CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209482Orig1s000

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW ADDENDUM

CLINICAL STUDIES

NDA/BLA #:	NDA 209482
Drug Name:	Fluticasone furoate/umeclidinium/vilanterol inhalation powder
Proposed Indication:	Long-term, once-daily, maintenance (b) (4) treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
Applicant:	GlaxoSmithKline
Dates:	NDA submitted: November 18, 2016 PDUFA due date: September 18, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Gregory Levin, PhD
Concurring Reviewers:	Robert Abugov, PhD Yongman Kim, PhD Thomas Permutt, PhD
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Sofia Chaudhry, MD Lydia Gilbert McClain, MD
Project Manager:	LeAnn Brodhead

Keywords: NDA review, clinical studies, combination drug, standard of evidence, factorial design

We refer the reader to our previous statistical review dated August 21, 2017 of NDA 209482 regarding the fixed dose combination of the inhaled corticosteroid (ICS) fluticasone furoate (FF), the long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC), and the long-acting β2 agonist (LABA) vilanterol (VI) for the treatment of chronic obstructive pulmonary disease. Our conclusions and recommendations have not changed. However, there have been additional discussions about the indication for FF/UMEC/VI. In particular, there has been consideration of an amended indication of the combination product "for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction with umeclidinium is desired or patients who are on umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol." Here, we provide commentary on the amended indication, and also discuss a potential alternative approach to justify approval of the NDA.

The amended INDICATIONS And USAGE section, which limits the population indicated for treatment with FF/UMEC/VI, may be helpful from a public health perspective in that it implicitly excludes the population of patients who are on Anoro (UMEC/VI). These are the patients who would be adding the ICS FF by stepping up to FF/UMEC/VI, and as discussed in our previous review, there are known adverse effects of ICSs and there is uncertainty about the contribution of FF to the efficacy of FF/UMEC/VI. However, even with the limited indication, approval of FF/UMEC/VI would represent approval of a fixed dose combination product, such that the regulation regarding fixed dose combination products (21 CFR 300.50) still applies. In particular, even for the amended indicated population of patients on FF/VI in whom additional treatment of airflow obstruction with umeclidinium is desired, the question about whether each of the three components of FF/UMEC/VI is contributing to its claimed effects is relevant. For example, it is possible that FF no longer contributes to effectiveness, or that the risks of FF exceed its benefit, once the effective LAMA UMEC has also been added as part of the treatment.

That being said, the Agency has often exercised flexibility in its interpretation of the combination rule, and we recognize that a scientific argument can be made that the regulation is satisfied without the support of clinical data directly evaluating the contributions of all three components. For example, based on internal discussions, it is our understanding that a conclusion may be reached that FF contributes to the effects of FF/UMEC/VI based on (1) previous findings that FF contributes to the effects of Breo (FF/VI); and (2) a pharmacologic rationale revolving around the differing mechanisms of action and expected effects of the three different components. We believe that, even with the amended indication, such an argument is needed to justify that the regulations for fixed dose combination products have been satisfied and to support a decision to approve FF/UMEC/VI. We defer to colleagues from other disciplines to support such an argument.

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/s/

GREGORY P LEVIN
09/18/2017

ROBERT ABUGOV
09/18/2017

YONGMAN KIM
09/18/2017

THOMAS J PERMUTT
09/18/2017
I concur.

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

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Table of Contents

1 EXECUTIVE SUMMARY 3

2 INTRODUCTION 3

2.1 BACKGROUND 3
2.2 HISTORY OF DRUG DEVELOPMENT 4
2.3 COMBINATION RULE 4

3 STATISTICAL EVALUATION 5

4 SUMMARY AND CONCLUSIONS 5

4.1 STATISTICAL ISSUES 5
4.2 CONCLUSIONS AND RECOMMENDATIONS 8

1 EXECUTIVE SUMMARY

This review considers the fixed dose combination product consisting of fluticasone furoate (FF) 100 mcg, umeclidinium (UMEC) 62.5 mcg, and vilanterol (VI) 25 mcg for treatment of chronic obstructive pulmonary disease (COPD). The applicant seeks marketing approval of FF/UMEC/VI based on data from Studies 200109 and 200110, which were randomized, double-blind, parallel-group, placebo-controlled, 12-week clinical trials evaluating UMEC 62.5 mcg as an add-on therapy for patients receiving background FF/VI treatment. Data from these two trials were previously reviewed under sNDA 205382/S-002, and we agree with the prior conclusion that UMEC is safe and effective for treatment of COPD in patients receiving background FF/VI. The Code of Federal Regulations (21 CFR 300.50) states that each component of a fixed dose combination product must make a contribution to its claimed effects. Given the results of Studies 200109 and 200110, as well as biopharmaceutics and clinical pharmacology data demonstrating equivalence of FF/UMEC/VI and UMEC + FF/VI, we agree that there is evidence that UMEC contributes to the claimed effects of FF/UMEC/VI. We also acknowledge that it might be reasonable to conclude that a direct evaluation of the contribution of VI to the effects of FF/UMEC/VI is not necessary, given that use of a long-acting muscarinic antagonist in combination with an inhaled corticosteroid is currently not an approved or commonly used treatment for COPD.

However, we do not believe that there is sufficient evidence supporting the contribution of FF to the claimed effects of FF/UMEC/VI to satisfy regulations for fixed combination products. The applicant has submitted no clinical data comparing the safety and effectiveness of FF/UMEC/VI with UMEC/VI. Furthermore, a reliable evaluation of the contribution of FF to the safety and effectiveness of FF/UMEC/VI is important from a public health perspective, given that Anoro (UMEC/VI) is an approved, safe and effective therapy, and that ICS products lead to known adverse effects such as an increased risk of pneumonia.

We recommend a complete response to NDA 209482. The lack of a comparison of FF/UMEC/VI with UMEC/VI is a key deficiency that can be addressed in a reliable and timely manner with results from an ongoing clinical trial being carried out by the applicant— Study CTT116855 is a randomized, double-blind, parallel-group, placebo-controlled, 52-week clinical trial in approximately 10,000 COPD patients designed to compare the safety and effectiveness of FF/UMEC/VI with FF/VI and UMEC/VI.

2 INTRODUCTION

2.1 Background

Chronic obstructive pulmonary disease (COPD) is a common, progressive disease that causes symptoms such as coughing and shortness of breath, and increases risks of disability and death. Patients with COPD may have chronic bronchitis and/or emphysema. Chronic bronchitis is characterized by inflammation of the lining of bronchial tubes that leads to increased mucus formation and airflow obstruction. In emphysema, the air sacs (alveoli) at the end of the smallest airways (bronchioles) in the lung are damaged and the amount of gas exchange is reduced.

Medications used to treat patients with COPD include bronchodilators and steroids. Bronchodilators, usually administered through an inhaler, relax muscles around the airways in order to improve airflow and relieve symptoms. There are two major types of bronchodilators: β2 agonists, which act on β2 receptors, and muscarinic antagonists, which inhibit the action of cholinergic nerves. Bronchodilators may be either short-acting or long-acting, and many have been approved by FDA for treatment of airflow obstruction in COPD. Fixed dose combinations of a long-acting β2 agonist (LABA) and an inhaled corticosteroid

(ICS), and of a LABA and long-acting muscarinic antagonist (LAMA), have also been approved for treatment of COPD. Standard of care treatment typically begins with a LABA or LAMA, with patients stepping up to an ICS/LABA or LAMA/LABA combination product if symptoms persist.

This review considers the fixed dose combination product consisting of fluticasone furoate (FF) 100 mcg, umeclidinium (UMEC) 52.6 mcg, and vilanterol (VI) 25 mcg for treatment of COPD.

2.2 History of Drug Development

The applicant has conducted several clinical trials to evaluate the safety and effectiveness of the components of FF/UMEC/VI as monotherapies and/or in various combinations. Incruse Ellipta (UMEC), Anoro Ellipta (UMEC/VI), and Breo Ellipta (FF/VI) are approved in the United States for treatment of COPD. This application seeks marketing approval of FF/UMEC/VI based on data from two randomized, double-blind, parallel-group, placebo-controlled, 12-week clinical trials evaluating UMEC 62.5 mcg as an add-on therapy for patients receiving background FF/VI treatment. Data from these two trials, Studies 200109 and 200110, were previously reviewed under sNDA 205382/S-002. The reviews concluded that there was sufficient evidence of safety and effectiveness to support the use of UMEC when used in patients receiving background FF/VI treatment, and the CLINICAL TRIALS section of the labeling for UMEC was revised to describe results from these two studies. The applicant is also conducting an ongoing randomized, double-blind, parallel-group, placebo-controlled, 52-week clinical trial, Study CTT116855, in COPD to compare the safety and effectiveness of FF/UMEC/VI with FF/VI and UMEC/VI. This trial is being carried out in approximately 10,000 patients, with the rate of moderate-to-severe COPD exacerbations as the primary efficacy endpoint.

We briefly highlight some relevant correspondence with the applicant during development of FF/UMEC/VI. In a pre-IND meeting May 7, 2012, FDA noted that the applicant would "be expected to provide data that justifies the use of the combination product over the individual components and the 2-component combination products that are relevant in the treatment of COPD, i.e., fluticasone furoate/vilanterol (FF/VI) and umeclidinium/vilanterol (UMEC/VI)." In an end-of-phase 2 meeting September 18, 2013, the applicant inquired whether the proposed phase 3 trial comparing FF/UMEC/VI with both FF/VI and UMEC/VI "meets the requirements under 21CFR §300.50 for a fixed-dose combination product" and FDA indicated the proposed phase 3 trial appeared reasonable. However, FDA minutes for a Type C meeting May 24, 2016 state that "GSK inquired if it already has adequate information to file an NDA" (based only on data from the two previously reviewed phase 3 trials demonstrating benefit of UMEC as an add-on to background FF/VI) and "FDA answered that there is adequate information to file an NDA…"

2.3 Combination Rule

The Code of Federal Regulations (21 CFR 300.50) states that "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." The contribution of a particular component to the "claimed effects" of a fixed dose combination product has often been supported through a conclusion that the fixed dose combination product has advantages in terms of safety or effectiveness over a product from which that respective component has been removed. For example, approval of LAMA/LABA combination products such as Anoro for treatment of COPD has been supported by (factorial) clinical trials establishing that the combination product is more effective than both the LAMA and LABA monotherapy components. On the other hand, approval of ICS/LABA combination products such as Breo for treatment of asthma has been supported by (1) clinical trials

comparing the ICS/LABA combination to the ICS monotherapy to establish the contribution of the LABA component to the effectiveness of the combination product; and (2) a conclusion that the ICS component contributes to the safety of the combination product, given known safety concerns (ICS/LABA products have a black box warning about asthma-related death) regarding the use of LABA without concomitant ICS in asthma—a clinical trial comparing the combination product to the LABA monotherapy is therefore not considered necessary or ethical.

3 STATISTICAL EVALUATION

There are no new relevant clinical data in this application, and therefore no additional statistical analyses have been conducted or reviewed. The reader is referred to the clinical review by Dr. Sofia Chaudhry and the statistical review by Dr. Yi Ren of sNDA 205382/S-002 for additional details on the design, analysis plan, and results of phase 3 Studies 200109 and 200110, which evaluated UMEC as an add-on therapy for patients receiving background FF/VI. We agree with the conclusions of Dr. Ren's review: there is convincing statistical evidence that UMEC is effective for treatment of COPD in patients receiving background FF/VI. Furthermore, the applicant has submitted results from biopharmaceutics and clinical pharmacology studies to support the conclusion that the fixed dose combination product FF/UMEC/VI, administered from a single inhaler, has equivalent safety and efficacy as UMEC plus FF/VI administered through separate inhalers. The reader is referred to the CMC and clinical pharmacology reviews for additional details on these studies and results. Given the safety and efficacy results of Studies 200109 and 20010, and the biopharmaceutics and clinical pharmacology bridging study results, we agree that there is sufficient evidence that FF/UMEC/VI is more effective than FF/VI for treatment of COPD. Therefore, there is evidence that UMEC contributes to the claimed effects of the fixed dose combination product.

However, the applicant's submission does not discuss why a conclusion that FF/UMEC/VI is more effective than FF/VI should be sufficient to conclude that FF/UMEC/VI is safe and effective for the treatment of COPD and to satisfy the regulations regarding fixed dose combination products. We discuss issues with the applicant's submission in the next section.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

We have identified the following important issues:

- Satisfaction of the combination rule

  The code of federal regulations states that each component must make a contribution to the claimed effects of the fixed dose combination product. We address the contribution of each of the three components of FF/UMEC/VI:

  (1) *Contribution of UMEC*: We agree that there is evidence from Studies 200109 and 200110 that UMEC contributes to the effectiveness of FF/UMEC/VI.

  (2) *Contribution of VI*: We acknowledge that it might be reasonable to conclude that a direct evaluation of the contribution of VI to the effects of FF/UMEC/VI is not necessary, given that use of a LAMA in combination with an ICS is currently not a commonly used standard-of-care

treatment for COPD.[1] COPD patients treated with FF/UMEC/VI in clinical practice would be expected to most often step up from ICS/LABA or LAMA/LABA therapy rather than from ICS/LAMA therapy, such that evaluations of the contributions of the LAMA and ICS components (UMEC and FF, respectively) rather than the LABA component (VI) are the most relevant and important from a public health perspective. Such a conclusion might be in line with a proposed revision (Federal Register Vol. 80 No. 246) to the regulations on prescription fixed-combination drugs stating that FDA may waive a requirement in scenarios where demonstration of the contribution of a component is considered "infeasible or medically unreasonable or unethical." It would also be consistent with the Division's pre-IND correspondence stating that the applicant would be expected to show superiority of FF/UMEC/VI over only the "2-component combination products that are relevant in the treatment of COPD, i.e., fluticasone furoate/vilanterol (FF/VI) and umeclidinium/vilanterol (UMEC/VI)." Alternatively, one could argue that the contribution of all three components should be established, given that standard of care is always evolving and may include ICS/LAMA therapy in the future. Thus, the lack of data demonstrating the contribution of VI to the effectiveness of FF/UMEC/VI would be an additional deficiency of this application.

(3) *Contribution of FF*: We do not agree that there is sufficient evidence that FF contributes to the claimed effects of FF/UMEC/VI. The applicant has submitted no clinical data comparing the safety and effectiveness of FF/UMEC/VI with UMEC/VI to support the contribution of FF to the claimed effects of the combination product. Furthermore, as discussed next, there is uncertainty about the contribution of FF and this evaluation is important from a public health perspective.

- Public health implications

Anoro (UMEC/VI) is an approved, safe and effective treatment for COPD, and it is likely that some patients receiving UMEC/VI in clinical practice will step up to FF/UMEC/VI, if the triple combination product is approved. Therefore, it is important from a public health perspective that such a step-up in therapy improves patient outcomes, i.e., that FF contributes to the effectiveness of the triple combination product. Furthermore, there are reasons to question whether any benefits achieved through the addition of FF to patients receiving UMEC/VI are worth the added risks. Although FDA concluded that there was sufficient support for the contribution of FF to the effectiveness of Breo (FF/VI) to support approval, the benefit of FF when added to VI appeared to be relatively small—there was not consistent evidence of an effect of FF on FEV1, and the estimated reduction in exacerbation rate achieved by adding FF was roughly one quarter of an event per person per year across the two phase 3 exacerbation trials (each with roughly 1,600 patients).[2] This corresponds to roughly 25 exacerbations prevented for every 100 patients treated for one year. In addition, there are known safety risks with the use of ICS products such as FF in patients with COPD. For example, FF can increase the risk of pneumonia—the risk was roughly doubled on FF/VI compared to VI across the two phase 3 exacerbation trials, with an estimated attributable risk of roughly 3% over the 52-week treatment period.[3] This corresponds to roughly 3 pneumonias caused for every 100 patients treated for one year. There were also estimates of the benefit and risk of FF when added to VI from a recent trial evaluating the effect of Breo on mortality.[4] This trial was much

[1] There are no ICS/LAMA fixed dose combination products approved in the United States. Furthermore, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 guidelines do not include LAMA + ICS as a recommended treatment.
[2] Detailed efficacy results are available in the statistical review by Dr. Kiya Hamilton.
[3] Detailed safety results are available in the medical review by Dr. Sofia Chaudhry.
[4] Detailed results are available in the Breo labeling.

larger, with over 16,000 patients, and was carried out in patients with less severe COPD than the previous phase 3 exacerbation studies. The magnitudes of both benefit and risk were smaller on the absolute scale in this trial than in the previous phase 3 trials: the estimates correspond to roughly 6 exacerbations prevented and 1.1 pneumonias caused for every 100 patients treated for one year with FF/VI instead of VI.

It is plausible that the benefits of FF when added to UMEC/VI could be less than when added to VI, given the known effectiveness of UMEC for treatment of COPD and the possibility that patients may reach a therapeutic plateau where benefits achieved through the addition of active ingredients may become diminished or absent. Therefore, there is uncertainty regarding whether the benefit-risk profile of adding FF to patients receiving background UMEC/VI is favorable, and the contribution of FF should be evaluated before approving FF/UMEC/VI for treatment of COPD. Fortunately, this evaluation is feasible and can be achieved in a timely manner, given that the applicant has an ongoing clinical trial designed to reliably answer this question by comparing the safety and effectiveness of FF/UMEC/VI with UMEC/VI (in addition to FF/VI).

- Regulatory implications

  Approval of FF/UMEC/VI in the absence of any clinical data comparing the safety and effectiveness of FF/UMEC/VI and UMEC/VI could also have important regulatory implications. It is unclear how one might justify the contribution of FF to the claimed effects of FF/UMEC/VI to support approval. However, one approach might be to extrapolate the contribution of FF to the effects of FF/UMEC/VI from previous conclusions that FF contributes to the effects of Breo (FF/VI). Reliance on such extrapolation may have an important effect on the interpretation of combination product regulations and on combination product development programs moving forward. For example, suppose that a sponsor conducts placebo-controlled clinical trials demonstrating that a LAMA and a LABA are safe and effective for treatment of COPD as monotherapies. The sponsor might then propose a fixed dose combination of the LAMA and LABA without any clinical trials comparing the combination product to the monotherapies, based on extrapolation of the contribution of the LAMA and LABA from the monotherapy studies. This approach would be in direct contrast to the current expectation that sponsors carry out a factorial design comparing the safety and effectiveness of LAMA/LABA combination products to the LAMA and LABA monotherapies to support approval for treatment of COPD. Alternatively, the sponsor could propose a fixed dose combination of the LABA with an ICS based on clinical trials comparing the ICS/LABA to the LABA monotherapy, along with extrapolation of the contribution of the LABA from the monotherapy studies. This approach would be in direct contrast to the current expectation that sponsors carry out a factorial design comparing the safety and effectiveness of ICS/LABA combination products to both the ICS and LABA monotherapies to support approval for treatment of COPD.

- Consistency with previous approval of sNDA 205382/S-002

  We believe that a decision against approval of FF/UMEC/VI would be consistent with the previous approval of sNDA 205382/S-002. sNDA 205382/S-002 focused on the use of UMEC in patients receiving background FF/VI treatment, and led to updates to the CLINICAL TRIALS section of the UMEC labeling to add results from the two studies supporting this condition of use. We agree that results from Studies 200109 and 200110 provide evidence supporting the condition of use and the labeling update for UMEC. However, such evidence is not sufficient here—there are additional important considerations for the evaluation of FF/UMEC/VI given that it is a new fixed dose combination product. In particular, regulations about fixed combination products are relevant to the review of FF/UMEC/VI but were not relevant to the previous UMEC supplement review.

Furthermore, the evaluation of the effects of FF when added to UMEC/VI (based on a comparison of FF/UMEC/VI to UMEC/VI) was not particularly relevant to UMEC labeling but has clear relevance to the evaluation of FF/UMEC/VI.

4.2 Conclusions and Recommendations

In summary, we conclude that there is insufficient evidence to support approval of FF/UMEC/VI for treatment of COPD. The applicant has submitted no clinical data comparing the safety and effectiveness of FF/UMEC/VI with UMEC/VI to support the contribution of FF to the claimed effects of the combination product. Therefore, regulations for fixed combination products (§ 300.50) have not been satisfied. Furthermore, a reliable evaluation of the contribution of FF to the safety and effectiveness of FF/UMEC/VI is important from a public health perspective, given that Anoro (UMEC/VI) is an approved, safe and effective therapy, and that ICS products lead to known adverse effects such as an increased risk of pneumonia.

We recommend a complete response to NDA 209482. The lack of a comparison of FF/UMEC/VI with UMEC/VI is a key deficiency that can be addressed in a reliable and timely manner with the results of the applicant's ongoing phase 3 clinical trial, Study CTT116855.

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/s/

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08/14/2017

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08/21/2017

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08/21/2017
I concur.

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209-482
Product Name:	Trelegy Ellipta (Fluticasone furoate/umeclidinium bromide /vilanterol)
Indication(s):	Maintenance treatment of COPD
Applicant:	GlaxoSmithKline
Dates:	Submitted: November 18, 2016
	PDUFA date: September 18, 2017
Review Priority:	Standard
Biometrics Division:	Division II
Statistical Reviewer:	Yi Ren, PhD
Concurring Reviewers:	Gregory Levin, PhD
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Sofia Chaudhry, MD
	Lydia Gilbert McClain, MD
Project Manager:	LeAnn Brodhead

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

No new clinical data

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	N/A. Studies 200109 and 200110 were previously reviewed under NDA 205382 supplement S002. Study CTT116853 is not considered relevant because of a non-US-approved comparator. Therefore, there is no new data to review.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	N/A
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	N/A
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	N/A
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	N/A

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	N/A. No new clinical data
Were analysis datasets provided?	N/A
Dataset structure (e.g., SDTM or ADaM)	N/A
Are the define files sufficiently detailed?	N/A
List the dataset(s) that contains the primary endpoint(s)	N/A
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	N/A
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	N/A
Safety data are organized to permit analyses	N/A

Content Parameter	Response/Comments
across clinical trials in the NDA/BLA.	

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.			√	
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			√	
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			√	
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).			√	
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements			√	

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

None 5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

We do not have any information requests. The following is a potential review issue:

Based on the Combination Rule (21 CFR 300.50), two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosing of each component is such that the combination is safe and effective for a significant patient population. Whether or not this submission satisfies the combination rule will be a potential review issue, given that the two previously reviewed studies showed only the contribution of umeclidinium bromide to the efficacy of the combination product.

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/s/

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01/10/2017

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