

EXCLUSIVITY SUMMARY

NDA # 207930

SUPPL # n/a

HFD # 570

Trade Name: Utibron Neohaler inhalation powder

Generic Name: indacaterol/glycopyrrolate

Applicant Name: Novartis Pharmaceuticals

Approval Date: October 29, 2015

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)

b) 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.

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:

c) Did the applicant request exclusivity?

YES NO

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

3 years

d) 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?

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# 022383	Arcapta Neohaler (indacaterol)	Approved
(b) (4)	(b) (4)	Withdrawn
NDA# 017558	Robinul injection (Eurohealth International Sarl)	Approved
(b) (4)	(b) (4)	Withdrawn
(b) (4)	(b) (4)	Withdrawn
NDA# 022571	Cuvposa oral solution (Merz Pharmaceuticals)	Approved
NDA# 012827	Robinul tablet (Shionogi)	Approved

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:

QVA149A2336, QVA149A2337

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"):

QVA 149A2336, QVA 149A2337

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		QVA 149A2336
IND #76377	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/> ! Explain:

Investigation #2		QVA 149A2337
IND #76377	YES <input checked="" type="checkbox"/>	! ! NO <input type="checkbox"/> ! 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 <input type="checkbox"/>		!
Explain:		! NO <input type="checkbox"/> ! 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:

Christine Ford, RPh

Title: Regulatory Project Manager

Date: October 29, 2015

Thru: Sandy Barnes, CPMS

Date: October 29, 2015

Name of Office/Division Director signing form:

Badrul A. Chowdhury, MD, PhD

Title: Director, Division of Pulmonary, Allergy, Rheumatology

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTINE H CHUNG
10/29/2015

BADRUL A CHOWDHURY
10/29/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 207930 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Utibron Neohaler Established Name: glycopyrrolate/indacaterol Dosage Form: inhalation powder		Applicant: Novartis Pharmaceuticals Agent for Applicant (if applicable):
RPM: Christine Ford		Division: DPARP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p><i>Note: 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.</i></p>
Actions <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>10/29/2015</u> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification needed).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

- | | |
|---|--|
| NDAs: Subpart H
<input type="checkbox"/> Accelerated approval (21 CFR 314.510)
<input type="checkbox"/> Restricted distribution (21 CFR 314.520)
Subpart I
<input type="checkbox"/> Approval based on animal studies

<input type="checkbox"/> Submitted in response to a PMR
<input type="checkbox"/> Submitted in response to a PMC
<input type="checkbox"/> Submitted in response to a Pediatric Written Request | BLAs: Subpart E
<input type="checkbox"/> Accelerated approval (21 CFR 601.41)
<input type="checkbox"/> Restricted distribution (21 CFR 601.42)
Subpart H
<input type="checkbox"/> Approval based on animal studies

REMS: <input type="checkbox"/> MedGuide
<input type="checkbox"/> Communication Plan
<input type="checkbox"/> ETASU
<input type="checkbox"/> MedGuide w/o REMS
<input type="checkbox"/> REMS not required |
|---|--|

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
^ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
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)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval 10/29/2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	7/6/15, 3/17/15
• Review(s) <i>(indicate date(s))</i>	7/6/15, 6/28/15, 3/13/15 2/26/15 – Information request
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 9/17/15 DMEPA: <input type="checkbox"/> None 8/12/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 10/21/15 OPDP: <input type="checkbox"/> None 10/19/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	9/16/15 (completed before filing)
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo <i>(indicate date)</i> ○ If yes, OC clearance for approval <i>(indicate date of clearance communication)</i> 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics <i>(approvals only)</i> <ul style="list-style-type: none"> • Date reviewed by PeRC 9/9/2015 If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <p><i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i></p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include previous action letters, as these are located elsewhere in package)</i> 	2015 – 10/26, 10/23, 10/21, 10/7, 9/18, 9/15, 8/14, 7/30, 6/1, 5/27, 5/11, 4/10, 3/12, and 1/12
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i> 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting <i>(indicate date of mtg)</i> 	<input type="checkbox"/> No mtg 3/19/14
<ul style="list-style-type: none"> • EOP2 meeting <i>(indicate date of mtg)</i> 	<input type="checkbox"/> No mtg 3/7/12, 9/27/11
<ul style="list-style-type: none"> • Mid-cycle Communication <i>(indicate date of mtg)</i> 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting <i>(indicate date of mtg)</i> 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i> 	
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Division Director Summary Review <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 10/29/2015
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 10/8/2015
<ul style="list-style-type: none"> PMR/PMC Development Templates <i>(indicate total number)</i> 	<input checked="" type="checkbox"/> None
Clinical	
Clinical Reviews	

<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review, also see CDTL review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	2015 – 9/24 and 3/2
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	9/24/15 Clinical review, page 18
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None QT-IRT 7/29/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 10/1/15, 9/10/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2015 – 10/15 (2), 9/25, 3/1
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2015 – 9/24, 2/24
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 10/1/15
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2015 – 9/24, 7/7, 2/19
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 5/26/2014 ECAC mtg Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2015 – 10/28, 2/3
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None Microbiology 3/10/15
Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	CMC review 10/28/15, pg 156
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable 10/28/15 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities

❖ For all 505(b)(2) applications:	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs:	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
• Notify the CDER BT Program Manager	
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u>	<input type="checkbox"/> Done
• Notify the Division of Online Communications, Office of Communications	
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done



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

ELECTRONIC CORRESPONDENCE

Date: October 26, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments – Prescribing Information

Total no. of pages including cover: 35

Comments: *Response requested no later than October 27, 2015*

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We refer to NDA 207923 for Seebri Neohaler and NDA 207930 for Utibron Neohaler. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

For Section 14.2 Confirmatory Trials:

We have reviewed your comments and proposed language regarding secondary endpoints. We have also reviewed the approved package inserts for similar drugs. Based on your comments, and our review, we have amended our language in the Utibron Neohaler package insert to be consistent with what is in the package insert of other approved drugs of the class (i.e., Anoro Ellipta). While it appears that we do not have prior precedence for inclusion of this language in the Seebri Neohaler (a single ingredient LAMA) package insert, we have included the language in the Seebri package insert for your consideration. The information we have included provides information to providers regarding how much improvement one can expect in peak FEV1 on Day 1 as compared to the end of study, in this case Day 85, after chronic dosing. Our proposed language also includes re-insertion of the onset of action language that was previously deleted. Note that we are using the definition of onset of action as pre-specified in your protocol. The language proposed by the Agency was arrived at after extensive internal discussion and deliberation; therefore, while you may propose minor changes/corrections to our labeling language, substantial changes will not be entertained at this time.

FDA edits were made as tracked changes to your proposed labeling emailed October 23, 2015, with official submission planned for October 26, 2015. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than October 27, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: review team in shrepoint/ 10.26.2015
cford/ 10.26.2015

Thru: BKarimi-Shah/ 10.26.2015

Initialed by: SBarnes/ 10.26.2015

Finalized: cford/ 10.26.2015

32 Page(s) of Draft Labeling have been Withheld in Full as b4
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/s/

CHRISTINE H CHUNG

10/26/2015

Christine Ford (formerly Chung)



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

ELECTRONIC CORRESPONDENCE

Date: October 23, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments – Patient labeling

Total no. of pages including cover: 22

Comments: *Response requested no later than October 27, 2015*

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We refer to NDA 207923 for Seebri Neohaler and NDA 207930 for Utibron Neohaler. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

FDA edits were made as tracked changes to your proposed labeling submitted October 15, 2015. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than October 27, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: DMPP-OPDP/ 10.21.2015
cford/ 10.23.2015

Thru: BKarimi-Shah/ 10.23.2015

Initialed by: SBarnes/ 10.23.2015

Finalized: cford/ 10.23.2015

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/s/

CHRISTINE H CHUNG

10/23/2015

Christine Ford (formerly Chung)



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

ELECTRONIC CORRESPONDENCE

Date: October 21, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments

Total no. of pages including cover: 40

Comments: *Response requested no later than October 23, 2015*

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We refer to NDA 207923 for Seebri Neohaler, NDA 207930 for Utibron Neohaler, and to your submission dated October 15, 2015. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

A. For both NDAs 207923 and 207930

1. Regarding Novartis Comment 3 (Section 2.3), we appreciate your correction and proposal to use the human systemic exposure (AUC_{0-24h}) of 0.221 base ng.h/mL derived from study CQVA149A2107. Further, we agree with your dose ratios, using the base values for systemic exposure (AUC) for both the clinical and nonclinical studies. As you stated, there were no appreciable differences in dose ratios using either the base or salt form.
2. Regarding Novartis Comment 4 (Section 2.4), we again appreciate your correction and proposal to use the human systemic exposure (AUC_{0-24h}) of 1.030 base ng.h/mL derived from study CQVA149A2107. Further, we agree with your proposed dose ratios.
3. We have considered your comments under Novartis Comment 5 (Section 2.5), but do not agree with your entire assessment. (b) (4)
[REDACTED]

In the case of glycopyrrolate, the combined eye findings in the rat and dog are a concern, and we consider them to be consistent with the mechanism of action of glycopyrrolate. Data and statements in your study reports clearly support that eye findings are test article related in both rats and dogs. Regarding the findings in the 39-week dog study, we agree with your assessment that the focal nuclear opacities may be incidental, (b) (4)

The eye findings of bilateral and unilateral lenticular changes (anterior capsular opacity, anterior prominent suture line, anterior slight cataract) in the rat, and conjunctivitis and corneal opacity in the dog remain as test article related findings in our proposed labeling. We have adjusted the dose ratios using the base form AUC_{0-24hr} for animal data, and the corrected clinical AUC_{0-24hr} value for glycopyrrolate, as shown in the table below. To simplify the labeling text, we have eliminated (b) (4) and stated the lower dose ratio between the sexes in rats and in dogs.

Study	Sex	Nonclinical dose corresponding to eye finding		Dose ratio for clinical dose of 31.2 mcg NVA237
		Achieved dose (mg/kg/day, salt form)	AUC (ng*hr/mL) (base form)	AUC = 0.221 ng*hr/mL (base form)
26 week rat	Both	4.98	334	1500
	Both	0.67	61.6	280
	Both	0.09	13.8	60
39 week dog	Male	0.33	80.9	370
	Female		32.8	150
	Male	0.12	21.3	100
	Female		33.6	150

Dose ratios are rounded

B. Only for NDA 207930 Utibron

1. Section 14.1 Dose Ranging Trials

We do not agree with your proposal/rationale to delete (b) (4) information from this section. The example you provide with respect to (b) (4) is not relevant; (b) (4)

(b) (4) We refer you to the package insert of (b) (4) for a more typical example. For this reason, we have re-inserted the (b) (4) information back into this section.

2. Section 14.2 Confirmatory Trials

- We acknowledge your removal of the table listing the secondary endpoints and reformatting into a narrative format. However, reporting the secondary endpoints with this degree of granularity is unnecessary. We have re-inserted the prior language describing that the results were significant for these parameters, without reporting the numbers.
- The (b) (4) is not appropriate for labeling claims, (b) (4) We have removed this statement.
- With respect to the SGRQ, we note your reference to Jones et. al.¹ Based on our review of this article, we disagree with your conclusion that (b) (4)

¹ Jones PW et al. Minimal Clinically Important Differences in Pharmacological Trials. Am J Respir Crit Care Med 2014; 189: 250 - 255.

(b) (4)

When evaluating a combination therapy in which one of the monocomponents has already shown a benefit over placebo, the most important comparison is not of the combination to placebo (as one would expect this comparison to be positive even in the setting that the second component contributes nothing), but of the combination to each component. In order to evaluate the benefit of the combination over each single entity, the authors advocate for a responder analysis and propose the term “minimum worthwhile incremental advantage” to describe the percentage of patients who would experience improvement at or above the MCID on adding one treatment to another, or comparing two active treatments. As the “minimum worthwhile incremental advantage” is not defined, the best way to communicate this information to providers is to provide information regarding the relevant pairwise comparisons between the combination product, monoproducts, and placebo. Therefore, we have described the results in more detail for the trial which demonstrated statistically significant pairwise comparisons, reporting both responder rates and odds ratios, and provided only odds ratios for the trial which trended in favor of “incremental benefit” of the combination over the monotherapies, without showing a statistically significant difference. This language communicates the data in a neutral matter without favoring one set of pairwise comparisons over another. We prefer reporting the SGRQ results of both trials, as we have done in the attached label, giving more detailed information for Trial 2. We discourage any labeling modification that proposes removal of Trial 1 results, as this will result in a change in our position as to which trial should be reported in detail in labeling. While you may propose minor modifications to our language, we discourage major changes to the SGRQ labeling language.

FDA edits were made as tracked changes to your proposed labeling submitted October 15, 2015. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) October 23, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 10.21.2015
BKarimi-Shah/ 10.21.2015
cford/ 10.21.2015

Initialed by: SBarnes/ 10.21.2015

Finalized: cford/ 10.21.2015

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CHRISTINE H CHUNG
10/21/2015



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

ELECTRONIC CORRESPONDENCE

Date: October 7, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments

Total no. of pages including cover: 67

Comments: *Response requested no later than October 15, 2015*

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We refer to NDA 207923 for Seebri Neohaler, NDA 207930 for Utibron Neohaler, and to your submission dated September 22, 2015. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

- We have reviewed your response dated September 22, 2015, and have the following comment to your response to Question 2, regarding study 0870596 entitled, “A subcutaneous fertility and early embryonic development study in rats”, as it applies to Section 13.1 of the proposed labeling language for glycopyrrolate. We agree with your application of the historical control data for the number of corpora lutea, implantation sites, live fetuses and pre-implantation losses at the mid-dose of 0.5 mg/kg/day. Thus, we agree that there appears to be no test article related effect on fertility and reproductive potential based on these parameters at the mid-dose of 0.5 mg/kg/day. However, the historical data did not cover these parameters at the high-dose of 1.5 mg/kg/day indicating adverse drug-related effects at this dose. We cannot agree that (b) (4)

(b) (4)

Thus, we have included language in the proposed labeling that states fertility was adversely affected at the dose of 1.5 mg/kg/day of glycopyrrolate in both males and females. To be consistent with the proposed dose of 15.6 mcg of glycopyrrolate (salt form), all nonclinical doses of glycopyrrolate have been represented in the label in the salt form. Therefore, in the case of the rat fertility data, we propose to use the dose of 1.88 mg/kg/day (salt form), which corresponds to 1.5 mg/kg/day (base form).
- Regarding labeling for both NDA 207923 and 207930, we have listed all doses for nonclinical studies in the salt form for glycopyrrolate, and in the base form for indacaterol.
- In calculating the dose ratios for glycopyrrolate, we have utilized the human systemic exposure (AUC) of 0.139 ng.h/mL (salt form), derived from study # CQVA149A2107 (0.111 ng*h/mL, base form), corresponding to the proposed dose of 31.2 mcg glycopyrrolate (salt form). The following table illustrates the how dose ratios were calculated for the nonclinical sections covering carcinogenicity, and reproductive and developmental effects.

Study	Route	Sex	Dose (mg/kg; salt)	AUC (ng.h/mL; salt)	Dose Ratio	Rounded	Study #
					Clinical	Clinical	
					AUC = 0.139 (ng.h/mL; salt)	AUC = 0.139 (ng.h/mL; salt)	
Carcinogenesis							
2 year rat	IH	Both	0.56	45.6	328.1	330	r670435
Reproductive and Development							
Fertility in rats	SC	Male	1.88	519	3733.8	3700	r870596
Fertility in rats	SC	Female	1.88	290	2086.3	2100	r870596
Fertility in rats	SC	Both	0.63	98.0	705.0	710	r870596
EFD in rats	IH	Female	3.83	388	2791.4	2800	r680006
EFD in rabbits	IH	Female	4.4	148	1064.7	1100	r870597
PPND in rats	SC	Female	1.88	290	2086.3	2100	r870598*

*AUC value extrapolated from study r870596.

4. In calculating the dose ratios for indacaterol, we have utilized the human systemic exposure (AUC) of 0.515 ng.h/mL (base form), derived from study #

CQVA149A2107, [REDACTED] (b) (4)

[REDACTED]. The following table illustrates the how dose ratios were calculated for the nonclinical sections covering carcinogenicity, and reproductive and developmental effects.

Study	Route	Sex	Dose (mg/kg; base)	AUC (ng.h/mL; base)	Dose Ratio	Rounded	Study #
					Clinical	Clinical	
					AUC = 0.515 (ng.h/mL; base)	AUC = 0.515 (ng.h/mL; base)	
Carcinogenesis							
2 year rat	IH	Both	2.09	116	225.2	230	320002
Reproductive and Development							
Fertility in rats	SC	Male	2.0	921	1788.3	1800	270074
Fertility in rats	SC	Female	2.0	694	1347.6	1300	270074
EFD in rats	SC	Female	1.0	345	669.9	670	270037
EFD in rabbits	SC	Female	1.0	795	1543.7	1500	270038
PPND in rats	SC	Female	0.3	114	221.4	220	270185*

*AUC value extrapolated from study 0270037.

5. Eye findings were identified in the pivotal chronic toxicology studies with NVA237 in rats and dogs. In the 26 week inhalation toxicology study (Study # r0580297/79031), rats received estimated achieved doses of 0 (air), 0 (vehicle: 1% magnesium stearate, 99% lactose monohydrate), 0.09, 0.67 and 4.98 mg/kg of NVA237 (salt form). Eye findings consisted of bilateral and unilateral lenticular changes (anterior capsular opacity, anterior prominent suture line, anterior slight cataract) that were observed at doses of 0.67 mg/kg and above (approximately 440 times and above the MRHD in adults on an AUC basis.) These findings were partially reversible.

In the 39 week inhalation toxicology study (Study #r0670548), beagle dogs were dosed with 0 (air), 0 (vehicle: 1% magnesium stearate, 99% lactose monohydrate),

0.030, 0.12, and 0.33 mg/kg (estimated achieved doses in salt form) through the inhalation route of exposure. Test article related ophthalmic findings were bilateral conjunctival hyperemia, corneal opacity, and focal nuclear opacity observed at 0.33 mg/kg (in male and female dogs at approximately 770 and 290 times the MRHD in adults on an AUC basis, respectively). These findings were reversible.

Regarding eye findings listed under Section 13.2 of both labels under NDAs 207923 and 207930, we calculated the dose ratios based on the following systemic exposures (AUCs):

Study	Sex	Nonclinical dose corresponding to eye finding		Dose ratio for clinical dose of 31.2 mcg NVA237
		Achieved dose (mg/kg/day, salt form)	AUC (ng*hr/mL) (salt form)	AUC = 0.139 ng*hr/mL (salt form)
26 week rat	Both	4.98	334	2400
	Both	0.67	61.6	440
	Both	0.09	13.8	100
39 week dog	Male	0.33	101.2	730
	Female		41.0	290
	Male	0.12	26.6	190
	Female		42.0	300

FDA edits were made as tracked changes to your proposed labeling submitted December 29, 2014. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) October 14, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: cford/ 10.6.2015

Initialed by: SBarnes/ 10.7.2015
JSohn, TRobison/ 10.7.2015
ETorjusen, BKarimi-Shah/ 10.7.2015

Finalized: cford/ 10.7.2015

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/s/

CHRISTINE H CHUNG

10/07/2015

Christine Ford (formerly last name Chung)



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

ELECTRONIC CORRESPONDENCE

Date: September 18, 2015

To: Bisola Ashiru Filchak, MPH Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) inhalation powder
NDA 207930 Utibron (indacaterol/glycopyrrolate) inhalation powder
FDA request for information – Nonclinical

Total no. of pages including cover: 3

Comments: *Information requested no later than September 22, 2015*

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder are currently under review, and we have the following request for information:

1. In proposed labeling for Utibron Neohaler, Section 8.3 states that “Indacaterol (including its metabolites) have been detected in the milk of lactating rats.” The Nonclinical Overview for NDA 207930 includes the following statement, “Indacaterol and/or its metabolites passed the placenta-blood-barrier in pregnant rats and were transferred rapidly into the milk of lactating rats (Study R02-0220) (Study R0700884).”

Provide the location of the study report(s) for R02-0220 and R0700884 in NDA 207930.

2. For study 0870596 entitled, “A subcutaneous fertility and early embryonic development study in rats,” the study report concluded that there were no test article related effects on fertility. Rats received subcutaneous (SC) doses of 0 (vehicle, 5% dextrose), 0.19, 0.63, 1.88 mg/kg/day (salt) to assess fertility.

You noted that the fertility index was generally low in all groups, including the control (control 72%, LD 60%, MD 84%, HD 60%). This effect was not dose dependent. You also noted that studies conducted “recently” in the same facility had fertility rates that ranged from 84% to 96%, and that only the MD had a fertility rate within the expected range. There is a concern that the cause of the decreased fertility rate may mask a test article related effect.

Further, at the MD and HD, there was a slight decrease in the litter mean number of corpora lutea (control 13.2, LD 13.6, MD 12.6, HD 11.0) and number of implantations (control 11.6, LD 12.3, MD 9.9, HD 7.9), which corresponded to a decreased number of live fetuses per litter (control 10.9, LD 11.6, MD 9.9, HD 7.9). The decrease in implantations and live fetuses at the MD and HD may be a result of increased preimplantation loss at the MD and HD (control 12.1%, LD 9.9%, MD 19.8%, HD 22.4%), compared to the control and LD. Based on these dose dependent trends, it is difficult to rule out an effect of the test article on these parameters.

It appears reasonable to conclude that fertility may have been adversely affected by the test article at the MD and HD, which are associated with decreased number of corpora lutea, implantations, and live fetuses, and increased preimplantation loss. Fertility does not appear to have been adversely effected at the LD of 0.19 mg/kg NVA237 (salt).

Provide further justification for your interpretation of a lack of test article related adverse findings in fertility parameters at the MD and HD.

Submit the requested information as official responses to the NDAs no later than September 22, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 9.17.2015
cford/ 9.17.2015

Initialed by: SBarnes/ 9.18.2015
JSohn, TRobison/ 9.18.2015

Finalized: cford/ 9.18.2015

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CHRISTINE H CHUNG
09/18/2015



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ELECTRONIC CORRESPONDENCE

Date: September 15, 2015

To: Bisola Ashiru Filchak, MPH Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) inhalation powder
NDA 207930 Utibron (indacaterol/glycopyrrolate) inhalation powder
FDA request for information – Nonclinical

Total no. of pages including cover: 3

Comments: *Information requested no later than September 21, 2015*

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder are currently under review, and we have the following request for information:

In the 39 week dog study (study #79334/0670548), ophthalmic findings were identified by a board certified ophthalmologist:

“...mucoid ocular discharge, conjunctival hyperemia, faint corneal opacities, evidence of previous corneal ulceration and in one animal of receiving 0.33/0.27 mg/kg/day, slight unilateral diffuse corneal edema accompanied by aqueous flare and superficial corneal vascularization. Findings were uni- or bilateral, mostly intermittent and mild, and no longer observed at the time of recovery”

The study report provides individual ophthalmological data for the findings mentioned above (pages 954 - 959), but no summary tables for these findings were provided. Provide a summary table indicating unilateral or bilateral eye findings to assist in our interpretation of the data. The study report should be subsequently amended to include this information.

Submit the requested information as official responses to the NDAs no later than September 21, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

NDA 207923
NDA 207930
Page 3

Drafted by: JSohn, TRobison/ 9.15.2015
cford/ 9.15.2015

Initialed by: SBarnes/ 9.15.2015

Finalized: cford/ 9.15.2015

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/s/

CHRISTINE H CHUNG
09/15/2015



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

ELECTRONIC CORRESPONDENCE

Date: August 14, 2015

To: Bisola Ashiru Filchak, MPH Jennifer Evans, PharmD Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159 862-778-6061	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com jennifer.evans@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) capsules for inhalation
NDA 207930 Utibron (indacaterol/glycopyrrolate) capsules for inhalation
FDA request for information – Statistics

Total no. of pages including cover: 3

Comments: *Information requested no later than August 21, 2015*

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Ubitron Neohaler (indacaterol/glycopyrrolate) capsules for inhalation are currently under review, and we have the following requests for information:

Provide tipping point sensitivity analyses to evaluate the impact of missing data for the primary endpoint in trials NVA237A2317, NVA237A2318, QVA149A2336, and QVA149A2337. These analyses should vary assumptions about average values of the relevant endpoint among the patients on NVA237, QVA149, QAB149 and placebo arms who withdrew from the trial early. Include the possibility that patients with missing data from the active arms had worse outcomes than patients with missing data from the placebo arm. Ensure that documentation submitted with your report defines the distributions used to generate values for withdrawn patients and explains how those distributions were obtained.

Provide the datasets and programs for all analyses. The analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

Submit the requested information as official responses to the NDAs no later than close of business (COB) August 21, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

NDA 207923
NDA 207930
Page 3

Drafted by: KHamilton, DPetullo/ 8.13.2015
cford/ 8.13.2015

Initialed by: SBarnes/ 8.13.2015

Finalized: cford/ 8.14.2015

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CHRISTINE H CHUNG
08/14/2015



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

ELECTRONIC CORRESPONDENCE

Date: July 30, 2015

To: Bisola Ashiru Filchak, MPH Jennifer Evans, PharmD Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159 862-778-6061	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com jennifer.evans@novartis.com	Phone number: 301-796-3420
Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Capsules for Inhalation NDA 207930 Utibron (indacaterol/glycopyrrolate) Capsules for Inhalation FDA request for information – Nonclinical and CMC	

Total no. of pages including cover: 4

Comments: *Information requested no later than August 12, 2015*

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Ubitron Neohaler (indacaterol/glycopyrrolate) Capsules for Inhalation are currently under review, and we have the following requests for information:

1. We note that your proposed acceptance criteria for degradants (b) (4) differ between NDA 207923 and NDA 207930. In NDA 207923, you propose a specification of NMT (b) (4) % for (b) (4) and NMT (b) (4) % for (b) (4). In NDA 207930, you propose a specification of NMT (b) (4) % for (b) (4) and NMT (b) (4) % for (b) (4).

Degradants exceeding (b) (4) % should be qualified by safety data from a 13-week animal study to support chronic use for maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis.

We note that the justification for the acceptance criteria of NMT (b) (4) % for (b) (4) and NMT (b) (4) % for (b) (4) is limited to data from your submitted 4-week Rat Study with Degradation Products (study #0870163), Mutagenicity Test Using Salmonella (study #0870161), and Induction of Chromosome Aberrations in Peripheral Blood Lymphocytes (study #0870162).

In order to address this issue you may either:

- a. Amend the specification to limit the acceptance criteria of (b) (4) and (b) (4) to NMT (b) (4) % for each degradant in NDA 207923.

OR

- b. Submit a 13-week rat study with safety data or submit additional justification to support the proposed acceptance criteria of NMT (b) (4) % for (b) (4) and NMT (b) (4) % for (b) (4) under NDA 207923.

2. We have the following questions regarding your Inhalation Embryo Fetal Development Study in Rats (study #900863/ 0680006). We refer to your following schedule from page 23 of your study report which states that the first day of treatment was on December 4, 2006 (which we interpret as corresponding to Gestation Day 6 for some animals) and the last treatment was on December 20, 2006 (which we interpret as corresponding to Gestation Day 17 for some animals).

Major activities	Date
Protocol signed	22-Nov-2006
Animal arrival	22-Nov-2006
Placement for mating	27-Nov-2006
Start of acclimatization/pretest/randomization	01-Dec-2006
Date of first treatment	04- Dec-2006
Date of last treatment	20- Dec-2006
Date of last cesarean	24- Dec-2006

- a. On page 118, the filter concentrations pre-study (Nov 24, 2006) for groups 4, 5, 6 appear to be positive for the NVA237. Confirm that these filter concentrations were obtained from testing of the chambers without animals present on November 24, 2006, prior to the dosing of animals with NVA237.
 - b. On pages 36-48, summary tables provided concentrations of NVA 237 from homogeneity data, and from chamber concentrations. Clarify the labels used for the tables. For example, on page 36, the first sample concentration is given for “sample position TA1”. Further, on page 39, the first sample concentration is given for “Rep 1”.
3. We have the following questions regarding your Inhalation Embryo Fetal Development Study in Rabbits (study #901910/0870597). We refer to your following schedule from page 23 of your study report which states that the first day of treatment was on April 20, 2009, and the last treatment was on May 5, 2009.

Major activities	Date
Protocol signed	15-Apr-2009
Animal arrival/start of acclimatization/pretest	15 and 17-Apr-2009
Animal randomization	18 to 21-Apr-2009
Date of first treatment	20-Apr-2009
Date of last treatment	05-May-2009
Date of last cesarean	15-May-2009

- a. On page 112, the pre-study (Apr 3, 2009) data for groups 2, 3, and 4 appear to be positive for the NVA237. Confirm that these filter concentrations were obtained from testing of the chambers without animals present on April 3, 2009, prior to the dosing of animals with NVA237.
- b. On pages 40-54, summary tables provided the concentrations of NVA 237 from homogeneity data, and from chamber concentrations. Clarify the labels used for the tables. For example, on page 40, the first sample concentration is given for “sample position GA1”. Further, on page 43, the first sample concentration is given for “Rep 1 7”.

Submit the requested information as official responses to the NDAs no later than close of business (COB) August 12, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison, AShaw, CBertha/ 7.30.2015
cford/ 7.30.2015

Initialed by: SBarnes/ 7.30.2015

Finalized: cford/ 7.30.2015

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/s/

CHRISTINE H CHUNG
07/30/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207930

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
Building 100
East Hanover, New Jersey 07936-1080

ATTENTION: Jennifer Evans, PharmD
Global Program Regulatory Director, Drug Regulatory Affairs

Dear Dr. Evans:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol and Glycopyrrolate Capsules for Inhalation, 27.5 mcg/15.6 mcg.

We also refer to your correspondence dated and received May 1, 2015, requesting review of your proposed proprietary name, Utibron Neohaler.

We have completed our review of the proposed proprietary name, Utibron Neohaler and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 1, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
07/06/2015

Ford, Christine

From: Ford, Christine
Sent: Monday, June 01, 2015 1:09 PM
To: Evans, Jennifer (jennifer.evans@novartis.com)
Cc: Ford, Christine
Subject: QT information request for clearance:: NDA 207930 indacaterol/glycopyrrolate

Dear Jennifer,

We refer to NDA 207930 for incadaterol/glycopyrrolate Neohaler. Regarding the QT study report, submit the following information.

1. Demographic dataset
2. QTcI correction factor (slope b in QTcI calculation) for each subject

We request that you submit the requested information as an official response to the NDA no later than close of business June 4, 2015, or provide a timeline for when the information will be submitted.

Please confirm receipt of this information request and contact me if you have any questions. Thanks.

Christine

Christine Ford, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG
06/01/2015

Executive CAC

Date of Meeting: May 26, 2015

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Timothy McGovern, Ph.D., OND IO, Member
Jane J. Sohn, Ph.D., DPARP, Presenting Reviewer (Acting Pharm Tox Supervisor)

Author of Minutes: Jane J. Sohn, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 207923, 207930

Drug Name: Glycopyrronium bromide (GP), GP/Indacaterol

Sponsor: Novartis

Novartis submitted results from a 2-year inhalation carcinogenicity study in rats and a 26-week oral carcinogenicity study in transgenic mice administered GP. The doses used in the studies were recommended by the Committee (see minutes dated 10/5/2006 (rat) and 2/24/10 (mouse) under IND 48655). Carcinogenicity studies with indacaterol alone were previously reviewed under NDA 22383.

Glycopyrronium bromide was negative in genetic toxicology testing based on results from the *in vitro* bacterial reverse mutation, human peripheral lymphocyte chromosomal aberration assay, and the *in vivo* rat micronucleus assay.

Rat Carcinogenicity Study

In a 2-year bioassay in Wistar rats (50 animals/sex/group), animals received GP by inhalation (nose-only) at doses of 0 (air, on loading rack in restraint tubes in separate room), 0 (air, rotated on a flow through chamber), 0 (vehicle: 1% magnesium stearate and 99% lactose monohydrate), 0.06, 0.17, 0.45 mg/kg/day GP through 60-minute exposures (estimated achieved doses, quaternary ammonium cation of the bromide salt). The first air control group (Air1) showed increased body weight compared to all other groups, and was not used for analysis. Statistical analyses were done against the vehicle control and second air control (Air2) groups.

No statistically significant neoplastic findings were observed in male or female rats. GP was associated with decreased body weight in males at all doses, and in HD females. NVA 237 had no effect on mortality. Systemic exposure (AUC) to GP was similar in both genders, and slight accumulation was observed at Week 52. Exposure was dose proportional between the LD and MD, but was slightly less than dose proportional between the MD and HD. Systemic exposures (AUC) at the HD exceeded the maximum anticipated clinical exposure in COPD patients by more than 300-fold.

Tg.rasH2 Mouse Carcinogenicity Study

In a 26-week bioassay, Tg.rasH2 mice (25/sex/group) received GP by oral gavage at 0 (vehicle: Deionized water), 10, 25, and 75 mg/kg/day in males, and 0 (vehicle), 10, 30, and 100 mg/kg/day in females. Positive control mice were administered N-methyl-N-nitrosourea (MNU; 75 mg/kg) by a single intraperitoneal injection on Day 1.

No statistically significant neoplastic findings were observed in male or female Tg.rasH2 mice. GP was associated with decreased body weight in male and female Tg.rasH2 mice. NVA 237 had no effect on mortality in Tg.rasH2 mice. Due to inconsistent exposure to GP, exposure to the metabolite CJL603 was measured. Systemic exposure (AUC) for CJL603 was detected in at least 2 of 3 HD male and female Tg.rasH2 mice at 0.5, 1, 3, and 7 hrs post dose. Based on limited data for CJL603, AUC increased in a roughly dose proportional manner.

As expected, MNU-treated Tg.rasH2 animals had increased mortality and neoplasia incidence, compared to control Tg.rasH2 animals.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in either male or female rats.

Mouse:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in either male or female Tg.rasH2 mice.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

/Division File, DPARP
/Timothy Robison, DPARP
/Jane Sohn, DPARP
/Carol Galvis, DPARP
/Christine Ford, DPARP
/ASeifried, OND IO

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/s/

JANE J SOHN
05/28/2015

ABIGAIL C JACOBS
05/28/2015



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

ELECTRONIC CORRESPONDENCE

Date: May 27, 2015

To: Bisola Ashiru Filchak, MPH Jennifer Evans, PharmD Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159 862-778-6061	Fax number: 301-796-9728
Email: bisola.ashiru@novartis.com jennifer.evans@novartis.com	Phone number: 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules
NDA 207930 indacaterol/glycopyrrolate Inhalation Powder Hard Capsules
FDA request for information – Clinical / Office of Scientific Investigations

Total no. of pages including cover: 3

Comments: *Information requested no later than June 3, 2015*

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NDA 207923 and 207930 for glycopyrrolate and indacaterol/glycopyrrolate Neohaler Inhalation Powder Hard Capsules are currently under review, and we have the following request for information:

- During the FDA site inspection of Dr. Pearle for Study NVA237A2317, the inspectors noted that randomization numbers were not available at the study site; only kit numbers were provided. Clarify how the randomization number corresponds to the kit number. Include other study protocols NVA237A2318, QVA149A2336, QVA149A2337, if applicable.
- The raw spirometry data provided at the study site for study NVA237A2317 (Dr. Pearle) does not correspond with the adjusted data submitted to the NDA. Submit clarification about how the raw spirometry data was adjusted in the NDA. Include other study protocols NVA237A2318, QVA149A2336, QVA149A2337, if applicable.

Submit the requested information as official responses to the NDAs no later than close of business (COB) June 3, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: ETorjusen, BKarimi-Shah, AOrencia/ 5.26.2015
cford/ 5.27.2015

Initialed by: SBarnes/ 5.27.2015

Finalized: cford/ 5.27.2015

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CHRISTINE H CHUNG
05/27/2015



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

ELECTRONIC CORRESPONDENCE

Date: May 11, 2015

To: Jennifer Evans, PharmD Global Program Regulatory Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-6061	Fax number: 301-796-9728
Email: jennifer.evans@novartis.com	Phone number: 301-796-3420

Subject: NDA 207930 indacaterol/glycopyrrolate Inhalation Powder Hard Capsules
FDA request for information: Nonclinical

Total no. of pages including cover: 3

Comments: *Information requested by no later than cob Thursday, May 14, 2015*

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NDA 207930 for indacaterol/glycopyrrolate Neohaler Inhalation Powder Hard Capsules is currently under review, and we have the following request for information:

1. We have the following questions regarding your 6-month rasH2 transgenic mouse carcinogenicity study (study #0770668/N109087).
 - a. In your anatomic pathology report, focal liver necrosis is included in your summary tables on pages 370 and 394. Liver necrosis, however, is listed as focal/multifocal throughout your individual animal Table 3. Provide clarification on the focal or multifocal nature of the observed liver necrosis.
 - b. Provide a definition for the acronym “HDN” listed on page 325 of your study report.
 - c. On page 976, it states that the “pathology results will be formally peer reviewed”, but no signed statement of peer review or name of the peer review pathologist could be found. Provide the location of such information, or provide further information regarding the peer review conducted.
 - d. On page 100, it states, “Stability was previously determined for concentrations and storage conditions used in this study [REDACTED]^{(b) (4)}, Project Nos. [REDACTED]^{(b) (4)}”. Provide the location of the study reports in your submission.
2. We have the following questions regarding your 2-year rat carcinogenicity study (study #0670435/79032).

On page 1496, you identify an ophthalmic finding, anterior cortical subcapsular lens, associated with administration of NVA237. While individual ophthalmological findings data is present starting on page 414, group summary data could not be found. Provide the location of group summary ophthalmic data, or submit the summary tables to the NDA.

Submit the requested information as an official response to the NDA no later than close of business Thursday, May 14, 2015, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 5.8.2015
cford/ 5.11.2015

Initialed by: SBarnes/ 5.11.2015

Finalized: cford/ 5.11.2015

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/s/

CHRISTINE H CHUNG
05/11/2015



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

ELECTRONIC CORRESPONDENCE

Date: April 10, 2014

To: Jennifer Evans, PharmD Global Program Regulatory Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-6061	Fax number: 301-796-9728
Email: jennifer.evans@novartis.com	Phone number: 301-796-3420

Subject: NDA 207930 indacaterol/glycopyrrolate Inhalation Powder Hard Capsules
FDA request for information from Office of Scientific Investigations

Total no. of pages including cover: 3

Comments: *Information requested by no later than cob Friday, April 17, 2015*

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notify us immediately by telephone at (301) 796-3420. Thank you.**

NDA 207930 for indacaterol/glycopyrrolate Neohaler Inhalation Powder Hard Capsules is currently under review, and we have the following request for information:

Provide clinical study subject data listings (a through g below) to capture the following, as applicable, and as 4 separate pdf files for the following sites:

Sites #5080 (Study A2336) and #5033 (Study A2337) [Dr. James Pearle, Fullerton, CA]
Sites #5082 (Study A2336) and #5027 (Study A2337) [Dr. Leonard Dunn, Clearwater, FL]

- a. Subject discontinuations (if applicable, sorted by treatment group and including the following variables: site subject number, screening visit date, randomization date, date of first dose/last dose, date of discontinuation, reasons for discontinuation)
- b. Subject assignment per treatment arm (randomization group, as applicable)
- c. Any protocol deviations or violations
- d. All adverse events - if applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE) [yes/no], death [yes/no]
- e. Primary study efficacy endpoint
- f. Relevant study efficacy endpoint/s (SGRQ scores)
- g. Concomitant medication list (non-study medications)

Submit the requested information as an official response to the NDA no later than close of business Friday, April 17, 2015, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: AOrencia/ 4.7.2015
cford/ 4.7.2015

Initialed by: SBarnes/ 4.8.2015
ETorjusen/ 4.9.2015
LGilbert-McClain for BKarimi-Shah/ 4.9.2015
AOrencia/ 4.10.2015

Finalized: cford/ 4.10.2015

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/s/

CHRISTINE H CHUNG
04/10/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207930

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
Building 100
East Hanover, NJ 07936-1080

ATTENTION: Jennifer Evans, PharmD
Global Program Regulatory Director
Drug Regulatory Affairs

Dear Dr. Evans:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol/Glycopyrrolate Capsules for Inhalation, 27.5 mcg/12.5 mcg.

We also refer to:

- Your correspondence, dated and received December 31, 2014, requesting reconsideration of your proposed proprietary name, (b) (4)
- Your amendment to the Request for Reconsideration of Proprietary Name Request, dated and received February 27, 2015

We have completed our review of the information submitted in support of the proposed proprietary name, (b) (4) and have concluded that your response has not alleviated the safety concerns described in the letter dated August 19, 2014. Therefore, we continue to find the use of the proposed proprietary name, (b) (4), unacceptable for the reasons listed:



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In summary, based on our evaluation of the information documented in our previous reviews along with the information provided as part of your reconsideration request for the proposed name [REDACTED] (b) (4), we conclude that the data submitted does not address our previous safety concerns regarding the potential for confusion between [REDACTED] (b) (4) and your proposed name, [REDACTED] (b) (4) for this product. Therefore, we maintain our objection to the use of this proposed proprietary name.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/17/2015



NDA 207930

**FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 100
East Hanover, NJ 07936-1080

Attention: Jennifer Evans, Pharm.D.
Global Program Regulatory Director

Dear Dr. Evans:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for indacaterol/glycopyrrolate Inhalation Powder Hard Capsules.

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 29, 2015.

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 October 1, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have however identified CMC deficiencies that may be addressed by your response to the following requests for information:

1. Institute controls on the particle size of (b) (4), QAB149 maleate drug substance, magnesium stearate, and lactose monohydrate, which are representative of the range of particle sizes of the lots used to manufacture the critical

clinical batches and commercial scale registration batches. Provide supportive data or the location of the referenced data supporting the proposed acceptance criteria.

2. Revise your analytical method for Aerodynamic Particle Size Distribution by (b) (4) to remove the allowance of (b) (4) inhalation, and utilize a target flow rate through the cascade impactor (b) (4). A total volume (b) (4) is excessive with respect to the typical volume of air withdrawn through such products by patients during use. In addition, propose acceptance criteria for your (b) (4) which reflect the data obtained under the new operating conditions.
3. Revise your analytical method for Delivered-Dose Uniformity by (b) (4) to utilize a target flow rate through the cascade impactor (b) (4).
4. Institute a stratified sampling plan throughout the filling process in the dosage form manufacturing process which includes in-process controls for Aerodynamic Particle Size Distribution (APSD) and Delivered Dose Uniformity (DDU) of both drug substances. Include additional sampling and testing after any significant event has occurred. A significant event is an operation that can affect the integrity of the in-process materials and, hence, their quality attributes (e.g., (b) (4)). We believe this is necessary since the (b) (4) in the formulation and, as such, (b) (4) during the capsule filling process which may influence these parameters, and therefore safety and efficacy. Provide an updated Master Batch Record which includes the above sampling.
5. Provide the results of stratified sampling and testing, included data analysis, for APSD and DDU throughout the filling process to assure that the proposed manufacturing process does not have a significant trend toward higher or lower delivered dose, or (b) (4).
6. Institute controls on blend uniformity during formulation manufacture ((b) (4) Indacaterol Maleate drug substance, Magnesium Stearate, and Lactose). Include these controls as well as the associated sampling plan in the revised Master Batch Record requested above.

We request that you also submit the following CMC information:

7. Control information for indacaterol maleate drug substance (specifications, analytical procedures, validation of analytical procedures, batch analyses and justification of specifications) was provided with NDA 207930. Confirm that no changes to this information are made relative to the approved, cross-referenced NDA 22383. Indicate if any changes have been submitted and approved in supplements.
8. Provide data to support the identification and assay of the extractables identified in 3.2.P.2.4.1.1
9. Provide an updated 356h to include all manufacturing facilities for the two drug substances, device and drug product. Indicate if testing is performed at the facility. For the drug product, specify the type i.e. processing, primary packaging and/or labeling are performed at the facility. Add testing facilities for release and stability if they are different from the manufacturing locations

10. Provide information on the solubility, hygroscopicity, and intrinsic dissolution differences between the [REDACTED] ^{(b) (4)} (if any) of indacaterol and glycopyrrolate. Explain how these differences (if any) could impact the drug product mean residence time in the lungs and the rate and extend of absorption.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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(s) 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 Christine Ford, Regulatory Project Manager, at (301) 796-3420.

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
03/12/2015



NDA 207930

INFORMATION REQUEST

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

Attention: Jennifer Evans, PharmD
Global Program Regulatory Director
Drug Regulatory Affairs

Dear Dr. Evans:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol/Glycopyrronium Dry Powder for Oral Inhalation, 27.5 mcg/15.6 mcg.

We also refer to your December 14, 2014 submission, containing the request for Proprietary Name requesting reconsideration of your proposed proprietary name, (b) (4).

We are reviewing your submission and have the following information request. We request a prompt written response by close of business, Friday, February 27, 2015, in order to continue our evaluation of your proprietary name.

In your (b) (4) Reconsideration request you reference a (b) (4) study and state: "The full report from the (b) (4) can be provided on request if the FDA wishes to review the details of that research." Submit the full report of the (b) (4) study for our review.

If you have any questions, please contact me, at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Nichelle Rashid
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NICHELE E RASHID
02/26/2015



NDA 207930

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 100
East Hanover, NJ 07936-1080

Attention: Jennifer Evans, Pharm.D.
Global Program Regulatory Director

Dear Dr. Evans:

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: indacaterol/glycopyrrolate Inhalation Powder Hard Capsules

Date of Application: December 29, 2014

Date of Receipt: December 29, 2014

Our Reference Number: NDA 207930

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 27, 2015, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

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, Allergy, and Rheumatology 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H CHUNG
01/12/2015



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: March 19, 2014 11:00 A.M. – 12:30 P.M.
Meeting Location: White Oak Building 22, Conference Room: 1311

Application Number: IND 76377
Product Name: QVA149 (indacaterol maleate/glycopyrronium bromide)
Indication: Chronic Obstructive Pulmonary Disease
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation (Novartis)

Meeting Chair: Badrul A. Chowdhury, Director
Meeting Recorder: Christine Chung, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, M.D., Deputy Director, DPARP
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP
Robert Lim, M.D., Clinical Reviewer, DPARP
Timothy Robison, Ph.D., Nonclinical Team Leader, DPARP
Andrew Goodwin, Ph.D., Nonclinical Reviewer, DPARP
Christine Chung, R.Ph., Regulatory Project Manager, DPARP
Ruthanna Davi, Ph.D., Biometrics Reviewer, Division of Biometrics II (DBII)
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCPII)
Craig Bertha, Ph.D., Acting CMC Lead, Division of New Drug Quality Assessment III

SPONSOR ATTENDEES:

Donald Banerji, M.D., Clinical Development
Eric Couture, Ph.D., Drug Regulatory Affairs
Maria Figliomeni, Ph.D., Medical Affairs
Emilie Gruen, Pharm.D., Drug Regulatory Affairs
Thomas Martin, M.D., Clinical Development
Francesco Patalano, M.D., Development
Paula Rinaldi, R.Ph., MPH, Drug Regulatory Affairs
Ann Shea, Drug Regulatory Affairs
Chau Thach, Ph.D., Statistics
Gretchen Trout, Drug Regulatory Affairs

BACKGROUND:

Novartis is developing fixed dose combination QVA149 (indacaterol 27.5mcg and glycopyrronium 12.5 mcg) for twice daily use in long-term, maintenance (b) (4) treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. Single ingredient Arcapta (indacaterol) was approved July 2011, and a NDA submission for NVA237 (glycopyrronium, IND 48655) is planned for the fourth quarter of calendar year 2014 (4Q2014). Novartis requested this pre-NDA meeting to discuss the content and format of the QVA149 NDA submission which is also planned for 4Q2014. The NVA237 NDA is planned to be submitted prior to the submission of the QVA149 NDA.

The briefing package was received February 18, 2014.

On March 18, 2014, Novartis emailed their responses and specified areas that they would like to further discuss with FDA during the meeting. Their comments are incorporated into the body of the minutes as well as provided as an Attachment.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics*; FDA's responses (meeting preliminary comments) in normal font; and Novartis' emailed responses also noted in *italics*. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND PRELIMINARY RESPONSES

Clinical / PK / Statistics

Question 1

Does the Agency agree with the proposed content and format of the Summary of Clinical Efficacy (SCE), including the pooling strategy?

FDA response

The proposed content and format of the Summary of Clinical Efficacy appears reasonable. However, while pooling of efficacy data may be helpful for exploratory analyses of treatment effects in smaller subpopulations of patients, the primary analyses of efficacy will be made based on individual results from each of your two phase 3 efficacy and safety studies.

Question 2

Does the Agency agree with the proposed pooling strategy for the Summary of Clinical Safety (SCS)?

FDA response

Your pooling strategy appears reasonable. However, given the ongoing safety concerns with anticholinergic agents, the adequacy of your long-term safety database will be a review issue.

Sponsor's request for clarification

Novartis would like to gain further understanding of the Agency's current safety concerns regarding this class of drugs.

Discussion:

Novartis noted that their safety database will include an adjudicated MACE analysis, as well as analyses of adverse events of special interest, including atrial fibrillation. Their safety data will include one long-term safety trial for the 27.5/12.5 mcg BID dose and two for the 110/50mcg qD dose. They believe that their safety database is comprehensive.

FDA responded that although the proposed analyses appear to be reasonable, the adequacy of the long-term safety database would be a review issue. With respect to the specific safety concerns for this class, the primary concerns are related to cardiovascular events. These concerns have been previously discussed at recent PADAC meetings for anticholinergic products. The FDA noted that at those meetings, the PADAC raised concerns regarding the size of the safety databases and whether or not population of patients studied was representative of the general COPD population. FDA also noted that majority of the patients in the QVA149 clinical program were from the non-U.S. program [QVA149 dose (110/50mcg qD)]. Data from the smaller U.S. program [QVA149 27.5/12.5mcg BID] would have to be placed into the context of the larger non-U.S. program.

Novartis inquired if the outcome of TIOSPIR would impact the safety review of QVA149.

FDA stated that at this time, they cannot determine if that would affect QVA149 review.

Question 3

Novartis plans to submit the narrative portion of the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) in Modules 2.7.3 SCE and 2.7.4 SCS respectively, with the appendices of data and integrated analyses in Module 5. Does the Agency agree with this proposal?

FDA response

This approach appears reasonable.

Question 4

Does the Agency agree with the safety information planned to be included in the 120-Day safety update?

FDA response

This appears reasonable.

Sponsor's request for clarification

Novartis acknowledges the Agency's response and will submit a protocol amendment for the interim analysis for NVA237 Study A2319, including a plan to maintain blinding, as

well as a statistical analysis plan by the end of April. At that time, we plan to request the Agency's feedback within 45 days.

Discussion:

FDA noted that the response was specific to Novartis' proposal for the 120-day update for QVA149. The response did *not* apply to NVA237 program.

The sponsor referred to their handout (Attachment 3).

Novartis reiterated the following information from the briefing package, "Novartis plans to cross-refer to the NVA237 NDA, including the 120-Day Safety Update that is planned to be submitted prior to the QVA149 120-Day Safety Update. In addition, Novartis acknowledges the Agency's Written Feedback dated November 21, 2013 for NVA237 (IND 48,655) and would like to note that the NVA237 NDA is planned to include [REDACTED] (b) (4)

[REDACTED]. The NVA237 120-Day safety update will include the full clinical study report for this study."

FDA stated that the NDA should be complete at the time of submission and that it should specifically include sufficient information to support long-term safety. FDA also noted that [REDACTED] (b) (4)

[REDACTED]. Should the sponsor decide to pursue this approach, the FDA recommended that the statistical analysis plan for the [REDACTED] (b) (4) associated with the efficacy analyses be submitted to the IND.

Novartis stated that they plan to submit the NDA for NVA237 prior to QVA149 but asked about acceptability of submitting QVA149 (combination product) NDA before the NVA237 (mono-product) NDA.

FDA responded that in the past applicants have chosen to submit either the mono-product or the combination product application first. However, if the combination product is submitted first, approval would be contingent on demonstration of safety and efficacy for the combination product *and* the mono-products. If the combination product NDA did not contain sufficient data to support the safety and efficacy of the mono-products, the combination product would not be approved. In the case of QVA149, because of the small size of the NVA237 safety database for the 12.5mcg BID dose, [REDACTED] (b) (4) and because further safety data would be pending for NVA237 at the time of QVA149 NDA submission, FDA would likely not consider the QVA149 NDA submission to contain sufficient data to support safety for the monoproduct NVA237. As such, submission of the QVA149 NDA prior to completion of the long-term safety trials for NVA237 would likely lead to a complete response.

FDA advised the sponsor to submit the NDA for the combination product after studies for NVA237 are complete.

Novartis asked again whether it would be acceptable to submit the NDA for QVA149 since there are no identified safety signals with the doses proposed (for glycopyrronium) in the combination product.

FDA responded that based on the information presented, the QVA149 NDA can probably be filed, but would likely be given a complete response for the reasons previously stated.

Question 5

Does the Agency agree with the proposals for providing the clinical and PK datasets in the NDA?

FDA response

We agree.

Question 6

Does the Agency agree with the proposed approach for handling the mixed data format in the NDA for QVA149?

FDA response

We agree with your proposal to provide efficacy data in both CDISC and legacy formats provided all variables are clearly defined and derivations are well-documented with appropriate links to the eCRF files and to the raw datasets. Further, ensure that the analysis datasets you submit include all data used to generate the results presented in your study report. In addition, provide the programs used for analyses of each efficacy variable proposed for inclusion on the product label or which precedes, in the analysis hierarchy, an efficacy variable proposed for inclusion on the product label. Also, include programs used for analyses of patient disposition.

Sponsor's request for clarification

Novartis acknowledges the Agency's feedback and proposes to provide the programs used for analyses of patient disposition only for the QVA149 27.5/12.5 mcg pivotal Studies A2336, A2337 and A2340. In these three studies, subjects who discontinued treatment were followed through the course of the study.

Discussion:

FDA stated that the sponsor's proposal is acceptable and recognized Novartis' efforts in collecting post-treatment discontinuation data, a practice that the Division is encouraging.

Question 7

Does the Agency agree with the proposal for submission of Case Report Tabulations (CRTs)?

FDA response

We agree with your proposal to provide data definition files and annotated CRFs for each clinical study dataset.

Your proposal for submission of population PK analysis data file and model control streams is adequate. In addition to final model, if applicable, you should submit the base model control stream and associated output files.

Question 8

Does the Agency agree with the proposal for submission of CRFs and SAE narratives?

FDA response

Include in your submission narratives for patients from the supportive trials (QVA149 110/50 program) who discontinued due to AEs. Otherwise, your proposal appears reasonable.

Regulatory

Question 9

Does the Agency agree with the overall proposed content and format of the NDA?

FDA response

The proposed content and format appear reasonable

Question 10

Novartis proposes to cross-reference the NDA 22-383 of Arcapta Neohaler (QAB149 – indacaterol) and the NDA of NVA237 (glycopyrronium) (planned to be submitted prior to the QVA149 NDA) for information related to the monotherapy components, including drug substance, non-clinical and clinical information. Does the Agency agree?

FDA response

Your proposal to cross reference drug substance, non-clinical, and clinical information related to the monotherapy components is reasonable. However, to facilitate review, consider submitting information related to NVA237 monotherapy dose/dose interval to this NDA rather than cross referencing the NDA for NVA237.

Sponsor's request for clarification

Novartis would like to discuss the content of both the QVA149 and NVA237 NDAs to support the dose selection for the NVA237 monotherapy component in the fixed-dose combination at the meeting (see attachment).

Discussion:

The sponsor referred to the slide entitled “Dose selection approach for NVA237 in QVA149” (see Attachment 2).

FDA stated that the approach for both NDAs appears reasonable. However, the adequacy of the dose-ranging will be a review issue.

Question 11

Could the Agency please clarify the regulatory review process intended for this application?

FDA response

As stated, QVA149 will not be under the provisions of the Program under PDUFA V. However, for non-Program applications, any additional information needed (requests for additional information and analyses) or any feedback that can be relayed will be communicated to you within a month following the mid-cycle meeting.

Determination of whether an Advisory Committee Meeting will be held will be made during the review cycle.

Question 12

Could the Agency please clarify the anticipated nomenclature (glycopyrrolate or glycopyrrolate) for the active ingredient for NVA237?

FDA response

The established name for the drug substance to be used is "glycopyrrolate" and the matching strength would be 12.5 mcg (corresponding to 15.6 mcg of glycopyrrolate bromide).

Sponsor's request for clarification

Novartis understands that the name "glycopyrrolate" is to be used for labeling purposes. In line with previous FDA feedback, Novartis had requested a new USAN for "glycopyrrolate" which has been denied by the USAN Council. Novartis would like to clarify that a new USAN is therefore not required to use "glycopyrrolate" for labeling purposes.

Discussion:

FDA stated that USAN has not provided a clear answer yet, so they will be contacting the USP liaison. They will plan to provide clarification in the official minutes of this meeting.

FDA Additional Comments

Clinical:

Clarify your intent to conduct clinical studies to assess the impact of your proposed QVA149 combination product (b) (4).

Sponsor's request for clarification

Novartis would like to clarify our intent with respect to the clinical studies to assess the (b) (4) at the meeting.

Discussion:

Novartis responded that they do not intend to (b) (4)

Nonclinical:

1. Provide a safety assessment of the components of the immediate packaging that are in direct contact with the capsule dosage forms for the shelf life of the drug product.
2. Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Draft Consensus Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 2 Version dated February 6, 2013).

Sponsor's request for clarification

Novartis would like to further understand the Agency's comment with respect to the request to provide a safety assessment of the components of the immediate packaging.

Discussion:

FDA noted that the device has already been approved, however, if any concerns are identified, nonclinical review will be requested.

Sponsor's request for discussion- Additional topic (time-permitting)

Novartis would like to understand the Agency's current thinking about patient-reported outcomes for key symptoms, such as shortness of breath in COPD.

Discussion:

FDA stated that patient reported outcomes (PRO's) may be acceptable; however discussion of a PRO's is beyond the scope of the current meeting.

Chemistry, Manufacturing, and Controls (CMC):

We remind you to submit *in vitro* CMC-related data (e.g., dose delivery, aerodynamic particle size distribution by cascade impaction) clearly demonstrating that, for the duration of the clinical studies, each strength of the combination drug product is pharmaceutically similar to the single ingredient monotherapy drug products, in terms of the delivery performance for each drug. Typically these data should be provided for our evaluation via the IND, prior to the commencement of your phase 3 clinical studies. In addition, we expect these data to be included in the pharmaceutical development section (P.2) of the NDA for the inhalation combination drug product.

PREA REQUIREMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and

each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)

<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ACTION ITEMS:

Action Item/Description	Owner	Due Date
USAN/USP follow-up regarding use of "glycopyrronium"	FDA	With meeting minutes, if possible

FOLLOW-UP TO ACTION ITEM:

It is acceptable to use "glycopyrrolate" for labeling purposes. For all future submissions for NVA237 applications, use "glycopyrrolate 15.6 mcg" for glycopyrronium 12.5 mcg; convert other doses accordingly.

ATTACHMENTS:

- Attachment 1 - Novartis' responses sent by email on March 18, 2014.
- Attachment 2 – Novartis' "Dose selection approach for NVA237 in QVA149"
- Attachment 3 – Novartis' handout at meeting "Clinical development overview" slides



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

Ann Shea, Director
Tel: 862-778-4567
Fax: 973-781-2565
Internet: ann.shea@novartis.com

March 18, 2014

Badrul Chowdhury, MD, PhD
Division Director
Food and Drug Administration
Division of Pulmonary and Allergy
Drug Products
Office of Drug Evaluation 2
5901-B Amundale Road
Beltsville, MD 20705-1266

IND 76,377

QVA149 (indacaterol and glycopyrronium)

**GENERAL CORRESPONDENCE:
Response to Pre-Meeting Comments for
March 19, 2014 (Type B) Meeting**

Dear Dr. Chowdhury,

Thank you for providing the preliminary meeting comments dated March 14, 2014. Please find below the topics that we would like to further discuss at the meeting.

Question 2 (Format and content of SCS)

The Agency noted that the pooling strategy appears reasonable; however, given the ongoing safety concerns with anticholinergic agents, the adequacy of the long-term safety database will be a review issue.

Novartis would like to gain further understanding of the Agency's current safety concerns regarding this class of drugs.

Question 4 (120-Day Safety Update)

Novartis acknowledges the Agency's response and will submit a protocol amendment for the interim analysis for NVA237 Study A2319, including a plan to maintain blinding, as well as a statistical analysis plan by the end of April. At that time, we plan to request the Agency's feedback within 45 days.

Question 6 (Mixed data format)

Novartis acknowledges the Agency's feedback and proposes to provide the programs used for analyses of patient disposition only for the QVA149 27.5/12.5 mcg pivotal Studies A2336, A2337 and A2340. In these three studies, subjects who discontinued treatment were followed through the course of the study.

Question 10 (Cross-referencing)

Novartis would like to discuss the content of both the QVA149 and NVA237 NDAs to support the dose selection for the NVA237 monotherapy component in the fixed-dose combination at the meeting (see attachment).

Question 12 (nomenclature for NVA237)

Novartis understands that the name “glycopyrronium” is to be used for labeling purposes. In line with previous FDA feedback, Novartis had requested a new USAN for “glycopyrronium” which has been denied by the USAN Council. Novartis would like to clarify that a new USAN is therefore not required to use “glycopyrronium” for labeling purposes.

FDA Additional Comments

Clinical:

Novartis would like to clarify our intent with respect to the clinical studies to assess the impact (b)
(4) at the meeting.

Nonclinical:

Novartis would like to further understand the Agency’s comment with respect to the request to provide a safety assessment of the components of the immediate packaging.

Additional topic (time-permitting)

Novartis would like to understand the Agency’s current thinking about patient-reported outcomes for key symptoms, such as shortness of breath in COPD.

If you have any questions regarding this submission, please do not hesitate to contact me at (862) 778-4567.

Sincerely,

Ann Shea
Director, Drug Regulatory Affairs

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immediately following this page

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

/s/

CHRISTINE H CHUNG
04/18/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 76377

MEETING MINUTES

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

Attention: Ann Shea
Drug Regulatory Affairs

Dear Ms Shea:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for QVA149 (indacaterol maleate and glycopyrronium bromide).

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2012. The purpose of the meeting was to discuss comments for End-of-phase 2 meeting dated, September 27, 2011.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-796-2284.

Sincerely,

{See appended electronic signature page}

Angela Ramsey R.N., M.S.N.

Project Coordinator

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Date and Time: March 7, 2012 at 9:30am -11:00am EST
Meeting Location: FDA White Oak, Building 22, Room 1315

Application Number: IND 76377
Product Name: QVA149 (indacaterol maleate and glycopyrronium bromide)
Indication: Chronic Obstructive Lung Disease
Sponsor/Applicant Name: Novartis

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D., Division Director
Meeting Recorder: Angela Ramsey, R.N., M.S.N., Project Coordinator

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lydia Gilbert-McClain, M.D., FCCP
Angela Ramsey, RN, MSN, Program Coordinator
Robert Lim, MD., Clinical Reviewer
Theresa Michele, MD, Clinical Team Leader
Craig Bertha, Chemistry Reviewer
Lokesh Jain, Clinical Pharmacologist Reviewer
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader
Molly Topper, Ph.D., Pharmacology Toxicology Supervisor
Atul Bhattaram, Ph.D., Clinical Pharmacologist Reviewer

SPONSOR ATTENDEES

Donald Banerji, M.D., Clinical Development, Sr. Global Program Medical Director
Hungta Chen, Ph.D., Integrated Information Science, Associate Director
Paul Colthorpe, Ph.D., Development, Global Program Head
Chris Compton, M.D., Clinical Development, Head, Primary Care
Eric Couture, Ph.D., Drug Regulatory Affairs, Global Head, Primary Care
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Greg Howe Regulatory CMC, Global Liaison
Rob Kowalski, Pharm.D., Drug Regulatory Affairs, Global Head
David Morris, M.D. Development, Global Head, Primary Care
Francesco Patalano, M.D., Development, Global Program Head
Romain Sechaud, Ph.D., Drug Metabolism & Pharmacokinetics, Senior Investigator
Ann Shea Drug Regulatory Affairs, Global Program Regulatory Director
Thomas Storm, Ph.D., Project Leader, Technical Research and Development

Gretchen Trout Drug Regulatory Affairs, FDA Liaison Office
Timothy Wright, M.D., Development, Global Head

1. BACKGROUND

Novartis submitted a Type B meeting request dated, December 16, 2011, to discuss comments from End-of Phase 2 meeting dated, September 27, 2011 for QVA149 (indacaterol maleate and glycopyrronium bromide). The February 15, 2012 meeting was rescheduled to March 7, 2012 at the request of Novartis. Novartis submitted background material dated, February 7, 2012. Upon review of the material, the Division responded via secure email on March 5, 2012. Novartis requested to continue the face-to-face meeting to clarify questions 4, 6, 7 and 2.

The content of the email are below. Any discussions that occurred during the meeting are captured directly under the relevant response. The sponsor's questions and clarifications are in ***bold italics***; the Division's response is in *italics*; and discussion is in normal font.

2. DISCUSSION

Quality

Question 1:

Does the Agency agree that the (b) (4) and QAB149 27.5 mcg monotherapy comparators are pharmaceutically equivalent to the indacaterol component of the (b) (4) and QVA149 27.5/12.5 mcg combination therapy drug products, respectively (i.e. same dose, formulation components, comparable APSD profiles and comparable EDU), and therefore can be used as part of the Novartis program to satisfy the requirements of 21 CFR 300.50 on fixed-combination prescription drugs for humans (combination rule)?

FDA Response:

Yes, we agree, assuming that the indacaterol Emitted Dose Uniformity data for the QAB149 27.5 mcg and the (b) (4) combination drug product are comparable.

We also acknowledge that you have not presented Emitted Dose Uniformity (EDU) or APSD profile data to support the pharmaceutical equivalence between the NVA237 monotherapy product ((b) (4) 12.5 mcg) and the QVA149 (b) (4) 27.5/12.5 mcg combination drug products proposed in the package; thus, no comments can be provided regarding that aspect of the development.

We do acknowledge, however, that we considered the fine particle mass (FPM) delivered from the NVA237 (b) (4) monotherapy product to be comparable to the NVA237 FPM from the (b) (4) QVA149 combination drug products as shown in the EOP2 meeting package.

Discussion

No discussion occurred.

Clinical Pharmacology

Question 2:

Does the Agency agree that the proposed clinical pharmacokinetic program is adequate to support registration of the QVA149 doses (b) (4) 27.5/12.5 mcg and the bridging of the clinical pharmacokinetic characteristics of indacaterol in QVA149 to QAB149 75 mcg (Arcapta™ Neohaler™) and that no additional clinical pharmacology bridging studies are required?

FDA Response:

Your proposed clinical pharmacology approach for registration of QVA149 products and for bridging of QVA149 products to QAB149 75 mcg and NVA237 products appears reasonable. However, we assume that NVA237 program will adequately address the dose adjustments for NVA237 based on intrinsic and extrinsic factors. Sufficiency of this information will be a review issue based on the results of the proposed PK studies. Also See Question 4 comment and response to Question 4a.

In population PK analysis, your proposed sample size and blood sampling schedule must have adequate power to characterize the effects of demographic variables and smoking history on pharmacokinetics of QAB149 and NVA237.

Clarification Question 2

With regard to your comments that dose adjustments for NVA237 based on intrinsic and extrinsic factors will be addressed, we do not expect that a change in dosing recommendation for NVA237 is required based on the data generated for (b) (4)

We propose to (b) (4)

Does the Agency agree that this is acceptable?

Discussion

The Division is unable to comment without reviewing the data; however, the approach seems reasonable.

Clinical

Question 3a:

Does the Agency agree with the design of the proposed NVA237 dose-frequency study

*(b) (4)
treatment arms?*

FDA Response:

We do not agree. As noted in the Pre-NDA meeting for NVA237 held on September 28, 2011, [REDACTED] (b) (4)

Discussion

No discussion occurred.

Question 3b:

Does the Agency agree with inclusion of open-label ipratropium?

FDA Response:

We have no objection to the use of open label ipratropium.

Discussion

No discussion occurred.

Question 3c:

Does the Agency agree that the [REDACTED] (b) (4) duration of the study is adequate?

FDA Response:

As noted in the post-SPA meeting dated 7/22/09, we recommend dose ranging studies of 28 days duration for NVA237. Based on previous dose-ranging studies A2208 and A2206, [REDACTED] (b) (4) study is of insufficient duration to determine the dose selection of NVA237.

Discussion

No discussion occurred.

Question 3d:

Does the Agency agree that the primary endpoint of [REDACTED] (b) (4) is acceptable?

FDA Response:

[REDACTED] (b) (4) is not an acceptable primary endpoint to determine dose/dosing frequency. [REDACTED] (b) (4). It would be of greater relevance to compare treatment effect in the 12-24 hour post-dose timeframe. A more appropriate endpoint would be trough FEV1.

You should note that assessment of optimal dose and dose frequency will be based on the totality of data and not any single endpoint.

Discussion

No discussion occurred.

Question 4:

The revised clinical development plan for the QVA149 Phase 3 studies includes evaluation of the efficacy and safety (b) (4) to support registration of the optimal dose/dosing regimen for the product.

FDA Comment:

(b) (4)

Additionally, while you have included pharmacokinetic (PK) measures in your program to bridge indacaterol 55mcg to Arcapta Neohaler 75mcg, you have not proposed a trial that would demonstrate a clinical link between the two formulations. The indacaterol 55mcg used in your trials must be sufficiently equivalent to Arcapta Neohaler 75 mcg based on pharmacodynamic measures to allow bridging of safety data. One potential approach would be to perform a dose response trial in asthmatic patients using your new formulation of indacaterol, Arcapta Neohaler 75mcg, (b) (4). If the indacaterol 55mcg treatment effect is similar to Arcapta Neohaler 75 mcg, then bridging may be appropriate.

Clarification Question 4a, 4b, 4c, 5 and 3a:

Development Program

Novartis acknowledges that further investigations of dose and dosing regimen are required. We propose to further characterize the dose and dosing regimen of NVA237 as part of the QVA149 Phase 3 development program. (b) (4)

(b) (4)

Also, since some of the questions posed in the Briefing Document regarding the proposed clinical studies are independent of a specific dose and dosing regimen, we would like to discuss a way forward to receiving your feedback prior to initiation of the full US QVA149 clinical development program.

Discussion

Novartis stated that [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Novartis asked if there could be agreement that NVA237 12.5mcg BID was the appropriate dose to move forward with. The Division responded that it would be reasonable to move forward with the NVA237 12.5 mcg BID dose, although final confirmation of this dose will finally be a review issue. Novartis stated that [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED] The Division did not have an issue with this approach, and agreed that 12.5 mcg BID would be reasonable to take forward.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Bridging of QAB monotherapy component

Novartis would also like to understand the Agency's rationale for performing a PD study to bridge from QAB149 55 mcg q.d. to QAB149 75 mcg q.d. in addition to a PK study to bridge safety. PK data will allow for a comparison of the systemic exposure from each product and long-term safety data are available [REDACTED] (b) (4), [REDACTED] for up to one year.

Discussion:

Novartis stated that PK study would provide a robust bridge for systemic toxicity, and asked for clarification with regard to the Division's rationale for a requiring bridging PD study and input for study design requirements. The Division stated that the purpose of the PD bridging study is to demonstrate similar local tolerability and efficacy between QAB149 55mcg and Arcapta Neohaler 75 mcg. The Division expects that, if possible, two or more doses of QAB149 will be compared to two or more doses of Arcapta Neohaler, including a dose higher than the 75 mcg approved dose. At a minimum, a single dose of QAB149 would be compared to Arcapta Neohaler 75mcg and a higher

dose of Arcapta Neohaler. The Division also stated that the Arcapta Neohaler doses must demonstrate dose separation, and that the comparison between QAB149 55mcg to the Arcapta Neohaler doses could be qualitative. The Division also stated that this PD study could be a single dose study, given the already existing data with indacaterol showing no further dose separation in longer duration trials.

Pharmaceutical equivalence

In Question 4a, the Agency pointed out that “you must assure that the monoproducts to be tested are pharmaceutically equivalent to the monocomponents of the combination product”. Novartis would like to clarify if the Agency has data requirements in addition to what was noted in Question 1

Discussion:

Novartis stated that the pharmacoequivalence will be demonstrated before moving forward and asked if the Division is looking for anything beyond what was noted in question 1. The Division stated that in addition to the requirements in question 1, PK, and PD have to match.

Question 4a:

Does the Agency agree with the rationale for dose selection of the monotherapy comparators for the QVA149 Phase 3 studies?

FDA Response:

We are unable to comment on your overall development program at this point. You have yet to define the optimum dose and dosing frequency of NVA237 and you must assure that the monoproducts to be tested are pharmaceutically equivalent to the monocomponents of the combination product.

Discussion:

See Pharmaceutical equivalence above.

Question 4b:

Does the Agency agree with the design and primary efficacy endpoints of Studies 1, 2 and 3?

- *Studies 1 and 2: FEV₁AUC_{0-24h} post-dose at Week 12 for evaluating the QVA149 o.d and b.i.d. dosing regimens?*
- *Study 3: FEV₁AUC_{0-12h} post-dose at Week 12 for evaluating the QVA149 b.i.d. dosing regimen?*

FDA Response:

See Question 4 comment and response to Question 4a.

Discussion

No discussion occurred.

Question 4c:

Does the Agency agree that 24-hour serial spirometry at Week 12 and Week 26 in a subset of patients in Studies 4 and 5 is adequate to support the replication of the primary efficacy endpoint in Studies 1, 2 and 3? Does the Agency agree that the totality of the data (Studies 1 – 5) would provide replication of doses and dosing regimens?

FDA Response:

See Question 4 comment and response to Question 4a.

Discussion

No discussion occurred.

Question 4d:

Does the Agency agree that the design, duration and endpoints of Studies 4 and 5 are adequate to (b) (4)

Does the Agency agree with the approach for (b) (4)

FDA Response:

We do not agree with your dose selection. See Question 4 comment and response to Question 3a.

Your blinding strategy may be acceptable; however, (b) (4)

Use of a double dummy design would increase interpretability of results and result in more robust data. (b) (4)

Clarification Question 4d

We acknowledge your response and will incorporate a double-dummy approach.

Novartis would like to clarify if the Agency's comment "... (b) (4)

?

Discussion

(b) (4)



Question 5:

Does the Agency agree that the timing of collection of the serial spirometric data in Studies 1, 2 and 3 (24-hour serial spirometry for all patients at Day 1 and Day 84) and Studies 4 and 5 (24-hour serial spirometry for a subset of patients at Day 1, Day 84 and Day 185) will be adequate to demonstrate duration of effect?

FDA Response:

See Question 4 comment and response to Question 4a.

Discussion

No discussion occurred.

Question 6:

Does the Agency agree that the proposed long-term safety data package, and the assessment of cardiovascular safety (QTc study and 24-hour Holter monitoring) will be adequate to assess the safety of the doses and dosing regimens of QVA149?

FDA Response:

We note that all proposed studies exclude patients with a history cardiac disease or atrial fibrillation. This is not representative of a 'real world' COPD population. As many patients who could benefit from this product would likely have cardiac co-morbidities, consider including these patients in your trials.

Your thorough QT study synopsis has been reviewed by the FDA QT-interdisciplinary team. Their comments will follow the question responses.

Clarification Question 6

Regarding the Agency's comment that "all proposed studies exclude patients with a history of cardiac disease or atrial fibrillation", please note that the Phase 3 studies do not have specific exclusion criteria for patients with cardiovascular risk. Also, they will not exclude patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months. Only patients with paroxysmal (e.g. intermittent) atrial fibrillation will be excluded. These criteria are the same as those used in the Arcapta Neohaler registration program. Does the Agency have any further guidance?

Meeting Minutes
Type B
March 7, 2012

OND/DPARP

[REDACTED] (b) (4)

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

/s/

ANGELA H RAMSEY
03/14/2012



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: September 27, 2011 at 1:30- 3:00 pm EST
Meeting Location: White Oak, Building 22, Conference Room 1315

Application Number: IND 76377
Product Name: QVA149 (indacaterol maleate and glycopyrronium bromide).

Indication: COPD
Sponsor/Applicant Name: Novartis Pharmaceuticals

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Angela Ramsey, R.N., M.S.N

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Robert Lim, MD., Clinical Reviewer
Theresa Michele, MD, Clinical Team Leader
Craig Bertha, Chemistry Reviewer
Alan Schroeder, Chemistry Lead
Prasad Peri, Chemistry Branch Chief
Timothy Robison, Pharmacology/Toxicology Team Leader
Molly Topper, Ph.D., Pharmacology/Toxicology Supervisor
Lokesh Jain, Clinical Pharmacologist Reviewer
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader
Angela Ramsey, RN, MSN, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Linda Armstrong, M.D., Drug Safety and Epidemiology
Donald Banerji, M.D., Respiratory Clinical Development
Paul Colthrope, Ph.D., Development, Global Program Head
Eric Couture, Ph.D., Drug Regulatory Affairs
Anton Drollman, M.D., Clinical Pharmacology
Hans-Juergen Fuelle, M.D., Drug Regulatory Affairs
Greg Howe, Regulatory CMC
Robert Kowalski, Pharm.D., Drug Regulatory Affairs

David Morris, M.D., Development, Respiratory, Global Head
Francesco Patalano, M.D., Development, Global Program Head
Bhavini Patel, Pharm.D., Regulatory Affairs, Global Program Regulatory Manager
Didier Renard, Ph.D., Modeling and Simulation
Romain Sechaud, Ph.D., Drug Metabolism and Pharmacokinetics
Donald Stanski, M.D., Modeling and simulation, Global Head
Thomas Storm, Ph.D., Project Leader, Technical Research and Development
Thomas Martin, M.D., Respiratory Clinical Development

BACKGROUND

Novartis submitted a Type B meeting request dated, June 24, 2011 to discuss their proposed program for a new fixed dose combination product of QVA149 for COPD patients. Novartis submitted their briefing package dated, August 31, 2011. Upon review of the material, the Division responded via fax on September 26, 2011. Novartis requested to discuss the Introductory Comments at the face-to-face meeting.

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant response. The sponsor's questions are in ***bold italics***; the Division's response is in *italics*; and the discussion is in normal font.

DISCUSSION

Introductory Comment:

Based on the information provided in your meeting package, we have significant concerns about your development program for (b) (4).

- (b) (4)
(b) (4)
To satisfy the combination product rule, the pharmaceutically equivalent monoproduct must be compared to the combination product in factorial studies. (b) (4). Therefore, in order to proceed with your development plan, you would be required to develop a QAB149 monoproduct that is pharmaceutically equivalent to the QAB149 component of the combination product (refer to question response 2).
- *Based on the data from NVA237 trial A2208, it is not clear if the appropriate dose for GP in the monoproduct is (b) (4)*
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Discussion:

Novartis provided the Division with handouts (see Attachment 1) in order to clarify the pharmaceutical characteristics of QVA149 compared to the indacaterol monoproduct and the dose of NVA237.

Pharmaceutical Characteristics of QVA 149 versus the indacaterol monoproduct: Referenced pgs 16-19

Novartis stated that their intent was to design a combination product (b) (4)
[Redacted]

[Redacted] Novartis adjusted the nominal dose of indacaterol (75 to 55mcg) in order to match FPM between the QVA149 and the indacaterol monoproduct. Based on the FPM match, Novartis believes that the QVA149 in the mono and combination product were equivalent (b) (4).

The Division acknowledged the CMC data and the dose adjustment, but stated that the products do not match with respect to the entire aerodynamic particle size profile (APSD) profile, therefore are not pharmaceutically equivalent. The Division also stated that (b) (4). Based on current knowledge, it is not known how the particle fractions are related to safety or efficacy. Due to this unknown, for an inhaled product to be equivalent, the whole APSD profile must match as a first step in development.

Novartis proposed further development of QVA149 with a PK study and asked if this would alleviate the Division's concerns with QVA149. The Division stated that a PK study would not be helpful for this inhaled product due to the unknowns regarding the relationship between particle fractions and safety/efficacy. Novartis asked the Division if there was a path forward potentially using (b) (4). The Division responded that (b) (4) and cannot (b) (4). Novartis again asked about potential paths forward. The Division stated that they cannot resolve this issue and therefore, cannot comment.

Novartis acknowledged that the Division does not agree that the indacaterol monoproduct is pharmaceutically equivalent to the indacaterol monocomponent in the QVA149 combination product, nor with Novartis' current proposal. Novartis further acknowledged that if they move forward with their proposed development program, it will be at their own risk.

Dose selection of NVA237 (Referenced slides 3-8)

Novartis stated that based on the data presented in briefing package, (b) (4) is an effective dose for NVA237. The Division responded that they disagreed. Based on the totality of the data (b) (4)

[Redacted] Therefore, the Division does not believe that (b) (4) is appropriate. The Division also referred back to previous interaction with Novartis regarding

NVA237 dosing. [REDACTED] (b) (4)

Regulatory

Question 1.

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 QVA149 from the requirements of the Pediatric Research Equity Act for patients under 18 years of age?

FDA Response

Submit a request for a waiver of pediatric study requirements in your NDA submission. An official determination will be made during the NDA review cycle.

We refer you to the Draft Guidance for Industry, "How to Comply with the Pediatric Research Equity Act" (<http://www.fda.gov/cder/guidance/6215dft.pdf>).

Discussion:

No discussion occurred.

Quality

Question 2.

Does the Agency agree that based on the presented technical data, the [REDACTED] (b) (4)

FDA Response

No, we do not agree. As part of your program to satisfy the requirements of the combination drug product rule, you should first start by developing monotherapy drug product that have the pharmaceutical equivalence to the combination drug product (i.e. same dose, comparable in vitro aerodynamic particle size distribution (APSD), same formulation components). [REDACTED] (b) (4)

Discussion:

No discussion occurred.

Non-clinical

Question 3.

Does the Agency agree that non-clinical safety studies conducted with the combination of QAB149 and NVA237 at a ratio of 3:1 qualify the QVA149 combination for clinical use at an adjusted dose ratio of 1.1:1?

FDA Response

Yes, we agree.

Discussion:

No discussion occurred.

Clinical Pharmacology

Question 4.

Does the Agency concur that the clinical pharmacokinetic package is adequate to support the
(b) (4),
(see Question 3.2.1)?

FDA Response

Please refer to Introductory Comments for dose adjustment of QAB149 in the fixed-dose combination. With respect to addressing the clinical pharmacology questions of dose adjustments based on DDI and for specific populations, your proposal appears reasonable; however, its sufficiency will be a review issue.

Discussion:

No discussion occurred.

Clinical

Question 5.

Does the Agency agree that
(b) (4),
for evaluation in the QVA149 Phase 3 clinical program?

FDA Response

No, we do not agree. See introductory comments.

Discussion:

No discussion occurred.

Question 6.

Does the Agency agree that the proposed two replicate Phase 3 pivotal 12-week placebo controlled studies evaluating the safety and efficacy of the combination product (b) (4)

FDA Response

No, we do not agree. See introductory comments.

Discussion:

No discussion occurred.

Question 7a.

Does the Agency agree that mean trough post-dose FEV₁ at 12 weeks is an appropriate primary efficacy variable for the pivotal Phase 3 studies evaluating the safety and efficacy of the combination product versus the monotherapies?

FDA Response

In general, trough FEV₁ is an appropriate primary endpoint for evaluation of LABA and LAMA products. However, as the dosing interval for NVA237 may be more frequent (b) (4) *the time point for this measurement is unclear. See introductory comments.*

Discussion:

No discussion occurred.

Question 7b.

Does the Agency agree that the timing of collection of the spirometric data in the Phase 3 studies (all population and in a subset of the overall population) will be adequate to demonstrate (b) (4) ***?***

Additionally, would these data allow for (b) (4) ***?***

FDA Response

No, we do not agree. See introductory comments.

Discussion:

No discussion occurred.

Question 8a.

Does the Agency agree that [REDACTED] (b) (4)
[REDACTED]
[REDACTED] ?

FDA Response

No, we do not agree. See introductory comments. [REDACTED] (b) (4)
[REDACTED]
[REDACTED] *Discussion of specific contents of the label is premature at this time.*

Discussion:

No discussion occurred.

Question 8b.

Does the Agency agree that [REDACTED] (b) (4)
Questionnaire is an appropriate secondary endpoint?

FDA Response

Information regarding the development and validation of this instrument is limited; therefore, we cannot agree that it is a valid instrument [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

Discussion:

No discussion occurred.

Question 9.

Does the Agency agree that [REDACTED] (b) (4)
[REDACTED]
[REDACTED] ?

FDA Response

No, we do not agree. See introductory comments.

Discussion:

No discussion occurred.

Question 10.

Novartis plans to perform a dedicated study that investigates [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

[REDACTED] (b) (4)

FDA Response

We do not agree. [REDACTED] (b) (4) See introductory comments.

The QT study summarized in this meeting package in conjunction with a study investigating [REDACTED] (b) (4) pending review of full protocols by QT interdisciplinary review team.

In addition, we note that you propose to use the [REDACTED] (b) (4) for this trial. As the participants in this study will be healthy volunteers, usage of that scale is inappropriate. We recommend usage of a more appropriate AE grading scale such as "Guidance for Industry: Toxicity grading scale for health adult and adolescent volunteers enrolled in preventive vaccine clinical trials" (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm>)

Discussion:

No discussion occurred.

Question 11a.

Does the Agency agree that [REDACTED] (b) (4)

FDA Response

No, we do not agree. See introductory comments.

Discussion:

No discussion occurred.

Question 11b.

Does the Agency agree with the standardized definition of [REDACTED] (b) (4) as outlined below?

FDA Response

The proposed definition seems reasonable.

Discussion:

No discussion occurred.

Question 12.

Does the Agency agree that the design proposed for the [REDACTED] (b) (4)
[REDACTED]
[REDACTED]?

FDA Response

We do not agree. See introductory comments. [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

Discussion:

No discussion occurred.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are

accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

/s/

ANGELA H RAMSEY
10/19/2011