

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203108Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 203108	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Striverdi Respimat Established/Proper Name: olodaterol Dosage Form: Inhalation Spray		Applicant: Boehringer-Ingelheim Agent for Applicant (if applicable):
RPM: Christine Chung		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>8/2/2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input type="checkbox"/> None CR 3/14/13
❖ 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 revised).

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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <i>(confirm chemical classification at time of approval)</i>	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Breakthrough Therapy designation	
<input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC	
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	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
<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	REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required
Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" 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)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	APPROVAL 8/1/14 Complete Response 3/14/13
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>	7/10/14, 1/2/13, 12/21/12 7/7/14, 12/21/12
• Review(s) <i>(indicate date(s))</i>	Telecons 9/21/12, 9/18/12
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 2/1/13 DMEPA: <input checked="" type="checkbox"/> 6/26/14, 1/18 and 1/10/13 DMPP/PLT (DRISK): 6/23/14 2/22/13 OPDP: <input checked="" type="checkbox"/> 2/20/13 SEALD: <input type="checkbox"/> None CSS: <input 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>	2/1/13
❖ 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

ing 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 10/10/12 <i>No pediatric record necessary</i> If PeRC review not necessary, explain: <u>Disease/condition does not occur in children</u> 	
<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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	2014- 7/8, 6/16, 1/14/14 2013- 2/22, 2/13, 1/24, and 1/11 2012- 11/2, 11/1, 10/30, 10/1, 9/28, 9/7, 8/30, 8/29, 8/20, 8/6, 7/27, 7/25, 7/24, 7/19, 7/12, and 5/23
<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>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input type="checkbox"/> N/A or no mtg WRO 2/12/14 <input type="checkbox"/> No mtg Meeting comments 9/28/2011 <input type="checkbox"/> No mtg 7/17/2008 2 separate - CMC, Clinical Addendum 1 - 8/12/2008 Addendum 2 - 9/4/2008 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input type="checkbox"/> No AC meeting 1/29/13
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	7/31/14, 3/14/13
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	7/30 and 7/29/14, 3/13/13
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	7/19/14, 1/31/13
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input checked="" type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	See CDTL reviews 7/11/14, 1/17/2013, 7/10/2012 <input type="checkbox"/> None
<ul style="list-style-type: 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>) 	MOR 1/17/2013, page 21

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	2/14/13, 10/22/12
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>) 	5/14/12 proposed 7/30/14, 2/15/13
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	3/22 and 3/1/2013, 1/18/13 (4)
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>)	1/17/13, 7/10/12
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>)	1/17/13, 7/12/12
❖ 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>)	2/26/13
• Supervisory Review(s) (<i>indicate date for each review</i>)	7/18/14, 1/24/13
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	7/11/14, 1/17/13, 6/26/12
❖ 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>)	12/13/12
❖ ECAC/CAC report/memo of meeting	7/11/12
❖ 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	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	See Decisional Summary Memos
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	3/11/13
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	6/23/14, 3/12/13, 11/8/12, 7/31/12, 7/17/12
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	2/7/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	P/T – 6/27/2012
❖ 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>	7/31/2012 (ONDQA review)
<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"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 6/16/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed 2/15/13 <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities

<p>For all 505(b)(2) applications:</p> <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done

EXCLUSIVITY SUMMARY

NDA # 203108

SUPPL # n/a

HFD # 570

Trade Name: Striverdi Respimat Inhalation Spray

Generic Name: olodaterol

Applicant Name: Boehringer-Ingelheim

Approval Date: 8/1/2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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:

d) Did the applicant request exclusivity?

YES NO

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

5 years per 21 CFR 314.108(b)(2)

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

YES NO

If the answer to the above question is 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#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

YES NO

If yes, explain:

=====
Person completing form:
Name: Christine Chung
Title: Regulatory Project Manager
Date: 7/23/2014
Thru: Sandy Barnes, CPMS
Office/Division Director signing form:
Name: Badrul A. Chowdhury, M.D., Ph.D.
Title: Director, DPARP

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
07/30/2014

BADRUL A CHOWDHURY
07/30/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203108

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
PO Box 368
Ridgefield, CT 06877

ATTENTION: Lorraine W. Sachs, M.S., RAC
Associate Director

Dear Ms. Sachs:

Please refer to your New Drug Application (NDA) dated June 2, 2014, received June 2, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olodaterol Inhalation Spray, 2.5 mcg per actuation.

We also refer to your June 13, 2014, correspondence, received June 13, 2014, requesting review of your proposed proprietary name, Striverdi Respimat.

We have completed our review of the proposed proprietary name, Striverdi Respimat and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your June 13, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Christine Chung, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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 on behalf of KELLIE A TAYLOR
07/10/2014



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

ELECTRONIC CORRESPONDENCE

Date: July 8, 2014

To: Lorraine W. Sachs, MS, RAC Associate Director, Regulatory Affairs	From: Christine Chung, RPh Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-791-5911	Fax number: 301-796-9728
Email: lorraine.sachs@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Striverdi (olodaterol) Respimat Inhalation Spray FDA Labeling comments July 8, 2014	

Total no. of pages including cover: 26

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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We refer to NDA 203108 for olodaterol, and we have the following labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes in the attached marked up label.

FDA edits were made as tracked changes to the clean version of your proposed label submitted June 13, 2014. The edits were primarily to make the language and format of the medication guide (MG) and instructions for use (IFU) consistent with current practices. In addition to the tracked changes edits, we also ask that you change the font of the MG and IFU to Verdana 11 point font. Any additional proposed changes you may have can be made in a similar fashion by using a clean version of the attached PI and edit using tracked changes.

Send your response to me via secure email at christine.chung@fda.hhs.gov by COB on Friday, July 11, 2014. Your response will subsequently need to be submitted officially to the NDA.

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

Drafted by: RLim, ADurmowicz/ 7.2.2014
Cchung/ 7.7.2014

Cleared by: SBarnes/ 7.7.2014

Finalized: cchung/ 7.8.2014

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



NDA 203108

**ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Lorraine W. Sachs, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Sachs:

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

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is August 2, 2014.

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

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
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
06/16/2014



NDA 203108

**MEETING REQUEST-
WRITTEN RESPONSES**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Lorraine W. Sachs, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Sachs:

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

We also refer to your correspondence dated December 20, 2013, received December 23, 2013, requesting a meeting to clarify issues regarding your planned response to the March 14, 2013, Complete Response letter.

Further reference is made to our Meeting Granted letter dated January 14, 2014, wherein we stated, as requested, that only written responses to your questions would be provided.

The enclosed document constitutes our written responses to the questions contained in your December 20, 2013, meeting request and background package.

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

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: NDA 203108
Product Name: olodaterol Respimat Inhalation Spray
Indication: Chronic obstructive pulmonary disease (COPD)
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
Regulatory Pathway: 505(b)(1)

BACKGROUND:

NDA 203108 for olodaterol Respimat Inhalation Spray was submitted May 14, 2012. A Complete Response action was taken on March 14, 2013, by the Agency due to current Good Manufacturing Practices (cGMP) deficiencies at the manufacturing facility. BI submitted a meeting request for Written Responses only to seek Agency feedback and agreement on the content and timing of BI's response to the Complete Response letter.

QUESTIONS AND PRELIMINARY RESPONSES

BI's questions in *italics font* are followed by the Division's responses in normal font.

Question 1: PRODUCT QUALITY

FDA has announced that they will re-inspect Boehringer-Ingelheim Pharma GbmH & Co. KG on February 24 – March 7, 2014. We would like to reach an understanding with the Division on what information or documentation from the inspection would be acceptable in our response to demonstrate satisfactory resolution of the cGMP deficiencies. This understanding will determine the timing for our response.

FDA response

The Division does not require any information or documentation from the inspection to be submitted to the application in the response to the complete response letter. The final compliance recommendation for the facility will be provided by the Office of Compliance after evaluation of the inspection report.

Question 2: LABELING

We have incorporated your proposed revisions to the draft labeling as attached to the Complete Response, dated March 14, 2013. In addition to the changes you indicated, we would like to include the following labeling changes which by their minor nature we will otherwise submit post-approval as annual reportable changes...

Do you concur that the above changes can be included in our final draft labeling without

delaying the review period?

FDA response

We concur.

Question 3: SAFETY UPDATE

Because the 1222.51/52 studies were of shorter duration (12 weeks) than the Phase 3 pivotal clinical trials (48 weeks), we intend to provide a pooled report of the safety results from these two studies, including case report forms and narratives for any deaths which occurred during the studies. At this time we do not plan to submit datasets from these studies with the safety update. Because of the 12 week duration of these studies, we do not think it is appropriate to integrate these results with the 48 week Phase 3 trial results. Do you concur with this proposal?

FDA response

While your approach regarding trials 1222.51/52 appears reasonable, if safety concerns are identified during review of this resubmission, these datasets may be requested.

Question 4: OTHER

We are hereby formally notifying the Agency that we intend to respond to the Complete Response letter at the earliest possible time following a successful re-inspection. Should this occur after the one year date of the Complete Response Letter, we will request an extension . We are also requesting your concurrence that this resubmission will be classified as a Class 1 Resubmission due to the nature of the submission elements with a 2 month review clock per PDUFA V. Because of the Product Quality issue that still must be addressed, we are planning to have a complete response ready for submission in early March 2014, assuming the Division is in agreement with the proposed scope of our resubmission as outlined in this document. We understand that the resubmission can only take place subsequent to the resolution of the GMP compliance issues at the manufacturing site.

FDA response

The classification of the resubmission will be made after preliminary review of the resubmission. If a re-inspection is needed, the resubmission would be classified as a Class 2 resubmission. If a re-inspection is not needed, the resubmission may be classified as a Class 1 resubmission after preliminary review of the resubmission.

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.

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/s/

CHRISTINE H CHUNG
02/12/2014



NDA 203108

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Lorraine W. Sachs, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Sachs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Striverdi Respimat (olodaterol) Inhalation Spray.

We also refer to your December 20, 2013, correspondence requesting a meeting to clarify issues regarding your planned response to the March 14, 2013, Complete Response letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

We agree that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a meeting will not be scheduled. Our goal date for providing our written responses is March 5, 2014.

We acknowledge that the background information for the meeting was included in the meeting request submission dated December 20, 2013, and that you do not plan to submit a separate briefing package. If the materials presented in the meeting request submission are inadequate to answer the questions, we may cancel the agreement to provide written responses. If we cancel the agreement to provide written responses, a new meeting request will be required.

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

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
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
01/14/2014

MEMORANDUM

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

Type of Meeting: Proprietary Name Review

Meeting Date: September 21, 2012; 1:30 PM
Meeting Location: Teleconference

Application: NDA 203108
Proposed Proprietary Name: (b) (4)
Established Name: Olodaterol
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Carol Holquist, Director, DMEPA
Meeting Recorder: Nichelle Rashid, Safety Regulatory Health Project Manager

FDA Attendees:

Office of Surveillance and Epidemiology

Carol Holquist, Director, DMEPA
Kellie Taylor, Deputy Director, DMEPA
Lubna Merchant, Team Leader, DMEPA
Nichelle Rashid, Safety Regulatory Health Project Manager

Applicant Attendees:

Boehringer Ingelheim Pharmaceuticals, Inc

Damon Daulerio (Associate Director, Regulatory Affairs, US)
Jeff Snyder (Executive Director, Regulatory Affairs, US)
Joanne Palmisano (VP, Regulatory Affairs, US)

Background:

DMEPA completed a name review of (b) (4) as an IND (OSE RCM #2011-3378 dated March 6, 2012), and found the name conditionally acceptable at that time. The name was submitted to the NDA on June 29, 2012, and found unacceptable due to the (b) (4) and therefore not acceptable for this product. DMEPA requested a teleconference to inform the Applicant of our findings on September 18, 2012. On September 21, 2012, Boehringer Ingelheim Pharmaceuticals, Inc requested a teleconference with DMEPA for additional clarifications of their findings.

Product Information

(b) (4) (Olodaterol) is used for Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. It will be available as 2.5 mcg per actuation.

Meeting Objectives

The objective of this meeting is to provide additional clarification with Boehringer Ingelheim Pharmaceuticals, Inc (BI) of our findings.

Discussion



DMEPA stated that there will be no extension of the PDUFA date of September 27, 2012.

Regulatory Options:

1. Produce evidence from (b) (4) to support your view that the (b) (4) and therefore does not warrant DMEPA finding the name unacceptable.
2. Withdraw the proposed name, (b) (4) and submit the alternate name, Striverdi, for review.
3. Submit a reconsideration letter for the proposed proprietary name, (b) (4)

Conclusions:

BI will discuss their regulatory options and will let DMEPA know the decision by COB, Wednesday, 09/26.

Addendum:

On September 26, 2012, BI notified DMEPA that they will be withdrawing the proposed proprietary name, (b) (4) and will submit a new proprietary name review request, Striverdi Respimat.

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/s/

LUBNA A MERCHANT
02/28/2013

MEMORANDUM

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

Type of Meeting: Proprietary Name Review

Meeting Date: September 18, 2012; 11:00 AM
Meeting Location: FDA White Oak, Bldg 22, Room 4396, Teleconference

Application: NDA 203108
Proposed Proprietary Name: (b) (4)
Established Name: Olodaterol
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Lubna Merchant, Team Leader, DMEPA
Meeting Recorder: Nichelle Rashid, Safety Regulatory Health Project Manager

FDA Attendees:

Office of Surveillance and Epidemiology

Kellie Taylor, Deputy Director, DMEPA
Lubna Merchant, Team Leader, DMEPA
Lissa Owens, Safety Evaluator, DMEPA
Nichelle Rashid, Safety Regulatory Health Project Manager

Applicant Attendees:

Boehringer Ingelheim Pharmaceuticals, Inc

Damon Daulerio (Associate Director, Regulatory Affairs, US)
Jeff Snyder (Executive Director, Regulatory Affairs, US)
Alan Hamilton (Medical Lead, BI Canada)
Carolanne Guzzo (Labeling, BI US)
Josephine King (Labeling, BI US)
Annette Wasmund (Regulatory Affairs, BI Germany)
Nadja Oellers (International Project Lead, BI Germany)
Astrid Hannich-Walter (Intellectual Property Rights, Germany)
David Milbauer (Marketing, BI US)
Juergen Roemhild (Legal Prescription Medicines, BI Germany)
Ernesto Pirsch_Alonso (Marketing, BI Germany)

Background:

DMEPA completed a name review of (b) (4) as an IND (OSE RCM #2011-3378 dated March 6, 2012) and found the name conditionally acceptable at that time. The

name was submitted to the NDA on June 29, 2012, and found unacceptable due to the (b) (4) and therefore not acceptable for this product. DMEPA requested a teleconference to inform the Applicant of their findings.

Product Information

(b) (4) (Olodaterol) is used for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. It will be available as 2.5 mcg per actuation.

Meeting Objectives

The objective of this meeting is to inform Boehringer Ingelheim Pharmaceuticals, Inc (BI) of our findings and inform them of their options.

Discussion

(b) (4)

Alternate Name: Striverdi

DMEPA also conveyed that (b) (4) in the alternate name, Striverdi. However, the name has not undergone a full evaluation for orthographically and phonetically similar names.

Regulatory Options:

1. [REDACTED] (b) (4) Submit an amendment with the change of the spelling of the name.
2. Withdraw the proposed name, [REDACTED] (b) (4) and submit the alternate name, Striverdi, for review.

Questions from Sponsor:

1. [REDACTED] (b) (4)
2. BI also asked if they had to resubmit labeling with the name change. DMEPA responded that the labeling review was not on the same review clock as the proprietary name review.

Conclusions:

BI will discuss their regulatory options and will let DEMPA know the decision by COB, Friday, 09/21.

Addendum:

On September 21, 2012, BI requested a teleconference to seek some additional clarification regarding the previous conversation on September 18, 2012.

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/s/

LUBNA A MERCHANT
02/28/2013



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

ELECTRONIC CORRESPONDENCE

Date: February 22, 2013

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Striverdi (olodaterol) Repimat FDA Labeling comments 2/22/2013	

Total no. of pages including cover: 29

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-3420. Thank you.**

We refer to NDA 203108 for olodaterol, and we have the following labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes in the attached marked up label.

Send your response to me via secure email at christine.chung@fda.hhs.gov by COB on Tuesday, February 26, 2013. Your response will subsequently need to be submitted officially to the NDA.

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

Drafted by: RLim, TMichele/ 2.22.13
Cchung/ 2.22.2013

Cleared by: SBarnes/ 2.22.2013

Finalized: cchung/ 2.22.2013

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/s/

CHRISTINE H CHUNG
02/22/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion and Division of Consumer Drug
Promotion**

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

Memorandum

Date: February 20, 2013

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

From: Matthew Falter, Regulatory Review Officer, Office of Prescription
Drug Promotion (OPDP), Division of Consumer Drug Promotion
(DCDP)

Roberta Szydlo, Regulatory Review Officer, OPDP, Division of
Professional Drug Promotion (DPDP)

CC: Lisa Hubbard, Acting Deputy Division Director, DPDP
Twyla Thompson, Group Leader, DCDP

Subject: NDA # 203108
OPDP labeling comments for STRIVERDI® RESPIMAT®
(olodaterol) Inhalation Spray (Striverdi Respimat)

OPDP has reviewed the proposed Package Insert (PI), Carton and Container Labeling, Medication Guide (MG), and Instructions for Use (IFU) for Striverdi Respimat submitted for consult on July 12, 2012.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "FDA olo PI 2-13-13.doc" that was sent via email from DPARP to OPDP on February 13, 2013. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP's comments on the MG and IFU are based on the proposed draft marked-up labeling titled "striverdi MG 1-17-13.doc" that was sent via email from DPARP to OPDP on February 13, 2013. OPDP's comments on the MG and IFU are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed carton and container labeling submitted by the applicant and available in the EDR at:

- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\5585a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\5583a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\5584a.pdf>
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- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\ct5582a.pdf>

We have no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions concerning the PI or carton and container labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions concerning the MG or IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
02/20/2013

MATTHEW J FALTER
02/20/2013



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

ELECTRONIC CORRESPONDENCE

Date: February 13, 2013

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Olodaterol Repimat FDA Labeling comments 2/13/2013	

Total no. of pages including cover: 15

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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are hereby notified that any review, disclosure, dissemination, copying, or other action based on the
content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-3420. Thank you.**

We refer to NDA 203108 for olodaterol, and we have the following labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes in the attached marked up label.

In addition, as a follow-up to your emailed request for clarification dated January 31, 2013, FDA re-analyzed data from the QT study. Based on this re-analysis, Section 12.2 of the PI has been updated, although the conclusions from the trial do not change. In the current analysis, a mixed model was used to obtain the point estimate and corresponding confidence intervals of ddQTcI for each treatment group. Adjustment for multiple testing was not applied for all BI 1744 treatment groups. The model includes treatment, timepoints, gender, sequences, period, baseline QTd and treatment by timepoints interaction as fixed effects. Each individual was defined as random effects.

Send your response to me via secure email at christine.chung@fda.hhs.gov by COB on Monday, February 18, 2013. Your response will subsequently need to be submitted officially to the NDA.

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

Drafted by: RLim, TMichele, RAbugov, JBuenconsejo/ 2.13.13
Cchung/ February 13, 2013

Cleared by: SBarnes/ 2.13.2013

Finalized: cchung/ 2.13.2013

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/s/

CHRISTINE H CHUNG
02/13/2013



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

ELECTRONIC CORRESPONDENCE

Date: January 24, 2013

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Olodaterol Repimat FDA Labeling comments 1/24/2013	

Total no. of pages including cover: 17

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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We refer to NDA 203108 for olodaterol, and we have the following labeling comments. Please note that comments for the Highlights of Prescribing Information, sections 6 and 14, and the Medguide are not included at this time; additional labeling changes will be forthcoming. Submit revised labeling incorporating changes in the attached marked up label.

Send your response to me via secure email at christine.chung@fda.hhs.gov by COB on Monday, February 4, 2013. Your response will subsequently need to be submitted officially to the NDA.

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

Drafted by: Cchung/ January 18, 2013

Cleared by: SBarnes/ 1.18.2013
Pji, SDoddapaneni/ 1.17.2013
CRivera-Lopez, MWood/ 1.22.2013
CBertha, ASchroeder, PPeri/ 1.24.2013
RLim/ 1.23.2013
TMichele/ 1.24.2013

Finalized: cchung/ 1.24.2013

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

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/s/

CHRISTINE H CHUNG
01/24/2013



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

ELECTRONIC CORRESPONDENCE

Date: January 24, 2013

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420

Subject: NDA 203108 Olodaterol Repimat
FDA information request: "BI Comments to FDA backgrounder"

Total no. of pages including cover: 3

Comments: Information requested no later than Friday, January 25, 2013

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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We refer to NDA 203108 for olodaterol and to “BI Comments to FDA backgrounder” for the Advisory Committee meeting scheduled for January 29, 2013. We have following request for information:

- 1.) Clarify how you calculated total fatal MACE events (percentages and numbers) in section 1 comment 8 of your document titled ‘BI Comments to FDA Backgrounder.’ You stated ‘Fatal MACE events occurred in (b) (4) in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively.’ We were unable to calculate the same numbers using the data from Tables 2.12.1 to 2.12.5 from the Summary of Clinical Safety Supplement Document (page 2,229-2,233).
- 2.) Note that we plan to issue an errata that will address all comments from section 1 of your document titled ‘BI Comments to FDA Backgrounder’ except for comments 2 and 11. We addressed comments in Section 2 only if considered relevant for the assessment of safety or efficacy.

Submit the requested information as an official response to the NDA no later than Friday, January 25, 2013.

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

Drafted by: RLim, TMichele, SSeymour/ 1.24.2013
Cchung/ 1.24.2013

Initialed by: SBarnes/ 1.24.2013

Finalized: cchung/ 1.24.2013

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/s/

CHRISTINE H CHUNG
01/24/2013



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

ELECTRONIC CORRESPONDENCE

Date: January 11, 2013

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Olodaterol Repimat FDA Labeling comments	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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Your NDA 203108 for olodaterol is currently under review, and we have the following initial labeling comments. Additional labeling changes may be forthcoming.

1. All Labels and Labeling

Although the established name is ½ the size of the proprietary name, it lacks prominence. Revise the established name so that it has a prominence commensurate to that of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

2. All Container Labels

Relocate the company logo so that it appears at the bottom of the label.

3. Professional Sample Label and Labeling

Revise the color of the statement, “Professional Sample: Not For Sale” from (b) (4) to improve readability.

4. Patient Instructions for Use

Remove the reference to the name (b) (4) and update it to reflect the current proposed proprietary name.

Submit your response to me via fax at 301-796-9728 or via email at christine.chung@fda.hhs.gov no later than Wednesday, January 16, 2013; or provide a timeline for when the information will be submitted. Your response will subsequently need to be submitted officially to the NDA.

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

Drafted by: Cchung/ January 11, 2013

Initialed by: MJordan-Garner for SBarnes/ January 11, 2013

Finalized: cchung/ January 11, 2013

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/s/

CHRISTINE H CHUNG
01/11/2013



NDA 203108

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

ATTENTION: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs

Dear Mr. Daulerio:

Please refer to your New Drug Application (NDA) dated May 14, 2012, received May 14, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Olodaterol Oral Inhalation, 2.5 mcg per actuation.

We acknowledge receipt of your September 26, 2012, correspondence, on September 27, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name, [REDACTED] ^{(b) (4)}. This proposed proprietary name request is considered withdrawn as of September 27, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Christine Chung, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
01/02/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203108

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

ATTENTION: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs

Dear Mr. Daulerio:

Please refer to your New Drug Application (NDA) dated May 14, 2012, received May 14, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Olodaterol Oral Inhalation, 2.5 mcg per actuation.

We also refer to your October 3, 2012, correspondence, received October 4, 2012, requesting review of your proposed proprietary name, Striverdi Respimat. We have completed our review of the proposed proprietary name, Striverdi Respimat and have concluded that it is acceptable.

The proposed proprietary name, Striverdi Respimat, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If **any** of the proposed product characteristics as stated in your October 3, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Christine Chung, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
12/21/2012



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

ELECTRONIC CORRESPONDENCE

Date: November 2, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Olodaterol Repimat FDA Request for information - Nonclinical	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Information requested by no later than Friday, November 9, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

With reference to the study entitled “*BI 1744 CL: 26-week inhalation toxicity study in rats with a 4-week recovery period, Amendment No. 1*” (Study no. 06B234, U08-1691-01-AMI), provide laboratory historical control data from age-matched animals from studies of comparable duration for the microscopic eye finding of epithelial atrophy (cornea) which was observed in thirteen 50 µg/kg animals, twenty-seven 200 µg/kg animals, and twenty-eight 4000 µg/kg animals. In addition, submit an assessment of the toxicological significance of this finding, which was increased in incidence and severity in drug-treated animals versus controls.

Submit the requested information as an official response to the NDA no later than Friday, November 9, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: CRivera-Lopez, MWood/ November 2, 2012
Cchung/ November 2, 2012

Initialed by: SBarnes/ November 2, 2012

Finalized: cchung/ November 2, 2012

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/s/

CHRISTINE H CHUNG
11/02/2012



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

ELECTRONIC CORRESPONDENCE

Date: November 1, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Olodaterol Repimat FDA Request for information - Clinical	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Information requested by no later than Friday, November 9, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

1. Provide your definition of MACE events, or provide the location of this information in your application.
2. Provide your definition of the pharmacovigilance (PV) endpoint stroke, or provide the location of this information in your application.
3. The cause of death for patient 14647 from trial 1222.14 was recorded as cerebrovascular accident; however, on table 2.1.7.2.2:1 in the summary of clinical safety, there are no deaths listed under the stroke PV. Was this event considered a MACE event, and if so, under which MACE category was this event recorded? Provide an explanation if this was not considered a MACE event.

Submit the requested information as an official response to the NDA no later than Friday, November 9, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RLim, TMichele/ October 31, 2012
Cchung/ November 1, 2012

Initialed by: SBarnes/ November 1, 2012

Finalized: cchung/ November 1, 2012

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/s/

CHRISTINE H CHUNG
11/01/2012



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

ELECTRONIC CORRESPONDENCE

Date: October 30, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-482-6346	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Repimat Request for information - Microbiology	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Information requested by no later than Friday, November 9, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

1. Your amendment dated September 28, 2012, contained a summary of results from 4 media fill conducted June 2011-April 2012. FDA's information request dated August 29, 2012, was meant to elicit a full accounting of units from recent media fills. Provide the following information for recent media fills: the number of units filled, the number of units rejected, the number of units incubated, and the number of positive units. Indicate the reason for rejection of units. Provide these data for batches 193198, 193200, 193201 and 292744.
2. Provide an explanation of why media fill batch 193199 was not included in revalidation studies (b) (4)

Submit the requested information as an official response to the NDA no later than Friday, November 9, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: JCole, BRiley/ October 30, 2012
Cchung/ October 30, 2012

Initialed by: SBarnes/ October 30, 2012

Finalized: cchung/ October 30, 2012

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/s/

CHRISTINE H CHUNG
10/30/2012



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

ELECTRONIC CORRESPONDENCE

Date: October 1, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Repimat Request for information - Statistical	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Information requested by no later than Thursday, October 11, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

Provide analysis datasets for adjudicated causes (SOC, PT, HLGT, HLT, SSC, PV, etc) of serious adverse events. Ensure that the datasets contain sufficient data so that each adjudicated event can be matched, by subject, time, and outcome, to a unique event in project level datasets AE103, AE204, and PVGAE204. In the datasets, you may either include all serious adverse events, with events flagged which were adjudicated, or you may instead include only adjudicated events; indicate in your documentation which of these alternatives you choose.

Submit the requested information as an official response to the NDA no later than Thursday, October 11, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RAbugov, JBuenconsejo/ September 27, 2012
Cchung/ September 28, 2012

Initialed by: SBarnes/ September 28, 2012

Finalized: cchung/ October 1, 2012

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/s/

CHRISTINE H CHUNG
10/01/2012



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

ELECTRONIC CORRESPONDENCE

Date: September 28, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Repimat Request for information - Clinical	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Information requested by no later than Wednesday, October 3, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following requests for information:

1. Provide the reference ranges for the clinical labs assayed in your phase 3 program, or provide the location of this information in your application.
2. Provide your definition for 'possibly clinically significant' lab abnormalities used in your phase 3 program, or provide the location of this information in your application.
3. In trial 1222.13, per protocol the IVRS was use to assign patient treatment boxes. After audit of site 2401 (Dr. De Salvo, Argentina), it appears that 7 patients were dispensed treatment boxes outside of the IVRS (patients 11947, 12079, 12104, 11935, 12052, 11931, and 12105). Clarify how randomization was performed for these patients.

Submit the requested information as an official response to the NDA no later than Wednesday, October 3, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RLim, TMichele/ September 26, 2012
Cchung/ September 26, 2012

Initialed by: SBarnes/ September 27, 2012

Finalized: cchung/ September 28, 2012

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/s/

CHRISTINE H CHUNG
09/28/2012



NDA 203108

**METHODS VALIDATION
MATERIALS RECEIVED**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Damon Daulerio, MBA
Associate Director
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Damon Daulerio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) Respimat (olodaterol) inhalation spray and to our July 24, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on September 6, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
09/07/2012



Food and Drug Administration
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Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: August 30, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Repimat Request for information - Statistics	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Information requested by no later than Wednesday, September 12, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

Provide datasets gentrt, adevent, and ae103 used by ae-risk-s1.sas in scs-supplement-10368901.pdf when invoking macro ae-risk.sas

Submit the requested information as an official response to the NDA no later than Wednesday, September 12, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RAbugov, JBuenconsejo/ August 29, 2012
Cchung/ August 29, 2012

Initialed by: SBarnes/ August 29, 2012

Finalized: cchung/ August 30, 2012

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/s/

CHRISTINE H CHUNG
08/30/2012



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

ELECTRONIC CORRESPONDENCE

Date: August 29, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420

Subject: NDA 203108 Oladaterol Repimat
Request for information – CMC: Microbiology

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by September 30, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

1. The bioburden sampling point should be [REDACTED] ^{(b) (4)}.
Revise the sampling point; the acceptance criteria may also be revised, as appropriate.
2. Provide a description of the growth media and incubation conditions for the environmental monitoring program.
3. Provide the following information for recent media fills: the number of units filled, the number of units incubated, and the number of positive units.
4. Provide the sterility test method verification studies.

Submit the requested information as an official response to the NDA no later than September 30, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: Jessica Cole, Bryan Riley/ August 28, 2012
Cchung/ August 29, 2012

Initialed by: SBarnes/ August 29, 2012

Finalized: cchung/ August 29, 2012

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/s/

CHRISTINE H CHUNG
08/29/2012



NDA 203108

DISCIPLINE REVIEW LETTER

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs

Dear Mr. Daulerio:

Please refer to your New Drug Application (NDA) dated and received May 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (olodaterol) Respimat Inhalation Spray, 2.5 mcg olodaterol per actuation.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. (b) (4)
2. (b) (4)
3. Revise the description of the manufacturing process for the drug substance that is provided in S.2.2 to include (b) (4), which are generally considered to be important operating conditions.
4. Revise description section S.2.2 to indicate where the (b) (4) (listed in S.2.3) is used (b) (4)
5. In the method validation report (document U11-1736-01) for the procedure for the determination of the content of the (b) (4) in the olodaterol, you state that “the potential impurities (b) (4) and the potential degradation product (b) (4) are (b) (4)” However, the chromatographic data demonstrating this specificity could not be

located. Provide these data or a clear reference to the location in the application where these are presented.

6. Revise method 032981-02 for determination of (b) (4) in the drug substance to include instructions for storage conditions and periods for the test solutions.
7. Provide confirmation that achieving the minimal resolution of (b) (4) peaks with the olodaterol drug substance assay method 032986-04, will assure sufficient resolution of the (b) (4) peak from the olodaterol. As both impurities are considered potential impurities in the olodaterol drug substance (although neither is said to have been observed above the reporting threshold according to S.3.2), provide justification for not including a resolution requirement for the (b) (4).
8. You state in the pharmaceutical development report in P.2 that (b) (4) and you indicate that this is “laid down in the manufacturing procedure.” Provide reference to the part(s) of the executed batch records provided in 3.2.R that specifically address (b) (4), as this was not clear.
9. Provide a description of the (b) (4) ” and provide some results from representative filled cartridge batches.
10. Provide more detailed information about the (b) (4) that are used in conjunction with the (b) (4) method.
11. Regarding impurity (b) (4), you state that you have not been able to identify a source of (b) (4) which reacts with the drug substance to form this degradant. Your summary statements in P.5.6 appear to imply that the low levels of (b) (4) reflect that there are only low levels of (b) (4) present, i.e., that all or most of the latter is being trapped by the reaction with the drug substance. Provide a short summary of what potential sources of (b) (4) you have considered (e.g., (b) (4)). Also indicate the detection/quantitation limit for (b) (4) in the formulation so that it will be possible to make a toxicological assessment if necessary (depending on the limit and what was observed).
12. Revise the list of stability commitments in P.8.2 to include the three month in-use study planned for product aged for 33 months under conditions of 30°C/75%RH, and indicate that these data will also be included in the NDA Annual Report.
13. Revise the method validation package to include a link to P.1 for the formulation composition.

14. The following comments pertain to the labels and labeling:

- a. Revise the DESCRIPTION section of the package insert to the following: “The drug product, (b) (4) RESPIMAT, is composed of a sterile, aqueous solution of olodaterol hydrochloride filled into a 4.5 mL plastic container...”
- b. Revise the Drug Listing Data Element table such that the “Basis of Strength” is “Olodaterol,” as the strength is 2.5 mcg per actuation.

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

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALAN C SCHROEDER

08/20/2012

I concur. Signed for Dr. Prasad Peri.



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

ELECTRONIC CORRESPONDENCE

Date: August 6, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Repimat Request for information - Statistics	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by August 18, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have the following request for information:

Provide the programs, macros, and analysis datasets used to analyze efficacy in dose ranging studies 1222 .3, .4, .5, .6, .26, .27, and .29. In addition, provide a document that explains the use of each program.

Submit the requested information as an official response to the NDA no later than Friday, August 18, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RAbugov, JBuenconsejo/ July 31, 2012
Cchung/ August 2, 2012

Initialed by: SBarnes/ August 2, 2012

Finalized: cchung/ August 6, 2012

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/s/

CHRISTINE H CHUNG
08/06/2012



NDA 203108

FILING COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs

Dear Mr. Daulerio:

Please refer to your New Drug Application (NDA) dated and received May 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (olodaterol) Respimat Inhalation Spray, 2.5 mcg olodaterol per actuation.

We also refer to your amendments dated June 7 and 29, 2012.

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 March 14, 2013.

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, midcycle, 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 January 31, 2013.

During our filing review of your application, we identified the following potential review issues:

1. In some of your phase 3 trials, the olodaterol treatment effect at 6 weeks is numerically greater than at 12 weeks. Whether or not this will affect your proposed (b) (4) will be a review issue.

2. Your proposed label states that the bronchodilator effect of olodaterol was maintained throughout the 48 week treatment period. However, based on preliminary analysis, in some of your phase 3 trials, the magnitude of olodaterol's bronchodilatory effect appeared to decrease over the 48 week treatment period. Inclusion of this maintenance claim will be a review issue.
3. You have included (b) (4) in your label. The appropriateness of its inclusion will be a review issue.
4. Inclusion of the (b) (4) from the 48 week phase 3 trials in the label (b) (4) is of minimal value as the proposed dosing interval is once daily.
5. (b) (4) Inclusion of (b) (4) related claims is unlikely to be permitted in the label.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We have the following request for information:

- A. If you have performed any long-term olodaterol trials in asthmatics, provide trial summaries. Include clinical trial reports if available.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. In the Highlights section for the Patient counseling information statement, include reference to the Instructions for Use (IFU) to state the following, "See 17 for PATIENT COUNSELING INFORMATION, Medication Guide, and Instructions for Use."
2. A horizontal line must separate the Table of Contents (TOC) from the Full Prescribing Information (FPI).
3. In the FPI, Section 17 include a reference to the IFU to state the following, "*See FDA-Approved Patient Labeling (Medication Guide and Instructions for Use).*"

We request that you resubmit labeling that addresses these issues by August 17, 2012. The resubmitted labeling will be used for further labeling discussions.

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 Medication Guide. 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 Medication Guide 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 Chung, 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
07/27/2012



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

ELECTRONIC CORRESPONDENCE

Date: July 25, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Information Request- Randomization codes	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

******* Submit requested information by June 27, 2012 *******

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol Respimat is currently under review, and we have following request for information:

Submit the randomization codes associated with the study site patient identification numbers (if not identical) for each of the clinical principal investigator study sites participating in the protocols listed below. Identify the name of the principal investigator associated with each of the study site numbers.

- (1) U.S. sites under Protocol 1222.11
- (2) U.S. sites under Protocol 1222.12
- (3) Argentina sites under Protocol 1222.13

Submit the requested information as an official response to the NDA as soon as possible but no later than COB Friday, July 27, 2012.

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

Drafted by: AOrencia/ July 25, 2012
cchung/ July 25, 2012

Initialed by: SBarnes/ July 25, 2012

Finalized: cchung/ July 25, 2012

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/s/

CHRISTINE H CHUNG
07/25/2012



NDA 203108

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Damon Daulerio, MBA
Associate Director
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Damon Daulerio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) Respimat (olodaterol) Inhalation Spray.

We will be performing methods validation studies on (b) (4) Respimat (olodaterol) Inhalation Spray, as described in NDA 203108.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

- 035324-01 Assay, identification, determination of degradation products
- 032977-05 Organic Impurities

Samples and Reference Standards

- 200 mg Olodaterol hydrochloride reference standard
- 200 mg Olodaterol hydrochloride drug substance
- 50 mg (b) (4) impurity standard
- 50 mg (w) (4) impurity standard
- 100 (w) (4) Respimat (olodaterol) Inhalation cartridges

Equipment

- 1 (b) (4)
- 1 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael Trehy, Ph.D.
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael Trehy, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/24/2012



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

ELECTRONIC CORRESPONDENCE

Date: July 19, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Request for information- Clinical Pharmacology	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

***Submit requested information as soon as possible but no later than
August 1, 2012***

Document to be mailed: YES NO

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ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
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are hereby notified that any review, disclosure, dissemination, copying, or other action based on the
content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-3420. Thank you.**

Your NDA 203108 for Olodaterol is currently under review, and we have following requests for information:

1. Submit the datasets and codes/scripts for reviewers to recreate the analyses described in the report entitled “Clinical Report- Pharmacokinetic Meta-Analysis Report” Doc. No. U10-2212-01. All model codes or control streams, output listings and scripts used to generate analyses and plots should be provided for all analyses performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
2. Submit all electronic clinical pharmacokinetic data sets as SAS transport files and a definition file which describes the contents of the electronic data sets. If possible, submit all data sets in CDISC SDTM format.
3. Submit a brief summary of the genotyping methods, tested alleles, and quality control procedures with regard to the UGT pharmacogenetic analyses, in addition to submitting each subject’s genotype data for the four genes in the meta-analysis dataset(s).

Submit the requested information as an official response to the NDA as soon as possible but no later than Wednesday, August 1, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: EShang, SDoddapaneni, SBrar, MPacanowski/ July 13, 2012
cchung/ July 19, 2012

Initialed by: SBarnes/ July 19, 2012

Finalized: cchung/ July 19, 2012

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/s/

CHRISTINE H CHUNG
07/19/2012



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

ELECTRONIC CORRESPONDENCE

Date: July 12, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol Repimat Request for information - Statistics	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by July 27, 2012

Document to be mailed: YES NO

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Your NDA 203108 for Olodaterol is currently under review, and we have following comments and request for information:

1. Provide efficacy database lock dates for studies 11, 12, 13, 14, 24, 25, 37, 38, 39, and 40.
2. For studies 11 and 12, provide documentation which shows how the sample size for the subset of patients on which FEV1 AUC0-12hr response was determined.
3. For studies 11 and 12, provide documentation which shows how the subset of patients for which FEV1 AUC0-12hr response was chosen.
4. Provide dataset ttm for disposition analyses of each of studies 11, 12, 13, 14, 24, 25, 37, 38, 39, and 40.
5. Provide the programs and macros used for the study specific and ISS safety analyses of studies, 11, 12, 13, 14, 24, 25, 37, 38, 39, and 40. In addition, provide a document that explains the use of each program. Ensure that your programs include those used for MACE analyses.
6. Explain empty observations in the adverse events (AE) datasets. For example, 45 in dataset ae103 for study 11, observations 21 through 27 for patient 3005 and observations 40 through 45 for patient 3009 are missing values for variables HLGT and HLT, and observation 44 for patient 3009 provides no MedDRA descriptions despite the fact that an exacerbation with an onset and end date is indicated.

Submit the requested information as an official response to the NDA no later than Friday, July 27, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RAbugov, JBuenconsejo/ July 12, 2012

Initialed by: SBarnes/ July 12, 2012

Finalized: cchung/ July 12, 2012

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/s/

CHRISTINE H CHUNG
07/12/2012

Executive CAC

Date of Meeting: July 10, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Alternate Member
Molly E. Shea, Ph.D., DPARP, Supervisor
Carol M. Rivera-Lopez, Ph.D., DPARP, Presenting Reviewer

Author of Draft: Carol M. Rivera-Lopez, Ph.D.

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

NDA # 203108

Drug Name: Olodaterol Respimat Inhalation Spray

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Boehringer Ingelheim Pharmaceuticals, Inc. submitted two 2-year carcinogenicity study results in mouse and rat under NDA 203108. The studies were conducted by (b) (4). The sponsor received ECAC concurrence for the olodaterol doses used in both studies (ECAC meeting minutes (facsimile) dated February 15, 2007).

Olodaterol was negative in the *in vitro* Ames mutagenicity and mouse lymphoma assays. In the *in vivo* micronucleus assay (intravenous), olodaterol produced an increase in the frequencies of micronucleated polychromatic erythrocytes. However, this was determined to be due to drug-enhanced compensatory erythropoiesis and not a direct genotoxic mechanism by olodaterol. Therefore, the overall genotoxicity assessment of olodaterol was judged to be negative.

Rat Carcinogenicity Study

In a 2-year carcinogenicity study, Wistar Han Crl: WI(Han) rats received 0 [vehicle control (0.01% benzalkonium chloride, 0.01% disodium EDTA, and 0.003% citric acid) or air control], 25.8, 75.9, or 270 µg/kg/day olodaterol (achieved doses) via inhalation by a snout-only exposure technique. No statistically significant tumor findings were observed in males. In females, olodaterol induced leiomyomas of the mesovarian tissue in 1 of 55 females at 25.8 µg/kg/day and 4 of 55 females at 270 µg/kg/day. The trend and pairwise assessments for this tumor finding are considered statistically significant (p=0.0092 for the trend and p=0.0494 for the pairwise high-dose assessment)). There was an increase in mortality in treated males relative to controls, but the increase was not dose-dependent or statistically significant. Female survival was not affected. Food consumption was greater among olodaterol-treated animals of both sexes. However, body weights were similar among all treatment groups in both sexes.

Mouse Carcinogenicity Study

In a 2-year carcinogenicity study, Crl:CD1 (ICR) mice received 0 [vehicle control (0.01% benzalkonium chloride, 0.01% disodium EDTA, and 0.003% citric acid) or air control], 26.1, 76.9, or 255 µg/kg/day olodaterol (achieved doses) via inhalation by a snout-only exposure technique. No statistically significant tumor findings were observed in males. In females, the incidences of benign uterine leiomyomas were higher at all dose levels when compared to the vehicle control group. Statistical significance was achieved at the high-dose level (255 µg/kg/day, p=0.0038). The incidences of malignant leiomyosarcomas were also increased in olodaterol-treated groups although statistical significance was only achieved at the middle-dose (76.9 µg/kg/day, p=0.0092). The incidences of combined benign uterine leiomyomas and malignant leiomyosarcomas were higher at all dose levels when compared to the vehicle control group. Statistical significance was achieved at doses \geq 76.9 µg/kg/day (p=0.0003 and 0.0018 for the mid- and high-dose, respectively). Survival was not affected in either males or females. A slight (transient) increase in body weight was observed in animals treated at \geq 76.9 µg/kg/day (both sexes) and was associated with greater food consumption.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study was positive for Olodaterol induced leiomyomas of the mesovarian tissue in females.

Mouse:

- The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study was positive for Olodaterol induced benign uterine leiomyomas and malignant leiomyosarcomas combined in females.

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

cc:\

/NDA 203-108 Division File, DPARP
/MShea, DPARP
/CRivera-Lopez, DPARP
/CChung, CSO/PM, DPARP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
07/11/2012

DAVID JACOBSON KRAM
07/11/2012

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/s/

CHRISTINE H CHUNG
07/08/2014



NDA 203108

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs

Dear Mr. Daulerio:

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: (b) (4) (olodaterol) Respimat Inhalation Spray

Date of Application: May 14, 2012

Date of Receipt: May 14, 2012

Our Reference Number: NDA 203108

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 July 13, 2012, 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

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

Sincerely,

{See appended electronic signature page}

Christine Chung, 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
05/23/2012



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

ELECTRONIC CORRESPONDENCE

Date: May 23, 2012

To: Damon Daulerio, MBA Associate Director, Drug Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: damon.daulerio@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 203108 Oladaterol- Request for information #1	

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by June 7, 2012

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

Your NDA 203108 for Olodaterol is currently under review, and we have following request for information:

1. For studies 11, 12, 13, 14, 24, and 25, files ae101.xpt, ae103.xpt, and ae104.xpt, studies 37 and 38, files ae191.xpt, ae192.xpt, ae193.xpt, and ae193e.xpt, studies 39 and 40, files ae191.xpt and ae197.xpt, provide xpt catalogues or programs to define the following formats: \$CONT1F, AEFUP1S, YN1F, PGQ1F, YNS1S, AESTC1S, SEX1F, AECTA1S, AEINT1S, and AEOUT1S.
2. For studies 11, 12, 13, 14, 24, 25, 37, and 38, files lbasco.xpt and linder.xpt, and studies 39 and 40 files lbasco21.xpt and linder21.xpt, provide xpt catalogues or programs to define the following formats: YN1F, AGEQ1F, UNIT2F, ALCCDC1F, PRJBCUSE, UNIT4F, UNIT1F, INFCON1F, UNIT5F, \$PAGE1F, NPND3F, NEGPOS1F, RACEI1F, BCUSE1F, BCUSEG1F, RACEA1F, RACEI1F, SEX1F, SMOKCD1F, and UNIT6F.
3. For parallel arm studies 11, 12, 13, and 14, provide analysis files as in adpft.xpt, but with missing visit values left as missing, without any imputation between visits for missing values. Include all data observed, including that collected on visits after discontinuation of treatment. In a separate column, provide a flag indicating whether or not the data was collected on visits with continued randomized treatment, after discontinuation of randomized treatment, or during use of rescue therapy.
4. Provide the programs and macros used for the efficacy, demographic, and disposition analyses for studies 11, 12, 13, 14, 24, 25, 37, 38, 39, and 40. In addition, provide a document that explains the use of each program.
5. Resubmit Letters of Authorization (LOAs) for the two Drug Master Files (DMFs) submitted (from Boehringer Ingelheim Pharma GmbH & Co. KG) on May 1, 2012. The original LOAs for these DMFs did not include the DMF numbers, because the DMF numbers had not yet been assigned.

Submit the requested information as an official response to the NDA by Thursday, June 7, 2012, or provide a timeline for when the information will be submitted.

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

Drafted by: RAbugov, JBuenconsejo/ May 21, 2012
ASchroeder, CBertha, PPeri/ May 18, 2012
cchung/ May 23, 2012

Initialed by: SBarnes/ May 23, 2012

Finalized: cchung/ May 23, 2012

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/s/

CHRISTINE H CHUNG
05/23/2012



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

Memorandum of Facsimile Correspondence

Date: November 30, 2011

To: Damon Daulerio
Associate Director, Drug Regulatory Affairs

Company: Boehringer Ingelheim Pharmaceuticals, Inc

Fax: 817-488-0215

Phone: 817-416-8073

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

Subject: IND 76,362; Comments

of pages:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPARP, Silver Spring, MD 20993.

Thank you.

IND 76,362
BI 1744 CL
Boehringer Ingelheim

We have reviewed your submission, dated Oct 7, 2011, received October 11, 2011, which contained clarifying questions regarding the Pre-NDA meeting comments we provided to you on September 29, 2011. For ease of reference, the questions and FDA responses dated September 29, 2011, are printed below in italics. We have the following responses (in bold font) to your clarifying questions:

Question 8.2.13 from September 1, 2011, briefing package:

Beta-agonist class effects: In light of the well established class effects of β -agonists, BI has developed specific rules to collapse various MedDRA preferred terms considered to be associated with the same β -agonist class effect. These collapsing rules, which were finalized prior to unblinding of data from the Phase 3 pivotal studies, are described in the SCS Supplement (Appendix 7).

Does the FDA agree with this approach?

FDA Response from September 28, 2011, Preliminary Comments:

In general, your proposal appears reasonable. We are unable to comment specifically at this time as we are unable to locate the collapsing rules in the submission. Provide the rules, or their location within your submission, prior to the meeting, so that we may comment more definitively.

BI Clarification from October 7, 2011, submission:

Appendix 2 of this submission contains a revised in-text table 2.1.7.5: 1 from the Summary of Clinical Safety. Also, for the collapsing rules, please refer to pre-NDA briefing package, volume 2, Appendix 7 (Mock Summary of Clinical Safety Supplement), Listing 2.2.9.1, pages 51-157.

Does the FDA agree with this approach?

FDA Response:

Your approach is reasonable.

8.2.19 from September 1, 2011, briefing package:

Based on the draft table of contents for Module 5, does the Division have any comments regarding the general organization and proposed content of Module 5?

FDA Response from September 28, 2011, Preliminary Comments:

From Clinical Pharmacology perspective, bioanalytical reports should be also listed in TABLE 5.2.

IND 76,362
BI 1744 CL
Boehringer Ingelheim

BI Clarification from October 7, 2011, submission:

The bioanalytical reports are not stand alone reports, but are included as appendices in the CTRs of those studies that included PK. Table 5.2 has been modified to identify these reports and is located in Appendix 3 of this submission.

Does the FDA agree with the revised Table 5.2?

FDA Response:

Your approach is reasonable

If you have any questions, please contact Eunice Chung-Davies at 301-796-4006.

IND 76,362
BI 1744 CL
Boehringer Ingelheim

Drafted: EChung-Davies/16NOV2011
Initialed: LJafari/30NOV2011
BKarimi-Shah/30NOV2011
EShang/30NOV2011
SDoddapaneni/30NOV2011

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/s/

EUNICE H CHUNG-DAVIES
11/30/2011



IND 76362

MEETING PRELIMINARY COMMENTS

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Damon Daulerio, M.B.A.
Associate Director, Drug Regulatory Affairs

Dear Mr. Daulerio

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for olodaterol Respimat Inhalation Spray.

We also refer to your July 29, 2011, correspondence, received August 1, 2011, requesting a meeting to discuss the proposed marketing application for olodaterol Respimat for COPD.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 29, 2011, between Boehringer Ingelheim and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes

of prescribing information are available at:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call Eunice Chung-Davies, at (301) 796-4006.

Sincerely,

{See appended electronic signature page}

Eunice Chung-Davies, Pharm.D.
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Questions and Responses

QUESTIONS AND RESPONSES

8.1 IND / End-of-Phase 2 Meeting: Outstanding Issues

8.1.1

BI has assessed all issues in the Regulatory History section as being fully resolved. Does the FDA agree?

Are there any other outstanding issues related to the interactions between BI and the FDA for olodaterol RESPIMAT that require resolution prior to the submission of the NDA?

Clinical Response:

The clinical issues raised at the End-of-Phase 2 and in subsequent interactions have been addressed appropriately. Whether full resolution of these issues has been achieved can be determined only at the time of NDA review. There do not appear to be any outstanding issues prior to NDA submission.

CMC Response:

The CMC related issues in the Regulatory History section have been fully resolved. There do not appear to be any outstanding issues prior to NDA submission.

Nonclinical Response:

We agree that the genetic toxicology findings have been adequately addressed. For the nonclinical rat histopathology finding of skeletal muscle necrosis, provide data to support that this finding was observed with formoterol as you suggested at the End-of-Phase 2 Meeting. Review of the rat embryo-fetal development study suggests that you have not dosed up to the maximal tolerated or feasible doses. Provide justification that this study is acceptable. There are no additional outstanding nonclinical issues that have been identified to date.

Clinical Pharmacology Response:

With regard to the renal impairment study, in severe renal impairment patients, C_{max} and AUC₀₋₄ increased by 137% and 135%, respectively. It is unknown at this stage if these increases are clinically significant and what if any dose adjustments are necessary. Whether data are needed in dialysis patients, mild and moderate renal impairment patients or not will be dependent on how severe renal impairment group is handled. In your NDA submission, provide an explanation on this aspect and how dialysis patients, mild and moderate renal impairment patients should be handled with respect to labeling.

8.2 Information to be submitted in the marketing application, including the proposed presentation and formatting of data.

Module 1

8.2.1

Based on the draft table of contents (Appendix 2) for Module 1, does the Division have any comments about the general organization and proposed content?

FDA Response:

We have no further comments.

8.2.2

Since all LABAs and all LABA containing products on the market have a Risk Evaluation Mitigation Strategy (REMS), BI is assuming that one will also be required for olodaterol RESPIMAT and that it should be similar in scope and content.

Does the FDA agree?

FDA Response:

We agree. The scope and content, although similar, will be dependent on the specific safety profile of olodaterol.

Can the FDA specify the timing as to when a proposed REMS would be required to be submitted (e.g. in the original NDA, towards the end of FDA's review)?

FDA Response:

The proposed REMS should be included at the time of NDA submission.

Module 2.7.1

Summary of Biopharmaceutic Studies and Associated Analytical Methods (Appendix 3)

8.2.3

Since no formulation changes and no relevant device changes were made throughout the development, and since olodaterol RESPIMAT Inhalation Spray is intended to be marketed at one dose only (5 µg), no relative BA/BE studies and no dose strength equivalence investigations were performed. Since olodaterol is administered via inhalation and the contribution of orally absorbed olodaterol to systemic concentrations is very low, no food effect studies were performed. Thus, it is proposed that the content of Module 2.7.1 will be restricted to a brief description of the formulation characteristics, an overview of the solution and device batches, doses, and bioanalytical methods used in the clinical studies with pharmacokinetic sampling, and a description of dose-proportionality of systemic exposure.

Does the FDA have any comments regarding the organization and/or proposed content in Module 2.7.1?

FDA Response: We do not have comments regarding the organization and/or proposed content in Module 2.7.1 at this time.

Module 2.7.2 Summary of Clinical Pharmacology Studies (Appendix 4)

8.2.4

Does the FDA have any comments regarding the organization and/or proposed content in Module 2.7.2?

FDA Response:

We do not have comments regarding the organization and/or proposed content in Module 2.7.2 at this time.

Module 2.7.3

Summary of Clinical Efficacy (SCE) (Appendix 5)

8.2.5

As explained in Section 1 of the Mock SCE, BI is proposing to not include a stand-alone ISE document; rather the following would constitute a complete integrated analysis in fulfillment of 21 CFR 314.50(d)(5)(v):

- *Narrative portion in SCE (2.7.3)*
- *Individual CTRs (5.3.5.1)*
- *Combined analysis reports with efficacy analyses (including sub-group analyses) based on pooled data from replicate studies (1222.11/12, 1222.13/14, 1222.24/25, 1222.39/40), (5.3.5.3)*

In support of the rationale for this approach, BI refers to the following excerpts from the FDA guidance document “Guidance for Industry. Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document” (April 2009):

There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2... In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3)...

If the narrative portion of the ISE or ISS is suitable for use in section 2.7.3 or 2.7.4, the narrative portion should be submitted only once and referenced in both Module 2 (section 2.7.3 or 2.7.4) and Module 5, section 5.3.5.3 (i.e., provide leaf elements in both locations)...

Based on this information, BI has taken the approach to split the integrated analysis of efficacy across specific sections/reports in Module 2 and Module 5, which together provide the

needed level of detail and also more detailed in-depth analyses to meet the requirements for an ISE. The specifics of this approach are described in the Mock SCE.

Since the NDA will be submitted as an eCTD, BI will make appropriate use of hyperlinking to ensure a seamless connection between Module 2.7.3 (SCE) and the respective tables and figures in the individual reports in Module 5.3.5.1 and the combined reports in Module 5.3.5.3.

BI intends to replicate the explanation of this approach provided in Module 2.7.3 into a stand-alone explanatory document in Section 5.3.5.3 for reference, in case a reviewer accesses Module 5.3.5.3 directly (rather than indirectly via the hyperlinks in Module 2.7.3).

Does the FDA agree with this proposal?

FDA Response: We agree.

If the FDA agrees to our proposal, then does the FDA agree that the explanation provided in the Mock SCE is adequate to fully inform the reviewer(s) of the overall structure of the integrated analysis of efficacy, especially in regards to the split across Module 2 and Module 5?

FDA Response: We agree.

8.2.6

Analyses in sub-populations: Section 3.3 of the SCE describes the results of comparisons across sub-populations. The sub-group analyses will focus on the pivotal, 48-week, parallel-group trials 1222.11/1222.12 and 1222.13/1222.14. BI considers that the 6 week cross-over studies (1222.24/1222.25, 1222.39/1222.40, 1222.37/1222.38) do not have sufficient numbers of patients to allow for meaningful comparisons across sub-populations. Pertinent to the NDA, the results of pulmonary function tests (FEV₁, FVC), will be analyzed for each trial by:

- ***Gender (male / female)***
- ***Age (≤65 years; > 65 years)***
- ***Race (Asian, White)***
- ***Region (US / Asia / Other in 1222.11/12; Europe / Asia / Other in 1222.13/14)***
- ***Use of long-acting muscarinic antagonists at baseline* (yes / no)***
- ***Use of short-acting muscarinic antagonists at baseline* (yes / no)***
- ***Use of xanthenes at baseline* (yes / no)***
- ***Use of inhaled steroids at baseline* (yes / no)***
- ***LABA use prior to study entry (yes / no)***
- ***Baseline disease severity (GOLD Stage II / GOLD Stage III / GOLD Stage IV)***
- ***Smoking status (current smoker / ex-smoker)***
- ***β₂-receptor haplotypes***

**** refer to definition in SCE***

Does the FDA agree with the defined sub-populations?

FDA Response:

Your choice of sub-populations is acceptable with the addition as outlined below.

Does the FDA have any suggestions regarding other sub-populations that should be considered?

FDA Response:

Include sub-population analyses based on beta-agonist reversibility as defined by the ATS/ERS criteria (reversible yes/no).

Include appropriate statistical assessment of the treatment-by-subgroup interaction in the overall group (e.g., utilization of a treatment-by-subgroup interaction term for endpoints that were analyzed using ANCOVA).

8.2.7

Does the FDA have any other comments regarding the organization and/or proposed content in Module 2.7.3?

FDA Response:

We have no further comments at this time.

Module 2.7.4

Summary of Clinical Safety (SCS) (Appendix 6)

8.2.8

Similar to the SCE / ISE proposal, BI is proposing to not include a stand-alone ISS; rather the following would constitute a complete integrated analysis in fulfillment of 21 CFR 314.50(d)(5)(vi):

- ***Narrative portion in SCS (2.7.4)***
- ***Individual CTRs (5.3.5.1)***
- ***Combined analysis reports with safety analyses based on pooled data from replicate studies (1222.11/12, 1222.13/14, 1222.24/25, 1222.39/40), (5.3.5.3)***
- ***SCS supplement (Appendix 7) with safety analyses (including sub-group analyses) based on pooled data from all long-term (48 week), parallel group studies (1222.11/12/13/14), pooled data from all short-term (6 week), cross-over studies (1222.24/25/37/38/39/40), and other studies within the clinical program (5.3.5.3)***

In support of the rationale for this approach, BI refers to the following excerpts from the FDA guidance document “Guidance for Industry. Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document” (April 2009):

There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2... In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3)...

If the narrative portion of the ISE or ISS is suitable for use in section 2.7.3 or 2.7.4, the narrative portion should be submitted only once and referenced in both Module 2 (section 2.7.3 or 2.7.4) and Module 5, section 5.3.5.3 (i.e., provide leaf elements in both locations)...

Based on this information, BI has taken the approach to split the integrated analysis of safety across specific sections/reports in Module 2 and Module 5, which together provide the needed level of detail and also more detailed in-depth analyses to meet the requirements for an ISS. The specifics of this approach are described in the Mock SCS.

Since the NDA will be submitted as an eCTD, BI will make appropriate use of hyperlinking to ensure a seamless connection between Module 2.7.4 (SCS) and the respective tables and figures in the individual reports in Module 5.3.5.1, the combined reports and SCS supplement in Module 5.3.5.3.

BI intends to replicate the explanation of this approach from Module 2.7.4 into a stand-alone explanatory document in Section 5.3.5.3 for reference, in case a reviewer accesses Module 5.3.5.3 directly (rather than indirectly via the hyperlinks in Module 2.7.4).

Does the FDA agree with this proposal?

FDA Response: We agree.

If the FDA agrees to our proposal, then does the FDA agree that the explanation provided in the Mock SCS is adequate to fully inform the reviewer(s) of the overall structure of the integrated analysis of safety, especially in regards to the split across Module 2 and Module 5?

FDA Response: We agree.

8.2.9

In consideration of the recent requirements for additional safety analyses for Arcapta and comments by the Agency in reference to (b) (4)

BI understands that similar analyses will be required for the olodaterol NDA. A draft adjudication committee charter including a statistical analysis plan is provided in Appendix 15. BI is seeking initial feedback on these documents at the pre-NDA meeting with the intention of subsequently submitting final documents to the FDA prior to implementation.

Does the FDA have any comments on the draft adjudication committee charter and/or statistical analysis plan?

FDA Response:

We have received the revised adjudication committee charter and statistical analysis plan. Your draft charter and statistical analysis plan appear reasonable.

8.2.10

SAE / AE Narratives: In Section 12.3 of each Phase 3 CTR, embellished narratives will be written for the following SAEs / AEs:

- (i) drug-related SAEs***
- (ii) fatal events***
- (iii) other relevant SAEs of interest (based on BI medical review).***
- (iv) non-serious AEs leading to discontinuation***

A template for the narratives is provided in Appendix 11. Narratives will be written on a per patient basis (i.e. multiple AEs/SAEs for a specific patient will be consolidated within one patient narrative). In addition, Section 15.4 of each CTR will include the original case narrative for all SAEs, as provided by the investigator and described within the CIOMS form in the BI safety database [ARISg].

Does the FDA agree with this approach?

FDA Response:

We do not agree with the submission of embellished narratives only for drug-related SAEs. Submit narratives for all SAEs from your phase 3 trials.

8.2.11

Exposure to olodaterol RESPIMAT monoprodut in the tiotropium+olodaterol fixed dose combination (FDC) program: BI is also developing a fixed dose combination product containing olodaterol and tiotropium as active substances (tiotropium + olodaterol RESPIMAT Inhalation Spray). The Phase 2 clinical program for tiotropium + olodaterol RESPIMAT Inhalation Spray was completed in Q1 2011 and the Phase 3 clinical program is currently in preparation. In some studies within the Phase 2 clinical program for tiotropium + olodaterol RESPIMAT Inhalation Spray: (i) olodaterol has been included as a comparator arm, and (ii) tiotropium and olodaterol were combined as a free or fixed combination. These studies do not provide long term data (>6 weeks) comparing olodaterol versus placebo. BI intends to submit CTRs for the completed studies in COPD from this clinical program within Module 5.3.5.4 "Other studies" of the NDA for olodaterol RESPIMAT. The overall extent of exposure, summary of adverse events and common adverse events have been integrated into the Phase 1/Phase 2 COPD database for olodaterol RESPIMAT within the NDA; thus accounting for patients administered olodaterol RESPIMAT monoprodut within the tiotropium+olodaterol FDC program. In addition, any safety concerns from these studies

related to the co-administration of tiotropium and olodaterol (in free or fixed combination) would be made note of in the SCS.

Does the FDA agree with this approach?

FDA Response:

Your approach is acceptable.

8.2.12

Analyses in sub-populations: Section 5 of the SCS describes the results of comparisons across sub-populations. The sub-group analyses will focus on the pivotal, 48-week, parallel-group trials 1222.11/1222.12 and 1222.13/1222.14. BI considers that the 6 week cross-over studies (1222.24/1222.25, 1222.39/1222.40, 1222.37/1222.38) do not have sufficient numbers of patients to allow for meaningful comparisons across sub-populations.

Safety data (adverse events) will be analyzed for each trial by:

- *Gender (male / female)*
- *Age (≤ 65 years; > 65 years)*
- *Race (Asian, White)*
- *Region (US / Asia / Other in 1222.11/12; Europe / Asia / Other in 1222.13/14)*
- *Use of long-acting muscarinic antagonists at baseline* (yes / no)*
- *Use of short-acting muscarinic antagonists at baseline* (yes / no)*
- *Use of xanthenes at baseline* (yes / no)*
- *Use of inhaled steroids at baseline* (yes / no)*
- *LABA use prior to study entry (yes / no)*
- *Baseline disease severity (GOLD Stage II / GOLD Stage III / GOLD Stage IV)*
- *Smoking status (current smoker / ex-smoker)*
- *Renal impairment (creatinine clearance >80 / $50-80$ / $30-50$ / <30 mL/min based on FDA guidance 1989)*
- *β_2 -receptor haplotypes*

** refer to definition in SCS*

Does the FDA agree with the defined sub-populations?

FDA Response:

Your choice of sub-populations is acceptable with the additions as outlined below.

Does the FDA have any suggestions regarding other sub-populations that should be considered?

FDA Response:

- 1) *Include sub-population safety analyses based on beta-agonist reversibility as defined by the ATS/ERS (reversible yes/no) for each trial.*

- 2) *Include safety analyses in patients with cardiac history.*
- 3) *For the sub-group of patients with cardiac history as well as the total safety database, we recommend that in order to see combined occurrence rates of medically similar adverse events, you collapse MedDRA preferred terms for adverse events of interest in addition to providing preferred terms. At a minimum, provide collapsed terms for myocardial infarction, atrial fibrillation, angina, stroke, congestive heart failure, tachycardia, and pneumonia, as well as other events as appropriate. As part of the NDA, provide a summary of your collapsing methodology. Also include an analysis of Major Adverse Cardiac Events (MACE).*

8.2.13

β-agonist class effects: In light of the well established class effects of β-agonists, BI has developed specific rules to collapse various MedDRA preferred terms considered to be associated with the same β-agonist class effect. These collapsing rules, which were finalized prior to unblinding of data from the Phase 3 pivotal studies, are described in the SCS Supplement (Appendix 7).

Does the FDA agree with this approach?

FDA Response:

In general, your proposal appears reasonable. We are unable to comment specifically at this time as we are unable to locate the collapsing rules in the submission. Provide the rules, or their location within your submission, prior to the meeting, so that we may comment more definitively.

8.2.14

The MedDRA classification versions for the individual studies as well as the combined reports will be the version in effect when the database for the trial was locked and the trial was unblinded (both members of each replicate pair of trials used the same MedDRA version). The MedDRA classification version 14.0 will be used for the SCS / SCS Supplement as this was the version in effect when the last Phase 3 trial was completed.

Does the FDA agree with the use of these specific MedDRA versions?

FDA Response: We agree.

8.2.15

Does the FDA have any other comments regarding the organization and/or proposed content in Module 2.7.4?

FDA Response:

We have no further comments.

Module 3

8.2.16

Based on the summary of information to be included for Module 3 (Appendix 8), does the Division have any comments regarding the general organization and/or proposed content in Module 3?

FDA Response:

The general organization of Module 3 is acceptable. The proposed contents appear sufficiently complete on its surface for the Agency to conduct the review. We have the following comments:

- 1. In control of excipients, it is not acceptable to merely state that the excipients are controlled to USP/NF requirements.*
- 2. Specify that at least an identification test is to be conducted on each lot of excipient to confirm its identity, and at least one full testing is to be conducted for each excipient at appropriate intervals; Further, provide a representative copy of the Certificate of Analysis (CoA) for each excipient used unless it is provided in the regional information section as part of executed batch records.*

Module 4

8.2.17

Based on the draft table of contents for Module 4 (Appendix 2), does the Division have any comments about the general organization and/or proposed content in Module 4?

FDA Response: No, we have no comments

Additional Nonclinical Comment:

Submit the completed final study reports for the rat and mouse carcinogenicity studies to the IND for review.

Module 5

8.2.18

Does the FDA agree with the organization of Table 5.2 (Appendix 9)?

FDA Response: Your organization of Table 5.2 is acceptable.

8.2.19

Based on the draft table of contents for Module 5, does the Division have any comments regarding the general organization and proposed content of Module 5?

FDA Response:

From Clinical Pharmacology perspective, bioanalytical reports should be also listed in TABLE 5.2.

8.3 Electronic Submission Proposal (Appendix 10)

8.3.1

Datasets: Data tabulation datasets and Analysis Datasets will be provided for all Phase 3 studies (1222.11/1222.12, 1222.13/1222.14, 1222.24/1222.25, 1222.37/1222.38, 1222.39/1222.40). For all other studies in the clinical development program, only data tabulation datasets will be provided. The SDTM standard domain models (SDTMIG version 3.1.2) will be used. Any custom domains required will follow the process documented in the CDISC SDTM Implementation guide. Analysis datasets will be provided in ADaM version 2.1 or BI proprietary format. A define.xml file will be included detailing the contents of each domain and analysis dataset.

Due to the use of validated reporting macros and pre-defined project specifications, certain analysis datasets identified in the eSubmission Proposal (Appendix 10) will not follow the CDISC structure. These analysis datasets will be provided in a BI proprietary format and a define.xml document will be created to detail the contents of the files. An example of a data set using each unique BI proprietary format have been included in Appendix 14.

Does the FDA agree with this proposal?

FDA Response: This is acceptable.

8.3.2

CRFs (i.e. PDF of completed eCRF data entry screens): In accordance with 21 CFR 314.50(f)(2), BI plans to submit CRFs, as defined above, for each randomized patient who died during the study and who discontinued study drug due to an adverse event for each trial in the clinical development program. BI proposes not to provide any other CRFs at the time of the NDA submission acknowledging that the FDA may request submission of other CRFs based on review of the NDA.

Does the FDA agree?

FDA Response: Your proposal is reasonable.

8.3.3

120-day safety update report: Study 1222.29 is a phase 2, randomised, double-blind, cross-over study to compare the 24-hour FEV₁-time profile of orally inhaled olodaterol, delivered with the Respimat[®] Inhaler, after 3 weeks of olodaterol once daily 5 µg [2 actuations of 2.5 µg], twice daily 2.5 µg [2 actuations of 1.25 µg] and placebo or after 3 weeks of once daily 10 µg [2 actuations of 5 µg], twice daily 5 µg [2 actuations of 2.5 µg] and placebo administration in patients with moderate to severe persistent asthma. This study was conducted as recommended by the FDA to compare different dosing frequencies in asthma to support the posology in COPD.

The clinical trial report for this study will be included into the NDA submission along with the interpretation and integration of the results within the SCE; however, BI does not intend to integrate the safety data into the SCS (i.e. not included in the pooled asthma dataset) nor include it in the adjudication analysis for the NDA submission. Any safety concerns would be addressed within the SCS for the NDA submission; however, the formal integration of the safety data from 1222.29 and inclusion into the adjudication will be provided to the FDA as part of the 120-day safety update report.

Additionally with respect to study 1222.29, the SDTM datasets will be included within the NDA submission. Assuming no unforeseen issues, this would also include those specific SDTM datasets that are relevant to the adjudication.

In addition, there will be 4 ongoing studies within the tiotropium+olodaterol fixed-dose combination program at the time of the NDA submission, 1237.5/1237.6 and 1237.13/1237.14, which will contain olodaterol RESPIMAT as comparator arm and therefore, would need to be included into the 120-day safety update report. The data from these studies will be blinded at the time of the NDA submission. As such, the 120-day safety update report is proposed to include a summary and table for each of the following for the timeframe of study start (September 2011) to March 21, 2012 (targeted date of NDA submission):

- ***Most frequent AEs***
- ***Serious AEs***
- ***IND safety reports***
- ***Deaths***
- ***Dropouts due to AEs***
- ***Disposition, extent of exposure (dose, duration, # of subjects)***
- ***Demographics***
- ***CRFs (if available) for those patients who've died, discontinued due to an AE, SAE***

Subsequent safety update reports will include the above mentioned information, as well as the following additional information for all unblinded studies:

- ***Integration of data into the SCS (i.e. cumulative safety exposure)***
- ***Narratives for all drug-related adverse events, fatal events, other serious adverse events, other adverse events judged to be of special interest because of clinical importance, and any adverse event leading to discontinuation***

Does the FDA agree with this proposal?

FDA Response:

Your NDA must be complete with the information you consider necessary for adequate review at the time of submission as significant safety data submitted later may not be integrated into the overall review. While your proposal may be reasonable, whether your safety database is adequate to support approval will depend on the quality of the safety data and the nature of adverse events observed with the drug product. We remind you that your proposed safety database at the time of NDA submission may not be adequate to overcome the need for a large post-marketing safety trial to evaluate serious respiratory adverse events in COPD patients.

In regards to study 1222.29, if something unforeseen arises that impacts the availability of those SDTM datasets that are specific to the adjudication by the targeted NDA submission date, then would the FDA accept the inclusion of these specific SDTM datasets into the 120-safety update report?

FDA Response:

Study 1222.29 will present crucial information regarding justification of the dose and dosing interval. Therefore, the SDTM datasets must be included at the time of submission. If additional safety data become available later in the review cycle, you may submit those data, but they may or may not be considered in the overall review.

8.3.4

BI plans to include the final data from the eCRFs in the case report form section. These are the data as approved by the investigator. BI does not plan to include the audit trail information. This is available upon request.

Does the FDA agree with this approach?

FDA Response: Yes.

8.3.5

Does the Division have any other comments related to the electronic submission proposal?

FDA Response: We have no further comments.

8.4 CONTENT AND FORMAT OF THE NDA

8.4.1

Does the FDA agree that the content and format of the NDA as described throughout the documents contained herein are adequate to support submission?

FDA Response: We agree.

We also have the following labeling comments:

- A. *All Container labels and Carton labeling: Revise the expression of strength to read '2.5 mcg per actuation' or '2.5 mcg/actuation' instead of [REDACTED] (b) (4)*
- B. *Carton labeling: On the side panel, relocate the strength statement to appear under the dosage form statement.*

Additional Comment

Include reports of all medication errors from the Phase 3 Clinical Trials, serious and non-serious, including those related to the device. All drug product units which patients believe are malfunctioning, should be returned to the sponsor for laboratory evaluation and testing.

8.4.2

As Olodaterol Respimat will be the second in a class of once-daily LABAs, BI is not aware of any precedent-specific issues that would immediately suggest the NDA will be the subject of an Advisory Committee to review the risk/benefit and approvability. Assuming no emergent safety issues arise, does the FDA have any comments on the prospects for an Advisory Committee review of the drug product?

FDA Response:

Olodaterol is a New Molecular Entity; therefore, olodaterol would likely be subject to an Advisory Committee review.

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/s/

EUNICE H CHUNG-DAVIES
09/28/2011



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

Memorandum of Facsimile Correspondence

Date: September 4, 2008

To: Damon Daulerio, MBA
Manager, Drug Regulatory Affairs

Company: Boehringer Ingelheim

Fax: (203) 791-6262

Phone: (203) 798-4988

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: IND 76,362; re: Addendum #2 to the July 11, 2008, meeting minutes

of Pages: 4

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Thank you.

MEMORANDUM OF TELECON

DATE: September 4, 2008

APPLICATION NUMBER: IND 76,362

BETWEEN:

Name: Damon Daulerio, Associate Director, Drug Regulatory Affairs
Phone: 1-817-416-8073
Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Akilah Green, MS, RN, Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products, HFD-570

SUBJECT: Addendum to the July 17, 2008, meeting minutes

In an email dated August 29, 2008, Damon Daulerio from Boehringer Ingelheim wrote,

In reading through the FDA's EoP2 Meeting Minutes, dated August 11, 2008, we noticed a minor discrepancy from our understanding on page 37 under the discussion for question 26. The FDA stated "...*BI should conduct in vitro studies to determine the inhibition/induction potential of these two metabolites on major CYP enzymes.*" We had pointed out in the meeting that although we have two major metabolites, only one is measurable in plasma following the inhalation of 5 and 10 mcg of BI 1744 CL, that being CD 992. The other metabolite, SOM 1552 BS, is not detectable. This was also noted on page 28 of the minutes under question 19. Based on this, we came away from the meeting with the understanding that we would only have to conduct the inhibition/induction studies on the one measurable metabolite (CD 992). Can you please confirm and advise if this should be/can be corrected in the official FDA minutes?

After speaking with Sandra Suarez, Ph.D., Clinical Pharmacology Reviewer, I communicated the following to Mr. Daulerio over the phone:

The following paragraph on page 37 of the July 17, 2008, meeting minutes reads:

Considering activity and concentration as definers of "major metabolites", the Agency agrees that there are only two major metabolites of BI 1744 CL. Therefore, BI should conduct in vitro studies to determine the inhibition/induction potential of these two metabolites on major CYP enzymes.

This paragraph should be changed to read:

Considering activity and concentration as definers of “major metabolites”, the Agency agrees that there is only one major metabolite of BI 1744 CL, that being CD 992. Therefore BI should conduct in vitro studies to determine the inhibition/induction potential of CD 992 on major CYP enzymes.

Akilah Green, MS, RN
Senior Regulatory Management Officer

Linked Applications

Sponsor Name

Drug Name

IND 76362

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

BI 1744 CL RESPIMAT INHALATION
SPRAY

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/s/

AKILAH K GREEN

09/04/2008



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

Memorandum of Facsimile Correspondence

Date: August 12, 2008

To: Damon Daulerio, MBA
Manager, Drug Regulatory Affairs

Company: Boehringer Ingelheim

Fax: (203) 791-6262

Phone: (203) 798-4988

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: IND 76,362; re: Addendum to the July 11, 2008, meeting minutes

of Pages: 3

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Thank you.

Dear Mr. Daulerio:

We are providing the recommended language below to explain the data discussed in the July 17, 2008, meeting minutes under question 23 for the Informed Consent. Modifications to this language can be considered after review of the in vivo micronucleus test (only summary data has been provided to date) and mechanistic study.

Several laboratory tests were conducted to determine whether BI 1744 can alter or otherwise damage DNA, the genetic material in the body's cells. These types of laboratory tests are always conducted to help determine if a new drug has any potential to cause cancer in humans. BI 1744 damaged genetic material in one test of rats treated with BI 1744 at significantly higher doses than those to be used in humans. This type of damage to genetic material has been associated with the development of cancer, although a positive test result does not necessarily mean that BI 1744 could cause genetic damage in humans or increase your risk of developing cancer. Additional laboratory testing is being conducted to evaluate the potential of BI 1744 to damage genetic material.

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

Linked Applications

Sponsor Name

Drug Name

IND 76362

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

BI 1744 CL RESPIMAT INHALATION
SPRAY

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/s/

AKILAH K GREEN

08/12/2008



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

Memorandum of Facsimile Correspondence

Date: August 11, 2008

To: Damon Daulerio, MBA
Manager, Drug Regulatory Affairs

Company: Boehringer Ingelheim

Fax: (203) 791-6262

Phone: (203) 798-4988

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: IND 76,392; re: July 17, 2008, meeting minutes

of Pages: 39

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Thank you.



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: July 17, 2008, 3:00-4:30 PM
Meeting Location: Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
10903 New Hampshire Avenue Building 22,
Conference Room 1419
Silver Spring, Maryland 20993
Application Number: IND 76,362
Product Name: BI 1744 Respimat Inhalation Spray
Received Briefing Package June 18, 2008
Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Requestor: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Meeting Recorder: Akilah Green, MS, RN
Senior Regulatory Management Officer
Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products

Sally Seymour, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products

Banu Karimi-Shah, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products

Molly Shea, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products

Timothy Robison, Ph.D., DABT, Pharmacology/Toxicology Acting Team Leader, Division of Pulmonary and Allergy Products

Akilah Green, M.S., R.N., Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products

Eunice Chung, Pharm.D., Consumer Safety Officer, Division of Pulmonary and Allergy Products

Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, Branch II

Ali Al-Hakim, Ph.D., Branch Chief, Division of Pre-Marketing Assessment I, Branch II

Alan Schroeder, Ph.D., Chemistry Reviewer, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Office of Clinical Pharmacology

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2,

Sandra Suarez-Sharp, Ph.D., Senior Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2,

Office of Biostatistics

Qian Li, Ph.D., Statistical Team Leader, Division of Biometrics II

Boehringer Ingelheim Attendees

Jeff Snyder, Executive Director, Drug Regulatory Affairs

Damon Daulerio, MBA, Associate Director, Drug Regulatory Affairs

Annette Wasmund, CDept, Drug Regulatory Affairs

Petra Moroni-Zentgraf, M.D., International Project Leader, CDept International Project Management

Bernd Disse, MD, Ph.D., Head, Therapeutic Area Respiratory Medicine

Alan Hamilton, Ph.D., Medical Project Leader (COPD)

Martina Brammer, M.D., Medical Project Leader (Asthma)

Larry Korducki, Ph.D., Project Statistician

Michael Nowak, Ph.D., R&D Project Leader, Department Project Management
R&D

Annerose Mauz Ph.D., Project Toxicologist, Department of Non-clinical Drug Safety

Esther Vock, Ph.D., Toxicology Expert, Department of Non-clinical Drug Safety

Andreas Greischel, Ph.D., Project Non-Clinical Pharmacokineticist, Department of Drug Metabolism and Pharmacokinetics

1.0 BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted a Type B meeting request dated May 16, 2008, to discuss the proposed Phase 3 development program in COPD, [REDACTED], and the non-clinical program to support the filing of an NDA for BI 1744 CL. BI's briefing package was dated June 8, 2008. Upon review of the briefing package, the Division responded to BI's questions via fax on July 16, 2008. The content of that fax is printed below. On July 17, 2008, BI submitted written responses for clarification and the content is included under the appropriate question below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. BI's questions are in ***bold italics***; FDA's original response is in *italics*; BI's response is in normal font; and discussion is in normal font.

2.0 DISCUSSION

CLINICAL - CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

2.1 QUESTION 1a-d

As described in Section 9.1.2 and 9.3.3 of the Briefing Package, the Phase 3 program for BI 1744 CL in COPD has been developed to support the registration requirements in both the US and EU: (i) trials 1222.11/1222.12 have been designed to provide substantial evidence of efficacy to support the registration requirements in the US, (ii) trials 1222.13/1222.14 have been designed to provide substantial evidence of efficacy to support the registration requirements in EU, and (iii) trials 1222.24/1222.25 have been designed to describe the 24 hour FEV₁-time profile of BI 1744 CL in support of the registration in both US and EU. Furthermore, trials 1222.11/12 and 1222.13/14 have also been designed to provide the long term safety assessment of BI 1744 CL to support the registration requirements in both the US and EU.

Lung function in trials 1222.11/1222.12 is intended to provide the primary evidence of efficacy of BI 1744 CL for the purpose of the US registration. Both FEV₁ and FVC will be measured at trough (pre-dose) and at 5 mins, 15 mins, 30 mins, 1 hour, 2 hours, and 3 hours post-dose at all clinic visits up to 12 weeks (i.e. the time-point of the primary efficacy analysis). FEV₁ AUC₀₋₃ response and trough [pre-dose] FEV₁ response after 12 weeks of treatment are defined as the co-primary efficacy endpoints (sequential testing: (1) FEV₁ AUC₀₋₃ superiority of BI 1744 CL (high dose) vs. placebo, (2) FEV₁ AUC₀₋₃ superiority of BI 1744 CL (low dose) vs. placebo, (3) trough FEV₁ superiority of BI 1744 CL (high dose) vs. placebo, (4) trough FEV₁ superiority of BI 1744 CL

(low dose) vs. placebo). Other lung function measurements (e.g. FEV_1 AUC_{0-3} and trough FEV_1 after 2 and 6 weeks treatment, peak FEV_1 after first dose, 2, 6 and 12 weeks of treatment, FEV_1 at each time-point up to 3 hours post-dose, FVC at each time-point up to 3 hours post-dose, FVC AUC_{0-3}) are listed as secondary endpoints.

In previous BI Phase 3 programs for once daily bronchodilators in COPD, the primary statistical analysis has used an analysis of covariance model with terms for treatment and centre as fixed classification effects and baseline as a continuous covariate including only data at the time of the primary endpoint. Any missing visit data were imputed using either last observation carried forward (LOCF) or least favorable observation carried forward (in case the patient discontinued due to worsening COPD). As it is now recognized that a likelihood-based mixed-effects model repeated measures approach (MMRM) is superior to LOCF methods for handling of missing data and provides more precise estimates of treatment differences, BI is proposing to use this method for the primary efficacy analysis in the long-term clinical trials 1222.11/1222.12 and 1222.13/1222.14 (although least favourable observation carried forward will still be included to address the issue of informative dropout).

Does the Agency agree that the primary evidence of efficacy of BI 1744 CL for the purpose of registration in the US will be based on the results from 1222.11/1222.12?

FDA Response:

In principle, we agree that the results of studies 1222.11 and 1222.12 will provide the primary data to assess the efficacy of BI 1744 CL, however, you plan several additional phase 3 clinical trials that will also provide efficacy data. The totality of the evidence from your phase 3 program will be used to evaluate the efficacy of BI 1744 CL.

Does the Agency agree that FEV_1 AUC_{0-3} and trough FEV_1 after 12 weeks of treatment are appropriate co-primary endpoints in 1222.11/1222.12 to assess bronchodilator efficacy of BI 1744 CL?

FDA Response:

While the primary endpoints of FEV_1 AUC_{0-3} and trough FEV_1 after 12 weeks of treatment may be reasonable to assess bronchodilator efficacy, studies 1222.11 and 1222.12 do not include sufficient serial spirometry time points to adequately describe the time profile of BI 1744 CL in the product label. We recommend that

you include serial spirometry testing at additional time points beyond 3 hours in studies 1222.11 and 1222.12.

BI Response:

As noted in the introduction to Q2, trials 1222.24/1222.25 are designed to describe the FEV₁-time profile of BI 1744 CL over the 24 hour dosing interval after chronic treatment in comparison to placebo and bid formoterol. In response to Q2, the Agency has stated that "...we agree that the proposed co-primary endpoints [FEV₁ AUC₀₋₁₂ and FEV₁ AUC₁₂₋₂₄] will evaluate the FEV₁ time profile over the 24 hour dosing interval."

(b) (4)

In this light, could the Agency clarify the rationale for the recommendation for inclusion of serial spirometry testing at additional time points beyond 3 hours in studies 1222.11 and 1222.12.

Discussion:

FDA commented that if pivotal studies 1222.11/1222.12 are to be the basis of approval, the FEV₁-time profile must be characterized in these studies over the 24-hour dosing interval. Although it is true that studies 1222.24/1222.25 will provide information to support the 24-hour dosing interval, these studies are only 6 weeks in duration, as opposed to the longer duration in the pivotal trials.

The Division inquired as to the difficulties of performing 24-hour spirometry in a subset of patients within the pivotal studies. BI explained that very few of their clinical sites have the appropriate infrastructure to accommodate patients for this period of time, and this was their primary reason for designing 1222.24/1222.25 as separate studies. Although the Division acknowledged the practical difficulties, the recommendation for 24-hour spirometry in the pivotal studies was firmly held. BI indicated that they would re-evaluate the 24 hour pulmonary function measurements and try to incorporate it into studies 1222.11/1222.12.

Does the Agency agree that the secondary endpoints described for studies 1222.11/1222.12 will provide adequate supportive evidence of the efficacy of BI 1744 CL?

FDA Response:

Yes, we agree with your proposed secondary endpoints, but we recommend that you also consider COPD exacerbations as an additional secondary efficacy variable.

Does the Agency agree with the use of the MMRM method for the primary efficacy analysis in studies 1222.11/1222.12?

FDA Response:

Yes, however, it is important to perform analyses using LOCF imputation method and other reasonable methods to ensure the treatment difference is robust.

Other comments:

- 1. For the closed testing procedures implemented in Phase III studies for co-primary endpoints and multiple dose levels, we recommend you conduct tests within dose levels first rather than within co-primary endpoints.*
- 2. We do not think that the missing data imputation approach is always conservative if the data missing due to worsening of symptoms or need for medication will be imputed with the least favorable data for that visit or time point. We leave this as a review issue and recommend that you consider additional imputation methods should be considered to ensure a robust treatment difference.*

BI Response:

BI will follow the agency's recommendations to perform the closed testing sequence within dose levels for primary lung function endpoints as well as provide additional method(s) of imputation. With regard to the second comment, does the Agency have any particular methods they advocate?

Discussion:

FDA stated that we do not have any particular methods in mind, only that missing data should be minimized.

2.2 QUESTION 2a-b

(b) (4)

the Agency

provided comments regarding the clinical development of BI 1744 CL. Specifically, the Agency commented that “in addition to justifying the clinical dose, you must justify the once daily dosing interval of BI 1744 CL. To do so, the dose response curve for BI 1744 throughout the entire dosing interval should be evaluated”. The Agency further clarified that “you will need to justify that your drug is safe and remains effective over the course of the proposed 24 hour dosing interval.”

As described in detail in Section 9.1.2 and 9.3.3 of the Briefing Package, the currently available non-clinical and clinical data support the proposed once daily dosing frequency for BI 1744 CL. The non-clinical experiments clearly show that BI 1744 CL has a duration of action of at least 24 hours at its fully effective dose, i.e. it is not necessary to overdose beyond the fully effective dose to achieve a 24 hour duration of action. In contrast, the b.i.d. LABA formoterol only has a 12 hour duration of action at its fully effective dose, but can achieve a 24 hour duration of action at doses greater than the fully effective dose. Clinical data from Phase 2 trials are consistent with the non-clinical data. In trial 1222.3, which included serial pulmonary function testing up to 24 hours post-dose, all doses from 2 µg to 20 µg had a significant effect on FEV₁ compared with placebo after 24 hours; furthermore, there was a clear dose-response relationship at both peak (within 3 hours post-dose) and after 24 hours, confirming that the 24 hour duration of action of BI 1744 CL is not simply a consequence of overdosing. Consistent results were also observed in the 4 week trial 1222.5 using once daily administration of BI 1744 CL, with a clear dose-response relationship at peak (within 3 hours post-dose), over the entire initial 6 hour post-dose period and at the 24 hour trough before the next administration.

In the Phase 3 program, trials 1222.24/1222.25 are designed to describe the FEV₁-time profile of BI 1744 CL over the 24 hour dosing interval after chronic treatment. Lung function will be measured at the following post-dose time-points after 6 weeks of treatment: 0.5 hrs, 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 12.5 hrs, 13 hrs, 14 hrs, 22 hrs, 23, hrs, 24 hrs. FEV₁ AUC₀₋₁₂ response and FEV₁ AUC₁₂₋₂₄ response are defined as co-primary endpoints (sequential testing: (1) FEV₁ AUC₀₋₁₂ superiority of BI 1744 CL (high dose) vs. placebo, (2) FEV₁ AUC₀₋₁₂ superiority of BI 1744 CL (low dose) vs. placebo, (3) FEV₁ AUC₁₂₋₂₄ superiority of BI 1744 CL (high dose) vs. placebo, (4) FEV₁ AUC₁₂₋₂₄ superiority of BI 1744 CL (low dose) vs. placebo). Other lung function measurements (e.g. FEV₁ at each time-point, FVC at each time-point) are listed as secondary endpoints.

(b) (4)

(b) (4)

In order to address this concern within the Phase 3 program for BI 1744 CL, BI has specifically included clinic visits after both 6 and 12 weeks of treatment in 1222.11/1222.12, in order to allow a comparison of the effects of BI 1744 CL at trough and up to 3 hours post-dose after 6 and 12 weeks of treatment.

Does the Agency agree with the designation of $FEV_1 AUC_{0-12}$ and $FEV_1 AUC_{12-24}$ as co-primary endpoints in studies 1222.24/1222.25?

FDA Response:

Yes, we agree that the proposed co-primary endpoints will evaluate the FEV_1 time profile over the 24 hour dosing interval. However, it is unclear that you have established that once-daily dosing is the appropriate dosing interval for BI 1744 CL. Although you have provided data that the fully effective dose is active over the 24 hour dosing interval, and that there is a dose response. However, this information does not mean that the optimal dosing regimens have been fully explored.

Does the Agency agree that the comparison of trough (pre-dose) FEV_1 and $FEV_1 AUC_{0-3}$ after 6 and 12 weeks of treatment in 1222.11/1222.12 provides an appropriate opportunity to assess whether the 24 hour FEV_1 -time profile of BI 1744 CL after 6 weeks of treatment in 1222.24/1222.25 is representative of the 24 hour FEV_1 -time profile of BI 1744 CL after 12 weeks of treatment?

FDA Response:

This approach is reasonable. However, if a large difference is noted between the response at 6 weeks versus that at 12 weeks, the 6 week duration of 1222.24/1222.25 could be problematic.

Discussion:

There was no discussion on questions 2a-b. BI accepted FDA's response.

2.3 QUESTION 3

US commercial Foradil[®] Aerolizer[®] is included as a treatment arm in trials 1222.24/1222.25, in order to compare the 24 hour FEV₁-time profiles of BI 1744 CL administered according to a once daily dosing regimen with the 24 hour FEV₁-time profile of Foradil[®] Aerolizer[®] administered according to the registered twice daily dosing regimen. BI considers this comparison of the 24 hour FEV₁-time profile of a q.d. LABA and b.i.d. LABA useful information for the prescribing physician that warrant inclusion in the product label of BI 1744 CL.

As highlighted in Section 7 of the draft clinical trial protocol for 1222.24, the following comparisons of BI 1744 CL vs. Foradil[®] Aerolizer[®] will be pre-specified as key secondary analyses (combined data from 1222.24 and 1222.25):

- Superiority in mean FEV₁ AUC₀₋₁₂ response in patients treated with BI 1744 CL 10 µg compared with those treated with formoterol, after 6 weeks*
- Superiority in mean FEV₁ AUC₁₂₋₂₄ response in patients treated with BI 1744 CL 10 µg compared with those treated with formoterol, after 6 weeks*
- Superiority in mean FEV₁ AUC₀₋₂₄ response in patients treated with BI 1744 CL 10 µg compared with those treated with formoterol, after 6 weeks*
- Superiority in mean FEV₁ AUC₀₋₁₂ response in patients treated with BI 1744 CL 5 µg compared with those treated with formoterol, after 6 weeks*
- Superiority in mean FEV₁ AUC₁₂₋₂₄ response in patients treated with BI 1744 CL 5 µg compared with those treated with formoterol, after 6 weeks*
- Superiority in mean FEV₁ AUC₀₋₂₄ response in patients treated with BI 1744 CL 5 µg compared with those treated with formoterol, after 6 weeks*

It is BI's perspective that the three analyses for each dose taken together (i.e. FEV₁ AUC₀₋₁₂ response, FEV₁ AUC₁₂₋₂₄ response, FEV₁ AUC₀₋₂₄ response, all tested 2-sided, $\alpha \leq 0.05$) provide an appropriate description of the relative lung function efficacy of qd BI 1744 CL vs. bid formoterol over the 24 hour dosing interval of BI 1744 CL.

(b) (4)

(b) (4)

FDA Response:

Although we agree that the comparison of 24 hour FEV1 time profile of your drug product with the b.i.d. Foradil Aerolizer will provide useful information for regulatory decision-making, (b) (4)

(b) (4)

(b) (4)

FDA Response:

(b) (4), we do not recommend combining the two studies for the analyses of the secondary endpoints. We expect consistent results from the two studies and that no multiplicity adjustment is necessary.

Discussion:

There was no discussion on questions 3a-b. BI accepted FDA's response.

2.4 QUESTION 4

As described in Section 9.3.4 of the Briefing Package, BI has selected 5 µg and 10 µg as the doses of BI 1744 CL to be taken into Phase 3.

Does the Agency agree with the selection of 5 µg and 10 µg BI 1744 CL for Phase 3?

FDA Response:

We agree that the 5mcg and 10mcg doses of BI 1744 CL are reasonable to evaluate in Phase 3. However, we remind you of our concern regarding establishing the appropriate dosing interval [See response to Question 2].

Discussion:

There was no discussion on question 4. BI accepted the FDA's response.

2.5 QUESTION 5a-b

The expected extent of exposure of BI 1744 CL in patients with COPD at the time of NDA submission is described in Section 9.3.6 of the Briefing Package. In summary, in the long term (48 week) Phase 3 trials, a total of 770 patients are planned to be randomized to each of 2 doses (5 µg, 10 µg) of BI 1744 CL. Taking into account that a certain proportion of patients will prematurely discontinue from the long-term Phase 3 trials, it is projected that approximately 700 patients will be treated at each dose for 24 weeks and that approximately 575 patients will be treated at each dose for 48 weeks.

Although the final country allocation is still pending, it is currently planned to conduct trials 1222.11/1222.12 in US, Germany, Australia, New Zealand, China, and Taiwan; to conduct trials 1222.24/1222.25 in US, Canada and Europe (specific countries still to be confirmed) and to conduct trials 1222.13/1222.14 in Canada, Germany, Italy, Brazil, Mexico, Argentina, Asia (countries still to be confirmed), Spain, Sweden, Norway, Denmark, Finland, Eastern Europe (countries still to be confirmed), South Africa, and the Netherlands.

Based on current estimates of the US contribution to patient recruitment in 1222.11/1222.12, it is projected that US patients will comprise approximately 15% of the patients treated long term with BI 1744 CL (400 US patients randomized in 1222.11/1222.12 out of a total of 2740 patients randomized in 1222.11/1222.12 and 1222.13/1222.14).

Does the Agency agree that an NDA that includes about 15% US patients will satisfy concerns about the adequate representation of US patients in the development program?

FDA Response:

We agree, as long as the study population and standard of care outside the US are similar to the US study population and standard of care.

BI Response:

Currently, we are planning for a significant contribution of patients from China in studies 1222.11 and 1222.12 (150 out of a total of 510 randomized patients in each study). To our understanding, there is a lower use of inhaled corticosteroids

(i.e. 20 vs. 60 %), long-acting beta-agonists and tiotropium in patients with COPD in China compared with the US, which may suggest some differences in the standard of care. Does the Agency have any specific concerns with these (or other potential differences) in the standard of care for patients with COPD and potential impact on the outcome of trials?

Discussion:

FDA commented that if there is no treatment difference, we do not have any concerns, as long as the error rate is controlled. The Division advised that randomization and stratification by country/center should be performed in case there is a treatment difference. BI stated that they will do a blocked randomization and that the primary endpoint will look at treatment interactions. Although BI does not anticipate a regional difference, they will perform the appropriate analyses of the data. The Division reminded BI that regional variation in treatment effect was at their own risk.

Does the Agency agree that the safety dataset of BI 1744 CL for the long-term once daily maintenance treatment in bronchospasm associated with COPD will be adequate to support the submission/review of an NDA in the US?

FDA Response:

The proposed safety database is in compliance with ICH guidelines. However, further investigation may be required if a safety signal is noted in your Phase 3 program.

2.6 QUESTION 6

In previous BI COPD trials, patients with asthma have been excluded from participation according to the following exclusion criterion:

Patients with a history of asthma, allergic rhinitis or atopy or a total blood eosinophil count $\geq 600/\text{mm}^3$. A repeat eosinophil count will not be conducted in these patients.

However, there are patients with a diagnosis of COPD who clearly do not have a history of asthma but may present with allergic rhinitis, atopy or an increased blood eosinophil count. In order to permit inclusion of these patients into the Phase 3 trials for BI 1744 CL in COPD, BI is considering modifying the exclusion criterion as follows:

Patients with a history of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not

have asthma. If a patient has a total blood eosinophil count $\geq 600/\text{mm}^3$, source documentation is required to verify that the increased eosinophil count is related to a non-asthmatic condition. A repeat eosinophil count will not be conducted in these patients.

Does the Agency agree?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 6. BI accepted the FDA's response to this question.

2.7 QUESTION 7

In the long-term (48 week), placebo-controlled trials 1222.11/1222.12 and 1222.13/1222.14, LABAs (i.e. formoterol, salmeterol) are excluded as concomitant therapy, but patients using anticholinergic drugs as concomitant therapy at study entry are eligible, and are not required to wash-out of these drugs prior to study enrolment. The randomization scheme will include stratification based on the use of tiotropium as concomitant therapy at study entry to ensure an appropriate balance of patients on tiotropium across treatment groups. Concomitant therapy will be monitored during the study and restrictions taken if there is a risk that a disproportionately large number of patients (> 60%) using tiotropium as concomitant therapy are entered into the study. For patients enrolled in the study who are not using tiotropium as concomitant therapy at study entry, the patient will be discontinued from the trial if initiation of maintenance treatment with tiotropium is required during the first 12 weeks of the treatment period (i.e. up to the primary efficacy analysis). If initiation of maintenance treatment with tiotropium is required after 12 weeks, the patient may continue in the trial.

Does the Agency agree with this approach?

FDA Response:

The inclusion and stratification of patients by treatment with tiotropium is appropriate.

Discussion:

There was no discussion on question 7. BI accepted FDA's response.

2.8 QUESTION 8

The single dose QT study 1222.8 was conducted in parallel with the Phase 2 study 1222.5. As such, the following exclusion criteria were applied in the protocol for 1222.5, in accordance with ICH E14 recommendations when the effects of an NCE on QTc have not yet been characterized :

- *a marked baseline prolongation of QT/QTc interval (e.g. repeated demonstration of a QTc interval > 450 ms)*
- *a history of additional risk factors for Torsade de Pointes (TdP) (e.g. heart failure, hypokalemia, family history of Long QT Syndrome)*
- *medications that prolong the QT/QTc interval since the effects of BI 1744 CL on QT/QTc interval have yet to be characterized*

As described in Section 9.2.1 of the Briefing Package, study 1222.8 showed the expected effect of BI 1744 CL on QTc, consistent with other β -agonists. In accordance with ICH E14 recommendations for clinical trial evaluation after completion of a thorough QT/QTc study, the effects of BI 1744 CL in the target patient population will be investigated by: (i) removing the aforementioned exclusion criteria related to baseline QT/QTc prolongation, risk factors for TdP, and medications that prolong QT/QTc from the Phase 3 protocols, (ii) including extensive ECG monitoring (in all patients) and Holter monitoring (in a subgroup of patients) in the long-term trials 1222.11/1222.12 and 1222.13/1222.14.

Does the Agency agree with this approach?

FDA Response:

Given that the results of study 1222.8 are still under review, and the pharmacokinetic profile of BI 1744 CL is unknown in special populations, we cannot agree with removing the exclusion criteria related to baseline QT/QTc prolongation, risk factors for TdP, and medications that prolong QT/QTc.

BI Response:

We will include the relevant exclusion criteria in the final protocols for all Phase 3 studies. However, does the Agency foresee an opportunity for a protocol amendment to remove or modify the aforementioned exclusion criteria, dependent on the Agency's review of the results of 1222.8?

Discussion:

The Division stated that a protocol amendment to remove the exclusions stated above would be reasonable once the TQt study has been reviewed. The Division clarified BI's intent of opening up the trial to a more general population, including those with cardiac risk factors and risk of QT prolongation, in order to investigate the safety of BI 1744 CL in a controlled trial setting. The Division recommended that the exclusion criteria remain in the protocol until the study has been reviewed internally.

Post Meeting Addendum:

In post-meeting discussion, the Division revisited this issue and felt that that the exclusion criteria regarding QT prolongation as stated in question 8 above could be removed from Phase 3 studies.

2.9 QUESTION 9

(b) (4)
the Agency commented that the single dose QT study 1222.8 may not be sufficient and that a multiple dose study may be warranted. (b) (4)
further relevant information is now available: (i) the QT study 1222.8 has been completed (results described in Section 9.2.1 of the Briefing Package and Clinical Trial Report submitted to IND 76,362 SN 0029 on June 17, 2008) (ii) data regarding the accumulation of relevant metabolites SOM 1522 BS (pharmacologic activity at the human beta 1 and beta 2 adrenoceptors) and CD 992 BS (currently considered to be main metabolite) are available indicating no relevant accumulation (results described in Section 12.1 of the Briefing Package), (iii) intrinsic factors influencing the PK have been identified (described in Section 9.4 of the Briefing Package), (iv) the doses of BI 1744 CL to be taken into Phase 3 have been selected.

Based on this new information, does the Agency agree that the QT study 1222.8, which included single doses of 10, 20, 30 and 50 □g BI 1744 CL, sufficiently characterizes the effects of BI 1744 CL on QTc, and that an additional study evaluating the effects of BI 1744 CL on QTc after multiple dosing is not necessary?

FDA Response:

Review of the QT study is ongoing. We are unable to provide comments at this time.

Discussion:

There was no discussion on question 9. BI accepted FDA's response.

2.10 QUESTION 10

Does the Agency agree, contingent upon review and acceptability of the data, that the Phase 3 program based on studies 1222.11/1222.12, 1222.13/1222.14 and 1222.24/1222.25 is adequate to support the submission/review of an NDA for the indication "long-term, once daily, maintenance (b) (4) with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema"?

FDA Response:

The program appears adequate to support the submission and review of an NDA for your product.

(b) (4)

(b) (4)

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(b) (4)



CLINICAL – PHARMACOKINETICS

2.18 QUESTION 18

Considering that BI 1744 CL is administered via inhalation, and based on the fact that plasma concentrations of BI 1744 BS following oral administration are much lower compared to those following inhalation of the same dose, BI

concludes that the investigation of the effect of food on the PK of BI 1744 BS is not necessary for submission (further rationale is given in Section 9.4.2.1 of the Briefing Package).

Does the agency agree that the investigation of the effect of food on the PK of BI 1744 BS is not necessary for submission?

FDA Response:

Yes, we agree that the investigation of the effect of food on the PK of BI 1744 BS is not necessary for submission. This is based on the assumption that the possible increase in the systemic exposure of BI 1744 BS and relevant metabolites by food intake may be of clinical irrelevance.

Discussion:

There was no discussion on question 18. BI accepted FDA's response.

2.19 QUESTION 19

As described in Section 9.4.2.2 of the Briefing Package, the PK in COPD patients has been sufficiently characterized by collecting PK data in the Phase 2b study (1222.5) and by subsequently analyzing them with respect to the following covariates: renal function (mild and moderate renal impairment as opposed to normal renal function), weight, age, race (restricted to the comparison of blacks and whites), and sex.

(b) (4)

(b) (4)

FDA Response:

No, we do not agree. PK assessment in Phase 3 trials may not be needed to further characterize the PK of BI 1744 CL; however, we believe it is needed to further characterize the PK/PD safety relationship of the drug and its major metabolites for the following reasons:

- *The variability in PK parameters appears to be higher than 50% which could preclude a dose-response (safety) relationship based on Phase 3 data.*
- *The length of the Phase 2 trials may not be sufficient for characterizing a PK/PD (safety) relationship.*

Therefore, we recommend that you assess the PK of the parent drug and major metabolites in Phase 3 trials to further characterize the PK/PD safety relationship. The PK characterization can be achieved by collecting trough samples at steady state.

It is premature to reach a conclusion about the lack of dosing adjustment with respect to any of the aforementioned covariates. (b) (4)

BI Response:

We agree to the Agency's recommendation to include PK in Phase 3 trials 1222.11 and 1222.12. Since C_{pre,ss} concentrations can only be quantified in a limited number of patients following inhalation of 5 and 10 µg BI 1744 CL, we intend to sample at t_{max} (~10 minutes post-dose) at steady state.

We agree to the assessment of parent drug.

Regarding the metabolites identified to date [the evaluation of the human ADME study is pending, so there is the possibility that further metabolites will be identified]:

- the active metabolite SOM 1522 BS is not detectable in plasma following inhalation of 5 and 10 µg BI 1744 CL
- BI 1744 CL is mainly metabolized by glucuronidation. According to the FDA guideline Safety Testing of Metabolites: "Phase II conjugation reactions generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation. However, if the conjugate forms a toxic compound such as acylglucuronide, additional safety assessments may be needed." This line of reasoning provided the foundation for the proposal from BI that no further data are required regarding a toxicological qualification of the metabolites (Q25), which was accepted by the Agency.

Therefore, we propose not to assess any metabolites in Phase III [under the proviso that no unique metabolites are identified in the human ADME study]. Does the Agency agree?

In the Phase 3 trials 1222.11 and 1222.12, we propose to measure potassium levels (at 1 and 3 hours post-dose as in the Phase IIb study 1222.5) as a representative PD parameter for the further description of the PK / PD (safety) relationship. Does the Agency agree?

Discussion:

FDA stated that we agree with BI's proposal. We recommend that BI keep the blood samples in case there are unexplainable events not attributed to the parent compound. BI should measure potassium, ECG, and vital signs. BI should also review other labels in this class. In addition, the Agency inquired about the enzymes involved in the glucuronidation process and added that any polymorphic variation in UGT enzymes involved in the metabolism of BI 1744CL needs to be characterized.

2.20 QUESTION 20

Taking into account in vitro CYP inhibition data and the low plasma concentrations of BI 1744 BS following inhalation of the therapeutic dose, BI concludes that in vivo drug-drug interaction (DDI) studies assessing the influence of BI 1744 CL as inhibitor are not necessary. Furthermore, considering the in vitro studies on CYP identification and minor importance of CYP-catalysed metabolic pathways, and based on the fact that systemic exposure of patients with decreased activity of CYP2C8 and CYP2C9 is not different when compared to the wild-type allele carriers (as described in Section 9.4.2.3 of the Briefing Package), (b) (4)

Does the agency agree that no in vivo drug-drug interaction studies assessing BI 1744 CL as inhibitor (b) (4) *are necessary?*

FDA Response:

We agree with your proposal to not conduct in vivo drug-drug interaction studies (DDI) assessing BI 1744 CL as an inhibitor. (b) (4)

It appears that the CYP enzymes contribute less than 30% to the overall metabolic clearance. In addition, it appears that the systemic exposure in homozygotes was not different from that in heterozygotes for the relevant polymorphic forms of both enzymes CYP 2C8 and 2C9. However, the percent contribution is based on animal studies and the systemic exposure comparisons were based on $AUC_{0-6\text{ hrs}}$ instead of AUC_{τ} .

Therefore, before making a conclusion on the need for in vivo DDI studies (using BI 1744 CL as substrate) we request that you reanalyze the systemic exposure data of homozygotes vs. heterozygotes for the relevant polymorphic forms for both enzymes using AUC_{τ} rather than $AUC_{0-6\text{ hrs}}$. In addition, provide the percent contribution of relevant CYP enzymes in the overall elimination of BI 1744 CL in humans.

BI Response:

BI will re-analyze the data with respect to $AUC_{\tau,ss}$. $AUC_{0-6,ss}$ was chosen as a measure for systemic exposure because determination of the terminal half-life (and thus extrapolation beyond the last quantifiable plasma concentration) was only reasonable in a limited number of patients (5 μ g: 1/80; 10 μ g: 31/86; 20 μ g: 52/79) due to the low plasma concentrations. Pre-dose plasma concentrations at steady state ($C_{pre,ss}$) which were used as 24 hour plasma concentrations to determine the $AUC_{0-24,ss}$, could only reasonably be quantified in a limited number of patients: (5 μ g: 9 / 80 patients; 10 μ g: 42 / 86 patients; 20 μ g: 65 / 79). Thus, restricting the analysis to $AUC_{\tau,ss}$ will decrease the available data for the assessment.

Thus, if there is no major difference between the results based on $AUC_{\tau,ss}$ and $AUC_{0-6,ss}$, does the Agency agree to take $AUC_{0-6,ss}$ as a basis for the assessment?

Based on the ^{14}C human ADME study, BI will obtain a more precise estimate regarding the CYP contribution to the overall elimination. Provided that the CYP contribution is less than or equal to 30% of the overall elimination, does the Agency agree that no additional clinical study to assess BI 1744 CL as substrate of CYP2C8 and CYP2C9 is necessary?

Discussion:

FDA requested that BI provide the rationale for $AUC_{0-6,ss}$. BI should re-analyze the data with respect to AUC_t (area under the curve from time zero to the last measurable concentration) and $AUC_{0-24\text{hrs}}$. In addition, if the individual contribution of CYP 2C8 and CYP 2C9 to the overall elimination of BI 1744 CL

is < 25%, an additional clinical study to assess BI 1744 CL as substrate of CYP2C8 and CYP2C9 may not be necessary.

2.21 QUESTION 21

The PK/PD relationship of BI 1744 CL (cAMP, K⁺, ECGs, vital signs) has been investigated in the Phase 1 and Phase 2 programs for BI 1744 CL, as described in Section 9.4.2.4 of the Briefing Package. (b) (4)

(b) (4)

(b) (4)

FDA Response:

No, we don't agree. The length of the Phase 2 trials may not be sufficient for the characterization of the PK/PD (safety) relationship. Therefore, we recommend that you further investigate the PK/PD (safety) relationship in Phase 3 trials (see response to question 19).

Discussion:

There was no discussion on question 21. BI accepted FDA's response.

NON-CLINICAL

2.22 QUESTION 22

A description of the preclinical pharmacological and toxicological studies conducted and the respective results, as well as a description of the ongoing and planned pharmacological/toxicological studies is given in Section 10.1.1 of the Briefing Package.

Does the Agency agree that the non-clinical development program as presented is adequate to support the NDA filing for BI 1744 CL?

FDA Response:

Based on the nonclinical summary data you provided, no NOAEL was identified in the 26-week repeat dose rat study due to observations of hypertrophy and necrosis of the skeletal muscles at all doses. Provide an explanation for the findings of skeletal muscle necrosis. The determination of the adequacy of the nonclinical program is pending review of the recently submitted nonclinical studies.

BI Response:

In the 26-wk rat study, a dose dependent hypertrophy of the skeletal musculature was observed, with overall incidences (i.e., males and females combined) of 0/40, 27/40, 39/40, and 35/40 for Control, 49, 200 and 3400 µg/kg/day, respectively. This is an anabolic, i.e., receptor mediated, pharmacodynamic class effect common to beta-2-agonists.

Also, muscle fiber necrosis was noted in all groups, including control animals; single fiber necrosis was found sporadically in the skeletal muscle of 10/40, 19/40, 20/40, and 20/40 rats of Control, 49, 200 and 3400 µg/kg/day, respectively. Disseminated fiber necrosis, i.e., a slightly higher degree of the alteration was observed in the individual groups at incidences of 0/40, 0/40, 1/40, and 6/40. Overall, the incidence of muscle fiber necrosis in BI 1744 CL treated rats was higher than in control animals, and the degree of the necrosis, i.e., the incidence of the affected muscle fibers within a given muscle was slightly more severe at 3400 µg/kg/day than at lower dosages. Necrosis of muscle fiber groups was not observed.

Muscle hypertrophy in general is said to be associated with a change in S/V ratio, i.e. "Surface to Volume ratio", with the oxygen supply relative to the increased volume being diminished. This disturbance of the energy metabolism may be enforced by exercise of skeletal musculature. Thus, the increased incidence of skeletal single fiber necrosis in BI 1744 CL treated rats is considered secondary to the well-known effect of beta-2 agonists inducing skeletal muscle hypertrophy. For other beta-2 agonists, skeletal hypertrophy as well as skeletal single fiber necrosis have been also reported in rat toxicity studies, e.g. formoterol.

Therefore, for the present 26-week rat study, the NOAEL had been set to 200 µg/kg/day, except for the findings due to exaggerated pharmacological effects. A NOEL could not be defined in this study. Even for the low dose of 49 µg/kg/day in this study, an exposure multiple versus the clinical exposure at 10 µg q.d., based on AUC of ~30 can be given. An exposure multiple of ~140 can be given for the NOAEL.

Based on this explanation, does the FDA have any further comments?

Discussion:

FDA acknowledged that body weight gain and hypertrophy of the musculature have been observed as anabolic effects with this drug class. However, based on FDA's experiences with other long acting beta agonists (LABAs), necrosis of the musculature has not been observed. BI expressed that they have experience with other LABAs that have induced musculature necrosis and referred to data from formoterol. FDA clarified that a detailed review of the recently submitted data, including the chronic toxicology studies, is not complete. Upon completion of the review of these studies we may request the formoterol data from BI to support their argument. BI offered to submit the formoterol data of musculature necrosis prior to Phase 3 clinical studies. FDA recommended that BI wait to submit these data until requested as additional information may be needed after final review of the chronic toxicology studies.

2.23 QUESTION 23

BI 1744 CL was negative in the in vitro genotoxicity battery and rat bone marrow assay after inhalation exposure. However it induced a slight increase in micronuclei with signs for erythropoiesis in an additional rat bone marrow micronucleus assay after intravenous application up to sub-lethal doses. The increase in micronuclei was observed at doses that showed severe tachycardia and extreme reductions in blood pressure as seen in a separate pharmacology study. Significant tachycardia and low blood pressure are known to induce hypoxia with a consequent release of erythropoietin. The data suggest that the increases in micronuclei formation are due to the exaggerated pharmacological action of BI 1744 CL (details and results given in Section 10.1.2 in the Briefing Package).

(b) (4)
We are performing an additional study to confirm the mechanism. (b) (4)

FDA Response:

We can not agree at this time. Based on the in vivo rat intravenous micronucleus study results, BI 1744 did induce micronuclei formation suggestive of genotoxic potential. Your proposed mechanism of induction of micronuclei formation due to hypoxia-induced-erythropoiesis is being taken into consideration. You should provide additional information to support your rationale.

The positive genetic toxicity findings will need to be included in the Informed Consent for future studies, the Investigator's Brochure, and in the product label. Provided the data support your proposed mechanism of micronuclei formation, the product label will include this explanation for the positive result.

Phase 3 clinical studies with COPD (b) (4) patients may proceed.

The adequacy of genetic toxicity studies to support NDA filing will be evaluated following the receipt of this mechanistic study.

BI Response:

The additional information on the results of a mechanistic study with a single intravenous dose of 40 mg/kg in male rats was just finalized and an interim report was recently submitted (SN0034 dated July 14, 1008). The results will be incorporated into the next update of the Investigator Brochure and the section regarding genotoxicity adjusted accordingly.

Upon review, if the FDA accepts the adequacy of the genotoxic and mechanistic studies and consents with erythropoiesis as mode of action for the induction of micronuclei, BI suggests to describe BI 1744 CL as not genotoxic and to exclude all the details of the genotoxicity studies in the Informed Consent since there is no risk for patients receiving therapeutic dose levels. Does the FDA agree?

BI would like to discuss the information on the label again in due time.

Discussion:

FDA stated at this time, whether due to secondary effects or due to direct effects of BI 1744 treatment, a positive signal for induction of micronuclei formation was observed. The current study assessing the mechanism of action for this induction has not yet been received or reviewed. FDA will consider these data when evaluating the genetic toxicology studies. Based on the data available at this time, the Informed Consent should include the positive genetic toxicity study results. BI expressed concern that inclusion of these data is not a true representation of BI 1744's genetic toxicity potential. Furthermore, BI felt expression of these data would not be meaningful to the patient. FDA will provide recommended language to explain these data for the Informed Consent after a complete review of the data.

2.24 QUESTION 24

(b) (4)

Does the Agency consider the study as adequate for this purpose?

FDA Response:

Yes, the study appears adequate.

Discussion:

There was no discussion on question 24. BI accepted FDA's response.

2.25 QUESTION 25

In the toxicity studies performed for BI 1744 CL, the parent drug was the only analyte measured in toxicokinetics, i.e. metabolites were not formally qualified according to the recently published FDA guidance on Safety Testing of Drug Metabolites. Considering the low doses and the metabolism data available for BI 1744 CL, which reveals a large extent of Phase 2 (glucuronidation) metabolic reactions, BI is of the opinion that formal qualification of metabolites of BI 1744 CL is not required to support NDA filing for BI 1744 CL (details and results given in Section 10.1.4 of the Briefing Package).

Does the Agency agree that no further data are required regarding a toxicological qualification of the metabolites?

FDA Response:

Based on the summary data provided in the Briefing Package, no additional qualification studies are needed. However, review of the recently submitted nonclinical studies is pending.

Discussion:

There was no discussion on question 25. BI accepted FDA's response.

2.26 QUESTION 26

Considering the effective concentrations of the known most potent enzyme inducing compounds and the anticipated human therapeutic dose of BI 1744

CL (detailed figures are given in Section 10.1.5 of the Briefing Package), (b) (4)

Does the Agency agree?

FDA Response:

No, we do not agree. We recommend that you conduct an in vitro study to determine the enzyme induction potential of BI 1744 CL.

BI Response:

We consider an *in vitro* P450 enzyme induction study on BI 1744 CL. An *in vitro* study on the inhibition of BI 1744 CL on P-gp transport of digoxin was recently completed and showed an IC₅₀ value of more than 300 μM, i.e. far above therapeutic plasma levels.

Additional Clinical Pharmacology Comments:

We recommend that you conduct the following studies:

- *An in vitro metabolism study to determine the inhibitory/induction characteristics of the major metabolites.*
- *An in vitro study to determine the effect (induction/inhibition) of BI 1744 CL on P-gp transporter.*
- *A renal impairment study including patients with mild, moderate, and severe disease, and patients receiving dialysis.*
- *Reanalyze the data in terms of effect of covariates in the PK of BI 1744 CL considering AUCτ rather than AUC0-6hrs. The analysis of effect of race should not be limited to the black, white, and Japanese populations.*

BI Response (Bullets 1 and 2):

Related to your recommendation, how would you define major metabolites for BI 1744 CL in this context?

Due to the very low dose of parent compound given (5 or 10 μg), the exposure to the metabolites are very low. Therefore, in the human situation, an enzyme inhibition/induction via the metabolites is highly unlikely. We therefore consider *in vitro* inhibition/induction studies on the metabolites not to be required. Does the FDA agree?

Also regarding your recommendation: as the methods for *in vitro* evaluation of P-gp induction are not well understood and the mechanism of CYP3A and P-gp induction are similar, we consider it to be sufficient to conduct an enzyme induction study on BI 1744 CL (see above). Does the FDA agree?

Discussion:

Considering activity and concentration as definers of “major metabolites”, the Agency agrees that there are only two major metabolites of BI 1744 CL. Therefore, BI should conduct *in vitro* studies to determine the inhibition/induction potential of these two metabolites on major CYP enzymes.

FDA agrees that an enzyme induction study is sufficient.

BI Response (Bullet 4):

As outlined in the reply to Q20 above, $AUC_{0-6,ss}$ was chosen as measure for systemic exposure because determination of the terminal half-life (and thus extrapolation beyond the last quantifiable plasma concentration) was only reasonable in a limited number of patients (5 μ g: 1/80; 10 μ g: 31/86; 20 μ g 52/79) due to the low plasma concentrations.

BI will re-analyze the data with respect to $AUC_{\tau,ss}$. However, taking into account the low plasma concentrations, does the Agency agree that the analysis of the effect of covariates on the PK of BI 1744 BS can be based on $AUC_{0-6,ss}$, rather than $AUC_{\tau,ss}$?

Discussion:

The Agency stated that the data should be re-analyzed with respect to AUC_t and $AUC_{0-24hrs}$.

Additional Nonclinical Comments:

- *Any impurities or degradation products exceeding ICH recommended qualification thresholds for an NDA submission as per ICH Guidances Q3AR and Q3BR will need to be qualified for safety.*
- *Provide adequate safety qualification for any identified leachables and extractables.*

Discussion:

FDA questioned whether patients would be able to interchange the canisters since this is the third product using the Respimat device, (b) (4)

(b) (4) BI stated that the device is not intended to be reusable. A lot of effort would be required to remove the canister once inserted. Further, the device and medication canister will be co-packaged and assembled by the patient; (b) (4)

(b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that remained open at the end of the meeting that would require further discussion.

4.0 ACTION ITEMS

There were no action items that were identified during the meeting.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts provided at the meeting.

Drafted by: Green/July 31, 2008
Initialed by: Karimi-Shah/August 11, 2008
Seymour/August 11, 2008
Li/August 6, 2008
Suarez/August 6, 2008
Shea/August 1, 2008
Robison/August 1, 2008
Chowdhury/August 11, 2008
Finalized: Green/August 11, 2008

6
b

Linked Applications

Sponsor Name

Drug Name

IND 76362

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

BI 1744 CL RESPIMAT INHALATION
SPRAY

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

/s/

AKILAH K GREEN

08/11/2008



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

Memorandum of Facsimile Correspondence

Date: August 11, 2008

To: Damon Daulerio, MBA
Manager, Drug Regulatory Affairs

Company: Boehringer Ingelheim

Fax: (203) 791-6262

Phone: (203) 798-4988

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: IND 76,392; re: July 17, 2008, CMC meeting minutes

of Pages: 18

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Thank you.



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: July 17, 2008, 11:00-12:30 PM
Meeting Location: Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
10903 New Hampshire Avenue Building 22,
Conference Room 1315
Silver Spring, Maryland 20993
Application Number: IND 76,362
Product Name: BI 1744 Respimat Inhalation Spray
Received Briefing Package June 18, 2008
Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Requestor: Damon Daulerio, MBA
Associate Director, Drug Regulatory Affairs
Meeting Chair: Ali Al-Hakim, Branch II Chief
Meeting Recorder: Akilah Green, MS, RN
Senior Regulatory Management Officer
Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II

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Banu Karimi-Shah, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products

Akilah Green, M.S., R.N., Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products

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

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Alan Schroeder, Ph.D., Senior Chemistry Reviewer, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

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Xiaohui Mei, Ph.D., Manager, CMC Regulatory Affairs, US

1.0 BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted a Type B meeting request dated May 16, 2008, to discuss the current status of their CMC development program and also to obtain the Division's concurrence and/or feedback on specific CMC development topics which will have a direct influence on the CMC information that will support a future NDA. BI's briefing package was dated June 8, 2008. Upon review of the briefing package, the Division responded to BI's questions via fax on July 15, 2008. The content of that fax is printed below. On July 16, 2008, BI submitted written responses for clarification and the content is included under the appropriate question below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. BI's questions are in ***bold italics***; FDA's original response is in *italics*; BI's response is in normal font; and discussion is in normal font.

2.0 DISCUSSION

Introductory Comment:

Your CMC package relies upon the assumption that the BI 1744 Respimat device will perform in a similar fashion to the Spiriva Respimat device that is currently under review.

(b) (4)

Should

there be observed differences in data during evaluation of your future NDA for BI 1744 Respimat, you will need to provide additional data to justify these differences.

2.1 QUESTION 1

Does FDA have any comments on BI's control strategy, including the list of tests / type of analytical procedures proposed for control of the drug substance? (refer to Section SI.4)

FDA Response to Question 1:

We have the following comments:

- *Include clarity of solution in addition to color in the specification.*
- *(b) (4) cannot be called starting materials. Provide manufacturing and controls information for them in the NDA. (b) (4) should be controlled in the drug substance since it possesses a structural alert moiety (potential genotoxin).*

- *All impurities containing structural alert moieties should be controlled to NMT (b) (4) mcg/TDI or justified by qualification.*
- *Provide data in the NDA to demonstrate that the residual solvents found in the starting materials are not found in the drug substance or that the levels are insignificant from a safety perspective.*
- *Although the approach for the control strategy of the drug substance appears reasonable, the actual evaluation will be done during review of the NDA.*

BI's Request for Discussion:

With respect to the designation of (b) (4) as starting materials, BI would appreciate a discussion of a risk-based approach to designation of starting materials that relies on both data and the company's quality system.

An Ames test has been performed on the (b) (4) compound which was negative. BI would appreciate FDA's confirmation that no additional genotoxicity studies will be required. We have never observed this impurity using the validated HPLC method with QL of (b) (4)%. We propose to control this impurity as an ordinary impurity according to the ICH unspecified impurity limit of NMT (b) (4)%.

Discussion:

FDA commented that (b) (4) are not simple compounds. They are close to the drug substance, but it is not clear if they are commercially available or well-characterized in the literature. If they would be considered starting materials, their manufacture would not be covered under GRMP. In addition, if their source is changed, their impurity profiles may also change, adding the risk of unknown impurities. BI may have a drug substance that is sufficiently pure in the NDA, but if the supplier changes we can not be sure of the quality of the product. Regarding testing for the potential for genotoxicity, this will require future input from the pharmacology/toxicology reviewers. BI may also provide adequate information and data to evaluate whether the (b) (4) in (b) (4) does or doesn't survive the (b) (4)

BI indicated that they would like to have a separate discussion on the starting material once they have completed their studies and submit the data. They plan to do a risk based approach.

2.2 QUESTION 2

Does FDA agree with the proposed primary stability studies including the test parameters for the drug substance? (refer to Section Sl. 7)

FDA Response to Question 2:

See Response to Question 1 (Bullets 1 and 5).

2.3 QUESTION 3

Does FDA agree with the recommended drug product characterization studies proposed to be performed and the concentrations to be used for the studies? (refer to Section P.2.2)

FDA Response to Question 3:

- *Your proposed list of characterization studies is reasonable to support clinical trials, with the exception of the in vitro dose proportionality data. Full evaluation of the supporting data will be done during review of the NDA.*
- *Provide results of in vitro dose proportionality for the two strengths of the product to be used in the clinical trials.*
- *For studies that you indicate as having already demonstrated certain drug product characteristics, provide the relevant data in the NDA or provide a reference or electronic link for ease of review of the supporting data. The adequacy of the approach will be determined during review of the NDA (see introductory comment).*
- *Provide comparative performance data (e.g., APSD and DDU, Plume Geometry) for a range of formulations you have used in your studies/development.*

BI's Request for Discussion:

With respect to FDA's first bullet point, we would like to clarify that the proposed characterization studies are intended to support the future NDA and commercial product, but will not necessarily be completed for support of the Phase 3 clinical program.

With reference to FDA's second bullet point, BI is collecting SCU and APSD data on each of the two strengths of the inhalation solution. However, we would appreciate clarification of FDA's request for *in vitro* proportionality data since the formulation is a solution.

We would like to discuss with FDA the data we will provide in our NDA to support the position that certain characterization studies need not be performed for BI 1744 Respimat®.

Finally we will appreciate FDA's agreement to the proposed concentrations of BI 1744 formulation for the temperature cycling and cleaning studies (per the last part of Question 3).

Discussion:

FDA noted that BI's proposal pertaining to the first bullet point, appears reasonable. Regarding the second bullet point, since BI is using both strengths in the clinical trial, we want to see in vitro data to support the clinical trial results, providing additional proof that device performance is not affected by strength.

BI also presented slides as part of the discussion on question 3 (the slides are attached at the end of the minutes). FDA questioned BI about the how the device works with regard to the locking mechanism and the ability of the patient to receive medication if not operating the device properly, thereby defeating the locking mechanism. BI stated that the patient may empty the device if only doing partial turns (<180°) for the cocking procedure. BI indicated that such misuse of the product would not produce a normal spray. In addition, partial turning does not count as a dose.

FDA stated that we are concerned and want assurance that the performance of the device will not change due to the change in formulation. BI should provide justification and appropriate data to justify the characterization studies which were not performed. We acknowledge that certain characterization studies are obviously not strength dependent; for example, dropping the unit. We do need to see strength-dependent data for Aerodynamic Particle Size Distribution (APSD), delivered dose uniformity, and plume geometry data. The more data provided the better.

FDA concurs with the proposal to test only the (b) (4) strength for the temperature cycling studies, and to test only the (b) (4) strength for development of the cleaning instructions, since in each case, the proposed strength to be used would be expected to be the worst case situation.

2.4 QUESTION 4

Does FDA agree with the (b) (4) strategy for endotoxins, and agree that this approach could obviate the need for final product endotoxin testing? (refer to Section P.2.5)

FDA Response to Question 4:

- *Your proposal is reasonable. However microbiological aspects of the drug product and its manufacturing process are subject to a microbiological review in the NDA.*
- [REDACTED] (b) (4)
- *The Agency recommends considering* [REDACTED] (b) (4)

BI's Request for Discussion:

BI uses Water for Injection, USP for the manufacture [REDACTED] (b) (4)
[REDACTED] Water for Injection, USP is
controlled to less than (b) (4) USP Endotoxin Unit per mL. [REDACTED] (b) (4)

Discussion:

FDA agrees with BI's statement.

2.5 QUESTION 5

Does FDA agree to the proposed test parameters for control of the drug product (e.g. regulatory and alternative procedures for SCU and PSD) and BI's approach on justification of alternative procedures and specifications for the proposed testing parameters? (refer to Section P.5)

FDA Response to Question 5:

- *We note that there is a potential for evaporation during testing of Spray Content Uniformity (SCU) via the gravimetric method. The method should be evaluated under varying environmental conditions or conditions should be tightly controlled in the method to avoid variability. The acceptability of this approach will depend upon evaluation of the supporting data in the NDA.*
- *Your approach of testing APSD appears reasonable. However, this will be determined upon review of the NDA.*
- *Your approach for leachables appears reasonable, but our evaluation will be dependent on the data that you provide in the NDA.*
- *You should provide baseline data to characterize plume geometry.*

BI's Request for Discussion:

BI would appreciate clarification of FDA's comment on characterization of plume geometry.

Discussion:

This should have been included in our discussion of Question 3. FDA commented that the information is needed for future reference. BI can address the issue of the adequacy of their criteria for plume geometry in the NDA. BI noted that they are investigating this with photography of the aerosol plume with cameras fixed 90 degrees apart. BI questioned if it is necessary to perform testing for plume geometry at release. FDA stated that partial blockage of the orifice may be picked up with plume geometry. BI commented that other tests would also pick up orifice blockage.

2.6 QUESTION 6

Does FDA agree to BI's proposal for the introduction of Physician samples and the studies proposed to demonstrate equivalent performance for a 28 actuation device as compared to the 60 actuation commercial product? (refer to Section P.5)

FDA Response to Question 6:

- *We expect that the drug product used in the physician sample will be studied using a normal stability protocol, as with all physician samples, to determine appropriate shelf life.*
- *Performance of the physician sample drug product should be satisfactory through out its shelf life.*
- *In the NDA, clarify your rationale for doing one time studies to investigate the performance of the physician sample drug product. If you plan to place your physician sample on normal stability, the performance of the sample will be evaluated.*

BI's Request for Discussion:

BI would like to clarify that the same shelf life (b) (4) will be proposed for the physician samples as for the commercial product. We would like to discuss the rationale for one time studies on the physician samples. The physician samples are identical to the commercial product with the only difference being a locking mechanism after approximately 28 actuations instead of 60 actuations. One of the one time studies will evaluate the performance parameters for the physician samples at dose 1 and 14 (1 dose = 2 actuations).

Discussion:

FDA asked for clarification of the proposed “one time studies” for the physician samples. FDA stated that batches of the physician sample have to be tested at release and put on stability at regular intervals. BI noted that every batch of physician samples will be released like the commercial batch and questioned whether they had to do formal stability testing. The same batch release testing performed for the commercial batch will be used for the physician sample. Commercial stability batches will be placed on stability (per the stability protocol). FDA stated that we will have to discuss the proposal not to test physician sample batches on stability internally. There may be cGMP issues with this proposal.

2.7 QUESTION 7

Does FDA agree that for the proposed phase 3 clinical trial, BI will investigate all apparently malfunctioning Respimat® inhalers, however, normally functioning inhalers need not be tested based on the consistent good results obtained from previous Spiriva®, Combivent® and Berodual Respimat® clinical studies? (refer to Section P. 5)

FDA Response to Question 7:

- *Your approach is reasonable from a CMC perspective.*
- *It would be to your advantage to test some normally functioning units in the event that malfunctioning units tested different in some manner or frequency from those of other Respimat drug products (Spiriva, Combivent etc.).*
-  (b) (4)

Discussion:

There was no discussion on question 7. BI accepted FDA’s response.

2.8 QUESTION 8

Does FDA agree with BI's proposal that the in-use studies performed during development (chemical stability after insertion of the cartridge) and intermittent use (from Spiriva Respimat Inhalation Spray) are acceptable for the NDA of BI 1744 Respimat Inhalation Spray? (refer to Section P.8)

FDA Response to Question 8:

- *You have shown summary data of the in-use studies for BI 1744 Respimat that seem to indicate that the performance (APSD and Delivered Mass) does not change significantly from initial values.*
- *Ensure that the in-use studies also provide results on degradants, particulate matter, and other stability parameters.*

- *In the NDA, provide your rationale for relying on the in-use studies (submitted in the meeting package) along with the complete listing of parameters used for stability testing including performance data, to support your in-use shelf life.*
- *Ensure that the in-use studies are conducted over the shelf life of the drug product.*
- *The evaluation of the expiration dating period will be a review issue.*

Discussion:

There was no discussion on question 8. BI accepted FDA's response.

2.9 QUESTION 9

Does FDA agree with the proposed primary stability studies for the drug product? (refer to Section P.8)

FDA Response to Question 9:

- *Your approach is reasonable from a CMC perspective.*
- *Include "Clarity of Solution" in the specifications.*
- *Include testing for "Particulate Matter" during the stability testing and also during in-use studies. You have not provided any assurance of the lack of particulate shedding from the container closure system on stability.*
- *Provide the content of edetate sodium and benzalkonium chloride as a percent of target (label claim) in addition to mg/mL.*

BI's Request for Discussion:

BI will perform Particulate Matter testing in the in use studies (per FDA's comments on Question 8) and for release testing. BI has collected data on particulates in the primary stability studies for both Spiriva[®] and Combivent[®] Respimat[®] products demonstrating no change in the number per size range over 12 month long term storage. The container closure system used in Spiriva[®] Respimat[®] and Combivent[®] Respimat[®] is identical to the one used for BI 1744 Respimat[®]. These data can be submitted in the NDA for BI 1744 and we would like to discuss with FDA if this is acceptable in lieu of testing particulates in the primary stability study of BI 1744 Respimat[®].

Discussion:

FDA agrees with BI's response.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that remained open at the end of the meeting that would require further discussion.

4.0 ACTION ITEMS

There were no action items that were identified during the meeting. [Note: FDA agreed to internally discuss the proposal to not test physician samples in a stability program.]

5.0 ATTACHMENTS AND HANDOUTS

Attached is the slide presentation provide by BI at the meeting during the discussion of question 3.

(b) (4)



6 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Drafted: Green/July 30, 2008
Initialed: Al-Hakim/August 4, 2008
Schroeder/August 4, 2008
Finalized: Green/August 11, 2008

Linked Applications

Sponsor Name

Drug Name

IND 76362

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

BI 1744 CL RESPIMAT INHALATION
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AKILAH K GREEN

08/11/2008