

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203975Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder) FOR ORAL INHALATION USE
Applicant	GlaxoSmithKline
Application/Supplement Number	NDA 203975
Type of Application	Original
Indication(s)	For the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease .
Office/Division	ODEII/DPARP
Division Project Manager	Leila Hann
Date FDA Received Application	December 18, 2012
Goal Date	December 18, 2013
Date PI Received by SEALD	December 12, 2013
SEALD Review Date	December 13, 2013
SEALD Labeling Reviewer	Debra Beitzell
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Extend horizontal lines on either side of headings to extend over the entire width of the column (see Appendix A).*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Insert bolded 4-digit year of application approval.*

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Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.
- Comment:
- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
- Comment:
- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
- Comment:
- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
- Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
- Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
- Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
- Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
- Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Insert bolded month and year of application approval.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification 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 practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

DEBRA C BEITZELL
12/13/2013

ERIC R BRODSKY
12/13/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

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

PATIENT LABELING REVIEW

Date: November 19, 2013

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Matthew Falter, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)
and Instructions for Use (IFU)

Drug Name (established name): ANORO ELLIPTA (umeclidinium/vilanterol)

Dosage Form and Route: Inhalation Powder

Application Type/Number: NDA 203975

Applicant: GlaxoSmithKline

1 INTRODUCTION

On December 18, 2012, GlaxoSmithKline (GSK) submitted, for the Agency's review, a New Drug Application (NDA) for ANORO ELLIPTA (umeclidinium/vilanterol) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology (DPARP) on January 4, 2013, and February 4, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ANORO ELLIPTA (umeclidinium/vilanterol) inhalation powder.

2 MATERIAL REVIEWED

- Draft ANORO ELLIPTA (umeclidinium/vilanterol) MG and IFU received on December 18, 2012 and received by DMPP on November 6, 2013.
- Draft ANORO ELLIPTA (umeclidinium/vilanterol) MG and IFU received on December 18, 2012 and received by OPDP on November 6, 2013.
- Draft ANORO ELLIPTA (umeclidinium/vilanterol) Prescribing Information (PI) received on December 18, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 6, 2013.
- Draft ANORO ELLIPTA (umeclidinium/vilanterol) Prescribing Information (PI) received on December 18, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on November 6, 2013.
- Approved BREO ELLIPTA (fluticasone furoate and vilanterol) inhalation power labeling dated May 10, 2013 (DMPP and OPDP).
- Approved TUDORZA PRESSAIR (aclidinium bromide inhalation powder) labeling dated July 23, 2012 (OPDP).
- Approved SPIRIVA HandiHaler (tiotropium bromide inhalation powder) labeling dated November 4, 2011 (OPDP).

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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

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/s/

TWANDA D SCALES
11/19/2013

MATTHEW J FALTER
11/19/2013

MELISSA I HULETT
11/19/2013

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

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

Memorandum

Date: November 15, 2013

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

From: Matthew Falter, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Group Leader, OPDP

Subject: NDA # 203975
OPDP Labeling Comments for ANORO ELLIPTA
(umeclidinium and vilanterol inhalation powder) FOR ORAL
INHALATION USE (Anoro Ellipta)

Reference is made to DPARP's February 4, 2013, consult request for OPDP's comments regarding the proposed Package Insert (PI), Medication Guide (MG), Instructions for Use (IFU), and Carton and Container labeling for Anoro Ellipta.

OPDP has revised the proposed PI. Our comments on the proposed PI are based on the proposed draft marked-up labeling titled "2013_11_06NDA203975LabelConsultants.doc" that was sent via email from DPARP to OPDP on November 6, 2013. OPDP's comments on the proposed PI are provided directly in the marked-up document attached (see below).

OPDP's has reviewed the proposed Carton and Container Labeling submitted by the applicant and available in the EDR at:

- <\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-125-25mgsmpltraylabel.pdf>
- <\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-125-25mgtraylabel.pdf>
- <\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgbacklabel.pdf>

- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgcarton.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgfrontlabel.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mginstcarton.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mginstfrontlabel.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mginsttraylabel.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgsmplcarton.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgsmpltraylabel.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgtraylabel.pdf](#)
- [\\cdsesub1\evsprod\nda203975\0000\m1\us\114-labeling\1141-draft\draft-62-5-25mgsmplfrontlabel.pdf](#)

OPDP does not have any comments on the proposed Carton and Container labels at this time.

OPDP's review and comments on the proposed MG and proposed IFU was conducted jointly with the Division of Medical Policy Programs (DMPP). This review will be submitted under separate cover at a later date.

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

If you have any questions regarding this review, please contact Matthew Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

MATTHEW J FALTER
11/15/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 12, 2013

Reviewer: Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, M.S., PharmD
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Anoro Ellipta
(Umeclidinium and Vilanterol inhalation powder)
62.5 mcg/25 mcg

Application Type/Number: NDA 203975

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2013-125

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review responds to a consult from the Division of Pulmonary Allergy and Rheumatology Products (DPARP) to evaluate the proposed container labels, carton and insert labeling, and patient instructions for use for Anoro Ellipta NDA 203975 for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the June 7, 2013 labeling submission.

- Active Ingredient: Umeclidinium and Vilanterol
- Indication of Use: Long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
- Route of Administration: Oral inhalation
- Dosage Form: Inhalation Powder
- Strength: 62.5 mcg/25 mcg per actuation
- Dose and Frequency: 1 inhalation once daily
- How Supplied: Light grey and red plastic inhaler containing 2 double-foil strips. The inhaler is packaged within a moisture-protective foil tray with a desiccant and a peelable lid. It is supplied as 30 blisters on each double-foil strip and an institutional pack with 7 blisters on each double foil strip. The inhaler is not reusable.
- Storage: Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place away from direct heat or sunlight. Discard after the counter reads “0” or 6 weeks after removal from the moisture-protective foil tray, whichever comes first.

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) searched the FDA Adverse Event Reporting System (FAERS) database for any medication error reports. Refer to Appendix A for a description of the FAERS database. We also reviewed the Anoro Ellipta labels, instructions for use, and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

Since the Ellipta device is currently marketed (Breo Ellipta), we searched the FAERS database using the strategy listed in Table 1 to see if there are any device related or labeling issues.

Table 1: FAERS Search Strategy	
Date	No date limitation
Drug Names	(Breo Ellipta)
MedDRA Search Strategy	Medication Errors HLT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

There were no reports retrieved from this search.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 18, 2012 (Appendix A)
- Carton Labeling submitted December 18, 2012 (Appendix B)
- Insert Labeling submitted June 7, 2013 (no image)
- Patient Instructions for Use submitted June 7, 2013 (no image)

2.3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Anoro Ellipta is composed of Umeclidinium and Vilanterol which are not currently marketed, making this combination product a new molecular entity. The Ellipta device is currently marketed (Breo Ellipta) and is to be integrated with the drug product and not available alone. There are other similar currently marketed products (i.e. Advair Diskus) that present as an integrated device with the drug product. (b) (4)

We did not retrieve any errors with the currently marketed Ellipta. We compared the label and labeling of Anoro Ellipta and Breo Ellipta to ensure that they are well differentiated from each other.

We note there are areas in the label, labeling, and the instructions for use that can be improved upon to decrease confusion and to increase readability. We provide our recommendations in section 4.1

3 CONCLUSIONS

DMEPA concludes that the proposed labels, labeling and instructions for use can be improved to increase the readability and prominence of important information on the label to mitigate any confusion.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

5.1 Comments to the Applicant:

A. All Container Labels

1. Revise the word 'Ellipta' in the proprietary name so that it is presented in the same color as the word 'Anoro'. As presented the word Ellipta utilizes a gray font over the pink background and is difficult to read.
2. Unbold the statement 'Rx Only', as presented this statement competes for prominence with the proprietary name.

B. All Carton Labeling

1. See above A1-A2
2. Remove the (b) (4) from the principle display panel to decrease clutter.
3. As presented, the directions on the side panel may cause confusion as patients may read across the line. Revise these to be presented in a stepwise manner that reads from left to right and top to bottom omitting the line in the middle. See example below:

1. OPEN

Slide the cover down until you hear a "click"

Add existing graphic

2. INHALE

- While holding the inhaler.....
- Don't breathe out...
- Put the mouthpiece...
- Take one long...

Add existing graphic

- Remove the inhaler....
- You may not be able...

3. CLOSE

- Then slide the cover
- Remember to....

C. Patient Instructions for Use

1. Each step throughout the IFU should be numbered as Step 1, Step 2.

2. Include a picture for each corresponding step and label the pictures as Figure A, Figure B.
3. In all pictures each individual component should be labeled.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

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/s/

LISSA C OWENS
09/12/2013

LUBNA A MERCHANT
09/13/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 5, 2013

TO: Leila P. Hann, Regulatory Project Manager
Jennifer Pippins, M.D., Medical Officer
Susan Limb, M.D., Cross Discipline Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203975

APPLICANT: Glaxo Group Limited, d/b/a GlaxoSmithKline

DRUG: umeclidinium-vilanterol dry powder for inhalation (Anoro™ Ellipta™)

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard review

INDICATION: Chronic obstructive pulmonary disease

CONSULTATION REQUEST DATE: February 4, 2013 (signed)
INSPECTION SUMMARY GOAL DATE: October 18, 2013
DIVISION ACTION GOAL DATE: December 18, 2013
PDUFA DATE: December 18, 2013

I. BACKGROUND:

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation caused by both progressive parenchymal destruction and disease of the small airways. Pharmacologic treatment guidelines recommend an incremental approach as the disease state worsens. A treatment option proposed by the Sponsor is the combination of an orally inhaled long-acting muscarinic antagonist (LAMA) such as umeclidinium and an orally inhaled selective long acting beta-2 adreno-receptor agonist (LABA) such as vilanterol.

Two adequate and well-controlled clinical studies were submitted in support of the Sponsor's NDA. The CDER review division selected a single foreign site in Denmark for Study DB2113361 and one domestic site for Study DB2113373 for inspection based on the high number of enrolled patients, large number of drop-outs, and a large efficacy effect size.

Study DB2113361

Study DB2113361 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The primary objective was to evaluate the efficacy and safety of GSK573719 (umeclidinium) /GW642444 (vilanterol) inhalation powder 125/25 mcg, GSK573719 (umeclidinium) inhalation powder 125 mcg, GW642444 (vilanterol) inhalation powder 25 mcg, and placebo when administered once daily via a novel dry powder inhaler (NDPI) over a 24-week treatment period in subjects with COPD. The primary measure of efficacy was trough (pre-bronchodilator and pre-dose) FEV1 at the clinic visit on Treatment Day 169. Trough FEV1 on Treatment Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at the Week 24 Visit).

Study DB2113373

Study DB2113373 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The primary objective of the study was to evaluate the efficacy and safety of GSK573719 (umeclidinium)/GW642444 (vilanterol) inhalation powder, GSK573719 (umeclidinium) inhalation powder, GW642444 (vilanterol) inhalation powder, and placebo when administered once-daily via a novel dry powder inhaler over 24-weeks in subjects with COPD. The primary efficacy endpoint was the pre-dose trough FEV1 on Treatment Day 169. Trough FEV1 on Treatment Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at the Week 24 Visit).

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Jesper Sonne, M.D. Copenhagen, Denmark	Protocol DB2113361/ Site #086085 N=19	April 29 - May 2, 2013	VAI
Gregory J. Feldman, M.D. Spartanburg, S.C.	Protocol DB2113373/ Site #087869 N=35	May 6 - 10, 2013	NAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

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

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed out, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Jesper Sonne, M.D./Protocol DB2113361 Site #086085

DanTrials ApS
 c/o Bispebjerg Hospital
 Bygning 15B
 Bispebjerg Bakke 23
 Copenhagen, 2400 Denmark

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from April 29 to May 2, 2013. A total of 45 subjects were screened and 19 subjects were enrolled. Fourteen subjects completed the study.

An audit of 34 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the

primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events (SAEs) at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not maintaining adequate clinical records. The following regulatory deficiencies are selected relevant examples: (1) Source documentation did not identify the research staff who documented the information. For example, the concomitant medications log for Subjects #3301, #3297, and #3293 did not include the identity of the staff who recorded the information. (2) Source documentation study records were not documented adequately, accurately or completely. For example, medication logs for Subject #3276 had “sticky notes” containing subject’s withdrawal of consent for being administered the medication, and Subject #3289 had “sticky notes” containing the patient’s medication dosages.

The List of Inspectional Observations (Form FDA 483) was communicated to the DPARP Medical Team who did not consider the above findings as significant. Dr. Sonne responded adequately to these observations in a letter dated May 16, 2013.

c. Assessment of data integrity:

The regulatory deficiencies noted above are considered minor and non-critical. Data submitted by this clinical site appear acceptable for this specific indication.

2. Gregory Feldman, M.D./Protocol DB2113373 Site #087869

South Carolina Pharmaceutical Research
1330 Boiling Springs Rd., Suite 2100
Spartansburg, S.C. 29303

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from May 6 to 10, 2013. A total of 41 subjects were screened and 35 subjects were enrolled. Twenty three subjects completed the study.

An audit of the 10 enrolled subjects’ records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this NDA, a single U.S. clinical investigator site for Study DB2113373 (Gregory Feldman, M.D.) and a single foreign clinical investigator site for Study DB2113361 (Jesper Sonne, M.D.) were inspected in support of this application.

No deficiencies were observed for Dr. Feldman's clinical study site. The final regulatory classification was NAI (No Action Indicated). Minor regulatory deficiencies were observed for Dr. Sonne's clinical study site for not maintaining adequate records. The final regulatory classification was VAI (Voluntary Action Indicated).

The study data collected appear generally reliable in support of the requested indication.

{See appended electronic signature page}

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

CONCURRENCE:

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/s/

ANTHONY J ORENCIA
09/06/2013

JANICE K POHLMAN
09/06/2013

KASSA AYALEW
09/06/2013

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2013-054
APPLICATION NUMBER	NDA 203975
LETTER DATE/SUBMISSION NUMBER	#1
PDUFA GOAL DATE	December 18, 2013
DATE OF CONSULT REQUEST	April 16, 2013
REVIEW DIVISION	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
MEDICAL REVIEWER	Jennifer R. Pippins
REVIEW DIVISION PM	Leila P. Hann
SEALD REVIEWER(S)	Jessica Voqui
REVIEW COMPLETION DATE	June 21, 2013
ESTABLISHED NAME	Umeclidinium bromide/vilanterol
TRADE NAME	Anoro Ellipta
APPLICANT	GlaxoSmithKline (GSK)
ENDPOINT(S) CONCEPT(S)	Dyspnea with daily activities
MEASURE(S)	Shortness of Breath with Daily Activities (SOBDA) Questionnaire
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
INDICATION	Long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
INTENDED POPULATION(S)	Adult patients (≥ 40 years of age) with an established clinical history of COPD, a post-bronchodilator FEV ₁ of $\leq 70\%$ predicted and FEV ₁ /FVC ratio < 0.70 , and ≥ 10 -pack years smoking history

SEALD Review

Jessica Voqui

NDA 203975

Anoro Ellipta (umeclidinium bromide / vilanterol)

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) regarding NDA 203975. The sponsor proposes Shortness of Breath with Daily Activities (SOBDA) Questionnaire for the measurement of dyspnea with daily activities for use as an exploratory endpoint in planned clinical trials in adult patients (≥ 40 years of age) with an established clinical history of COPD, a post-bronchodilator FEV₁ of $\leq 70\%$ predicted and FEV₁/FVC ratio < 0.70 , and ≥ 10 -pack years smoking history.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

In previous correspondences and discussions with the sponsor during the early instrument development under IND 050703, detailed advice was provided to the sponsor in advance of the clinical trials submitted for this application to provide guidance in developing a well-defined and reliable measure and avoid interpretability issues. [REDACTED] (b) (4)

[REDACTED] the interpretability issue may have been overcome and our recommendation would be more favorable. [REDACTED] (b) (4)

SEALD Review

Jessica Voqui

NDA 203975

Anoro Ellipta (umeclidinium bromide / vilanterol)

[Redacted] (b) (4)

B. SEALD COMMENTS

The DPARP requested that SEALD review the adequacy of the SOBDA instrument t [Redacted] (b) (4)

SEALD has previously reviewed the SOBDA and provided advice to the sponsor during the early development of this instrument under IND 050703. In response to the Agency’s feedback and advice, the sponsor reanalyzed qualitative study data and provided additional information, but did not make any major changes to the instrument itself since the most recent SEALD review (Papadopoulos 06/21/13). [Redacted] (b) (4)

[Redacted]

[Redacted] (b) (4)

C. STUDY ENDPOINT REVIEW

The sponsor has had ongoing discussions with the Agency regarding development programs for several products indicated for COPD, [Redacted] (b) (4)

SEALD Review

Jessica Voqui

NDA 203975

Anoro Ellipta (umeclidinium bromide / vilanterol)

The SOBDA has been previously reviewed by SEALD (Miskala 03/14/08; Papadopoulos 06/21/10) for IND 050703, which is referenced in the current NDA. (b) (4)

These comments were included in a letter to the sponsor dated June 30, 2010 that was followed up with a teleconference on July 27, 2010.

This NDA (203975) currently under review includes a PRO Evidence Dossier that provides additional information to address these concerns.

1 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

Shortness of Breath with Daily Activities (SOBDA) Questionnaire (Appendix A)

The final version of the SOBDA is a 13-item questionnaire that is administered in an electronic diary (eDiary). Each item is framed as, "How short of breath were you when you [performed this activity] today?" and includes the following activities:

- putting on long pants or stockings
- putting on shoes (sandals)
- washing yourself
- reaching above your head to put things away
- cleaned or fixed something at floor level
- put things away in the cupboard or shelf at chest level
- putting things away at knee level
- prepared food or a meal
- picked up light objects off the floor
- carried objects at your side like bags or baskets
- walked at a slow pace
- walked up 3 stairs
- walked up 8 stairs

Subjects respond to the items based on their activities that day and complete the eDiary each evening just prior to bedtime. The response options range from: *Not at all*; *Slightly*; *Moderately*; *Severely*; and *So severe that I did not do the activity today*; or *I did not do the activity today*.

SEALD Review

Jessica Voqui

NDA 203975

Anoro Ellipta (umeclidinium bromide / vilanterol)

Prior versions: Other versions that were developed earlier in the process were included in the Dossier.

User manual: The SOBDA User Manual Version 2.0 is also included in the Dossier.

Scoring: A weekly mean SOBDA score ranging from 1–4 is calculated based on the mean of seven days. Higher scores indicated more severe dyspnea with daily activities. Each daily score is computed from the mean of the scores on the 13 items. Response options for each item are assigned by weighted scores between 1-4 based on measurement theory methods.

Missing data: To calculate the weekly mean SOBDA score, at least four of the seven days must be complete. For the daily score, at least seven items out of thirteen must not be missing. Items with the response “I did not do the activity today” are set to missing.

2 TARGET PRODUCT PROFILE

(b) (4)

The SOBDA has been evaluated for this purpose as part of the GSK573719/GW642444 phase III clinical development program.”

(b) (4)

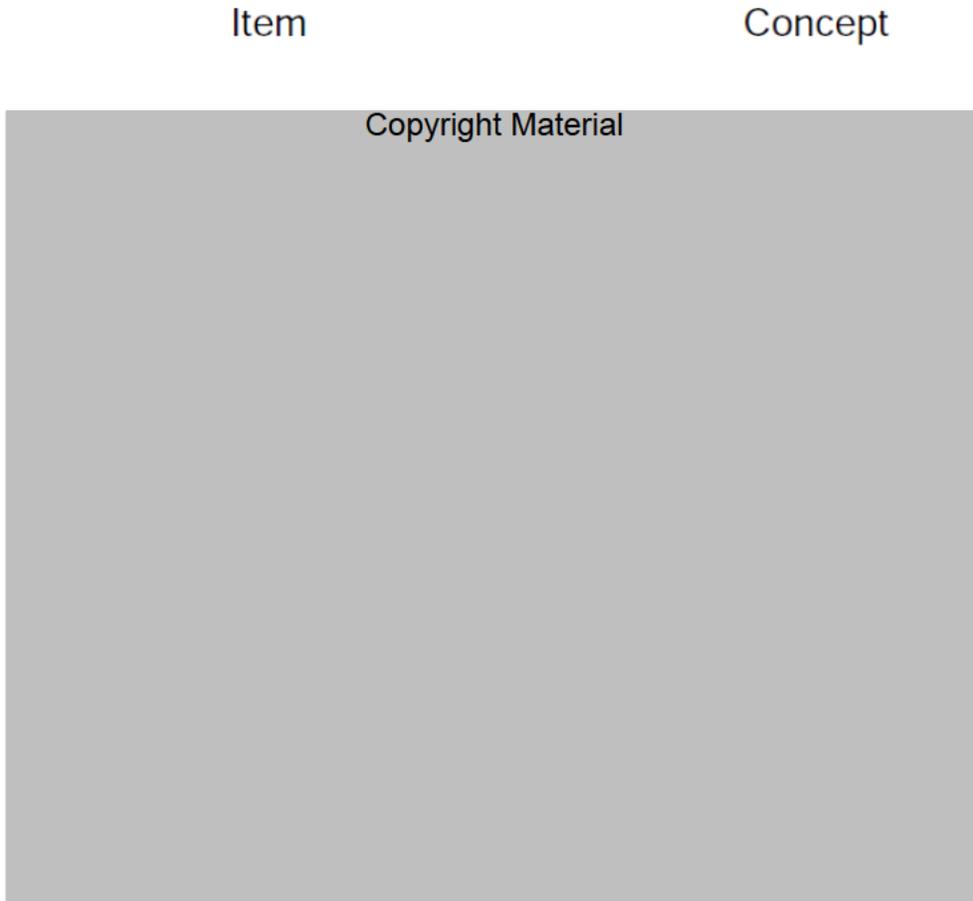
3 ENDPOINT MODEL

Table 1 Typical Efficacy Endpoint Hierarchy for General Clinical Trials in COPD

Primary Endpoint	Measurement Tools
Airflow obstruction	Spirometry (i.e., FEV ₁)
Secondary Endpoints	Measurement Tools
(b) (4)	PRO Daily Symptom Diary (e.g., SOBDA) Exercise tolerance (e.g., six-minute walk) COPD-specific assessment of Health Related Quality of Life [e.g. St Georges Respiratory Questionnaire (SGRQ)]

4 CONCEPTUAL FRAMEWORK

Figure 3 The SOBDA Conceptual Framework (Item - Concept)



5 CONTENT VALIDITY

The PRO Evidence Dossier includes detailed information regarding the instrument development, including qualitative research. The content validity has already been reviewed by SEALD (Papadopoulos 06/21/10), [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

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/s/

JESSICA VOQUI
06/21/2013

LAURIE B BURKE
06/24/2013

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

NDA	203975
Brand Name	Anoro Ellipta
Generic Name	Umeclidinium-Vilanterol
Sponsor	GlaxoGroup (d/b/a GSK)
Indication	Treatment for Chronic Obstruction Pulmonary Disease (COPD)
Dosage Form	Inhalation powder
Drug Class	Muscarinic receptor antagonist
Therapeutic Dosing Regimen	125/25 mcg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	500 mcg and 500/100 mcg
Submission Number and Date	SDN 001/18 Dec 2012
Review Division	DPARP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effects of a therapeutic dose of UMEC/VI 125/25 mcg and suprathereapeutic dose of UMEC 500 mcg were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, and between UMEC 500 mcg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between UMEC/VI 500/100 mcg and placebo was 10.7 which is higher than the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 6, indicating that assay sensitivity was established.

In this randomized, placebo-controlled, incomplete block, four-period crossover repeat dose study, 86 healthy subjects received UMEC/VI 125/25 mcg, UMEC/VI 500/100 mcg, UMEC 500 mcg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for UMEC/VI (125/25 mcg and 500/100 mcg), UMEC 500 mcg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
UMEC/VI 125/25 mcg	10 min	4.6	(2.0, 7.1)
UMEC/VI 500/100 mcg	30 min	8.2	(5.7, 10.7)
UMEC 500 mcg	30 min	-1.8	(-4.3, 0.7)
Moxifloxacin 400 mg*	4	9.3	(7.2, 11.5)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 6.1 ms.

An increase in heart rate was also observed. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo and UMEC/VI 500/100 mcg and placebo were 10.5 and 22.3 bpm, respectively.

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for UMEC/VI (125/25 mcg and 500/100 mcg) and UMEC 500 mcg for $\Delta\Delta\text{HR}$ (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{HR}$ (bpm)	90% CI (bpm)
UMEC/VI 125/25 mcg	10 min	8.8	(7.1, 10.5)
UMEC/VI 500/100 mcg	10 min	20.5	(18.8, 22.3)
UMEC 500 mcg	16 h	2.2	(0.3, 4.1)

An increase in $\Delta\Delta\text{QTcF}$ is observed with increasing concentration of VI. There is no relationship between UMEC concentration and $\Delta\Delta\text{QTcF}$. The suprathreshold dose (500/100 mcg) of UMEC/VI produces mean C_{max} values 4.2-fold the mean C_{max} for the therapeutic dose (125/25 mcg) at steady state for VI. Following repeat dosing of inhaled vilanterol, up to 2.4-fold accumulation is expected at steady state. It is expected from single dose drug interaction study that co-administration of VI with ketoconazole, the $\text{AUC}(0-t)$ will be 90% higher suggesting an increase in half-life of VI. The C_{max} was not affected. However, upon multiple administration of the drug with ketoconazole, higher C_{max} (greater than 2.4-fold) is expected because of accumulation and increase in half-life. The concentrations achieved at the suprathreshold dose for VI at steady state are likely to be above those for the predicted worst case scenario (drug interaction with ketoconazole) for VI. The suprathreshold dose (500/100 mcg) of UMEC/VI produces mean C_{max} values 4.2-fold the mean C_{max} for the therapeutic dose (125/25 mcg) at steady state for UMEC. Following repeat dosing of inhaled UMEC, up to 1.5- to 2-fold accumulation is expected at steady state. The concentrations achieved at the suprathreshold dose for UMEC at steady state are likely to be above those for the predicted worst case scenario (accumulation due to repeated dose) for UMEC.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

12.2 Pharmacodynamics

(b) (4)



Reviewer's Comments: We have not reviewed the data referenced in the paragraph labeled "cardiovascular effects."

2.2 QT-IRT'S PROPOSED LABEL

QT-IRT's label recommendations are suggestions only. We defer final label decisions to the Division.

12.6. Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, multiple dose, placebo- and positive-controlled crossover study in 86 healthy volunteers. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 4.6 (7.1) ms and 8.2 (10.7) ms for umeclidinium/vilanterol 125/25 and umeclidinium/vilanterol 500/100, respectively.

A dose-dependent increase in heart rate was also observed. The maximum mean (95% upper confidence bound) difference in heart rate from placebo after baseline correction was 8.8 (10.5) beats/min and 20.5 (22.3) beats/min seen 10 minutes after dosing for umeclidinium/vilanterol 125/25 and umeclidinium/vilanterol 500/100, respectively.

3 BACKGROUND

3.1 PRODUCT INFORMATION

GSK573719 is a long-acting, inhaled, muscarinic receptor antagonist (or anticholinergic) bronchodilator. It is currently under development for the treatment of chronic obstructive pulmonary disease (COPD). GW642444 is a potent and selective long-acting β 2 agonist. GSK573719 in combination with Vilanterol are in development as inhaled treatments for

Chronic Obstructive Pulmonary Disease (COPD). [REDACTED] (b) (4)

[REDACTED] The Novel Dry Powder Inhaler (Novel DPI) delivers both GSK573719 and Vilanterol, as the inhalation powder.

3.2 MARKET APPROVAL STATUS

Umeclidinium bromide/vilanterol is not marketed in any country in the world.

3.3 PRECLINICAL INFORMATION

Reviewer's comments: GSK573719 blocks hERG currents in a concentration-dependent manner. The IC50 is 3-fold the clinical exposure achieved with a single dose of 1000 µg.

3.4 PREVIOUS CLINICAL EXPERIENCE

More than 4000 subjects are included in the sponsor's safety database. Cases of QT prolongation (less than 1% incidence) and ventricular tachycardia were reported during this clinical program in subjects exposed to UMEC or VI, and placebo. One case of sudden death was reported in a subject treated with VI 25 mcg. No torsade de pointes were reported in this program.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of UMEC's and VI's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 104,479. The sponsor submitted the study report DB2114635 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, placebo-controlled, incomplete block, four period crossover, repeat dose study to evaluate the effect of the inhaled GSK573719/vilanterol combination and GSK573719 monotherapy on electrocardiographic parameters, with moxifloxacin as a positive control, in healthy subjects.

4.2.2 Protocol Number

DB2114635

4.2.3 Study Dates

Initiation Date: 09-JAN-2012

Completion Date: 05-JUN-2012

4.2.4 Objectives

Primary objective: [REDACTED]

- To estimate the effect of umeclidinium (UMEC, GSK573719)/vilanterol (VI, GW642444) 125/25 mcg on the QT interval using Fridericia's correction (QTcF) as compared with placebo after 10 days' dosing
- To estimate the effect of UMEC 500 mcg (four times the highest combination dose being evaluated in Phase III trials) on the QTcF interval as compared with placebo after 10 days' dosing

Secondary objectives:

- To estimate the effect of UMEC/VI 500/100 mcg (four times the highest combination dose being evaluated in Phase III trials) on the QTcF interval as compared with placebo after 10 days' dosing
- To estimate the effect of UMEC/VI 125/25 mcg and 500/100 mcg on the individual QT correction (QTci) and Bazett's correction (QTcB) interval as compared with placebo after 10 days' dosing
- To estimate the effect of UMEC 500 mcg, on the QTci and QTcB interval as compared with placebo after 10 days' dosing
- To estimate the effect of a single oral dose of 400 mg moxifloxacin on the QTcF interval as compared with placebo on Day 10
- To estimate the effect of a single oral dose of 400 mg moxifloxacin on the QTci and QTcB interval as compared with placebo on Day 10
- To estimate the effect of all active treatments on other cardiac electrophysiological parameters as compared with placebo after 10 days' dosing
- To characterize the pharmacokinetic profiles of UMEC and VI when administered in combination via novel dry powder inhaler (NDPI)
- To characterize the pharmacokinetic profile of supra-therapeutic dose of UMEC when administered as monotherapy via NDPI
- To explore the relationship between pharmacokinetic concentration and QT

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, placebo-controlled, four-period incomplete block crossover study in healthy male and female subjects. Screening took place within 28 days prior to the first dose. Eligible subjects were randomized to receive four of five possible, 10-day repeat dose treatments. Treatments were placebo with a moxifloxacin placebo on Day 10, placebo with moxifloxacin (400 mg) on Day 10, UMEC/VI combination (125/25 mcg) with moxifloxacin placebo on Day 10, UMEC/VI combination (500/100 mcg) with moxifloxacin placebo on Day 10, or UMEC (500 mcg) with moxifloxacin placebo on Day 10. Treatment periods were separated by a washout of at least 10 days. The overall duration of each subject's participation in the study, from screening to follow-up, was approximately 16 weeks. A follow-up visit was held within 10 days of the final dose.

Treatment periods were separated by a washout of at least 10 days. The overall duration of each subject's participation in the study, from screening to follow-up, was approximately 16 weeks. A follow-up visit was held within 10 days of the final dose.

4.2.5.2 Controls

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

4.2.5.3 Blinding

All treatments were double blind except for moxifloxacin (400 mg) and moxifloxacin placebo controls, given as a single-blind single dose on Day 10 of the appropriate treatment period.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

All subjects were randomly assigned to 1 of 5 treatments (A, B, C, D A or E) to one of the twenty possible sequences of regimens provided in the table below:

- A: Placebo 1–10 Single inhalation from matching placebo NDPI once
- B: Moxifloxacin positive control
- C: UMEC 500 mcg supra-therapeutic dose
- D: UMEC/VI 125/25 mcg therapeutic dose
- E: UMEC/VI 500/100 mcg suprathapeutic dose

Table 3: Sequences of Treatment Regimens

A	E	D	C
B	A	E	D
C	B	A	E
D	C	B	A
E	D	C	B
A	B	C	D
B	C	D	E
C	D	E	A
D	E	A	B
E	A	B	C
A	D	B	E
B	E	C	A
C	A	D	B
D	B	E	C
E	C	A	D
A	C	E	B
B	D	A	C
C	E	B	D
D	A	C	E
E	B	D	A

4.2.6.2 Sponsor's Justification for Doses

The effects of inhaled UMEC/VI combination were assessed at the anticipated therapeutic clinical dose as well as the inhaled UMEC/VI combination and UMEC monotherapy at a higher suprathereapeutic dose representing a four times multiple of the anticipated clinical dose.

Reviewer's Comment: The suprathereapeutic dose (500/100 mcg) of UMEC/VI produces mean C_{max} values 4.2-fold the mean C_{max} for the therapeutic dose (125/25 mcg) at steady state for VI. Following repeat dosing of inhaled vilanterol, up to 2.4-fold accumulation is expected at steady state. It is expected from single dose drug interaction study that co-administration of VI with ketoconazole, the AUC(0-t) will be 90% higher suggesting an increase in half-life of VI. The C_{max} was not affected. However, upon multiple administration of the drug with ketoconazole, higher C_{max} (greater than 2.4-fold) is expected because of accumulation and increase in half-life. The concentrations achieved at the suprathereapeutic dose for VI at steady state are likely to be above those for the predicted worst case scenario (drug interaction with ketoconazole) for VI. The suprathereapeutic dose (500/100 mcg) of UMEC/VI produces mean C_{max} values 4.2-fold the mean C_{max} for the therapeutic dose (125/25 mcg) at steady state for UMEC. Following repeat dosing of inhaled UMEC, up to 1.5- to 2-fold accumulation is expected at steady state. The concentrations achieved at the suprathereapeutic dose for UMEC at steady state are likely to be above those for the predicted worst case scenario (accumulation due to repeated dose) for UMEC. Since the concentrations achieved by the suprathereapeutic dose covers the worst case scenario for VI and UMEC, the suprathereapeutic dose is adequate.

4.2.6.3 Instructions with Regard to Meals

Subjects were given standard meals and snacks during the following time intervals: 4 h–4.5 h, 10 h \pm 0.5 h and 14–16 h post-dose. Water was permitted *ad libitum* except for 1 h either side of dosing.

Reviewer's Comment: This is a product for inhalation. Thus food effects are not anticipated.

4.2.6.4 ECG and PK Assessments

ECG and PK sampling on day 10 of the treatment period is shown in **Table 4**. ECG and PK samples were collected pre-dose, 5 min, 10 min, 30 min, 1 h, 2h, 4 h, 8 h, 12 h, 16h and 24 after drug administration.

Table 4: PK and ECG Sampling on Days 9-10, Periods 1-4

Procedure	Treatment Periods 1-4																		
	Day 9	Day 10																	
		Pre-dose	0	5 min	10 min	15 min	30 min	45 min	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	16 h	24 h
Drugs of abuse screen	X																		
Alcohol and CO breath test	X																		
Safety laboratory tests	X																		X
Pregnancy test	X ¹																		
Vital signs ²		X			X				X		X			X			X		X
12-Lead ECG ³		X							X					X		X	X	X	X
12-Lead Holter ECG ⁴		X		X	X		X		X		X		X		X	X	X	X	X
Dosing	X		X																
Pharmacokinetic samples		X		X	X		X		X		X		X		X		X	X	X
Adverse event check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Meals and snacks ⁵	X												X	X		X			

1. Urine pregnancy tests were not performed on female subjects whose post-menopausal status had been confirmed at screening.
 2. Three measurements taken throughout.
 3. Those 12-lead ECGs obtained pre-dose and at 1, 8, 12 and 24 h post-dose were reviewed by the clinical unit physician for safety purposes.
 4. Triplicate measurements were taken.
 5. Subjects were given standard meals and snacks during the following time intervals: 4 h-4.5 h, 10 h ±0.5 h and 14-16 h post-dose. Water was permitted *ad libitum* except for 1 h either side of dosing.
- CO=carbon monoxide; ECG=electrocardiogram.

Source: Sponsor’s Table 5 from Clinical Study report

Reviewer’s Comment: ECG/PK samples were collected frequently enough to monitor the effects of the drug over a 24-hour interval. Frequent samples were collected around T_{max} (5-15 min) of the drug in order to detect changes in the QT interval at maximum drug concentrations. The ECG and PK samples were collected at steady state on day 10.

4.2.6.5 Baseline

The sponsor used pre-dose QTc values on day 10 as baseline.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor’s Results

4.2.8.1 Study Subjects

Of the 103 (48 female and 55 male) subjects enrolled the study, 86 subjects (83%) completed the study.

Demographics	
Age in years, Mean (range)	33.1 (19-63)
Sex, n (%)	
Female:	48 (47)
Male:	55 (53)
Body Mass Index (kg/m ²), Mean (range)	23.37 (19.2-29.5)
Height (cm), Mean (range)	171.7 (153-195)
Weight (kg), Mean (range)	69.29 (46.4-102.1)
Ethnicity, n (%)	
Hispanic or Latino:	1 (<1)
Not Hispanic or Latino:	102 (>99)
Race, n (%)	
African American/African Heritage	21 (20)
Asian – Central/South Asian Heritage	10 (10)
Asian – East Asian Heritage	1 (<1)
Asian – South East Asian Heritage	1 (<1)
White – White/Caucasian/European Heritage	68 (66)
Mixed Race	2 (2)

a. Including 1 subject who reached protocol-defined stopping criteria due to a liver event.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was baseline-adjusted mean differences between UMEC/VI 125/25 mcg and placebo, and between UMEC 500 mcg and placebo on Day 10. The sponsor used an analysis of covariance (ANCOVA) model and the results are presented in Table 5. This model included period, time, treatment, and time-by-treatment interaction as fixed effect terms, subjects as a random effect, and subject and period baseline QTcF were included as covariate. The upper limits of the 2-sided 90% CIs for UMEC/VI 125/25 mcg, UMEC/VI 500/100 mcg and UMEC 500 mcg were below 10 ms.

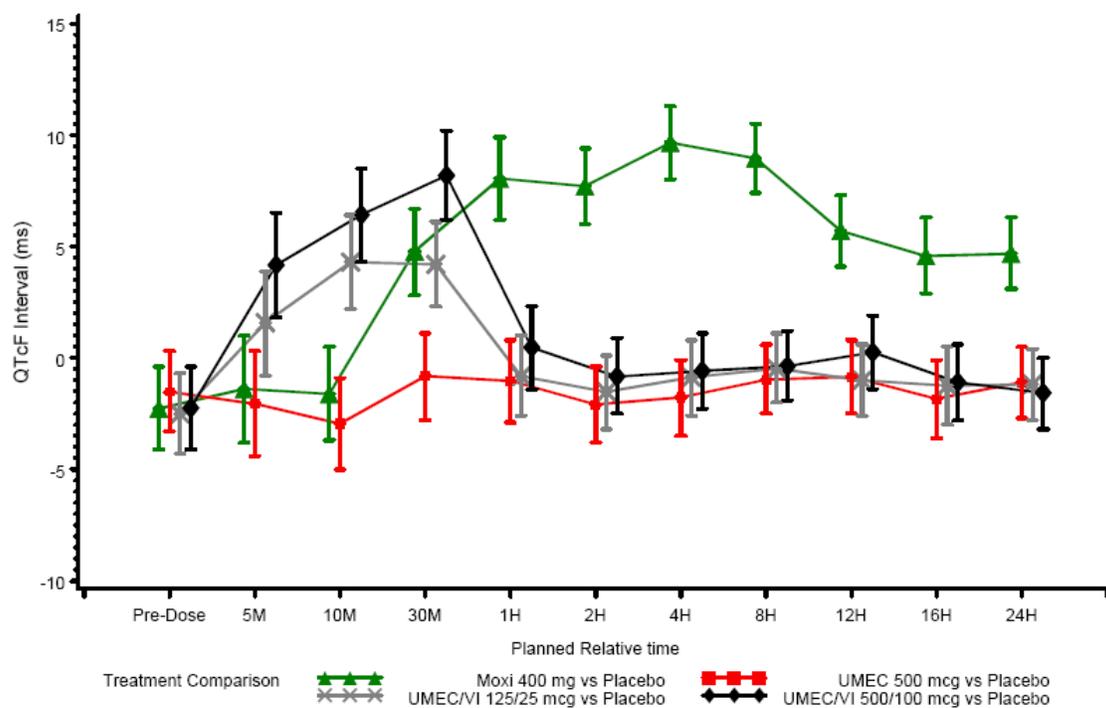
Table 5: Sponsor Results $\Delta \Delta$ QTcF for UMEC/VI 125/25mcg, UMEC/VI 500/100 mcg, UMEC 500 mcg and Moxifloxacin 400 mg

Time Point	Adjusted Means (msec)					Treatment Difference (90% CI) (msec)			
	Pbo (A)	Moxi 400 mg (B)	UMEC 500 mcg (C)	UMEC/VI 125/25 mcg (D)	UMEC/VI 500/100 mcg (E)	B – A	C – A	D – A	E – A
Pre-dose	0.6	-1.6	-0.9	-1.9	-1.6	-2.3 (-4.1,-0.4)	-1.5 (-3.3, 0.3)	-2.5 (-4.3,-0.7)	-2.2 (-4.1,-0.4)
5 mins	-1.9	-3.3	-4.0	-0.3	2.2	-1.4 (-3.8, 1.0)	-2.1 (-4.4, 0.3)	1.6 (-0.8, 3.9)	4.2 (1.8, 6.5)
10 mins	1.7	0.1	-1.2	6.0	8.2	-1.6 (-3.7, 0.5)	-2.9 (-5.0,-0.9)	4.3 (2.2, 6.4)	6.4 (4.3, 8.5)
30 mins	-1.6	3.2	-2.4	2.6	6.6	4.8 (2.8, 6.7)	-0.8 (-2.8, 1.1)	4.2 (2.3, 6.1)	8.2 (6.2,10.2)
1 h	0.0	8.1	-1.0	-0.8	0.5	8.1 (6.2, 9.9)	-1.0 (-2.9, 0.8)	-0.8 (-2.6, 1.0)	0.5 (-1.4, 2.3)
2 h	0.5	8.2	-1.6	-1.1	-0.4	7.7 (6.0, 9.4)	-2.1 (-3.8,-0.4)	-1.5 (-3.2, 0.1)	-0.8 (-2.5, 0.9)
4 h	0.5	10.1	-1.3	-0.4	-0.1	9.7 (8.0, 11.3)	-1.8 (-3.5,-0.1)	-0.9 (-2.6, 0.8)	-0.6 (-2.3, 1.1)
8 h	-7.7	1.3	-8.7	-8.2	-8.0	9.0 (7.4, 10.5)	-1.0 (-2.5, 0.6)	-0.5 (-2.0, 1.1)	-0.4 (-1.9, 1.2)
12 h	-4.5	1.2	-5.3	-5.5	-4.3	5.7 (4.1, 7.3)	-0.8 (-2.5, 0.8)	-1.0 (-2.6, 0.6)	0.3 (-1.4, 1.9)
16 h	2.2	6.7	0.3	0.9	1.1	4.6 (2.9, 6.3)	-1.8 (-3.6,-0.1)	-1.2 (-3.0, 0.5)	-1.1 (-2.8, 0.6)
24 h	-2.9	1.8	-4.0	-4.1	-4.5	4.7 (3.1, 6.3)	-1.1 (-2.7, 0.5)	-1.2 (-2.8, 0.4)	-1.6 (-3.2, 0.0)

Pbo=placebo; Moxi=moxifloxacin; CI=confidence interval.

Source: Clinical Study Report No., Section 5.1, Table 10, Pg 34/647

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our analyses results are similar as provided by the sponsor.



4.2.8.2.2 Assay Sensitivity

The sponsor used the same ANCOVA model to analyze the Δ QTcF effect for moxifloxacin. The analysis results were presented in Table 5. The lower limit of the two-sided 90% CI was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and Δ QTc $>$ 60 ms.

4.2.8.3 Safety Analysis

There were no serious adverse events. Four subjects had AEs that led to withdrawal from the study.

Subject 103 was withdrawn for non-drug related gastroenteritis that began 6 days after the first UMEC/VI 125/25 mcg dose.

Subject 116, was withdrawn after 9 days of UMEC/VI 500/100 mcg dosing in Period 1 due to intermittent palpitations and chest pain of mild intensity. The palpitations began 11 minutes after the first dose and lasted 8 days; the chest pain began 6 days after the first dose and lasted 5 days. Both AEs were considered possibly related to study medication by the investigator.

Subject 144 was withdrawn for non-drug related contact dermatitis that began 11 days after the first inhaled placebo dose.

Subject 192 was withdrawn for an alanine aminotransferase (ALT) increase >3 x the upper limit of normal that began 8 days after the first inhaled placebo dose and was attributed to (blinded) study medication by the investigator.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK parameters on day 10 are presented in Table 6 (UMEC) and Table 7 (VI). The concentration-time profiles on day 10 for UMEC and VI are shown in Figure 1 and Figure 2. Following administration of 500/100 mcg of UMEC/VI (supratherapeutic dose) C_{max} and $AUC_{0-\tau}$ values of UMEC in the thorough QT study were 4.2-fold and 4.3-fold values seen with 125/25 mcg of UMEC/VI, the highest intended clinical dose. Following administration of 500 mcg of UMEC (supratherapeutic dose of UMEC) C_{max} and $AUC_{0-\tau}$ values of UMEC were 4.6-fold and 4.9-fold values seen with 125/25 mcg of UMEC/VI. Following administration of 500/100 mcg of UMEC/VI C_{max} and $AUC_{0-\tau}$ values of VI were 4.5-fold and 4.3-fold values seen with 125/25 mcg of UMEC/VI.

Table 6: Sponsor’s Mean PK parameters for UMEC on Day 10

Parameter	Treatment	N	n	Geometric Mean	95% CI	CVb(%)
C_{max} (pg/mL)	UMEC 500 mcg	75	73	1541	(1412, 1682)	38.8
	UMEC/VI 125/25 mcg	75	74	334	(294, 379)	59.1
	UMEC/VI 500/100 mcg	73	70	1400	(1285, 1525)	37.1
$AUC_{0-\tau}$ (h*pg/mL)	UMEC 500 mcg	75	73	2444	(2278, 2623)	31.0
	UMEC/VI 125/25 mcg	75	74	495	(431, 569)	65.6
	UMEC/VI 500/100 mcg	73	70	2145	(1977, 2328)	35.2
t_{max} (h)*	UMEC 500 mcg	75	73	0.10	(0.08, 0.23)	NA
	UMEC/VI 125/25 mcg	75	74	0.10	(0.08, 0.15)	NA
	UMEC/VI 500/100 mcg	73	70	0.10	(0.08, 0.12)	NA
t_{last} (h)*	UMEC 500 mcg	75	73	24.08	(23.98, 24.25)	NA
	UMEC/VI 125/25 mcg	75	74	24.08	(0.10, 24.25)	NA
	UMEC/VI 500/100 mcg	73	70	24.08	(24.08, 24.25)	NA
$t_{1/2}$ (h)	UMEC 500 mcg	75	47	25.9	(23.7, 28.3)	0.1
	UMEC/VI 125/25 mcg	75	37	19.1	(12.6, 29.0)	110.9
	UMEC/VI 500/100 mcg	73	36	25.2	(22.4, 28.4)	0.2
CL/F (L/h)	UMEC 500 mcg	75	73	205	(191, 220)	31.0
	UMEC/VI 125/25 mcg	75	73	244	(216, 276)	56.9
	UMEC/VI 500/100 mcg	73	70	233	(215, 253)	35.2
V/F (L)	UMEC 500 mcg	75	47	7749	(6890, 8716)	41.7
	UMEC/VI 125/25 mcg	75	37	7857	(6225, 9918)	79.3
	UMEC/VI 500/100 mcg	73	36	8418	(7375, 9607)	40.6
λ_z	UMEC 500 mcg	75	47	0.027	(0.024, 0.029)	31.2
	UMEC/VI 125/25 mcg	75	37	0.036	(0.024, 0.055)	195.9
	UMEC/VI 500/100 mcg	73	36	0.027	(0.024, 0.031)	36.5

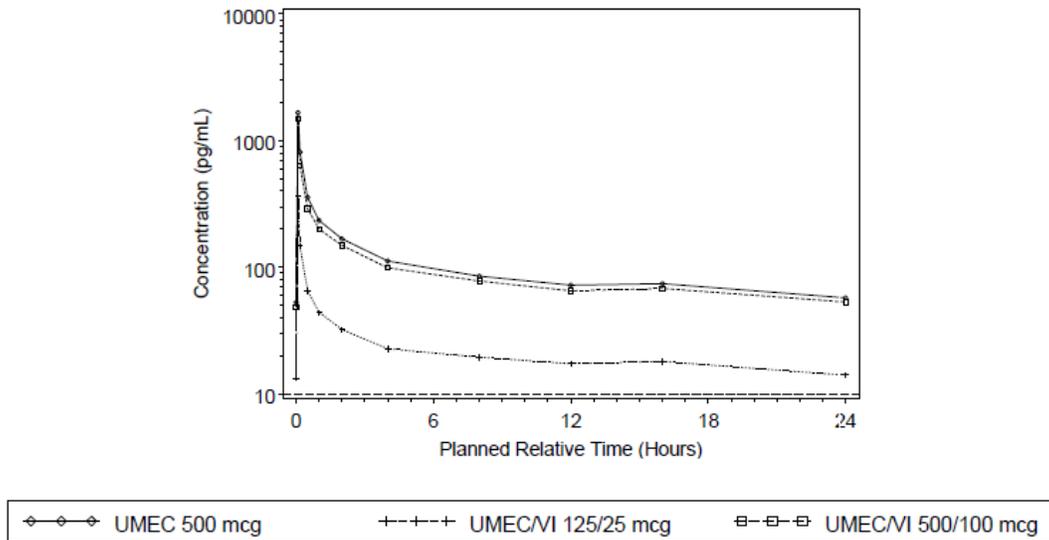
Source Data: Table 11.2

*Presented as median and range.

NA=not applicable; CVb=between-subject coefficient of variation.

Source: Table 15 in Clinical Study report

Figure 1: Sponsor’s Mean UMEC concentration-time profiles on Day 10



Source: Figure 11.3 in Clinical Study report.

Table 7: Sponsor’s Mean PK parameters for VI on Day 10

Parameter	Treatment	N	n	Geometric Mean	95% CI	CVb(%)
C _{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	340	(307, 376)	45.9
	UMEC/VI 500/100 mcg	73	70	1518	(1416, 1627)	29.8
AUC(0-τ) (h*pg/mL)	UMEC/VI 125/25 mcg	75	74	429	(379, 486)	57.6
	UMEC/VI 500/100 mcg	73	70	1824	(1728, 1924)	22.9
t _{max} (h)*	UMEC/VI 125/25 mcg	75	74	0.10	(0.08, 0.15)	NA
	UMEC/VI 500/100 mcg	73	70	0.10	(0.08, 0.22)	NA
t _{last} (h)*	UMEC/VI 125/25 mcg	75	74	16.02	(0.52, 24.25)	NA
	UMEC/VI 500/100 mcg	73	70	24.08	(24.08, 24.25)	NA
t _{1/2} (h)	UMEC/VI 125/25 mcg	75	55	10.52	(8.43, 13.12)	97.8
	UMEC/VI 500/100 mcg	73	62	19.22	(17.68, 20.90)	33.9
CL/F (L/h)	UMEC/VI 125/25 mcg	75	74	58.2	(51.4, 65.9)	57.6
	UMEC/VI 500/100 mcg	73	70	54.8	(51.9, 57.9)	22.9
V/F (L)	UMEC/VI 125/25 mcg	75	55	890	(783, 1010)	49.8
	UMEC/VI 500/100 mcg	73	62	1526	(1383, 1684)	40.2
λ _z	UMEC/VI 125/25 mcg	75	55	0.066	(0.053, 0.082)	97.8
	UMEC/VI 500/100 mcg	73	62	0.036	(0.033, 0.039)	33.9

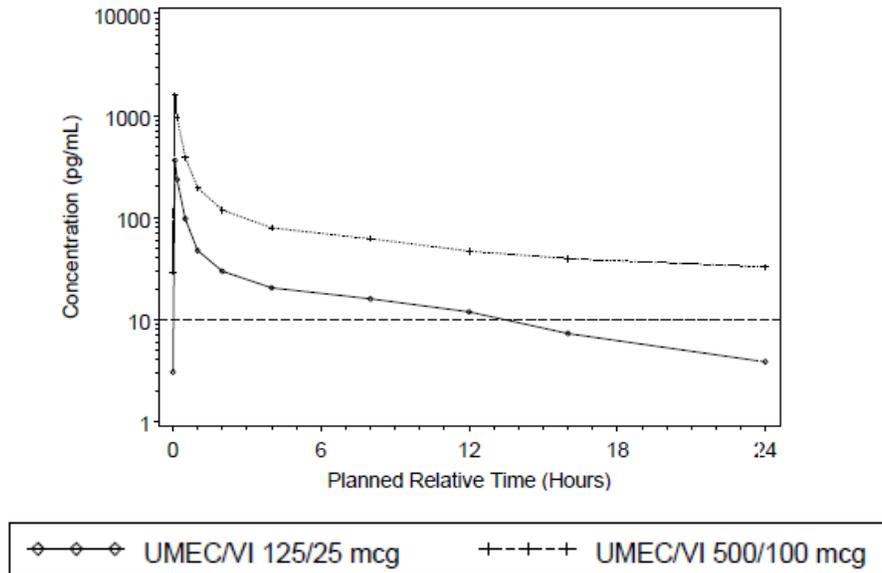
Source Data: [Table 11.4](#)

*Presented as median and range.

NA=not applicable; CVb=between-subject coefficient of variation.

Source: Table 16 in Clinical Study report

Figure 2: Sponsor's Mean VI concentration-time profiles on Day 10



Source: Figure 11.6 in Clinical Study report

4.2.8.4.2 Exposure-Response Analysis

A nonlinear mixed-effect model successfully described the relationship between QTcF, UMEC, and VI with additive drug effects of UMEC and VI. In this mixed-effects analysis of study DB2114635, time-matched observed UMEC and VI plasma concentrations were used to develop a systemic exposure-response model describing the concentration-QTcF effect of these drugs in healthy subjects. A nonlinear mixed-effects model successfully described the relationship between QTcF, UMEC, and VI with model terms for baseline, placebo, drug effects of UMEC and VI. The QTc prolongation effect of VI systemic exposure was adequately described by a saturable relationship. The decreasing QTc effect of UMEC systemic exposure was adequately described by a linear model. Simulations of the model typical parameters were carried out at the geometric mean observed C_{max} for each treatment. As shown in Table 8 for the suprathreshold monotherapy, the estimated mean UMEC drug effect was -2.38 msec (-3.82, -0.85 msec 90% PI) at the geometric mean observed UMEC C_{max}. The combined additive drug effect was estimated to be 5.39 msec (4.40, 6.47) and 5.22 msec (3.72, 6.80) for the therapeutic and suprathreshold combinations, respectively. Decreased QTcF following UMEC monotherapy, along with increased QTcF observed for the combination therapies in this study suggest the effect is possibly attributable to the VI component of the combination treatment. The sponsor investigated the time-lag between concentration and effect. As shown in Figure 4, the $\Delta \Delta$ QTcF closely tracked the time-course of plasma VI concentrations for both the therapeutic and suprathreshold combination treatments. With no evidence of a substantial time-delay in concentration-effect, direct-effect models were used to relate VI and UMEC concentrations to time-matched QTcF measurements.

Table 8: Sponsor’s Mean QTcF model predictions from exposure-response analysis

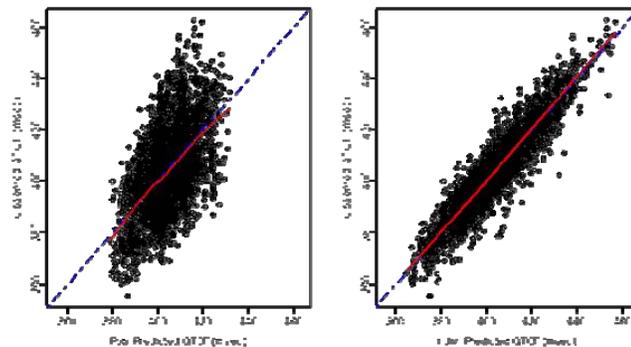
Treatment	Observed Geometric Mean C _{max} ¹		Mean (90% PI) QTcF		
	UMEC (pg/mL)	VI (pg/mL)	UMEC (msec)	VI (msec)	Total (msec)
UMEC 500 mcg	1531	NA	-2.38 (-3.82, -0.85)	NA	-2.38 (-3.82, -0.85)
UMEC/VI 125/25 mcg	321	335	-0.50 (-0.80, -0.18)	5.89 (4.89, 6.91)	5.39 (4.40, 6.47)
UMEC/VI 500/100 mcg	1290	1394	-2.01 (-3.22, -0.72)	7.23 (5.88, 8.55)	5.22 (3.72, 6.80)

PI=Prediction Interval, NA= Not Applicable

1. geometric means of individual C_{max} values. These exclude the five subjects who were missing ECG data and only include time-matched PK obs.

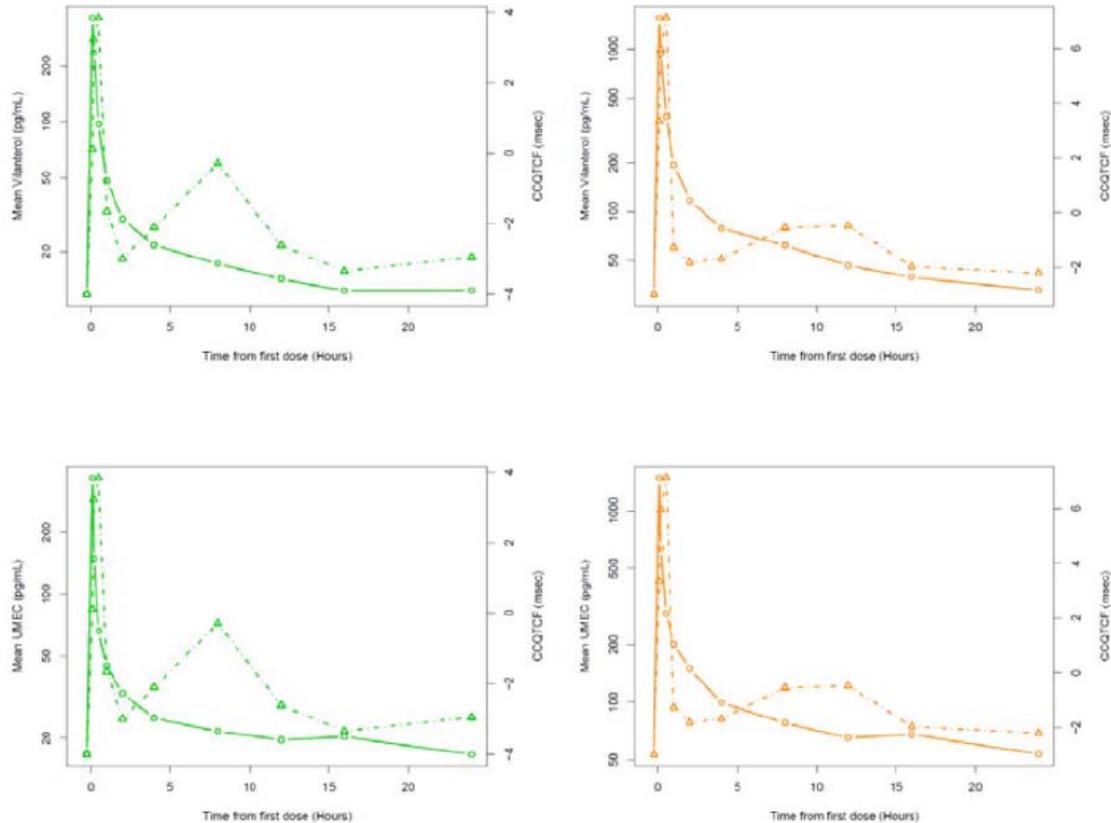
Source: Sponsor’s Table 17 in Clinical Study report

Figure 3: Diagnostic plots from the Sponsor’s Model



Source: Figure 40 of Attachment 2 of Clinical Study report

Figure 4: Sponsor’s Mean profiles for VI (upper) or UMEC (lower) plasma concentration (solid lines) and $\Delta\Delta QTcF$ (dashed lines) versus time from dose for therapeutic (left panel) and suprathreshold (right panel) combination treatment periods.



Best Available Copy

Source: Figure 25 of Attachment 2 of Clinical Study report

Reviewer’s Analysis: A plot of $\Delta\Delta QTcF$ vs. UMEC concentrations is presented in Figure 7 with no evident exposure response relationship. A plot of $\Delta\Delta QTcF$ vs. VI concentrations is presented in Figure 8 which shows an increase in $\Delta\Delta QTcF$ with increasing VI concentration.

5 REVIEWERS’ ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

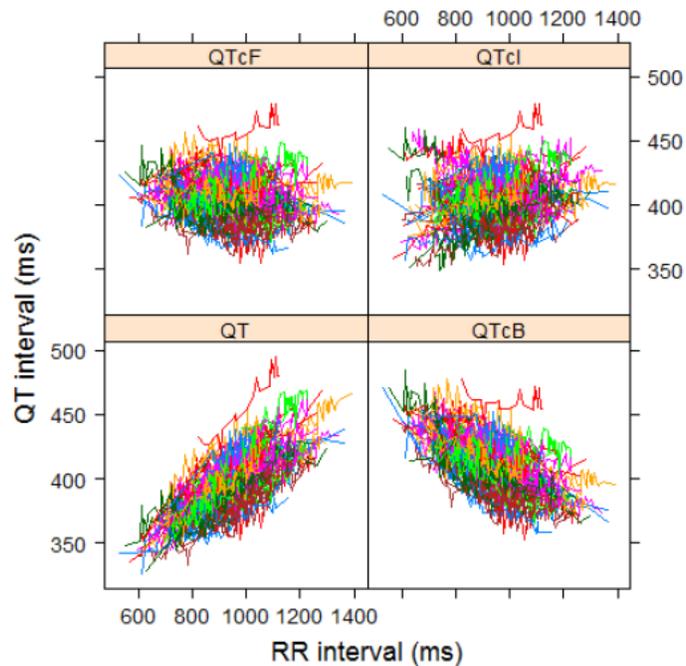
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 9, it appears that QTcF is better than QTcI and QTcB. To be consistent with the sponsor’s analyses, this reviewer used QTcF for primary statistical analyses.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Moxifloxacin 400 mg	74	0.0072	74	0.0022	74	0.0040
Placebo	77	0.0049	77	0.0020	77	0.0031
UMEC 500 mcg	76	0.0048	76	0.0017	76	0.0032
UMEC/VI 125/25 mcg	78	0.0079	78	0.0019	78	0.0025
UMEC/VI 500/100 mcg	76	0.0090	76	0.0014	76	0.0027
All	103	0.0061	103	0.0007	103	0.0023

The QT-RR interval relationship is presented in Figure 5 together with the Bazett's (QTcB), Fridericia (QTcF), and an Individual (QTcI) corrections.

Figure 5: QT, QTcB, QTcF, QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, between UMEC/VI 500/100 mcg and placebo, and between UMEC 500 mcg and placebo are 7.1 ms, 10.7, and 0.7 ms, respectively.

Table 10: Analysis Results of Δ QTcF(ms) and $\Delta\Delta$ QTcF(ms) for UMEC/VI 125/25 mcg, UMEC/VI 500/100 mcg, and UMEC 500 mcg

Time (h)	Placebo	UMEC 500 mcg				UMEC/VI 125/25 mcg				UMEC/VI 500/100 mcg			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
5 min	-1.9	72	-5.1	-3.2	(-6.1, -0.3)	71	-0.1	1.8	(-1.1, 4.7)	68	2.1	4.0	(1.1, 6.9)
10 min	1.7	73	-2.2	-4.0	(-6.5, -1.4)	74	6.3	4.6	(2.0, 7.1)	68	8.0	6.3	(3.7, 8.9)
30 min	-1.7	73	-3.5	-1.8	(-4.3, 0.7)	74	2.9	4.5	(2.1, 7.0)	68	6.5	8.2	(5.7, 10.7)
1	-0.0	73	-2.0	-2.0	(-4.3, 0.4)	73	-0.5	-0.4	(-2.8, 1.9)	68	0.4	0.5	(-1.9, 2.8)
2	0.4	73	-2.8	-3.2	(-5.5, -0.9)	73	-0.9	-1.3	(-3.6, 1.0)	67	-0.6	-1.1	(-3.4, 1.3)
4	0.9	71	-2.6	-3.5	(-5.9, -1.1)	70	-0.2	-1.1	(-3.5, 1.3)	69	-0.3	-1.1	(-3.6, 1.3)
8	-7.5	73	-9.7	-2.2	(-4.4, 0.0)	73	-7.8	-0.2	(-2.5, 2.0)	70	-8.0	-0.5	(-2.7, 1.8)
12	-4.2	70	-6.3	-2.1	(-4.4, 0.2)	72	-5.2	-1.0	(-3.3, 1.3)	68	-4.2	-0.0	(-2.3, 2.3)
16	2.4	70	-0.8	-3.2	(-5.6, -0.8)	72	1.3	-1.1	(-3.5, 1.3)	70	1.1	-1.3	(-3.7, 1.1)
24	-2.6	72	-5.2	-2.6	(-4.8, -0.3)	70	-4.0	-1.4	(-3.6, 0.9)	69	-4.4	-1.7	(-4.0, 0.5)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 11. The largest unadjusted 90% lower confidence interval is 7.2 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 6.1 ms, which indicates that an at least 5 ms QTcF effect of moxifloxacin can be detected from the study.

Table 11 : Analysis Results of Δ QTcF(ms) and $\Delta\Delta$ QTcF(ms) for Moxifloxacin 400 mg

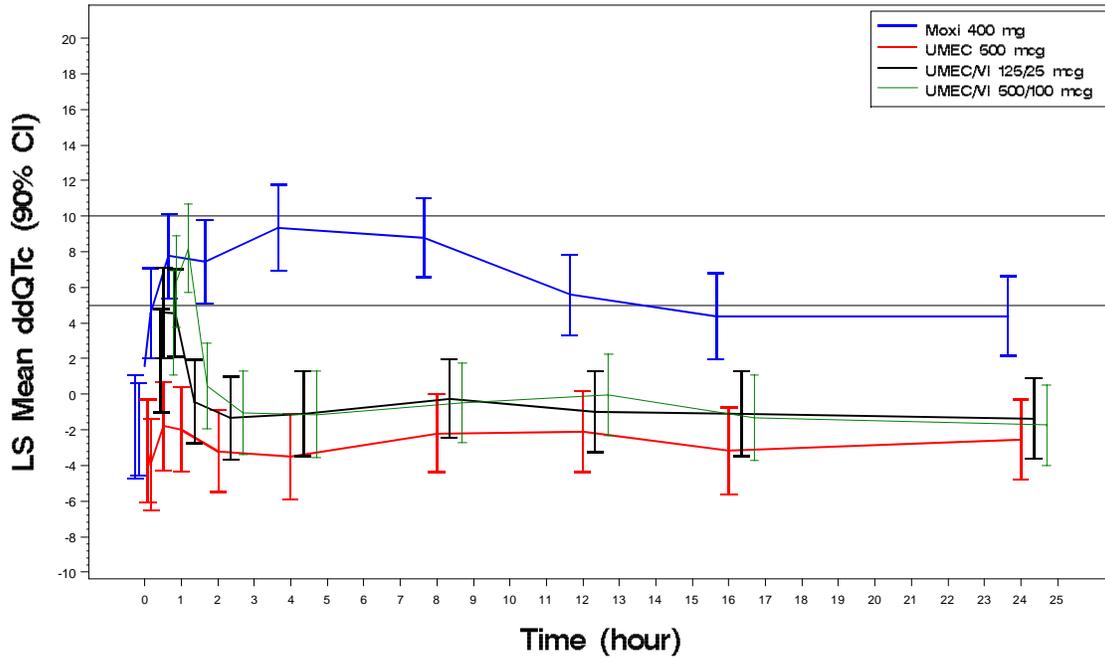
Time (h)	Placebo	Moxifloxacin 400 mg				
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF		
	LS Mean	N	LS Mean	LS Mean	90% CI	Adj 90% CI *
5 min	-1.9	69	-3.7	-1.8	(-4.4, 0.7)	(-5.8, 2.2)
10 min	1.7	69	-0.3	-2.0	(-4.2, 0.3)	(-5.5, 1.6)
30 min	-1.7	68	2.9	4.5	(2.3, 6.7)	(1.1, 7.9)
1	-0.0	68	7.7	7.8	(5.7, 9.8)	(4.5, 11.0)
2	0.4	70	7.9	7.4	(5.4, 9.5)	(4.3, 10.6)
4	0.9	70	10.2	9.3	(7.2, 11.5)	(6.1, 12.6)
8	-7.5	71	1.2	8.8	(6.8, 10.7)	(5.7, 11.8)
12	-4.2	71	1.4	5.6	(3.6, 7.6)	(2.5, 8.7)
16	2.4	72	6.8	4.4	(2.3, 6.5)	(1.1, 7.6)
24	-2.6	71	1.7	4.4	(2.4, 6.3)	(1.3, 7.4)

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

5.2.1.3 Graph of $\Delta\Delta$ QTcF over Time

Figure 6 displays the time profile of $\Delta\Delta$ QTcF for different treatment groups and moxifloxacin 400 mg.

Figure 6: Mean and 90% CI $\Delta\Delta$ QTcF Time Course for and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 m, and between 480 ms and 500 ms. No subject's QTcF is above 480 ms.

Table 12: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
Moxifloxacin 400 mg	72	69 (95.8%)	3 (4.2%)
Placebo	76	76 (100%)	0 (0.0%)
UMEC 500 mcg	73	72 (98.6%)	1 (1.4%)
UMEC/VI 125/25 mcg	76	75 (98.7%)	1 (1.3%)
UMEC/VI 500/100 mcg	73	73 (100%)	0 (0.0%)

Table 13 lists the categorical analysis results for Δ QTcF. No subject's change from baseline is above 60 ms.

Table 13: Categorical Analysis for Δ QTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
Moxifloxacin 400 mg	71	69 (97.2%)	2 (2.8%)
Placebo	75	74 (98.7%)	1 (1.3%)
UMEC 500 mcg	71	71 (100%)	0 (0.0%)
UMEC/VI 125/25 mcg	74	73 (98.6%)	1 (1.4%)
UMEC/VI 500/100 mcg	72	71 (98.6%)	1 (1.4%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, and between UMEC/VI 500/100 mcg and placebo, and between UMEC 500 mcg are 10.5 bpm, 22.3 bpm, and 4.1 bpm, respectively. Table 15 presents the categorical analysis of HR. Four subjects who experienced HR interval greater than 100 bpm are in UMEC/VI 500/100-mcg group.

Table 14: Analysis Results of Δ HR (bpm) and $\Delta\Delta$ HR (bpm) for UMEC/VI 125/25 mcg, UMEC 500 mcg, and UMEC/VI 500/100 mcg, and Moxifloxacin 400 mg

Time (h)	Placebo	Moxifloxacin 400 mg				UMEC 500 mcg				UMEC/VI 125/25 mcg				UMEC/VI 500/100 mcg			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
5 min	1.7	69	1.0	-0.7	(-2.3, 1.0)	72	2.1	0.4	(-1.2, 2.1)	71	6.9	5.2	(3.6, 6.9)	68	17.6	16.0	(14.3, 17.6)
10 min	-0.4	69	-0.8	-0.4	(-2.2, 1.3)	73	-0.7	-0.3	(-2.0, 1.4)	74	8.5	8.8	(7.1, 10.5)	68	20.2	20.5	(18.8, 22.3)
30 min	0.2	68	0.9	0.7	(-0.8, 2.2)	73	0.5	0.3	(-1.2, 1.8)	74	4.4	4.3	(2.8, 5.8)	68	13.2	13.0	(11.5, 14.5)
1	-0.1	68	1.9	2.0	(0.4, 3.5)	73	0.0	0.1	(-1.4, 1.6)	73	1.9	2.0	(0.5, 3.5)	68	9.3	9.3	(7.8, 10.9)
2	-1.1	70	0.9	2.0	(0.5, 3.6)	73	0.0	1.1	(-0.4, 2.7)	73	1.4	2.5	(0.9, 4.1)	67	7.9	9.1	(7.5, 10.7)
4	-0.9	70	1.7	2.7	(1.1, 4.3)	71	1.0	1.9	(0.3, 3.5)	70	1.6	2.5	(0.9, 4.2)	69	7.8	8.7	(7.1, 10.3)
8	1.4	71	2.9	1.6	(-0.1, 3.3)	73	3.5	2.2	(0.5, 3.9)	73	3.2	1.9	(0.2, 3.6)	70	10.1	8.8	(7.1, 10.5)
12	3.8	71	6.2	2.4	(0.5, 4.3)	70	5.9	2.1	(0.2, 4.0)	72	5.2	1.4	(-0.5, 3.3)	68	11.0	7.2	(5.4, 9.1)
16	-0.4	72	1.6	2.1	(0.2, 3.9)	70	1.8	2.2	(0.3, 4.1)	72	1.1	1.5	(-0.3, 3.3)	70	6.6	7.0	(5.2, 8.9)
24	2.3	71	2.9	0.6	(-0.9, 2.1)	72	4.0	1.7	(0.2, 3.2)	70	4.3	2.1	(0.6, 3.6)	69	8.4	6.1	(4.6, 7.7)

Table 15: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR \geq 100 bpm
Moxifloxacin 400 mg	72	72 (100%)	0 (0.0%)
Placebo	76	76 (100%)	0 (0.0%)
UMEC 500 mcg	73	73 (100%)	0 (0.0%)
UMEC/VI 125/25 mcg	76	76 (100%)	0 (0.0%)
UMEC/VI 500/100 mcg	73	69 (94.5%)	4 (5.5%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, between UMEC/VI 500/100 mcg and placebo, and between UMEC 500 mcg are 3.0 ms, 1.6, and 3.4 ms, respectively. Table 17 presents the categorical analysis of PR. Three subjects who experienced PR interval greater than 200 ms are in UMEC 500-mcg, UMEC/VI 125/25-mcg, and UMEC 500/100-mcg groups.

Table 16: Analysis Results of Δ PR(ms) and $\Delta\Delta$ PR(ms) for UMEC/VI 125/25 mcg, UMEC 500 mcg, and UMEC/VI 500/100 mcg, and Moxifloxacin 400 mg

	Placebo		Moxifloxacin 400 mg				UMEC 500 mcg				UMEC/VI 125/25 mcg				UMEC/VI 500/100 mcg			
	Δ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	
5 min	-4.4	69	-2.7	1.6	(-0.8, 4.0)	72	-4.8	-0.4	(-2.8, 2.0)	71	-4.7	-0.4	(-2.8, 2.0)	68	-8.4	-4.0	(-6.4, -1.6)	
10 min	-3.2	69	-0.9	2.3	(-0.1, 4.7)	73	-2.1	1.0	(-1.3, 3.4)	74	-4.8	-1.7	(-4.0, 0.7)	68	-11.9	-8.7	(-11.1, -6.3)	
30 min	-1.1	68	-0.9	0.2	(-2.1, 2.4)	73	-1.5	-0.4	(-2.7, 1.8)	74	-4.0	-3.0	(-5.2, -0.7)	68	-8.7	-7.6	(-9.9, -5.4)	
1	-2.1	68	-1.6	0.5	(-1.6, 2.6)	73	-1.6	0.5	(-1.5, 2.5)	73	-1.1	1.0	(-1.0, 3.0)	68	-5.3	-3.2	(-5.2, -1.1)	
2	-2.0	70	-2.6	-0.6	(-2.7, 1.5)	73	-2.5	-0.5	(-2.5, 1.6)	73	-1.8	0.2	(-1.9, 2.2)	67	-4.3	-2.3	(-4.4, -0.2)	
4	-2.8	70	-5.1	-2.4	(-4.5, -0.2)	71	-2.9	-0.2	(-2.3, 2.0)	70	-2.1	0.7	(-1.4, 2.8)	69	-4.3	-1.5	(-3.6, 0.7)	
8	-5.7	71	-7.0	-1.3	(-3.4, 0.7)	73	-6.0	-0.3	(-2.4, 1.7)	73	-6.6	-0.9	(-2.9, 1.2)	70	-6.1	-0.4	(-2.5, 1.6)	
12	-3.4	71	-5.3	-1.9	(-4.0, 0.1)	70	-4.8	-1.4	(-3.5, 0.7)	72	-4.3	-0.9	(-3.0, 1.1)	68	-5.3	-1.9	(-4.0, 0.2)	
16	1.2	72	1.0	-0.2	(-2.4, 2.0)	70	-0.6	-1.8	(-4.0, 0.5)	72	0.5	-0.7	(-2.9, 1.5)	70	-0.6	-1.8	(-4.1, 0.4)	
24	-2.2	71	-1.5	0.7	(-1.2, 2.5)	72	-2.5	-0.3	(-2.1, 1.6)	70	-1.7	0.5	(-1.4, 2.3)	69	-2.8	-0.6	(-2.4, 1.3)	

Table 17: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR \geq 200 ms
Moxifloxacin 400 mg	72	70 (97.2%)	2 (2.8%)
Placebo	76	73 (96.1%)	3 (3.9%)
UMEC 500 mcg	73	70 (95.9%)	3 (4.1%)
UMEC/VI 125/25 mcg	76	75 (98.7%)	1 (1.3%)
UMEC/VI 500/100 mcg	73	70 (95.9%)	3 (4.1%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 18. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, between UMEC/VI 500/100 mcg and placebo, and between UMEC 500 mcg are 0.8 ms, 1.7 ms, and 1.0 ms, respectively. Table 19 presents the categorical analysis of QRS. Four subjects who experienced QRS interval greater than 110 ms are in UMEC 500-mcg, UMEC/VI 125/25-mcg, and UMEC 500/100-mcg groups.

Table 18: Analysis Results of Δ QRS(ms) and $\Delta\Delta$ QRS(ms) for UMEC/VI 125/24 mcg, UMEC 500 mcg, and UMEC/VI 500/100 mcg, and Moxifloxacin 400 mg

Time (h)	Placebo	Moxifloxacin 400 mg				UMEC 500 mcg				UMEC/VI 125/25 mcg				UMEC/VI 500/100 mcg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
5 min	0.1	69	-0.3	-0.4	(-1.3, 0.5)	72	-0.2	-0.3	(-1.2, 0.6)	71	-0.4	-0.5	(-1.4, 0.4)	68	-0.6	-0.7	(-1.6, 0.2)
10 min	0.2	69	-0.0	-0.2	(-1.1, 0.6)	73	0.0	-0.2	(-1.0, 0.7)	74	-0.0	-0.3	(-1.1, 0.6)	68	0.2	-0.1	(-0.9, 0.8)
0.5	-0.0	68	-0.2	-0.2	(-1.1, 0.7)	73	-0.1	-0.0	(-0.9, 0.8)	74	-0.1	-0.1	(-1.0, 0.8)	68	0.7	0.8	(-0.1, 1.7)
1	-0.0	68	-0.1	-0.1	(-1.0, 0.8)	73	0.1	0.1	(-0.7, 1.0)	73	-0.2	-0.2	(-1.1, 0.7)	68	0.2	0.2	(-0.6, 1.1)
2	-0.0	70	-0.2	-0.2	(-1.2, 0.7)	73	-0.4	-0.4	(-1.3, 0.6)	73	-0.4	-0.4	(-1.4, 0.5)	67	-0.2	-0.2	(-1.1, 0.8)
4	-0.0	70	-0.3	-0.3	(-1.1, 0.6)	71	0.0	0.1	(-0.8, 0.9)	70	-1.0	-0.9	(-1.8, -0.1)	69	0.1	0.1	(-0.8, 1.0)
8	-0.3	71	-0.9	-0.6	(-1.5, 0.2)	73	-0.4	-0.1	(-1.0, 0.7)	73	-1.3	-1.0	(-1.8, -0.2)	70	-0.8	-0.5	(-1.4, 0.3)
12	0.2	71	-0.1	-0.3	(-1.1, 0.5)	70	-0.0	-0.2	(-1.0, 0.6)	71	-0.4	-0.5	(-1.4, 0.3)	68	-0.3	-0.5	(-1.4, 0.3)
16	0.5	72	0.2	-0.3	(-1.1, 0.5)	70	0.4	-0.2	(-1.0, 0.6)	72	0.1	-0.5	(-1.3, 0.4)	70	0.6	0.1	(-0.7, 0.9)
24	0.1	71	-0.5	-0.6	(-1.5, 0.2)	72	-0.0	-0.1	(-0.9, 0.8)	70	-0.7	-0.8	(-1.7, 0.1)	69	-0.7	-0.8	(-1.7, 0.1)

Table 19: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS \geq 110 ms
Moxifloxacin 400 mg	72	67 (93.1%)	5 (6.9%)
Placebo	76	73 (96.1%)	3 (3.9%)
UMEC 500 mcg	73	69 (94.5%)	4 (5.5%)
UMEC/VI 125/25 mcg	76	73 (96.1%)	3 (3.9%)
UMEC/VI 500/100 mcg	73	70 (95.9%)	3 (4.1%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcF and UMEC concentrations is visualized in Figure 7 with no evident exposure-response relationship. The relationship between $\Delta\Delta$ QTcF and VI concentrations is visualized in Figure 8 with an increase in $\Delta\Delta$ QTcF with increasing VI concentrations. A log-linear model was used to describe the relationship between $\Delta\Delta$ QTcF and VI concentrations and the parameter estimates from the model are provided in Table 20. The predicted $\Delta\Delta$ QTcF at C_{\max} of the drug from the model is shown in Table 21.

Figure 7: $\Delta\Delta$ QTcF vs. UMEC concentration

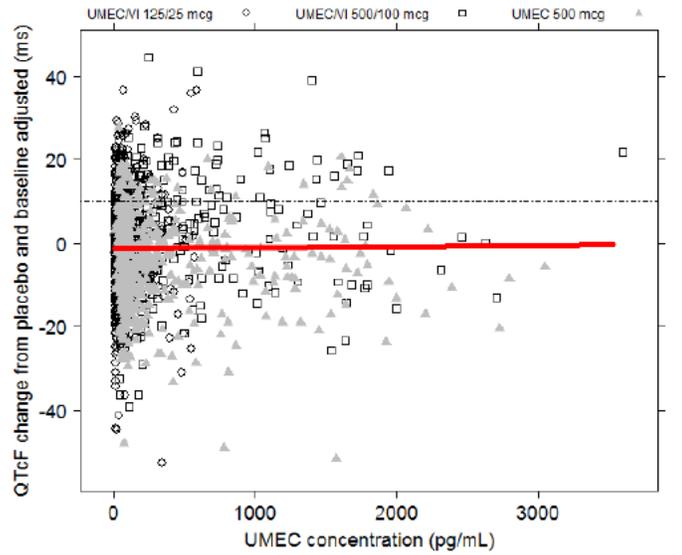


Figure 8: $\Delta\Delta$ QTcF vs. VI concentration

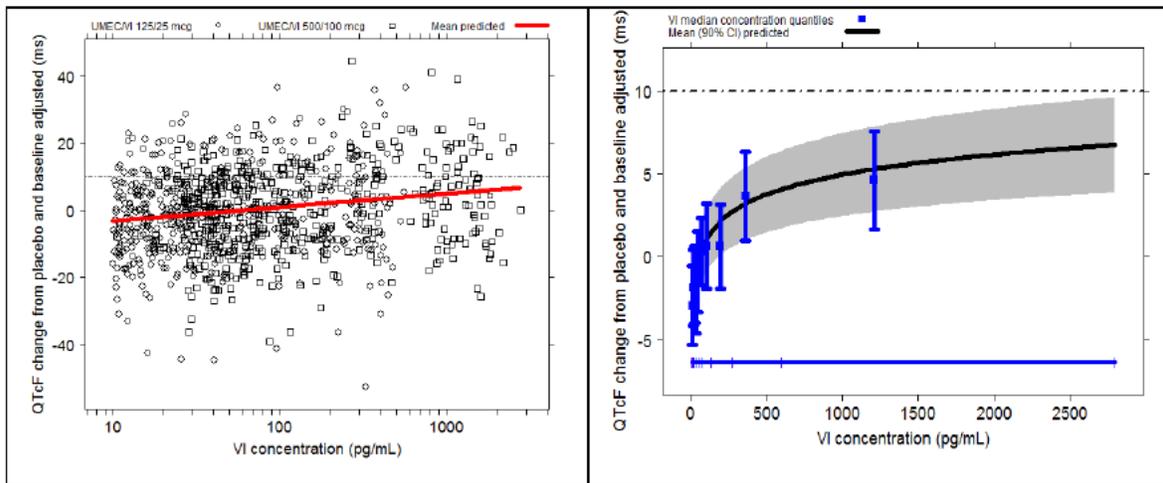


Table 20: Model Parameters for the concentration- $\Delta\Delta$ QTcF model

Parameter	Estimate	pvalue	IIV
Model 1: $\Delta\Delta$ QTcF = Intercept + slope * VI Concentration			
Intercept (ms)	-7.05 (-9.53; -4.58)	<.0001	9.26
Slope (ms per log pg/mL)	1.74 (1.24; 2.24)	<.0001	1.63
Residual Variability (ms)		8.5	

Table 21: Mean $\Delta\Delta$ QTcF predictions at Cmax from concentration- $\Delta\Delta$ QTcF analysis

Treatment	UMEC Concentration	Mean (msec)	(90%CI)	VI Concentration	Mean (msec)	(90%CI)
UMEC/VI 125/25 mcg	321 pg/mL	-1.23	(-2.89; 0.438)	335 pg/mL	3.06	(0.897; 5.23)
UMEC/VI 500/100 mcg	1290 pg/mL	-0.969	(-3.5; 1.56)	1390 pg/mL	5.54	(2.92; 8.16)
UMEC 500 mcg	1530 pg/mL	-0.904	(-3.73; 1.92)			

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 96 % of the ECGs were annotated in multiple leads, with less than 0.4 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

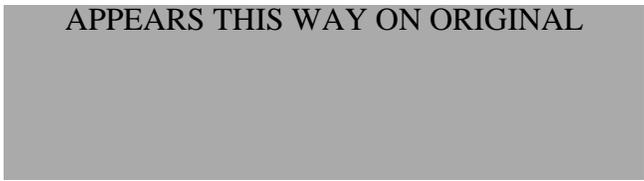
As shown in Table 17 and Table 19, there were several subjects with PR > 200 ms or QRS > 110 ms. In no case the effect was >15% from baseline values and no post-baseline PR was > 210 ms or QRS > 118 ms, these values are not clinically relevant.

5.4.4 HR

UMEC/VI combination increases HR. Mean effect for UMEC/VI 125/25 mcg was 8.8 bpm, and for UMEC/VI 500/100 mcg 20.5 bpm.

Four subjects had HR > 100 bpm, with increase over baseline > 30% all in the UMEC/VI 500/100 mcg. The maximal HR value reported was 109 bpm which is 33% higher than the baseline value.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

GSK573719 Highlights of Clinical Pharmacology

Therapeutic dose	<p>The GSK573719 Novel DPI contains an active strip, containing a blend of either 62.5 or 125 mcg micronised GSK573719A (bromide salt), lactose monohydrate and magnesium stearate.</p> <p>GSK573719/GW642444 Inhalation Powder in the Novel Dry Powder Inhaler containing two blister strips. One strip contains a blend of either 62.5 or 125 mcg micronised GSK573719A, lactose monohydrate and magnesium stearate. The second strip contains a blend of 25 mcg micronised GW642444M, lactose monohydrate and magnesium stearate.</p>	
<p>GSK573719</p> <p>Maximum dose tested/ maximum dose tolerated</p>	<p>Maximum dose tested and well tolerated:</p> <p>in COPD patients: 1000 µg once daily administered for 14 days (study AC4113073)</p> <p>in healthy CYP2D6 extensive and poor metabolizers: 1000 µg once daily administered for 7 days (study AC4110106)</p> <p>Japanese healthy subjects: 1000 µg once daily administered for 7 days (study AC4113377)</p>	
Principal adverse events	<p>Most adverse events were mild or moderate in intensity. The incidence of SAEs was low and comparable across GSK573719 doses, and there were no fatal SAEs. The incidence of AEs was generally similar among the placebo and GSK573719 125 mcg and 250 mcg doses, and slightly higher for the 500 mcg dose of GSK573719. Cough and headache were the most common adverse events.</p>	
GSK573719 Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Geometric Mean (%CV) C_{max} and AUC following 1000 µg via novel DPI:</p> <p>In healthy volunteers (AC4110106):</p> <p>C_{max} 1.565 ng/mL (34%).</p> <p>AUC(0-24) 1.833 ng.h/mL (36%)</p> <p>In COPD patients (AC4105211):</p> <p>C_{max} 1.5284 ng/mL (54%).</p> <p>AUC(0-8) 2.029 ng.h/mL (70%)</p>
	Multiple Dose	<p>Geometric Mean (%CV) C_{max} and AUC following 1000 µg via novel DPI</p> <p>In healthy volunteers (AC4110106):</p> <p>C_{max} 1.756 ng/mL (64%)</p> <p>AUC(0-24) 3.575 ng.h/mL (30%)</p>

		In COPD patients (AC4113073): C _{max} 1.60 ng/mL (87%) AUC(0-24) 3.78 ng.h/mL (101%)
Range of linear PK	More than dose proportional over range 62.5 – 1000 mcg GSK573719 Novel DPI (AC4113073).	
Accumulation at steady state	Accumulation ratios (Day 14 to Day 1) ranged from 1.3 – 1.8 for C _{max} and 1.1 – 2.4 for AUC with once-daily dosing. (study AC4113073).	
Metabolites	Major route of metabolism in human hepatocytes were O-dealkylation (M14). Following daily inhaled administration of GSK573719 for 7 days at a dose of 1 mg to healthy male subjects, who were either normal or poor CYP2D6 metabolisers, parent and M14 were the only drug-related components detected in human plasma extracts and urine.	
Absorption	Absolute Bioavailability	Absolute bioavailability of GSK573719 Novel DPI was 12.82 (43.7) (AC4112008)
	T _{max}	Median (range): Healthy subjects: 0.08 h (0.08 h-0.25 h) following single and repeat dose (study AC4110106). COPD patients: 0.08 h (0.067 h – 0.35 h) following repeat dose 125 mcg GSK573719 Novel DPI on Day 28 (study AC4113589).. Metabolites not quantifiable in plasma.
Distribution	V _{ss} /F/ V _{ss} for IV solution	Geometric Mean (%CV): 2717 L (53%) 1000mcg GSK573719 Novel DPI; 14.5 L (34%).65mcg GSK573719 IV solution (study AC4112008)
	% bound	Plasma protein binding: 88%
Elimination	Route	Primary route is likely to be biliary excretion. Approximately 130 µg (13%) was absorbed in the systemic circulation via the lungs and approximately 1.8% of the total inhaled dose (~ 16.6 µg) was excreted unchanged in urine over the dosing interval. These results indicate that ~13% of the lung deposited/absorbed dose of GSK573719 in systemic circulation was excreted unchanged in urine.

	Terminal t½	Mean (%CV) parent: 2.5 h (79%) (single dose 1000mcg GSK573719 Novel DPI) (AC4112008). Urinary Terminal t½ : 19h (44%) single dose; 35h (67%) (repeat dose 100mcg GSK573719 Novel DPI) (AC4110106) Metabolites not quantifiable in plasma.
	CL/F CL for IV solution	Geometric Mean (%CV): 752 L/h (58%) (1000mcg GSK573719 Novel DPI; 91 L (33%) . 11.9 L/h (56%) 65mcg GSK573719 IV solution (study AC4112008)
Intrinsic Factors	Age	No evidence for marked changes in Cmax and AUC
	Sex	No evidence for marked changes in Cmax and AUC
	Race	No evidence for marked changes in Cmax and AUC
	Hepatic & Renal Impairment	To be determined.
Extrinsic Factors	Drug interactions	The results of study AC4110106 for both plasma and urine PK data suggested no difference in GSK573719 systemic exposure between healthy volunteers and a CYP2D6 poor metabolizer population. The results of Study DB2113950 support the position that GSK573719 Inhalation Powder and GSK573719/ GW642444 Inhalation Powder are unlikely to have a clinically significant drug-drug interaction with Pgp transporter inhibitors.
	Food Effects	Not determined
Expected High Clinical Exposure Scenario	To be determined. No high clinical GSK573719 systemic exposure scenarios expected based on in vitro drug-drug interaction liability.	

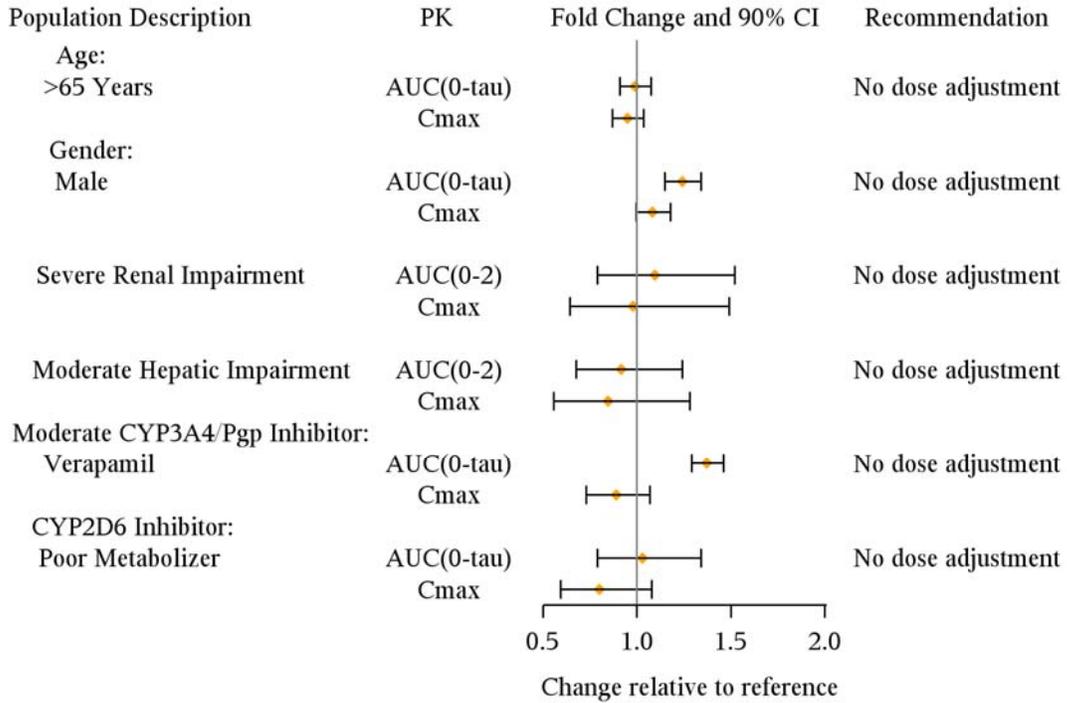
Vilanterol Highlights of Clinical Pharmacology

Therapeutic dose	25 mcg vilanterol (VI; GW642444M in lactose) once daily via inhalation from an Investigational Product Inhaler either as the individual component or in combination with the inhaled corticosteroid fluticasone furoate (FF).	
Maximum tolerated dose	100 mcg VI, single and repeat once daily dosing via DISKUS device to healthy subjects (GSK Study B2C108784) or as a single dose via Investigational Product Inhaler as the individual component (GSK Study B2C106180) or as FF/VI (800/100mcg) (GSK Study HZA102934).	
Principal adverse events	Common adverse events ($\geq 5\%$) from Phase IIb individual clinical studies with VI (3 to 50mcg) include headache in both asthma and COPD patients and nasopharyngitis in COPD patients. The rates were generally comparable between VI and placebo.	
Maximum dose tested	Single Dose	100 mcg VI administered via Investigational Product Inhaler to healthy subjects (GSK Studies HZA105871 and B2C106180) and asthma patients (GSK Study B2C111401).
	Multiple Dose	100 mcg VI, administered once daily for 14 days, to healthy subjects via DISKUS device (GSK Study B2C108784).
Exposures Achieved at Maximum Tested Dose	Single Dose	Geometric Mean (CV%) C _{max} and AUC: C _{max} 929pg/mL (30.4%) AUC(0-t) 734pg.h/mL (37.2%)
	Multiple Dose	Geometric Mean (CV%) C _{max} and AUC: C _{max} 932pg/mL (17.9%) AUC(0-t) 913pg.h/mL (25.7%)
Range of linear PK	Apparent proportionality over dose range 25 - 100 mcg VI administered via DISKUS device (GSK Studies B2C108784 and B2C106996). Approximate proportionality over dose range 6.25 - 100 mcg VI administered via Investigational Product Inhaler (GSK Study B2C111401).	
Accumulation at steady state	Highest extent of accumulation was 72-99% following once daily dosing to COPD patients (25 mcg VI in combination with 400 mcg FF via Investigational Product Inhaler (GSK Study HZC111348).	
Metabolites	GW630200 [M1] (O-dealkylation of VI) and GSK932009 [M2] (O-dealkylation of VI followed by oxidation). Both metabolites are at least 2500-fold less potent than VI on the beta2-adrenoreceptor.	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability of inhaled VI was estimated to be 22-35% following FF/VI (800/100 mcg) (HZA102934)

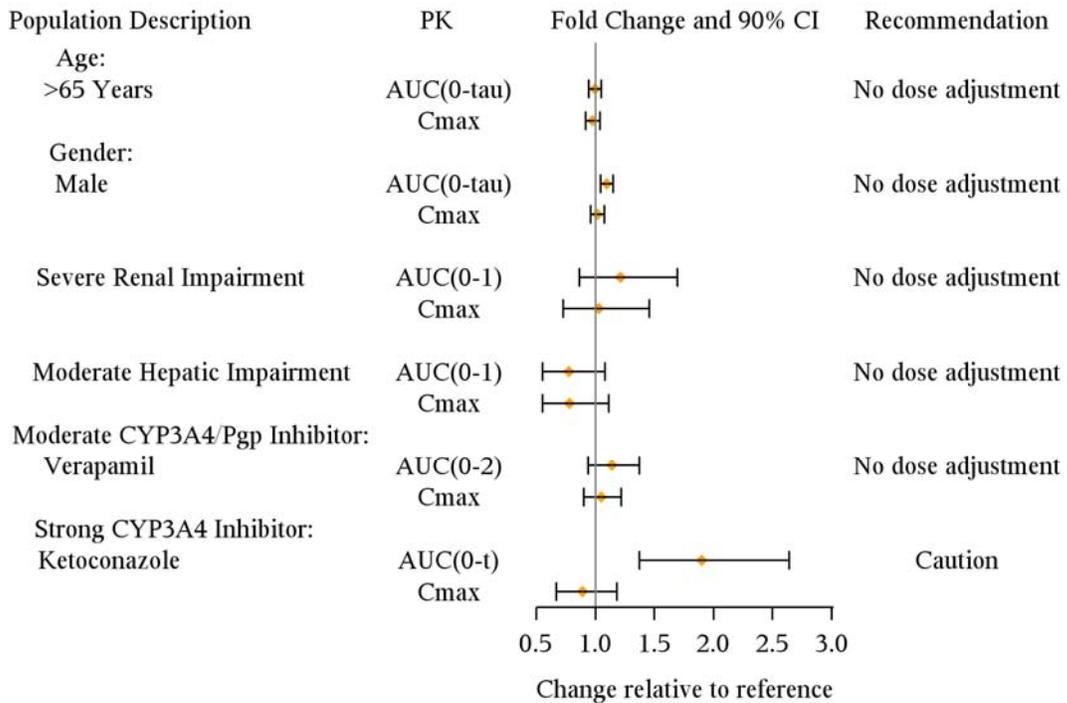
	Tmax	<p>Median (range) Parent VI :</p> <p>Asthma patients: 0.17h (0.1h, 0.6h) following single dose (25 mcg VI via Investigational Product Inhaler (GSK Study B2C111401)</p> <p>COPD patients: 0.17h (0.08h, 0.27h) following once daily dosing (25 mcg in combination with 400 mcg FF via Investigational Product Inhaler (GSK Study HZC111348)</p> <p>Major metabolites:</p> <p>Not quantifiable in plasma following inhaled administration at therapeutic doses (Lower limit of quantification 90 pg/mL for GW630200 [M1] and 180 pg/mL for GSK932009 [M2]).</p>
Distribution	Vd/F or Vd	Vdss 165 L (129, 211) (GSK Study HZA102934).
	% bound	Mean (range) plasma protein binding: 97.2% (95.8 – 97.6).
Elimination	Route	<p>Primary route is metabolism. Major in vitro metabolites are GW630200 (M1) and GSK932009 (M2).</p> <p>Urine primary route of excretion</p> <p>Renal elimination of parent VI was <2% of the administered dose (GSK Study B2C106180).</p>
	Terminal t½	<p>Mean (CV%):</p> <p>Parent: Not determined, terminal profile not adequately defined due to low exposure (\leqLLQ 10 pg/ml) following inhaled dosing. Metabolites not quantifiable in plasma.</p>
	CL	108 L/h (86.2, 135) (GSK Study HZA102934)).
Intrinsic Factors	Age	No evidence for marked changes in Cmax (GSK Studies B2C109575 and B2C111045).
	Sex	No evidence for a marked gender difference in Cmax (GSK Studies B2C109575 and B2C111045).
	Race	Not determined.

	Hepatic & Renal Impairment	Hepatic: to be determined in all impairment severities. Renal: to be determined in severe impairment only. The effect of renal impairment on parent VI is expected to be minimal (<2% of the dose is excreted in urine as parent).
Extrinsic Factors	Drug interactions	Repeat dose co-administration of FF/VI (200/25 mcg) with ketoconazole (400 mg) in comparison with FF/VI (200/25 mcg) with placebo resulted in greater VI exposure. Mean VI AUC(0-t [∞]) and C _{max} were increased by 65% (90% CI: 38% to 97%) and 22% (90% CI: 8% to 38%), respectively (HZA105548). There was no significant increase in VI systemic pharmacodynamic effects (heart rate and potassium). Co-administration of inhaled VI with FF did not affect GW642444 systemic exposure (GSK Studies HZA105871, HZA102940).
	Food Effects	No food interaction study has been conducted. Whilst a significant portion of an inhaled dose may be swallowed an effect on VI systemic availability is not anticipated as any absorbed VI appears to undergo extensive 1 st pass metabolism (oral bioavailability estimated < 2% oral dose) (GSK study B2C106180).
Expected High Clinical Exposure Scenario	To be determined (for AUC) in the hepatic impairment study.	

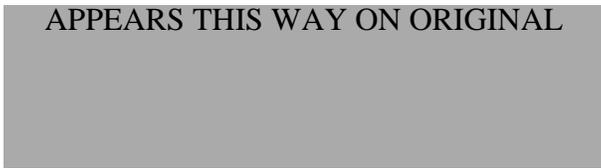
Impact of Factors on Umeclidinium PK



Impact of Factors on Vilanterol PK



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

/s/

MOH JEE NG
05/06/2013

QIANYU DANG
05/06/2013

ANSHU MARATHE
05/08/2013

KEVIN M KRUDYS
05/08/2013

MONICA L FISZMAN
05/09/2013

NORMAN L STOCKBRIDGE
05/09/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203975 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Anoro-Ellipta Established/Proper Name: umeclidinium-vilanterol Dosage Form: powder for inhalation Strengths: 62.5/25 µg and 125/25 µg		
Applicant: Glaxo Group, LTD (d/b/aGSK) Agent for Applicant (if applicable):		
Date of Application: 12/18/2012 Date of Receipt: 12/18/2012 Date clock started after UN:		
PDUFA Goal Date: 12/18/2013		Action Goal Date (if different):
Filing Date: 02/18/2013		Date of Filing Meeting: 01/18/2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 and 4		
Proposed indication(s)/Proposed change(s): maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 74696, 77855, 104479, 106616				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			X																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>			X																	
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		X																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including: X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #			X	
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?	X			
• If yes, were all of them submitted on time?	X			
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) Tray			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			PLT sent 01/03/2013, CMC Micro and Sterility sent 02/15/2013
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 17, 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 25, 2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 18, 2013

BLA/NDA/Supp #: NDA 203975

PROPRIETARY NAME: Anoro-Ellipta

ESTABLISHED/PROPER NAME: umeclidinium - vilanterol

DOSAGE FORM/STRENGTH: 62.5/25 µg and 125/ 25 µg

APPLICANT: GlaxoGroup d/b/a/ GlaxoSmithKline

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema

BACKGROUND: NME NDA 203975 submitted December 18, 2013 by GlaxoGroup

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Leila P. Hann	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Susan Limb		N
Clinical	Reviewer:	Jennifer R. Pippins	Y
	TL:	Susan Limb	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jianmeng Chen, Ping Ji	Y, Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Gregory Levin	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jane Sohn	Y
	TL:	Timothy Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Craig Bertha, Arthur Shaw	Y, Y
	TL:	Alan Schroeder, Prasad Peri	Y, Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Anthony Orenca	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lissa Owens	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Yasmin Choudhry	N
	TL:	Kendra Worthy	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Linda Ng Lydia Gilbert-McClain Badrul Chowdhury Dipti Kalra Twanda Scales Nicole Vesely Matthew Falter Nichelle Rashid Vibhakar Shah Sally Seymour		Y Y Y Y Y Y Y Y N Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? 	<input checked="" type="checkbox"/> YES

<p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Date if known:</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES</p> <p>X NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL</p>	<p><input type="checkbox"/> Not Applicable</p>

<p>(PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p>X Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curtis Rosebraugh	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): May 10, 2013	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Mid Cycle Meeting: May 10, 2013 Mid Cycle Communication: May 14, 2013 Labeling Planning Meeting: May 13, 2013 Wrap-Up Meeting: October 16, 2013	
Comments: In The Program	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

Drafted by: L. Hann/ January 28, 2013
Cleared by: S. Barnes/ January 31, 2013
Finalized by: L. Hann/ February 04, 2013

APPEARS THIS WAY ON ORIGINAL



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

/s/

LEILA P HANN
02/19/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203975

Application Type: New NDA

Name of Drug: Anoro Ellipta/ umeclidinium-vilanterol

Applicant: Glaxo Group, d/b/a GlaxoSmithKline

Submission Date: December 18, 2012

Receipt Date: December 18, 2012

1.0 Regulatory History and Applicant's Main Proposals

NME NDA 203975 submitted December 18, 2013 by GlaxoGroup for the maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 15, 2013. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- NO** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *“Milk proteins & ingredients” - these two items should be separated and in bulleted form*

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **“See 17 for PATIENT COUNSELING INFORMATION”**

If a product **has** FDA-approved patient labeling:

- **“See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.”**
- **“See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.”**

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- NO** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment: *At end of TOC: F,P,I, not capitalized.*

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification 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.”

Comment: Not verbatim statement:

“compared WITH rates” - should be TO

“observed in practice” - should be “observed in CLINICAL practice”

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Should not be in italics.*

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/s/

LEILA P HANN
02/05/2013



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

NDA FILING REVIEW

NDA #: 203975
Drug Name: Umeclidinium bromide/vilanterol Inhalation Powder
Indication(s): Treatment of airflow obstruction in chronic obstructive pulmonary disorder
Applicant: GlaxoSmithKline
Stamp Date(s): February 1, 2013

Biometrics Division: Division of Biometrics II
Statistical Reviewer: Gregory Levin, Ph.D.
Concurring Reviewers: Joan Buenconsejo, Ph.D.

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team: Jennifer Pippins, M.D., Medical Reviewer
Susan Limb, M.D., Medical Team Leader
Project Manager: Leila Hann

Keywords: NDA filing review

INTRODUCTION

The applicant has submitted the results of several studies to support the efficacy and safety of the umeclidinium (UMEC) / vilanterol (VI) combination inhalation powder for once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disorder (COPD). UMEC, a long-acting muscarinic antagonist, and VI, a long-acting beta₂-antagonist, have not been approved by the FDA as monotherapies. The four clinical trials supporting the primary efficacy of the UMEC / VI combination product are studies DB2113361, DB2113373, DB2113360, and DB2113374, which we will refer to as studies 361, 373, 360, and 374, respectively. These were randomized, double-blind, parallel-group, 24-week clinical trials in COPD patients with moderate to very severe airflow obstruction and an extensive cigarette smoking history. Studies 361 and 373 were placebo-controlled, while studies 360 and 374 were controlled against the active treatment tiotropium. All four studies included both monotherapy and combination therapy treatment arms, but the choice of monotherapy arm(s) and dose of UMEC (either 62.5 or 125 mcg) differed across studies. The pre-specified primary efficacy endpoint was the change from baseline in mean trough FEV₁ at Day 169. The pre-specified secondary efficacy endpoint was the change from baseline in weighted mean FEV₁ 0 to 6 hours post-dose on Day 168. A number of other efficacy endpoints were pre-specified, including additional spirometry measurements, Shortness of Breath with Daily Activities (SOBDA) score, rescue salbutamol use, COPD exacerbation, and St. George's Respiratory Questionnaire (SQRQ) score.

FILING SUMMARY

There are no filing issues from a statistical perspective. We are able to locate necessary data files, summaries, and reports, and data sets are accessible and appropriately documented. Safety and efficacy were investigated by gender, racial, and age subgroups.

POTENTIAL REVIEW ISSUES

We have identified the following topics to be further assessed as part of the statistical review of this application: (1) evidence supporting the contribution of VI to the efficacy of the combination therapy, (2) the potential impact of missing data on the reliability of efficacy and safety results, and (3) evidence supporting the approval of both doses of the combination product (containing UMEC 62.5 and 125 mcg).

With respect to the impact of missing data, we do not find the sensitivity analyses provided by the applicant 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 FEV₁ prior to dropout likely declined or went completely away once the patient stopped taking the therapy. We request that the applicant provides 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.

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/s/

GREGORY P LEVIN
02/01/2013

JOAN K BUENCONSEJO
02/01/2013
I concur.