

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203975Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203975

SUPPL #

HFD #

Trade Name Anoro Ellipta

Generic Name umeclidinium bromide/vilanterol trifenate

Applicant Name Glaxo Group (d/b/a GSK)

Approval Date, If Known 12/18/2013

### 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 X 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 X 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 X      NO

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?  
YES       NO X

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

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

2. Is this drug product or indication a DESI upgrade?  
YES       NO X

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 X NO

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

NDA# 204275

fluticasone furoate/vilanterol trifenate

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 X 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 X 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 X

(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 X

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:

Trials DB2113361, DB2113373, DB2113360, DB2113374, DB2113359, DB2114417, DB2114418

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 <input type="checkbox"/>	NO X
Investigation #2	YES <input type="checkbox"/>	NO X
Investigation #3	YES <input type="checkbox"/>	NO X
Investigation #4	YES <input type="checkbox"/>	NO X
Investigation #5	YES <input type="checkbox"/>	NO X
Investigation #6	YES <input type="checkbox"/>	NO X
Investigation #7	YES <input type="checkbox"/>	NO X

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 <input type="checkbox"/>	NO X
Investigation #2	YES <input type="checkbox"/>	NO X
Investigation #3	YES <input type="checkbox"/>	NO X
Investigation #4	YES <input type="checkbox"/>	NO X
Investigation #5	YES <input type="checkbox"/>	NO X
Investigation #6	YES <input type="checkbox"/>	NO X
Investigation #7	YES <input type="checkbox"/>	NO X

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

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

Trials DB2113361, DB2113373, DB2113360, DB2113374, DB2113359,  
DB2114417, DB2114418

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

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

Investigation #1		!
		!
IND # 106616	YES X	! NO <input type="checkbox"/>
		! Explain:

Investigation #2  
IND # 106616      YES X      !  
! NO   
! Explain:

Investigation #3  
IND # 106616      YES X      !  
! NO   
! Explain:

Investigation #4  
IND # 106616      YES X      !  
! NO   
! Explain:

Investigation #5  
IND # 106616      YES X      !  
! NO   
! Explain:

Investigation #6  
IND # 106616      YES X      !  
! NO   
! Explain:

Investigation #7  
IND # 106616      YES X      !  
! NO   
! Explain:

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

Investigation #1      !  
!

YES   
Explain:

! NO   
! Explain:

Investigation #2

!  
!

YES   
Explain:

! NO   
! 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 X

If yes, explain:

=====

Name of person completing form: Leila P. Hann  
Title: Regulatory Project Manager  
Date: December xx, 2013

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.  
Title: Division Director

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LEILA P HANN  
12/18/2013

BADRUL A CHOWDHURY  
12/18/2013

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203975 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Anoro Ellipta Established/Proper Name: umeclidinium – vilanterol Dosage Form: powder for inhalation		Applicant: Glaxo Group d/b/a GSK Agent for Applicant (if applicable):
RPM: Leila P. Hamm		Division: DPARP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>December 18, 2013</u></li> </ul>	X AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	X None	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (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).

<p>❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only): 1 and 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC             </p> <p>                 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             </p> <p> <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             </p> <p>                 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             </p> <p>                 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             </p> <p>Comments:</p>	
<p>❖ 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)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p> <input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other             </p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

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

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

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

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

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

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

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

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

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

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

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

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

❖ Copy of this Action Package Checklist <sup>4</sup>	Yes
<b>Officer/Employee List</b>	
❖ 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> )	X Included
Documentation of consent/non-consent by officers/employees	X Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Approval 12/18/2013
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	12/13/2013
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	12/18/2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<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
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	12/13/2013 (as part of PI draft)
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	12/18/2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	12/10/2013
<ul style="list-style-type: none"> <li>❖ Proprietary Name                     <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	03/19/2013 03/19/2013
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 02/05/2013 <input checked="" type="checkbox"/> DMEPA 09/13/2013 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 11/19/2013 <input checked="" type="checkbox"/> ODPD (DDMAC) 11/15/2013 <input checked="" type="checkbox"/> SEALD 12/13/2013, 06/24/2013 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	02/19/2013
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included 12/18/2013
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                     <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)                     <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>08/14/2013</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	X Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	11/06/2013, 11/05/2013, 10/21/2013, 10/18/2013, 10/08/2013, 09/12/2013, 09/06/2013, 08/21/2013, 08/13/2013, 08/08/2013, 08/07/2013, 07/22/2013, 07/18/2013, 06/27/2013, 06/06/2013, 06/06/2013, 05/16/2013, 05/14/2013, 05/10/2013, 04/29/2013, 04/16/2013, 04/11/2013, 03/15/2013, 03/13/2013, 02/28/2013, 02/04/2013, 12/31/2012, 12/06/2013, 12/11/2013,
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 12/06/2013
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	X N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 01/18/2012
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 10/29/2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	09/10/2013
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	Minutes
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/18/2013
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/26/2013
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/09/2013
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	08/15/2013, 02/01/2013
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	X None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ 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> )	Primary review 08/15/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 05/09/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	<input type="checkbox"/> None 08/27/2013
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 09/06/2013, 08/21/2013, 07/18/2013
<b>Clinical Microbiology</b> X None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	X None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	X None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 08/16/2013, 02/01/2013
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	X None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	X None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 08/16/2013, 02/01/2013
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	X None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/13/2013
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 08/11/2013
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/25/2013, 05/23/2013, 04/25/2013, 01/23/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	X None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc 04/09/2013, 04/02/2013
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 04/11/2013 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input 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>	<input type="checkbox"/> None 12/16/2013,
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	X None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/26/2013, 08/20/2013, 08/15/2013, 02/15/2013, 01/30/2013
❖ Microbiology Reviews X 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>	<input type="checkbox"/> Not needed April 03, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	08/20/2013
<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	
X NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: X Acceptable 08/23/2013 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (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 type="checkbox"/> Completed X Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/  
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LEILA P HANN  
12/18/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have labeling comments regarding your December 11, 2013 response to our Information Request of December 06, 2013. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the application.

The labeling changes are shown in the attached marked up label.

In order to facilitate the review of your NDA submission, submit revised labeling incorporating the comments listed above no later than COB, December 12, 2013. If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ December 11, 2013  
Cleared by: S. Limb/ December 11, 2013  
S. Barnes/ December 11, 2013  
Finalized by: L. Hann/ December 11, 2013

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

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/s/  
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LEILA P HANN  
12/11/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following labeling comments regarding your October 28, 2013 response to our Information Request of November 06, 2013. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the application.

1. The orientation of the inhaler device in carton labeling is inconsistent with the orientation shown in Figures E, F, G and I of the Medication Guide. Revise carton labeling to maintain consistency with the Medication Guide.
2. Provide figures with higher resolution if possible. For Figure 3, reconcile the symbols in the figure and the legend.

In order to facilitate the review of your NDA submission, submit revised labeling incorporating the comments listed above no later than COB, December 10, 2013. If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ December 03, 2013  
Cleared by: J. Pippins/ December 06, 2013  
S. Limb/ December 06, 2013  
J. Sohn/ December 04, 2013  
T. Robison/ December 04, 2013  
J. Chen/ December 04, 2013  
P. Ji/ December 04, 2013  
S. Brar/ December 04, 2013  
A. Shaw/ December 04, 2013  
C. Bertha/ December 04, 2013  
P. Peri/ December 04, 2013  
B. Chowdhury/ December 06, 2013  
S. Barnes/ December 06, 2013  
Finalized by: L. Hann/ December 06, 2013

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/s/  
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LEILA P HANN  
12/06/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. The label attached to our November 05, 2013 Information Request was a previous version and the current version has been attached to this document.

We have the following labeling comments regarding your October 28, 2013 response to our Information Requests of October 08, and 21, 2013. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the application.

1. In Section 6.1, revise the description of the patient population for the 6-months trials so that the summary statistics are based on the n=7,433 population as opposed to the (b) (4) population. In Section 14. Provide corresponding information in Section 14.2. In addition, include a sentence that specifies the size of the population used in the efficacy analysis.
2. Provide a source to allow us to confirm the (b) (4) included in the introduction to Section 14.
3. Section 14.1, Figure 3 and Figure 4

Present mean change from baseline in FEV1 not adjusted for placebo (include plot of placebo in the figure).

4. Your comments regarding the "USE IN SPECIFIC POPULATIONS and NONCLINICAL TOXICOLOGY" sections are shown in plain text followed by our comments in italics.

Section 8.1 Pregnancy/Teratogenic effects/Umeclidinium: It is unclear what value for systemic exposure to umeclidinium in human subjects has been used to calculate the overages quoted for rats and rabbits in this section. The original values have been updated in line with those defined in the NDA using a human systemic exposure (AUC) to umeclidinium of 0.3124 ng.h/mL following administration of ANORO ELLIPTA (see Table below).

FDA response

*The value used for human systemic exposure to umeclidinium is 0.3124 ng.h/mL.*

Section 8.1 Pregnancy/Teratogenic effects/Umeclidinium: GSK considers that the reference to the fetal skeletal variation should be removed since this finding is considered unrelated to treatment. In the rat EFD study (see study report WD2007/00764) whilst there were some slightly higher incidences in some frequently occurring skeletal changes in treated groups compared to the concurrent control group, including unossified ventral arch of the 1<sup>st</sup> cervical vertebra, these were considered unrelated to treatment as there were no test-article related dose responses and these parameters can be considered to be variants that can occur regularly in a population with no adverse effects on embryofetal development.

FDA response

*We accept removal of the statement regarding fetal skeletal variation.*

Section 8.3 Nursing Mothers/Umeclidinium: Contrary to the statement in Sentence 2, the excretion of umeclidinium into breast milk has not been examined in animals. Therefore GSK suggests this sentence should be revised as indicated in the revised label.

### FDA response

We do not agree. While the statement, “the excretion of umeclidinium into breast milk has not been examined in animals”, is true, the absence of data based on the lack of studies is not informative in this case, and might not be accurate. In study number 2011N118595, you stated on page 234 that the umeclidinium was “quantifiable in two out of 54 pups from dams dosed with GSK573719, on post natal Day 10”. The pups were most likely exposed to umeclidinium in breast milk, considering that the pups themselves were not dosed, and the half-life of umeclidinium precludes the possibility that this is a result of in utero exposure.

**Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility/Umeclidinium:** The systemic exposures in male or female mice at the respective doses of 295 / 200 mcg/kg/day are similar therefore the exposure multiples have been altered to reflect this (see Table below). The systemic exposure multiple seen at 294 mcg/kg/day in female rats has been changed in line with that quoted in the submission (see Table below).

### FDA response

We do not agree. Your stated values are consistent with the Agency’s values for the carcinogenicity study in male mice (AUC of 8.21 ng.h/mL with a rounded dose ratio of 25, based on the reduced dose of 295 mcg/kg/day), but not for the carcinogenicity study in female mice (study no. 2012N131664). At 26 weeks, females had an exposure of 6.87 ng.h/mL, associated with a dose of 200 mcg/kg/day. Data from 26 weeks is used as this best represents the long-term exposure to the test article. This results in a dose ratio of 22, which is rounded to 20 for labeling. The tables from page 75 of your study report are shown below:

#### **Initial doses: 60 minutes exposure**

Parameter+	Week	Male			Female		
		Estimated Achieved Dose					
		58.6 µg/kg/day	188 µg/kg/day	533 µg/kg/day	20.8 µg/kg/day	63.7 µg/kg/day	200 µg/kg/day
AUC <sub>(0-t)</sub> (ng.h/mL)	4	4.15	1.50	16.0	1.01	7.10	9.65
	26	NC	1.78	8.47	NC	1.51	6.87
C <sub>max</sub> (ng/mL)	4	2.49	1.27	4.14	0.429	1.59	3.16
	26	0.430	0.387	2.75	0.244	0.935	3.64

+Calculated values derived by multiplying the dose normalised data by the overall estimated achieved dose.

NC Not calculated; insufficient data to define AUC

#### **Reduced doses: 30 minutes exposure**

Parameter+	Week	Male		
		Estimated Achieved Dose		
		32.2 µg/kg/day	102 µg/kg/day	295 µg/kg/day
AUC <sub>(0-t)</sub> (ng.h/mL)	4 #	1.53	3.28	8.21
C <sub>max</sub> (ng/mL)	4 #	0.611	0.781	4.03

+Calculated values derived by multiplying the dose normalised data by the overall estimated achieved dose.

# Week 4 at the reduced dose (Study Week 76)

**Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility/Vilanterol:** The systemic exposure multiples achieved in the carcinogenicity studies in rats or mice given vilanterol have been changed in line with those quoted in the submission (see Table below).

<b>Study</b>	<b>Dose</b>	<b>Systemic Exposure (AUC)</b>	<b>Approximate multiple of human</b>
EFD in rats with umeclidinium	278 mcg/kg/day	<sup>a</sup> 16.2 ng.h/mL	52 times
EFD in rabbits with umeclidinium	180 mcg/kg/day	61.4 ng.h/mL	197 times
Carcinogenicity study in mice with umeclidinium	295 mcg/kg/day (M)	8.21 ng.h/mL	25 times
	200 mcg/kg/day (F)	8.26 ng.h/mL	25 times
Female fertility in rats with umeclidinium	294 mcg/kg/day	<sup>a</sup> 16.2 ng.h/mL	52 times
Carcinogenicity study in mice with vilanterol	29500 mcg/kg/day	3590 ng.h/mL	5800 times
	615 mcg/kg/day	135 ng.h/mL	220 times

<b>Study</b>	<b>Dose</b>	<b>Systemic Exposure (AUC)</b>	<b>Approximate multiple of human</b>
Carcinogenicity study in rats with vilanterol	84.4 mcg/kg/day	911 ng.h/mL	15 times
Human umeclidinium	62.5 mcg/day	0.3124 ng.h/mL	-
Human vilanterol	25 mcg/day	0.6147 ng.h/mL	-
a = systemic exposure taken from 13 week inhaled study in rats given similar dose			

**FDA response**

*Regarding carcinogenicity studies conducted with vilanterol, clarify the sources of the systemic exposure (AUC) values shown in your table. The stated systemic exposures (AUC) for vilanterol in your study reports differ from the ones provided in your Response to FDA Request for Information. Specifically, we note differences with the values provided for mice on page 60 of the report (study # 2011N119325), excerpted below. We calculate the average systemic exposure (AUC) of males and females at week 26 to be 4853 ng.h/mL (associated with a dose of 29500 mcg/kg/day), and 128.5 ng.h/mL (associated with a dose of 615 mcg/kg/day). The corresponding rounded dose multiples are 7800 and 210.*

*Study #2011N119325: Table of toxicokinetic parameters for vilanterol in mice (p. 60 of study report)*

Parameter+	Week	Male					
		Estimated Achieved Dose					
		0 µg/kg/day	6.4 µg/kg/day	62 µg/kg/day	615 µg/kg/day	6150 µg/kg/day	29500 µg/kg/day
GW642444M							
AUC <sub>(0-t)</sub>	Week 4	NQ	14.1	46.1	143	880	2428
(ng.h/mL)	Week 26	NQ	3.20	27.3	125	1052	4012
C <sub>max</sub>	Week 4	NQ	2.60	19.2	34.1	305	729
(ng/mL)	Week 26	NQ	0.520	9.05	37.5	418	1127

Parameter+	Week	Female					
		Estimated Achieved Dose					
		0 µg/kg/day	6.4 µg/kg/day	62 µg/kg/day	615 µg/kg/day	6150 µg/kg/day	29500 µg/kg/day
GW642444M							
AUC <sub>(0-t)</sub>	Week 4	NQ	13.1	52.3	139	750	2230
(ng.h/mL)	Week 26	NQ	1.31	13.8	132	996	5694
C <sub>max</sub>	Week 4	NQ	2.67	12.2	34.7	429	605
(ng/mL)	Week 26	NQ	0.736	5.39	76.9	502	1227

In addition, we note a difference for the systemic exposure reported for rats in study # 2010N10925 (table from p. 54 of the study report is excerpted below). The systemic exposure is 11.95 ng.h/mL, based on the average of the AUC values for males and females at Week 26, for the dose of 84.4 mcg/kg/day. The associated dose multiple is rounded to 20 for the label.

Study # 2010N10925: Table of toxicokinetic parameters for vilanterol in rats (p.54 of study report) GW642444

Parameter+	Week	Male				Female			
		Estimated Achieved Dose				Estimated Achieved Dose			
		10.5 µg/kg/day	84.4 µg/kg/day	223 µg/kg/day	657 µg/kg/day	10.5 µg/kg/day	84.4 µg/kg/day	223 µg/kg/day	657 µg/kg/day
AUC <sub>(0-t)</sub>	Week 4	NC	5.63	14.4	36.0	NC	6.94	18.5	38.4
(ng.h/mL)	Week 26	0.839	11.4	19.3	67.5	0.429	12.5	18.9	72.9
C <sub>max</sub>	Week 4	0.302	2.84	7.47	12.5	0.255	3.33	6.73	13.3
(ng/mL)	Week 26	1.04	4.41	6.56	26.8	0.381	5.79	6.89	32.5

+ Calculated values derived by multiplying the dose-normalized data (refer to Appendix 5) by the overall estimated achieved dose

NC: Not calculated due to insufficient data

Regarding your dose multiple of 52 for the rat EFD and rat female fertility studies, we accept it as it is more conservative. We note that you used the extrapolated systemic exposure (AUC) value of 16.2 ng.h/mL, which is the average AUC of males and females at Weeks 4 and Weeks 13 in a 13 week study (study #WD2007/02012). Our calculations were made using AUC values from a 28 day study in rats (study #WD2005/0142); the 28 day dosing duration of this study more closely approximates the dosing in the rat EFD (study # WD2007/00764) and female fertility studies (study # WD2007/00763).

Regarding your dose multiple of 197 for the rabbit EFD study, we acknowledge that it is correct. We have rounded it to 200 for the label.

To facilitate clear communication, we have provided edits to the table you provided in your "Response to FDA Request for Information":

Study	Dose (mcg/kg/day)	Systemic exposure (ng.h/mL)	Approximate dose multiple
EFD in rats with UMEC	278	16.2 (extrapolation from 13 week rat study)	50
EFD in rabbits with UMEC	180	61.4	200
Carcinogenicity in mice with UMEC	M: 295	8.21	25
	F: 200	6.87	20
Female fertility in rats with UMEC	294	16.2 (extrapolation from 13 week rat study)	50
Carcinogenicity in mice with VI	29500	4853	7800
	615	128.5	210
Carcinogenicity in rats with VI	84.4	11.95	20

Additional comment

*We note that you have altered the text under section 12.1 Mechanism of Action. The original text has been restored to remain consistent with the labels for other products in the same Established Pharmaceutical Classification.*

In order to facilitate the review of your NDA submission, submit revised labeling incorporating the comments listed above no later than COB, November 18, 2013. If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ October 29, 2013  
Cleared by: J. Pippins/ November 06, 2013  
S. Limb/ November 06, 2013  
J. Sohn/ November 04, 2013  
T. Robison/ November 04, 2013  
J. Chen/ November 04, 2013  
P. Ji/ November 04, 2013  
S. Brar/ November 04, 2013  
A. Shaw/ November 04, 2013  
C. Bertha/ November 04, 2013  
P. Peri/ November 04, 2013  
S. Barnes/ November 06, 2013  
Finalized by: L. Hann/ November 06, 2013

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

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/s/  
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LEILA P HANN  
11/06/2013



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 21, 2013**

<b>To:</b> Vicki Gunto Global Regulatory Affairs	<b>From:</b> Leila P. Hann
<b>Company:</b> Glaxo Group, d/b/a GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> vicki.x.gunto@gsk.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 203975 (Anoro Ellipta) Information Request

**Total no. of pages including cover:** 41

**Comments:** The attached label includes the edits and comments sent October 08, 2013.

**Document to be mailed:** YES xNO

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

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/s/  
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LEILA P HANN  
10/21/2013



NDA 203975

**METHODS VALIDATION  
MATERIALS RECEIVED**

Glaxo Group Limited  
Attention: Susan M. Holmes, M.S. Director, Global CMC Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709  
FAX: (919) 483-5381

Dear Susan M. Holmes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ANORO ELLIPTA (umeclidinium bromide and vilanterol trifenate) Inhalation Powder and to our September 9, 2013, FAX requesting sample materials for methods validation testing.

We acknowledge receipt on October 17, 2013, 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  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
10/18/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following preliminary labeling comments. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the application.

1. Revise Section 5.6 so as to include results from the MACE and CV AESI analyses. Make appropriate corresponding changes to the Highlights Section.
2. In Section 6.1 after the first introductory paragraph and before the 6-month trial subsection include a description of the overall clinical program, using an approach consistent with the Breo Ellipta label.
3. In Section 6.1, the 6-month trial subsection, describe the patient population in a manner consistent with the Breo Ellipta label.
4. Revise adverse event table and text in Section 6 to show AEs occurring at a rate  $\geq 1\%$  and at a frequency greater than placebo.
5. You may propose the addition of adverse events occurring at a frequency of  $< 1\%$  to Section 6. Provide a rationale for the selection of specific adverse events.
6. Section 14.1, Figure 3:
  - a. Delete (b) (4).
  - b. Present mean change from baseline in FEV1 not adjusted for placebo. The treatment groups represented in the figure should include the following: placebo, and umeclidinium 15.6 mcg, 31.25 mcg, 62.5 mcg, and 125 mcg.
7. In Section 14.1 add a new figure presenting Day 1 data from Trial AC4115321.
8. In Section 14.1, revise figure 4 so that it presents mean change from baseline in FEV1 not adjusted for placebo. The treatment groups represented in the figure should include the following: placebo, and vilanterol 3.0 mcg, 6.25 mcg, 12.5 mcg, 25 mcg, and 50 mcg.
9. In Section 14.2 reorient table 2 so that it is in the same configuration as table 2 in the Breo Ellipta label.
10. In Section 14.2 add a second graph to figure 6 that presents data from Day 1.
11. In Section 14.2, revise the discussion of peak FEV1 results by first defining peak FEV1 and then reporting differences in mean changes relative to placebo at Day 1, in a manner consistent with the Breo Ellipta label.
12. In Section 14.2 after the discussion of peak FEV1 add a description of the results for time to onset, using the same definition for time to onset as defined in the Breo Ellipta label.

13. Revise Section 12.3, record the accumulation for UMEC and VI with repeat dosing of inhaled ANORO ELLIPTA in COPD patients under Absorption section, and calculate the effective half life for UMEC and VI in COPD patients under Elimination section.
  - a. Absorption: Following repeat dosing of inhaled ANORO ELLIPTA, steady state was achieved within xx days with xx fold accumulation.
  - b. Elimination: The effective elimination half-life for....., is xx hours.
14. As the exposure of VI is not consistent in BREO ELLIPTA and ANORO ELLIPTA, the VI PK characteristics (ADME) derived from FF/VI studies are not used for labeling. For VI PK in special population and drug-drug interaction, we consider all studies done with VI, UMEC/VI, and FF/VI, and use the worst case scenario (largest observed change in AUC or Cmax) in the labeling. Therefore, the renal impairment paragraph under section 12.3 is revised as “Vilanterol systemic exposure (AUC(0-24)) was 56% higher in subjects with severe renal impairment compared with healthy subjects.” Please revise the figure 1 to reflect this change.
15. Revise Section 16 as follows:

ANORO ELLIPTA is supplied as a disposable light grey and red plastic inhaler containing a foil blister strip with 30 blisters. The inhaler is packaged within a moisture protective foil tray with a desiccant and a peelable lid (NDC 0173-0869-10).

ANORO ELLIPTA is also supplied in an institutional pack of a disposable light grey and red plastic inhaler containing a foil blister strip with 7 blisters. The inhaler is packaged within a moisture protective foil tray with a desiccant and a peelable lid (NDC 0173-0869-06).

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

Discard ANORO ELLIPTA 6 weeks after opening the foil tray or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart
16. Add a statement regarding cardiovascular safety in Section 17 corresponding to the information in the Warnings and Precautions.

In order to facilitate the review of your NDA submission, submit revised labeling incorporating the comments list above no later than COB, October 14, 2013. If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ October 03, 2013  
Cleared by: J. Pippins/ October 07, 2013  
S. Limb/ October 07, 2013  
J. Sohn/ October 07, 2013  
T. Robison/ October 07, 2013  
J. Chen/ October 07, 2013  
P. Ji/ October 07, 2013  
S. Brar/ October 07, 2013  
A. Shaw/ October 07, 2013  
C. Bertha/ October 07, 2013  
P. Peri/ October 07, 2013  
S. Barnes/ October 07, 2013  
Finalized by: L. Hann/ October 08, 2013

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/s/  
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LEILA P HANN  
10/08/2013

5 Pages Have Been Withheld As Duplicative. The Material For the Pulmonary-Allergy Drugs Advisory Committee Meeting for September 10, 2013 Can Be Found at FDA.gov



NDA 203975

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

GlaxoSmithKline  
Attention: Susan M. Holmes, M.S.  
Director, Global CMC Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709  
FAX: (919) 483-5381

Dear Susan Holmes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ANORO ELLIPTA (umeclidinium bromide and vilanterol trifenate) inhalation powder.

We will be performing additional methods validation studies on ANORO ELLIPTA (umeclidinium bromide and vilanterol trifenate) inhalation powder, as described in NDA 203975.

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

**Method, current version**

Determination of Umeclidinium and Vilanterol Identity and Uniformity of Emitted Dose in Umeclidinium/Vilanterol Inhalation Powder by HPLC

**Samples and Reference Standards**

- 200 mg umeclidinium bromide drug substance
- 200 mg umeclidinium bromide reference standard
- 100 mg umeclidinium bromide test mix/resolution check reference material
- 60 blisters strips (30-blister strip)
- 60 blisters strips (7-blister strip)

**Equipment to be returned**



(b) (4)

**Equipment not to be returned**

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials. Please note new address shown below.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
645 S Newstead Ave  
St. Louis, MO 63110

Please notify me upon receipt of this letter. 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, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
09/06/2013

## Rivera, Luz E (CDER)

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**From:** Rivera, Luz E (CDER)  
**Sent:** Thursday, August 08, 2013 4:12 PM  
**To:** 'susan.m.holmes@gsk.com'  
**Subject:** NDA 203975

Good afternoon Ms. Holmes,

We are reviewing your NDA 203975 and request additional information to continue our evaluation.

- Specify the time considered for the zero time for the stability studies. It should be the date on which the active ingredients are blended with the excipients.

Please submit the information requested by email to me ([Luz.E.Rivera@fda.hhs.gov](mailto:Luz.E.Rivera@fda.hhs.gov)) and officially submit to the application.

Please acknowledge the receipt of this request

Thank you,  
Luz E Rivera, Psy.D.  
LCDR, US Public Health Service  
Regulatory Health Project Manager  
FDA/CDER/OPS/ ONDQA  
Division of New Drug Quality Assessment III  
[luz.e.rivera@fda.hhs.gov](mailto:luz.e.rivera@fda.hhs.gov)  
301 796 4013

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/s/  
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LUZ E RIVERA  
08/08/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following requests for information:

1. Provide a table that describes the ECG and Holter findings leading to patient withdrawal for the primary efficacy trials (DB2113361, DB2113373, DB2113360, DB2113374) and for the long-term safety trial (DB2113359).
2. Modify the following tables from your submission dated April 26, 2013:

**A. Table 1. Summary of Exposure (Primary Efficacy Trials, Long-Term Safety Trials, Other Trials, FF/VI Trials)**

Modify Table 1 by adding a column for UMEC/VI 500 mcg/25 mcg. Confirm that the numbers presented in this table include data from Investigator 040688 in Trial DB2113360.

	Placebo	UMEC/V I 62.5/25	UMEC/V I 125/25	UMEC/ VI 500/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N	N
Primary Efficacy Trials	555	842	832		418	629	1034	423
Long-Term Safety Trial	109	N/A	226		N/A	227	N/A	N/A
Other Trials	788	282	272		252	325	241	91
FF/VI Trials	412	N/A	N/A		N/A	N/A	1226	N/A
Overall Total	1864	1124	1330		670	1181	2501	514

Note: N=Number of patients in the ITT population for all trials except for AC4115408, AC4113073, and AC4115321, for which N represents the number of patients in the mITT population; patients in crossover trials are counted once under each treatment received

**B. Table 2. Summary of On-Treatment or Post-Treatment Fatal Adverse Events (Primary Efficacy Trials, Long-Term Safety Trial, Other Trials, FF/VI Trials)**

Modify Table 2 by adding a column for UMEC/VI 500 mcg/25 mcg, adding in values for N, and confirming the percentages. Confirm that the N you provide includes data from Investigator 040688 in Trial DB2113360.

	Placebo	UMEC/V I 62.5/25	UMEC/V I 125/25	UMEC/V I 500/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials	2* (<1)	5 (<1)	1 (<1)		3 (<1)	2 (<1)	6 (<1)	2 (<1)
Long-Term Safety Trial	1 (<1)	--	0		--	4 (2)	--	--
Other Trials#								

	0	1 (<1)	0		0	1 (<1)	0	0
FF/VI Trials		--	--		--	--		--
	2 (<1)	--	--		--	--	16 (1)	--
Overall Total								
	5 (<1)	6 (<1)	1 (<1)		3 (<1)	7 (<1)	22 (<1)	2 (<1)

Note: N=Number of patients in the ITT population for all trials except for AC4115408, AC4113073, and AC4115321, for which N represents the number of patients in the mITT population; patients in crossover trials are counted once under each treatment received; some trials included additional treatment arms to those shown here

Note: n(%) = number (percentage) of deaths for each trial grouping

\*A post-treatment death reported after trial closure for a patient in the placebo group of Trial DB2113373 is not included in this count

\*A death reported for the VI 6.25 mcg treatment group of Trial B2C111045 is not included in this table

**C. Table 3. Summary of On-Treatment Non-Fatal Serious Adverse Events (Primary Efficacy Trials, Long-Term Safety Trial, Other Trials, FF/VI Trials)**

Modify Table 3 by adding a column for UMEC/VI 500 mcg/25 mcg, adding in values for N, and confirming the percentages. Confirm that the N you provide includes data from Investigator 040688 in Trial DB2113360.

	Placebo	UMEC/V I 62.5/25	UMEC/V I 125/25	UMEC/V I 500/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials								
	24 (4)	47 (6)	43 (5)		27 (6)	35 (6)	54 (5)	20 (5)
Long-Term Safety Trial		--			--		--	--
	7 (6)	--	14 (6)		--	15 (7)	--	--
Other Trials								
	11 (1)	6 (2)	9 (3)		2 (<1)	6 (2)	9 (4)	0
FF/VI Trials		--	--		--	--		--
	20 (5)	--	--		--	--	14 7 (12 )	--
Overall Total								
	62 (3)	53 (5)	66 (5)		29 (4)	56 (5)	21 0 (8)	20 (4)

Note: N=Number of patients in the ITT population for all trials except for AC4115408, AC4113073, and AC4115321, for which N represents the number of patients in the mITT population; patients in crossover trials are counted once under each treatment received; some trials included additional treatment arms to those shown here

Note: n(%) = number (percentage) of deaths for each trial grouping  
Note: This table includes on-treatment events

3. Confirm that that the ITT population presented in the following tables and figures include data from Investigator 040688 in Trial DB2113360:
  - A. Submission dated April 26, 2013
    - i. Table 88A
    - ii. Table 4
  - B. ISS submitted December 18, 2012
    - i. Table 138
4. Clarify whether or not the ITT population presented in the following tables and figures (all from the ISE submitted on December 18, 2012) exclude data from Investigator 040688 in Trial DB2113360:
  - A. Table 84
  - B. Figure 18
  - C. Table 3.36
  - D. Table 3.35
  - E. Table 3.144
  - F. Table 3.145
  - G. Table 3.41
  - H. Table 3.40
  - I. Table 3.43
  - J. Table 3.42

In order to facilitate the review of your NDA submission, provide the requested information no later than COB, Wednesday, August 07, 2013. If answers to questions 2-4 are available sooner, please send them.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ August 07, 2013  
Cleared by: J. Pippins/ August 07, 2013  
S. Limb/ August 07, 2013  
S. Barnes/ August 07, 2013  
Finalized by: L. Hann/ August 07, 2013

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/s/  
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LEILA P HANN  
08/07/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following requests for information:

We noticed that you used PBPK modeling to predict the combined effect of CYP2D6 genetic polymorphism and P-gp Transporter Inhibition on systemic exposure of UMEC. You should submit PBPK modeling and simulation report and model files for further review.

The report should include:

1. A summary of model input parameters. This can be compiled in the table format with parameter name, parameter values (mean and/or variability), source of the parameter values and assumptions being made. Generally, software version should also be provided. In addition, any modification of the default values of the parameter input of a particular version should be declared and justified.
2. Steps of model development in a logical manner. The process starts with model building using *in silico*, *in vitro* and *in vivo* data, which is followed by model verification/modification (simulating known situations) and model prediction (simulating unknown situations). Keep in mind that comparison of simulations with observed plasma exposure data is often not sufficient for developing confidence in PBPK models. Biological/physiological plausibility of the model should be evaluated and discussed during model building and verification. Parameters with less certainty yet likely more influence on the model prediction should be tested using sensitivity analysis. All statistical methods used should be clearly stated.
3. The details of experimental design of the simulations. Such details should include, but are not limited to, demographics of virtual population(s), number of trials, number of subjects in each trial, dosing scheme, and sampling scheme.
4. Specifically, simulated urinary excretion of UMEC should be provided. Your simulation of unknown situations should consider the intended route of administration (e.g. inhalation) and dose of UMEC. Submit model files used to generate the final PBPK simulations (compound and population files, such as .cmp for both UMEC and verapamil, .lbr, and .wks). The model files should be executable using SimCYP software Version 12.2. These files may be submitted via CD.

In order to facilitate the review of your NDA submission, provide the requested information no later than COB, Thursday, August 01, 2013.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ July 22, 2013  
Cleared by: P. Ji/ July 22, 2013  
P. Zhao/ July 22, 2013  
S. Brar/ July 22, 2013  
S. Barnes/ July 22, 2013  
Finalized by: L. Hann/ July 22, 2013

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/s/  
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LEILA P HANN  
07/22/2013



NDA 203975

**METHODS VALIDATION  
MATERIALS RECEIVED**

Glaxo Group Limited  
Attention: Susan M. Holmes, M.S. Director, Global CMC Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709  
FAX: (919) 483-5381

Dear Susan M. Holmes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ANORO ELLIPTA (umeclidinium bromide and vilanterol trifenate) Inhalation Powder and to our May 22, 2013, e-mail requesting sample materials for methods validation testing.

We acknowledge receipt on June 21, 2013, 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  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
06/27/2013



NDA 203975

**MID-CYCLE COMMUNICATION**

GlaxoSmithKline  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D., R.A.C.  
Global Regulatory Affairs

Dear Dr. Gunto:

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

We also refer to the teleconference between representatives of your firm and the FDA on May 14, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** May 14, 2013 from 3:00 PM – 4:00 PM

**Application Number:** NDA 203975  
**Product Name:** Anoro Ellipta  
**Indication:** COPD  
**Applicant Name:** GlaxoSmithKline, Ltd.

**Meeting Chair:** Susan Limb  
**Meeting Recorder:** Leila P. Hann

**FDA ATTENDEES**

Sara Stradley, (Acting) Associate Director of Regulatory Affairs, Office of Drug Evaluation II  
Gregory Levin, Ph.D., Biometrics Reviewer, Division of Biometrics II (DBII)  
Joan Buenconsejo, Ph.D., Team Leader, DBII  
Jennifer R. Pippins, M.D., M.P.H., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Susan Limb, M.D., Clinical Team Leader, DPARP  
Leila P. Hann, Regulatory Project Manager, DPARP

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (4), Independent Assessor

**APPLICANT ATTENDEES**

Mary Sides, Global Regulatory Affairs  
Patrick Wire, Senior Director, Global Regulatory Affairs  
Elaine Jones, Medicine Development Project Leader  
Jean Brooks, Statistician  
Stephanie Harris, Clinical  
Chris Kalberg, Clinical  
Dennis Kelleher, Clinical  
Bik Chopra, Safety Assessment

**1.0 INTRODUCTION**

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 or may not be able to consider your response before we take an action on your application during this review cycle.

**2.0 SIGNIFICANT ISSUES**  
Clinical and Biometrics

1. Insufficient support for the [REDACTED] (b) (4)

[REDACTED] (b) (4)

2. Insufficient support for [REDACTED] (b) (4)

[REDACTED] (b) (4)

**3.0 INFORMATION REQUESTS**

No information requests were made by the Division during the meeting.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

No major safety concerns were noted by the Division during the meeting.

**5.0 ADVISORY COMMITTEE MEETING**

The Division stated that the AC meeting will be held on September 10, 2013. Likely topics for discussion are the characterization of dose response and dose selection. Additional topics that may arise include the ethics of placebo controlled trials and the racial distribution of the populations evaluated. The Applicant asked if the Division would continue to consider all the

available data if the higher dose is withdrawn. The Division affirmed that that all data would be considered in the evaluation of the proposed product.

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The Division noted that the late cycle meeting will be held on August 22, 2013.

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/s/  
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LEILA P HANN  
06/06/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following requests for information:

- Regarding the study “GSK573719A: INHALED EMBRYO-FETAL DEVELOPMENT STUDY IN RATS” (study no. WD2007/00764), we noted a possible dose-dependent effect on brain hemorrhage. Specifically, hemorrhages of the cerebellum were noted at the MD and HD (4/22 litters MD, 3/19 litters HD), and those within the cerebral hemisphere were noted only at the HD (2/19 litters).

In addition, if all brain hemorrhages are pooled, regardless of location, there remains a potential dose-dependent effect (control 2/22 litters, LD 2/20 litters, MD 4/22 litters, HD 5/19 litters). Our interpretation of the data, based on the provided summary table (p. 54 of study report) and individual line listings is provided below:

Group	Fetuses			
	1	2	3	4
Number examined	136	123	135	113
<b>Brain hemorrhages</b>				
between cerebral hemisphere and mid brain	2	3	-	1
cerebellum	-	-	4 (fetus #7, 8, 4, 6)	3 (fetus #6, 10, 1)
within cerebral hemisphere	-	-	-	2 (fetus #3, 9)
3rd ventricle	-	-	1 (fetus #8)	-
all locations	2	3	4	5

Group	Litters			
	1	2	3	4
Number examined	22	20	22	19
<b>Brain hemorrhages</b>				
between cerebral hemisphere and mid brain	2	2	-	1
cerebellum	-	-	4 (dam #47, 52, 56, 64)	3 (dam #78, 84, 85)
within cerebral hemisphere	-	-	-	2 (dam #79, 87)
3rd ventricle	-	-	1 (dam #52)	-
all locations	2	2	4	5

Your analysis of the data in the study report, however, includes the following statement only combining the cerebellum, and between the cerebral hemisphere and mid-brain. It is not clear why only these 2 regions were combined, and why the incidences in your following text are not consistent with the table on p. 54 of your study report.

Excerpt from p. 29 of the study report, with the two combined locations underlined:

“The incidence of subdural haemorrhages on the cerebellum and between the cerebral hemisphere and mid-brain was slightly higher in all treated groups, when compared with the concurrent control group. A total of 4 fetuses from 3 litters, 4 fetuses from 4 litters or 4 fetuses from 4 litters showed this abnormality at doses of 0.0317, 0.0969 or 0.278 mg/kg/day respectively compared to 2 fetuses from 2 litters in the control group. In the absence of a dose response and in light of the low numbers affected, this is considered unrelated to treatment.”

Excerpt from table on p. 54 of the study report:

**Fetal examinations - minor visceral abnormalities - group incidences**

Group	Fetuses				Litters					
	1	2	3	4	1	2	3	4		
Number examined	136	123	135	113	22	20	22	19		
Number affected	2	4	8	7	2	3	7	6		
<b>Visceral abnormalities</b>										
Brain	dilated 3 <sup>rd</sup> ventricle		-	-	1	-	-	1	-	
Eye(s)	variation in lens size		-	1	-	-	1	-	-	
<b>Haemorrhages</b>										
Brain	between cerebral hemisphere and mid brain		2	3	-	1	2	2	-	1
	cerebellum		-	-	4	3	-	-	4	3
	within cerebral hemisphere		-	-	-	2	-	-	-	2
	3 <sup>rd</sup> ventricle		-	-	1	-	-	1	-	-
Eye/surrounding tissue	aqueous humour		-	-	2	-	-	2	-	-
	vitreous humour		-	-	1	1	-	-	1	1

Note: Individual fetuses/litters may occur in more than one category.

- Provide your assessment of these findings.
- In your statement from p. 29, it is not clear why a “total of 4 fetuses from 3 litters” showed hemorrhage (cerebellum and between the cerebral hemisphere and mid-brain) at the dose of 0.0318 mg/kg/day. Your provided table appears to show 3 fetuses from 2 litters with hemorrhage at the reference locations and dose. Please clarify your statement.
- Provide historical control data for these findings. Ensure that it contains historical control data from animals of similar age in studies of similar duration, from the same testing laboratory, stating the dates the study(ies) were initiated, the incidence of the relevant findings in each study, and an overall mean incidence and range from all studies.

In order to facilitate the review of your NDA submission, provide the requested information no later than 12:00 pm (noon), Tuesday, June 11, 2013.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ June 05, 2013  
Cleared by: J. Sohn/ June 05, 2013  
              T. Robison/ June 05, 2013  
              S. Barnes/ June 05, 2013  
Finalized by: L. Hann/ June 06, 2013

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/s/  
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LEILA P HANN  
06/06/2013



NDA 203975

**INFORMATION REQUEST**

Glaxo Group Limited d/b/a GlaxoSmithKline.  
Attention: Susan Holmes, M.S.  
Director, CMC Regulatory Affairs  
Five Moore Drive, P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Ms. Holmes:

Please refer to your New Drug Application (NDA) submitted December 18, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ANORO™ ELLIPTA™ (umeclidinium and vilanterol) Inhaled Powder.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by May 23, 2013) in order to continue our evaluation of your NDA.

1. The specifications should include references to test methods (See ICH Topic Q 6 A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances). Provide a complete copy of each test method used in your release and stability testing, and clearly identify each method with a unique method ID and version number.
2. The umeclidinium bromide (UB) and VI (Vilanterol) Identity and Content Uniformity of Emitted Dose by HPLC method describes two doses that are collected from each of 10 inhalers, along with information to outline the typical doses collected. Such a description may be confusing and not easy for an analyst new to the method to follow. Therefore we recommend that you include a table to illustrate which doses are collected in the procedure as part of the method. An example of such a table is shown below for your consideration.

	Dose No																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Inhaler 1	*			*																										
Inhaler 2							*				*																			
Inhaler 3													*			*														
Inhaler 4																				*			*							
Inhaler 5																												*		*
Inhaler 6	*			*																										
Inhaler 7							*				*																			
Inhaler 8													*			*														
Inhaler 9														*						*			*							
Inhaler 10																												*		*

3. Your drug product specifications table includes a (b) (4) (as noted in footnote L). In Section P.5.6 (Justification of Specifications) you state (3.2.P.5.6.2.8.1):

“Tolerance intervals have been calculated using the batches contained within the database described in Section 1.”

The database described in Section 1 includes, in addition to the clinical batches used in Phase III studies, “Primary stability batches including data obtained following storage at the long term storage condition (25°C/60% RH) for up to 12 months within secondary packaging.”

In order for long-term storage stability data and in-use stability data to be used to support the calculation of the tolerance interval you must provide an analysis of the test results for all of the samples tested, including an analysis to demonstrate the sources of variability e.g. within batch, between batch, storage time, and in-use storage time.

Alternatively you can amend the drug product specifications table to remove the (b) (4) (b) (4) testing acceptance criterion.

4. Provide the following information regarding your Near Infrared (NIR) method used for (b) (4) —

(b) (4)

5. Based on the submitted data we have determined that the (b) (4) as measured by (b) (4) may be underestimated by (b) (4) due to (b) (4) by the test sample in a (b) (4) during the test time frame. Therefore we recommend that the (b) (4) acceptance limit in the drug product specification table be changed from (b) (4)
6. Regarding the Dose Content Uniformity and Dose Content Uniformity through Life test:

- a. Prespecify the alternative sample sizes (b) (4)  
[Redacted]
  - b. Your sampling approach should be such that the probability of a given batch passing will not change with an increase in sample size. (b) (4)  
[Redacted]
7. Provide in vitro dose delivery data demonstrating the effect of a mis-use scenario where (b) (4)  
[Redacted]
  8. In the container closure section (P.7.), the method for determination of particulates only quantifies particulates (b) (4)  
[Redacted]
  9. The Agency notes that you have indicated in section P.3.3 that regulatory action for minor post approval changes to processing parameters (PP) would be taken in conformance with regulations and guidance. We would like to remind you that, if a change to a PP has a substantial or moderate potential impact to product quality (e.g., as might occur in the case of changes beyond ranges previously studied), you should conform to the requirements for regulatory notification as described in CFR 314.70 (b) or (c).

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

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/  
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PRASAD PERI  
05/16/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following comments regarding the clinical pharmacology related sections in the proposed labeling:

1. Revise sections 7 and 12 with respect to both format and content based on the approved BREO ELLIPTA labeling.
2. The VI exposure is higher in the UMEC/VI program as compared to FF/VI program, therefore, the applicability of relevant PK data from FF/VI program to this product should be carefully thought through. Please assess the VI related statements in the labeling and make revisions accordingly. For example, (b) (4)  
 should not be used in the NDA203975 labeling.
3. Figure 1 and 2 are duplicate plots for UMEC. Please use  $AUC_{\tau}$  (after multiple dose) or  $AUC_{inf}$  (after single dose) to generate forest plots. In addition, poor CYP2D6 metabolizer study cannot be used as a CYP2D6 inhibition study for UMEC.

Please submit revised labeling incorporating the above comments. Additional labeling comments will be provided as our review continues.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ May 14, 2013  
Cleared by: S. Doddapaneni/ May 13, 2013  
S. Barnes/ May 14, 2013  
Finalized by: L. Hann/ May 14, 2013

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/s/  
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LEILA P HANN  
05/14/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following requests for information:

1. Regarding the study “GSK573719A: Subcutaneous Embryo-Fetal Development Study in Rabbits” (study no. CD2010/00253/00), please provide the following:
  - a. The section on dosing solution analysis references study no. WD2010/00081/00. Please state the location of this study in your NDA submission, or provide a copy of the study.
  - b. Historical control data are referenced in analyzing observed malformations and variations. Provide a copy of the referenced historical control document “GSK Reproductive Toxicology Historical Control Compendium”. Ensure that it contains historical control data from animals of similar age in studies of similar duration, from the same testing laboratory, stating the dates the study(ies) were initiated, the incidence of the relevant findings in each study, and an overall mean incidence and range from all studies. Separate data based upon the sex of the animals in each study.
2. In the study report titled “GSK573719A AND GW642444M: A 4-WEEK COMBINATION INHALATION TOXICITY STUDY IN DOGS” (study no. 2010N109790), some statements are made in the text that do not appear to be reflected in the Clinical Observation Summary Tables (Tables 1 and 2). For example, the study report states, “Swelling of the neck was seen...in both animals given 220/234 GW642444/GSK573719 µg/kg/day (Group 4). The finding was first observed during dosing and was still present immediately post dose in affected animals.”

Provide corrected summary tables, or clarify where findings are represented in the summary tables and how they correspond to the text.

In order to facilitate the review of your NDA submission, provide the requested information no later than 12:00 pm (noon), Friday, May 17, 2013. If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ May 09, 2013  
Cleared by: J. Sohn/ May 09, 2013  
T. Robison/ May 09, 2013  
M. Jordan Garner/ May 09, 2013  
Finalized by: L. Hann/ May 10, 2013

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/s/  
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LEILA P HANN  
05/10/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following request for information:

1. In the summary of clinical pharmacology studies, we note that the exposure of VI is 2-3 fold higher after administration of UMEC/VI compared to FF/VI in both healthy subjects and COPD patients, as summarized in the following table. Please clarify and address these findings.

Study	Subjects	Treatment	Days of dosing	Geometric mean	
				AUC <sub>(0-24)</sub> (pg*h/ml)	C <sub>max</sub> (pg/ml)
DB2114635	Healthy	UMEC/VI 125/25 mcg	10	429	340
DB2113361, DB2113373	COPD	UMEC/VI 125/25 mcg, VI 25 mcg	Phase III, steady state	614.7	127.9
HZA102936, HZA105548, HZA113970, HZA111789	Healthy	FF/VI 200/25 mcg VI 25mcg	7	213.9	130.5
HZC111348, HCZ110946, HZC112206, HZC112207	COPD	FF/VI 50/25, 100/25, 200/25, 400/25 mcg	Phase III, steady state	265.7	43.2

Source: Table 11, Table 26, Table 78 and Table 79, 2.7.2, clin pharm summary

In order to facilitate the review of your NDA submission, provide the requested information no later than 12:00 pm (noon), Tuesday, May 07, 2013.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ April 29, 2013  
Cleared by: J. Chen/ April 29, 2013  
S. Doddapaneni/ April 29, 2013  
S. Barnes/ April 29, 2013  
Finalized by: L. Hann/ April 29, 2013

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/s/  
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LEILA P HANN  
04/29/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following clinical comments and/or request(s) for information:

- 1) Clarify if the adjudication of non-fatal SAEs presented in Tables 104 and 105 of the ISS includes only on-treatment events, post-treatment events, or both on-treatment and post-treatment events.
- 2) Revise Tables 88 and 90 of the ISS so that SOC is included, along with PT.
- 3) Provide the tables outlined below, noting the following:
  - The term “Primary Efficacy Trials” refers to trials DB2113361, DB2113373, DB2113360, and DB2113374
  - The term “Long-Term Safety Trial” refers to trial DB2113359
  - The term “Other Trials” refers to trials DB2114417, DB2114418, AC4115408, AC4113589, B2C111045, DB2113120, AC4113073, and AC4115321
  - The term “FF/VI Trials” refers to trials HZC102871, HZC102970, HZC112206, HZC112207

**Table 1. Summary of Exposure**

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Primary Efficacy Trials							
Long-Term Safety Trial							
Other Trials							
FF/VI Trials							
Overall Total							

**Table 2. Deaths (on-treatment or post-treatment)**

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials							
Long-Term Safety Trial							
Other Trials							
FF/VI Trials							
Overall Total							

**Table 3. Non-fatal SAEs (on-treatment)**

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials							
Long-Term Safety Trial							
Other Trials							
FF/VI Trials							
Overall Total							

**Table 4. Non-fatal SAEs (on-treatment) by SOC and PT, Primary Efficacy Trials**

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any non-fatal SAE							
SOC							
PT							
PT							
PT, etc.							
SOC							
PT							
PT							
PT, etc.							

**Table 5. Non-fatal SAEs (on-treatment) by SOC and PT, Long-term Safety Trial**

	Placebo	UMEC/VI 125/25	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
Any non-fatal SAE			
SOC			
PT			
PT			
PT, etc.			
SOC			
PT			
PT			
PT, etc.			

In order to facilitate the review of your NDA submission, provide the requested information no later than 12:00 pm (noon), Tuesday, April 30, 2013.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ April 15, 2013  
Cleared by: J. Pippins/ April 15, 2013  
S. Limb/ April 15, 2013  
S. Barnes/ April 15, 2013  
Finalized by: L. Hann/ April 16, 2013

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/s/  
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LEILA P HANN  
04/16/2013

## **Executive CAC**

Date of Meeting: April 9, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Karen Davis Bruno, Ph.D., DMEP, Alternate Member  
Tim Robison, Ph.D., DPARP, Team Leader  
Jane J. Sohn, Ph.D., DPARP, Presenting Reviewer

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

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

NDA # 203975

Drug Name: Umeclidinium-Vilanterol

Sponsor: GlaxoSmithKline

### Background:

The sponsor is developing umeclidinium (GSK573719A), a muscarinic acetylcholine receptor (mAChR) antagonist, as part of a combination product with vilanterol, a long acting beta-2 agonist (LABA) for the treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD). Results from 2-year carcinogenicity studies in mice and rats administered inhaled GSK573719A were submitted by the sponsor. Carcinogenicity studies with vilanterol alone were previously reviewed under NDA 204275, which is for vilanterol in combination with fluticasone furoate, a corticosteroid.

### Mouse Carcinogenicity Study

The sponsor conducted a 2-year bioassay in CD-1 mice (75/sex/group) with GSK573719A by inhalation (nose only). Initial doses were based on MTD determined in a 13 week toxicology study (ECAC minutes 6/3/09). Female mice received nominal doses of 0 (1% magnesium stearate in lactose), 20, 60, and 200 mcg/kg/day throughout the study (60 minute exposures). Males initially received nominal doses of 0 (1% magnesium stearate in lactose), 60, 200, and 600 mcg/kg/day (60 minute exposures). Doses were decreased at Week 67 for males only to 0, 30, 100, and 300 mcg/kg/day (30 minute exposures), based on loss of body weight in dosed males, with concurrence from the ECAC (minutes 2/18/11).

There were no treatment-related neoplastic findings based on the lack of statistical significance for both trend and pair-wise statistical analysis. Histiocytic sarcomas (whole body) were noted in females dosed with the test article (control 1, LD 1, MD 5, HD 5), but the findings were not statistically significant by trend analysis and pair-wise analysis, and were within historical control data (1.7 to 11.7%) for females, based on data

submitted by the sponsor. Additional historical control data from Crl: CD1 mice from (b) (4) (updated March 2010) showed that 1.67 to 11.67% of animals were diagnosed with histiocytic sarcomas in their facility.

#### Rat Carcinogenicity Study

The sponsor conducted a 2-year bioassay in Crl: CD (Sprague Dawley) rats (65/sex/group) with GSK573719A by inhalation (nose only). Initial doses were based on the MTD determined from a 13-week inhalation toxicology study (ECAC minutes 6/3/09). The recommended doses were 0 (1% magnesium stearate in lactose), 30, 100, and 300 mcg/kg/day (60 minute exposures). Effective from Week 73, doses were reduced to target doses of 15, 50, and 150 mcg/kg/day (30 minute exposures) with ECAC concurrence (minutes 2/18/11). Based on data up to Week 70, the sponsor noted decreases in body weight gains and proposed lower doses. The nonclinical reviewer determined that data up to 70 weeks showed minimal effects on survival and absolute body weights, but that reduced doses would provide large multiples over systemic exposure achieved with the MRHD.

There were no treatment-related neoplastic findings based on the lack of statistical significance. Neoplastic findings observed with increased incidences in test article-treated groups were basal cell tumors in females (skin; control/LD/MD 0, HD 3) and lymphomas in males (whole body; control 0, LD 1, MD 0, HD 3), but these did not achieve statistical significance for trend and pair-wise comparison, and were within historical control values. For basal cell tumors of the skin, the sponsor provided historical control data (0.0 to 4.6%) that covered the incidence of 3/65 (4.6%) in the reviewed study. For lymphomas, historical control data (0.91 to 6.00%) for Crl: CD rats diagnosed with lymphocytic lymphomas (whole body) from (b) (4) covered the incidence of 3/65 (4.6%) in the reviewed study.

#### **Executive CAC Recommendations and Conclusions:**

##### **Rat:**

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

##### **Mouse:**

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

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

cc:\

/Division File, DPARP  
/Timothy Robison, DPARP  
/Jane J. Sohn, DPARP  
/Leila P. Hann, DPARP  
/ASeifried, OND IO

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/s/  
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ADELE S SEIFRIED  
04/11/2013

DAVID JACOBSON KRAM  
04/11/2013



NDA 203975

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

GlaxoSmithKline  
Attention: Susan M. Holmes, M.S.  
Director, Global CMC Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709  
FAX: (919) 483-5381

Dear Susan Holmes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ANORO ELLIPTA (umeclidinium bromide and vilanterol trifenate) inhalation powder.

We will be performing methods validation studies on ANORO ELLIPTA (umeclidinium bromide and vilanterol trifenate) inhalation powder, as described in NDA 203975.

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

**Method, current version**

- Determination of Umeclidinium bromide content in Umeclidinium bromide by HPLC
- Determination of drug-related impurities content in Umeclidinium bromide by HPLC
- Determination of Umeclidinium blister content uniformity in Umeclidinium/Vilanterol inhalation powder by HPLC
- Umeclidinium drug-related impurities content by blister by HPLC

**Samples and Reference Standards**

- 200 mg umeclidinium bromide drug substance
- 200 mg umeclidinium bromide reference standard
- 100 mg umeclidinium bromide test mix/resolution check reference material
- 20 blisters strips (30-blister strip)
- 20 blisters strips (7-blister strip)

**Equipment**

[Redacted area] (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: MVP Sample Custodian  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email ([michael.trehy@fda.hhs.gov](mailto:michael.trehy@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
04/11/2013



NDA 203975

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Glaxo Group Limited, England  
c/o GlaxoSmithKline  
Five Moore Drive  
Research Triangle Park, NC 27709

ATTENTION: Mary Sides  
Director, Global Regulatory Affairs

Dear Ms. Sides:

Please refer to your New Drug Application (NDA) dated December 18, 2012, received December 18, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Umeclidinium and Vilanterol Powder for Oral Inhalation, 62.5 mcg/25 mcg and 125 mcg/25 mcg.

We also refer to your December 19, 2012, correspondence, received December 19, 2012, requesting review of your proposed proprietary name, Anoro Ellipta. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your December 19, 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, Leila Hann, at (301) 796-3367.

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/  
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CAROL A HOLQUIST  
03/19/2013

Your NDA 203975 submitted on December 18, 2012 is currently under review. We have the following nonclinical comments and/or request(s) for information:

- 1) Regarding your 104-week carcinogenicity study with inhaled GSK573719A conducted in Crl:CD(SD) rats (study BVR1357/R28862), we note that bilateral opacity on the posterior position of the lens was increased in a dose-dependent manner in males (control 2/39, LD 5/46, MD 5/43, HD 8/48). Severity was not reported for this finding, therefore it is unknown if severity increases with dose. Provide severity data, if it is available.

In addition, provide all available historical control data from Crl:CD(SD) rats of similar age in studies of similar duration, from the same testing laboratory, stating the dates the study(ies) were initiated, the incidence of the relevant findings in each study, and an overall mean incidence and range from all studies. Separate data based upon the sex of the animals in each study. Published scientific references may also be referenced. A toxicological assessment of this finding should also be provided.

In order to facilitate the review of your NDA submission, provide the requested information no later than 12:00 pm (noon), Monday, March 26, 2013.

If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted by: J. Sohn/ March 15, 2013  
Cleared by: T. Robison/ March 15, 2013  
S. Barnes/ March 15, 2013  
Finalized by: L. Hann/ March 15, 2013

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/s/  
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LEILA P HANN  
03/15/2013

## Liu, Youbang

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**From:** Liu, Youbang  
**Sent:** Wednesday, March 13, 2013 8:54 AM  
**To:** 'Susan Holmes'  
**Cc:** Hann, Leila  
**Subject:** Information Request for NDA 203975

NDA 203975

Glaxo Group Limited d/b/a GlaxoSmithKline.  
Attention: Susan Holmes, M.S.  
Director, CMC Regulatory Affairs  
Five Moore Drive, P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Ms. Holmes

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 203975 dated December 18, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

- Provide the complete Specifications (Test, Analytical procedure, and Acceptance Criteria) for both of the drug substance umeclidinium bromide and vilanterol trifenate in the NDA. Provide complete copies of the analytical procedures and methods validation reports for each of the procedures. State whether these are identical to the information in the DMF 26339 for umeclidinium bromide and DMF 25906 for vilanterol trifenate.

Please acknowledge the receipt of this email and the time line of the amendment submission.

Kind Regards,

*Youbang Liu, Ph.D.*  
Regulatory Project Manager  
Division III, ONDQA/OPS/CDER/FDA  
10903 New Hampshire Avenue  
Building 21, Room 2649  
Silver Spring, MD 20993  
Phone: (301) 796-1926

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/s/  
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YOUBANG LIU  
03/13/2013



NDA 203975

**FILING COMMUNICATION**

GlaxoSmithKline  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Mary V. Sides  
Director, Global Regulatory Affairs

Dear Ms. Sides:

Please refer to your New Drug Application (NDA) dated December 18, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Anoro Ellipta (umeclidinium bromide-vilanterol) inhalation powder at 65.5/25 µg and 125/25 µg.

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**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is December 18, 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, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 27, 2013. In addition, the planned date for our internal mid-cycle review meeting is May 10, 2013. We are currently planning to hold an advisory committee meeting to discuss this application.

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

1. We note that your rationale for proposing [REDACTED] (b) (4)

nature. The adequacy of the data to support approval of both doses will be a review issue.

2. We note your proposal to include results from [REDACTED] (b) (4)  
[REDACTED]
3. The inclusion of results [REDACTED] (b) (4) in the product label is potentially problematic. While the results are of clinical interest, we question whether these results are necessary to support a regulatory action and believe these results may be more appropriately described in the literature as they pertain to the practice of medicine.
4. [REDACTED] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. 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 request that you submit the following information:

1. Provide 4 samples of the drug product.

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

1. Each contraindication should be bulleted when there is more than one contraindication.
2. The following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”
3. In Adverse Reactions, the following verbatim statement should precede the presentation of adverse reactions: “*Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.*”
4. Section 17, “See FDA-approved patient labeling (Medication Guide and Instructions for Use)” should not be in italics.

We request that you resubmit labeling that addresses these issues by March 19, 2013. 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.

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), 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 Leila P. Hann, Regulatory Project Manager, at (301) 796-3367.

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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BADRUL A CHOWDHURY  
02/28/2013

Your application is currently under review and we have the following information request:

In assessing the potential impact of missing data on the reliability of results, we do not find the sensitivity analyses you provided to be sufficient. All four multiple imputation approaches (missing at random, copy differences from control, last mean carried forward, and last mean -25 mL/year carried forward) more or less impute post-dropout data by preserving the mean treatment effect that was observed prior to discontinuation. This may not be appropriate, since any positive effects of the bronchodilator on FEV<sub>1</sub> prior to dropout likely declined or went completely away once the patient stopped taking the therapy. We request that you provide results based on additional sensitivity model(s) that do not preserve the pre-dropout treatment effect after patients stop taking the therapy. For example, one approach of interest would multiply impute missing data *in all treatment arms* using the missing at random model *in the control arm*. In other words, the analysis would be based on a multiple imputation model that copies *actual outcomes* from control rather than copying *differences in outcomes* from control. The control arm should be placebo in studies 361 and 373, and tiotropium in studies 360 and 374.

If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 04, 2013  
Cleared by: S. Barnes/ February 04, 2013  
G. Levin/ February 04, 2013  
J. Buenconsejo/ February 04, 2013  
Finalized by: L. Hann/ February 04, 2013

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/s/  
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LEILA P HANN  
02/04/2013



NDA 203975

**NDA ACKNOWLEDGMENT**

GlaxoSmithKline  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Mary V. Sides  
Director, Global Regulatory Affairs

Dear Ms. Sides:

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: Anoro-Ellipta (umeclidinium bromide-vilanterol)  
Inhalation powder, 62.5/25 µg and 125/25 µg

Date of Application: December 18, 2012

Date of Receipt: December 18, 2012

Our Reference Number: NDA 203975

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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LEILA P HANN  
12/31/2012



IND 106616

**MEETING MINUTES**

GlaxoSmithKline  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709

Attention: Mary Sides  
Director

Dear Ms. Sides:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK573719/GW642444.

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2012. The purpose of the meeting was to discuss the progress of the Phase 3 program and discuss the content and format of the non-clinical pharmacology/toxicology, clinical pharmacology, and the clinical efficacy and safety of the planned NDA for COPD.

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

If you have any questions, call me at (301) 796-4006.

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:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** January 18, 2012, 3:00 P.M. to 4:30 P.M.  
**Meeting Location:** White Oak Campus Bldg 22 Room 1311  
**Application Number:** IND 106616  
**Product Name:** GSK573719/GW642444 (vilanterol)  
**Indication:** COPD  
**Sponsor/Applicant Name:** GSK  
**Meeting Chair:** Badrul Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Eunice Chung-Davies, Pharm.D.

**FDA ATTENDEES**

Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Jennifer R. Pippins, M.D., MPH., Clinical Reviewer, DPARP  
Susan Limb, M.D., Clinical Team Leader, DPARP  
Timothy Robison, Ph.D., Nonclinical Team Leader, DPARP  
Feng Zhou, M.S., Statistics Reviewer, Division of Biometrics II  
Joan Buenconsejo, Ph.D., Acting Statistics Team Leader, Division of Biometrics II  
Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II  
Suresh Doddapaneni, Ph.D., Deputy Director, Division of Clinical Pharmacology II  
Teresa McMillan, Pharm.D., Safety Evaluator, Division of Medication Errors Prevention and Analysis  
Zachary Oleszcuk, Pharm.D., Safety Team Leader, Division of Medication Errors Prevention and Analysis  
Eunice Chung-Davies, Pharm.D., Sr. Regulatory Management Officer, DPARP

**SPONSOR ATTENDEES**

Darrell Baker, Senior Vice President, Respiratory Medicine Development Center  
Jean Brooks, Manager, Respiratory Medicine Development Center Statistics  
Sally Bruce, Director, Global Regulatory Affairs  
Susan Fayinka, Director, Medicines and Process Delivery  
Mauri Fitzgerald, Vice President, Global Regulatory Affairs  
Alison Hofmann, MD, Director, Respiratory Medicine Development Center

Meeting Minutes  
PreNDA Meeting

Division of Pulmonary, Allergy, and Rheumatology Products

C. Elaine Jones, Ph.D., Vice President, Medicine Development Leader  
Mary Sides, Director, Global Regulatory Affairs

## 1. BACKGROUND

Ms. Mary Sides of GlaxoSmithKline requested a type B PreNDA meeting with the Division of Pulmonary, Allergy, and Rheumatology Products to discuss the progress of their Phase III program and discuss the content and format of the nonclinical pharmacology/toxicology, clinical pharmacology, and clinical efficacy and safety of the planned NDA for COPD. The meeting was granted on August 10, 2011. Preliminary comments (*in italics*) to GSK's December 12, 2011, briefing package questions (*in bold italics*) were sent to the GSK on January 12, 2012. Any discussion from the January 18, 2012, face to face meeting are in normal font below.

## 2. DISCUSSION

### *Introductory Comment:*

- *We remind you of the discussion that took place at the EOP2 meeting held on October 29, 2010, at which time we commented on the absence of a clear dose-response based on the phase 2b data, and recommended the evaluation of lower doses, and we note your decision to carry forward two doses of the GSK573719/VI combination (62.5/25 mcg and 125/25 mcg) in the phase 3 program. Without the results of these trials, which are currently ongoing, we are unable to confirm that the appropriate dose and dosing interval have been selected.*
- *The clinical development program for GSK573719/VI must include a full characterization of both of the monotherapy components, including replicate evidence of the efficacy of each of the monotherapies. In addition, substantial evidence of the efficacy and safety of GSK573719/VI as compared to each of the monotherapy components must be provided. Typically, this evidence would come from replicate trials with statistically significant, positive results.*
- *We have concerns regarding your plan to submit the NDA for the GSK573719/VI combination product prior to that for the GSK571319. Typically, the submission of a New Drug Application for a combination product NDA follows the full development of the monotherapies comprising the combination. As we expect that GSK571319 will have been fully characterized for the purposes of the combination program, we recommend that you submit the NDA for GSK571319 first. We also note that the appropriateness of marketing a combination product without component monotherapies available will be a review issue. A relevant patient population for the proposed combination product must be identified.*
- *We recommend that you provide justification for the choice of a placebo-control design in planned studies in the NDA submission.*

### Discussion:

The sponsor wished to clarify the Agency's rationale behind the comment, "the appropriateness of the marketing of a combination product without the component monotherapies will be a review issue." FDA stated that this will not be a filing issue. However, whether it is an approval issue will depend on the data. Generally, combination products are intended for patients who do not achieve sufficient benefit from a single

ingredient product. If the single ingredient product is not available, then the intended target population is not immediately apparent.

The sponsor stated that they anticipate that their combination product will be used in the moderate to severe COPD population. They anticipate that trials will demonstrate that use of the combination product in this population results in substantial improvement of airflow that is superior to that obtained with the single ingredient product.

FDA commented that there may be a patient population for whom treatment with the long-acting muscarinic antagonist (LAMA) alone would be suitable. The sponsor stated that they intend to market the LAMA monocomponent. While the LAMA monocomponent may be appropriate for patients with milder COPD, the sponsor anticipates its use primarily as an add-on therapy to existing therapeutics, such as inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) combination products.

FDA noted the current availability of tiotropium as a LAMA monotherapy. If the clinical program were to provide substantial evidence of benefit for the GSK571319/vilanterol combination over an existing LAMA monotherapy like tiotropium, those results would be useful for identifying an appropriate patient population for the combination. GSK agreed to providing a rationale for the target patient population in the NDA application for FDA's review.

#### ***CMC Question from Cover Letter***

***GSK will request a CMC specific pre-NDA meeting in mid-2012 to discuss CMC aspects of the NDA. GSK would appreciate earlier feedback on a general CMC content question to initiate document preparation as soon as possible. As the Division are aware, two product strengths are currently being studied in Phase 3 clinical trials and the product strength of the to be marketed product has yet to be determined. Therefore, GSK proposes to include full CMC information covering both product strengths in the NDA as these data have contributed significantly to the development and scientific understanding of the product. Does the Agency agree with this approach?***

#### ***Division Response:***

*The NDA should include all information for the drug product strength(s)/formulation(s) proposed for marketing. Other strengths/formulations used for clinical studies should be adequately described along with appropriate data, in the P2 (pharmaceutical development) section of the NDA. Provide a table to correlate the relevant information (e.g., strength, batch number, clinical trial number, etc.) for all batches of drug product used in clinical studies.*

No discussion occurred.

#### ***Section 5: Regulatory***

- 1. Does the Division agree with the proposal for submission of the NDA and 120-Day Safety Update for completed and ongoing studies with GSK573719/VI, including***

**provision of relevant data with fluticasone furoate/VI Inhalation Powder or VI Inhalation Powder as a monotherapy for (b) (4) COPD to obtain a first-cycle approval (described in Section 5)?**

Division Response:

*Adequate safety data to support the application is expected at the time of NDA filing. While the proposed content of the NDA submission and 120-day safety update appear reasonable, we note that we will not be able to conduct a substantive review of information submitted at the 120-day safety update; as a result, this additional data has limited capacity to support a regulatory action.*

No discussion occurred.

### **Section 6: Clinical Pharmacology and Biopharmaceutics**

- 2. Clinical pharmacology studies examining the bronchodilator properties of GSK573719 and VI in subjects with COPD will be summarised in m.2.7.2. Other pharmacological effects unrelated to efficacy (including heart rate, blood pressure, QTc interval, plasma glucose, and blood potassium) will be discussed in section m.2.7.4. Is this acceptable to the Division?**

Division Response:

*Your proposal appears reasonable.*

No discussion occurred.

- 3. Does the Division agree that, if the results of study AC4115487 (see Section 3.2.1) provide sufficient evidence that the small pharmacodynamic effect observed between (b) (4) (b) (4) the two-strip configurations of the 62.5mcg and 125mcg GSK573719 monotherapy products is of minimal clinical significance and dose ranging data from the phase IIb studies (AC4113073, AC4113589 and AC4115321) are supportive of the intended marketed dose, that no additional studies are required (b) (4) (b) (4)**

Division Response:

*As noted previously in the EOP2 meeting, the (b) (4) GSK573719 when (b) (4) vs. a double-strip device fell in the range of (b) (4) which is considered substantial from a CMC perspective and clouds the interpretability of results from the factorial-design trials. We recommended reformulating the monocomparators to be used in the factorial-design trials (b) (4) providing data demonstrating that there is no relevant clinical difference. If you believe that results from study AC4115487 provide that data, submit those data in the NDA. The adequacy of the data will depend on how these data fit into the overall clinical program. For example, data from AC4115487 may be sufficient to bridge between the dose-ranging trials conducted with the double-strip device and the GSK573719 (b) (4) device intended for marketing. On the*

*other hand, providing sufficient justification for use of (b) (4) device in the pivotal factorial design poses a higher hurdle.*

Discussion:

FDA asked for clarification of the formulation of the monotherapies used in the pivotal trials, namely, whether or not the monotherapies were (b) (4) double-strip devices. The sponsor replied that they were (b) (4). FDA stated that this may be problematic with regards to the interpretation of data from the factorial-design clinical trials, noting that it is critical that the combination product provide the same amount of drug product as the monotherapies. FDA noted that the difference in (b) (4) for GSK571319 exceeded the upper limit (b) (4) that previously has been considered to be an acceptable magnitude of difference.

The sponsor stated that their single dose study shows no clinical difference so they believe that their magnitude of difference is potentially reasonable despite the fact that it is outside the Agency's upper limit (b) (4). The sponsor stated that their clinical program was based on FDA's prior advice against the use of unnecessary excipients in the monoproducts as well as FDA's recommendation for a single, PK bridging trial. Given that the (b) (4) is higher for the monotherapy, the sponsor also noted that difference is to their disadvantage for the purposes of demonstrating superiority of the combination over the monotherapies.

FDA acknowledged that the Agency's current position is a departure from advice previously given. The change in position stems from an effort to maintain consistency across other development programs which have encountered similar issues. FDA requested that the sponsor provide justification for the use (b) (4) device in the factorial design trials in the NDA application. The acceptability of the justification will be a review issue.

- 4. Does the Division agree that the results of the ADME study (AC4112014, described in Section 3.2.2.1) support GSK's proposal to conduct hepatic and renal impairment studies and that product labeling with respect to hepatic and renal impairment will be commensurate with those findings?**

Division Response:

*You are proposing to submit (a) PK results of GSK573719 Inhalation Powder, GSK573719/VI Inhalation Powder, and fluticasone furoate/VI in subjects with severe renal impairment and (b) in subjects with moderate hepatic impairment for GSK573719 Inhalation Powder and GSK573719/VI Inhalation Powder and in subjects with mild, moderate, and severe hepatic impairment for fluticasone furoate/VI. You will assume no PK interaction between VI and fluticasone for VI PK conclusions. Further, due to technical difficulties, you are proposing to assess in vitro protein binding of GSK573719 and VI from sourced donors with severe renal impairment in a separate assessment and not assess protein binding of VI in moderate hepatic impairment subjects. Although, it is possible that you may be able to come up with appropriate labeling in renal and hepatic impairment subjects, in light of the several variables involved in this approach and with no data in hand at this time, we are unable to agree.*

5. ***Where necessary to more completely describe the clinical pharmacology of VI, data may be used from early phase clinical pharmacology studies in healthy volunteers, COPD patients and asthma patients, using a variety of VI formulations and devices and from studies with fluticasone furoate /VI studies in which only fluticasone furoate /VI treatment arms were tested to describe the pharmacological effects of VI unrelated to efficacy, including heart rate, blood pressure, QTc interval, plasma glucose, and blood potassium. Use of data from these early VI studies and studies with fluticasone /VI studies will be specifically noted in m2.7.2. All clinical pharmacology studies containing VI will be included in m5. Is this acceptable to the Division?***

Division Response:

*Yes. However, since you are proposing to use data from early studies that used a variety of VI formulations and devices and from studies with fluticasone furoate /VI treatment arms, we recommend that you provide clear explanation in the NDA as to how data from each of these studies is pertinent to the final product.*

No discussion occurred.

**Section 7: Summary of Clinical Efficacy**

6. ***Does the Division agree with GSK's plans for the integration / pooling of the efficacy data including study grouping, subgroups, and country groupings and studies to be used to support dose and dosing interval justification for GSK573719 and VI which are to be discussed in the Integrated Summary of Efficacy and 2.7.3?***

Division Response:

*Yes, we agree.*

No discussion occurred.

7. ***Specific to the integration of patient level efficacy data, GSK plans to integrate efficacy data from the four primary efficacy studies conducted for GSK573719/VI Inhalation Powder (DB2113361/ DB2113373 and DB2113360/DB2113374) and not to integrate efficacy data from other studies conducted as part of the GSK573719/VI Inhalation Powder, GSK573719 Inhalation Powder, and fluticasone furoate/VI Inhalation Powder (i.e. data from VI arms) development programs as described in Section 3.1 and Section 7. Does the Division agree with this approach?***

Division Response:

*While the presentation of pooled efficacy results is at your discretion, we will rely primarily on the efficacy results from the individual trials to support a regulatory action.*

No discussion occurred.

**Section 8: Summary of Clinical Safety**

8. ***Does the Division agree with GSK's plans for the integration / pooling of the safety data including study grouping, subgroups and country groupings, as discussed in Section 3.1 and Section 8?***

Division Response:

*Yes, we agree.*

No discussion occurred.

9. ***GSK intends to provide subject level integration for summaries of overall AEs, SAEs, Fatal AEs (deaths), AEs Leading to Withdrawal, Most Frequent AEs and AEs of Special Interest from 13 studies conducted for GSK573719/VI Inhalation Powder, GSK573719 Inhalation Powder, and fluticasone furoate/VI Inhalation Powder that were at least 4 weeks in duration and included a treatment arm for GSK573719/VI Inhalation Powder, GSK573719 Inhalation Powder, and/or VI Inhalation Powder as described in Section 3.1 and Section 8. Does the Division agree with the proposed approach?***

Division Response:

*Yes, we agree.*

No discussion occurred.

10. ***GSK intends to limit subject level integration of shifts for clinical laboratory tests, ECG and vital sign measurements to five Phase III studies for GSK573719/VI Inhalation Powder (DB2113361, DB2113373, DB2113360, DB2113374, and DB2113359) as described in Section 3.1 and Section 8. Subject level integration of AEs will also be done for these studies. Does the Division agree with the proposed approach?***

Division Response:

*Yes, we agree.*

No discussion occurred.

11. ***GSK intends to limit subgroup analyses of AEs to five Phase III studies for GSK573719/VI Inhalation Powder (DB2113361, DB2113373, DB2113360, DB2113374, and DB2113359) as described in Section 8. Does the Division agree with the proposed approach?***

Division Response:

*Yes, we agree.*

No discussion occurred.

12. ***GSK does not intend to describe safety data collected with VI Inhalation Powder in subjects with asthma, obtained as part of the fluticasone furoate/VI Inhalation Powder program. Does the Division agree with the proposed approach?***

Division Response:

*No, we do not agree. Include a high-level summary of the safety findings from the asthma program, including deaths, non-fatal SAEs, AEs leading to discontinuation, and common AEs.*

Discussion:

The sponsor stated that they would include a summary of the safety of vilanterol in asthma within the Integrated Summary of Safety (ISS), including data on deaths, nonfatal SAEs, AEs, etc., but that they were not planning to include individual study reports. FDA responded that this appears to be reasonable.

**13. Does the Division agree with the proposed list of adverse events of special interest as described in Section 8?**

Division Response:

*In addition to the events you have listed, include an evaluation of the following: pneumonia, events consistent with anticholinergic syndrome (in addition to urinary retention), and intestinal obstruction.*

Discussion:

The sponsor stated that they will add pneumonia and intestinal obstruction as FDA suggested. However, the sponsor wished to obtain clarification regarding the inclusion of events consistent with anticholinergic syndrome. FDA responded that we are interested in all anticholinergic symptoms (e.g., dry mouth, constipation, blurry vision, palpitations, tachycardia), and referred the sponsor to the descriptions included in the labels of other products. The sponsor asked whether FDA is also interested in somnolence for LAMAs. FDA responded affirmatively.

**14. GSK is proposing not to integrate AE data from GSK573719/VI, GSK573719, and relevant fluticasone furoate/VI clinical pharmacology studies with the later phase studies. Where appropriate, AEs from special population, electrocardiographic, and drug-drug interaction clinical pharmacology studies will be summarized in the relevant sections of the ISS. Listings of AEs of special interest and SAEs from all the clinical pharmacology studies will be provided in the NDA submission. Does the Division agree with this proposed approach?**

Division Response:

*Yes, we agree.*

No discussion occurred.

**15. GSK intends to include AE reports from the literature as part of the ISS and Summary of Clinical Safety. Does the Division agree that this reporting should be limited to nonclinical data and to orally inhaled long-acting muscarinic antagonist and long-acting beta-agonist clinical data in COPD?**

Division Response:

*Provide clarification regarding your plans to submit AE reports from the literature. You propose inclusion of nonclinical data, which is typically not included in the ISS and Summary of Clinical Safety.*

No discussion occurred.

- 16. GSK are proposing to provide narratives for all deaths and non-fatal SAEs and for subjects withdrawn from treatment due to an AE for all completed studies. For ongoing studies at the time of submission narratives would not be provided. Does the Division agree with the proposal for provision of narratives in this NDA?**

Division Response:

*No, we do not agree. In addition to what you propose, also provide narratives for all deaths and non-fatal SAEs for ongoing studies.*

No discussion occurred.

- 17. Some of the planned IIIb studies for GSK573719/VI Inhalation Powder and fluticasone furoate/VI Inhalation Powder (that include a VI alone treatment arm) will be ongoing at the time of the submission of the NDA for GSK573719/VI Inhalation Powder. GSK proposes to include synopses, but not to include data from these ongoing studies in the NDA. Any data for ongoing studies of fluticasone furoate/VI Inhalation Powder (that include a VI alone treatment arm) will be by cross-referenced to the relevant INDs (077855 and 074696). Does the Division agree with this approach?**

Division Response:

*Yes, we agree.*

No discussion occurred.

- 18. Does the Division agree with GSK's plan for adjudication of SAEs from the Phase IIIa studies conducted for GSK573719/VI Inhalation Powder as described in Section 8?**

Division Response:

*In general, we agree. The events chosen for adjudication should be both important and relevant to a LAMA and/or LABA. We recommend you refer to the adjudications conducted previously for other LAMA and LABA COPD products, the details of which are available in the public domain.*

Discussion:

The sponsor stated that they plan to adjudicate for deaths, hospitalizations, and intubations and asked whether that would be appropriate. FDA responded affirmatively and added that

an analysis of major adverse cardiac events (MACE) and respiratory-related adverse events such as those conducted in other COPD programs would also be appropriate.

**19. Does the Division agree that the size of the safety database for GSK573719/VI Inhalation Powder as described in Section 4 will provide an adequate safety database to support the NDA for GSK573719/VI Inhalation Powder?**

Division Response:

*While the size of the safety database ultimately depends on the nature of the safety data observed, the current proposal appears to be reasonable.*

No discussion occurred.

**Section 9: Statistics**

**20. GSK submitted the Summary Document Analysis Plans (SDAP) for the ISE and ISS for Division comment in November 2011. Does the Division agree with the proposed statistical methodology as outlined in the SDAPs and the associated briefing document?**

Division Response:

*Yes, we agree. In addition, add the annual rate of exacerbation in "Other endpoints" for the integrated analyses (section 3.2 in SDAP for the ISE).*

Discussion:

The sponsor stated that with regard to the annual rates, the majority of their patients withdraw due to exacerbations. However, they do allow for them to stay for the safety analyses. The sponsor asked if they could keep to their original plan to evaluate time to first exacerbation. FDA responded affirmatively.

**21. Subjects who had previously received GSK573719, VI, GSK573719/VI or fluticasone furoate/VI were not allowed to participate in the phase III program for GSK573719/VI, except for the exercise studies DB2114417 and DB2114418 of cross-over design. The number of subjects participating in more than one study is expected to be small, and may be counted twice in these integrated summaries. Does the Division agree with this approach?**

Division Response:

*Yes, we agree. Include a variable (flag) to indicate these patients in the pooled and individual study datasets. Of note, we generally use the results from the individual studies to support any claims in the label. Pooled analyses are not usually very helpful in this regard with the exception of required analyses by subpopulation, like age, sex and race; etc.*

No discussion occurred.

**Section 11: Non-Clinical Development**

- 22. A comprehensive package of nonclinical studies on GSK573719 and GW642444 (as individual NCE's) in accordance with the ICH M3 (R) Guidelines will be available at the time of file. In addition, combination toxicology studies on GSK573719/GW642444 up to one months' duration (rat and dog) and up to 3 months' duration in one species (dog) have been completed. Does the Division agree that no further nonclinical studies are required to support the registration of GSK573719/GW642444 Inhalation Powder?**

Division Response:

We agree that no further nonclinical studies are required to support the registration of GSK573719/GW642444 Inhalation Powder.

For the NDA, provide structures of impurities and intermediates of the drug substance and drug product. Refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R2)] and degradants in drug products [ICH Q3B(R2)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Impurities or intermediates that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" (December 2008) for assessment of impurities to support clinical studies for an IND and NDA.

No discussion occurred.

- 23. Future clinical studies are planned to**

(b) (4)

(b) (4)

(b) (4)

Division Response:

No discussion occurred.

### **Section 13: Labeling**

- 24. GSK intend to describe the Phase IIb dose ranging data for GSK573719 and VI in the Clinical Trials section of the application along with data from the Phase III development program. This includes discussion of the Phase III studies which include a tiotropium arm as these studies are pivotal to the approval of the application (Studies DB2113360 and DB2113374). Does the Division have any comment on the inclusion of the dose-ranging data for GSK573719 and VI and relevant comparator data for tiotropium?**

Division Response:

While it is premature to comment on labeling at this time, we find your proposal to include dose-ranging data in the Clinical Trials section to be reasonable in principle. We note, however, that information regarding an active comparator is typically not included in a product label unless necessary to support the proposed use in the intended patient population. Provide adequate justification in the NDA if you choose to include comparator data for tiotropium in the proposed product label.

No discussion occurred.

- 25. GSK propose to include in the Clinical Trials section a discussion of the results from the primary and secondary endpoints, as well as selected "Other" endpoints such as supplemental (b) (4) provided statistical significance is achieved. Does the Division have any comment the inclusion of this data?**

Division Response:

It is premature to comment on labeling at this time. Propose the inclusion of information you assess to be necessary to adequately inform the user.

No discussion occurred.

- 26. GSK intend to submit the proposed proprietary name in 1Q 2012. Does the Division have any preliminary comments on the proposed process for review of proprietary names according to the February 2010 guidance for evaluation of proprietary names and when would feedback be expected?**

Division Response:

Submit the proposed name in accordance with Guidance on Complete Submission.  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> For an

*IND, the expected completion date is 180 days from the date of complete submission. If the proposed proprietary name is submitted under the NDA, the expected completion date is 90 days from the date of complete submission.*

*The proposed proprietary name will also be reviewed 90 days prior to the expected date of approval of the NDA.*

*We recommend submitting your name as early as possible in the IND phase once your dose has been established.*

No discussion occurred.

### **Section 13: Risk Evaluation and Mitigation Strategy**

- 27. Does the Division agree with the proposal to submit a proposed risk evaluation and mitigation strategy (REMS) that is in-line with the current REMS requirements for LABA containing COPD medications?**

Division Response:

*It is premature to comment on REMS at this time, prior to an evaluation of the safety profile of the product.*

No discussion occurred.

### **Section 16: GSK573719 Monotherapy**

- 28. GSK is planning to submit the NDA for GSK573719 Inhalation Powder subsequent to the GSK573719/VI Inhalation Powder NDA submission. GSK intends to include in the GSK573719 Inhalation Powder NDA data from replicate studies evaluating the efficacy and safety of the addition of (b) (4) (b) (4) in patients with COPD to obtain information for health care professionals should the products be used together. A description of these studies is provided in Section 15 and Appendix 8. Does the Division agree that the conduct of replicate clinical trials evaluating the safety and efficacy of (b) (4) (b) (4) alone will support inclusion of data from these studies in the Clinical Trials section of the prescribing information for GSK573719 Inhalation Powder?**

Division Response:

*Refer to the Introductory Comment regarding the sequence of NDA submission. Regarding the inclusion of data from trials comparing (b) (4) (b) (4) we believe that such information falls under the practice of medicine and inclusion of data in the label is unlikely to be warranted.*

Discussion:

(b) (4)

FDA stated that the Agency will be reluctant to place this type of information in the product label, as the decision to put a (b) (4) falls under the practice of medicine. Trials evaluating (b) (4) may be more appropriate for publication in the medical literature.

The sponsor asked whether there is any way to obtain feedback on the robustness of the proposed trials, as these trials may be used to support promotional materials. FDA responded that the sponsor may submit the protocols for comment. The sponsor also asked if FDA's position would be different if (b) (4) to which FDA replied in the negative.

*ADDITIONAL COMMENTS:*

- 1. Provide all raw data sets, as well as analysis data sets (including all efficacy and safety variables) used to generate the results presented in your study reports. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.*
- 2. Include all SAS programs used for creating analysis dataset from submitted raw datasets and all SAS programs used for efficacy and main safety analyses. In addition, provide a document that explains what each SAS programs are used for.*
- 3. Provide all analysis data sets and SAS programs used to generate the results in the ISE and ISS reports.*

*For more information, refer to*

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

### **3.0 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.

### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

N/A

### **5.0 ACTION ITEMS**

N/A

### **6.0 ATTACHMENTS AND HANDOUTS**

N/A

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EUNICE H CHUNG-DAVIES  
02/03/2012



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2  
**Meeting Date and Time:** October 29, 2010; 3-4:30 P.M. E.S.T.  
**Meeting Location:** White Oak Bldg 22 Room 1309  
**Application Number:** IND 106,616  
**Product Name:** GSK573719/GW642444 Inhalation Powder  
**Received Briefing Package** September 24, 2010  
**Sponsor Name:** GlaxoSmithKline  
**Meeting Requestor:** Mary Sides  
**Meeting Chair:** Badrul A. Chowdhury  
**Meeting Recorder:** Eunice Chung-Davies

**Meeting Attendees:**

**FDA Attendees**

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Susan Limb, M.D., Clinical Team Leader, DPARP

Jennifer R. Pippins, M.D., M.P.H., Clinical Reviewer, DPARP

Molly Topper, Ph.D., Nonclinical Supervisor, DPARP

Tim Robison, Ph.D., Nonclinical Reviewer, DPARP

Joan Buenconsejo, Ph.D., Acting Statistics Team Leader, Division of Biometrics II

Feng Zhou, Ph.D., Statistics Reviewer, Division of Biometrics II

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II

Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Sofia Chaudhry, M.D., Clinical Review, DPARP

Antoine El Hage, Ph.D., Clinical Reviewer, DSI

Eunice Chung-Davies, Pharm.D., Senior Regulatory Management Officer,  
DPARP

**Sponsor Attendees**

Darrell Baker, Vice President, Medicine Development Center Head

Jean Brooks, MSc., Associate Director, Biostatistics

Glenn Crater, M.D., Director, Clinical Development

Susan Fayinka, Director, Pharmaceutical Development

Mauri Fitzgerald, Vice President, Global Regulatory Affairs

C. Elaine Jones, Ph.D., Medicine Development Leader, Clinical Development

Chris Kalberg, Ph.D., Director, Clinical Development

Dennis Kelleher, Ph.D., Manager, Clinical Pharmacology, Clinical Development

Mary Sides, Associate Director, Global Regulatory Affairs

Gill Stemp, Manager, Safety Assessment Europe

Andrea Terron, Director, Safety Assessment Europe

## 1.0 BACKGROUND

Ms. Mary Sides of GSK requested an EOP2 meeting to discuss the nonclinical, clinical and statistical aspects of the Phase III program for GSK573719 Inhalation Powder as a monotherapy and GSK573719/GW642444 Inhalation Powder as a combination for the long-term maintenance of treatment of airflow obstruction and the relief of dyspnea with daily activities, associated with COPD. FDA provided responses (*italics*) to the sponsor's questions (**bold italics**) in the briefing package, dated September 24, 2010, on October 27, 2010. Discussion that took place at the October 29, 2010, face-to-face meeting, is in normal font.

## 2.0 QUESTIONS AND RESPONSES AND DISCUSSION

### *Nonclinical*

#### *Question 9.1.1.*

***A list of completed, ongoing or proposed non-clinical studies for the individual components, GSK573719 and GW642444, alone and in combination is provided in attachment 2. Are the data from the non-clinical toxicology studies adequate to support initiation of the proposed Phase III clinical trials with the combination product and subsequent registration of the combination product?***

#### *FDA Response:*

*The data appears to be inadequate at this time with specific reference to the histopathological examinations of organs and tissues in the 13-week toxicology study with the combination of GSK573719 and GW642444 in dogs.*

*This study was intended to determine if the observed toxic effects observed with the combination of GSK573719 + GW642444 are consistent with toxic effects observed with monoproducts alone (i.e., there is no evidence of additive or synergistic toxic effects). Further, the study should attempt to identify a NOAEL.*

*Several findings were identified at increased incidences in the lungs, larynx, and trachea from dogs that received the combination of GSK573719 + GW642444 at a dose of 177/183 µg/kg/day (Group 5); however, lower dose groups were not examined in order to determine if a NOAEL could be identified. Further, it is noted that pre-adaptation or tolerance phase was used for Group 5, which might have potentially protected animals from subsequent exposure to higher doses. Groups 3 and 4 need to be examined to ensure that there were no additional findings due to the use of a tolerance phase for Group 5.*

Organ/Tissue	Finding
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Lung	perivascular/peribronchial/subpleural inflammatory cell infiltrate, G1
Lung	aggregates of alveolar macrophages
Larynx	mucosa: mixed inflammatory cell infiltrate, G1-G2
Trachea	mucosa: mixed inflammatory cell infiltrate, G1

*Organs and tissues from dogs that received monoproducts (GSK573719 or GW642444 alone) were, in general, not submitted to the histopathological examination. This makes the direct comparison of findings with the combination product and monoproducts difficult or essentially impossible. The only potential comparisons are to rely on findings from other toxicology studies with monoproducts alone; however, these studies were conducted under differing experimental conditions and doses. This renders the comparisons inexact and inadequate.*

*Provide histopathological examinations of all tissues for combination groups that received 23/29 and 60/72 µg/kg/day (Groups 3 and 4). The control group (Group 1) needs to be reexamined by the pathologist along with drug treatment groups in order to have a valid comparison. Tissues, in which findings were identified for Groups 3, 4, or 5, should also be examined for monoproducts groups (Groups 6 and 7).*

**Question 9.1.2.**

***Inhaled combination toxicity studies with GSK573719 and GW642444 of up to 28 days duration in the rat and dog and up to 13 weeks duration in the dog have been completed. A further 28-day toxicity in the dog is ongoing and data will be available prior to the start of the Phase III trials. Does the Agency agree that, based on results of these combination studies, that no further nonclinical studies on the combination are required to support Phase III or registration?***

*FDA Response:*

*We cannot provide a definitive response to this question at this time. The need for any additional nonclinical studies will be assessed following review of the histopathology data for the 13-week combination toxicology study in dogs requested in Question 9.1.1 and the 28-day combination study in dogs to determine the effect of a pre-adaptation phase.*

**Question 9.1.3.**

***Interstitial, bronchoalveolar and granulomatous inflammation in the lung were observed at all doses in the dog 28-day study. Due to the histopathological appearance of the lesions, it was considered likely that this lung pathology was a result of accidental inhalation and deposition of exogenous material in the lung. This hypothesis has been further substantiated in subsequent studies in the dog with***

***GSK573719 alone or in combination with GW642444. Does the Division agree that the induction of granulomas in the dog has been adequately explained and resolved?***

*FDA Response:*

*We agree that the induction of granulomas in the dog has been adequately explained and resolved.*

***Question 9.1.4.***

***GSK have conducted 28-day and 13-week dog combination toxicology studies evaluating GSK573719/GW642444 in combination at various dose levels. A subsequent 28-day dog combination study is ongoing to assess the effect of a pre-adaptation phase used in the previous dog combination studies on cardiovascular function/parameters; the study report will be submitted within 30 days of initiating the long-term safety study (i.e. mid Nov 2010). Given that for the proposed Phase III clinical dose (125mcg), adequate safety margins already exists from a non-pre-adapted dose in the 13 week combination study at the 1:1 ratio, GSK believe it is safe to proceed with combination clinical studies longer than 12 weeks duration. Does the Division agree?***

*FDA Response:*

*We cannot provide a definitive response to this question at this time. The adequacy of nonclinical support for combination clinical studies longer than 12 weeks duration will be assessed following review of the histopathology data for the 13-week combination toxicology study in dogs requested in Question 9.1.1 and the 28-day combination study in dogs to determine the effect of a pre-adaptation phase.*

*The proposed clinical doses of GSK573719 and GW642444 in the combination product need to be adequately supported by NOAELs identified in the 6-month rat and 9-month dog toxicology studies with the individual monoproducts as well as the 13-week combination toxicology study in the dog. A NOAEL for the 13-week combination toxicity study has not yet been established.*

Discussion:

The Sponsor expressed their thinking that the nonclinical information in their briefing package was comprehensive enough to start Phase 3 studies in humans. They noted that histopathological findings in the 3 month combination study were consistent with findings for each of the monoproducts alone and there was no evidence for any additive or synergistic effect with the combination. Further, the observed findings were not considered adverse. Thus, they did not believe that there was any need to examine additional groups in the combination study. FDA responded that we have expressed numerous concerns regarding the use of a pre-adaptation or tolerance phase for Group 5 as this might lead to protective effects for various tissues and mask any potential toxic effects of the combination. The primary concern was for the heart; however, protective effects for other tissues could not be excluded. FDA further stated that the sponsor should

have examined Groups 3 and 4 to ensure the pre-adaptation or tolerance phase used for Group 5 did not mask any potential toxic effects of the combination. The 28-day dog study was designed to assess the effects of the pre-adaptation phase with specific reference to the heart. It might provide supportive data for the use of Group 5 from the 3-month combination study; however, it does not alleviate the need to examine all tissues from Groups 3 and 4. The data from the 28-day study is unknown at this time.

The sponsor agreed to examine all the tissues for Groups 3 and 4 in the 13 week combination study with dogs. As stated in the response to Question 9.1.1., tissues in which findings were identified for Groups 3, 4, or 5, should also be examined for monoproducts groups (Groups 6 and 7). The FDA agreed. It was also confirmed that the 28-day dog study to assess the effects of pre-adaptation should be submitted prior to the human study protocol.

The sponsor inquired how long it would take for FDA to review the data if they submit the data by the end of November with the clinical trial. FDA discouraged the sponsor from submitting the clinical protocol without prior agreement that the nonclinical data are adequate. FDA stated that it could not pinpoint a time, however, the nonclinical reviewer will give it high priority and review the data as soon as it is submitted.

The sponsor stated that their intent is to start their study in humans as soon as possible after the animal data is complete. FDA acknowledged this.

### ***Clinical Pharmacology***

#### ***Question 9.2.1.***

***Does the Division agree that the clinical pharmacology program completed and ongoing to date when combined with the proposed studies to be conducted during Phase III will be adequate to describe the clinical pharmacology, potential for drug-drug interactions, and co-variant pharmacokinetics of GSK573719 Inhalation Powder and the combination product GSK573719/GW642444 Inhalation Powder?***

#### ***FDA Response:***

*Yes, your program appears acceptable.*

Discussion:

No discussion required

#### ***Question 9.2.2.***

***Does the Division agree that the results of the verapamil drug interaction study***

***DB2113950 adequately describes the low probability of a clinically significant drug-drug interaction between Pgp substrate inhibitors and GSK573719 such that no additional drug-interaction studies are required and the exclusion of strong Pgp inhibitors is not required in Phase III studies for GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder?***

FDA Response:

*Yes, your rationale appears acceptable.*

Discussion:

No discussion required

***Question 9.2.3.***

***Does the Division agree the results of study AC4110106, a study of repeat inhaled doses of GSK573719 in a healthy population of cytochrome P450 2D6 poor metabolizers, adequately describe the low probability of a clinically significant drug-drug interaction with concomitant use of GSK573719 Inhalation Powder and 2D6 inhibitors and that no additional studies are required and the exclusion of 2D6 poor metabolizers is not required in Phase III studies for GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder?***

FDA Response:

*Yes, your rationale appears acceptable.*

Discussion:

No discussion required

***Clinical***

***Question 9.3.1.***

***Does the Division agree that the completed Phase IIb studies for GSK573719 Inhalation Powder provide adequate data to demonstrate a once-daily dosing interval?***

FDA Response:

*No, we do not agree. Confirmation of the dosing interval should be preceded by adequate dose-ranging. See our response to Question 9.3.2.*

Discussion:

The sponsor asked what the FDA is looking for with regard to the determination of nominal dose and dosing interval. FDA replied that, as stated in the response to Question 9.3.2, there seems to be no clear discrimination among doses in terms of trough FEV1. In the absence of a demonstrated dose response, it is difficult for FDA to draw conclusions about the appropriateness of the sponsor's proposed nominal dose and dosing interval.

Focusing on dosing interval, the sponsor commented that the 62.5 mcg twice daily dose did not perform better than the once daily dose, and added that anti-cholinergic products tend to have a flat dose response curve. FDA acknowledged that the information provided by the sponsor is supportive of a once daily dosing interval; however, in the absence of a demonstrated dose response, there is a concern that the once daily dosing interval may be the result of a nominal dose that is higher than necessary. The sponsor stated that the totality of the data demonstrates that 62.5 mcg is not as effective as 125 mcg.

FDA acknowledged that there are not many examples of anti-cholinergic products and that it is uncertain if a clear dose response curve can be demonstrated for this class of therapeutics. Nevertheless, what is certain is that at some dose, the product will not work. It remains important to obtain some sense of dose response in order to address whether the chosen dose is at the optimal portion of the dose response curve. FDA further stated that dose selection needs to be considered in the context of heightened concerns about anti-cholinergic safety; the safety of tiotropium is still an open question. If a safety issue is identified with the proposed 125 mcg dose, the Division will question whether lower doses may have had more acceptable safety profiles with similar efficacy. In addition, dose selection influenced by the goal of demonstrating superiority to another product, which is a goal that the sponsor may or may not have, can complicate matters. The sponsor stated that their dose selection is not based on a goal of demonstrating superiority to tiotropium, rather, the development program includes trials comparing the proposed product to tiotropium because of European regulatory requirements.

FDA summarized its view on a path forward: generation of a good FEV1 dose response curve in the patient population of interest. Demonstration of an ineffective dose would also aid in supporting the sponsor's choice of dose.

The sponsor expressed that the 62.5 dose data was characterized by a high degree of variability; FDA responded that trough FEV1 tends to be a variable measure, however, we would take into account the entire FEV1 curve in our review. FDA noted that exploring a nominal dose and dose frequency at the same time can be very difficult; it is preferable to explore nominal dose and dosing frequency in a sequential fashion (first nominal dose, then dosing frequency). The sponsor asked whether they could establish a nominal dose based on the results of a single dose study. FDA responded that this was a reasonable approach FDA suggested a cross-over study, using either ipratropium or tiotropium as a benchmark to assure assay sensitivity. Enrichment of the population for anti-cholinergic sensitivity may also assist in demonstration of a dose response. The sponsor referred to a single dose study that evaluated the 30 mcg, 60 mcg, and 125 mcg doses in COPD patients, stating that the lowest dose did not demonstrate efficacy, while the two higher doses did. The sponsor added that in a single dose, healthy, ipratropium-responsive volunteer study, no effect was observed at the 10 mcg or 20 mcg dosing

levels. FDA agreed that these were supportive data, but noted that these data would be more convincing in a COPD population, who can be quite sensitive to anti-cholinergic effects.

**Question 9.3.2.**

***Does the Division agree that the 125mcg once-daily dose of GSK573719 Inhalation Powder is the optimal dose to evaluate individually and in combination with the LABA GW642444 Inhalation Powder in Phase III?***

FDA Response:

*No, we do not agree. The summary information provided indicates that no clear dose response was observed in terms of trough FEV<sub>1</sub>, the proposed primary efficacy variable for the pivotal phase 3 trials. We recommend exploration of lower doses. Assess the full time profile FEV<sub>1</sub> curve after dosing, rather than relying only on one time point at trough. Consider assessing the nominal dose first, then exploring the dosing frequency.*

Discussion:

See discussion in 9.3.1.

**Question 9.3.3.**

***Does the Division agree that the Phase I and IIa data for GSK573719 Inhalation Powder in combination with GW642444 Inhalation Powder provide an appropriate basis for progression to Phase III for GSK573719/GW642444 Inhalation Powder?***

FDA Response:

*From a clinical perspective, pending resolution of issues raised in response to your questions 9.3.1 and 9.3.2 above, the proposal appears reasonable. Also see the response to 9.1.1 regarding the adequacy of nonclinical data to support dosing in the Phase 3 trials.*

Discussion:

See discussion in 9.3.1.

**Question 9.3.4.**

***Does the Division agree that based on findings from clinical studies conducted to date for GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder, no further assessment of the gall bladder is required in clinical trials other than standard adverse event monitoring?***

FDA Response:

*Yes, we agree.*

Discussion:

No discussion required.

***Question 9.3.5.***

***Does the Division agree that enrolment of women of childbearing potential who have a negative pregnancy test at screening and are using appropriate contraceptive methods is acceptable in the proposed Phase III studies?***

*FDA Response:*

*Yes, the proposed enrollment of women of childbearing potential who have a negative pregnancy test at screening and are using appropriate contraception is acceptable.*

Discussion:

No discussion required.

***Question 9.3.6.***

***Does the Division agree that conducting replicate 6-month pivotal studies evaluating GSK573719/GW642444 Inhalation Powder, GSK573719 Inhalation Powder, GW642444 Inhalation Powder, and placebo within each study:***

***a. are sufficient to fulfill the requirements of 21 CFR 300.50 for fixed-combination prescription drugs,***

***b. are sufficient to demonstrate the efficacy of the GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder, and***

***c. support the proposed indication for both GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder for the long-term maintenance treatment of airflow obstruction associated with COPD, including emphysema and chronic bronchitis?***

*FDA Response:*

*The general trial design of the proposed replicate 6-month trials appears reasonable. We note the choice of trough FEV1 as the primary endpoint. We ask that you justify the use of this endpoint in the NDA submission. While the choice of primary endpoint is at*

*your discretion, we remind you that the totality of the data will be examined during NDA review including post-dose serial FEV1 time curves and supportive non-spirometric parameters.*

*In addition, we have the following comments about the proposed Phase 3 program:*

- 1) As previously discussed during the June 8, 2010, meeting for the related ICS/LABA product (fluticasone furoate/vilanterol; IND 77,855), we remind you that dose selection for the LABA component of the combination should be supported by robust pharmacodynamic information in a bronchodilator-sensitive population.*
- 2) The generalizability of the data to a broad COPD population, including both patients with emphysema and those with chronic bronchitis, will depend on the characteristics of the patient population enrolled.*

Discussion:

No discussion required.

***Question 9.3.7.***

***Does the Division agree that the primary endpoint of trough FEV1 proposed for the replicate 6-month pivotal studies is adequate for evaluation of 1) the individual products and 2) the combination product to demonstrate that the individual products contribute to the efficacy of the combination product?***

*FDA Response:*

*See our response to Question 9.3.6.*

Discussion:

No discussion required.

***Question 9.3.8.***

***Does the Division agree that the size of the database, the length of patient exposure, and the proposed safety monitoring, including the extent of cardiovascular safety monitoring, will provide an adequate safety database to support the NDA for GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?***

*FDA Response:*

*While the proposed safety database appears reasonable at this time, the adequacy of the safety database will depend on the totality of the data. Additional information may be required depending on the nature of the safety findings observed during Phase 3.*

Discussion:

No discussion required.

***Question 9.3.9.***

***Does the Division agree that 1) subjects who participated in previous GW642444 studies are eligible to participate in any of the proposed Phase III studies for GSK573719/GW642444 Inhalation Powder and 2) subjects who participated in previous studies for GSK573719 Inhalation Powder are eligible to only participate in the Phase III studies comparing GSK573719/GW642444 Inhalation Powder and tiotropium?***

*FDA Response:*

*We prefer that you enroll treatment-naïve patients in your pivotal Phase 3 clinical trials.*

Discussion:

No discussion required.

***Question 9.3.10.***

***Does the Division agree that the measures proposed to ensure a consistent standard of care across regions in the proposed global, multicenter Phase III studies are adequate to allow these data to support approval for the use of GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder in a US population?***

*FDA Response:*

*The generalizability of the data generated by the Phase 3 trials, which draw only 30% of their total enrollment from North America, to the U.S. population will be a review issue. Ensure adequate representation of patients of African descent in your program.*

Discussion:

The sponsor clarified that the study will draw approximately 20-25% of its population from America, and that this group will be representative of the United States population.

The sponsor stated that based on prior experience, the proportion of African Americans recruited is expected to be quite low (approximately 1-2%). This is despite efforts to improve the recruitment of African American patients in the U.S. One attempt to address this lack of diversity will be the recruitment of European patients of African descent. The

sponsor also stated that they will be recruiting South American and Asian patients. FDA stated that the issue of adequately diverse representation in clinical trials has been widely discussed in public forums, and that the Agency would be remiss to not continue bringing it to the attention of sponsors. Nevertheless, FDA stated that it understands the difficulties faced by the sponsor and that the proposed approach is reasonable.

**Question 9.3.11.**

***Does the Division agree that a GW642444 arm is not required in the 12 month safety study DB2113359?***

FDA Response:

*Yes, we agree.*

Discussion:

No discussion required.

**Question 9.3.12.**

***Does the Division agree that the replicate 6-month studies comparing GSK573719/GW642444 Inhalation Powder to tiotropium via the HandiHaler are adequately designed, including the blinding strategy,*** (b) (4)

(b) (4)

FDA Response:

*A demonstration of superiority to an active comparator such as tiotropium is not a regulatory requirement and appears intended primarily for promotional purposes. Therefore, we have no comment on the proposed trial design. However, we caution you that the intention to demonstrate superiority to an active comparator may compromise the selection of an optimally safe dose.*

Discussion:

No discussion required.

**Question 9.3.13.**

***GSK plan to evaluate patient ease of use of the Novel DPI and the HandiHaler in the 6-month studies comparing GSK573719/GW642444 Inhalation Powder to tiotropium.***

***Does the Division agree that the proposed approach to evaluate patient ease of use***

(b) (4)

FDA Response:

*We are unable to comment on the acceptability of the proposed approach based on the information provided. For advisory comments, we recommend that you submit the following information:*

- 1) *The questionnaire to evaluate patient ease of use of the novel DPI compared to Handihaler*
- 2) *The study protocol which describes the target population and manner in which the questionnaire will be administered*

(b) (4)

Discussion:

No discussion required.

***Question 9.3.14.***

***Does the Division agree that the replicate exercise studies comparing GSK573719/GW642444 Inhalation Powder, GSK573719 Inhalation Powder, GW642444 Inhalation Powder, and placebo are adequately designed***

(b) (4)

FDA Response:

*We note that exercise endurance is multi-factorial and influenced by many factors, including ones unrelated to COPD. As a result, it will be difficult to attribute changes in exercise endurance time solely to a beneficial effect of the proposed product on the lungs. Other factors which may confound exercise capacity, such as cardiovascular fitness, muscle tone, joint mobility, and balance, will need to be addressed.*

Discussion:

The sponsor wished to obtain feedback on the choice of endurance shuttle test for the proposed trial, commenting that this assessment would be more useful in the evaluation of COPD patients and less artificial than a treadmill test or other exercise challenge models. FDA noted that while the shuttle test has some advantages, at the same time it is still dependent on patient motivation. FDA stated that our comments were not focused on the choice of instrument, but rather on the general challenges

(b) (4)

(b) (4)

FDA stated that it will be important to connect any effects of the proposed product on exercise to its bronchodilatory effect. Moreover, given that this is new territory, the topic would be discussed in a public forum.

**Question 9.3.15.**

***Does the Division agree that the data from the dose-ranging studies for GSK573719 Inhalation Powder (which contains two strips, i.e. an active strip and a nonactive strip) can be utilized to select a single dose to progress to Phase III pivotal studies for both the single-strip Novel DPI for the monotherapy product and a two-strip Novel DPI for GSK573719/GW642444 Inhalation Powder?***

FDA Response:

*Based on the information provided, we note differences in the aerodynamic particle size distribution (APSD) in the presence and absence of a non-active strip. Given these differences, we have concerns that the use of a single-strip comparator in the factorial design pivotal trials for GSK573719/GW642444 will not be appropriate for satisfying the requirements of the Combination Rule.*

*Dose ranging information obtained from the two-strip device may be used to support dose selection for a single-strip monotherapy product; however, clinical bridging data will be required to characterize and support the differences between the two-strip and single-strip products. Should you choose to develop a single-strip monotherapy product for marketing, additional safety information may be required depending on the extent of the differences.*

Discussion:

The sponsor inquired why the use of a single-strip comparator in the factorial design pivotal trials for GSK573719/GW642444 would impact the ability to satisfy the combination rule. FDA stated that

(b) (4)  
(b) (4)  
(b) (4). Hence, the interpretability of data from the factorial design pivotal trial would be clouded.

The sponsor stated that they could add the second (nonactive) strip to the monotherapy device, noting, however, that this would expose users to unnecessary excipient, and that previous guidance from FDA had discouraged this. FDA responded that the previous guidance was provided prior to data being available regarding this pharmaceutical interaction. FDA outlined two options open to the sponsor: adding in a second non-active strip to the monotherapy, or obtaining bridging data to justify reliance on the data generated by the single-strip monotherapy device. The sponsor noted that the (b) (4) monotherapy device actually puts the sponsor at a disadvantage, making it more difficult to demonstrate superiority of the combination product to monotherapy. FDA reiterated that choosing to use the single-strip monotherapy device will result in data that is difficult to interpret, moreover, also at issue

is the difficulty that would be faced by providers and patients when switching from the combination product to monotherapy.

(b) (4)

from a CMC perspective. FDA will require data demonstrating that there is no relevant clinical difference; such data may be obtained from a single dose PK/PD study.

***Question 9.3.16.***

***Does the Division agree with GSK's proposal to compare the two-strip Novel DPI for GSK573719/GW642444 Inhalation Powder with the single strip Novel DPI for the monotherapy products in the pivotal Phase III studies to support registration of GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?***

***FDA Response:***

*See our response to 9.13.15.*

Discussion:

No discussion required.

***Question 9.3.17.***

***Does the Division agree that the population pharmacokinetics sampling to be conducted during the planned Phase III studies will be adequate to evaluate population co-variants; e.g. age and gender among the general population of prescribed patients?***

***FDA Response:***

*Yes, your program appears acceptable.*

Discussion:

No discussion required.

***Question 9.3.18.***

(b) (4)

FDA Response:

*In your Phase 3 studies, your calculated sample size of 1005 subjects in Study DB2113361/3373, and 292 subjects in Study DB2113360/3374 is acceptable. Assuming your analysis population consists of all randomized subjects and taking into consideration your proposal to handle missing data, sample size need not be increased to allow for dropouts. Otherwise, increasing the sample size is reasonable to allow adequate safety data. Of note, the study has to demonstrate clinically meaningful and statistically significant treatment differences on the primary efficacy endpoint of FEV<sub>1</sub>.*

*We noted that your sample size of 190 subjects was calculated based on a two-sample t-test for the exercise endurance study. Because this is a crossover design study, applying a two-sample t-test is not recommended.*

Discussion:

The sponsor stated that they plan to increase the sample size to allow for patient dropouts. They also stated that given their primary endpoint is at the end of the treatment (Visit 9), missing data due to patient dropout will be a problem even if they apply mixed model repeated measures.

The Division stated that we understand the potential loss of power due to patient dropout. However, because the Sponsor is applying mixed model repeated measures that uses all observed data from all randomized patients to analyze their primary endpoint, we do not agree with the reason for inflating the sample size.

Nonetheless, increasing the sample size is acceptable and the Division reminded the Sponsor that our assessment will not just be on the statistical significance, but also on the clinical meaningfulness of the treatment effect.

**Question 9.3.19.**

***GSK intend to conduct a clinical study to evaluate the safety of fluticasone furoate/GW642444 Inhalation Powder and GSK573719/GW642444 Inhalation Powder given concomitantly in patients with COPD. Does the Division have any feedback on the design of the study?***

FDA Response:

*We have no comments at this time.*

Discussion:

No discussion required.

### ***Labeling***

#### ***Question 9.4.1.***

***Does the Division have any preliminary comments on the draft wording for the INDICATIONS AND USAGE section and the DOSAGE AND ADMINISTRATION section of the package inserts for GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?***

#### ***FDA Response:***

*The evaluation of dyspnea presents many challenges, and the successful development of a patient reported outcome instrument to measure dyspnea and/or shortness of breath is without precedent. We refer you to the meeting of the Pulmonary-Allergy Drugs Advisory Committee held on September 6, 2002, as well as the May 10, 2010, discussion of the SOBDA instrument (IND 50,703), which addressed the difficulties associated with attempts to measure dyspnea and to claim dyspnea as an indication.*

Discussion:

No discussion required.

#### ***Question 9.4.2.***

***Does the Division have any preliminary comments on inclusion of studies from the Phase III development program in the clinical trials section of the labelling for GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?***

#### ***FDA Response:***

*We have no specific comments at this time. In general, we note that the inclusion of active comparator data will be a review issue.*

Discussion:

No discussion required.

### **ADDITIONAL COMMENTS**

*Statistics Comments:*

1. *You propose to apply Mixed Model Repeated Measures to evaluate treatment difference at Visit 9 (Day 169). In general, this approach is generally acceptable. However, we would like to caution you that the reasons for dropout may vary for which some may likely be due to treatment-related adverse events. Therefore it may be difficult to justify the assumption of missing data at random.*

*In the protocol, discuss potential mechanisms which may cause FEV<sub>1</sub> data to be missing, and how those mechanisms affected your selection of the primary analysis method. We also recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in a different direction from the result of the primary analysis.*

*Refer to the National Research Council of the National Academy's report, titled "The Prevention and Treatment of Missing Data in Clinical Trials" for further information.*

## Discussion:

The Sponsor stated that they understood our comments and will be providing a more detailed description of their approach to handle missing data in their protocols. They asked the Division if we have further suggestions on how to handle missing data. The Division replied that we do not have any specific advice on what methods to use. We noted from their synopsis that they plan to use last observation carried forward approach to impute missing data as part of their sensitivity analysis. Unless they have sound justification, we cautioned them about the use of LOCF, in particular when there are treatment-related dropouts. We refer them again to the NAS report for more information about missing data.

2. *You stated that you are anticipating a 30% dropout rate. We recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned.*
3. *In the briefing package, you stated that "all available data collected until the time of study discontinuation will be included in the intent-to-treat analysis for subjects who withdraw from the study." In your protocol, clarify if you intend to use the data collected after patient withdraws from treatment.*

## Discussion:

The Sponsor clarified that if a patient drops out of the study, they will conduct a follow-up visit/assessment within 30 days either by bringing the patient in or by phone. They do not plan to include any data collected after a patient drops out in the efficacy analysis. The sponsor asked whether this is the information that FDA is looking for. FDA stated affirmatively and that it was not clear from the package. FDA further stated that the sponsor should try to prevent loss to follow up and to clearly document the reasons for dropout (e.g. adverse event or lack of efficacy). The sponsor acknowledged this and indicated that this is what they intend to do. FDA further advised the sponsor to make sure that the informed consent form is very clear and ensure that the patient is aware of their expectations in order to prevent missing data.

#### Additional Discussion:

The sponsor inquired about what FDA's thoughts were on long acting muscarinic antagonists (LAMAs) and intranasal corticosteroids (ICSs) in combination for asthma. FDA responded that this topic has been brought up in many forums and it remains an open question. While the scientific community generally views LAMAs as having poor efficacy for asthma, there is some support for the use of LAMA/ICS combinations, particularly among patients with severe asthma. FDA raised the issue that perhaps this severe population is actually comprised of individuals with COPD, as opposed to true asthmatics. Hence, it would be important for the sponsor to clearly define the patient population being targeted for a proposed LAMA/ICS product.

The sponsor inquired about whether a pediatric plan would be needed for this COPD program. FDA responded that a COPD program will not require a pediatric plan.

The sponsor inquired about whether a large safety trial will be required to support product registration for a COPD indication. FDA responded that this issue would require internal discussion. The sponsor also noted that if the LAMA/LABA and LAMA/ICS products were both available, some providers and COPD patients might choose to use the products concurrently; the sponsor asked FDA what would be required to address this issue. FDA responded that this topic would be best discussed at a later time.

The Division of Scientific Investigations provided documents to the sponsor describing a voluntary pilot program to which they are being invited.

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

**4.0 ACTION ITEMS**

**5.0 ATTACHMENTS AND HANDOUTS**

Drafted by: Eunice Chung-Davies/November 1, 2010

Initialed by: Timothy Robison/November 2, 2010

Molly Topper/November 2, 2010

Joan Buenconsejo/November 5, 2010

Jennifer Pippins/ November 5, 2010

Susan Limb/ November 5, 2010

Badrul A. Chowdhury/November 17, 2010

Finalized by: EChung-Davies/November 17, 2010

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/s/

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EUNICE H CHUNG-DAVIES  
11/17/2010

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 203975

**LATE-CYCLE MEETING MINUTES**

GlaxoSmithKline  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D., R.A.C.  
Global Regulatory Affairs

Dear Dr. Gunto:

Please refer to your New Drug Application (NDA) dated December 18, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Anoro Ellipta, (umeclidinium bromide/vilanterol trifenatate) inhalation powder 62.5mcg/25mcg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 22, 2013.

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

If you have any questions, call Leila P. Hann, Regulatory Project Manager at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Susan Limb, M.D.  
Clinical Team Leader  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** August 22, 2013 at 2:00 PM – 3:30 PM  
**Meeting Location:** FDA, White Oak Building 22, Room 1313

**Application Number:** NDA 203975  
**Product Name:** umeclidinium bromide/vilanterol trifenate  
**Applicant Name:** Glaxo Group, (d/b/a GSK)

**Meeting Chair:** Susan Limb, M.D.  
**Meeting Recorder:** Leila P. Hann

**FDA ATTENDEES**

Curtis Rosebraugh, M.D., Director, Office of Drug Evaluation II (ODEII)  
Mary Parks, M.D., Deputy Director, ODEII  
Badrul A. Chowhdury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Lydia I. Gilbert-McClain, M.D., Deputy Director, DPARP  
Sally Seymour, M.D., Deputy Director for Safety, DPARP  
Susan Limb, M.D., Clinical Team Leader, DPARP  
Jennifer R. Pippins, M.D., M.P.H., Clinical Reviewer, DPARP  
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP  
Marcie Wood, Ph.D., Non-Clinical Supervisor, DPARP  
Craig Bertha, Ph.D., Acting Chemistry, Manufacturing, and Controls Lead, Division of New Drug Quality Drug Assessment II  
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCPII)  
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, DCPII  
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, DCPII  
Gregory Levin, Ph.D., Biometrics Reviewer, Division of Biostatistics II  
Nichelle Rashid, Senior Regulatory Health Project Manager, Office of Surveillance and Epidemiology (OSE)  
Lissa C. Owens, Pharm.D., Safety Evaluator, Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention and Analysis, OSE  
Jessica Voqui, Regulatory Review Officer, Study Endpoints and Labeling Development  
Eileen Wu, Pharm.D., Safety Evaluator Team Leader, Division of Pharmacovigilance I (DPVI), OSE  
Jasmine Gatti, M.D., Safety Reviewer, DPVI, OSE  
Leila P. Hann, Regulatory Health Project Manager, DPARP

**EASTERN RESEARCH GROUP ATTENDEES**

<sup>(b) (4)</sup>, Independent Assessor

## **APPLICANT ATTENDEES**

Christine Elaine Jones, Vice President, Medicine Development Leader  
Alison Church, Director, Clinical Development  
Patrick Wire, Senior Director, Global Regulatory Affairs  
Jean Brooks, Director, Clinical Statistics  
Vicki Gunto, Ph.D., Director, Global Regulatory Affairs  
Mauri Fitzgerald, Vice President, Global Regulatory Affairs  
John Finkle, Vice President, Global Clinical Safety and Pharmacovigilence

## **1.0 BACKGROUND**

NDA 203975 was submitted on December 18, 2012 for Anoro Ellipta (umeclidinium bromide/vilanterol trifenate).

Proposed indication(s): maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema

PDUFA goal date: December 18, 2013

FDA issued a Background Package in preparation for this meeting on August 13, 2013.

## **2.0 DISCUSSION**

### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

### 2. Discussion of Substantive Review Issues – 15 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Cardiovascular safety

**Discussion:** The Agency noted small imbalances in cardiovascular events favoring placebo. The applicant acknowledged that there are potential cardiovascular safety signals and inquired which data are the most concerning to the Agency. The Agency responded that the totality of the data is being reviewed, with a focus on the results for MACE, and particularly non-fatal MI, as well as cardiovascular adverse events of special interest (AESI). The key question is whether or not the data are sufficient to support safety and are adequate to allow for appropriate labeling, or, alternatively, if additional data are needed either pre-marketing or postmarketing.

- Umeclidinium dose selection

**Discussion:** The Agency will discuss umeclidinium dose selection during the AC, which may inform the committee's discussion of safety. The applicant inquired if the Spiriva

Respimat data that is expected to be presented at an upcoming European Respiratory Society conference will be part of the Agency's presentation. The Agency responded that it will only briefly refer to the recently completed trial..

3. Information Requests – 5 minutes

- Clinical information request dated August 7, 2013

**Discussion:** On August 16, 2013, the applicant responded to the above mentioned information request (IR). The applicant noted that in the IR, the Agency expressed concern regarding withdrawals due to ECG and Holter abnormalities and asked if the Agency needed any additional data regarding this concern. The Agency responded that it has no current plans for additional information requests.

4. Discussion of Upcoming Advisory Committee Meeting – 15 minutes

**Discussion:** Vilanterol data will be presented at a very high level. While vilanterol dose selection was discussed at the PADAC meeting for Breo Ellipta, there are members of the committee who may have not attended that meeting. The applicant asked what type of SAE data will be presented – i.e., adjudicated or unadjudicated. The Agency plans to present the unadjudicated events; in general, the results of the adjudicated and unadjudicated analyses are consistent with each other. The results of both the broad and narrow MACE analyses will be discussed. The applicant proposed exchanging the slides in advance of the meeting. The Agency responded that they would not be able to commit to providing the Applicant with slides ahead of the usual due date.

5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- Pending discussion at Advisory Committee meeting

**Discussion:** The Agency noted that the best approach for discussion at the AC may be the one that preserves the most flexibility. The Agency inquired if the applicant is planning on performing additional efficacy studies, as this would enlarge the safety database. The applicant responded that a lung function study is currently ongoing. The applicant noted that they intend to present efficacy data pertaining to the SGRQ, rescue medication use, and exacerbations.

6. REMS or Other Risk Management Actions

- None anticipated

7. Clinical

- a. Cardiovascular safety: Review of the data indicates some imbalances between the active treatment arms and placebo. Namely, there is an imbalance in cardiac ischemia AESIs in the Primary Efficacy trials, and in the long-term safety trial, there is an imbalance in early discontinuations secondary to ECG or Holter abnormalities.

Whether these imbalances represent a cardiac safety signal and whether additional safety data are needed to characterize the potential risk are topics for discussion.

- i. Clinical information request sent August 7, 2013

**Discussion:** Discussion can be found under #2 – Cardiovascular safety.

#### Statistics

- Umeclidinium dose selection: In light of a potential safety signal as described above, the issue of appropriate dose selection for umeclidinium is brought to the forefront. The dose-ranging data suggest that doses lower than 62.5 mcg may be efficacious.

**Discussion:** Discussion can be found under #2 – Umeclidinium dose selection.

8. Additional Applicant Data – (Applicant)

- Complete study report for protocol DB2116133

**Discussion:** The applicant clarified that they are not planning to present this study at the AC but will answer questions if they are raised. The Agency requested that any comments made by the Applicant pertaining to this trial at the AC be prefaced by a statement indicating that the FDA has not had a chance to verify these data.

9. Major labeling issues – 15 minutes

- Umeclidinium dose ranging information for Day 1 and Day 7

**Discussion:** Regarding the umeclidinium dose ranging data for Day 1 and Day 7, figures may be needed in the label.

- Inclusion of active comparator trials

**Discussion:** While the active comparator trials may provide information pertinent to the practice of medicine, data from these trials are not appropriate for the product label. The Agency also questioned whether an efficacy comparison of a LAMA/LABA product to a LAMA monotherapy was fair. The applicant noted that physicians may be able to benchmark to tiotropium. The applicant inquired if these concerns would also be an issue for the umeclidinium monotherapy label. The Agency stated that it was not able to comment on that label at this time.

- Description of cardiac safety data

**Discussion:** The Agency noted that the proposed label does not discuss cardiovascular safety.

- Inclusion of SGRQ and rescue medication data

**Discussion:** The benefit on SGRQ or rescue medication has not been replicated for the 62.5/25 mcg dose. The applicant suggested that the results for the 125/25 mcg dose provide replication. The Agency clarified that the principle would have worked in the opposite direction but is not applicable here; i.e., data for the lower dose may be used to support the higher dose, but not the other way around. The Agency stated that an additional well-controlled, adequately designed trial replicating a clinically meaningful benefit for SGRQ may be sufficient (b) (4)

#### 10. Discussion of Minor Review Issues – 10 minutes

- SGRQ: Efficacy based on SGRQ has not been replicated for the proposed dose of umeclidinium/vilanterol 62.5 mcg/25 mcg.

**Discussion:** Discussion can be found under #9 – Inclusion of SGRQ and rescue medication data.

- SOBDA: The content validity of the SOBDA instrument and the ability of patients to discriminate among the response options have been raised as review issues.
- Rescue medication: A benefit for rescue medication usage has not been replicated for the proposed dose of umeclidinium/vilanterol 62.5 mcg/25 mcg.

**Discussion:** Discussion can be found under #9 – Inclusion of SGRQ and rescue medication data.

#### 11. Review Plans – 5 minutes

- a. Review of responses to outstanding information requests
- b. Obtain feedback from Advisory Committee panel
- c. Completion of consults and tertiary reviews
- d. Completion of inspections
- e. Labeling discussions (as needed)

#### 12. Wrap-up and Action Items – 5 minutes

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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LEILA P HANN  
09/12/2013



NDA 203975

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

GlaxoSmithKline  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D., R.A.C.  
Global Regulatory Affairs

Dear Dr. Gunto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anoro Ellipta, (umeclidinium bromide/vilanterol trifenate) inhalation powder 62.5mcg/25mcg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 22, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Leila P. Hann, Regulatory Project Manager, at (301) 796-3367.

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** August 22, 2013 at 2:00 PM – 3:30 PM  
**Meeting Location:** FDA, White Oak Building 22, Room 1313

**Application Number:** NDA 203975  
**Product Name:** umeclidinium bromide/vilanterol trifenatate  
**Indication:** maintenance treatment of patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema  
**Sponsor/Applicant Name:** Glaxo Group, (d/b/a GSK)

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical/Statistics

- Cardiovascular safety: Review of the data indicates some imbalances between the active treatment arms and placebo. Namely, there is an imbalance in cardiac ischemia AESIs in the Primary Efficacy trials, and in the long-term safety trial, there is an imbalance in early discontinuations secondary to ECG or Holter abnormalities. Whether these imbalances represent a cardiac safety signal and whether additional safety data are needed to characterize the potential risk are topics for discussion.
- Umeclidinium dose selection: In light of a potential safety signal as described above, the issue of appropriate dose selection for umeclidinium is brought to the forefront. The dose-ranging data suggest that doses lower than 62.5 mcg may be efficacious.

## **ADVISORY COMMITTEE MEETING**

**Date of AC meeting:** September 10, 2013

**Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management:** August 20, 2013

### **Potential questions and discussion topics for AC Meeting are as follows:**

The main issues for discussion are cardiovascular safety and umeclidinium dose selection. We anticipate that AC members will be requested to discuss and vote on the following: 1) the strength of the efficacy data [REDACTED] (b) (4), with consideration of the umeclidinium dose range explored and the factorial contribution of the individual components to the combination; 2) the adequacy and strength of the safety data, with particular consideration of the cardiovascular safety data and the appropriateness of dose selection; and 3) the overall risk-benefit of umeclidinium/vilanterol 62.5 mcg/25 mcg for the proposed indication.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

### **1. Introductory Comments – 5 minutes (RPM/CDTL)**

Welcome, Introductions, Ground rules, Objectives of the meeting

### **2. Discussion of Substantive Review Issues – 15 minutes**

Each issue will be introduced by FDA and followed by a discussion.

- Cardiovascular safety
  - Umeclidinium dose selection
3. Information Requests – 5 minutes
    - Clinical information request dated August 7, 2013
  4. Discussion of Upcoming Advisory Committee Meeting – 15 minutes
  5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
    - Pending discussion at Advisory Committee meeting
  6. REMS or Other Risk Management Actions
    - None anticipated
  7. Clinical
    - Cardiovascular safety: Review of the data indicates some imbalances between the active treatment arms and placebo. Namely, there is an imbalance in cardiac ischemia AESIs in the Primary Efficacy trials, and in the long-term safety trial, there is an imbalance in early discontinuations secondary to ECG or Holter abnormalities. Whether these imbalances represent a cardiac safety signal and whether additional safety data are needed to characterize the potential risk are topics for discussion.
      - i. Clinical information request sent August 7, 2013

#### Statistics

- Umeclidinium dose selection: In light of a potential safety signal as described above, the issue of appropriate dose selection for umeclidinium is brought to the forefront. The dose-ranging data suggest that doses lower than 62.5 mcg may be efficacious.
8. Additional Applicant Data – (Applicant)
    - Complete study report for protocol DB2116133
  9. Major labeling issues – 15 minutes

- Umeclidinium dose ranging information for Day 1 and Day 7
- Inclusion of active comparator trials
- Description of cardiac safety data
- Inclusion of SGRQ and rescue medication data

10. Discussion of Minor Review Issues – 10 minutes

- SGRQ: Efficacy based on SGRQ has not been replicated for the proposed dose of umeclidinium/vilanterol 62.5 mcg/25 mcg.
- SOBDA: The content validity of the SOBDA instrument and the ability of patients to discriminate among the response options have been raised as review issues.
- Rescue medication: A benefit for rescue medication usage has not been replicated for the proposed dose of umeclidinium/vilanterol 62.5 mcg/25 mcg.

11. Review Plans – 5 minutes

- Review of responses to outstanding information requests
- Obtain feedback from Advisory Committee panel
- Completion of consults and tertiary reviews
- Completion of inspections
- Labeling discussions (as needed)

12. Wrap-up and Action Items – 5 minutes

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/s/  
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LYDIA I GILBERT MCCLAIN  
08/13/2013  
Acting Division Director