

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204275Orig1s000

OTHER REVIEW(S)

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

Product Title	BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder), for oral inhalation use
Applicant	Glaxo Group, LTD
Application/Supplement Number	NDA 204275
Type of Application	Original Application
Indication(s)	Treatment of chronic obstructive pulmonary disease
Established Pharmacologic Class ¹	Inhaled corticosteroid and long-acting beta ₂ -adrenergic agonist
Office/Division	ODEII/DPARP
Division Project Manager	Angela Ramsey
Date FDA Received Application	July 12, 2012
Goal Date	May 12, 2013
Date PI Received by SEALD	May 2, 2013
SEALD Review Date	May 6, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **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 (not applicable):** This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

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: DPARP will grant a waiver of the 1/2 page HL limit in the approval letter.

- 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:

- NO** 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: Insert cross reference after first statement under D&A heading (i.e., "(2)").

- 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*

Selected Requirements of Prescribing Information

• 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:

Boxed Warning

YES

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:

Selected Requirements of Prescribing Information

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and 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 established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 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:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

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

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Insert month of revision date.*

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:

- 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.

Selected Requirements of Prescribing Information

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 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:

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
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)

Selected Requirements of Prescribing Information

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

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

Comment:

Adverse Reactions

- YES** 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 practice.”

Selected Requirements of Prescribing Information

Comment:

- 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

- YES** 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:

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/s/

DEBRA C BEITZELL
05/06/2013

LAURIE B BURKE
05/06/2013

**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: April 9, 2013

Reviewer(s): 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

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Breo Ellipta (Fluticasone Furoate 100 mcg and
Vilanterol 25 mcg inhalation powder)

Application Type/Number: NDA 204275

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2012-1685

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

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1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling, and instructions for use for Breo Ellipta NDA 204275 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Breo Ellipta is composed of Fluticasone Furoate and Vilanterol. Fluticasone Furoate is currently marketed (e.g. Flonase, Flovent); however, Vilanterol is not currently marketed, making this combination product a new molecular entity. Additionally, the Ellipta device is not currently marketed and is to be integrated with the drug product and not available alone.

The name was evaluated in a separate review OSE RCM #2012-2898.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 6, 2012 proprietary name submission.

- Active Ingredient: Fluticasone Furoate and Vilanterol
- Indication of Use: (b)(4) COPD
- Route of Administration: Oral Inhalation
- Dosage Form: Powder for Inhalation
- Strength: 100 mcg/25 mcg
- Dose and Frequency: 1 inhalation once daily
- How Supplied: A disposable light grey and blue plastic inhaler containing 2 double-foil strips, each with 30 blisters. The institutional pack contains 2 double-foil strips, each with 14 blisters.
- Storage: Store at room temperature, 20°C to 25°C (68° to 77°F), in a dry place away from direct heat or sunlight:

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Breo Ellipta labels, instructions for use, and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

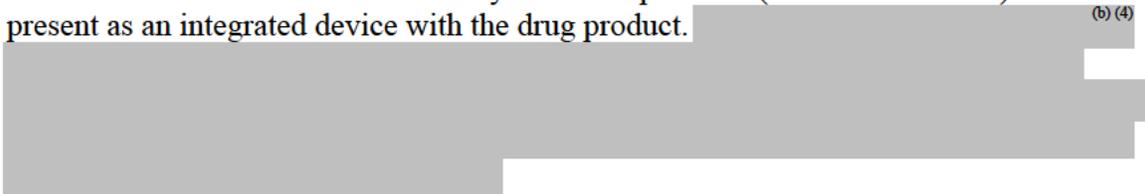
Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

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

- Container Labels submitted July 12, 2012 (Appendices B, D, and F)
- Carton Labeling submitted July 12, 2012 (Appendices C, E, and G)
- Insert Labeling submitted July 12, 2012 (no image)
- Instructions for Use submitted July 12, 2012 (no image)

2.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Breo Ellipta is composed of Fluticasone furoate and Vilanterol. Fluticasone Furoate is currently marketed (e.g. Flonase, Flovent); however, Vilanterol is not currently marketed, making this combination product a new molecular entity. Additionally, the Ellipta device is not currently marketed 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 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 discussed the following recommendations for the instructions for use with Patient Labeling: 1) Each step throughout the IFU should be numbered as Step 1, Step 2, etc. 2) Include a picture for each corresponding step and label the pictures as Figure A, Figure B, etc. 3) In all pictures each individual component should be labeled. They will incorporate these and additional recommendations in their review. We provide our recommendations for the container and carton labeling 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.

4 RECOMMENDATIONS

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

4.1 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 'Breo'. As presented the word Ellipta utilizes a (b) (4) font over the blue 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 Theravance logo 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....

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.

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/s/

LISSA C OWENS
04/09/2013

LUBNA A MERCHANT
04/09/2013

SCOTT M DALLAS
04/09/2013

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

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

Memorandum

Date: April 9, 2013

To: Angela Ramsey, Senior 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., Acting Group Leader, OPDP

Subject: NDA # 204275
OPDP Labeling Comments for BREO ELLIPTA (fluticasone
furoate and vilanterol inhalation powder) FOR ORAL
INHALATION (Breo Ellipta)

OPDP has reviewed the proposed Package Insert (PI), Carton and Container Labeling, Medication Guide (MG), and Instructions for Use (IFU) for Breo Ellipta submitted for consult on July 24, 2012.

OPDP's comments on the PI were provided under separate cover and submitted into DARRTS on April 4, 2013.

OPDP's comments on the MG and IFU are based on the proposed draft labeling titled "clean Breo Ellipta MG IFU .doc" that was sent via email from the Division of Medical Policy Products (DMPP) to DPARP and OPDP on April 5, 2013. OPDP's comments on the MG and IFU are provided directly in the marked-up document attached (see below).

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

- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgbacklabel.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgcarton.pdf>

- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgfrontlabel.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mginstcarton.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mginstfrontlabel.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mginsttraylabel.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgsmppfrontlabel.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgsmplcarton.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgsmpltraylabel.pdf>
- <\\cdsesub1\EVSPROD\NDA204275\0020\m1\us\114-labeling\1141-draft\draft-100-25mgtraylabel.pdf>

OPDP's comments on the proposed carton labeling are as follows:

- From a promotional perspective, OPDP does not have any objections to including IFU on the carton labeling as long as it is complete and not false or misleading in any way. However, we defer to the Division of Medication Error Prevention and Analysis concerning the appropriateness of this presentation from a regulatory perspective.
- OPDP is concerned that the presentation of abbreviated IFU on the proposed carton labeling may imply that these are the complete directions to ensure proper use of Breo Ellipta. OPDP recommends revising the carton labeling to include a directive for patients to read the complete IFU included as part of the FDA-approved patient labeling. In addition, we recommend for the carton IFU to be revised to include revisions as recommended by DMPP.

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

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
04/09/2013

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

PATIENT LABELING REVIEW

Date: April 5, 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)

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

Drug Name (established name): BREO ELLIPTA (fluticasone furoate/vilanterol)

Dosage Form and Route: Inhalation Powder

Application Type/Number: NDA 204275

Applicant: GlaxoSmithKline

1 INTRODUCTION

On July 12, 2012, GlaxoSmithKline (GSK) submitted, for the Agency's review, a New Drug Application (NDA) for BREO ELLIPTA (fluticasone furoate/vilanterol) indicated for the maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD). On July 29, 2012, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BREO ELLIPTA (fluticasone furoate/vilanterol).

This review is written in response to a request by DPARP for DMPP to review the Applicant's proposed MG and IFU for BREO ELLIPTA (fluticasone furoate/vilanterol). DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review will be provided to DPARP under separate cover.

2 MATERIAL REVIEWED

- Draft BREO ELLIPTA (fluticasone furoate/vilanterol) MG and IFU received on July 12, 2012 and received by DMPP on March 22, 2013.
- Draft BREO ELLIPTA (fluticasone furoate/vilanterol) Prescribing Information (PI) received on July 12, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 22, 2013.

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. We have reformatted the MG and IFU documents using the Verdana font, size 11.

In our 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 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 on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP 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.

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/s/

TWANDA D SCALES
04/05/2013

MELISSA I HULETT
04/05/2013

LASHAWN M GRIFFITHS
04/05/2013

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

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

Memorandum

Date: April 4, 2013

To: Angela Ramsey, Senior 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., Acting Group Leader, OPDP

Subject: NDA # 204275
OPDP Labeling Comments for BREO ELLIPTA (fluticasone
furoate and vilanterol inhalation powder) FOR ORAL
INHALATION (Breo Ellipta)

OPDP has reviewed the proposed Package Insert (PI) for Breo Ellipta submitted for consult on July 24, 2012.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "Breo Label – FDA Draft-CLEAN (10-12-12).doc" that was sent via email from DPARP to OPDP on March 22, 2013. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP's comments on the Carton and Container Labeling, Medication Guide, and Instructions For Use will be provided under separate cover.

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
04/04/2013



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 28, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Angela Ramsey, DPARP

Subject: QT-IRT Consult to NDA 204275

This memo serves as an addendum to our original review for NDA 204275 dated 10/21/2012

QT-IRT Comments for DPARP

There was a typographical error in our labeling recommendations in our original review. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction for the fluticasone furoate 800 mcg/vilanterol 100 mcg dose is 9.6 (12.2), not ^{(b) (4)} as stated in the review. Therefore, our recommended labeling language is as follows:

12.6 Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, multiple dose, placebo- and positive-controlled crossover study in 85 healthy volunteers. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 4.9 (7.5) ms and 9.6 (12.2) ms seen 30 minutes after dosing for fluticasone furoate 200 mcg/vilanterol 25 mcg and fluticasone furoate 800 mcg/vilanterol 100 mcg, respectively.

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 7.8 (9.4) beats/min and 17.1 (18.7) beats/min seen 10 minutes after dosing for fluticasone furoate 200 mcg/vilanterol 25 mcg and fluticasone furoate 800 mcg/vilanterol 100 mcg, respectively.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

KEVIN M KRUDYS
03/28/2013

NORMAN L STOCKBRIDGE
03/28/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 15, 2013

TO: Angela Ramsey, Regulatory Project Manager
Sofia Chaudhry, M.D., Medical Officer
Susan Limb, M.D., Medical Officer, 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

Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204275

APPLICANT: GlaxoSmithKline

DRUG: vilanterol-fluticasone furoate (Breo™ Ellipta™)

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: standard review

INDICATION: chronic obstructive pulmonary disease (COPD)

CONSULTATION REQUEST DATE: September 4, 2012 (signed)
INSPECTION SUMMARY GOAL DATE: April 12, 2013 (original)
DIVISION ACTION GOAL DATE: May 12, 2013

PDUFA DATE:

May 12, 2013

I. BACKGROUND:

COPD, a progressive disease, is characterized by chronic airflow limitation caused by both parenchymal destruction and disease of the small airways. Vilanterol is a novel beta-2 adreno-receptor agonist. Current marketed and approved combination products (eg, inhaled corticosteroid with long acting beta-agonist (LABA)) require twice daily administration for COPD. The sponsor proposes that a once daily inhaled combination of corticosteroid with a LABA (e.g., vilanterol) may potentially improve patient compliance.

Two adequate and well-controlled clinical studies were submitted in support of the sponsor's NDA. As part of the clinical site audit, DPARP selected a single foreign site and a single U.S. site for Study HZC102871, and a single U.S. site for Study HZC112206, principally based on the highest number of randomized patients. The foreign site was also selected based on a reported high percentage of fatal pneumonias at that site.

Study HZC102871

HZC102871 was a randomized, double-blind, parallel-group, multi-center study evaluating three dosage strengths of fluticasone furoate/GW642444 versus one dosage strength of GW642444 alone given once daily in the morning. The primary objective of this study was to evaluate the safety and efficacy of fluticasone furoate/GW642444 50 mcg/25 mcg QD, fluticasone furoate/GW642444 100 mcg/25 mcg QD, and fluticasone furoate/GW642444 200 mcg/25 mcg QD versus GW642444 25 mcg QD on the annual rate of moderate and severe exacerbations in subjects with COPD over a 52 week treatment period. This study assessed the contribution of the inhaled corticosteroids on reducing the rate of exacerbations when used in combination with a fixed dose of a LABA (GW642444) in subjects with COPD. Patients aged 40 years and older with a diagnosis of COPD, post-bronchodilator spirometry evidence of disease, and a history of exacerbations were eligible for study inclusion. Subjects with asthma were excluded. The primary study endpoint was the annual rate of moderate and severe exacerbations of COPD.

Study HZC112206

HZC112206 was a multicenter, randomized, stratified (by smoking status), double-blind, placebo controlled, parallel-group study, to evaluate the efficacy and safety of fluticasone furoate/GW642444 inhalation powder 50 mcg/25 mcg QD, fluticasone furoate/GW642444 inhalation powder 100 mcg/25 mcg QD, fluticasone furoate inhalation powder 100 mcg QD, GW642444 inhalation powder 25 mcg QD, and placebo when administered via the novel dry powder inhaler over a 24-week treatment period in subjects with COPD. Patients aged 40 years and older, with a diagnosis of COPD and post-bronchodilator spirometry evidence of disease were eligible. Subjects with asthma were excluded. The co-primary efficacy endpoints were the weighted mean Clinic Visit Forced Expiratory Volume in One Second (FEV1) 0-4 hours post-dose (to evaluate the

contribution of GW642444) on Treatment Day 168 (Visit 11), and change from baseline in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV1 (to evaluate the contribution of fluticasone furoate and the 24-hour effect of GW642444) on Treatment Day 169 (Visit 12).

II. RESULTS:

Name of CI City, State	Protocol/Study Site/n, number of subjects	Insp. Date	Final Classification*
Richard E. Martinez, MD Boerne, TX	Protocol HZC102871 Site #068982 n=29 subjects enrolled	October 22-25, 2012	Preliminary: NAI
Joven Roque Gonong, M.D. Quezon City, Philippines	Protocol HZC102871 Site #69772 n=54 subjects enrolled	November 26-30, 2012	Preliminary: VAI
Edward M. Kerwin, M.D. Medford, OR	Protocol HZC112206 Site #069133 n=28 subjects enrolled	October 10-17, 2012	Preliminary: NAI
GlaxoSmithKline Durham, NC	Sponsor	December 17-19, 2012	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 and findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or complete review of EIR is pending. Once a final letter is issued by CDER to the inspected entity and the file is closed out, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

- 1. Richard E. Martinez, M.D./HZC102871 Site #068982**
Boerne, TX

- a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.811, from October 22 to 25, 2012. A total of 47 subjects were screened and 29 subjects were enrolled. Ten subjects withdrew or were terminated and 19 subjects completed the study.

An audit of 14 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 (100% of enrolled patients) 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. ORA staff discussion items at the close-out of the clinical site audit with the clinical investigative site management included:

(1) Bone metabolism marker blood specimens were not collected at Visit #11 for Subjects #108173 D-C and #103174 R-C. Failure to collect these specific laboratory tests was described as "inadvertent" by the clinical investigator. Additionally, bone metabolism marker blood specimens for the following subjects were not sent out for analyses for Subjects #103193 E-M, #103194 L-S, #103195 DCC, and #103196 #CJH. The clinical investigator mentioned that the sponsor gave instructions to destroy the collected specimens.

(2) Scheduled chest x-rays were not performed for Subjects #103165 EJC, #103159 C-B, #103195 DCC, and #103173 due to COPD exacerbation episodes. The clinical site records showed due diligence in attempting to complete these tests.

OSI Reviewer Comment:

This medical officer does not consider these sporadic protocol violations to be significant. Lack of chest x-ray completion was considered a protocol deviation. The unanalyzed bone metabolism markers were not central to the primary study objectives or clinical study hypotheses. DPARP did not consider these ORA observations relevant.

c. Assessment of data integrity:

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

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Joven Roque Gonong, M.D./HZC102871 Site #69772
Quezon City, Philippines

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from November 26 to 30, 2012. A total of 78 subjects were screened and 54 subjects were enrolled and randomized. Forty-two subjects completed the study.

An audit of the 23 screened and/or 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. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not conducting the study according to investigational plan and not maintaining adequate case histories or records.

(1) The investigation was not conducted according to the specified plan. Specifically,

- (a) The protocol required notification of the Sponsor Monitor when study drug storage temperatures exceeded 25°C. During a study monitoring visit, a storage temperature greater than 25°C was identified. The Sponsor impact assessment of these observations was that the investigational drug was still acceptable for use, as samples were not exposed to temperatures exceeding 40°C.

However, subsequent storage temperatures exceeding 25°C (ranging from 25.5 to 26.6°C) on more than 100 occasions were observed. The clinical site did not inform the Study Monitor.

- (b) Subject #1111265 EBA Visit #6's spirometry could not be performed due to a COPD exacerbation during the visit.

(2) There were deficiencies in maintaining accurate, adequate or complete case histories.
For example,

(a) For eligible Subject #111082 CBS at Visit #1 (Screening), the respiratory questionnaire section for review of systems (page 2) and subject eligibility questionnaire entries (page 5) were left blank. However, run-in medication was dispensed on March 11, 2010.

(b) For eligible Subject #111083 FZZ at Visit #1 (Screening) on March 11, 2010, respiratory questionnaire section for review of systems (page 2), reversibility test (Page 4), and subject eligibility (page 5) questionnaire entries were left blank.

Dr. Gonong responded adequately to the List of Inspectional Observations on December 10, 2012. His corrective and preventive action plans appeared adequate.

These minor regulatory deficiencies were referred to DPARP and were considered by the DPARP medical team as non-critical.

The DPARP medical team also inquired about the case histories for patients with fatal pneumonias for the following patients: Subject #111084 (fluticasone-vilanterol), Subject #111089 (fluticasone-vilanterol), Subject # 111092 (vilanterol), Subject #111126 (vilanterol), Subject #111128 (fluticasone-vilanterol), Subject #111165 (fluticasone-vilanterol), and Subject 111168 (fluticasone-vilanterol). Communication from the ORA field staff indicated that for the seven patients with fatal pneumonia reviewed at Dr. Gonong's site, relatives refused further diagnostic testing or patient intubation due to cost burden. Thus, available COPD patient management procedures may have been limited.

c. Assessment of data integrity:

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

**3. Edward M. Kerwin, M.D./HZC112206 Site #069133
Medford, OR**

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from October 10 to 17, 2012. A total of 37 subjects were screened and 28 subjects were enrolled. Twenty patients completed the study.

An audit of 11 randomized 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.

While a Form FDA 483 was not issued, the following relevant items were discussed at the close-out of this clinical site audit:

(1) Although known or suspected history of alcohol or drug abuse within the past two years was an exclusion criterion, the study protocol did not have clear measures or criteria for defining alcohol abuse. One unidentified subject (Note: study number not provided) was noted to have 28 alcohol drinks per week.

(2) Subject #131549 and Subject #131552 had long Fridericia corrected QTc intervals at Visit #1 (Screening), but these patients were eventually randomized into the study without two additional ECG readings to confirm a prolonged QTc [Note: Per protocol, all potentially exclusionary QT measurements (corrected or uncorrected) should be confirmed by two additional readings at least five minutes apart].

c. Assessment of data integrity:

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

SPONSOR

4. GlaxoSmithKline

Durham, NC

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from December 17 to 19, 2012.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The Sponsor maintained adequate oversight of the clinical trial. Monitoring of clinical investigator sites appeared to be adequate. The Sponsor took appropriate steps to bring noncompliant sites into compliance. At the conclusion of the inspection, no List of Inspectional Observations (Form FDA 483) was issued.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this NDA, a single U.S. clinical investigator site for Protocols HZC102871 and HZC112206, a single foreign clinical investigator site for Protocol Study HZC102871, and the Sponsor were inspected in support of this application.

No regulatory deficiencies were observed for Richard E. Martinez, M.D., Edward M. Kerwin, M.D., and the Sponsor (GSK). The preliminary classification for these inspections was NAI (No Action Indicated). Regulatory deficiencies of a non-critical nature related to not conducting the study according to the protocol and incomplete record keeping were observed for Joven R. Gonong, M.D. Preliminary classification for this inspection was related to not conducting the study according to the protocol and incomplete record keeping VAI (Voluntary Action Indicated).

Based on review of inspectional findings for these clinical investigator and Sponsor sites, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and final review of the EIRs.

{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:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
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Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
03/15/2013

JANICE K POHLMAN
03/15/2013

SUSAN D THOMPSON
03/15/2013

Consult – Fracture Risk with Fluticasone Furoate /Vilanterol Inhaler

To: Sofia Chaudhry, MD, DPARP

From: Stephen Bienz, MD, Clinical Reviewer, DRUP

Through: Theresa Kehoe, MD, Clinical Team Leader, DRUP
Hylton Joffe, MD, MMSc, Division Director, DRUP

Re: Fracture risk with Fluticasone Furoate/Vilanterol inhaler

Application: NDA 204,275

Consult Tracking #: 372

Date of Consult: October 2, 2012

Date Completed: November 29, 2012

1 Executive Summary

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) has consulted the Division of Reproductive and Urologic Products (DRUP) regarding fracture risk with a proposed combination long-acting inhaled corticosteroid/beta adrenergic device for COPD, Breo Ellipta (fluticasone furoate/vilanterol) 100/25 mcg QD.

There is some evidence in Trial HZC102871 for increased risk of bone fracture over a year with the fluticasone component of the inhaler with a dose dependent increase in fractures. In this trial, there is also lowered bone formation marker osteocalcin with higher fluticasone consistent with a corticosteroid bone effect. The fracture findings are not confirmed in Trial HZC102970, a similarly designed study. Osteocalcin was not measured in Trial HZC102970. Bone mineral density (BMD) was not obtained in either study.

Patients with COPD frequently have a number of risk factors which may make them more susceptible to osteoporosis and fracture including smoking, advanced age, hypogonadism, physical inactivity, malnutrition, low weight, and chronic inflammation. Evidence for increased fractures with corticosteroid inhaler use in COPD in the literature is mixed with often negative results, although a recent meta-analysis, Loke 2011, finds a modest 21-27% increase in risk.

Although subjects with COPD appear to be at increased risk of osteoporosis, probably related to the risk factors noted above, evidence for further BMD loss with inhaled corticosteroids is also mixed, with many studies with negative results. A small but

significant decrease in osteocalcin, a marker of bone formation and the most commonly followed bone turnover marker in studies of corticosteroid inhalers in COPD, is the most common positive finding in studies reviewed for this consult. A decrease in osteocalcin is consistent with a corticosteroid effect.

See the response to the questions below for further thoughts.

Questions:

1. Do the adverse event data for bone fractures in NDA 204275 indicate an increased risk of fracture for the proposed product, Breo Ellipta 100/25 mcg QD?

DRUP response: No. There is some evidence in Trial HZC102871 for increased risk of bone fracture with the fluticasone component of the inhaler with a dose dependent increase in fractures. There is also lowered bone formation marker osteocalcin with higher fluticasone consistent with a corticosteroid bone effect. However, the fracture findings are not confirmed in the similarly designed Trial HZC102970.

Inhaled corticosteroid usage in all treatment groups prior to the treatment period and more systemic corticosteroid usage during dosing for flares in the lower or no fluticasone groups may contribute to difficulty in showing a difference in osteocalcin and fractures between treatment groups.

As you are aware, there is some evidence in the literature that inhaled corticosteroids may contribute to fracture risk, especially in COPD patients, who appear at baseline to be at increased fracture risk probably secondary to age, smoking, and other factors. That evidence is balanced by many studies showing no increase in fractures.

We do suggest mention in the label that subjects with COPD may be at increased risk of osteoporosis, that the inhaler potentially may further increase fracture risk, and of the need to appropriately treat osteoporosis, whether diagnosed by BMD testing or fragility fracture.

2. Are there additional data/studies that should be conducted to further evaluate the risk?

DRUP response: A study to confirm the effect of fluticasone furoate on fracture would be interesting but would of necessity be large, long, and, due to complications with the treating of flares and perhaps other issues (e.g. retention), will likely not provide definitive results, and so cannot be recommended. The large ongoing placebo-controlled Trial HZC113782, evaluating survival in subjects with COPD and cardiovascular disease with the fluticasone furoate/vilanterol inhaler, may provide useful data regarding fracture risk, and should be evaluated relative to that risk once completed.

A study to confirm the effect of inhaled fluticasone furoate on bone turnover markers or BMD in subjects with COPD newly randomized to inhalers would not give a final answer regarding fracture risk. Osteocalcin and serum carboxy-terminal cross-linking telopeptide of collagen (CTX) have already been evaluated in Trial HZC102871, and, although other

bone turnover markers could be evaluated, further useful information is unlikely to be obtained. A BMD study, given other risk factors leading to bone loss in patients with COPD and the history of non-definitive BMD studies with other corticosteroid inhalers, may well also not provide useful information, and so cannot be recommended.

2 Introduction

DPARP requests that DRUP evaluate studies in NDA 204,275 for increased fracture risk with the long-acting combination corticosteroid/ beta adrenergic inhaler fluticasone furoate/vilanterol. Specific questions are:

1. Do the adverse event data for bone fractures in NDA 204275 indicate an increased risk of fracture for the proposed product, Breo Ellipta 100/25 mcg QD?
2. Are there additional data/studies that should be conducted to further evaluate the risk?

3 Background

Although a causative role has not been shown, patients with COPD are at increased risk of osteoporosis and fracture. Associated risk factors such as smoking, advanced age, hypogonadism, physical inactivity, malnutrition, low weight, and chronic inflammation may play a role. Oral corticosteroids used to treat COPD additionally contribute to lower BMD and higher fracture risk. However, studies and reviews have been inconsistent regarding showing an association between inhaled corticosteroids and increased fracture risk or loss of BMD (Jorgensen 2008, Loke 2011). A recent meta-analysis suggests a modest increase in fracture risk (21-27%) in subjects with COPD treated with inhaled corticosteroids for at least 6 months (Loke 2011). The bone formation marker osteocalcin, the most frequently studied of the bone turnover markers in COPD, has been reported to be lowered with higher doses of inhaled corticosteroids (Jones 2002).

Systemic corticosteroids have been shown to decrease bone formation with an early brief increase in resorption as well, decrease BMD, and increase fracture risk. Fracture risk increases early and exceeds that expected for the degree of bone loss. As bone loss is primarily trabecular, the pattern of fracture is similar to that of postmenopausal osteoporosis with vertebral body, hip, and other non-vertebral fractures increased despite a different mechanism for bone loss with corticosteroids (Maricic 2011).

The oral bioavailability of fluticasone furoate is low (1.3%) and similar to fluticasone propionate, largely due to extensive first-pass metabolism. The absolute bioavailability when delivered as inhaled fluticasone furoate/vilanterol dry powder is 15% (NDA submission, Module 2.7.2 Summary of Clinical Pharmacology, Kelly 2003). The systemic equivalence of fluticasone furoate to prednisone appears not to have been previously calculated, but, expressed in milligrams, is estimated to be several times less based on structure and lung effects.

Reviewer comment: An expected 15 mcg daily of systemic fluticasone furoate with this inhaler seems unlikely to cause major systemic corticosteroid effects. This is confirmed by lack of effect in the cortisol suppression study HZA106851.

Fluticasone furoate is a corticosteroid approved since 2007 as a nasal spray for allergic rhinitis at a dose of 110 mcg once daily (for adults). No mention of bone mineral density (BMD) or fracture is found in the label.

A related corticosteroid, fluticasone propionate, is approved for asthma at doses up to 1,000 mcg twice daily and in combination with salmeterol (long acting beta agonist) for asthma and COPD at doses up to 500 mcg twice daily (the recommended dose for COPD is 250 mcg twice daily). Nasal spray products are dosed at 200 mcg daily. The label for fluticasone propionate 500, 250, or 100mcg/salmeterol 50 mcg with the indication for COPD (Advair Diskus) includes a Warning and Precaution regarding the potential for BMD reduction:

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post-menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating ADVAIR DISKUS and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

2-Year Fluticasone Propionate Study: A 2-year study of 160 patients (females aged 18 to 40 years, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

3-Year Bone Mineral Density Study: Effects of treatment with ADVAIR DISKUS 250/50 or salmeterol 50 mcg on BMD at the L1-L4 lumbar spine and total hip were evaluated in 186 patients with COPD (aged 43 to 87 years) in a 3-year double-blind study. Of those enrolled, 108 patients (72 males and 36 females) were followed for the entire 3 years. BMD evaluations were conducted at baseline and at 6-month intervals. Conclusions cannot be drawn from this study regarding BMD decline in patients treated with ADVAIR DISKUS versus salmeterol due to the inconsistency of treatment differences across gender and between lumbar spine and total hip. In this study there were 7 non-traumatic fractures reported in 5 patients treated with ADVAIR DISKUS and 1 non-traumatic fracture in 1 patient treated with salmeterol. None of the non-traumatic fractures occurred in the vertebrae, hip, or long bones.

3-Year Survival Study: Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 patients (females and males aged 40 to 80 years) with COPD in the 3-year survival study. BMD evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be drawn from this study because of the large number of drop outs (>50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD. Fracture risk was estimated for the entire population of patients with COPD in the survival study (N = 6,184). The probability of a fracture over 3 years was 6.3% for ADVAIR DISKUS, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

Reviewer comment: The difference in fracture risk between groups in the 3-Year Survival Study was not statistically significant (Ferguson 2009).

Advair Diskus was the only fluticasone propionate product found indicated for COPD.

Symbicort (budesonide 80 and 160 mcg/formoterol fumarate 4.5 mcg) is another corticosteroid/long acting beta adrenergic inhaler indicated for COPD at 2 inhalations of the 160/4.5 dosage twice daily. The first paragraph of a Warnings and Precautions section is essentially identical to that for Advair Diskus, and that is followed by:

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm²). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Much less information on bone effect was found in labels for corticosteroid inhalers indicated for asthma only.

This is the first NDA for **Vilanterol** (GW642444), a long acting beta adrenergic agonist.

4 Review of the provided trials and data

Trial Number HZC102871, titled “A 52-week efficacy and safety study to compare the effect of three dosage strengths of fluticasone furoate/GW642444 inhalation powder with GW642444 on the annual rate of exacerbations in subjects with chronic obstructive pulmonary disease”, was a multicenter, multinational, randomized, double blind study in 1622 subjects comparing fluticasone furoate/vilanterol inhaler at 50/25 mcg, 100/25 mcg,

and 200/25 mcg to vilanterol 25 mcg alone dosed once daily in the morning via “novel dry powder inhaler” (NDPI). Subjects were at least 40 years of age with COPD and at least one moderate or severe COPD exacerbation in the prior year. During a 4 week run-in period all subjects received open-label fluticasone propionate 250 mcg/salmeterol 50 mcg bid prior to randomization. Subjects were not routinely supplemented with calcium and vitamin D. Bone endpoints were safety endpoints and included bone fractures and the bone turnover markers serum carboxy-terminal cross-linking telopeptide of collagen (sCTX) and osteocalcin. Fractures were reported on a separate case report form sheet in addition to being reported as adverse events, but were not adjudicated. Bone mineral density was not done.

Mean subject age was 64 years. About 59% of subjects were male. About 82% of subjects were White. BMI averaged 27. Prior to run-in, 68% of subjects were listed as having taken inhaled corticosteroids and 7% systemic corticosteroids, although no oral corticosteroids were allowed within 30 days of screening and run-in. During the study, about 4% of subjects were on a bisphosphonate and 3% on estrogen. Treatment groups were similar in these characteristics. Dropout rates were similar between treatment groups (23 to 28%).

On treatment fractures in Trial HZC102871 are shown in Table 1. More subjects with fractures were noted in the fluticasone/vilanterol inhaler treatment groups (7 – 9) than in the vilanterol group (2) over the one year of the study. When fragility fractures are considered (excluding fractures of the skull, face, hands, and feet), there appears to be a dose response, with 2 fractures in the vilanterol group and 3, 7, and 8 respectively in the fluticasone/vilanterol 50/25, 100/25, and 200/25 groups. Nominal statistical significance was found for subjects with fracture comparing the FF/VI 200/25 group ($p=0.036$) and overall (summed) fluticasone groups ($p=0.040$) to vilanterol alone (as calculated by this reviewer, not included in study report) but this was not reflected with fragility fractures, although a trend was noted. This increase in fractures in the fluticasone groups and dose response may indicate an increased fracture risk with inhaled fluticasone, although low event rates limit conclusions.

A longer time on steroids may lead to increased fracture risk. As many of the subjects in this study were on inhaled steroids before enrollment, that effect may or may not be apparent. Time to fragility fracture was divided into quartiles in Table 1. Only in the fluticasone/vilanterol 100/25 treatment group did fractures appear to increase later in the treatment period (86% of fractures later than Day 180, 43% later than Day 270). The interpretation of this is unclear.

The notes to Table 1 document a lack of consistency in location and even number of fractures between sources in the study report and datasets which made evaluation difficult and may indicate errors in collecting and evaluating these data on the part of the Applicant.

Table 1, On-Treatment Fractures in Trial HZC102871 Over One Year

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N	409	408	403	402

Total subjects with fx	2	8	7	9
P-value (fx) ¹		0.064	0.105	0.036
Non-traumatic fracture ²	0	3	2	5
Fragility fractures ³	2	3	7	8
P-value (fragility fx) ¹		0.686	0.105	0.062
Thoracic spine			2 ^a	2
Lumbar spine				1
Hip (inf. pubic ramus per narrative)				1 ^a
Wrist		1 ⁴	2	
Radius			1 ⁴	
Humerus			1 ⁴	
Rib ⁵	2	2	2	1
Sternal				1 ⁶
Knee				1 ⁷
Tibia				2 ^{8, b}
Hand				1
Foot		5		1 ^{9, a}
Fragility fractures at ≥ Day 90 (%)	2 (100)	2 (67)	7 (100)	4 (50)
Fragility fractures at ≥ Day 180 (%)	2 (100)	2 (67)	6 (86)	2 (25)
Fragility fractures at ≥ Day 270 (%)	2 (100)	1 (33)	3 (43)	1 (13)
Source: Clinical Study Report HZC102871 Table 7.38 and AE dataset				
1 Difference from the vilanterol group in subjects with fracture by Fisher's Exact Test. Calculated by reviewer. For the summed fluticasone groups p=0.040 for fx, 0.191 for fragility fx				
2 Traumatic fracture is not defined, but is determined by a checkbox on the case report form (CRF)				
3 Excludes fractures of the skull, face, hands, and feet				
4 Classified as "arm" on bone fracture CRF				
5 As the number of ribs fractured is usually not listed, each incident of fractured ribs is counted once				
6 Classified as "chest" on bone fracture CRF				
7 Classified as "leg" on bone fracture CRF				
8 These classified together as one fracture "other" on bone fracture CRF				
9 Classified as "ankle" on bone fracture CRF, foot in other sources and treated with walking boot				
a Two fractures on the same day				
b Bilateral fractures on the same day				

Change from Baseline over the 52 weeks of Trial HZC102871 in serum carboxy-terminal cross-linking telopeptide of collagen (sCTX) and osteocalcin is shown in Table 2 and Table 3. There was no significant difference in change over 52 weeks between the vilanterol and the fluticasone furoate/vilanterol treatment groups in the bone resorption marker sCTX (ratio of change for the combination inhaler treatment groups not significantly different from that of vilanterol alone, see Table 2).

Table 2, Serum CTX Change over 52 Weeks in Trial HZC102871

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N (Baseline)	402	397	389	388
sCTX, mcg/L (geom. mean)	0.347	0.337	0.335	0.320
n (End of study)	347	353	357	340
sCTX, mcg/L (geom. mean)	0.387	0.354	0.353	0.352
n Ratio (EOS/Baseline)	341	342	346	328
Geom Mean Ratio (EOS/Baseline)	1.133	1.058	1.056	1.078
Ratio compared to VI25		0.933	0.932	0.952
P-value		0.184	0.172	0.345
Source: Clinical Study Report HZC102871 Tables 7.54, 7.55, 7.56				

Borderline significant difference in change over 52 weeks between the vilanterol group and the highest dose fluticasone furoate/vilanterol treatment group in the bone formation marker osteocalcin was noted ($p=0.047$), with a dose-trend noted also in the lower dose fluticasone treatment groups (see Table 3). This pattern indicates perhaps a reduction in osteocalcin with increased doses of fluticasone furoate, although the 9% reduction seen in the 200 mcg fluticasone treatment group was not large. What is seen is consistent with the usual glucocorticoid induced pattern for bone turnover markers of stable bone resorption with decreased bone formation, however, and so appears to be likely relevant and to indicate some glucocorticoid effect on bone is occurring.

Complicating interpretation is that all subjects were on inhaled glucocorticoids for at least one month prior to baseline and there was a trend for fewer subjects in the fluticasone furoate/vilanterol 200/25 mcg treatment group to have COPD exacerbations requiring systemic steroids (19% reduction, $p=0.064$ compared to vilanterol). Both of these interventions would be expected to reduce differences between treatment groups for bone turnover marker change.

Table 3, Osteocalcin Change over 52 Weeks in Trial HZC102871

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N (Baseline)	402	396	389	390
Osteocalcin, mcg/L (geom.. mean)	15.16	14.18	14.89	14.12
n (End of study)	348	353	356	341
Osteocalcin, mcg/L (geom.. mean)	16.45	15.51	15.12	14.11
n Ratio (EOS/Baseline)	342	341	345	330
Geom Mean Ratio (EOS/Baseline)	1.09	1.07	1.02	0.99
Ratio compared to VI25		0.98	0.93	0.91
P-value		0.683	0.128	0.047

Source: Clinical Study Report HZC102871 Tables 7.54, 7.55, 7.57

Scans for bone density (DXA, CT) were not done in this study.

Conclusions: More fractures were noted in the fluticasone/vilanterol inhaler treatment groups (7 – 9) than in the vilanterol group (2). When fragility fractures are considered, there appears to be a dose response, with 2 fractures in the vilanterol group and 3, 7, and 8 respectively in the fluticasone/vilanterol 50/25, 100/25, and 200/25 groups. This increase in fractures in the fluticasone groups and dose response may indicate an increased fracture risk with inhaled fluticasone although the low event rates limit conclusions. (Note: Statistical evaluation of fracture between groups was not done in the study report. Using Fisher’s Exact Test and subjects with fracture, the only group statistically different from the vilanterol group was the fluticasone/vilanterol 200/25 group with $p=0.036$. Summing all fluticasone groups yields $p=0.040$)

Bone turnover markers indicate little change in the marker of bone resorption sCTX, but a small (9%) nominally significant drop in the bone formation marker osteocalcin with the highest dose of fluticasone, and a trend at lower doses. As the usual pattern in glucocorticoid induced effects on bone turnover markers is for stable bone resorption and reduced bone formation as seen to a small degree here, it is likely bone turnover markers

in Trial HZC102871 indicate some effect of inhaled fluticasone on bone. Difference in osteocalcin may have been greater if subjects had not been on inhaled glucocorticoids for at least a month prior to baseline and if as many subjects on the highest dose of fluticasone had required systemic steroids for COPD flares as in the vilanterol group.

Although not conclusive, the data from Trial HZC102871 support an increased fracture risk with this fluticasone/vilanterol inhaler when used for COPD, particularly with 100 or more mcg of fluticasone furoate daily.

Trial Number HZC102970, a study designed similarly to HZC102871 and titled identically “A 52-week efficacy and safety study to compare the effect of three dosage strengths of fluticasone furoate/GW642444 inhalation powder with GW642444 on the annual rate of exacerbations in subjects with chronic obstructive pulmonary disease”, was a multicenter, multinational, randomized, double blind study in 1633 subjects comparing fluticasone furoate/vilanterol inhaler at 50/25 mcg, 100/25 mcg, and 200/25 mcg to vilanterol 25 mcg alone dosed once daily in the morning via NDPI. Subjects were at least 40 years of age with COPD and at least one moderate or severe COPD exacerbation in the prior year. During a 4 week run-in period all subjects received open-label fluticasone propionate 250 mcg/salmeterol 50 mcg bid prior to randomization. Subjects were not routinely supplemented with calcium and vitamin D. Bone fractures were a safety endpoint and were collected both as adverse events and on a fracture case report form sheet. Fractures were not adjudicated. Bone turnover markers and bone mineral density were not done in this trial.

Mean subject age was 64 years. About 55% of subjects were male. About 88% of subjects were White. BMI averaged 27. Prior to run-in, 74% of subjects were listed as having taken inhaled corticosteroids and 5% systemic corticosteroids, although no oral corticosteroids were allowed within 30 days of screening and run-in. During the study, about 5% of subjects were on a bisphosphonate and 4% on estrogen. Treatment groups were similar in these characteristics.

In Trial HZC102970, 6 subjects fractured on vilanterol over one year, while 7, 12, and 5 subjects fractured in the fluticasone/vilanterol 50/25, 100/25, and 200/25 treatment groups respectively (see Table 4). Although fractures increase with increasing fluticasone through 100 mcg, that pattern is clearly broken with the 200 mcg fluticasone group. A similar pattern is seen with fragility fractures. There also does not appear to be a pattern of higher numbers of fragility fractures with longer treatment with fluticasone as noted when the time to fracture is divided into quartiles (see Table 4).

The notes to Table 4 document a lack of consistency in location and number of fractures between sources in the study report and datasets. Two fractures were found in a narrative which were not reported in the report or datasets otherwise. These inconsistencies made evaluation difficult and may indicate errors in collecting and evaluating fracture data on the part of the Applicant.

Table 4, On-Treatment Fractures in Trial HZC102970 Over One Year

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
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N	409	412	403	409
Total subjects with fracture ¹	6	7	12	5
P-value (fx)*		1.000	0.093	1.000
Non-traumatic fracture ²	2	1	4	4
Subjects with fragility fracture ³	5	7	10	4
P-value (fragility fx)*		0.773	0.203	1.000
Thoracic spine	1	1	2 ^b	
Lumbar spine				1 ⁴
Hip	1	2		1
Wrist	1	1 ⁵	1	1
Humerus		1 ^a	1	
Clavicle			1	
Scapula	1			
Rib ⁶		2 ^a	4	1
Pelvis	1		1	
Patella		1		
Ankle		1 ⁵	1	
Hand				1
Foot	1		2 ⁷	
Fragility fractures at ≥ Day 90 (%)	4 (80)	7 (88)	6 (60)	3 (75)
Fragility fractures at ≥ Day 180 (%)	3 (60)	4 (50)	5 (50)	1 (25)
Fragility fractures at ≥ Day 270 (%)	0	3 (38)	3 (30)	1 (25)

Source: Clinical Study Report HZC102970 Table 7.38, AE dataset, and fracture dataset

Note: Subject 118352 in the VI 25 treatment group developed a patella and an arm fracture in a fall 33 days after last investigational product. As this was beyond the 7 day protocol follow-up period, these fractures are not included above

* Difference from the vilanterol group in subjects with fracture by Fisher's Exact Test. Calculated by reviewer. For the summed fluticasone groups p=0.672 for fx, 0.649 for fragility fx

1 If two or more fractures occurred on the same date in a subject, it was considered one fracture "incident".

One subject in the FF/VI 50/25 group had two fracture incidents

2 Traumatic fracture is not defined, but is determined by a checkbox on the case report form (CRF)

3 Excludes fractures of the skull, face, hands, and feet

4 As the lumbar spine fracture occurred post-treatment but within the 7 day follow-up period, it is included

5 Same subject on different days

6 As the number of ribs fractured is usually not listed, each incident of fractured ribs is counted once

7 Clinical Study Report HZC102970 Table 7.07 lists this as 3 fractures but does not report the ankle fracture in this treatment group

a Subject 116853 narrative lists rib and humeral fracture in motorcycle accident on Day 165 not in AE listings or datasets

b Subject with two acute compression fractures in narrative rather than 1

Bone turnover markers were not done in Trial HZC102970. Scans for bone density (DXA, CT) were also not done in this study.

Conclusions: In Trial HZC102970, there is little indication of an increased fracture risk with fluticasone with 6 subjects fracturing on vilanterol over one year, while 7, 12, and 5 subjects fractured in the fluticasone/vilanterol 50/25, 100/25, and 200/25 treatment groups respectively. There did also not appear to be an increased fracture risk with more time on fluticasone. Both high use of steroid inhalers prior to the study in all treatment groups and lower use of systemic steroids for flares on-study in subjects on 200 mcg fluticasone daily may have masked any difference.

Combined One Year Study Fractures: Fractures were totaled from Studies HZC102871 and HZC102970 in Table 5. About twice as many subjects with fracture occurred in the fluticasone/vilanterol groups than the vilanterol alone groups (total fractures 8 with vilanterol and 15, 19, and 14 respectively with fluticasone/vilanterol 50/25, 100/25, and 200/25). Only the fluticasone/vilanterol 100/25 group showed statistically significant difference from the vilanterol group in subjects with fracture (nominal $p=0.033$), as calculated by the reviewer. There does not appear to be dose dependence for the increased fracture risk except when evaluating non-traumatic fractures (2 with vilanterol and 4, 6, and 9 respectively with fluticasone/vilanterol 50/25, 100/25, and 200/25). As the definition of “traumatic” was left to the discretion of the investigator with apparently little instruction, it is difficult to evaluate the significance of that finding.

Table 5, Fractures from Trials HZC102871 and 102970 Combined

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N	818	820	806	811
Total subjects with fracture	8	15	19	14
P-value (fx)*		0.207	0.033	0.205
Non-traumatic fracture ²	2	4	6	9
Subjects with fragility fracture ³	7	10	17	12
P-value (fragility fx)*		0.478	0.040	0.259
Source: Table 1 and Table 4				
* Difference from the vilanterol group in subjects with fracture by Fisher’s Exact Test. Calculated by reviewer. For the summed fluticasone groups $p=0.062$ for fx, 0.127 for fragility fx				
1 If two or more fractures occurred on the same date in a subject, it was considered one fracture “incident”				
2 Traumatic fracture is not defined, but is determined by a checkbox on the case report form (CRF)				
3 Excludes fractures of the skull, face, hands, and feet				

Trial Number HZC112206 entitled A 24-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (GW685698)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared with Placebo in Subjects with Chronic Obstructive Pulmonary Disease (COPD), was a multinational, randomized, double blind, placebo controlled trial comparing fluticasone furoate/vilanterol 50/25 and 100/25 mcg against fluticasone 100 mcg, vilanterol 25 mcg, and placebo once daily on change in FEV₁. A total of 1030 subjects with COPD and at least age 40 were given a 2 week run-in with albuterol/salbutamol prn which was continued during the trial.

Mean subject age was 63 with 67% males and 72% Whites. Treatment groups were similar for these characteristics.

As many or more subjects with fracture occurred in the placebo and vilanterol groups (3 and 2) than in the fluticasone and fluticasone/vilanterol 50/25 and 100/25 groups (2, 0, and 1 respectively) (see Table 6). The number of fractures is small and the time for effect (24 weeks) is short, so interpretation is difficult.

Table 6, On Treatment Fractures in Trial HZC112206

	Placebo	VI 25	FF 100	FF/VI 50/25	FF/VI 100/25
N	207	205	206	206	206

Total subjects with fracture	3	2	2	0	1
Subjects with fragility fracture ¹	3	2	1	0	1
Coccyx	1				
Rib			1		
Clavicle		1 ²			
Radius (distal)	1 ³				
Wrist	1 ³				
Patella					1
Knee		1 ²			
Multiple	1 ^{4,5}	1 ⁵			
Foot			1		
Source: Clinical Study Report HZC112206 Table 7.05, AE dataset					
1 Excludes fractures of the skull, face, hands, and feet					
2 Same subject, same day					
3 Same subject, same day, listed separately, unclear if different bones					
4 Found in narrative only					
5 Motor vehicle accident					

Trial Number HZC112207, also entitled A 24-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (GW685698)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared with Placebo in Subjects with Chronic Obstructive Pulmonary Disease (COPD), was a multinational, randomized, double blind, placebo controlled trial comparing fluticasone furoate/vilanterol 100/25 and 200/25 mcg against fluticasone 100 and 200 mcg, vilanterol 25 mcg, and placebo once daily on change in FEV₁. A total of 1224 subjects with COPD and at least age 40 were given a 2 week run-in with albuterol/salbutamol prn which was continued during the trial.

Mean subject age was 62 with 72% males and 94% Whites. Treatment groups were similar for these characteristics.

No more than two fractures occurred in any treatment group (see Table 7). The number of fractures is small and the time for effect (24 weeks) is short, so interpretation is difficult.

Table 7, On Treatment Fractures in Trial HZC112207

	Placebo	VI 25	FF 100	FF 200	FF/VI 100/25	FF/VI 200/25
N	205	203	204	203	204	205
Total subjects with fracture	0	1	1	2	2	0
Subjects with fragility fracture ¹	0	1	1	2	1	0
Lumbar spine		1				
Rib			1			
Arm				1		
Humerus					1	
Tibia				1 ²		
Fibula				1 ²		
Hand					2 ³	
Source: Clinical Study Report HZC112205 Table 7.05, AE dataset						
1 Excludes fractures of the skull, face, hands, and feet						
2 Same subject, same day						
3 Two distal phalanges, same day						

Trial Number HZC113782 is an ongoing multicenter, multinational, randomized, double-blind study comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone furoate 100 mcg, vilanterol 25 mcg, and placebo in about 16,000 subjects with COPD with or at increased risk of cardiovascular disease on survival. The primary evaluation is to be performed after the required number of events is reached, which is expected after 15 to 44 months. Although fractures will only be recorded as adverse events and interpretation will be complicated by the treating of flares and perhaps other issues such as retention, the large size and duration of this placebo-controlled study allow it to potentially provide interesting data with regard to the risk of fracture with inhaled fluticasone furoate.

5 Summary

Trial HZC102871 shows significantly more subjects with fracture in the highest fluticasone furoate/vilanterol inhaler group (200/25 mcg) over one year (nominal $p=0.036$), with numerically more fractures in the other fluticasone groups and statistically more fractures in the summed fluticasone groups compared to vilanterol (nominal $p=0.040$). These findings were not confirmed in the similarly designed Trial HZC102970. Inhaled corticosteroid use prior to the treatment period by all treatment groups and more use of systemic corticosteroids during the trial in treatment groups with less or no fluticasone complicate the interpretation of this data.

No bone mineral density data are available in these studies. Osteocalcin and CTX, markers of bone turnover, were followed in Trial HZC102871. Although no statistically significant change from vilanterol was found for CTX, the fluticasone furoate/vilanterol 200/25 mcg showed a statistically significant 9% decrease for osteocalcin compared to vilanterol alone (nominal $p=0.047$), with a pattern of decreasing osteocalcin with increasing doses of fluticasone. Again, prior inhaled corticosteroid use by all treatment groups and more use of systemic corticosteroids during the trial in treatment groups with less or no fluticasone complicate the interpretation of these data. Although the decrease in osteocalcin is small, the pattern of reduced bone formation markers is consistent with corticosteroid effect.

In the literature there is most consistently a suggestion of osteocalcin decrease with inhaled corticosteroids. BMD and fracture findings have been less consistent, but a recent meta-analysis suggests a modest increase in fracture risk (21-27%) in subjects with COPD treated with inhaled corticosteroids for at least 6 months (Loke 2011). Patients with COPD may have a number of risk factors making them more susceptible to osteoporosis and fracture compared to asthma patients including smoking, advanced age, hypogonadism, physical inactivity, malnutrition, and low weight. Chronic inflammation may also contribute to fracture risk in the COPD population. It would appear what should be a very small systemic corticosteroid dose may be enough to further increase fracture risk, but the data are not conclusive.

A study to confirm the effect of fluticasone furoate on fracture would be interesting but would of necessity be large, long, and, due to complications with the treating of flares and perhaps other issues (e.g. retention), will likely not provide definitive results, and so

cannot be recommended. The large ongoing placebo-controlled Trial HZC113782, evaluating survival in subjects with COPD and cardiovascular disease with the fluticasone furoate/vilanterol inhaler, may provide useful data regarding fracture risk, and should be evaluated relative to that risk once completed.

A study to confirm the effect of inhaled fluticasone furoate on bone turnover markers or BMD in subjects with COPD newly randomized to inhalers would likely not give a final answer regarding fracture risk. Osteocalcin and CTX have already been evaluated, and, although other bone turnover markers could be evaluated, further useful information is unlikely to be obtained. A BMD study, given other risk factors leading to bone loss in patients with COPD and the history of non-definitive BMD studies with other corticosteroid inhalers, may well also not provide useful information, and so cannot be recommended.

The increase of risk factors for osteoporosis with COPD, the potential for increasing fracture risk with the inhaler, and the need to appropriately treat osteoporosis, whether diagnosed by BMD testing or fragility fracture, should be mentioned in the label.

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/s/

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12/11/2012

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12/12/2012

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12/12/2012

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

NDA	204275
Brand Name	Breo Ellipta
Generic Name	Fluticasone Furoate (FF)/ GW642444M (vilanterol (VI))
Sponsor	GlaxoSmithKline
Indication	Maintenance treatment of Chronic Obstruction Pulmonary Disease (COPD)
Dosage Form	Inhalation Powder
Drug Class	Fluticasone furoate: Corticosteroid GW642444: Long-acting β 2 agonist (LABA)
Therapeutic Dosing Regimen	Fluticasone furoate: 200 mcg once daily GW642444M: 25 mcg once daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Fluticasone furoate: 800 mcg once daily GW642444M: 100 mcg once daily
Submission Number and Date	SDN 001/12 Jul 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

The largest upper bounds of the 2-sided 90% CI for the mean difference between FF/IV 200/25 mcg and placebo were below 10 ms. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between FF/IV 800/100 mcg and placebo was above 12.2 ms 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 4, indicating that assay sensitivity was established.

In this randomized, four-way crossover repeat dose study, 85 healthy subjects received FF/VI 200/25 mcg, FF/VI 800/100 mcg, placebo, and a single oral dose of 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 FF/VI (200/25 mcg and 800/100 mcg) for $\Delta\Delta\text{QTcF}$ and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
FF/VI 200/25 mcg	30 min	4.9	(2.3, 7.5)
FF/VI 800/100 mcg	30 min	9.6	(7.0, 12.2)
Moxifloxacin 400 mg*	4	14.3	(11.9, 16.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 11.1 ms

An increase in heart rate was also observed. The largest upper bounds of the 2-sided 90% CI for the mean differences between FF/VI 200/25 and placebo, and between FF/VI 200/25 and placebo were 9.4 bpm and 18.7 bpm, respectively.

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for FF/VI (200/25 mcg and 800/100 mcg) for $\Delta\Delta\text{HR}$ (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{HR}$ (ms)	90% CI (ms)
FF/VI 200/25 mcg	10 min	7.8	(6.2, 9.4)
FF/VI 800/100 mcg	10 min	17.1	(15.5, 18.7)

The supratherapeutic dose (FF/VI 800/100 mcg) produces mean C_{max} values of FF and VI that are 3.3-fold and 4.6-fold, respectively, the mean C_{max} for the therapeutic dose (200/25 mcg). These concentrations are above those for the predicted worst case scenario for FF (drug interaction with ketoconazole) and VI (hepatic impairment).

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

12.2 Pharmacodynamics

(b) (4)

2.2 QT-IRT'S PROPOSED LABEL

Our recommendations are suggestions only. We defer final labeling decisions to the review division.

12.6 Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, multiple dose, placebo- and positive-controlled crossover study in 85 healthy volunteers. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 4.9 (7.5) ms and [REDACTED]^{(b) (4)} ms seen 30 minutes after dosing for fluticasone furoate 200 mcg/vilanterol 25 mcg and fluticasone furoate 800 mcg/vilanterol 100 mcg, respectively.

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 7.8 (9.4) beats/min and 17.1 (18.7) beats/min seen 10 minutes after dosing for fluticasone furoate 200 mcg/vilanterol 25 mcg and fluticasone furoate 800 mcg/vilanterol 100 mcg, respectively.

3 BACKGROUND

3.1 PRODUCT INFORMATION

GW642444 is a potent and selective β_2 -adrenoceptor agonist. It has similar potency and greater intrinsic activity at β_2 -adrenoceptors than salmeterol, but less than formoterol. GW642444 has a rapid onset and long duration of action.

3.2 MARKET APPROVAL STATUS

Fluticasone furoate is the active ingredient of fluticasone furoate nasal spray suspension, which was first approved by the FDA on 27 April 2007 for treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older

(VERAMYST™ Nasal Spray). Since that time, fluticasone furoate nasal spray suspension has been approved (trade mark AVAMYST™) in 108 countries. To date, VI or the combination of FF/VI are not currently and have never been registered or marketed anywhere in the world.

3.3 PRECLINICAL INFORMATION

From eCTD 2.6.3

Organ Systems Evaluated	Species (Strain)	Method of Admin.	Concentration	Salt	No. Per Sex Per Group	Noteworthy Findings	GLP	Report No. (Study No.)
hERG assay	HEK293 cells	In vitro	0.31 to 30.7 mcM (0.15 to 14.9 mcg/mL)	H	NA	GW642444 inhibited hERG tail current in a concentration-dependent manner. The IC ₂₅ , IC ₅₀ and IC ₇₅ values for GW642444 inhibition of hERG tail current were 2.0, 4.8 and 12.6 mcM (0.99, 2.3 and 6.1 mcg/mL), respectively.	Yes	FD2003/00330/00 (V24776)
Purkinje fibre assay	Dog (beagle)	In vitro	1.0 to 100 mcM (0.49 to 49 mcg/mL)	H	NA	At stimulation frequencies of 0.5 and 1 Hz, exposure to GW642444 at concentrations of 1 and 10 mcM caused a concentration-dependant depolarization of RMP and decreases in UA, MRD and APD. At 100 mcM GW642444 action potentials could not be elicited in 3 of the 4 test substance treated fibres. In the remaining fibre RMP, UA and APD were further reduced compared to the effects observed at 10 mcM GW642444 (the effect on MRD was similar to the effects observed at 10 mcM) at 1 Hz. This fibre became spontaneous at 0.5 Hz. Due to these effects meaningful statistical analysis could not be performed at 0.5 and 3 Hz. These results are consistent with inhibition of cardiac potassium (IK1) and sodium channels although an additional inhibition of cardiac channels cannot be ruled out.	Yes	FD2003/00323/01 (V24650)

Organ Systems Evaluated	Species (Strain)	Method of Admin.	Dose ^a (mcg/kg)	Salt	No. Per Sex Per Group	Noteworthy Findings	GLP	Report No. (Study No.)
Single dose cardiovascular study	Dog (beagle)	Intravenous (infusion ^c)	0, 0.1, 0.3, 1	H	4M	Transient increases in heart rate were observed at 0.3 and 1 mcg/kg GW642444, which were moderate (approximately 60 bpm) at 1 mcg/kg.	Yes	FD2003/00275/00 (D24478)
Single dose cardiovascular study	Dog (beagle)	Intravenous (infusion ^c)	0, 0.1, 0.3, 1	M	4M	At 1 mcg/kg a small transient decrease in blood pressure and an increase in heart rate were observed. At 0.3 mcg/kg a smaller increase in heart rate was observed. At 0.3 and 1 mcg/kg reductions in PR, RR, QT and QT _{cL} interval were observed, attributed to the changes in heart rate. At 0.1 mcg/kg a very small prolongation of QT and QT _{cL} interval was observed.	Yes	FD2005/00097/00 (D28014)

Key:

a = Estimated achieved dose for inhaled studies.
b = 3 additional animals/group included for toxicokinetic investigations.
c = 1 minute infusion.
NOAEL = No observed adverse effect level.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

ECG evaluations in the six-month lung function studies indicated that:

- Mean for maximum post-baseline changes in QTc(F) were similar for the placebo group (10.3 msec) and for all active treatment groups (9.4 to 10.4 msec).
- Repeated measures analysis of QTc(F) data showed no statistically significant differences between any active treatment group compared with placebo, any FF/VI

combination groups compared with VI 25, or between either the FF/VI 100/25 and FF 100 or the FF/VI 200/25 and FF 200 monotherapy groups, the latter observations suggesting no increased VI systemic effect with co-administration of FF.

- The percentages of subjects with one or more prolonged QTc(F) intervals (i.e., greater than 450 msec) at any time post-baseline were low and similar across all active treatment groups (3% to 6%) and placebo (2%). No subjects in any group had a prolonged QTc(F) value >500 msec. The occurrences of changes from baseline in QTc(F) ≥ 30 msec were low across the treatment groups (5% to 10% in active treatment groups, 8% in placebo group) with changes from baseline of >60 msec very infrequent (<1% across all treatment groups) and these were all pre-dose values.
- Repeated measures analysis of heart rate from ECG evaluations showed few statistically significant differences at any time-point for heart rate; where statistically significant differences were noted, these differences, in the range of 1 to 2 bpm, were not considered clinically important.
- Abnormal ECG findings assessed by centralized over-readers and finding considered of potential clinical importance were in general similar across the treatment groups and the categories of ECG changes of potential clinical importance observed were similar across the treatment groups.

Overall, over the six-month lung function studies, the one-year exacerbation studies, and the supporting shorter-term studies, there was no indication of a clinically important effect of FF/VI, VI, or FF on ECGs.

Reviewer's comments: There were no reports of QTc > 500 ms. The incidence in reports of sudden deaths was similar in the placebo and study drug arms.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of fluticasone furoate's and GW642444M's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 77,855. The sponsor submitted the study report HZA102936 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, four-way crossover repeat dose study to evaluate the effect of the inhaled fluticasone furoate/GW642444M (vilanterol) combination on electrocardiographic parameters, with moxifloxacin as a positive control, in healthy subjects

4.2.2 Protocol Number

HZA102936

4.2.3 Study Dates

Initiation Date: 23 Jun 2010

Completion Date: 04 Jan 2011

4.2.4 Objectives

Primary objective:

- To demonstrate the lack of effect of fluticasone furoate (FF)/vilanterol (VI; GW642444M) 200/25 mcg (the highest combination dose being evaluated in Phase III trials) on the QTcF interval as compared with placebo after 7 days' dosing.

Secondary objectives:

- To estimate the effect of FF/VI 800/100 mcg (four times the highest combination dose being evaluated in Phase III trials) on the QTcF interval as compared with placebo after 7 days' dosing.
- To estimate the effects of FF/VI 200/25 mcg and 800/100 mcg on QTci and QTcB as compared with placebo after 7 days' dosing (time matched and/or categorical/outlier analysis).
- To estimate the effect of a single oral dose of moxifloxacin 400 mg on the QTcF interval compared with placebo on Day 7.
- To characterise the pharmacokinetic profiles of VI and FF when administered via novel dry powder inhaler (DPI).
- To characterise the relationship between plasma VI concentrations and electrocardiogram (ECG) parameters (QTcF, QTci, QTcB, QT) and heart rate.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, placebo-controlled, four-way crossover study design in healthy male and female subjects.

4.2.5.2 Controls

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

4.2.5.3 Blinding

Blinding will be maintained by the use of a double-dummy medication method with all subjects receiving an inhaled dose and an oral dose for each treatment period. Inhaled fluticasone furoate/GW642444M and inhaled placebo will be administered under double blind conditions. Moxifloxacin will be administered under single-blind conditions. Moxifloxacin will not be over-encapsulated to avoid potential issues with drug release. Blinding the moxifloxacin and non-matched placebo will be achieved by blind-folding the subjects.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

All subjects were randomized to receive the following treatments over four treatment periods:

- Inhaled FF/VI 200/25 mcg combination once daily on Days 1–7 with a single dose placebo tablet on Day 7.
- Inhaled FF/VI 800/100 mcg combination once daily on Days 1–7 with a single dose placebo tablet on Day 7.
- Placebo inhaler once daily on Days 1–7 with a single dose oral moxifloxacin (400 mg) on Day 7.
- Placebo inhaler once daily on Days 1–7 with a single dose placebo tablet on Day 7.

The overall duration of each subject's participation in the study, from screening through to follow-up, was approximately 13 weeks. This consisted of a screening visit within 28 days of the first dose, four treatment periods lasting 7 days with a washout period of at least 7 days between them and a follow-up visit within 14 days of the final dose.

4.2.6.2 Sponsor's Justification for Doses

The therapeutic FF/VI combination treatment (200/25 mcg) was administered once daily for 7 days, which was a sufficient duration to achieve steady-state for both components. This dose was selected as it is the maximum dose that was administered in Phase III studies with the FF/VI combination.

The supra-therapeutic FF/VI combination treatment (800/100 mcg) was administered once daily for 7 days, which was a sufficient duration to achieve steady-state for both components [GlaxoSmithKline Document Number [GM2004/00283/05](#); GlaxoSmithKline Document Number [SM2003/00028/08](#)]. This dose was selected as VI 100 mcg was the highest dose administered in Phase I/IIa studies and is known to produce systemic pharmacodynamic effects, including QTcF and QTcB prolongation. The supratherapeutic FF/VI combination treatment of 800/100 mcg ensured that the ratio of FF:VI was the same as for the therapeutic combination dose.

Reviewer's Comment: The Sponsor's dose selection is acceptable. The supratherapeutic dose results in FF and VI C_{max} that are 3.3-fold and 4.6-fold the C_{max} at the intended clinical dose. These exposures cover the expected high clinical scenario for FF (ketoconazole drug-drug interaction) and VI (hepatic impairment).

4.2.6.3 Instructions with Regard to Meals

Doses will be administered after an overnight fast.

Reviewer's Comment: Administration in the fasted state is acceptable. Although a portion of the dose is swallowed, both products undergo extensive first pass metabolism.

4.2.6.4 ECG and PK Assessments

On Day -1, triplicate ECG measurements were taken pre-dose. On Day 1, triplicate ECG measurements were collected at pre-dose and 1 h post-dose. On Day 7, ECG and PK measurements were collected pre-dose and 5, 10, and 30 mins, and 1, 2, 4, 8, 12, 16 and 24 h post-dose.

Reviewer's Comment: The timing of ECG/PK collection is adequate to capture the potential QT effect at T_{max} of VI (10 minutes) and fluticasone furoate (30 minutes) and any delayed effect.

4.2.6.5 Baseline

The sponsor used pre-dose QTc on Day 1 as baseline values.

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

The study enrolled 85 healthy males or females, 18 to 65 years of age, with a normal 12-lead ECG and BMI (18.5 to 29 kg/m²). At least 66 subjects completed the study.

Demographics	
Age in years, median [range]	28.0 [18–65]
Sex, n (%)	
Female:	36 (42)
Male:	49 (58)
Body mass index in kg/m ² , mean (standard deviation)	23.86 (2.87)
Height in cm, mean (standard deviation)	169.7 (8.5)
Weight in kg, mean (standard deviation)	68.95 (11.22)
Ethnicity, n (%)	
Hispanic or Latino:	10 (12)
Not Hispanic or Latino:	75 (88)
Race, n (%)	
African American/African heritage	9 (11)
Asian – Japanese/ East Asian/South East Asian heritage	4 (5)
Asian – Central/South Asian heritage	10 (12)
White – White/Caucasian/European heritage	60 (71)
African American/African heritage and White	1 (1)
Asian and White	1 (1)

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between FF/IV (100/25 mcg and 800/100 mcg) and placebo in QTcF on Day 7. The sponsor used a mixed effects model and the results are presented in Table 3. This model included period, time, treatment, and time-by-treatment interaction as fixed effect terms. Baseline QTcF was included as a covariate and subject as random effect. Time was fitted as a repeated using an unstructured covariance. The upper limits of the 2-sided 90% CI for the FF/IV 100/25 mcg were below 10 ms. However, the upper limits of the 2-sided 90% CI for the FF/IV 800/100 occurred at 30 minutes post-dose [9.6 ms; 7.2, 12.0] was above 10 ms. This was the only time point where the upper 90% CI exceeded 10 ms.

Table 3: Sponsor Results $\Delta \Delta$ QTcF for FF/VI 200/25 mcg, FF/VI 800/100 mcg, and Moxifloxacin 400 mg

Time point	Least Square Means (msec)			Treatment Difference (90% CI) (msec)			
	FF/VI 200/25 mcg	FF/VI 800/100 mcg	Placebo	Moxifloxacin 400 mg	FF/VI 200/25 mcg - Placebo	FF/VI 800/100 mcg - Placebo	Moxifloxacin 400 mg - Placebo
Pre-dose	0.9	1.4	2.3	4.0	-1.3 (-3.4, 0.7)	-0.8 (-2.9, 1.2)	1.8 (-0.3, 3.8)
5 minutes	-5.7	-0.2	-5.6	-6.2	-0.1 (-2.6, 2.3)	5.4 (3.0, 7.9)	-0.5 (-3.0, 1.9)
10 minutes	6.4	9.5	2.1	3.2	4.3 (2.0, 6.6)	7.4 (5.1, 9.7)	1.2 (-1.1, 3.5)
30 minutes	4.8	9.9	0.3	5.1	4.5 (2.1, 6.9)	9.6 (7.2, 12.0)	4.8 (2.4, 7.2)
1 h	3.0	5.4	2.0	13.5	1.0 (-0.9, 3.0)	3.4 (1.4, 5.3)	11.5 (9.5, 13.4)
2 h	2.1	3.8	2.4	13.9	-0.4 (-2.3, 1.6)	1.4 (-0.5, 3.3)	11.5 (9.6, 13.5)
4 h	1.5	2.9	2.6	15.8	-1.1 (-3.0, 0.7)	0.3 (-1.6, 2.1)	13.2 (11.4, 15.1)
8 h	-5.6	-5.0	-5.5	5.9	-0.1 (-1.8, 1.7)	0.5 (-1.3, 2.3)	11.4 (9.6, 13.1)
12 h	-3.4	-2.8	-1.9	6.2	-1.5 (-3.1, 0.1)	-0.9 (-2.5, 0.7)	8.1 (6.5, 9.7)
16 h	4.4	4.6	5.8	14.5	-1.3 (-3.3, 0.6)	-1.2 (-3.1, 0.8)	8.7 (6.8, 10.7)
24 h	-3.4	-3.8	-1.7	5.1	-1.6 (-3.4, 0.2)	-2.1 (-3.9, -0.3)	6.9 (5.1, 8.7)

Source data: Table 10.1

CI = confidence interval; FF = fluticasone furoate; VI = vilanterol.

Source: Clinical Study Report No., Section 10.2.1, Table , Pg 46/661

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. We used QTcF as primary endpoint. The largest upper bound of the 2-sided 90% CI for the mean difference between FF/IV 800/100 and placebo is 12.2 ms.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the Δ QTcF effect for moxifloxacin. The analysis results were presented in Table 3. The lower limit of the two-sided 97.5% CI was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2. Our results are similar to the sponsor's findings.

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 AEs (SAEs) and no subjects were withdrawn from the study due to an AE.

Adverse events of special interest occurring in more than one subject are presented below.

Adverse event	Placebo	FF/VI 200/25	FF/VI 800/100	Moxifloxacin	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
N	84	81	80	79	85
Any event	35 (42)	38 (47)	49 (61)	46 (58)	71 (84)
Headache	18 (21)	19 (23)	17 (21)	14 (18)	38 (45)
Palpitations	2 (2)	1 (1)	12 (15)	4 (5)	16 (19)
Dizziness	1 (1)	1 (1)	8 (10)	3 (4)	13 (15)
Nausea	0	1 (1)	2 (3)	9 (11)	11 (13)
Dysmenorrhoea	2 (2)	3 (4)	4 (5)	3 (4)	8 (9)
Anxiety	0	2 (2)	5 (6)	0	7 (8)
Oropharyngeal pain	1 (1)	1 (1)	6 (8)	0	7 (8)
Tremor	0	2 (2)	6 (8)	0	7 (8)
Upper respiratory tract infection	1 (1)	3 (4)	2 (3)	3 (4)	7 (8)
Diarrhoea	1 (1)	2 (2)	0	3 (4)	6 (7)
Presyncope	1 (1)	0	2 (3)	3 (4)	6 (7)
Abdominal pain	1 (1)	1 (1)	0	3 (4)	5 (6)
Abdominal pain upper	2 (2)	1 (1)	1 (1)	1 (1)	4 (5)
Cough	0	0	2 (3)	2 (3)	4 (5)
Dry mouth	0	3 (4)	1 (1)	1 (1)	4 (5)
Fatigue	0	1 (1)	4 (5)	1 (1)	4 (5)
Asthenia	0	1 (1)	0	2 (3)	3 (4)
Chest pain	1 (1)	1 (1)	0	1 (1)	3 (4)
Dermatitis contact	3 (4)	0	0	0	3 (4)
Dysphonia	0	1 (1)	2 (3)	1 (1)	3 (4)
Influenza	1 (1)	1 (1)	0	1 (1)	3 (4)
Nasopharyngitis	1 (1)	0	0	2 (2)	3 (4)
Somnolence	0	0	2 (3)	1 (1)	3 (4)
Toothache	2 (2)	0	0	1 (1)	3 (4)
Throat irritation	1 (1)	0	1 (1)	1 (1)	3 (4)

Reviewer's comments: No AES of concern as per ICH E14 guidance were reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 4 (fluticasone furoate) and Table 5 (vilanterol). For fluticasone furoate, C_{max} and AUC values in the thorough QT study were 3.3-fold and 3.8-fold, respectively, values seen following administration of 800/100 mcg compared with 200/25 mcg drug, the intended clinical dose. For vilanterol, C_{max} and AUC values in the thorough QT study were 4.6-fold and 9.1-fold, respectively, values seen following administration of 800/100 mcg compared with 200/25 mcg drug.

Table 4: Summary of Fluticasone Furoate Pharmacokinetic Parameters (Day 7) following Inhaled Administration of FF/VI (200/25 and 800/100 mcg)

Parameter	Treatment	N	n	n*	Geometric mean (CV%)	95% confidence intervals
AUC(0–24) (pg.h/mL)	FF/VI 200/25	81	71	1	507 (37.9)	465, 553
	FF/VI 800/100	80	80	0	1921 (43.4)	1751, 2107
AUC(0–t) (pg.h/mL)	FF/VI 200/25	81	80	1	398 (90.1)	335, 472
	FF/VI 800/100	80	80	0	1927 (43.8)	1755, 2115
Cmax (pg/mL)	FF/VI 200/25	81	80	0	39.7 (35.7)	36.8, 42.9
	FF/VI 800/100	80	80	0	130 (32.3)	122, 140
Tmax(h) ¹	FF/VI 200/25	81	80	0	1.07 (0.08, 8.08)	NA
	FF/VI 800/100	80	80	0	2.05 (0.08, 8.08)	NA

Source data: Table 11.3 and Table 11.4.

¹median (range); FF = fluticasone furoate; VI = vilanterol.

NA = Not applicable;

n = Number of subjects with non-missing observations (including imputed non-calculable values);

n*=Number of subjects for whom parameter cannot be derived because of non-calculable concentrations.

AUC non-calculable values imputed by 0.5 x lowest observed AUC (i.e., AUC(0–24): 0.5 x 200.1; AUC(0–t): 0.5 x 27.5).

Source: Study Report, Table 16, Page 54.

Table 5: Summary of Vilanterol Pharmacokinetic Parameters (Day 7) following Inhaled Administration of FF/VI (200/25 and 800/100 mcg)

Parameter	Treatment	N	n	n*	Geometric mean (CV%)	95% confidence intervals
AUC(0–24) (pg.h/mL)	FF/VI 200/25	81	57	2	85.0 (76.6)	71.0, 102
	FF/VI 800/100	80	74	0	775 (36.6)	714, 842
AUC(0–t) (pg.h/mL)	FF/VI 200/25	81	74	2	59.8 (77.7)	51.0, 70.2
	FF/VI 800/100	80	74	0	755 (40.1)	691, 826
Cmax (pg/mL)	FF/VI 200/25	81	74	1	115 (56.9)	102, 130
	FF/VI 800/100	80	74	0	527 (37.2)	485, 573
Tmax(h) ¹	FF/VI 200/25	81	73	1	0.083 (0.083, 0.550)	NA
	FF/VI 800/100	80	74	0	0.100 (0.083, 0.267)	NA

Source data: Table 11.5 and Table 11.6

¹median (range); FF = fluticasone furoate; VI = vilanterol.

NA = Not applicable;

n = Number of subjects with non-missing observations (including imputed non-calculable values);

n*=Number of subjects for whom parameter cannot be derived because of non-calculable concentrations.

AUC non-calculable values imputed by 0.5 x lowest observed AUC (i.e., AUC(0–24): 0.5 x 32.4; AUC(0–t): 0.5 x 18.3);

Cmax non-calculable values imputed by 0.5 x LLQ (i.e., 0.5 x 10).

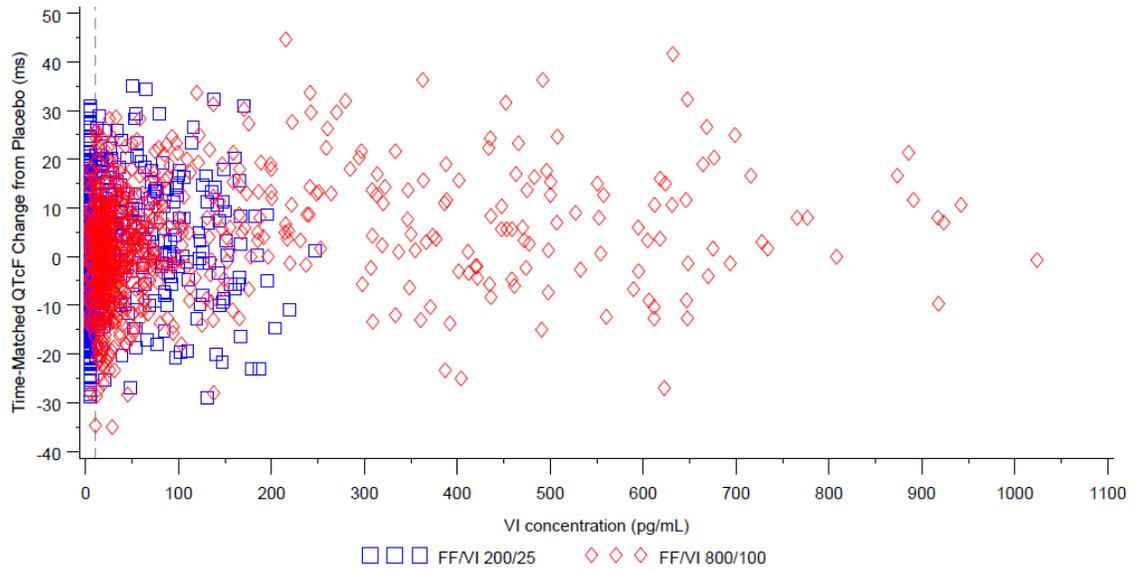
Source: Study Report, Table 17, Page 55.

4.2.8.4.2 Exposure-Response Analysis

The Sponsor did not conduct exposure-response analysis for FF because results from a previous study with a 4000 mcg FF dose showed no effect on QTcF. A slope-intercept linear model was used to describe the relationship between VI plasma concentrations and time-matched difference from placebo in change from baseline QTcF. The model

included baseline QTcF as a significant covariate on the intercept. A plot of the relationship is illustrated in Figure 1 and the parameter estimates of the model are presented in Table 6.

Figure 1: Relationship between Time-Matched QTcF Change from Placebo and VI Concentrations



Source: Study Report, Figure 13.6, Page 591.

Table 6: Parameter Estimates of Exposure-Response Model for QTcF

Parameter	Estimate [95% CI]	Precision (%CV)
Intercept (msec)	74.6 [40.1, 109]	23.6
Slope (msec)	0.00751 [0.00400, 0.0110]	25.0
Baseline covariate effect	4.53 [1.98, 7.08]	28.7
Inter-subject variability in intercept (%)	0.446 [-0.177, 1.07]	71.3
Residual error	50.7 msec [39.2, 62.2]	712

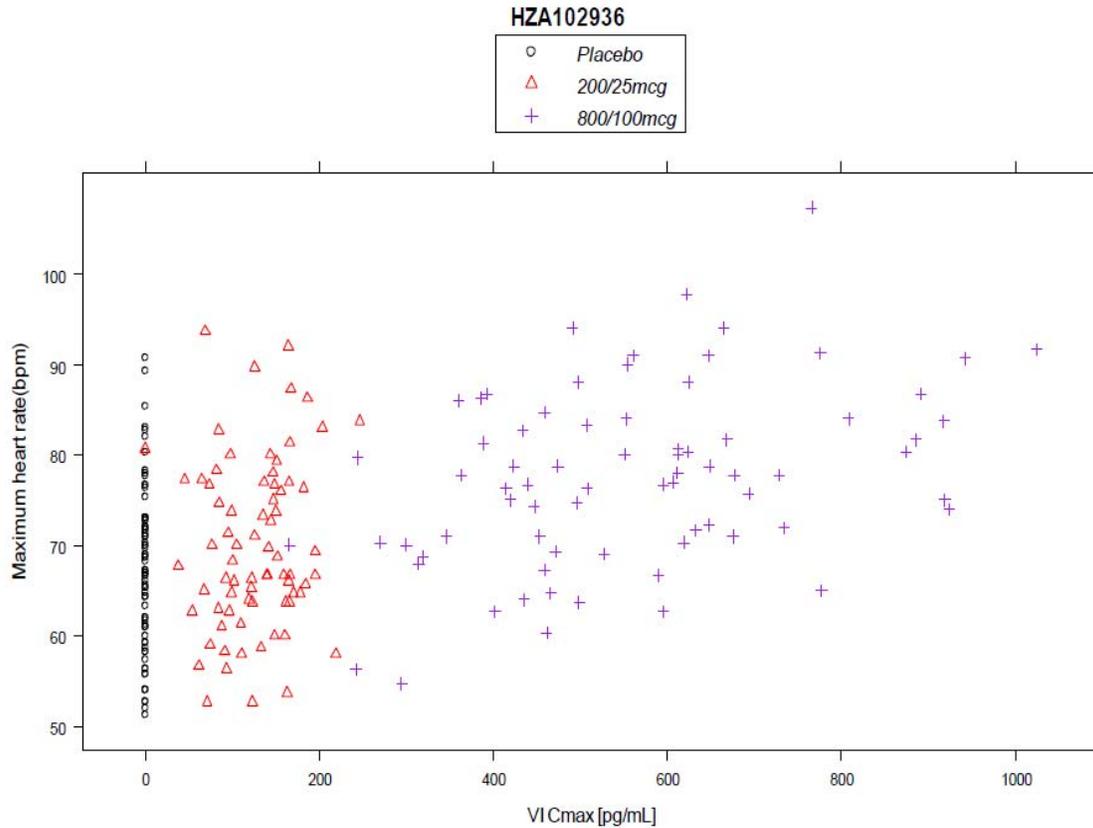
Source data: Table 13.5

CI=confidence interval; CV=coefficient of variation.

Source: Study Report, Table 18, Page 57.

A similar analysis was performed to describe the relationship between VI maximum concentration and maximum heart rate. A plot of the relationship is illustrated in Figure 2 and parameter estimates of the model are presented in Table 7.

Figure 2: Relationship between Maximum Heart Rate and VI C_{max}



Source: Study Report, Figure 13.3, Page 642.

Table 7: Parameter Estimates of the Exposure-Response Model for Maximum Heart Rate

Parameter	Estimate [95% CI]	Precision (%CV)
Intercept (bpm)	23.6 [15.2, 32.0]	7.40
Slope (bpm)	0.0173 [0.0150, 0.0200]	18.3
Baseline covariate effect	1.86 [0.839, 2.88]	28.0
Inter-subject variability in intercept	0.0132 [-0.001, 0.0270]	11.5
Inter-subject variability in baseline	0.485 [-0.354, 1.32]	88.2
Residual error	24.2 bpm [16.8, 31.6]	492

Source data: Table 13.10

CI=confidence interval; CV=coefficient of variation.

Source: Study Report, Table 19, Page 58.

Reviewer's Analysis: The Reviewer's analysis is presented in Section 5 of this review.

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 8, it appears that QTcF and QTcJ are equally better than QTcI and QTcB. The results produced by both QTcF and QTcJ are very similar. To be consistent with the sponsor's analyses, we choose to present QTcF results.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method							
	QTcB		QTcF		QTcI		QTci (e)*	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
FF/VI 200/25	81	0.0067	81	0.0024	81	0.0040	81	0.0027
FF/VI 800/100	80	0.0096	80	0.0025	80	0.0039	80	0.0024
Moxifloxacin 400 mg	79	0.0062	79	0.0040	79	0.0076	79	0.0056
Placebo	84	0.0056	84	0.0040	84	0.0051	84	0.0027
All	85	0.0065	85	0.0026	85	0.0039	85	0.0020

*Individual QTci values were subsequently calculated as follows:

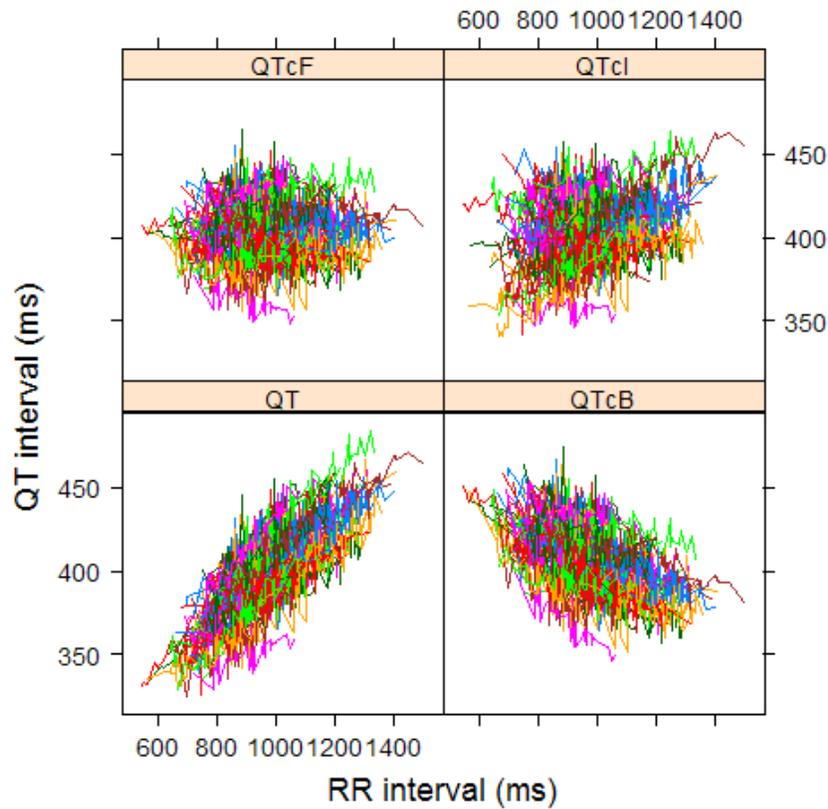
$QT_{ci} = QT + \beta (1-RR)$ where β was the estimate of the correction factor obtained in step 1 from the respective model.

For QTci typically nine time points were used for calculation. As ECGs were taken in triplicate this meant 27 readings per subject.

An alternative exploratory derivation for individual QTc linear correction [QTci(e)] was also undertaken as the above QTci did not provide an adequate correction (as indicated by a positively correlated QTcI:R-R interval relationship). This was derived as above, except that in step 1 all baseline and placebo data were used in fitting the linear regression model i.e., all drug-free values. Hence up to an additional 15 time points were used (pre-dose Day 1 for each period i.e., four extra time points over the four periods and 11 time points from Day 7 for the period in which placebo was taken) leading to a total of 24 time points or 72 ECG readings. Regulatory guidelines suggest that a large set of drug-free QT-RR measurements for each participant is required for QTci to be accurate.

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF and 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 is listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between FF/VI 200/25 mcg and placebo, and between FF/VI 200/25 mcg and placebo are 7.5 ms and 12.2 ms, respectively.

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for FF/VI 200/25 mcg, FF/VI 800/100 mcg, and Moxifloxacin 400 mg

	Placebo	FF/VI 200/25 mcg				FF/VI 800/100 mcg				Moxifloxacin 400 mg				
	Δ QTcF	Δ QTcF		Δ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		
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	*Adj. 90% CI
5 min	-6.2	78	-5.4	0.8	(-1.9, 3.4)	78	-0.8	5.4	(2.8, 8.1)	77	-6.3	-0.1	(-2.8, 2.5)	(-3.8, 3.5)
10 min	1.9	78	6.7	4.8	(2.2, 7.4)	78	8.8	6.9	(4.3, 9.5)	76	3.6	1.7	(-0.9, 4.3)	(-1.8, 5.3)
30 min	-0.1	79	4.8	4.9	(2.3, 7.5)	78	9.5	9.6	(7.0, 12.2)	77	5.2	5.3	(2.7, 7.9)	(1.7, 8.9)
1	1.7	79	2.8	1.1	(-1.2, 3.4)	80	4.7	3.0	(0.7, 5.3)	77	13.7	12.0	(9.7, 14.4)	(8.8, 15.2)
2	1.6	80	2.0	0.4	(-1.9, 2.7)	80	3.3	1.7	(-0.5, 4.0)	77	14.1	12.4	(10.2, 14.7)	(9.3, 15.6)
4	1.9	79	1.7	-0.3	(-2.6, 2.0)	80	2.7	0.8	(-1.5, 3.1)	77	16.2	14.3	(11.9, 16.6)	(11.1, 17.4)
8	-6.1	79	-5.5	0.6	(-1.5, 2.7)	80	-5.4	0.7	(-1.4, 2.8)	75	6.1	12.1	(10.0, 14.3)	(9.2, 15.1)
12	-2.5	80	-3.3	-0.8	(-2.9, 1.2)	80	-3.0	-0.5	(-2.5, 1.5)	75	6.4	8.9	(6.8, 11.0)	(6.1, 11.7)
16	5.8	78	4.6	-1.2	(-3.4, 1.0)	78	4.7	-1.1	(-3.4, 1.1)	76	14.7	8.9	(6.6, 11.1)	(5.8, 11.9)
24	-2.0	79	-3.9	-1.9	(-4.1, 0.3)	77	-3.9	-1.9	(-4.0, 0.3)	76	5.6	7.6	(5.4, 9.8)	(4.6, 10.6)

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

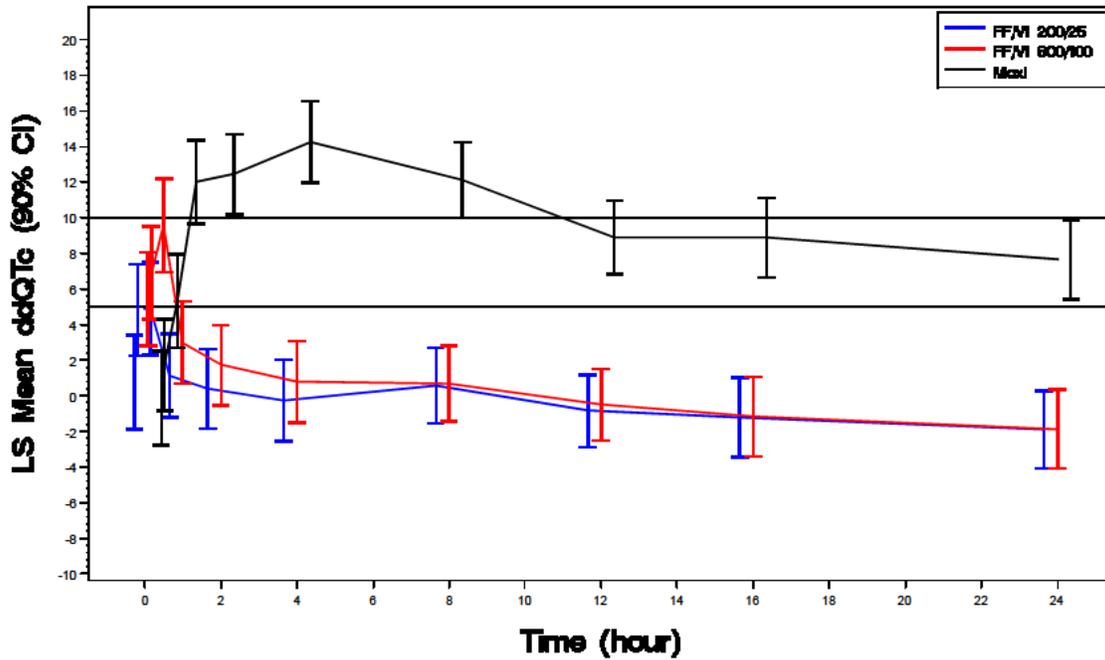
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 11.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 11.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

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

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcF Time Course for FF/VI 200/25 mcg, FF/VI 800/100 mcg, and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
FF/VI 200/25 mcg	80	80 (100%)	0 (0.0%)
FF/VI 800/100 mcg	80	80 (100%)	0 (0.0%)
Moxifloxacin 400 mg	77	73 (94.8%)	4 (5.2%)
Placebo	83	83 (100%)	0 (0.0%)

Table 11 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 11: Categorical Analysis of Δ QTcF

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
FF/VI 200/25 mcg	80	80 (100%)	0 (0.0%)
FF/VI 800/100 mcg	80	77 (96.3%)	3 (3.8%)
Moxifloxacin 400 mg	77	65 (84.4%)	12 (15.6%)
Placebo	81	81 (100%)	0 (0.0%)

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 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between FF/VI 200/25 and placebo, and between FF/VI 200/25 and placebo are 9.4 bpm and 18.7 bpm, respectively. Table 13 presents the categorical analysis of HR. Three subjects who experienced HR interval greater than 100 bpm was in FF/VI groups.

Increases in time-matched heart rate were seen at both FF/VI doses with maximum effects seen 10 minutes after dosing. This was particularly evident for the FF/VI 800/100 mcg dose where the mean heart rate increased by 17 bpm compared with placebo. In comparison with placebo, mean maximum heart rate (0-4h) increased by 4 bpm and 12 bpm after dosing with FF/VI 200/25 mcg and 800/100 mcg, respectively, while weighted mean heart rate was increased by 3 bpm and 8 bpm, respectively.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR for FF/VI 200/25 mcg, FF/VI 800/100 mcg, and Moxifloxacin 400 mg

Time (h)	Placebo	FF/VI 200/25 mcg				FF/VI 800/100 mcg				Moxifloxacin 400 mg			
	Δ 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
5 min	3.3	78	5.8	2.5	(0.8, 4.1)	78	11.8	8.5	(6.8, 10.1)	77	1.9	-1.4	(-3.0, 0.3)
10 min	-0.9	78	6.9	7.8	(6.2, 9.4)	78	16.2	17.1	(15.5, 18.7)	76	-0.6	0.3	(-1.3, 1.9)
30 min	-0.4	79	5.0	5.3	(3.7, 6.9)	78	12.3	12.6	(11.0, 14.2)	77	0.8	1.1	(-0.5, 2.7)
1	-0.5	79	2.2	2.7	(1.1, 4.3)	80	7.1	7.6	(6.0, 9.1)	77	2.3	2.8	(1.3, 4.4)
2	-1.1	80	0.6	1.8	(0.3, 3.2)	80	5.0	6.1	(4.7, 7.6)	77	0.6	1.7	(0.2, 3.1)
4	-1.0	79	0.5	1.5	(0.1, 2.9)	80	4.4	5.4	(4.1, 6.8)	77	-0.0	1.0	(-0.4, 2.4)
8	1.4	79	2.9	1.5	(0.1, 3.0)	80	7.1	5.7	(4.2, 7.1)	75	2.5	1.2	(-0.3, 2.6)
12	3.4	80	5.6	2.2	(0.7, 3.6)	80	9.0	5.6	(4.1, 7.0)	75	3.9	0.5	(-1.0, 2.0)
16	-1.5	78	-0.2	1.3	(-0.2, 2.8)	78	2.1	3.6	(2.1, 5.1)	76	-1.2	0.3	(-1.2, 1.8)
24	1.1	79	2.2	1.1	(-0.2, 2.3)	77	3.4	2.3	(1.0, 3.6)	76	1.0	-0.2	(-1.4, 1.1)

Table 13: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR >=100 bpm
FF/VI 200/25 mcg	80	79 (98.8%)	1 (1.3%)
FF/VI 800/100 mcg	80	77 (96.3%)	3 (3.8%)
Moxifloxacin 400 mg	77	77 (100%)	0 (0.0%)
Placebo	83	83 (100%)	0 (0.0%)

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 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between FF/VI 200/25 and placebo, and between FF/VI 800/100 and placebo are 2.7 ms and 0.8 ms, respectively. Table 13 presents the categorical analysis of PR. Five subjects who experienced PR interval greater than 200 ms were in FF/VI both groups.

Table 14: Analysis Results of Δ PR and $\Delta\Delta$ PR for FF/VI 200/25 mcg, FF/VI 800/100 mcg, and Moxifloxacin 400 mg

Time (h)	Placebo	FF/VI 200/25 mcg				FF/VI 800/100 mcg				Moxifloxacin 400 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
	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	-3.7	78	-4.5	-0.8	(-2.9, 1.3)	78	-6.9	-3.2	(-5.3, -1.1)	77	-2.9	0.8	(-1.3, 2.9)
10 min	-0.8	78	-3.7	-2.9	(-5.0, -0.7)	78	-9.0	-8.1	(-10.3, -5.9)	76	-1.6	-0.8	(-3.0, 1.4)
30 min	0.3	79	-3.9	-4.2	(-6.3, -2.1)	78	-7.2	-7.5	(-9.6, -5.3)	77	-0.5	-0.9	(-3.0, 1.3)
1	0.5	79	-0.6	-1.1	(-3.3, 1.0)	80	-3.8	-4.3	(-6.4, -2.1)	77	-0.9	-1.5	(-3.6, 0.7)
2	-1.3	80	-1.9	-0.6	(-2.7, 1.5)	80	-3.2	-1.9	(-4.0, 0.2)	77	-3.5	-2.2	(-4.3, -0.1)
4	-2.3	79	-2.1	0.2	(-1.7, 2.1)	80	-4.4	-2.1	(-4.0, -0.2)	77	-4.5	-2.2	(-4.1, -0.2)
8	-5.9	79	-6.4	-0.4	(-2.5, 1.6)	80	-8.5	-2.5	(-4.6, -0.5)	75	-8.4	-2.5	(-4.5, -0.4)
12	-6.2	80	-6.4	-0.2	(-2.2, 1.9)	80	-8.8	-2.6	(-4.6, -0.6)	75	-6.5	-0.3	(-2.4, 1.7)
16	-0.3	78	-0.6	-0.3	(-2.3, 1.8)	78	-4.1	-3.8	(-5.9, -1.8)	76	-0.9	-0.7	(-2.7, 1.4)
24	-2.0	79	-1.2	0.8	(-1.1, 2.7)	77	-3.1	-1.1	(-3.0, 0.8)	76	-3.4	-1.5	(-3.4, 0.5)

Table 15: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR ≥200 ms
FF/VI 200/25	80	75 (93.8%)	5 (6.3%)
FF/VI 800/100	80	79 (98.8%)	1 (1.3%)
Moxifloxacin 400 mg	77	72 (93.5%)	5 (6.5%)
Placebo	83	77 (92.8%)	6 (7.2%)

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 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between FF/VI 200/25 and placebo, and between FF/VI 200/25 and placebo are 2.7 ms and 0.8 ms, respectively. Table 15 presents the categorical analysis of QRS.

Table 16: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for FF/VI 200/25 mcg, FF/VI 800/100 mcg, and Moxifloxacin 400 mg

	Placebo	FF/VI 200/25				FF/VI 800/100				Moxifloxacin 400 mg			
	Δ QRS	Δ QRS	$\Delta\Delta$ QRS	$\Delta\Delta$ QRS	Δ QRS	$\Delta\Delta$ QRS	Δ QRS	$\Delta\Delta$ QRS	Δ QRS	$\Delta\Delta$ QRS	Δ QRS	$\Delta\Delta$ QRS	
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
5 min	-0.1	78	-0.3	-0.2	(-1.3, 0.9)	78	0.8	0.9	(-0.2, 2.0)	77	-0.7	-0.6	(-1.7, 0.5)
10 min	0.6	78	0.2	-0.5	(-1.6, 0.6)	78	1.5	0.8	(-0.2, 1.9)	76	-0.3	-0.9	(-2.0, 0.2)
30 min	0.3	79	0.6	0.4	(-0.7, 1.4)	78	2.3	2.0	(0.9, 3.1)	77	-0.4	-0.7	(-1.8, 0.4)
1	0.2	79	0.5	0.3	(-0.7, 1.3)	80	1.7	1.5	(0.5, 2.5)	77	-0.1	-0.2	(-1.3, 0.8)
2	0.3	80	0.5	0.2	(-0.8, 1.2)	80	1.3	1.0	(0.0, 2.0)	77	0.0	-0.3	(-1.3, 0.8)
4	0.1	79	0.5	0.4	(-0.6, 1.4)	80	1.0	0.9	(-0.1, 1.9)	77	-0.1	-0.2	(-1.3, 0.8)
8	-0.2	79	-0.1	0.1	(-0.9, 1.1)	80	-0.2	-0.0	(-1.0, 1.0)	75	-0.5	-0.4	(-1.4, 0.7)
12	0.2	80	0.1	-0.1	(-1.1, 0.9)	80	0.0	-0.2	(-1.2, 0.8)	75	0.0	-0.2	(-1.2, 0.9)
16	0.9	78	0.9	-0.1	(-1.1, 1.0)	78	1.1	0.2	(-0.9, 1.3)	76	0.7	-0.2	(-1.3, 0.9)
24	0.6	79	0.3	-0.3	(-1.3, 0.8)	77	0.6	0.0	(-1.0, 1.0)	76	0.1	-0.5	(-1.5, 0.6)

Table 17: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS ≥ 110 ms
FF/VI 200/25	80	76 (95.0%)	4 (5.0%)
FF/VI 800/100	80	78 (97.5%)	2 (2.5%)
Moxifloxacin 400 mg	77	75 (97.4%)	2 (2.6%)
Placebo	83	79 (95.2%)	4 (4.8%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profiles are illustrated in Figure 5 (FF) and Figure 6 (VI).

Figure 5: Mean FF Concentration-Time Profiles for 200/25 mcg (blue line) and 800/100 mcg (red line) FF/VI

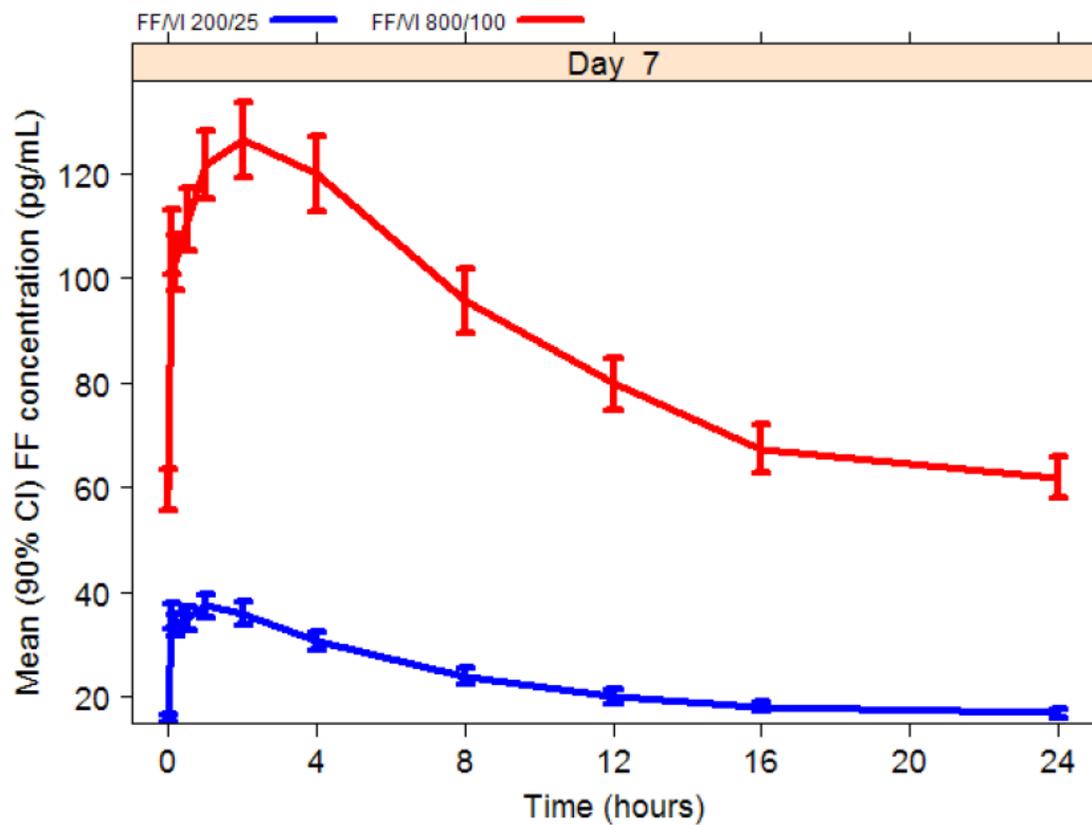
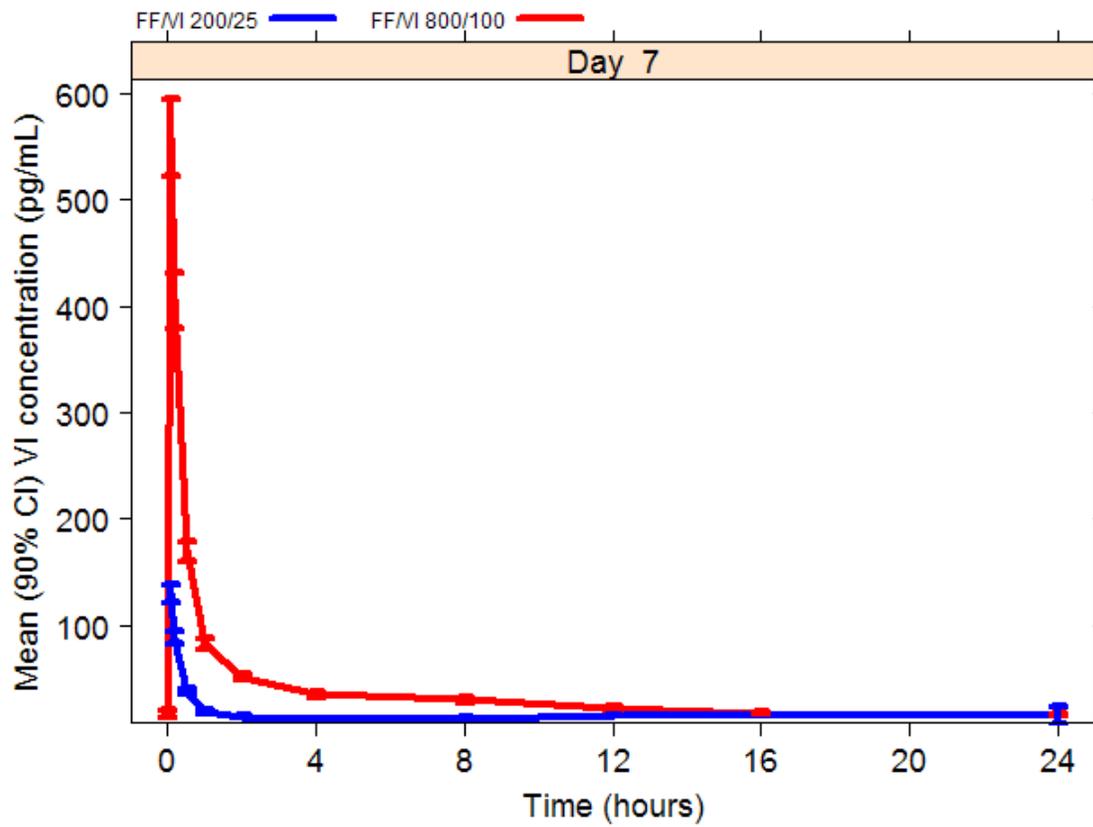
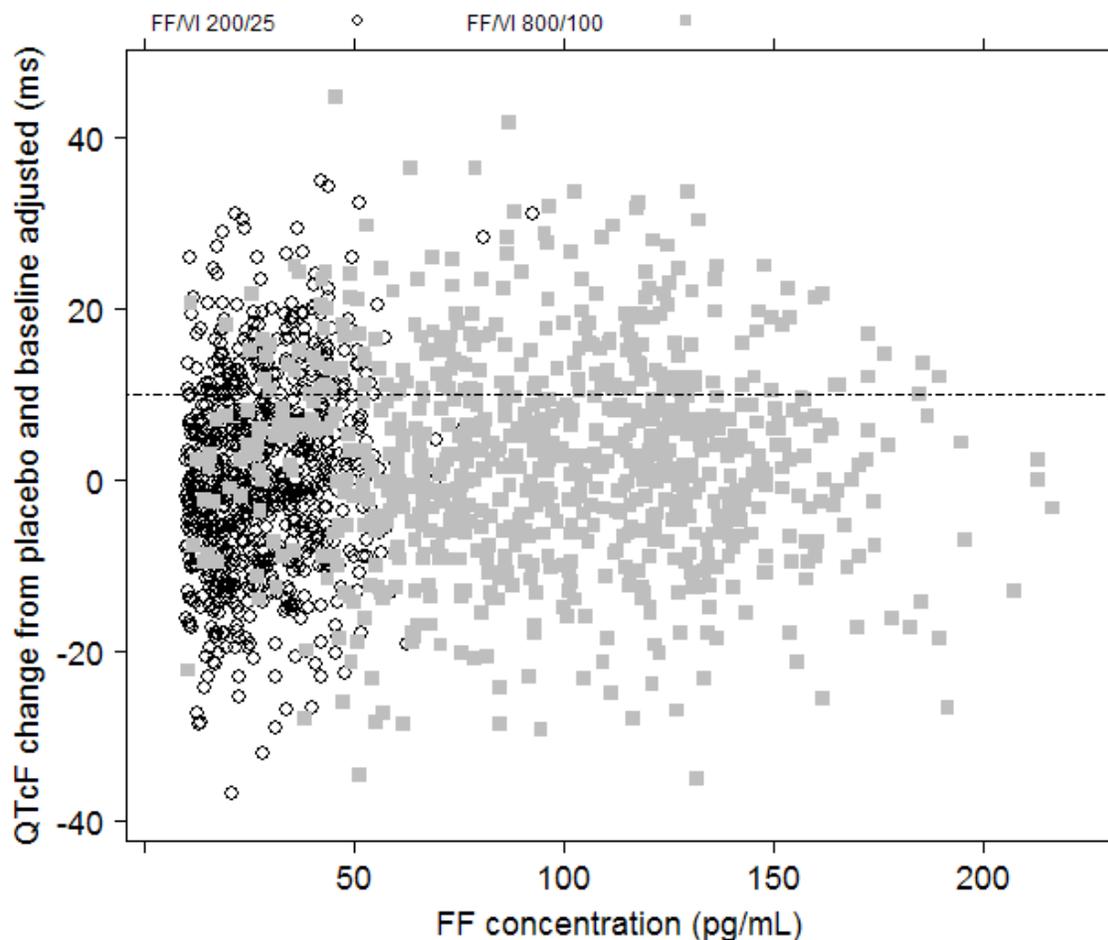


Figure 6: Mean VI Concentration-Time Profiles for 200/25 mcg (blue line) and 800/100 mcg (red line) FF/VI



The relationship between $\Delta\Delta Q_{TcF}$ and FF concentrations is visualized in Figure 7 with no evident exposure-response relationship.

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



The relationship between $\Delta\Delta$ QTcF and VI concentrations was investigated by linear mixed-effects modeling. VI concentrations were log-transformed after examining the model fit.

The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

In all three models a significant slope was identified. Model 1 was used for further analysis since the model with intercept was found to fit the data best.

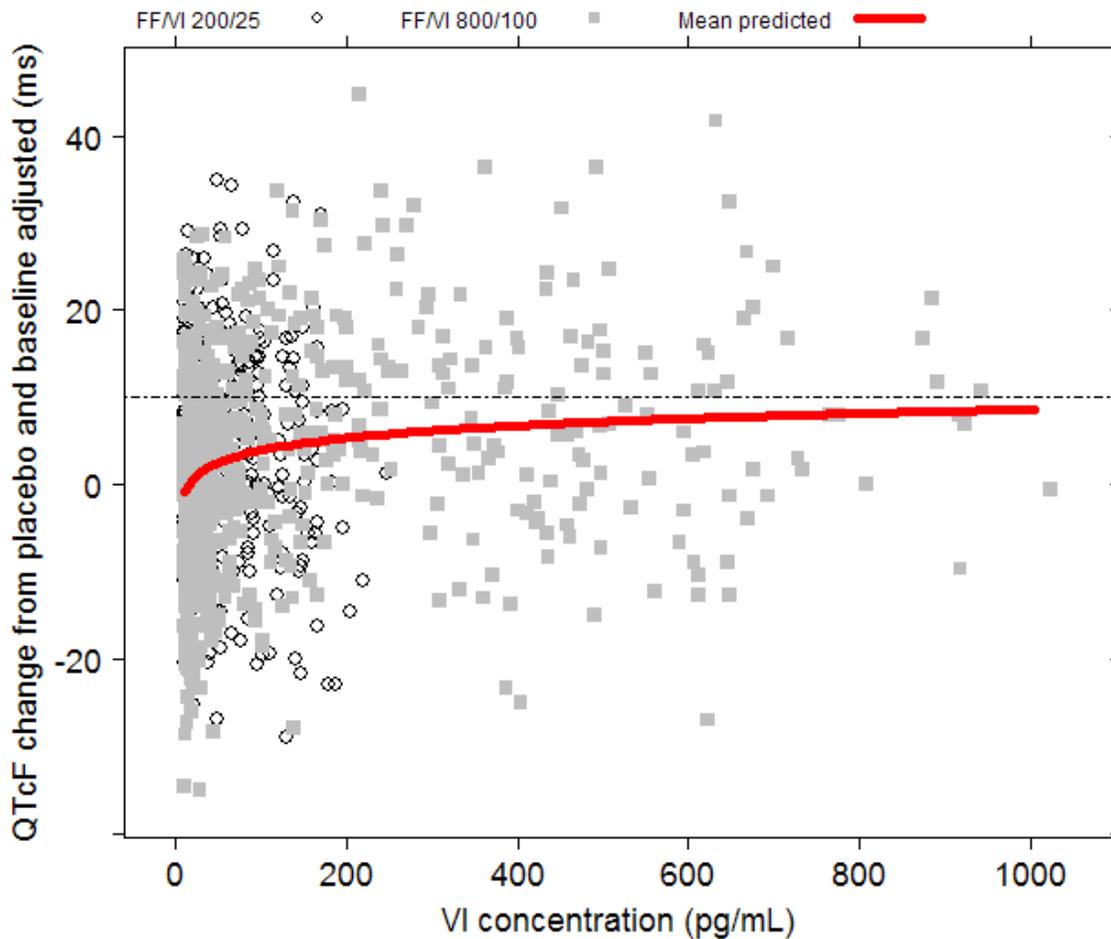
Table 18: Exposure-Response Analysis of VI Associated $\Delta\Delta$ QTcF Prolongation

Parameter	Estimate	P-value	Inter-individual Variability (%)

$\Delta\Delta QTcF = \text{Intercept} + \text{slope} * \text{VI concentration}$			
Intercept (ms)	-5.5 (-7.7; -3.2)	0.0001	8.1
Slope (ms per pg/mL)	2.0 (1.56 2.5)	<.0001	1.5
Residual Variability (ms)	8.7		

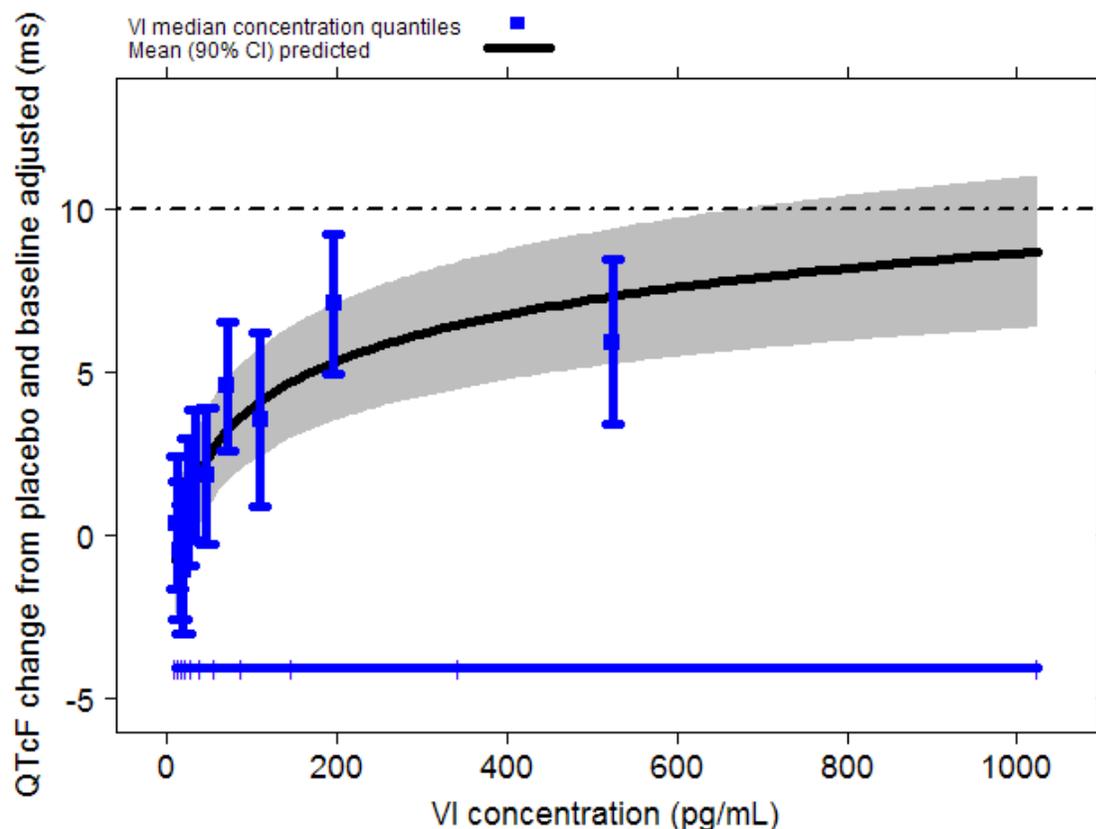
The relationship between VI concentrations and $\Delta\Delta QTcF$ is visualized in Figure 8.

Figure 8: $\Delta\Delta QTcF$ vs. VI Concentrations with Mean Prediction (solid red line)



The goodness-of-fit plot in Figure 9 shows the observed median-quantile VI concentrations and associated mean (90% CI) $\Delta\Delta QTcF$ together with the mean (90% CI) predicted $\Delta\Delta QTcF$.

Figure 9: Observed Median-Quantile VI Concentrations and Associated Mean (90% CI) $\Delta\Delta$ QTcF (colored dots) with the Mean (90% CI) Predicted $\Delta\Delta$ QTcF (black line with shaded grey area)

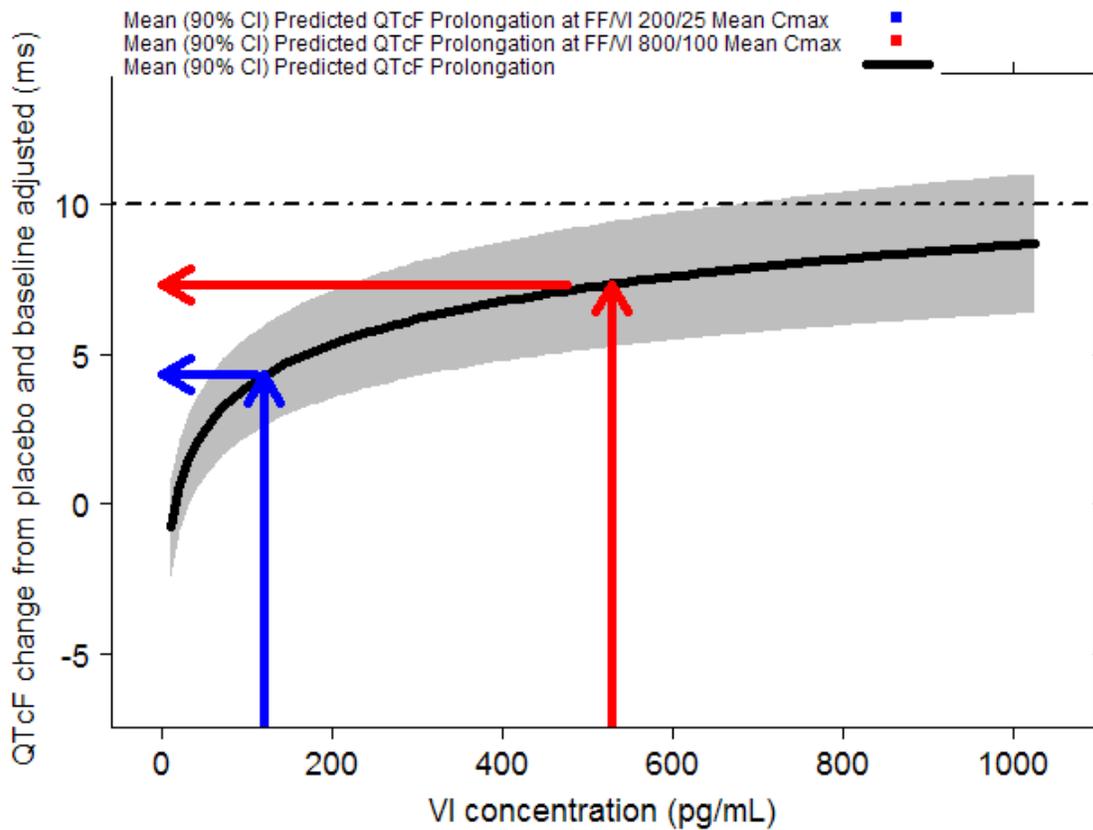


The predicted $\Delta\Delta$ QTcF at the geometric mean peak VI concentration can be found in Table 19 and visualized in Figure 10.

Table 19: Predicted $\Delta\Delta$ QTcF Interval at Geometric Mean Peak VI Concentration Using Model 1.

	Treatment	Concentration	Pred	95%CI
1	FF/VI 200/25 mcg	120 pg/mL	4.3	(2.6; 6.0)
2	FF/VI 800/100 mcg	528 pg/mL	7.3	(5.2; 9.4)

Figure 10: Mean (90% CI) Predicted $\Delta\Delta$ QTcF at Geometric Mean C_{max}



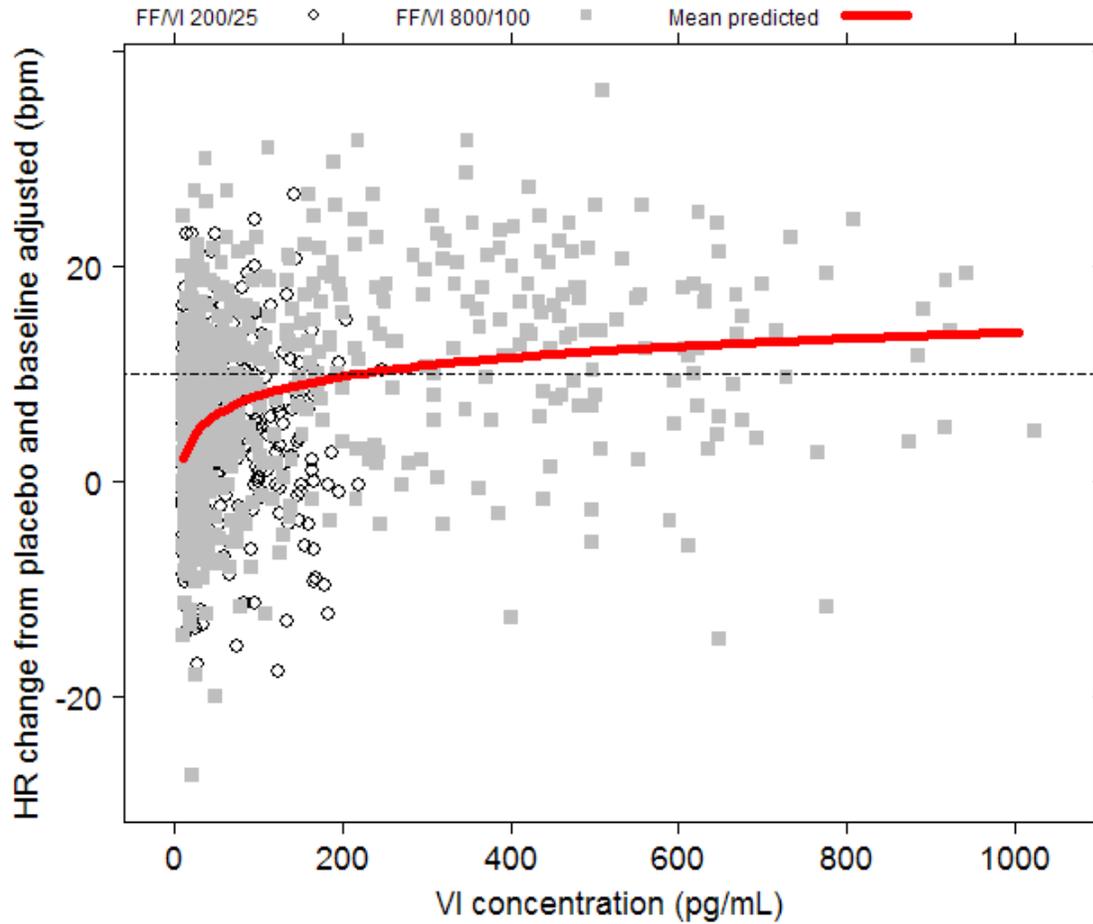
A similar approach was used to quantify the relationship between VI concentrations and heart rate. The parameters of the final model are presented in Table 20.

Table 20: Exposure-Response Analysis of VI Associated $\Delta\Delta$ HR Prolongation

Parameter	Estimate	P-value	Inter-individual Variability (%)
$\Delta\Delta$ HR=Intercept + slope*VI concentration			
Intercept (bpm)	-3.8 (-5.2; -2.4)	<0.0001	4.6
Slope (bpm per pg/mL)	2.6 (2.3 2.8)	<0.0001	0.5
Residual Variability (bpm)	5.8		

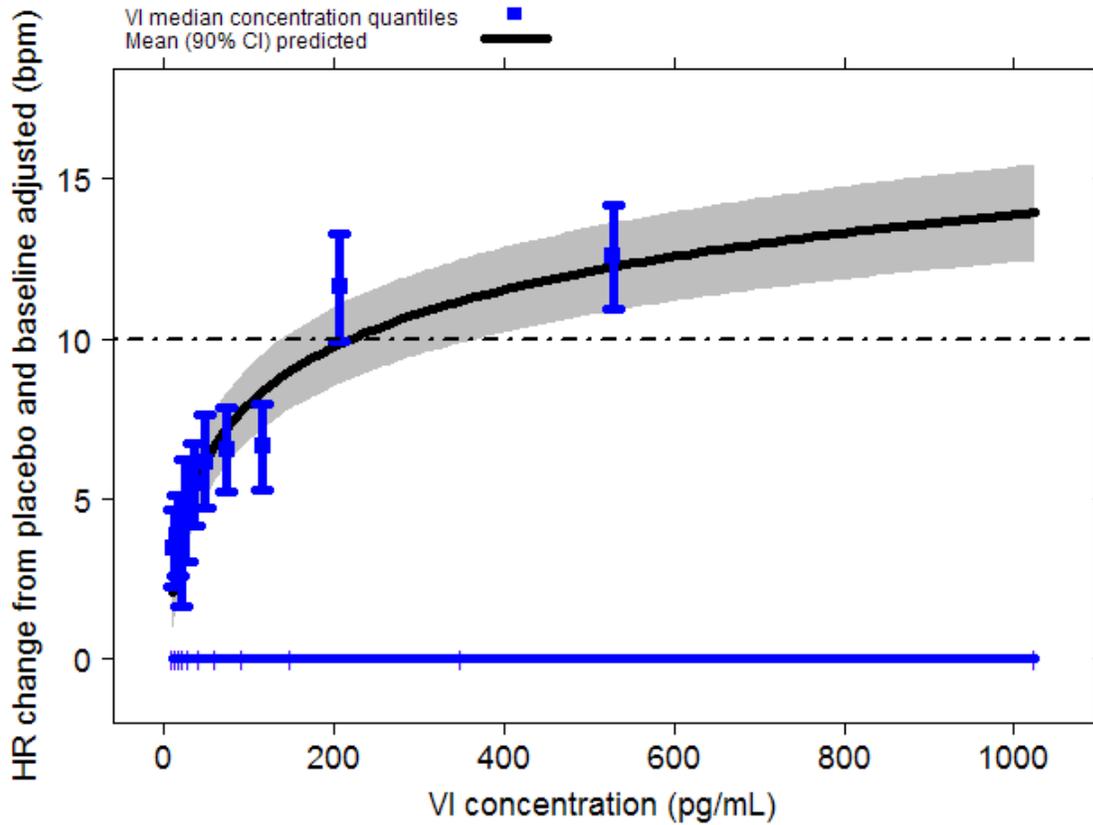
The relationship between VI concentrations and $\Delta\Delta$ HR is visualized in Figure 11.

Figure 11: $\Delta\Delta$ HR vs. VI Concentrations with Mean Prediction (solid red line)



The goodness-of-fit plot in Figure 12 shows the observed median-quantile VI concentrations and associated mean (90% CI) $\Delta\Delta$ HR together with the mean (90% CI) predicted $\Delta\Delta$ HR.

Figure 12: Observed Median-Quantile VI Concentrations and Associated Mean (90% CI) $\Delta\Delta$ HR (colored dots) with the Mean (90% CI) Predicted $\Delta\Delta$ HR (black line with shaded grey area)

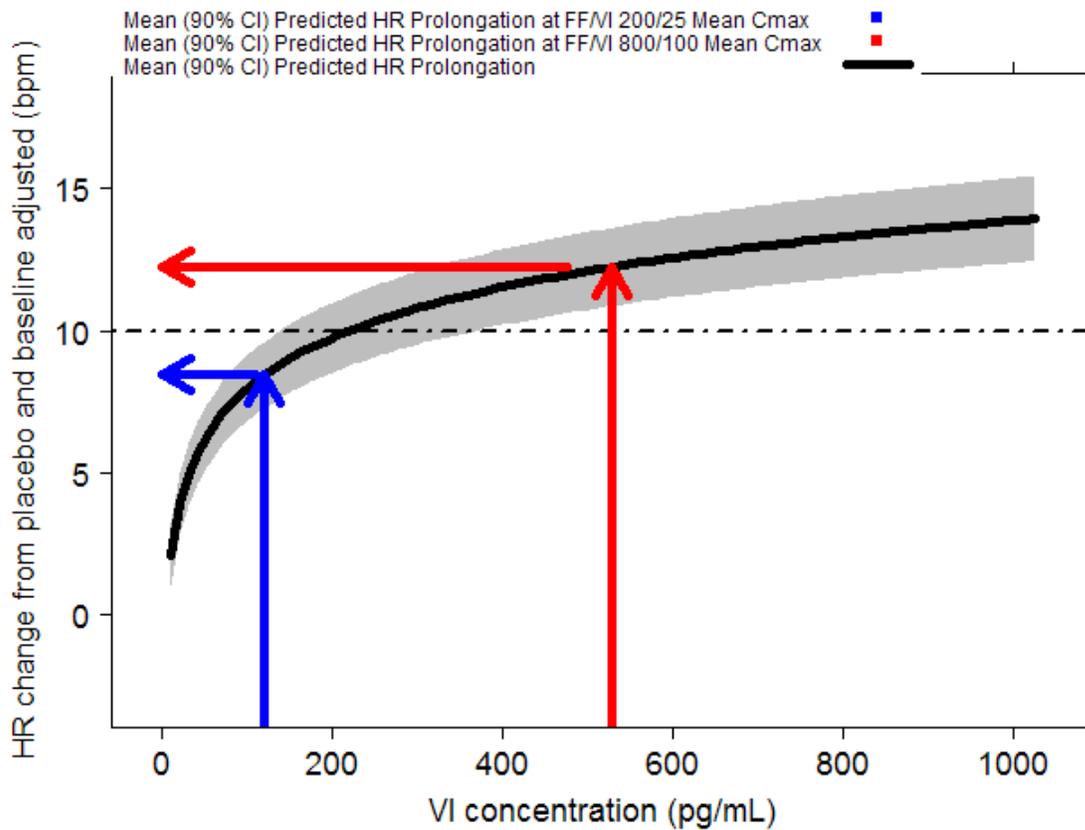


The predicted $\Delta\Delta$ HR at the geometric mean peak VI concentration can be found in Table 21 and visualized in Figure 13.

Table 21: Predicted $\Delta\Delta$ HR Interval at Geometric Mean Peak VI Concentration Using Model 1.

	Treatment	Concentration	Pred	95%CI
1	FF/VI 200/25 mcg	120 pg/mL	8.5	(7.3; 9.6)
2	FF/VI 800/100 mcg	528 pg/mL	12.2	(10.9; 13.6)

Figure 13: Mean (90% CI) Predicted $\Delta\Delta$ HR at Geometric Mean C_{max}



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 0.04% 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

Five subjects had a PR >200 ms and four subjects had a QRS >110 ms, none were clinically meaningful.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Fluticasone Furoate (FF) Highlights of Clinical Pharmacology

Therapeutic dose	Up to 200 mcg FF (in lactose) once daily via inhalation from a novel dry powder inhaler (NDPI) either alone or in combination with the LABA vilanterol (VI, GW642444M).	
Maximum tolerated dose	Maximum doses administered: 4000 mcg single dose, 2000 mcg repeat dose. Dose limited by corticosteroid pharmacology (cortisol suppression)	
Principal adverse events	Common adverse events ($\geq 5\%$) from Phase IIa and IIb individual clinical studies with fluticasone furoate (25 to 800 mcg) include headache, nasopharyngitis, oral candidiasis and dysphonia. With the exception of oral candidiasis (increasing incidence with dose), the rates were comparable between fluticasone furoate and placebo.	
Maximum dose tested	Single Dose	4000 mcg [GSK Study FFA10001 & FFR101888]
	Multiple Dose	2000 mcg once daily for 14 days [GSK Study FFA10002]
Exposures Achieved at Maximum Tested Dose	Single Dose	Geometric mean (CV%): [GSK Study FFA10001] Cmax 437 pg/mL (33%) AUC(0-inf) 8126 pg.h/mL (43%)
	Multiple Dose	Geometric mean (CV%) [GSK Study FFA10002] Cmax 459 pg/mL (42%) AUC(0-inf) 3586 pg.h/mL (47%)
Range of linear PK	50 mcg to 2000 mcg (once daily). Following administration of FF/VI via NDPI, FF systemic exposure as measured by AUC(0-t ⁺), was dose proportional. The lack of dose proportionality for FF Cmax was considered to be due to rate limited absorption from the lung, which is well characterised for FF and is supported by tmax being observed at later times as the FF dose increased (median tmax: FF/VI 200/100 mcg 5 minutes, FF/VI 400/100 mcg 10 minutes and FF/VI 800/100 mcg 60 minutes). This is not considered to be of clinical relevance [GSK Study HZA102932].	
Accumulation at steady state	Geometric Mean (CV%) 68% (19%) to 90% (34%) (once daily)	
Metabolites	Predominant route of metabolism: hydrolysis of the thioester moiety to give 17- β -carboxylic acid metabolite. The only other routes of metabolism identified from the drug-related material present in faecal extracts involved defluorination and hydroxylation. None of the metabolites have significant pharmacological activity compared to parent.	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability of inhaled FF was estimated to be 13-18% following FF/VI administration (800/100 mcg) [GSK Study

		HZA102934]
	Tmax	Median (range) 0.50h (0.08h to 3.00h) [GSK Study HZA105871] Major metabolite (GW694301X) not measurable in plasma followed inhaled administration at doses up to 2000 mcg (LLQ 10 pg/mL)
Distribution	Vd	Geometric mean (CV%) [GSK Study FFA10003] 704 L (47%)
	% bound	>99% bound to plasma proteins
Elimination	Route	Metabolism ($\geq 90\%$) considered to be biliary [GSK Study FFR10008] Renal (<3% dose) [GSK Study FFR10008]
	Terminal t _{1/2}	Geometric mean (CV%) [GSK Study FFA10003] 22 h (23%) to 25.0 h (10%) No metabolites measurable in plasma
	CL	Geometric mean (CV%) [GSK Study FFA10003] 71.8 L/h (22%)
Intrinsic Factors	Age	No effect on PK [population PK modeling]
	Sex	No effect on PK [population PK modeling]
	Race	Higher systemic FF exposure following inhaled dosing with both 200 mcg and 800 mcg once daily in Chinese, Japanese and Korean subjects compared with Caucasian subjects. At FF 800 mcg, where the pharmacokinetic data were more robust due to higher systemic exposure in all populations, geometric mean ratios for C _{max} and AUC (Day 1 or Day 8) ranged from 35% to 76% greater and 46% to 77% greater, respectively. Similar differences were seen following 200mcg once daily dosing. Following FF 800 mcg for 7 days, absolute bioavailability ranged from 36% to 55% higher in the Asian populations, compared with Caucasian subjects [GSK Study HZA113477]. Results from deconvolution analysis suggested that following inhaled administration FF resided

		<p>in the lung of Chinese, Japanese and Korean subjects longer (average MAT approximately double) than for Caucasian subjects and hence provided opportunity for the greater bioavailability.</p> <p>There was no evidence for a difference in serum cortisol weighted mean between Caucasians and Chinese or Korean healthy subjects following 7 days of once daily inhaled FF 200 mcg. There was an average 22% (90% CI: 12–30%) lower serum cortisol weighted mean in Japanese subjects compared with Caucasian subjects following 7 days of once daily inhaled FF 200 mcg.</p> <p>All FF treatments were safe and well tolerated with no marked quantitative or qualitative differences in safety endpoints between the ethnic groups.</p>
	<p>Hepatic & Renal Impairment</p>	<p>Following repeat dosing of FF/VI for 7 days, there was an increase in FF systemic exposure (on average, less than two-fold as measured by AUC(0–24)) in subjects with hepatic impairment compared with healthy subjects. Dose-normalised FF systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B and C, respectively), suggesting that the increase in FF systemic exposure seen in these subjects represents the maximum likely to be seen in any subjects with hepatic impairment [GSK Study HZA111789].</p> <p>Repeat dose FF/VI had no clinically relevant effects on weighted mean serum cortisol in subjects with mild hepatic impairment (200/25 mcg) or severe hepatic impairment (100/12.5 mcg). In subjects with moderate hepatic impairment (200/25 mcg) weighted mean (0–24 h) serum cortisol was reduced by on average 34% (90% CI: 11% decrease to 51% decrease) compared with healthy subjects. Inhaled FF/VI was well tolerated in hepatically impaired and healthy subjects.</p> <p>Severe renal impairment (CrCl <30 mL/min) had no effect on the pharmacokinetics of FF when administered as a FF/VI repeat dose 200/25 mcg for 7 days [GSK Study HZA113970].</p>

		There was no evidence of a difference between subjects with severe renal impairment and healthy subjects in systemic effects that might be attributable to the administration of an inhaled corticosteroid (weighted mean serum cortisol). Repeat dose FF/VI (200/25 mcg) was well tolerated in healthy subjects and in subjects with severe renal impairment.
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 FF exposure. Mean VI AUC(0-24) and Cmax were increased by 36% (90% CI: 16% to 59%) and 33% (90% CI: 12% to 58%), respectively. There was an increase in steroid mediated systemic effects: weighted mean serum cortisol (0–24 h) was, on average, 27% lower (95% CI: 14, 38) with FF/VI and ketoconazole co-administration when compared with FF/VI and placebo co-administration [GSK Study HZA105548]. Co-administration of inhaled FF with VI did not affect the systemic exposure of either component compared to administration alone [GSK Studies HZA105871, HZA102940]
	Food Effects	No food interaction study has been conducted. Although a significant portion of the inhaled dose is swallowed an effect of food on FF systemic bioavailability is not anticipated as any absorbed FF undergoes extensive first pass metabolism. Data from up to 2000mcg once daily FF show no capacity limitation on the first pass effect.
Expected High Clinical Exposure Scenario	From ketoconazole DDI study [GSK Study HZA105548]: Geometric means following 7 days repeat dose with FF/VI 200/25 mcg: Cmax 82.5 pg/mL and AUC(0-24) 970 pg.h/mL.	

Vilanterol Highlights of Clinical Pharmacology

Therapeutic dose	25 mcg vilanterol (VI; GW642444M in lactose and magnesium stearate) once daily via inhalation from a Novel Dry Powder 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 inhaler to healthy subjects [GSK Study B2C108784] or as a single dose via Novel Dry Powder as the individual component [GSK Study B2C106180] or as FF/VI (800/100 mcg) [GSK Study HZA102934].	
Principal adverse events	Common adverse events ($\geq 5\%$) from Phase IIb individual clinical studies with VI (3 to 50 mcg) 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 Novel Dry Powder 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 inhaler [GSK Study B2C108784].
Exposures Achieved at Maximum Tested Dose	Single Dose	Geometric Mean (CV%) C _{max} and AUC: C _{max} 929 pg/mL (30.4%) AUC(0-t) 734 pg.h/mL (37.2%)
	Multiple Dose	Geometric Mean (CV%) C _{max} and AUC: C _{max} 932 pg/mL (17.9%) AUC(0-t) 913 pg.h/mL (25.7%)
Range of linear PK	Apparent proportionality over dose range 25 - 100 mcg VI administered via DISKUS inhaler [GSK Studies B2C108784 and B2C106996]. Approximate proportionality over dose range 6.25 - 100 mcg VI administered via Novel Dry Powder Inhaler [GSK Study B2C111401]. Equivalence of VI exposure across the three FF/VI dosage strengths of 50/25, 100/25 and 200/25 mcg was demonstrated as the 90% confidence intervals for the slope of AUC _(0-t) and C _{max} were completely contained within the pre-specified equivalence ranges of (0.80, 1.25) and (0.70, 1.43), respectively.	
Accumulation at steady state	Highest extent of accumulation based on AUC _(0-t) (AUC to a common time point within an individual) was on average was 72-99% following once daily dosing to COPD patients (25 mcg VI in combination with 400 mcg FF via Novel Dry Powder 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	Median (range) Parent VI : Asthma patients: 0.17 h (0.1h, 0.6 h) following single dose (25 mcg VI via Novel Dry Powder Inhaler[GSK Study B2C111401]) COPD patients: 0.17 h (0.08 h, 0.27 h) following once daily dosing (25 mcg in combination with 400 mcg FF via Novel Dry Powder Inhaler [GSK Study HZC111348]) Major metabolites: Not quantifiable in plasma following inhaled administration at therapeutic dose (Lower limit of quantification 90 pg/mL for GW630200 [M1] and 180 pg/mL for GSK932009 [M2]).
Distribution	Vd/F or Vd	Vdss 165 L (95% CI: 129, 211) [GSK Study HZA102934].
	% bound	Mean (range) plasma protein binding: 97.2% (95.8 – 97.6).
Elimination	Route	Primary route is metabolism. Major in vitro metabolites are GW630200 (M1) and GSK932009 (M2). Urine primary route of excretion Renal elimination of parent VI was <2% of the administered dose [GSK Study B2C106180].
	Terminal t _{1/2}	Mean (CV%): Parent: Not determined, terminal profile not adequately defined due to low exposure (≤LLQ of 10 pg/ml) following inhaled dosing. Metabolites not quantifiable in plasma.
	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	Cross study comparison have shown VI systemic exposure in Japanese subjects to be similar to that seen in predominantly Caucasian subjects.
	Hepatic & Renal Impairment	<p>There was no effect of hepatic impairment on VI systemic exposure (dose-normalised Cmax and dose-normalised AUC(0–24) on Day 7) following repeat dose administration of FF/VI 200/25 mcg to subjects with mild or moderate hepatic impairment (Child-Pugh A and B, respectively) and FF/VI 100/12.5 mcg to subjects with severe hepatic impairment (Child-Pugh C) [GSK Study HZA111789].</p> <p>There were no clinically relevant effects of the FF/VI combination on beta-adrenergic systemic effects (heart rate or serum potassium) in subjects with hepatic impairment compared with healthy subjects. Although the VI dose was 12.5 mcg in subjects with severe hepatic impairment, significant beta-adrenergic systemic pharmacodynamic effects would not be predicted at 25 mcg. Inhaled FF/VI was well tolerated in hepatically impaired and healthy subjects.</p> <p>Severe renal impairment (CrCl <30 mL/min) had no effect on the pharmacokinetics of VI when administered as a FF/VI repeat dose 200/25 mcg for 7 days [GSK Study HZA113970].</p> <p>There was no evidence of a difference between subjects with severe renal impairment and healthy subjects in systemic effects that might be attributable to the administration of either a long-acting beta agonist (maximum heart rate and minimum serum potassium). Repeat dose FF/VI (200/25 mcg) was well tolerated in healthy subjects and in subjects with severe renal impairment.</p>

Extrinsic Factors	Drug interactions	<p>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 Cmax were increased by 65% (90% CI: 38% to 97%) and 22% (90% CI: 8% to 38%), respectively [GSK Study HZA105548]. There was no significant increase in VI systemic pharmacodynamic effects (heart rate and potassium).</p> <p>Co-administration of inhaled VI with FF did not affect VI systemic exposure [GSK Studies HZA105871, HZA102940].</p>
	Food Effects	<p>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 1st pass metabolism (oral bioavailability estimated < 2% oral dose) [GSK study B2C106180].</p>
Expected High Clinical Exposure Scenario	<p>From hepatic impairment study [GSK Study HZA111789]:</p> <p>Geometric means following 7 days repeat dose with FF/VI 200/25 mcg: Cmax 206 pg/mL and AUC(0-24) 678 pg.h/mL.</p>	

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/s/

KEVIN M KRUDYS
10/30/2012

MOH JEE NG
10/31/2012

QIANYU DANG
10/31/2012

MONICA L FISZMAN
10/31/2012

NORMAN L STOCKBRIDGE
10/31/2012

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 # 204275 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Breo Ellipta Established/Proper Name: fluticasone furoate/vilanterol Dosage Form: Inhalation Powder Strengths: 100/25 mcg		
Applicant: GlaxoSmithKline Agent for Applicant (if applicable):		
Date of Application: July 11, 2012 Date of Receipt: July 12, 2012 Date clock started after UN:		
PDUFA Goal Date: May 12, 2013		Action Goal Date (if different): May 10, 2013
Filing Date: September 10, 2012		Date of Filing Meeting: August 30, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1,4		
Proposed indication(s)/Proposed change(s): COPD		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input checked="" 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	
<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 type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input 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)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<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 (if OTC product):				
List referenced IND Number(s): 77855, 48647, 70297, 74696 (b)(4)				
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>	✓			
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>	✓			
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>	✓			
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>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<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 <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <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 <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>																				
<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>																				
<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>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th data-bbox="203 1446 495 1482">Application No.</th> <th data-bbox="495 1446 773 1482">Drug Name</th> <th data-bbox="773 1446 1060 1482">Exclusivity Code</th> <th data-bbox="1060 1446 1349 1482">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																
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 will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<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? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>✓</p>																		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			✓	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	✓			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		✓		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
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?			✓	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	✓			
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>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
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)?	✓			
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)?	✓			

<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>	✓			
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>	✓			
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>			✓	
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>			✓	
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>	✓			
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			
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>			✓	
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>				
<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>		✓		
Proprietary Name	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>	✓			Conditionally Acceptable 7.26.12
REMS	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>	✓			
Prescription Labeling	<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) <input checked="" type="checkbox"/> Carton labels			

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"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	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>	✓			
Is the PI submitted in PLR format? ⁴	✓			
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>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> 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? <i>If no, request in 74-day letter.</i>				

4

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

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)	✓			OT Review Team
<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): March 16, 2011 and March 31, 2009	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 14, 11- CMC				
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		✓		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 30, 2012

BLA/NDA/Supp #: 204275

PROPRIETARY NAME: BREO ELLIPTA

ESTABLISHED/PROPER NAME: fluticasone furoate/vilanterol

DOSAGE FORM/STRENGTH: 100/25mcg Inhalation Powder

APPLICANT: GlaxoSmithKline

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): COPD

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Angela Ramsey	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Susan Limb		Y
Clinical	Reviewer:	Sofia Chaudhry	Y
	TL:	Susan Limb	Y
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:	Lokesh Jain Jainmeng Chen	Y Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	David Hoberman	
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Tim 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 Xiaobin Shen	Y
	TL:	Alan Schroeder Prasad Peri	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Atul Bhattaram	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lissa Owens	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Nichelle Rashid, OSE PM		Y
Other attendees	Teena Thomas, OSE PM		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <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 checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<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? <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> 	<input checked="" type="checkbox"/> YES Date if known: March 2013 <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason: NME

<ul style="list-style-type: none"> ○ <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> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<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>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<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 pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<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
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<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

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<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
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<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>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<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>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Angela Ramsey	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): December 5, 2012	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	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 checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<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)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	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]
<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.

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

/s/

ANGELA H RAMSEY
09/18/2012

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: 204275

Application Type: NDA

Name of Drug: Breo Ellipta (fluticasone furoate and vilanterol) Inhalation Powder

Applicant: GlaxoSmithKline

Submission Date: July 11, 2012

Receipt Date: July 12, 2012

1.0 Regulatory History and Applicant's Main Proposals

GlaxoSmithKline submitted a New Drug Application for Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder in the treatment of COPD.

The proposed labeling submitted for Breo Ellipta includes Prescribing Information in SPL format, MedGuide and carton/container labeling.

OSE, OPDP, and PLT were consulted to review proposed labeling.

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.

In addition, the following labeling issues were identified:

1. Excessive length in the HL. The length of the HL section must be less or equal to one-half the page.

RPM PLR Format Review of the Prescribing Information

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 October 15, 2012. 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:

- NO** 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).

Selected Requirements of Prescribing Information (SRPI)

Comment:

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

- YES** 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:
- NO** 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)

- N/A** 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:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

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:

YES

Selected Requirements of Prescribing Information (SRPI)

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:

- YES** 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:

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

N/A

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

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 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:

- 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

- YES** 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:

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

/s/

ANGELA H RAMSEY
09/18/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division:

Mail Code: HF

Consulting Reviewer Name: Quynh Nhu Nguyen

Building/Room #: WO 66/2531

Phone #: 301-796-6273

Fax #:

Email Address: QuynhT.Nguyen@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: DPARP

Mail Code: HF

Requesting Reviewer Name: Sofia Chaudhry, MD

Building/Room #: WO 22/3215

Phone #: 301-796-4157

Fax #:

Email Address: sofia.chaudhry@fda.hhs.gov

RPM/CSO Name and Mail Code: Angela Ramsey 6-2284

Requesting Reviewer's Concurring

Supervisor's Name: Susan Limb, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: September 18, 2012

Requested Completion Date: November 30, 2012

Submission/Application Number: 204275
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: July 12, 2012

Official Submission Due Date: May 10, 2013

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

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/s/

ANGELA H RAMSEY
09/18/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: November 29, 2012

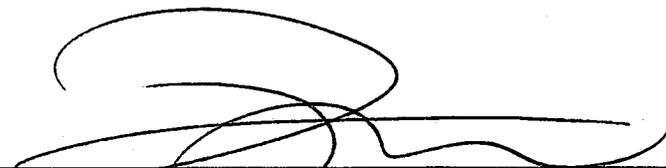
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGRID

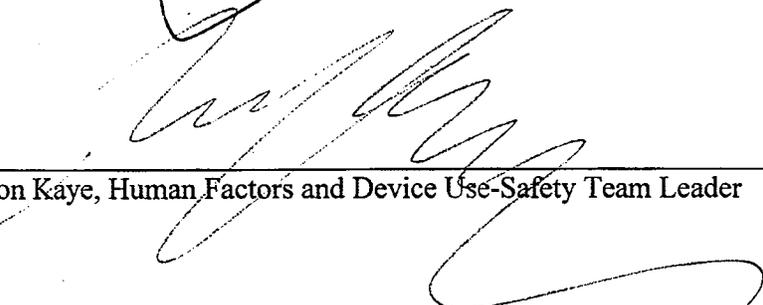
TO: Sofia Chaudhry, Medical Officer, CDER/OND/ODEII/DPARP
Angela Ramsey, Regulatory Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: NDA 204275
Drug: Fluicasone furoate/vilanterol inhalation power
Device: Breo Ellipta Inhaler
CDRH CTS Tracking: ICC1200181, CON1219008



QuynhNhu Nguyen, Combination Products Human Factors Specialist

11/29/2012
Date



Ron Kaye, Human Factors and Device Use-Safety Team Leader

11/29/2012
Date

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CDRH Human Factors Review

Overview and Recommendations

The Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of the NDA 204275 submitted by GlaxoSmithKline for the Breo Ellipta inhaler product.

The Sponsor has undertaken a number of formative usability studies during the design development process of the product, which lead to several design improvements prior to performing a final validation study with the proposed commercial product. While the study results showed high success in use performance and positive subjective feedback, there are several issues that will need to be addressed with respect to pediatric users, and users with manual dexterity limitations.

Reviewer's Recommendations

To complete the review of the human factors information, the reviewer requests that the following deficiencies be transmitted to the Sponsor so that the Sponsor can provide clarification/additional information to address the issues.

With respect to the human factors information that you included in the submission, you reported that you have conducted several formative studies included patients (ages 7 and 83 years) and patients with limited grip function and manual dexterity. Another study was conducted with pediatrics to determine whether the inhaler could be used by children unsupported by an adult. In addition, your validation study included 47 inhaler users (12 – 55+ years of age) and 15 professional/lay caregivers. Please address the following:

- 1) We are not clear the smallest pediatric age that you expect to use the proposed product. Your validation study was conducted with users with the age 12 and above but prior formative studies were conducted with users with the age of 7 and above.
- 2) The validation study report was not clear on whether or not pediatric users (ages <18) were able to use the product independently or with the assistance of a caregivers. If caregiver assistance was provided in this study, please describe the use scenario and the nature of assistance provided. If assistance is required for use with this product, please

ensure that the product labeling/instructions for use and your communication to prescribing physicians clearly specify this requirement.

- 3) The validation study report was not clear on the inclusion of users who might have manual dexterity limitations. Please clarify. Also, please provide a characterization of potential limitations with COPD patients, and discuss how your product design has been validated to safeguard against potential use related issues that might occur with patients whose limitations might be more severe than others.

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 204275
Applicant: GlaxoSmithKline
Drug Constituent: Fuidcasone Furoate/Vilanterol
Device Constituent: Breo Ellipta Inhaler
Intended Use: Treatment of COPD
User Population: patients un-assisted aged 7 years and older
Review Material: Submission dated July 12, 2012, Sequence 000, Section 3.2.P.2.4.3.3.9.2

CDRH Human Factors Involvement History

Date	Involvements
9/18//2012	CDRH HF team was requested to provide a consultative review
11/30/2012	CDRH HF team provided review recommendation to CDER

Summary of Review Materials

This review covers the human factors related information in section 3.2.P.2.4.3.3.9.2 of the Original NDA submission. The Sponsor has undertaken a number of formative usability studies during the design development process of the product, which lead to several design improvements prior to performing a final validation study with the proposed commercial product. A summary of the changes made to the product is provided here:

- A modification was made to the dose counter mechanism to address a defect in the Dose Counter kick over mechanism which operates the decimals gear at numbers 30 to 29, 20 to 19, 10 to 9 and 0 to red flag for a 30 dose inhaler
- An audible click has been added to the commercial inhaler, similar to that already used in commercial Diskus inhalers, to help indicate to the user that the Mouthpiece Cover has been fully opened.

The formative studies included patients (ages 7 and 83 years) and patients with limited grip function and manual dexterity. In addition, a study was undertaken with pediatrics to determine whether the inhaler could be used by children unsupported by an adult.

The validation study included 47 inhaler users (12 – 55+ years of age) and 15 professional/lay caregivers. The participants were given an opportunity to familiarize themselves with the inhaler device and read the Patient Information Leaflet independently. The participants were also permitted to actuate the device more than once in an effort to become familiar with the device. Then, the participants were asked to prepare and use the device; however, the inhalation step was simulated; there was no drug in the device. Once the participants completed the use procedures, the participants completed a short self-administered questionnaire. The questionnaire assessed the participant's understanding and interpretation of various scenarios with the counter on the device (e.g., counts down by 1 each time the cover is opened, displays half red when fewer than 10 doses remain, etc.). For the critical tasks, patients and caregivers demonstrated very high

scores (98% - 100%) in using the inhaler correctly. The self-administered questionnaire results showed 94% -100 participants understood the four key directions, and warnings.

While the study results showed high success in use performance and positive subjective feedback, there are several issues that will need to be addressed with respect to pediatric users, and users with manual dexterity limitations. The reviewer requests that the following deficiencies be transmitted to the Sponsor so that the Sponsor can provide clarification/additional information to address the issues.

Background

Device Description: The container closure system for Fluticasone Furoate/Vilanterol Inhalation Powder comprises GlaxoSmithKline's novel dry powder inhalation delivery system containing two pre-filled separate multi-dose blister strips and a mechanism to deliver simultaneously the contents from a single blister from each of the two blister strips. The inhaler incorporated a dose counter that displays to total number of doses remain in the inhaler. When the inhaler is empty, the dose counter shows a red square indicating that the inhaler needs to be replaced.

A 30 dose commercial pack and a 14 dose sample/institutional pack are available to provide up to 30 days or 14 days therapy respective with once a day dosing frequency. The packs use the same container closure system and differ only in the blister strip length and the number of blister pockets.



Figure 1: Proposed Inhaler



Figure 2: Exploded View of The Inhaler

The operation of the inhaler is designed to be simple, easy and intuitive for the patient to use. There are three operating steps:

1. Open mouthpiece cover (with a click sound to indicate that the cover is fully open)
2. Inhale dose
3. Close mouthpiece cover

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

/s/

ANGELA H RAMSEY
12/07/2012
Ramsey for Nguyen