study is the trough FEV1, be aware that the entire FEV1 curve is of interest to the Division. Consider incorporating an assessment of the curve (such as AUC) into the dose selection rules.*

Comment:
Regarding inclusion of FEV_1AUC into the dose selection rules, several studies have demonstrated continuous bronchodilation over 24 hours (A2208, A2217, A2218). The Phase 3 program will capture further data to demonstrate the FEV_1 curve. The previous dose-ranging studies demonstrated that trough FEV_1 is a good criterion for dose selection. Including two variables in the dose selection rules would increase the need for interpretation of the efficacy results. Therefore, the decision rules are based on trough FEV_1.

Discussion:
Novartis stated that the dose selection rules should be kept simple and acknowledged the importance of FEV_1AUC. They further commented that trough FEV_1 is an appropriate measure for dose selection. Novartis believes that the AUC is well addressed in that the phase 3 program includes a subset of 440 patients in which extensive data will be provided regarding FEV_1AUC. The Division responded that the comment regarding FEV_1 AUC was for Novartis to consider because the Division will review not only the trough FEV_1, but also other variables, such as peak FEV_1 and FEV_1 AUC as part of the assessment of dose selection.

19. *Add a statement to the protocol indicating that no efficacy claims will be made as a result of the interim analysis.*

Comment:
Novartis agrees

20. *The statistician and programmer who prepare the interim analysis report should be independent of DMC and the sponsor. The DMC (make-up, conduct, and actions) should be independent from the sponsor.*

Comment:
Novartis confirms that the DMC is independent from Novartis.

Novartis believes that it can ensure adequate confidentiality with separation of the Novartis independent statistician and programmer from trial activities.

Discussion:
The Division clarified that the expectation is that the statistician and programmer providing data to the DMC should be independent of the company and that independence from trial activities may not be sufficient. Novartis responded that although these individuals would be Novartis employees, they would be physically and organizationally separated from those involved in this

clinical trial and that confidentiality agreements would be put in place to help insure that data was not leaked. Novartis indicated that they are aware that the burden of proof for establishing that appropriate "firewalls" are in place is their responsibility. The Division commented that at present we are not convinced that the necessary "firewalls" can be maintained while using this type of structure and that there have been numerous examples where information has been leaked when using such a structure. Novartis commented that hiring external consultants to fulfill these roles would not necessarily solve the problem and in fact, they have had some experience that indicated that leaking of information was more likely under this scenario than when using independent company employees. The Division indicated that if the decision is made to use an internal statistician and programmer, standard operating procedures on monitoring the adaptation process and for interactions among the DMC, statistician, and programmer need to be established a priori and submitted for review and documentation before trial initiation.

Post Meeting Request:
Submit confidentiality agreements mentioned in the above Discussion. At the time of NDA submission, submit a document that describes the actual monitoring processes, the extent of compliance, and any potential impact on study results.

Question #2b
Is the proposed statistical analysis plan adequate and acceptable to support approval of indacaterol?

Response:
If the following comments are satisfied, the proposed statistical analysis plan is adequate and acceptable to support demonstration of the efficacy of indacaterol.

21. As the LOCF approach is proposed for imputing the trough FEV1 at week 12. The trough FEV1 should be measured at the same time point at each visit.

Comment:
Novartis agrees and will ensure consistency of the timing of measurement of trough FEV_1 up to week 12.

22. Since the assignment of tiotropium is open-label, the non-inferiority comparison of indacaterol to tiotropium will not be adequate (b) (4)

Comment:
Novartis acknowledges the Agency's comment.

Discussion:
Novartis indicated the difficulty in blinding the study for a comparative (b) (4) They proposed a separate, smaller study with a double-dummy design, involving a third party that would administer the blinded drug to the patient. The sponsor asked if such a study would be adequate to (b) (4). Although unable to comment on the details of such a study without prior review, the Division acknowledged the difficulty with blinding tiotropium. The Division suggested that Novartis consider asking subjects to guess which drug they had received to assess the effectiveness of blinding procedures. Both Novartis and the Division agreed that the

suggestion was appropriate since certain drugs have a distinct taste and side effects, such as dry mouth.

23. *The non-inferiority test comparing indacaterol and tiotropium relies on a pre-defined non-inferiority margin that requires justification. The protocol should clearly justify the choice of the non-inferiority margin. This justification should be based on both statistical reasoning and clinical judgment as described in the International Conference on Harmonization E10 document.*

Comment:
Novartis acknowledges the Agency's comment and will include the justification of the choice of non-inferiority margin in the protocol.

24. *The methods for handling missing data are of concern given that the drop-out rate is expected to be high (30%). You propose to use the LOCF approach imputing the trough FEV1 at week 12. You should pre-specify and provide sensitivity analyses to demonstrate the robustness of the efficacy findings to the missing data. Analyses imputing the worst-observed value for the missing data may be useful in this regard. Similarly, sensitivity analyses assessing the impact of the missing data on the percentage of poor symptom control days are needed. Consider an analysis where missing diary entries result in the symptom control for that day being considered poor.*

Comment:
Novartis anticipates that the drop-out rate for the analysis of the primary endpoint (FEV_1 at 12 weeks) is expected to be only 15% (a 30% drop-out rate is expected only for the secondary endpoint 'Days of Poor Control', which is measured after 52 weeks of treatment). To help provide robust conclusions (in support of the primary LOCF analysis), Novartis will develop a statistical plan with various approaches, such as multiple imputation methods, mixed effects models, and conservative imputation (e.g., worst case type) schemes.

Discussion:
Novartis acknowledged the importance of documenting missing data. They indicated that the expected drop-out rate for the primary endpoint will be 15%. They also noted that a plan (as described in the preceding paragraph) which includes sensitivity analysis and worse case scenario will be implemented to thoroughly address the missing data. The Division responded that this was acceptable.

Question #2c
Does the Agency agree that Study B2355S can be of 6 months duration to support approval, given that Study B2334 provides replicate efficacy data and 1-year safety data?

Response:
If you plan to carry forward the 300 or 600mcg dose of indacaterol, then B2335S could be 6 months duration. However, if you decide to carry forward a dose other than 300 or 600mcg, then Study B2334 will not provide replicate efficacy and safety data. Keep in mind that your program should meet the ICH guidelines for population exposure to assess clinical safety (ICH-E1A).

Comment:
Novartis acknowledges the Agency's comment.

Question #2d
Does the Agency agree that if the 150 µg and/or 75 µg doses are demonstrated in Study B2335S to be the doses with adequate efficacy, replicate 6-month safety and efficacy data on these doses will be sufficient to support approval, when coupled with the 1-year safety data from Study B2334?

Response:
If you choose the 75 or 150mcg dose based upon the results of Study B2335S and you provide replicate efficacy and safety data for the 75 or 150mcg dose, Study B2334 may be sufficient for the one year safety data. However, in this situation it is your risk to conduct the one year study (Study B2334) with higher doses (300 and 600mcg).

Comment:
Novartis acknowledges the Agency's comment.

Question #3
Does the Agency agree that development in asthma of a fixed dose combination product of indacaterol with an asthma approved dry powder formulation inhaled corticosteroid does not require that phase 3 studies for indacaterol as a monotherapy in asthma be conducted prior to the phase 3 studies of the fixed dose combination?

Response:
In principle, you do not need to establish indacaterol as monotherapy in asthma prior to developing a combination product containing indacaterol and an approved dry powder corticosteroid for asthma. However, your development program must establish that each component makes a contribution to the claimed effects. In addition, long-term safety of indacaterol in the treatment of asthma will need to be addressed in the clinical development program.

Comment:
Novartis acknowledges the Agency's comment.

Additional comments:
25. Address the potential for off-label use in asthma in your development program for indacaterol in the treatment of COPD.

Comment:
Novartis would like to ask the Agency to clarify if their comment on the potential off-label use in asthma is intended to be addressed during the COPD development program, or once the product is approved.

Discussion:
The Division stated that ongoing changes in the market place and the safety profile of Novartis' product may impact any plan to address off-label use in asthma, precluding any further comments at this time. Novartis asked if it would be appropriate to address the off-label use in a

risk management plan. The Division noted that last week there was a drug approved for COPD and presently there are 1 or 2 drugs marketed for COPD only. A risk management plan may not be sufficient if it is known by the time of Novartis' NDA application that similar risk management plans and labeling have not been effective. The Division reiterated that no further comment could be made at this time.

(b) (4)

27. We recommend you submit your protocols for review prior to conducting the study.

Comment:
Novartis acknowledges the Agency's comment.

Additional Discussion
The Division inquired if Novartis plans to develop the product as a single molecular entity for asthma. Novartis stated that an appropriate strategy is under discussion (b) (4) The Division commented the approach may have implications relative to Comment 25.

If you have any questions, you may contact Ms. Carol Hill, Regulatory Project Manager, at 301-796-1226.

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/s/

Carol F. Hill
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