CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208798Orig1s000

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 AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208-798 and NDA 208-799
Drug Name:	ArmonAir RespiClick (Fluticasone Propionate) 55, 113, and 232 mcg BID AirDuo RespiClick(Fluticasone Propionate and Salmeterol Xinafoate) 55/14, 113/14, and 232/14 mcg BID
Indication(s):	Fluticasone propionate (Fp) multidose dry powder inhaler (MDPI) is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Fp MDPI is not indicated for the relief of acute bronchospasm Fluticasone propionate/salmeterol MDPI is an inhaled corticosteroid plus a long-acting beta agonist indicated for (b) (4) treatment of asthma (b) (4) in patients aged 12 years and older. Fluticasone propionate/salmeterol MDPI is not indicated for the relief of acute bronchospasm
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.
Date(s):	Submission Date: March 28, 2016 PDUFA due date: January 27, 2017
Review Priority:	Standard
Biometrics Division:	DB II
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Keywords: 505(b)(2) Pathway, Combination drug, Missing data, Sensitivity Analysis, Analysis of Covariance

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1 EXECUTIVE SUMMARY

Teva Branded Pharmaceutical Products R&D, Inc. (Teva) submitted two new drug applications (NDAs): NDA 208798 in support of fluticasone propionate (Fp) inhalation powder at proposed dose strengths of 50, 100, and 200 mcg twice daily (BID) and NDA 208799 in support of a fixed dose combination of fluticasone propionate/salmeterol (FS) at proposed dose strengths of 50/12.5, 100/12.5 and 200/12.5 mcg BID, both using Teva's multidose dry powder inhaler (MDPI), to the Food and Drug Administration (FDA) for the treatment of asthma, with the proposed indications as follows:

> NDA 208798
>
> *"Fluticasone propionate (Fp) multidose dry powder inhaler (MDPI) is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Fp MDPI is not indicated for the relief of acute bronchospasm."*
>
> NDA 208799
>
> *"Fluticasone propionate/salmeterol MDPI is an inhaled corticosteroid plus a long-acting beta agonist indicated for* (b) (4) *treatment of asthma* (b) (4) *in patients aged 12 years and older. Fluticasone propionate/salmeterol MDPI is not indicated for the relief of acute bronchospasm."*

Both monotherapy use of inhaled corticosteroids (ICS) and concomitant use of ICS and long-acting beta$_2$-agonists (LABA) are well-established and recommended approaches for the treatment of asthma (NHLBI, NAEPP, 2007). GSK's Flovent Diskus (Fp) and Advair Diskus (FS) are established drugs for asthma approved by the FDA. Teva's two NDAs are filed through the 505(b)(2) pathway with Flovent Diskus and Advair Diskus as reference products, respectively. While the 505(b)(2) pathway is appropriate for dry powder inhaler products that combine an existing approved drug and a novel inhaler device, allowing certain application elements, such as preclinical data, to be referenced, the process does not free the applicant from the responsibility to provide necessary clinical studies to establish the safety and effectiveness of the proposed products in light of the differences between the referenced products and the new products. The design and structure of the clinical program became a critical issue in this sense for the current two applications. In addition, the applicant's intention to match doses with marketed doses of Flovent and Advair without establishing dose separation within the new drugs, considerations about the combination rule requirement in the situation of the incomplete factorial design due to safe concerns with mono-therapy use of LABA in asthmatic patients, and other factors are issues we faced and tried to address during the review process.

The two drugs were developed in parallel sharing one common clinical development program including a total of 9 clinical studies. This statistical review focused on four efficacy and safety studies, which were all double-blind, 12-week, multicenter, randomized, parallel-group, placebo- and in the cases of phase 2 studies, also open-label active-controlled studies, in adolescents and adults with persistent asthma. The four studies enrolled persistent asthma patients with different

disease severity, as determined by the required asthma maintenance therapy ICS dose level prior to the study.

The two phase 2 trials Study 201 and Study 202 were dose-ranging trials that were both placebo- and active-controlled. Study 201 evaluated treatment effects of Fp 12.5, 25, 50, and 100 mcg BID over placebo in persistent asthma patients who were uncontrolled with non-steroidal maintenance therapy; it also included Flovent 100 mcg BID as a reference drug. Study 202 evaluated treatment effects of Fp MDPI 50, 100, 200 and 400 mcg BID over placebo in persistent asthma patients who were still symptomatic with high ICS dose maintenance therapy; it also included Flovent 250 mcg BID as a reference drug. For the dose-ranging portion, Study 201 demonstrated the superiority of test drug to placebo at proposed doses (50 mcg BID and 100 mcg BID) while Study 202 failed to show superiority of test drug to placebo at any proposed dose; none of the two studies were powered to demonstrate treatment effect differences between adjacent doses within study drug. For the active-controlled portion, as there was no established appropriate non-inferiority (NI) margin to show that the new drug is not worse than the active control, there was no formal NI test. In addition, as Study 202 failed to demonstrate superiority of either active control or study drug over placebo, there is reason to suspect that this active controlled trial may lack the expected assay sensitivity.

The two phase 3 trials Study 301 and Study 30017 were both confirmatory placebo-controlled studies. Study 301 evaluated efficacy of FS 50/12.5, FS100/12.5, Fp 50, and Fp 100 mcg BID in persistent asthma patients who were symptomatic despite low-dose or mid-dose ICS therapy. Study 30017 evaluated efficacy of FS 100/12.5, FS 200/12.5 mcg BID, Fp 100, and Fp 200 mcg BID in persistent asthma patients who were symptomatic despite mid-dose or high-dose ICS therapy. For FS MDPI, the trials were used to demonstrate the contribution of Salmeterol (Sx) to FS by comparing FS to Fp at each Fp dose level; for Fp MDPI, the trials were used to compare each Fp dose to placebo, with additional supportive evidence of efficacy of Fp over placebo from the phase 2 trials. As each trial covered only two pairs of FS vs. Fp comparisons, the two trials provide replicate data for FS 100/12.5 over Fp 100 only, and didn't provide replicate evidence for the contribution of Sx to FS over Fp on the proposed dose strengths of Fp 50 and Fp200.

Statistical evidence of efficacy for Fp MDPI as monotherapy at all three proposed dose strengths (Fp MDPI 50, 100, and 200 mcg BID) was demonstrated with respect to the primary endpoint change from baseline trough FEV_1. For Fp 50, in Study 201, the mean difference from placebo ***over*** the 12-week treatment period was 0.107 L (95% confidence interval [CI]: 0.027, 0.187; p = 0.009); in Study 301, mean difference from placebo ***at*** the end of the 12-week treatment period was 0.119 L (95% CI: 0.025, 0.212; p = 0.013). For Fp 100, in Study 201, the mean difference from placebo ***over*** the 12-week treatment period was 0.136 L (95% CI: 0.056, 0.216; p < 0.001); in Studies 301 and 30017, mean differences from placebo ***at*** the end of the 12-week treatment period were 0.151 L (95% CI: 0.057, 0.244; p = 0.002) and 0.123 L (95% CI: 0.038, 0.208; p = 0.005), respectively. For Fp 200, the efficacy over placebo was demonstrated in Study 30017 only, with an estimated mean difference from placebo at the end of 12-week treatment period of 0.276 L (95% CI: 0.191, 0.361; p <.001). Study 202 failed to demonstrate the efficacy of Fp MDPI at doses of 50, 100 and 200 over placebo in persistent asthma patients who were symptomatic despite being on high-dose ICS therapy.

In the ideal situation of a full factorial design, efficacy of the fixed dose combination FS at each proposed dose strength would be demonstrated through establishing statistically significant improvement in outcomes comparing FS with both Fp and Sx. This would demonstrate the contribution of both Fp and Sx to the efficacy of the combination product. However, due to the LABA safety concern, none of the FS containing trials under this program had an Sx monotherapy arm, that is, direct evaluation of the contribution of Fp to the combination was not possible.

The efficacy of FS 50/12.5 mcg was demonstrated in a single study, Study 301: 1) with statistically significant greater improvement compared with placebo for primary endpoints of standardized baseline-adjusted (SBA) FEV_1 $AUEC_{0\text{-}12h}$ and trough FEV_1 at Week 12 with estimated effect sizes of 0.325 L (95% CI: 0.203, 0.447; p <.001) and 0.266 L (95% CI: 0.172, 0.360; p <.001), respectively; 2) with statistically significant greater improvement compared with Fp 50 for SBA FEV_1 $AUEC_{0\text{-}12h}$ with estimated effect size of 0.131 L (95% CI 0.011, 0.250; p = 0.032) , as the efficacy of monotherapy Fp 50 was established earlier.

The efficacy of FS 100/12.5 mcg was demonstrated in both Study 301 and Study 30017, where statistically significant greater treatment differences in SBA FEV_1 $AUEC_{0\text{-}12h}$ were observed between FS 100/12.5 and placebo of 0.335 L (Study 301) and 0.322 (Study 30017); and in changes from baseline in trough FEV_1 of 0.262 L (Study 301) and 0.274 (Study 30017). As efficacy of Fp 100 was established earlier, the contribution of Sx to the efficacy of FS 100/12.5 mcg was demonstrated by statistically significant treatment differences of 0.179 L (Study 301) and 0.182 (Study 30017) between FS 100/12.5 and Fp 100 in SBA FEV_1 $AUEC_{0\text{-}12h}$.

The efficacy of FS 200/12.5 mcg was demonstrated in a single study, Study 30017, where statistically significant greater treatment differences of 0.326 L in SBA FEV_1 $AUEC_{0\text{-}12h}$ and 0.276 in change from baseline trough FEV_1 were observed between FS 200/12.5 and placebo. As efficacy of Fp 200 was established in the same study (without replication), the contribution of Sx to the efficacy of FS 200/12.5 mcg was demonstrated by the treatment difference of 0.179 L between FS 200/12.5 and Fp 200 in SBA FEV_1 $AUEC_{0\text{-}12h}$.

The contribution of Sx 12.5 mcg to the overall effectiveness of the combination was directly examined in the phase 3 studies. In support of the Sx contribution, after 12 weeks of treatment, patients assigned to receive FS 50/12.5, FS100/12.5 or FS 200/12.5 consistently showed statistically greater improvement in SBA FEV_1 $AUEC_{0\text{-}12h}$ than patients assigned to receive Fp only.

The potential impact of missing data on the reliability of efficacy results was assessed through a series of tipping point analyses conducted for each statistically significant comparison over change from baseline in trough FEV_1. In general, for each comparison, analyses treated missing data in the control arm as missing-at-random (MAR) and varied the degree of shifting to the MAR imputed values in the experimental treatment arm, in order to explore the space of missing-not-at-random (MNAR) assumptions. Assumptions were varied until reaching a tipping point at which the result of the comparison of interest changes from statistically significant to not statistically significant. In all comparisons, the tipping points were clinically implausible, in that

they ranged from 2-fold to 10-fold the size of the estimated treatment effects, such that these sensitivity analyses supported the primary analysis conclusions as briefed above.

Subgroup analyses were conducted to investigate the level of consistency of treatment effects across age, gender, racial and region subgroup levels. My examination confirmed the applicant's conclusion on consistency of treatment effect across subgroup levels. For subgroups of reasonable sizes (>10), across the endpoints and studies, there was no significant interaction between subgroups and treatment. Lack of a significant treatment-by-subgroup interaction should not be interpreted as evidence that no interaction exists. However, estimated effects were largely similar across the subgroups evaluated. Definite conclusions cannot be drawn due to limitations such as small sample size in some of the subgroups.

2 INTRODUCTION

2.1 Overview

2.1.1 Investigational Drug Background

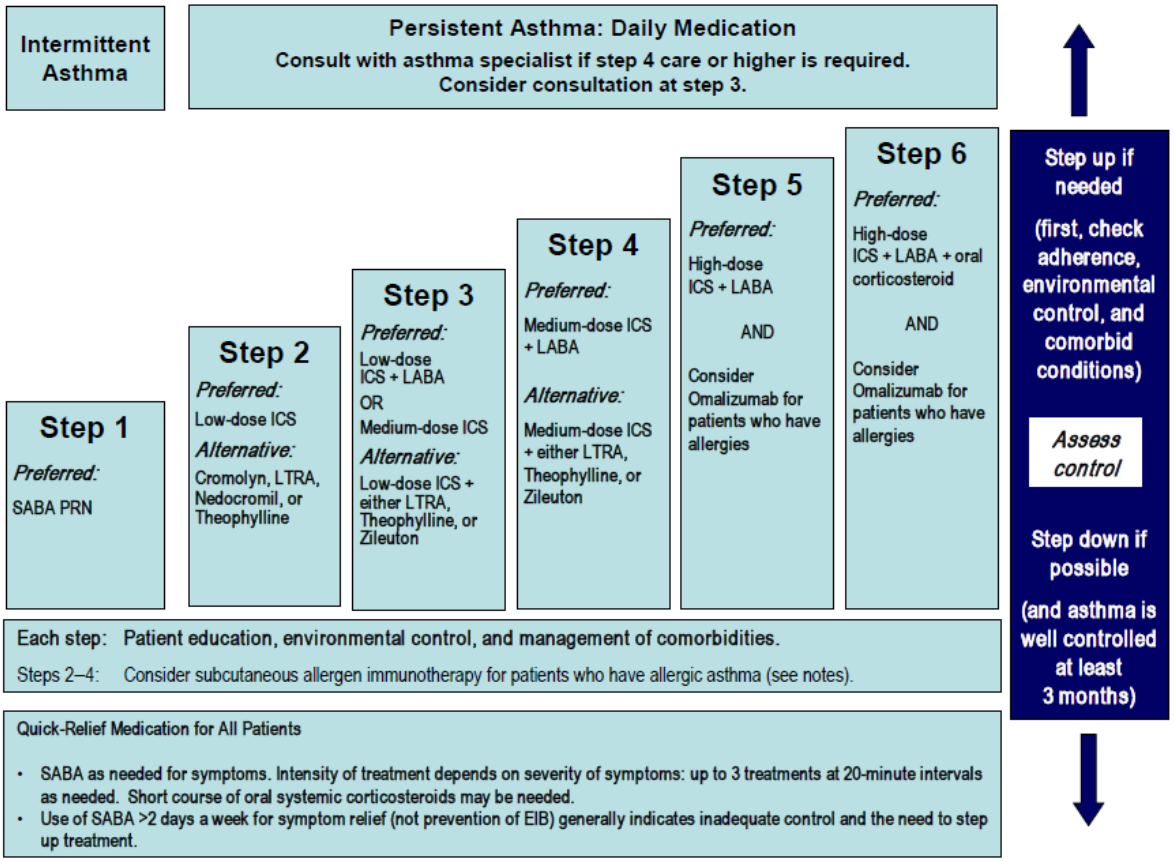
2.1.1.1 Drug Class and the Intended Indication

Asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations. Asthma drugs could be classified by their roles in the overall management of asthma, quick relief or long-term control. Fluticasone propionate is an inhaled corticosteroid (ICS) and salmeterol xinafoate is a long-acting beta agonist (LABA). Among long-term asthma control drugs, categorized by their predominant effect in treatment of asthma, ICS is effective in suppression of airway inflammation; LABA is used for the bronchodilator effect of relaxation of airway smooth muscle. GSK's Flovent Diskus (fluticasone propionate using the Diskus device) and Advair Diskus (fluticasone propionate/salmeterol xinafoate using the Diskus device) are both established maintenance treatments of asthma as prophylactic therapies in the US market.

Teva's investigational products, fluticasone propionate (Fp) inhalation powder, using the applicant's proprietary multi-dose dry powder inhaler (MDPI), referred to as Fp MDPI in the application, and the fixed dose combination product of fluticasone propionate/salmeterol xinafoate (FS) inhalation powder, also using MDPI, referred to as FS MDPI, were both proposed to be indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Teva's application for Fp MDPI and FS MDPI were filed through the 505(b)(2) application pathway with Flovent Diskus and Advair Diskus as reference products.

Asthma *severity* and *treatment recommendation* are both relative concepts that need to be defined in reference to each other in the context of asthma *control* (Taylor, 2008). International guidelines all recommend a step-wise approach for long term treatment of asthma. Among them, the NHLBI National Asthma Education and Prevention Program's Expert Panel Report 3 (NAEPP EPR 3, 2007) recommends a 6-step approach (Figure 1) that classifies *severity* (Figure 2) in patients after asthma becomes well controlled, by lowest level of *treatment* required to maintain *control*. According to the applicant, Fp MDPI is supplied in dose strengths of Fp at 50, 100, and 200 mcg twice daily (BID) for patients requiring ICS therapy (Reviewer's note: Steps 2 and 3 in NAEPP EPR 3) for treatment of asthma; FS MDPI is supplied in dose strengths of 50/12.5, 100/12.5, and 200/12.5 mcg with a fixed dose of salmeterol xinafoate (Sx) for patients requiring combination therapy (Reviewer's note: Steps 3, 4 and 5 in NAEPP EPR 3).

Figure 1 Step-wise approach to asthma treatment



Source: Figure 4-5 in NHLBI NAEPP EPR3, 2007.

Figure 2 Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control

Lowest level of treatment required to maintain control (See figure 4–5 for treatment steps.)	Classification of Asthma Severity			
	Intermittent	Persistent		
		Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

Source: Figure 3-4c in NHLBI NAEPP EPR3, 2007.

2.1.1.2 Overview of Development Program

Teva (IVAX before January 2006, when it was acquired by Teva) first brought the development plan for a combination of Fp and Sx delivered via a metered dry powder inhaler for asthma, intended as a similar product to GSK's Advair Diskus through the 505(b)(2) application pathway, to the FDA in July, 2005. Since then, there have been extensive communications between Teva and the Division of Pulmonary, Allergy, and Rheumatology Products (the Division or DPARP) on the overall and detailed elements in the design and conduct of the FS

and Fp MDPI dual development program. Table 1 provides a list of the meeting minutes or communications during this process. This subsection will first go over some of the key topics, the evolvement of which had shaped the development program, and then give an overview of the dual development program supporting both Fp MDPI and FS MDPI in its final executed shape. It is hoped that by elaborating on these topics upfront, it will facilitate understanding of the clinical trial design elements that will be discussed in detail in the Statistical Evaluation Section and clarify efficacy expectations in each trial, which ultimately guided this review.

Table 1 Statistics related regulatory interactions

IND (Date of documentation)	Type of Interaction	Summary of Statistics Related Contents
Pre-IND 72240 (December 23, 2005)	Teleconference	IVAX with the Division on December 5, 2005
Pre-IND 72240 (March 31, 2008)	Type C Teleconference	IVAX with the Division on March 25, 2008
Pre-IND 72240 (December 28, 2009)	Type B Pre-IND face to face meeting	Teva met with the Division on December 1, 2009.
Pre-IND 108838 (August 25, 2010)	Type B Pre-IND face to face meeting	Teva met with the Division on July 30, 2010. Agreed on • MMRM model as primary analysis for change from baseline trough FEV_1 in phase 2 Fp MDPI studies • A non-full-factorial phase 3 design due to safety concern with LABA, and • Division suggested assessment of Fp contribution with mid relative to low dose FS in the absence of Sx arm.
EOP 2 IND 108838 and IND 072240 (March 17, 2014)	End of Phase 2 Multidisciplinary face to face meeting	Teva met with the Division on February 18, 2014. Doses of Fp and Sx Teva plans to bring into phase 3 studies Teva plans to use study 201 to support Fp MDPI 50 and 100 mcg, and study 202 to support the Fp MDPI 200 mcg.
A Series of Correspondences between Teva and the Division of phase 3 endpoint selection and analysis method	Emails	The detail is covered in the Evaluation of Efficacy section of this review

Source: Reproduced from records by Reviewer

2.1.1.2.1 Key topics that shaped the development program

Between the applicant and the Division and within the Division, as the Teva FS MDPI program was the first combination drug inhaler development program following a 505(b)(2) application route, there was some evolution on trial design considerations before common agreements were reached and final decisions were made. I will mainly describe the final agreement and allude to earlier discussions when necessary.

2.1.1.2.1.1 The 505(b)(2) application pathway

Teva's (IVAX, acquired by Teva in 2006) plan was to develop a combination of fluticasone and salmeterol delivered via a metered dry powder inhaler for asthma that's comparable with Advair Diskus with the intention to seek approval through the 505(b)(2) pathway using Advair as the reference drug. The division responded that while the 505(b)(2) pathway is appropriate for dry powder inhaler products that combine an existing approved drug and a novel inhaler device, and certain application elements, such as preclinical data, can be referenced, the process does not free the applicant from the responsibility to provide necessary clinical studies to establish the safety and effectiveness of the proposed product in light of the differences between the referenced product and the new product. Through three Pre-IND meetings (2005, 2008, 2009) that followed, the Division guided the applicant on program design to meet the 505(b)(2) NDA pathway expectations in the context of a combination drug plus a device.

2.1.1.2.1.2 Assessment of Fp contribution in absence of a Salmeterol monotherapy arm

The FDA Combination Rule requires that to adequately demonstrate efficacy of a combination product like FS MDPI, each component of the product must be shown to make a contribution to the efficacy of the combination product. Due to the safety concerns with the use of LABA as first line therapy in asthma patients, it is not advisable to include a salmeterol-only arm. Assessment of the ICS contribution in the absence of a LABA-only arm became an issue. Two approaches were recommended by the Division to assess the Fp contribution: a) as contribution of Fp was demonstrated in the development program of Advair, by showing non-inferiority of FS MDPI to Advair, it can be used as a bridge to indirectly demonstrate the contribution of Fp to the combination; b) by demonstrating a greater treatment effect with a higher dose of FS over a lower dose of FS, contribution of Fp to the combination can be indirectly inferred. However, the non-inferiority approach was not adopted due to the following reasons. While the combination of a new device with approved drugs qualified the application through the 505 (b)(2) pathway, there is no established non-inferiority margin with respect to a primary FEV1 endpoint for a possible NI test of effects of the study drug with an approved reference drug in the US market. In addition, the applicant's final program didn't include Advair Diskus as an active control in the phase 3 studies of FS MDPI. While the phase 2 dose-ranging studies included Flovent Diskus arms both as reference and for assay sensitivity purposes, there was no plan for an NI test between the study drug and Flovent due to the NI margin concern.

2.1.1.2.1.3 Dose selection (EOP 2 Multidisciplinary Meeting Minutes Dated March 17, 2014: Q6 and Q7)

Teva proposed to study fluticasone propionate doses of 50 mcg, 100 mcg, and 200 mcg, both alone as Fp MDPI and in combination with salmeterol 12.5 mcg as FS MDPI. Teva stated that dose finding studies in phase 2 demonstrated that *the three Fp strengths, representing half the delivered dose corresponding to those in Flovent Diskus and Advair Diskus, provide comparable clinical efficacy and safety with lower systemic exposure; the 12.5 mcg strength of salmeterol MDPI, representing about one-quarter the delivered dose corresponding to salmeterol in Advair Diskus, provide comparable clinical efficacy and safety with lower systemic exposure*. The Division agreed with the proposed doses to be carried forward into the phase 3 studies.

The Division acknowledged Teva's goal of obtaining approval of three ICS doses, however, based on review of past applications, the Division commented that there will be difficulty in demonstrating incremental benefit and Teva may not be able to show dose separation.

2.1.1.2.1.4 Replication for Fp MDPI versus placebo (EOP 2 Multidisciplinary Meeting Minutes Dated March 17, 2014: Q8)

Teva proposed and the Division agreed that the two 12-week phase 2 studies can serve as replicates for the planned Fp versus placebo comparisons that will be part of the phase 3 efficacy studies, although the phase 2 studies were conducted in different patient populations. Study FpS-AS-201 will support the Fp MDPI 50 mcg and 100 mcg doses and Study Fp-AS-202 will support the Fp MDPI 200 mcg dose.

2.1.1.2.1.5 Replication for FS MDPI over Fp MDPI (EOP 2 Multidisciplinary Meeting Minutes Dated March 17, 2014: Q6 and Q7)

In the applicant's original proposed development program discussed at the EOP2 meeting, two phase 3 studies were planned to each investigate treatment groups of placebo, Fp MDPI and FS MDPI, with different doses included (Study 301: low Fp 50 and FS 50/12.5, Study 30017: mid and high Fp 100, 200 mcg and FS 100/12.5, FS 200/12.5). The Division pointed out that the plan didn't have replication of any of the combination treatment arms. The Division stated the general expectation of replicate evidence of efficacy over placebo of the lowest dose strength (Fp 50 mcg in this program). The Division also expressed concern with the low dose ICS/LABA combination, as asthma guidelines recommend that LABA add-ons should be started with mid-dose ICS. Therefore, it was recommended to add Fp 100 mcg and FS 100/12.5 mcg treatment arms to Study 301. Together with Study 30017 which covered Fp 100 mcg and FS 100/12.5 mcg, this allowed for replicate evaluation of FS 100/12.5 mcg, as well as provided a direct comparison of the Fp 50 and 100 mcg doses. It was also pointed out that the appropriateness of the combination FS 50/12.5 would be a review issue.

2.1.1.2.2 Overview of the development program supporting dual applications of Fp MDPI and FS MDPI

The clinical development program supporting dual applications for Fp MDPI and FS MDPI comprised 9 studies in total (Table 2). The 3 phase 1 studies (Studies FpS-AS-101, FpS-AS-102, and FSS-AS-10042) were all single-dose, crossover studies investigating the pharmacokinetic profiles of single doses Fp and FS and the reference drugs. One phase 2 study (Study FSS-AS-201) was a single-dose, crossover dose-ranging study of different doses of Sx each in combination with a fixed dose of Fp 100 mcg administered as a single dose. Two phase 2 studies, Studies FpS-AS-201 and FpS-AS-202, were dose-ranging studies of Fp with doses ranging (jointly) from 12.5 mcg to 400 mcg. These two phase 2 studies, together with two phase 3 studies, Studies FSS-AS-301 and FSS-AS-30017, were all double-blind, 12-week, multicenter, randomized, parallel-group, placebo- and in the cases of phase 2 studies, also open-label active-controlled studies, in adolescents and adults with persistent asthma. As these four studies

represented the key efficacy assessments within the development programs and this review is focused on efficacy aspects of the program, these four studies are selected for full statistical review and evaluation. Table 3 summarizes the number of investigational sites, study type, design, treatment arms, target patient population, and number of randomized patients in each arm for the four studies. Study FSS-AS-305 was a long-term (26 weeks), randomized, open-label, active-controlled, safety study of Fp MDPI in 2 strengths and FS MDPI in 2 strengths with active controls.

Table 2. Overview of the Clinical Program

Phase	Type	Studies	Fp (NDA 209798)	FS (NDA 209799)	Note
I	PK, safety, and tolerability	FpS-AS-101			
		FpS-AS-102			
		FSS-AS-10042			
II	Dose ranging	FpS-AS-201	✓		
		FpS-AS-202	✓		
		FSS-AS-201			Crossover Trial: Dose-ranging for Sx
III	Long term safety	FSS-AS-305			Active Control: Fp vs. Flovent HFA FS vs. Advair
	Efficacy and safety	FSS-AS-301	✓	✓	
		FSS-AS-30017	✓	✓	

Source: Reviewer

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SS transport format. Protocols, Reporting and Analysis Plans, Study Reports, correspondence, and data listings were accessed under the EDR link: \\CDSESUB1\evsprod\NDA208798\208798.enx, and \\CDSESUB1\evsprod\NDA208799\208799.enx.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented or became so upon information request. We were able to reproduce the results of all key analyses.

3.2 Evaluation of Efficacy

3.2.1 Studies overview

3.2.1.1 Phase 2 dose-ranging studies

The design purpose of the two phase 2 studies, Studies 201 and 202, was dose-ranging; if ideally carried out, they would have served three functions in the overall development program. First, as the applicant intended to develop 3 strengths of the Fp MDPI to allow flexibility in Fp dosing based on a patient's asthma severity, the two dose-ranging trials jointly spanned the intended persistent asthma population with a range of candidate doses of Fp MDPI for selection of the optimal doses to carry forward into phase 3 studies. Second, the two studies were both 12-week placebo controlled efficacy and safety studies for Fp MDPI that provided evaluation of the three proposed Fp doses against placebo, and therefore provided additional supportive evidence of efficacy beyond that provided by the phase 3 FS MDPI studies. Third, both studies included an active control arm for assay sensitivity and benchmarking.

The primary objective of Study 201 was to evaluate the dose response, efficacy and safety of 4 different doses of Fp (12.5, 25, 50 and 100 mcg) delivered as Fp MDPI when administered BID in subjects 12 years of age and older with persistent asthma uncontrolled on non-steroidal therapy. The primary objective of Study 202 was to evaluate the dose response, efficacy and safety of 4 different doses of Fp (50, 100, 200, 400 mcg in Study 202) delivered as Fp MDPI when administered BID in subjects 12 years of age and older with severe persistent asthma uncontrolled on high dose ICS therapy.

Table 3. List of studies reviewed

Study Number (Number used in this review) Number of Sites	Design	Treatment Groups (Duration: 12-week)	# of Randomized Subjects per Arm	Subject Population
FpS-AS-201 (201) 188 Sites	Phase 2, R, DB, placebo- and OL active-controlled, PG, MC, Dose-ranging	Fp MDPI 12.5 mcg 1 inhalation BID Fp MDPI 25 mcg 1 inhalation BID Fp MDPI 50 mcg 1 inhalation BID Fp MDPI 100 mcg 1 inhalation BID Flovent Diskus 100 mcg 1 inhalation BID Placebo MDPI 1 inhalation BID	103 104 104 103 104 104	Patients with persistent asthma that is **uncontrolled** on **non-steroidal** therapy
FpS-AS-202 (202) 180 Sites	Phase 2, R, DB, placebo- and OL active-controlled, PG, MC, Dose-ranging	Fp MDPI 50 mcg 1 inhalation BID Fp MDPI 100 mcg 1 inhalation BID Fp MDPI 200 mcg 1 inhalation BID Fp MDPI 400 mcg 1 inhalation BID Flovent Diskus 250 mcg 1 inhalation BID Placebo MDPI 1 inhalation BID	107 107 106 107 107 106	Patients with persistent asthma that is **uncontrolled** on **high**-dose ICS therapy
FSS-AS-301 (301) 129 Sites	Phase 3, R, DB, placebo-controlled, PG, MC	Fp MDPI 50 mcg 1 inhalation BID Fp MDPI 100 mcg 1 inhalation BID FS MDPI 50/12.5 mcg 1 inhalation BID FS MDPI 100/12.5 mcg 1 inhalation BID Placebo MDPI 1 inhalation BID	129 130 129 129 130	Patients with persistent asthma that required to have a **low-dose or mid-dose** ICS as part of asthma management plan, either as ICS monotherapy or an **ICS/LABA** combination
FSS-AS-30017 (30017) 147 Sites	Phase 3, R, DB, placebo-controlled, PG, MC	Fp MDPI 100 mcg 1 inhalation BID Fp MDPI 200 mcg 1 inhalation BID FS MDPI 100/12.5 mcg 1 inhalation BID FS MDPI 200/12.5 mcg 1 inhalation BID Placebo MDPI 1 inhalation BID	146 146 145 146 145	Patients with persistent asthma that required to have a **mid-dose or high-dose** ICS as part of asthma management plan, either as ICS monotherapy or an **ICS/LABA** combination

Source: Reviewer
Abbreviations: R = Randomized, DB = Double-Blind, OL = Open-Label, PG = Parallel-group, MC = Multicenter, BID = Twice a day

3.2.1.2 Phase 3 studies

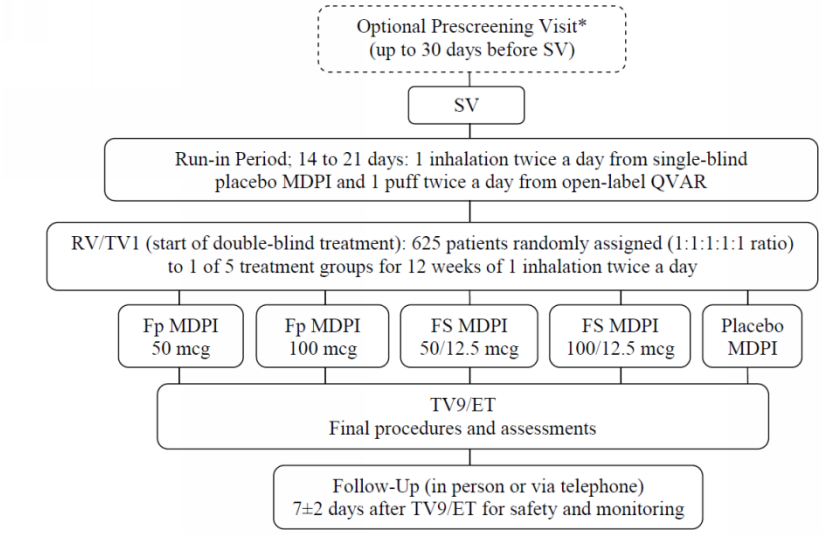
The two 12-week phase 3 efficacy and safety studies, Studies 301 and 30017, served two purposes in the overall development program: to support the approvals of both the ICS monotherapy Fp MDPI and the ICS/LABA combination FS MDPI. By carrying forward the selected 3 doses of Fp monotherapy from the dose-ranging studies, the phase 3 studies included both the Fp monotherapies and their corresponding FS combination of the same ICS strengths with the purpose to evaluate the efficacy and safety of Fp MDPI and the FS MDPI combination product at each selected Fp strength in persistent asthma patients symptomatic despite ICS therapy.

The primary objective of each phase 3 study was to evaluate the efficacy of Fp MDPI and FS MDPI when administered over 12 weeks in patients 12 years and older with persistent asthma. The secondary objectives on efficacy were: to evaluate the efficacy of Fp MDPI and FS MDPI based on patient-reported outcomes and secondary efficacy measures in patients with persistent asthma treated over 12 weeks.

3.2.2 Study design

The four studies were similar in design in that they shared a common overall structure, as illustrated using Study 301 schema (Figure 1) as an example. In general, all studies were comprised of four periods (pre-screening period, run-in period, double-blind treatment, and follow-up period) demarked by four visits (the screening visit (SV), the randomization visit (RV/TV1), the end of study visit (TV9/ET) and the follow-up visit (FU)). For patients whose previous stable asthma treatment regimen included a LABA component, there was an optional prescreening visit (PSV) up to 30 days before the screening visit (SV). For each key design elements, design features of each individual study will be summarized and presented in the order of study numbers to allow easy reference and contrast.

Figure 3. Overall Study Schema (Example study: Study 301)



Source: Applicant's Study 301 Protocol Figure 1.

3.2.2.1 Targeted patients severity level, experimental dose arms and key patient selection criteria

The applicant intended to develop three dose strengths of Fp (low, middle and high) and their corresponding FS combinations for approval. The phase 2 trials included a jointly broad dose range of Fp and selected three doses of Fp (50, 100, and 200 mcg BID) to carry forward into phase 3 studies. Aside from the Fp monotherapy arms, the phase 3 studies also included the corresponding FS arms to evaluate the LABA contribution to the combination. In this program, both the phase 2 dose-ranging part and the phase 3 confirmatory part each included two studies targeting different dose ranges. For each of the four studies, the subject populations were chosen to be representative of the intended patient population. For each study, the targeted patients' previous ICS level, the doses studied, and key patient selection criteria will be described in the following subsections.

3.2.2.1.1 Study 201

Study 201 enrolled patients with persistent asthma whose previous asthma was uncontrolled on non-steroidal maintenance therapy. The trial studied Fp at dose strengths of 12.5, 25, 50, and 100 mcg BID with a placebo control and Flovent Diskus 100 mcg as active control. For dose selection purpose, Flovent Diskus 100 mcg, which is the lowest approved dose for Flovent Diskus as maintenance treatment of asthma in patients aged 12 years and older, was used here as a benchmark for selecting the lowest effective Fp MDPI dose.

Key inclusion criteria at screening included: severity of disease assessed by a best forced expiratory volume in one second ($ppFEV_1$) was required to be 40% - 85% of the predicted normal value; reversibility of disease needed to be demonstrated by a ≥15% reversibility of FEV_1 within 30 minutes following 2-4 inhalations of albuterol/salbutamol inhalation aerosol; current asthma therapy permitted included SABA alone, non-corticosteroidal maintenance therapy, or low-dose ICS. ICS/LABA combinations were not permitted.

3.2.2.1.2 Study 202

Study 202 enrolled patients with severe persistent asthma whose previous asthma was uncontrolled on high dose of ICS (1000 mcg/day of Fp or an equivalent ICS). Of note, for persistent asthma patients who are treated with ICS, the highest recommended dose of Flovent Diskus is 500 mcg BID. The trial studied Fp at dose strengths of 50, 100, 200, and 400 mcg BID with a placebo control and Flovent Diskus 250 mcg BID as an active control. For dose selection purpose, this study was used to select the maximally effective dose of Fp MDPI and at the same time determined the range of effective dose of Fp MDPI as ICS monotherapy. Flovent Diskus 250 mcg, which is the highest approved dose of Flovent Diskus for the maintenance treatment of asthma, was used as the benchmark in this trial.

Key inclusion criteria at the screening visit were similar with those of Study 201 except: reversibility of disease needed to be demonstrated by a ≥12% (instead of 15% as in the other 3 studies) reversibility of FEV_1 within 30 minutes following 2-4 inhalations of albuterol/salbutamol inhalation aerosol; and current asthma therapy included stable high-dose

ICS monotherapy or ICS/LABA combination for at least four weeks. The list of permitted therapies and corresponding daily dose ranges is reproduced in Table 4, which includes dose ranges from all the four studies.

3.2.2.1.3 Study 301

Study 301 enrolled adolescents and adults 12 years of age and older who had persistent asthma and were symptomatic despite low-dose or mid-dose ICS therapy. The study included two sets of Fp and FS pairs at low and mid-dose of Fp: Fp 50 versus FS 50/12.5, Fp 100 versus FS 100/12.5 mcg BID and a placebo control. The study was designed to both evaluate the clinical benefit of adding a LABA to Fp and allow comparisons of Fp monotherapy or FS combination over placebo.

Key criteria for inclusion at screening included: the patient had persistent asthma with a $ppFEV_1$ between 40% and 85% per NHANES III; the patient had demonstrated at least 15% reversibility and at least a 200 mL increase from baseline FEV_1 (patients age 18 and older) within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol HFA MDI; and the patient was required to have a low-dose or mid-dose ICS as part of their asthma management plan, either as ICS monotherapy or an ICS/LABA combination for at least 1 month before providing information consent. The list of permitted therapies and corresponding daily dose ranges is reproduced in Table 4.

3.2.2.1.4 Study 30017

Study 30017 enrolled adolescents and adults 12 years of age and older who had persistent asthma and were symptomatic despite ICS therapy. The study included two sets of Fp and FS pairs at middle and high doses of Fp: Fp 100 versus FS 100/12.5, Fp 200 versus FS 200/12.5 mcg BID and a placebo control. The study was designed to both evaluate the clinical benefit of adding a LABA to Fp and allow comparison of Fp monotherapy or FS combination over placebo.

Key criteria for inclusion at screening were similar to those of Study 301 except for the current asthma therapy criterion. While patients were also required to have an ICS as part of their asthma management plan, either as ICS monotherapy or as an ICS/LABA for a minimum of 1 month before providing informed consent, the qualifying doses ranges of ICS were given only a lower bound to allow for enrollment of patients with mid- to high-dose of ICS, as contrast to the ranges given in Study 301 of a fixed range of low to mid-dose of ICS (Table 4).

Table 4. Qualifying ICS/LABA doses by study

Qualifying ICS (as ICS or ICS/LABA)	Dosage range (mcg/day)			
	Study 201*	Study 202	Study 301	Study 30017
Fluticasone HFA		≥880	88-500	>200
Fluticasone DPI	200	≥1000	50-500	>200
Budesonide HFA (80 or 160 mcg/dose)			80-480	>160
Budesonide HFA (100 or 200 mcg/dose)			100-400	>200
Budesonide DPI		≥1600	90-720	>200
Beclomethasone dipropionate DPI		≥2000		
Beclomethasone dipropionate HFA small particle (eg,		≥640	40-240	>160

Qualifying ICS (as ICS or ICS/LABA)	Dosage range (mcg/day)			
	Study 201*	Study 202	Study 301	Study 30017
QVAR 40 or 80 mcg/dose)				
Beclomethasone dipropionate HFA large particle (eg Beclate or Clenil Modulate, 50 or 100 mcg/dose)		≥2000	50-400	>300
Mometasone DPI (110 or 220 mcg/dose)		≥880	110-440	>220
Mometasone pMDI (100 or 200 mcg/dose)			200-400	>200
Ciclesonide HFA		≥640	80-240	>160
Flunisolide pMDI		≥2000	320-480	>320
Fluticasone/salmeterol HFA			90-500	>200
Fluticasone/salmeterol DPI			100-500	>200
Budesonide/formoterol MDI			80-480	>160
Budesonide/formoterol DPI			100-400	>200
Triamcinolone acetonide		≥2000		

Source: Reproduced from study protocols.
Note:
* Study 201 permitted asthma therapies required low-dose ICS with 100 mcg Fp BID or therapeutic equivalent.
When a qualifying ICS was not listed in a certain study, the corresponding cell is greyed out.

3.2.2.2 Study Procedures

This section covers the common study procedures across the four studies. When there are design features unique to a certain study, it will be covered in the following sections where individual studies are described.

3.2.2.2.1 Pre-screening Period

Across the four studies, for patients treated with ICS/LABA combination therapy prior to enrollment, there was a period for LABA discontinuation or ICS/LABA switch to ICS post PSV and 1 week prior to the SV, or a washout period for patients who were taking protocol prohibited medications. The patient's previous ICS/LABA asthma treatment was switched to an ICS regimen that was consistent with the ICS component of the patient's ICS/LABA. That is, one week prior to the SV, all patients were either on nonsteroidal therapy or on an ICS therapy.

Table 5 Pre-Screening and Run-In period

Medication Category	FpS-AS-301	FpS-AS-202	FSS-AS-301	FSS-AS-30017
Previous Asthma Treatment				
	Patients with persistent asthma that is **uncontrolled** on **non-steroidal** therapy	Patients with persistent asthma that is **uncontrolled** on **high**-dose ICS therapy	Patients with persistent asthma that required to have a **low-dose or mid-dose** ICS as part of asthma management plan, either as ICS monotherapy or an **ICS/LABA** combination	Patients with persistent asthma that required to have a **mid-dose or high-dose** ICS as part of asthma management plan, either as ICS monotherapy or an **ICS/LABA** combination

Medication Category	FpS-AS-301	FpS-AS-202	FSS-AS-301	FSS-AS-30017
Prior to Screening				
LABA	NA	LABA Discontinuation	LABA Discontinuation	LABA Discontinuation
Run-in Period				
Previous ICS (or other)	**Continue** NCS or ICS	Discontinue	Discontinue	Discontinue
Treatment received	**Single-blind**: 1 inhalation of **placebo** MDPI BID	**Single-blind**: 1 inhalation of **placebo** MDPI BID	**Single-blind**: 1 inhalation of **placebo** MDPI BID **Open-label**: 1 puff QVAR 40 mcg HFA MDI BID	**Single-blind**: 1 inhalation of Fp MDPI 50 mcg BID

Source: Reviewer. Summarized from study protocols.

3.2.2.2.2 Run-in Period

The purpose of the run-in period was to complete baseline safety evaluations, establish patient compliance, and to obtain baseline measures of asthma symptoms, rescue medication use, and peak expiratory flow (PEF) values. The four studies were different with respect to how previous treatments were handled, the run-in treatment regimen, and the blinding scheme (Table 5).The asthma diagnosis was required to be in accordance with the National Institutes of Health (NIH) definition.

3.2.2.2.3 Double-blind Period

At randomization, patients who met all of the inclusion/exclusion criteria were randomized at equal ratio into one of the treatment arms for the duration of the treatment period. All treatments were administered twice daily in a double-blind manner (aside from open-label active control in the phase 2 studies). All subjects continued albuterol/salbutamol HFA-MDI for use on an as needed basis for the relief of asthma symptoms throughout the treatment period.

3.2.3 Efficacy Endpoints

3.2.3.1 Phase 2 Studies

Corresponding to the primary objective of evaluating the dose response, efficacy and safety of Fp MDPI, the primary endpoint in Studies 201 and 202 was change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV_1 **over** the 12-week treatment period. This measure will be referred to from now on as *trough FEV_1*.

Secondary endpoints included change from baseline measures of other lung function variables: a) weekly average of daily trough morning PEF **over** the 12-week treatment period, b) weekly average of daily trough evening PEF over the 12-week treatment period, c) the percentage of

rescue-free 24-hour periods during the 12-week treatment period, and time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period.

3.2.3.2 Phase 3 Studies

With the common primary objective being to evaluate the efficacy of both Fp MDPI and FS MDPI when administered over 12 weeks, Studies 301 and 30017 both used two primary endpoints: change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV_1 **at** Week 12; and standardized baseline-adjusted area under the effect curve for forced expiratory volume in 1 second from time zero to 12 hours post-dose (SBA FEV_1 $AUEC_{0-12h}$) **at** Week 12. For each study, the SBA FEV_1 $AUEC_{0-12h}$ endpoint was assessed for a subset of 312 subjects who performed post-dose serial spirometry. This measure will be referred to from now on as *SBA FEV_1 $AUEC_{0-12h}$*.

Regarding the time point selection for trough FEV_1, the applicant originally proposed a standardized baseline-adjusted trough morning FEV1 area under the effect curve **over** the 12 week treatment period (SBA FEV_1 $AUEC_{0-12wk}$) calculated using the trapezoidal rule through a phase 3 study draft SAP submission. Upon review of the SAP, FDA statistical review team recommended a landmark endpoint, such as change from baseline in trough FEV_1 **at** week 12, which is commonly accepted in asthma trials as an appropriate measure of long term control.

Secondary efficacy endpoints evaluated efficacy of Fp MDPI and FS MDPI on additional spirometry parameters, patient reported outcomes, time to event endpoints and rescue medication use. They included: change from baseline measures of a) weekly average of the daily trough morning PEF **over** the 12-week treatment period, b) weekly average of the daily trough evening PEF **over** the 12-week treatment period, c) weekly average of the total daily asthma symptom score **over** Weeks 1 to 12, d) weekly average of total daily use of albuterol/salbutamol inhalation aerosol **over** Weeks 1 to 12, e) Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) score at Week 12 or at *Endpoint*, and time to event measures of f) time to patient withdrawal for worsening asthma during the 12-week treatment period, and g) time to 15% and 12% improvement from baseline in FEV_1 post-dose at TV1. Note that *Endpoint* was used in this program to denote the derived efficacy variable for Week 12 with last observation carried forward (LOCF) imputation for missing data.

3.2.4 Statistical Methodologies

3.2.4.1 Analysis Populations and (Data) Sets

Across the four studies, the applicant defined six populations/analysis sets: Intent-to-Treat (ITT) population, Full Analysis Set (FAS), Per-Protocol (PP) Population, Safety Population, Pharmacokinetic (PK) Analysis Set for the phase 2 dose-ranging trials, and the Serial Spirometry Subset (SSS) for the phase 3 studies. As this is an efficacy focused review, the definitions of the ITT population, FAS and SSS sets and the efficacy analyses they supported are described here.

3.2.4.1.1 ITT Population

The ITT population included all randomized subjects. Subjects were assigned based upon the treatment to which they were randomized regardless of treatment they actually received. While by its definition the ITT population in this program included all patients and was the appropriate population to support the estimation of the de facto or intent-to-treat estimand (i.e., the difference in outcomes at Week 12 in all randomized patients regardless of adherence), the study protocols designated it as a supportive population for efficacy analyses. Importantly, the ITT population was used for sensitivity analyses.

3.2.4.1.2 Full Analysis Set

The FAS included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 post-baseline trough FEV_1 assessment. In addition, pulmonary function test data collected within a 7-day window of visits in which patients took any prohibited asthma medications that were deemed as significantly confounding were excluded from analyses on the FAS. The FAS was chosen by the applicant as the primary analysis set for efficacy analyses.

3.2.4.1.3 Serial Spirometry Subset

In each of Studies 301 and 30017, a subset of randomized subjects who performed post-dose serial spirometry was used for assessment of the primary endpoint SBA FEV_1 $AUEC_{0\text{-}12h}$ at Week 12 and for other post-dose spirometry parameters. While the SSS is a subset of the randomized population, there were SSS-ITT and SSS-FAS sets nested within the SSS, defined in the same way as in the full randomized population.

3.2.4.2 Analysis Methods

For the primary efficacy endpoints, this section describes and discusses the primary analysis and sensitivity analysis methods planned and performed by the applicant. Due to the dual purposes of each trial, supporting both dose-ranging and efficacy testing of Fp MDPI over placebo in the phase 2 studies, and supporting both efficacy testing of FS MDPI over Fp MDPI and Fp MDPI over placebo in the phase 3 studies, primary analyses under each study were performed following a corresponding planned testing hierarchy for the purpose of controlling the type I error probability across the multiple comparisons. These hierarchical testing procedures will be described as necessary while the main focus of the subsections will be on discussion of primary analysis methods.

Due to their long-term nature, without any pre-planned missing data prevention efforts, it is expected that pulmonary trials like the trials under this program will incur a non-trivial to substantial amount of missing data. In a randomized controlled trial, the benefit of randomization to balance out known and unknown factors among the subjects may be reduced and treatment group comparisons may be biased by this missingness. At the trial design and conduct stage, the applicant did not plan to minimize the amount of missing data and stopped collecting information on key outcomes on subjects who discontinued their protocol specified treatment. As each statistical method for handling missing data is associated with assumptions on the mechanism of missingness, which are untestable, the applicant planned sensitivity analyses to assess the degree to which the treatment effects relied on the assumptions. The subsections

below describe the planned primary analysis methods, their related missing data handling methods, the underlying assumptions on the missingness mechanism, and corresponding planned sensitivity analyses.

3.2.4.2.1 Phase 2 Studies

3.2.4.2.1.1 Primary Analysis Method

In each of Studies 201 and 202, the primary endpoint was the change from baseline trough FEV_1 **over** the 12-week treatment period. The primary analysis was performed using a mixed model for repeated measures (MMRM) with covariates baseline trough FEV_1, gender, age, visit, treatment, and visit-by-treatment interaction based on the FAS dataset. For the four dose levels, a fixed-sequence multiple testing procedure was used to control the overall Type I error rate at the 0.05 level for the list of comparisons of interest. The hierarchy of testing (Table 6) consisted of two steps: first to test the linearity of dose response, where the logarithm of dose was defined as log(dose+1) to accommodate the case of a zero dose (placebo) and the response was the time averaged change from baseline trough FEV_1 over the treatment period estimated with the MMRM analysis; upon a statistically significant result in the first step, the second step was to test and estimate pairwise comparisons of each Fp MDPI dose over placebo with a two-sided test at the 0.05 level of significance starting with the highest Fp dose in the study. For the sequence of Fp MDPI doses, the testing was performed until a failed one stopped the procedure or all the doses were tested. The tests for trend and comparisons of Fp MDPI doses over placebo were all based on the FAS with Flovent Diskus data excluded. An unstructured covariance matrix was first used for model fitting, and upon a failure of the iterative procedure to converge, a compound symmetry covariance structure was used.

Comparisons of Fp MDPI dose groups with the Flovent Diskus group in trough FEV_1 over the 12-week treatment period was also examined based on MMRM analyses similar to the primary analyses. These analyses were carried out on the FAS dataset including the Flovent Diskus data. There was no adjustment for multiplicity in these comparisons.

Table 6. Phase 2 Studies: multiple testing procedure for comparisons on primary endpoint

	Test	
	Study 201	Study 202
Log-dose Linearity Test	To test the linear in log-dose time-averaged response trend over doses of Fp MDPI at 0, 12.5, 25, 50, 100 mcg BID	To test the linear in log-dose time-averaged response trend over doses Fp MDPI at 0, 50, 100, 200, 400 mcg BID
Pair-wise Comparison	Fp MDPI 100 mcg BID vs. Placebo	Fp MDPI 400 mcg BID vs. Placebo
	Fp MDPI 50 mcg BID vs. Placebo	Fp MDPI 200 mcg BID vs. Placebo
	Fp MDPI 25 mcg BID vs. Placebo	Fp MDPI 100 mcg BID vs. Placebo
	Fp MDPI 12.5 mcg BID vs. Placebo	Fp MDPI 50 mcg BID vs. Placebo

Source: Reviewer

3.2.4.2.1.2 Sensitivity Analysis

No imputation for missing data was planned based on two assumptions: the extent of missing data was predicted to be low, and by assuming the missing at random (MAR) missingness mechanism, it is valid to draw inference about treatment effects with maximum likelihood method based on incomplete observed data.

There were no pre-planned sensitivity analyses to test the robustness of the test results to violations in the assumed MAR missingness mechanism. Instead, supportive analyses were planned for the primary comparisons. Among them, there was a comparison of Fp MDPI with placebo **after** 12 weeks of therapy based on MMRM; and a comparison of Fp MDPI with placebo **after** 12 weeks of therapy based on ANCOVA. The ANCOVA analyses were performed on the modified datasets with missing data imputed with last observation carried forward (LOCF) method. The approach with MMRM estimates **at** Week 12 is consistent with time point selection recommended by the FDA as discussed earlier; however, this approach also assumes MAR missing data and therefore does not target the robustness of results to violation of MAR. In addition, the single imputation method LOCF has two main drawbacks: there is no scientific evidence that the last observed FEV_1 value will remain unchanged till the end of study; and the single imputation scheme does not properly reflect the uncertainty around the imputed missing data and results in an underestimation of the standard errors for treatment effects. With these problems, these two supportive analyses were not considered sufficient sensitivity analysis.

Therefore, for this review, tipping point analyses for trough FEV_1 over the 12-week treatment period similar to the approach used in phase 3 sensitivity analyses (described in more detail below) were conducted by this reviewer to check the robustness of positive study conclusions to violations of the assumed MAR.

3.2.4.2.2 Phase 3 Studies

3.2.4.2.2.1 Primary Analyses Methods

Studies 301 and 30017 employed two efficacy endpoints: trough FEV_1 **at** Week 12 and SBA FEV_1 $AUEC_{0\text{-}12h}$ **at** Week 12.

Analyses of trough FEV_1 were performed on the modified baseline observation carried forward imputed (described in detail later) FAS dataset using an ANCOVA model with covariates of baseline trough morning FEV_1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment. The baseline trough FEV_1 was the average of the 2 pre-dose FEV_1 measurements (30 minutes and 10 minutes) at the randomization visit.

The SAB FEV_1 $AUEC_{0\text{-}12h}$ endpoint was analyzed using an ANCOVA model with covariates of treatment, sex, (pooled) center, previous therapy (ICS or ICS/LABA), age, and baseline FEV_1. The primary analyses were conducted on the FAS population with LOCF used to handle missing data.

During the EOP2 meeting and based on reviews of the phase 3 study SAPs, FDA statistical reviewers gave comments on study design and conduct regarding minimization of missing data. The applicant's data collection plan didn't incorporate FDA's comments (EOP 2 meeting minutes, March 17, 2014) that they should continue to collect efficacy data even if patients discontinue treatment to allow for an assessment of the treatment effect in the entire study population regardless of patients' adherence to treatment. Instead, across the studies, patients who discontinued study medication also dropped out of study. The collected data therefore do not support a reliable evaluation of the de facto estimand.

The applicant's primary data analysis of trough FEV_1 at week 12 was based on the so called baseline observation carried forward method (as in the applicant's document). I will use the notation m-BOCF to differentiate it from the typical BOCF method, with *m* denoting modified. The m-BOCF method imputed missing values with either baseline data or the last observed post baseline FEV_1 measurement (LOCF): when the last observed post baseline measurement was worse than baseline, that measurement was used for Week 12 analysis; when the last observed post baseline measurement was better than the baseline value, the baseline value was used for Week 12 analysis.

The applicant did not clearly state what estimand was being targeted by the proposed primary analysis. Furthermore, we discussed the problems with LOCF earlier. For the two phase 3 studies, the m-BOCF imputation relies on either BOCF or LOCF. While the m-BOCF method may seem to be more conservative than LOCF, it still inherits the problems with single imputation methods as commented in the National Research Council Report on Prevention and Treatment of Missing Data in Clinical Trials (NRC Panel on Handling Missing Data in Clinical Trials, 2010).

> *Two problems with single imputation are (1) inferences (tests and confidence intervals) based on the filled-in data can be distorted by bias if the assumptions underlying the imputation method are invalid, and (2) statistical precision is overstated because the imputed values are assumed to be true.*

3.2.4.2.2.2 Sensitivity Analysis Methods

The applicant planned and conducted two types of sensitivity analyses regarding the trough FEV_1 endpoint: 1) a tipping point analysis by assuming MAR in the placebo group and MNAR in the active treatment groups and 2) a cumulative proportion of responder analysis. This subsection describes the rationale and proposed algorithm of each method.

3.2.4.2.2.2.1 Trough FEV_1 - Tipping Point Analysis

The purpose of a tipping point analysis is to evaluate the sensitivity of results to violations in missing data assumptions by finding out the size of the change from MAR that tips statistically significant results to become not statistically significant. In the phase 3 studies, the trough FEV_1 was measured at baseline and Weeks 1, 2, 3, 4, 6, 8, 10 and 12. In the applicant's proposed tipping point analysis, trough FEV_1 missing data from Week 1 to Week 12 was imputed with multiple imputation. For the change from baseline in trough FEV_1 over the 12-week treatment periods, it was performed in steps:

1. A multiple imputation step with SAS PROC MI performed on the observed trough FEV_1 data for ITT subjects from baseline to Week 12.
    a. For each subject with a non-monotone missing pattern, Markov-Chain Monte Carlo (MCMC) was used to impute their missing values 10 times. Ten datasets with monotone missing pattern were generated.
    b. Based on the monotone missing patterned datasets generated by Step 1.a, all missing post-baseline data were imputed sequentially with covariates constructed from their corresponding sets of preceding trough FEV_1 assessments plus treatment arm using the regression method.
2. For treatment groups assumed MAR, no shift was added on the imputed trough FEV_1 values. For the active treatment groups assumed MNAR, a positive constant shift was subtracted from the imputed trough FEV_1 values. The shift started at 0 and was increased in a repeated process until the treatment effect is no longer significant at 0.05 level in step 5.
3. For each of the 10 complete (they may not be, will be discussed later) datasets after imputation, the MMRM model was fitted to estimate treatment differences and corresponding p-values.
4. The 10 sets of MMRM results were combined with SAS PROC MIANALYZE, which combines estimates using Rubin's rule.
5. Steps 2 to 4 were repeated with different values of the shift parameter until the tipping point was reached.

3.2.4.2.2.2.2 Trough FEV_1 - Cumulative Responder Plot (CRP) Analysis

Cumulative responder curves (i.e., empirical distribution functions) on change from baseline in trough FEV_1 at Week 12 were developed as follows. Each patient was classified as having been successfully or unsuccessfully treated according to whether or not the patient reached a certain threshold for the change from baseline in trough FEV_1 at the study primary time-point (Week 12). This dichotomization of the change from baseline in trough FEV_1 was repeated across a range of possible thresholds, in this case from minimum of the observed change from baseline value across study treatment arms to the maximum. Patients with missing change from baseline trough FEV_1 data at the primary time-point were classified as unsuccessfully treated for all thresholds. In the continuous responder plot, the x-axis displays the thresholds required to classify a patient as a successfully treated patient. Then a corresponding rank sum statistic based on Mann-Whitney-Wilcoxon test was calculated on the modified data. That is, output of the cumulative responder plot is in the form of an empirical distribution function plot and a corresponding p-value for a test comparing ranks of any of the two distributions of interest.

In a cumulative responder plot constructed as above, it is anticipated that for each treatment arm there is an initial drop from 100% to the completer rates of that arm on the y-axis, corresponding to the proportions of patients who dropped out in that arm since patients with missing change from baseline data were classified as unsuccessfully treated for all thresholds.

3.2.4.2.2.2.3 SBA FEV_1 $AUEC_{0\text{-}12h}$ - Sensitivity Analysis

For the SBA FEV_1 $AUEC_{0\text{-}12h}$ endpoint, upon which there were two scheduled post-baseline assessments (Week 1 and Week 12), the primary analysis method was an ANCOVA on Week 12 data with LOCF imputation. For this endpoint, the applicant considered LOCF an MAR type of imputation and BOCF an MNAR type of imputation and planned a sensitivity analysis with BOCF for missing data due to withdrawal caused by worsening of asthma and LOCF for the rest of the missing data.

As discussed previously, being a primary analysis method, both BOCF and LOCF are single imputation methods with which the estimated effects may be biasedand the related precision overestimated. While both LOCF and BOCF imputation assume MNAR missing data, they evaluate only a single alternative assumption in the MNAR space and therefore do not systematically explore the space of plausible alternative missing data assumptions. A tipping point sensitivity analysis is such a systematic searching tool; and a tipping point analysis similar to the one planned for the trough FEV_1 endpoint would ideally have also been performed for the SBA FEV_1 $AUEC_{0\text{-}12h}$ comparisons. However, such analyses were not carried out by the applicant. Given the findings of the tipping point analyses for the primary trough FEV1 endpoint, and the supportive nature of the SBA FEV_1 $AUEC_{0\text{-}12h}$ evaluation, we did not carry out additional sensitivity analyses in this review.

3.2.4.3 Multiplicity Control

3.2.4.3.1 Phase 2 Studies

Tests and multiplicity control for the multiple primary endpoint comparisons were described earlier. Upon demonstration of the significance of all primary comparisons (Table 6), testing of secondary efficacy variables at the 4 dose levels proceeded in the sequential manner as illustrated in Table 7 for Study 201. While this procedure allowed for type I error control within each endpoint (row-wise) or each dose comparison over placebo (column-wise), it did not control the overall Type I error.

Table 7. Study 201: sequence of testing secondary variables at dose levels

Endpoint	Hypothesis Testing				
	Overall Trend Test	100 mcg BID vs Placebo	50 mcg BID vs Placebo	25 mcg BID vs Placebo	12.5 mcg BID vs Placebo
Change from baseline in weekly average of daily trough AM PEF over the 12-week Treatment Period	→	↓→	↓→	↓→	↓
Change from baseline in weekly average of daily PM	→	↓→	↓→	↓→	↓

PEF over the 12-week Treatment Period					
Change from baseline in the percentage of rescue-free 24-hour periods during the 12-week Treatment Period		↓→	↓→	↓→	↓
Time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week Treatment Period		→	→	→	□

Source: Study SAP

3.2.4.3.2 Phase 3 Studies

A fixed-sequence multiple testing procedure was used to control the overall Type I error rate at the two-sided 0.05 level for the two primary endpoints at different doses in the order described in Table 8. The plan was that if all the primary comparisons were significant, then inferential testing would be performed for the secondary efficacy endpoints for the two study drugs (FS MDPI and Fp MDPI) and at two strength levels (Fp 50 mcg BID and Fp 100 mcg BID) in the order described below for Fp MDPI (Table 9) and FS MDPI (Table 10) for study 301. Control procedures were similar in study 30017, only at different dose levels. FDA provided the following comments on the plan:

> *As studies FSS-AS-301 and FSS-AS-30017 are designed to support two NDAs, it is acceptable to separate the sequential testing strategies for each NDA. However, we note that your proposed sequential testing procedure within each NDA does not control the overall type I eror at 0.05 across the multiple secondary endpoints and multiple dose comparisons.*

The applicant did not modify the approach in response to the FDA comments, so the results will need to be interpreted in the context of a multiple testing procedure that does not appropriately control the Type I error probability across all primary and secondary endpoint comparisons.

Table 8. Phase 3 studies: multiple testing procedures for primary endpoints

Endpoint	Drug	Dose Comparison	
		Study 301	Study 30017
SBA FEV_1 $AUEC_{0\text{-}12h}$	FS vs. Fp	100/12.5 vs. 100	200/12.5 vs. 200
		50/12.5 vs. 50	100/12.5 vs. 100
	FS vs. Placebo	100/12.5 vs. Placebo	200/12.5 vs. Placebo
		50/12.5 vs. Placebo	100/12.5 vs. Placebo
Δ Trough FEV_1	FS vs. Placebo	100/12.5 vs. Placebo	200/12.5 vs. Placebo
		50/12.5 vs. Placebo	100/12.5 vs. Placebo
	Fp vs. Placebo	100 vs. Placebo	200 vs. Placebo
		50 vs. Placebo	100 vs. Placebo

Source: Reviewer

Table 9. Study 301: sequence of testing secondary endpoints for Fp MDPI

Secondary Endpoint	Hypothesis Testing	
	Fp MDPI 100 mcg vs. Placebo	Fp MDPI 50 mcg vs. Placebo
[A] Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓
[B] Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 to 12	↓ →	↓
[C] Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutomol inhalation aerosol (number of inhalations) over weeks 1 to 12	↓ →	↓
[D] Time to patient withdrawal for worsening asthma during the 12-week treatment period	↓ →	↓
[E] Change from baseline in the AQLQ(S) (patients ≥18 years of age only) score at endpoint	→	

Source: Study SAP

Table 10. Study 301: sequence of testing secondary endpoints for FS MDPI

Secondary Endpoint	Hypothesis Testing				
	FS MDPI 100/12.5 mcg vs. Placebo	FS MDPI 50/12.5 mcg vs. Placebo	FS MDPI 100/12.5 mcg vs. Fp MDPI 100 mcg	FS MDPI 50/12.5 mcg vs. Fp MDPI 50 mcg	FS MDPI 50/12.5 mcg vs. Fp MDPI 100 mcg
[A] Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓ →	↓ →	↓ →	↓
[B] Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 to 12	↓ →	↓ →	↓ →	↓ →	↓
[C] Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutomol inhalation aerosol (number of inhalations) over weeks 1 to 12	↓ →	↓ →	↓ →	↓ →	↓
[D] Time to patient withdrawal for worsening asthma during the 12-week treatment period	↓ →	↓ →	↓ →	↓ →	↓
[E] Change from baseline in the AQLQ(S) (patients ≥18 years of age only) score at endpoint	→	→	→	→	

Source: Study SAP

3.2.4.4 Subgroup analysis

Subgroup analyses were performed for the co-primary efficacy endpoints by sex (male and female), by age group (12 to 17, 18 to 64, ≥65 years), by race (white, black, and other), and by region (US and non-US).

3.2.5 Overall Demographic and Baseline Characteristics

An overview of demographics and clinically important baseline variables across the four studies is given in Table 11. In line with the program rationale, the study population differed between the low-(Study 201), low- to medium-(Study 301), medium- to high-(Study 30017), and high-dose (Study 202) ICS studies. Subjects in the high-dose study, Study 202, tended to be older, had less adolescent subjects (1%), and had lower baseline FEV_1 and percentage predicted FEV_1, while subjects in the low-dose or low- to medium-dose studies, Study 201 and Study 301, tended to be younger, had more adolescent subjects, and had higher baseline FEV_1 and percentage predicted FEV_1; Study 30017 values fell in between. There were higher proportions of female than male subjects in each study. The majority of subjects were whites in each study. Studies 201 and 202 didn't report on subjects' previous asthma therapy. In Study 301, the proportion of subjects treated with ICS/LABA combination products at screening (29%) was lower than that of Study 30017 (45%).

Table 11. Summary of demographics and select baseline characteristics by study (ITT)

		Uncontrolled on Low-Dose ICS	Uncontrolled on High-Dose ICS	Low or Medium-Dose ICS	Medium or High-Dose ICS
		Study 201 N=622	Study 202 N=640	Study 301 N=647	Study 30017 N=728
Sex	F	358 (58%)	379 (59%)	364 (56%)	439 (60%)
	M	264 (42%)	261 (41%)	283 (44%)	289 (40%)
Age	Mean (SD)	39.9 (15.87)	49.0 (13.46)	41.5 (17.60)	44.7 (15.95)
	Median (Min, Max)	40.0 (12, 81)	51.0 (12, 83)	43.0 (12, 86)	46.5 (12, 84)
Age Group	12-17 Years	52 (8%)	9 (1%)	86 (13%)	45 (6%)
	18-64 Years	535 (86%)	563 (88%)	494 (76%)	608 (84%)
	65+ Years	35 (6%)	68 (11%)	67 (10%)	75 (10%)
Country	United States	433 (70%)	298 (47%)	360 (56%)	427 (59%)
	Other Countries	189 (30%)	342 (53%)	287 (44%)	301 (41%)
Race	White	527 (85%)	565 (88%)	515 (80%)	588 (81%)
	Black or African American	81 (13%)	65 (10%)	113 (17%)	120 (16%)
	Other Races	14 (2%)	10 (2%)	19 (3%)	20(3%)
Previous Asthma Therapy	ICS			461 (71%)	399 (55%)
	ICS/LABA			186 (29%)	329 (45%)

		Uncontrolled on Low-Dose ICS	Uncontrolled on High-Dose ICS	Low or Medium-Dose ICS	Medium or High-Dose ICS
		Study 201 N=622	Study 202 N=640	Study 301 N=647	Study 30017 N=728
Qualifying airway reversibility (%) at Screening	N	622	547	647	728
	Mean (SD)	26.9 (13.25)	28.9 (19.70)	29.9 (17.40)	29.5 (14.96)
	Median (Min, Max)	22.4 (3.9, 118.3)	21.2 (-8.4, 175.0)	24.0 (10.0, 133.0)	25.0 (2.0, 132.0)
Baseline FEV_1 (L)	N	619	637	641	722
	Mean (SD)	2.2 (0.64)	2.0 (0.59)	2.2 (0.60)	2.1 (0.63)
	Median (Min, Max)	2.1 (0.8, 4.3)	1.9 (0.7, 4.6)	2.1 (0.8, 4.1)	2.0 (0.8, 4.1)
Percent Predicted FEV_1 (%) at Screening	N	622	628	641	722
	Mean (SD)	66.0 (11.16)	63.6 (11.32)	67.5 (10.61)	65.2 (10.73)
	Median (Min, Max)	67.2 (40.0, 94.8)	63.3 (26.3, 92.2)	69.0 (41.0, 92.0)	66.0 (40.0, 85.5)

Source: Reviewer

3.2.6 Overall Patient Disposition

Across the four studies, patients who discontinued study medication also dropped out of the study. This approach led to considerable dropout, especially in the phase 2 studies. The protocols pre-specified reasons that a subject would withdraw or to be withdrawn. While some of the primary reasons for withdrawal were named differently between the phase 2 studies and phase 3 studies, they can be generally grouped into the categories: Adverse Event, Lack of Efficacy, Compliance, and Administrative Reasons. Table 12 is provided to facilitate comparison of the disposition rates across studies.

Table 12. Summary of disposition by study (ITT)

	Uncontrolled on Low-Dose ICS	Uncontrolled on High-Dose ICS	Low or Medium-Dose ICS		Medium or High-Dose ICS	
	Study 201	Study 202	Study 301	Study 301 SSS	Study 30017	Study 30017 SSS
Randomized	622	640	647	312 (100%)	728	312 (100%)
ITT	622 (100%)	640 (100%)	647 (100%)	312 (100%)	728 (100%)	312 (100%)
Full Analysis set	611 (98%)	630 (98%)	640 (99%)	312 (100%)	720 (99%)	312 (100%)
Completer	483 (78%)	459 (72%)	602 (93%)	294 (94%)	650 (89%)	277 (89%)
Non-Completer	139 (22%)	181 (28%)	45 (7%)	18 (6%)	78 (11%)	35 (11%)
Adverse Event						
Adverse Event	5 (<1%)	5 (<1%)	12 (2%)	5 (2%)	8 (1%)	4 (1%)
Lack of Efficacy						

	Uncontrolled on Low-Dose ICS	Uncontrolled on High-Dose ICS	Low or Medium-Dose ICS		Medium or High-Dose ICS	
	Study 201	Study 202	Study 301	Study 301 SSS	Study 30017	Study 30017 SSS
Met Stopping Criteria for Worsening Asthma	54 (9%)	112 (18%)				
Lack of Efficacy			6 (<1%)	3 (<1%)	9 (1%)	6 (2%)
Disease Progression			4 (<1%)	2 (<1%)	24 (3%)	12 (4%)
Compliance						
Protocol Violation	38 (6%)	45 (7%)	3 (<1%)	2 (<1%)	6 (<1%)	1 (<1%)
Non-Compliance to Study Medication	2 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Administrative						
Applicant Required Subject to Be Withdrawn	11 (2%)	2 (<1%)				
Physician Decision	2 (<1%)	4 (<1%)				
Withdrawal by Subject	19 (3%)	10 (2%)	9 (1%)	5 (2%)	19 (3%)	9 (3%)
Lost To Follow-up	6 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)
Pregnancy	2 (<1%)	0	0	0	1 (<1%)	1 (<1%)
Other			6 (<1%)	0	6 (<1%)	0

Source: Reviewer

3.2.7 Results by Study

3.2.7.1 Dose-ranging study - Study 201

3.2.7.1.1 Study 201 – Demographics, Baseline Characteristics, and Disposition

Study 201 evaluated the dose response, efficacy and safety of Fp MDPI at doses of 12.5, 25, 50 and 100 mcg BID versus placebo for 12 weeks in adolescent and adult subjects with persistent asthma uncontrolled on nonsteroidal therapy. Flovent Diskus 100 mcg BID was included for assay sensitivity and to allow assessment of the relative magnitude of response of doses of Fp MDPI compared with Flovent Diskus 100 mcg BID.

Among the 622 subjects included in the ITT population, demographics and baseline disease characteristics were similar across the six treatment groups (Table 13). There was a higher percentage of females (58%) than males (42%). The mean age was 39.3 years with 86% adult subjects (18-64 years of age). This was a global trial with US subjects comprising 70% of the total population. The majority of subjects were white (85%). All subjects had to demonstrate reversibility of disease and the mean reversibility was 26.9% at screening. Mean percentage predicted FEV_1 was 66% at screening and mean baseline FEV_1 was 2.2 L.

Table 13. Study 201: Demographic and Baseline Characteristics (ITT Population)

		Fp MDPI				Placebo MDPI BID	Flovent Diskus 100mcg BID	Total
		12.5mcg BID	25mcg BID	50mcg BID	100mcg BID			
	Category	103	104	104	103	104	104	622
Sex	F	57 (55%)	63 (61%)	60 (58%)	60 (58%)	55 (53%)	63 (61%)	358 (58%)
	M	46 (45%)	41 (39%)	44 (42%)	43 (42%)	49 (47%)	41 (39%)	264 (42%)
Age (Years)	Mean (SD)	41.0 (16.94)	42.4 (16.02)	39.1 (16.06)	36.9 (15.34)	39.7 (15.28)	40.0 (15.34)	39.9 (15.87)
	Median (Min, Max)	42.0 (12, 74)	45.0 (12, 78)	41.0 (12, 72)	35.0 (12, 73)	38.0 (12, 77)	38.0 (12, 81)	40.0 (12, 81)
Age Group	12-17 Year	10 (10%)	7 (7%)	14 (13%)	9 (9%)	5 (5%)	7 (7%)	52 (8%)
	18-64 Year	85 (83%)	90 (87%)	86 (83%)	88 (85%)	93 (89%)	93 (89%)	535 (86%)
	65+ Years	8 (8%)	7 (7%)	4 (4%)	6 (6%)	6 (6%)	4 (4%)	35 (6%)
Country	United States	68 (66%)	70 (67%)	76 (73%)	80 (78%)	69 (66%)	70 (67%)	433 (70%)
	Ukraine	18 (17%)	19 (18%)	17 (16%)	11 (11%)	14 (13%)	17 (16%)	96 (15%)
	Hungary	5 (5%)	4 (4%)	4 (4%)	4 (4%)	11 (11%)	2 (2%)	30 (5%)
	Bulgaria	5 (5%)	7 (7%)	4 (4%)	3 (3%)	6 (6%)	4 (4%)	29 (5%)
	Israel	3 (3%)	0	0	4 (4%)	1 (<1%)	4 (4%)	12 (2%)
	Poland	2 (2%)	0	2 (2%)	1 (<1%)	2 (2%)	4 (4%)	11 (2%)
	Croatia	0	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (2%)	5 (<1%)
	Serbia	1 (<1%)	3 (3%)	0	0	0	1 (<1%)	5 (<1%)
	Spain	1 (<1%)	0	0	0	0	0	1 (<1%)
Race	White	91 (88%)	91 (88%)	90 (87%)	85 (83%)	85 (82%)	85 (82%)	527 (85%)
	Black	10 (10%)	11 (11%)	12 (12%)	14 (14%)	17 (16%)	17 (16%)	81 (13%)
	Asian	1 (<1%)	2 (2%)	2 (2%)	4 (4%)	0	1 (<1%)	10 (2%)
	American Indian	1 (<1%)	0	0	0	1 (<1%)	0	2 (<1%)
	Native Hawaiian	0	0	0	0	1 (<1%)	0	1 (<1%)
	Other	0	0	0	0	0	1 (<1%)	1 (<1%)
Qualifying airway reversibility (%)	N	103	104	104	103	104	104	622
	Mean (SD)	26.7 (12.01)	26.0 (11.86)	24.3 (10.63)	27.6 (12.92)	30.6 (17.84)	26.2 (12.50)	26.9 (13.25)
	Median (Min, Max)	23.2 (14.5, 76.4)	21.3 (14.6, 83.2)	21.7 (3.9, 68.4)	22.2 (14.5, 71.3)	24.1 (9.0 , 118.3)	22.6 (13.9, 82.9)	22.4 (3.9, 118.3)
Baseline FEV_1 (L)	N	102	104	104	103	103	103	619
	Mean (SD)	2.2 (0.68)	2.2 (0.60)	2.2 (0.64)	2.3 (0.66)	2.2 (0.60)	2.2 (0.67)	2.2 (0.64)
	Median (Min, Max)	2.1 (0.8, 4.2)	2.2 (1.0, 3.8)	2.3 (1.0, 4.0)	2.3 (0.8, 4.3)	2.1 (1.1, 4.0)	2.1 (0.8, 3.9)	2.1 (0.8, 4.3)
Percent Predicted FEV_1 (%)	N	103	104	104	103	104	104	622
	Mean (SD)	66.1 (11.71)	66.9 (10.81)	66.3 (11.04)	66.1 (11.22)	65.5 (10.62)	65.1 (11.73)	66.0 (11.16)
	Median (Min, Max)	67.8 (41.6, 86.0)	68.8 (40.1, 87.3)	66.6 (42.4, 94.8)	67.4 (40.1, 85.2)	66.2 (41.8, 89.5)	66.2 (40.0, 83.7)	67.2 (40.0, 94.8)

Source: Reviewer

3.2.7.1.2 Study 201 - Analysis Populations and Disposition

A total of 622 subjects were randomized to treatments and included in the ITT population. Among the 622 ITT subjects, 483 (78%) completed and 139 (22%) discontinued the treatment and study early. The trial used predetermined *stopping criteria for worsening asthma* based on post baseline lung function tests or incidence of asthma exacerbation, resulting in withdrawal of 19% of patients in the placebo group, which is more than two times the withdrawal rate of any of the active treatment groups. An average rate of 9% in the total population withdrew due to these lack of efficacy criteria. The trial defined *protocol violation* criteria consisted of less than 80% compliance to study drug or any protocol deviation that was deemed by the clinical study leader as a protocol violation, resulting in 10% of placebo patients withdrawing and an average of 6% total patient withdrawal. The placebo group (10%) and Fp MDPI 12.5 mcg BID group (9%) had the highest rates of dropout due to *protocol violation*.

Table 14 Study 201: Patient populations and discontinuation by reason

	Fp MDPI (BID)				Placebo MDPI BID	Flovent Diskus 100mcg BID	Total
	12.5mcg BID	25mcg BID	50mcg BID	100mcg BID			
Randomized	103	104	104	103	104	104	622
ITT	103 (100%)	104 (100%)	104 (100%)	103 (100%)	104 (100%)	104 (100%)	622 (100%)
Full Analysis set	102 (99%)	101 (97%)	102 (98%)	102 (99%)	102 (98%)	102 (98%)	611 (98%)
Completer	79 (77%)	83 (80%)	92 (88%)	82 (80%)	63 (61%)	84 (81%)	483 (78%)
Non-Completer	24 (23%)	21 (20%)	12 (12%)	21 (20%)	41 (39%)	20 (19%)	139 (22%)
Met Stopping Criteria for Worsening Asthma	8 (8%)	7 (7%)	4 (4%)	9 (9%)	20 (19%)	6 (6%)	54 (9%)
Protocol Violation	9 (9%)	6 (6%)	5 (5%)	2 (2%)	10 (10%)	6 (6%)	38 (6%)
Withdrawal by Subject	4 (4%)	2 (2%)	2 (2%)	5 (5%)	5 (5%)	1 (<1%)	19 (3%)
Applicant Required Subject to Be Withdrawn	2 (2%)	3 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (3%)	11 (2%)
Lost To Follow-up	0	1 (<1%)	0	2 (2%)	2 (2%)	1 (<1%)	6 (<1%)
Adverse Event	0	0	0	1 (<1%)	2 (2%)	2 (2%)	5 (<1%)
Non-Compliance to Study Medication	1 (<1%)	0	0	0	0	1 (<1%)	2 (<1%)
Physician Decision	0	0	0	1 (<1%)	1 (<1%)	0	2 (<1%)
Pregnancy	0	2 (2%)	0	0	0	0	2 (<1%)

Source: Reviewer

3.2.7.1.3 Study 201 - Primary Efficacy Results

3.2.7.1.3.1 Study 201 - Planned Analyses Results

The primary analyses of change from baseline in trough FEV_1 over 12 weeks were analyzed with an MMRM model based on observed FAS data. The top part of Table 15 is the summary of

mean change from baseline in trough FEV_1 values over 12 weeks with Flovent Diskus data excluded from the analyses. The lower part is the summary with Flovent Diskus data included in the analyses. The two sets of analyses had similar results regarding comparisons between the Fp MDPI doses and placebo, while the analyses with Flovent Diskus data allowed a numerical assessment of the Fp MPDI treatment effect relative to the marketed product Flovent at a dose of 100 mcg BID.

The primary analysis, the two-sided linear in log-dose time-averaged trend test on trough FEV_1 over the 12-week treatment period demonstrated a statistically significant positive trend (Reviewer's p=0.0004, Table 39 in Appendix). Per the planned fixed-sequence testing procedure, the statistical significance in linear trend test allowed further comparisons of Fp MDPI doses with placebo.

The mean change from baseline trough FEV_1 values ranged from 0.149 L to 0.226 L across the Fp MDPI treatment groups. Statistically significant differences were observed in favor of Fp MDPI 100, 50, and 25 mcg BID relative to placebo; no statistically significant difference was observed between the Fp 12.5 mcg BID treatment group and placebo. Of particular note, there was evidence of effects for the Fp doses of 50 and 100 mcg that have been proposed for marketing. Estimated differences between the Fp MDPI doses and the active control Flovent Diskus 100 mcg BID were largely close to zero, with no statistical evidence of differences in efficacy (all comparisons had confidence intervals covering zero) while the sample sizes were not powered for non-inferiority test as there were no established NI margin for such comparisons. Numerically speaking, Fp MDPI 25 and 50 mcg had the most similar mean treatment effects with Flovent Diskus 100 mcg.

The pre-defined criteria including *stopping criteria for worsening asthma* contributed to the high rate of dropout in the phase 2 studies, including Study 201, which makes the interpretation of the results difficult. The primary analysis method, MMRM, assumes a missing-at-random missingness mechanism, which is an unverifiable and likely implausible assumption. As discussed in the Section 3.2.4, the applicant conducted supportive analyses were not considered sufficient sensitivity analysis to appropriately evaluate the potential impact of missing data.

Table 15. Primary Analysis of Change from Baseline Trough FEV_1 over the 12-Week Treatment Period by Treatment Group (Full Analysis Set)

	Placebo MDPI	Flovent Diskus 100 mcg BID	Fp MDPI			
			12.5 mcg BID	25 mcg BID	50 mcg BID	100 mcg BID
Excluding Flovent Diskus 100 mcg BID Data						
N	N=102		N=102	N=101	N=102	N=102
LS Mean Change from Baseline (L) (SE)(95% CI)	0.136 (0.029) (0.080, 0.192)		0.171 (0.029) (0.114, 0.227)	0.225 (0.029) (0.168, 0.282)	0.241 (0.028) (0.185, 0.297)	0.270 (0.029) (0.214, 0.326)
Difference vs. Placebo, CI, p-value			0.036 (-.044,	0.091 (0.010,	0.107 (0.027,	0.136 (0.056,

	Placebo MDPI	Flovent Diskus 100 mcg BID	Fp MDPI			
			12.5 mcg BID	25 mcg BID	50 mcg BID	100 mcg BID
			0.117) 0.377	0.171) 0.027	0.187) 0.009	0.216) <.001
Including Flovent Diskus 100 mcg BID Data						
N	N=102	N=102	N=102	N=101	N=102	N=102
LS Mean Change from Baseline (L) (SE)(95% CI)	0.136 (0.029) (0.080, 0.192)	0.249 (0.028) (0.194, 0.305)	0.172 (0.028) (0.117, 0.228)	0.228 (0.028) (0.172, 0.283)	0.242 (0.028) (0.187, 0.297)	0.271 (0.028) (0.215, 0.326)
Difference vs. Placebo, CI, p-value		0.113 (0.034, 0.192) 0.005	0.036 (-.043, 0.115) 0.370	0.091 (0.012, 0.171) 0.024	0.106 (0.028, 0.185) 0.008	0.135 (0.056, 0.214) <.001
Difference vs. FLOVENT DISKUS 100 mcg BID, CI, p-value			-.077 (-.155, 0.002) 0.055	-.022 (-.100, 0.057) 0.590	-.007 (-.085, 0.071) 0.866	0.022 (-.057, 0.100) 0.587

Source: Reviewer

Statistical significance was achieved for tests in the hierarchy of pre-planned treatment comparisons above Fp MDPI 12.5 mcg BID vs. placebo (Table 16). Therefore, there was statistical evidence of efficacy for the Fp MDPI 25 mcg, 50 mcg, and 100 mcg BID doses in this study.

Table 16. Study 201: Results for Primary Efficacy Endpoint According to Applicant's Multiple Testing Procedure

Category	Test	Result*
Log-dose Linearity Test	To test the linearity in log-dose time-averaged trend over doses Fp MDPI at 0, 12.5, 25, 50, 100 mcg BID	p=0.0004
Pair-wise Comparison	Fp MDPI 100 mcg BID vs. Placebo	0.136 (0.056, 0.216) <.001
	Fp MDPI 50 mcg BID vs. Placebo	0.107 (0.027, 0.187) 0.009
	Fp MDPI 25 mcg BID vs. Placebo	0.091 (0.010, 0.171) 0.027
	Fp MDPI 12.5 mcg BID vs. Placebo	0.036 (-.044, 0.117) 0.377

Source: Reviewer
Note: * Results reported in this table are from the FAS with Flovent Diskus data excluded. Cell for failed test was greyed out.

3.2.7.1.3.2 Study 201 - Sensitivity Analyses Results

3.2.7.1.3.2.1 Tipping Point Analysis

The applicant didn't plan or conduct any sensitivity analyses for Study 201. As there was a substantial amount of missing data in the primary analysis which was based on the MAR assumption, I performed a tipping point analysis per the steps described in phase 3 statistical methodology section for change from baseline in trough FEV_1 over the 12-week treatment period to assess the effects of missing data.

Per the hierarchy of comparisons over primary efficacy endpoint, Table 17 displays the tipping points I derived for each comparison with the estimated treatment effect based on the primary analyses as a reference. Negative shifts were applied to imputed missing values of patients in the Fp MDPI dose groups while 0 shift was applied to the placebo group. For the three dose groups (Fp 25, 50 and 100) that were demonstrated by the primary analysis (MMRM) to be effective treatments: in the case of Fp 25, the size of the negative shift (-0.043) needed to change the result from statistically significant to not statistically significant was about half the size of the estimated treatment effect over placebo (0.091); for the proposed dose Fp MDPI 50, the size of the tipping point was about twice that of the treatment effect over placebo; in the case of proposed dose Fp 100, the size of the tipping point (-0.345) was a little less than three times the size of the estimated treatment effect (0.136). I consider these sensitivity analysis results to support the conclusions of the primary analysis.

Table 17. Study 201: Tipping Point Analysis Results (Unit: L)

Category	Test	Result*	Tipping Point
Pair-wise Comparison	Fp MDPI 100 mcg BID vs. Placebo	0.136 (0.056, 0.216) <.001	-0.345
	Fp MDPI 50 mcg BID vs. Placebo	0.107 (0.027, 0.187) 0.009	-0.203
	Fp MDPI 25 mcg BID vs. Placebo	0.091 (0.010, 0.171) 0.027	-0.043
	Fp MDPI 12.5 mcg BID vs. Placebo	0.036 (-.044, 0.117) 0.377	

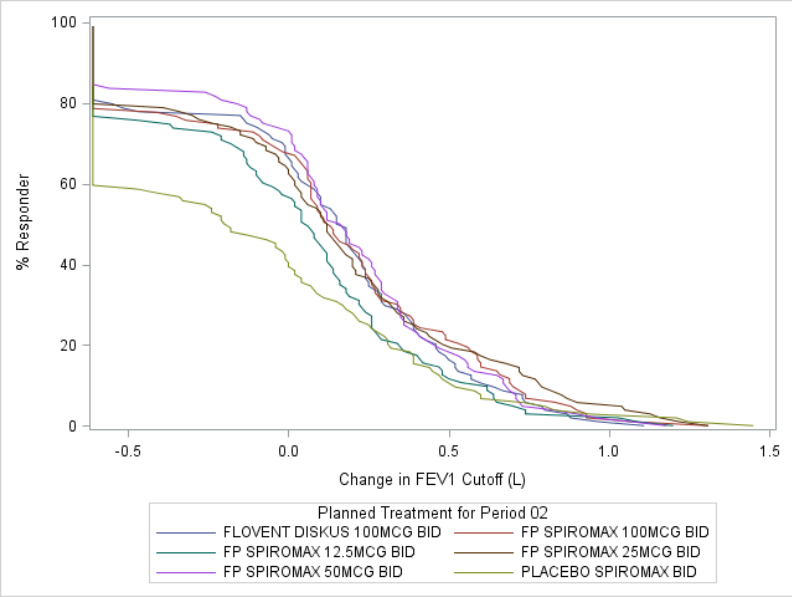
Source: Reviewer
Note: * Results reported in this table are from the FAS with Flovent Diskus data excluded. Cell for failed test was greyed out.

3.2.7.1.3.2.2 Cumulative Responder Plot

Figure 4 provides continuous responder curves (i.e., empirical distribution functions) on change from baseline in trough FEV_1 for Study 201. These presentations are developed as described in Section 3.4.2. As shown in Figure 4, there is an initial drop from 100% to approximately 74% for the placebo arm, corresponding to the 26% of patients who dropped out in placebo since patients with missing change from baseline data were classified as unsuccessfully treated for all thresholds. Generally, across the treatment arms, lack of improvement in FEV_1 from baseline was more frequent in the placebo or low-dose Fp monotherapy groups. Also evident from the figure is that there is clear separation between the placebo and Fp groups.

For each pair of comparison, a corresponding rank sum statistic based on the Mann-Whitney-Wilcoxon test was calculated on the modified data (Table 18). Results from the Mann-Whitney-Wilcoxon tests are largely consistent with the primary results and provide reassurance that the overall conclusions that Fp doses are more effective than placebo in terms of trough FEV_1 are reliable despite the missing data.

Figure 4. Cumulative Responder Plot for Change from Baseline in Trough FEV_1 (Study 201, ITT)



Source: Reviewer

Table 18. Summary of Wilcoxon Rank Sum test on comparisons of interest based on modified data – Study 201 (ITT Population, Change from baseline trough FEV_1)

Comparison	Wilcoxon Two-Sample Test Two-sided p-value
Fp MDPI 100 mcg BID Placebo MDPI	0.0008
Fp MDPI 50 mcg BID Placebo MDPI	<0.0001
Fp MDPI 25 mcg BID Placebo MDPI	0.0011
Fp MDPI 12.5 mcg BID Placebo MDPI	0.0315

Source: Reviewer

3.2.7.2 Dose-ranging study - Study 202

3.2.7.2.1 Study 202 – Demographics, Baseline Characteristics, and Disposition

Study 202 evaluated the dose response, efficacy and safety of Fp MDPI at doses of 50, 100, 200 and 400 mcg BID versus placebo for 12 weeks in subjects with persistent asthma uncontrolled on high-dose ICS therapy. The study also included Flovent Diskus 250 mcg BID for assay sensitivity and to allow numerical assessment of the relative magnitude of response of the doses of Fp MDPI compared with Flovent Diskus 250 mcg BID.

Among the 640 subjects included in the ITT population, demographics and baseline disease characteristics were roughly similar across the six treatment groups in the ITT population (Table 19). There was a higher proportion of female subjects (59%). The mean age was 49.0 years. There were only 9 (1%) adolescent subjects in the study. The majority of subjects were adults

(88%). This was a global trial with US subjects comprising 47% of the total population. White subjects comprised 85% of the total population. All subjects had to demonstrate reversibility of disease at screening and the mean reversibility was 28.9%. Mean baseline FEV_1 was 2.0 L and mean percentage predicted FEV_1 was 66% at screening. The demographics and disease characteristics were consistent with the targeted study population.

Table 19. Study 202: Demographic and Baseline Characteristics (ITT Population)

		Fp MDPI				Placebo MDPI BID	Flovent Diskus 250mcg BID	Total
	Category	50mcg BID	100mcg BID	200mcg BID	400mcg BID			
N		107	107	106	107	106	107	640
Sex	F	63 (59%)	55 (51%)	66 (62%)	72 (67%)	65 (61%)	58 (54%)	379 (59%)
	M	44 (41%)	52 (49%)	40 (38%)	35 (33%)	41 (39%)	49 (46%)	261 (41%)
Age (Years)	Mean (SD)	47.9 (14.59)	48.7 (12.48)	47.7 (14.18)	50.9 (13.32)	49.8 (12.87)	49.2 (13.26)	49.0 (13.46)
	Median (Min, Max)	50.0 (13, 78)	51.0 (14, 75)	47.5 (12, 77)	54.0 (14, 70)	52.0 (14, 78)	51.0 (14, 83)	51.0 (12, 83)
Age Group	12-17 Year	2 (2%)	3 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	9 (1%)
	18-64 Year	94 (88%)	99 (93%)	90 (85%)	90 (84%)	94 (89%)	96 (90%)	563 (88%)
	65+ Years	11 (10%)	5 (5%)	15 (14%)	16 (15%)	11 (10%)	10 (9%)	68 (11%)
Country	United States	52 (49%)	58 (54%)	49 (46%)	50 (47%)	43 (41%)	46 (43%)	298 (47%)
	Ukraine	14 (13%)	20 (19%)	23 (22%)	17 (16%)	24 (23%)	22 (21%)	120 (19%)
	Hungary	10 (9%)	7 (7%)	12 (11%)	11 (10%)	9 (8%)	5 (5%)	54 (8%)
	Bulgaria	10 (9%)	4 (4%)	5 (5%)	5 (5%)	12 (11%)	10 (9%)	46 (7%)
	Poland	9 (8%)	7 (7%)	5 (5%)	12 (11%)	4 (4%)	8 (7%)	45 (7%)
	Germany	5 (5%)	5 (5%)	10 (9%)	8 (7%)	9 (8%)	7 (7%)	44 (7%)
	Romania	3 (3%)	3 (3%)	1 (<1%)	3 (3%)	3 (3%)	6 (6%)	19 (3%)
	Greece	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (2%)	6 (<1%)
	Israel	2 (2%)	1 (<1%)	0	0	1 (<1%)	0	4 (<1%)
	Serbia	0	0	0	1 (<1%)	0	1 (<1%)	2 (<1%)
	Spain	1 (<1%)	0	0	0	0	0	1 (<1%)
	New Zealand	0	1 (<1%)	0	0	0	0	1 (<1%)
Race	White	96 (90%)	94 (88%)	93 (88%)	91 (85%)	96 (91%)	95 (89%)	565 (88%)
	Black	9 (8%)	12 (11%)	12 (11%)	13 (12%)	8 (8%)	11 (10%)	65 (10%)
	Asian	1 (<1%)	1 (<1%)	1 (<1%)	2 (2%)	2 (2%)	0	7 (1%)
	American Indian	0	0	0	0	0	1 (<1%)	1 (<1%)
	Native Hawaiian	1 (<1%)	0	0	0	0	0	1 (<1%)
	Other	0	0	0	1 (<1%)	0	0	1 (<1%)
Qualifying airway reversibility	N	93	94	94	85	92	89	547
	Mean (SD)	31.6 (22.42)	27.3 (14.72)	30.4 (25.16)	28.3 (19.01)	28.9 (19.09)	26.8 (15.66)	28.9 (19.70)

	Category	Fp MDPI				Placebo MDPI BID	Flovent Diskus 250mcg BID	Total
		50mcg BID	100mcg BID	200mcg BID	400mcg BID			
N		107	107	106	107	106	107	640
	Median (Min, Max)	20.0 (11.8, 127.0)	23.0 (12.0, 69.0)	21.1 (-8.4, 175.0)	21.0 (0.0, 82.5)	21.3 (11.6, 91.8)	21.5 (11.8, 92.8)	21.2 (-8.4, 175.0)
Baseline FEV_1 (L)	N	107	107	104	106	106	107	637
	Mean (SD)	2.1 (0.65)	2.1 (0.58)	2.0 (0.57)	2.0 (0.63)	2.0 (0.56)	2.0 (0.59)	2.0 (0.59)
	Median (Min, Max)	2.0 (1.0, 4.6)	2.0 (0.9, 3.7)	2.0 (1.0, 3.7)	1.9 (0.9, 3.9)	1.9 (0.9, 3.6)	1.9 (0.7, 4.0)	1.9 (0.7, 4.6)
Percent Predicted FEV_1 (%)	N	106	105	105	104	103	105	628
	Mean (SD)	63.4 (11.15)	63.8 (9.83)	63.0 (12.80)	65.5 (11.57)	63.4 (9.79)	62.6 (12.47)	63.6 (11.32)
	Median (Min, Max)	62.9 (40.1, 91.9)	63.3 (41.7, 84.3)	63.9 (31.8, 92.2)	66.9 (40.0, 84.4)	62.3 (43.1, 90.9)	61.8 (26.3, 89.5)	63.3 (26.3, 92.2)

Source: Reviewer

3.2.7.2.2 Study 202 - Analysis Populations and Disposition

A total of 640 subjects were randomized to treatment and all 640 were in the ITT population (Table 20), of which 459 (72%) completed the study and 181 (28%) withdrew early. The most common primary reasons for withdrawal was still *met stopping criteria for worsening of asthma and protocol violation*, as in Study 201, which was given by 112 subjects (18%). The percentage of subjects giving *met stopping criteria for worsening of asthma* as the primary reason for withdrawal was 31% in the placebo group, and 12% to 18% in the active treatment groups.

Table 20 Study 202 Patient populations and discontinuation by reason

	Fp MDPI				PLACEBO MDPI BID	FLOVENT DISKUS 250mcg BID	Total
	50mcg BID	100mcg BID	200mcg BID	400mcg BID			
Randomized	107	107	106	107	106	107	640
ITT	107 (100%)	107 (100%)	106 (100%)	107 (100%)	106 (100%)	107 (100%)	640 (100%)
Full Analysis Set	107 (100%)	106 (99%)	102 (96%)	107 (100%)	105 (99%)	103 (96%)	630 (98%)
Completer	82 (77%)	87 (81%)	75 (71%)	80 (75%)	58 (55%)	77 (72%)	459 (72%)
Non-Completer	25 (23%)	20 (19%)	31 (29%)	27 (25%)	48 (45%)	30 (28%)	181 (28%)
Met Stopping Criteria for Worsening of Asthma	16 (15%)	13 (12%)	19 (18%)	16 (15%)	33 (31%)	15 (14%)	112 (18%)
Protocol Violation	5 (5%)	4 (4%)	10 (9%)	6 (6%)	8 (8%)	12 (11%)	45 (7%)
Withdrawal by Subject	1 (<1%)	1 (<1%)	0	2 (2%)	4 (4%)	2 (2%)	10 (2%)
Adverse Event	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	5 (<1%)
Physician Decision	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	4 (<1%)

	Fp MDPI				PLACEBO MDPI BID	FLOVENT DISKUS 250mcg BID	Total
	50mcg BID	100mcg BID	200mcg BID	400mcg BID			
Applicant Required Subject to Be Withdrawn	1 (<1%)	0	0	0	1 (<1%)	0	2 (<1%)
Non-compliance to Study Medication	0	0	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Lost to Follow-up	0	0	0	1 (<1%)	0	0	1 (<1%)

Source: Reviewer

3.2.7.2.3 Study 202 - Primary Efficacy Results

The primary analysis of change from baseline in trough FEV_1 **over** 12 weeks was analyzed with an MMRM model carried out on the FAS. The primary analysis, the trend test of linear log-dose response in change from baseline trough FEV_1 over 12 weeks did not show a statistically significant result (applicant: p-value = 0.0604, reviewer: p-value = 0.0866), thus disallowing the subsequently planned comparisons between Fp MDPI doses and placebo. Table 40 in Appendix lists the Fp doses and SAS Proc IML generated linear coefficients used in the linear trend contrast statement.

In pairwise comparisons, there was no evidence of treatment effects for any of the Fp doses as compared to placebo (all the confidence intervals of treatment differences of Fp from placebo cover 0). There was a small numerical trend toward higher differences with higher Fp dose. Comparison between the active control Flovent Diskus 250 mcg BID (a mid-dose ICS that is on the market) and placebo was not statistically significant, raising questions about the assay sensitivity (ability to detect differences if such differences exist) of the study.

Table 21 presents the summary of results based on MMRM analyses carried over the FAS. The mean change from baseline trough FEV_1 values ranged from 0.053 L to 0.127 L across the Fp MDPI treatment groups. No statistically significant differences were observed in comparisons of Fp MDPI doses relative to placebo. Importantly, the active control Flovent 250 was included in the study for assay sensitivity and no statistically significant difference was observed for Flovent 250 versus placebo. The estimated differences between the Fp MDPI doses and Flovent 250 were largely close to zero, with no statistical evidence of differences (all comparisons had confidence intervals cover zero). Of note, the sample sizes were not powered for non-inferiority test as there were no established margins for such comparisons.

Trial 202 had the highest rate of dropout among the four studies. The applicant conducted several supportive analyses as planned (described in Section 3.2.4). Among them, analysis of the change from baseline trough FEV_1 endpoint at the end of the 12-week treatment period using LOCF to handle missing data showed that Fp MDPI 200 mcg BID and Flovent 250 mcg BID had statistically significantly greater increases in FEV_1 over placebo. As discussed earlier, LOCF is not an appropriate approach for handling missing data in this context. This review will conduct no sensitivity analysis given the failed primary test results.

Table 21. Primary Analysis of Change from Baseline Trough FEV_1 over the 12-Week Treatment Period by Treatment Group (Full Analysis Set)

	Placebo MDPI	Flovent Diskus 250 mcg BID	Fp MDPI			
			50 mcg BID	100 mcg BID	200 mcg BID	400 mcg BID
Excluding Flovent Diskus 250 mcg BID Data						
N	N=105		N=107	N=106	N=101	N=106
LS Mean Change from Baseline (L) (SE)(95% CI)	0.057 (0.026) (0.005, 0.109)		0.053 (0.026) (0.002, 0.104)	0.100 (0.026) (0.049, 0.150)	0.094 (0.027) (0.041, 0.146)	0.127 (0.026) (0.075, 0.179)
Difference vs. Placebo, CI, p-value			-.004 (-.077, 0.068) 0.905	0.043 (-.030, 0.115) 0.248	0.036 (-.037, 0.110) 0.329	0.070 (-.003, 0.143) 0.060
Including Flovent Diskus 250 mcg BID Data						
N	N=105	N=103	N=107	N=106	N=101	N=106
LS Mean Change from Baseline (L) (SE)(95% CI)	0.061 (0.027) (0.009, 0.113)		0.056 (0.026) (0.005, 0.107)	0.101 (0.026) (0.050, 0.152)	0.098 (0.027) (0.046, 0.151)	0.132 (0.027) (0.080, 0.184)
Difference vs. Placebo, CI, p-value		0.034 (-.040, 0.108) 0.365	-.005 (-.078, 0.068) 0.893	0.040 (-.033, 0.113) 0.279	0.038 (-.036, 0.111) 0.319	0.071 (-.003, 0.144) 0.058
Difference vs. FLOVENT DISKUS 250 mcg BID, CI, p-value			-.039 (-.112, 0.034) 0.294	0.006 (-.067, 0.079) 0.867	0.004 (-.070, 0.077) 0.926	0.037 (-.037, 0.110) 0.328

Source: Reviewer

3.2.7.3 Confirmative study - Study 301

3.2.7.3.1 Study 301 - Demographics, Baseline Characteristics, and Disposition

Study 301 compared the efficacy and safety of FS MDPI 50/12.5, FS MDPI 100/12.5, Fp MDPI 50, Fp MDPI 100 mcg BID and placebo administered for 12 weeks in adolescent and adult patients with persistent asthma who were symptomatic despite low-dose or mid-dose ICS therapy.

A total of 647 subjects were included in the ITT population. The demographics (Table 22) showed that the percentage of female subjects (56%) in the ITT population were slightly higher than that of males (44%). The mean age was 41.5 years. There were 86 (13%) adolescent subjects. This trial was conducted in the United States, Canada and five European countries. The number of subjects randomized across countries ranged from 3 (<1%) in Canada to 360 (56%) in the US. The majority of subjects were white (80%).

The overall mean FEV_1 reversibility was 29.9% at screening. The overall mean baseline FEV_1 was 2.2 L. The overall percent predicted FEV_1 was 67.5% at screening. Prior to the study, the majority of subjects were on ICS monotherapy (71%) as compared to 29% of subjects on ICS/LABA combination therapy.

Table 22. Study 301: Demographic and Baseline Characteristics (ITT Population)

	Category	Fp MDPI		FS MDPI		Placebo MDPI 0 mcg	Total
		50 mcg BID	100 mcg BID	50/12.5 mcg BID	100/12.5 mcg BID		
N		129	130	129	129	130	647
Sex	F	75 (58%)	76 (58%)	71 (55%)	72 (56%)	70 (54%)	364 (56%)
	M	54 (42%)	54 (42%)	58 (45%)	57 (44%)	60 (46%)	283 (44%)
Age (Years)	Mean (SD)	43.3 (17.96)	40.6 (17.16)	41.4 (18.61)	41.0 (17.00)	40.9 (17.35)	41.5 (17.60)
	Median (Min, Max)	43.0 (12, 79)	44.0 (12, 75)	41.0 (12, 86)	43.0 (12, 74)	44.0 (12, 78)	43.0 (12, 86)
Age Group	12-17 Years	13 (10%)	18 (14%)	19 (15%)	19 (15%)	17 (13%)	86 (13%)
	18-64 Years	93 (72%)	102 (78%)	97 (75%)	100 (78%)	102 (78%)	494 (76%)
	65+ Years	23 (18%)	10 (8%)	13 (10%)	10 (8%)	11 (8%)	67 (10%)
Country	United States	70 (54%)	78 (60%)	68 (53%)	74 (57%)	70 (54%)	360 (56%)
	Poland	25 (19%)	16 (12%)	21 (16%)	20 (16%)	18 (14%)	100 (15%)
	Russia	12 (9%)	15 (12%)	17 (13%)	13 (10%)	15 (12%)	72 (11%)
	Hungary	11 (9%)	11 (8%)	15 (12%)	12 (9%)	11 (8%)	60 (9%)
	Ukraine	8 (6%)	8 (6%)	5 (4%)	8 (6%)	11 (8%)	40 (6%)
	Czech Republic	3 (2%)	1 (<1%)	3 (2%)	1 (<1%)	4 (3%)	12 (2%)
	Canada	0	1 (<1%)	0	1 (<1%)	1 (<1%)	3 (<1%)
Race	White	107 (83%)	93 (72%)	109 (84%)	105 (81%)	101 (78%)	515 (80%)
	Black or African	18 (14%)	30 (23%)	19 (15%)	20 (16%)	26 (20%)	113 (17%)
	Asian	1 (<1%)	4 (3%)	1 (<1%)	4 (3%)	1 (<1%)	11 (2%)
	Other	2 (2%)	2 (2%)	0	0	2 (2%)	6 (<1%)
	American Indian	0	1 (<1%)	0	0	0	1 (<1%)
	Native Hawaiian	1 (<1%)	0	0	0	0	1 (<1%)
Qualifying airway reversibility (%)	N	129	130	129	129	130	647
	Mean (SD)	31.8 (21.18)	29.8 (17.25)	29.2 (16.75)	29.5 (16.64)	29.4 (14.73)	29.9 (17.40)
	Median (Min, Max)	25.0 (12.0, 120.0)	23.0 (14.0, 106.0)	22.0 (14.0, 97.0)	25.0 (15.0, 133.0)	25.0 (10.0, 95.0)	24.0 (10.0, 133.0)
Baseline FEV_1 (L)	N	129	129	128	126	129	641
	Mean (SD)	2.1 (0.63)	2.2 (0.57)	2.3 (0.65)	2.2 (0.55)	2.2 (0.56)	2.2 (0.60)
	Median (Min, Max)	2.0 (0.8, 4.1)	2.1 (0.9, 3.9)	2.2 (1.0, 3.9)	2.1 (1.1, 3.8)	2.1 (1.0, 3.9)	2.1 (0.8, 4.1)
Percent Predicted	N	129	129	128	126	129	641
	Mean (SD)	66.5 (9.87)	67.1 (9.66)	69.7 (10.87)	67.1 (11.22)	67.0 (11.19)	67.5 (10.61)

	Category	Fp MDPI		FS MDPI		Placebo MDPI 0 mcg	Total
		50 mcg BID	100 mcg BID	50/12.5 mcg BID	100/12.5 mcg BID		
N		129	130	129	129	130	647
FEV_1 (%)	Median (Min, Max)	67.5 (45.0, 84.0)	68.0 (47.5, 85.5)	72.0 (41.0, 85.0)	69.5 (41.5, 92.0)	69.5 (41.0, 83.5)	69.0 (41.0, 92.0)
Pre-screening Asthma Therapy	ICS	89 (69%)	83 (64%)	90 (70%)	97 (75%)	102 (78%)	461 (71%)
	ICS/LABA	40 (31%)	47 (36%)	39 (30%)	32 (25%)	28 (22%)	186 (29%)

Source: Reviewer

3.2.7.3.2 Study 301 - Analysis Populations and Disposition

A total of 647 subjects were randomized to treatment and were in the ITT population (Table 23). In the ITT population, 602 (93%) subjects completed and 45 (7%) withdrew early. There was no predominant primary reason for withdrawals. The top reasons (numerically) for withdrawal was adverse event (2%), withdrawal by subject (1%), while the percentages of other reasons were all less than 1%. The placebo group had a considerably higher dropout rate (13%) compared with all the other arms. Within the placebo group, adverse event (5%) and lack of efficacy (3%) were the top contributors to dropout.

Within the Serial Spirometry Subset, the ITT population (100%) and FAS population (100%) included all the randomized SSS subjects. The overall early withdrawal rate was 6% within the SSS. The pattern of common primary reasons for withdrawals within the SSS was similar to that of the overall population.

Table 23. Study 301 Patient populations and disposition by reason

Analysis Group	Placebo	Fp MDPI (BID)		FS MDPI (BID)		Total
		50 mcg	100 mcg	50/12.5 mcg	100/12.5 mcg	
Full Study Set						
Randomized	130	129	130	129	129	647
ITT	130 (100%)	129 (100%)	130 (100%)	129 (100%)	129 (100%)	647 (100%)
Full Analysis Set	129 (99%)	128 (99%)	129 (99%)	128 (99%)	126 (98%)	640 (99%)
Completed Study	113 (87%)	121 (94%)	121 (93%)	121 (94%)	126 (98%)	602 (93%)
Non-Completers	17 (13%)	8 (6%)	9 (7%)	8 (6%)	3 (2%)	45 (7%)
Adverse Event	6 (5%)	1 (<1%)	2 (2%)	3 (2%)	0	12 (2%)
Withdrawal by Subject	2 (2%)	3 (2%)	2 (2%)	2 (2%)	0	9 (1%)
Lack of Efficacy	4 (3%)	1 (<1%)	0	1 (<1%)	0	6 (<1%)
Other	1 (<1%)	0	1 (<1%)	1 (<1%)	3 (2%)	6 (<1%)
Disease Progression	2 (2%)	1 (<1%)	1 (<1%)	0	0	4 (<1%)
Lost to Follow-Up	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	4 (<1%)
Protocol Violation	1 (<1%)	1 (<1%)	1 (<1%)	0	0	3 (<1%)
Non-compliance	0	0	1 (<1%)	0	0	1 (<1%)
Serial Spirometry Subset (SSS)						

Analysis Group	Placebo	Fp MDPI (BID)		FS MDPI (BID)		Total
		50 mcg	100 mcg	50/12.5 mcg	100/12.5 mcg	
SSS-Randomized	60 (100%)	63 (100%)	72 (100%)	56 (100%)	61 (100%)	312 (100%)
SSS-ITT	60 (100%)	63 (100%)	72 (100%)	56 (100%)	61 (100%)	312 (100%)
SSS-Full Analysis Set	60 (100%)	63 (100%)	72 (100%)	56 (100%)	61 (100%)	312 (100%)
SSS-Completer Set	54 (90%)	57 (90%)	69 (96%)	53 (95%)	61 (100%)	294 (94%)
SSS-Non-Completers	6 (10%)	6 (10%)	3 (4%)	3 (5%)	0	18 (6%)
Adverse Event	2 (3%)	1 (2%)	1 (1%)	1 (2%)	0	5 (2%)
Withdrawal by Subject	0	2 (3%)	1 (1%)	2 (4%)	0	5 (2%)
Lack of Efficacy	2 (3%)	1 (2%)	0	0	0	3 (<1%)
Disease Progression	1 (2%)	1 (2%)	0	0	0	2 (<1%)
Protocol Violation	0	1 (2%)	1 (1%)	0	0	2 (<1%)
Lost to Follow-Up	1 (2%)	0	0	0	0	1 (<1%)

Source: Reviewer

3.2.7.3.3 Study 301 - Primary Efficacy Results

3.2.7.3.3.1 Study 301 - Planned Analyses Results

A summary of the SBA FEV_1 $AUEC_{0\text{-}12h}$ analysis results at Week 12 is provided in Table 24. The least square mean of SBA FEV_1 $AUEC_{0\text{-}12h}$ values ranged from 0.254 L in the Fp MDPI 100 mcg BID group to 0.408 L in the FS MDPI 100/12.5 mcg BID group. Statistically significant differences were first observed in favor of the combination drugs relative to the single ingredient counterparts: FS 100/12.5 treatment relative to Fp 100 and FS 50/12.5 treatment relative to Fp 50. Following the pre-planned fixed-sequence multiple testing procedure, statistically significant differences were observed in favor of the combination drugs relative to placebo: FS 100/12.5 treatment relative to placebo and FS 50/12.5 treatment relative to placebo.

Table 24. Primary Analysis of Standardized Baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ (L) at Week 12 by Treatment Group (Full Analysis Set – Serial Spirometry Subset)

	Placebo MDPI	Fp MDPI		FS MDPI	
		50 mcg BID	100 mcg BID	50/12.5 mcg BID	100/12.5 mcg BID
N	N=60	N=63	N=72	N=56	N=61
LS Mean SBA FEV_1 (L) (SE)(95% CI)	0.074 (0.049) (-.022, 0.170)	0.268 (0.046) (0.178, 0.358)	0.254 (0.043) (0.169, 0.339)	0.399 (0.048) (0.305, 0.493)	0.408 (0.046) (0.317, 0.500)
Difference vs. Placebo, 95% CI, p-value		0.195 (0.078, 0.312) 0.001	0.180 (0.067, 0.294) 0.002	0.325 (0.203, 0.447) <.001	0.335 (0.216, 0.453) <.001
Difference vs. Fp MDPI 50 mcg BID, 95% CI, p-value			-.014(-.126, 0.098) 0.802	0.131(0.011, 0.250) 0.032	0 140(0.023, 0 256) 0.019
Difference vs. Fp MDPI 100 mcg BID, 95% CI, p-value				0.145(0.028, 0.261) 0.015	0 154(0.041, 0 267) 0.008

Source: Reviewer

A summary of the mean change from baseline in trough FEV_1 (m-BOCF) is provided in Table 25. The mean change from baseline trough FEV_1 values ranged from 0.172 L in the Fp 50 mcg BID group to 0.319 L in the FS 50/12.5 mcg BID group. Statistically significant differences were observed in favor of doses of both FS MDPI and Fp MDPI relative to placebo.

Table 25. Primary Analysis of Change from Baseline Trough FEV_1 at Week 12 by Treatment Group (Full Analysis Set)

	Placebo MDPI	Fp MDPI		FS MDPI	
		50 mcg BID	100 mcg BID	50/12.5 mcg BID	100/12.5 mcg BID
N	N=129	N=128	N=129	N=128	N=126
LS Mean Change from Baseline (L) (SE)(95% CI)	0.053 (0.035) (-.015, 0.122)	0.172 (0.035) (0.104, 0.240)	0.204 (0.034) (0.137, 0.271)	0.319 (0.035) (0.250, 0.388)	0.315 (0.035) (0.246, 0.385)
Difference vs. Placebo, CI, p-value		0.119(0.025, 0.212) 0.013	0.151(0.057, 0.244) 0.002	0.266(0.172, 0.360) <.001	0.262(0.168, 0.356) <.001
Difference vs. Fp MDPI 50 mcg BID, CI, p-value			0.032(-.062, 0.126) 0.502	0.147(0.053, 0.242) 0.002	0.144(0.049, 0.238) 0.003
Difference vs. Fp MDPI 100 mcg BID, CI, p-value					0.111(0.017, 0.206) 0.020

Source: Reviewer

Statistical significance was achieved for the hierarchy of pre-planned treatment comparisons with respect to the primary endpoints (Table 26). Therefore, this study provided evidence of efficacy for Fp 50 and 100 mcg BID, and for FS 50/12.5 mcg and 100/12.5 mcg, as well as evidence of the contribution of the LABA component to the efficacy of the two combination products.

Table 26. Study 301: Results in for Primary Efficacy Endpoints According to Applicant's Multiple Testing Procedures

Endpoint	Drug	Dose Comparison	
		Study 301	Results
SBA FEV_1 $AUEC_{0-12h}$	FS vs. Fp	100/12.5 vs. 100	0.154(0.041, 0.267) 0.008
		50/12.5 vs. 50	0.131(0.011, 0.250) 0.032
	FS vs. Placebo	100/12.5 vs. Placebo	0.335 (0.216, 0.453) <.001
		50/12.5 vs. Placebo	0.325 (0.203, 0.447) <.001
Δ Trough FEV_1	FS vs. Placebo	100/12.5 vs. Placebo	0.262(0.168, 0.356) <.001
		50/12.5 vs. Placebo	0.266(0.172, 0.360) <.001
	Fp vs. Placebo	100 vs. Placebo	0.151(0.057, 0.244) 0.002
		50 vs. Placebo	0.119(0.025, 0.212) 0.013

Source: Reviewer

3.2.7.3.3.2 Study 301 - Sensitivity Analyses Results

3.2.7.3.3.2.1 Study 301 – Tipping Point Analysis Results for Trough FEV_1

For each of the comparisons in the hierarchy of tests for primary endpoints (Table 8), Table 27 includes four type of results: 1) reviewer's primary analysis results according to the applicant's pre-planned analysis methods, 2) for trough FEV_1, the estimates of treatment effect from an MMRM analysis over the 12-week treatment period as a reference for the interpretation of plausibility of tipping points, as the applicant's proposed tipping point analysis was based on an MMRM model, 3) the reviewer's tipping points, and 4) the applicant reported tipping points. The purpose of juxtaposing these results is to use the primary analysis results and MMRM results in the case of trough FEV_1 as a reference to judge the reasonability of the tipping point.

In terms of change from baseline trough FEV_1, for the comparison of FS 50/12.5 over placebo, the estimated treatment effect at Week 12 was 0.266 L from the m-BOCF ANCOVA model, and the estimated treatment effect over the 12-week treatment period from the MMRM based on observed data was 0.256 L, while the tipping point was -2.39 (reviewer's result) and -2.60 (applicant's result). Therefore, an assumption that missing outcomes on the experimental treatment arm tended to be roughly ten-fold worse than the magnitude of the overall effect size was needed to shift the MNAR imputation to tip the statistically significant result to not statistically significant (while assuming missing-at-random missing data on the placebo arm). While most of the reviewer's tipping points are slightly smaller than the applicant reported ones, the qualitative interpretation of the findings does not change. For most of the comparisons, an assumption of roughly 6-(0.76 vs. 0.119 in Fp 50 vs. placebo) to 16-fold (-4.34 v. 0.262 in FS 100/12.5 vs. placebo) shifts relative to the magnitude of treatment effect was needed to tip the positive decision on treatment efficacy. These assumptions are considered very unlikely to be plausible. In addition, considering the study mean baseline FEV_1 was 2.0 L, and the range of tipping points was -0.84 L to -3.97 L, it is noted that some assumptions are not even biologically possible. With these considerations, the tipping point sensitivity analysis results confirmed the validity of the positive primary analysis results, which were based on missing data handling methods that may have potentially violated the true unknown missingness mechnism.

Table 27. Study 301: Tipping Point Analysis Results for Trough FEV_1 (Unit: L)

Endpoint	Drug	Planned Comparison	Primary Analysis Result	Estimated Effect from MMRM Over 12 weeks treatment period	Tipping Point	
					Applicant's	Reviewers
Δ Trough FEV_1	FS vs. Placebo	100/12.5 vs. Placebo	0.262(0.168, 0.356) <.001	0.243 (0.164, 0.322) <.001	-5.48	-4.34
		50/12.5 vs. Placebo	0.266(0.172, 0.360) <.001	0.256 (0.177, 0.335) <.001	-2.60	-2.39
	Fp vs. Placebo	100 vs. Placebo	0.151(0.057, 0.244) 0.002	0.150 (0.072, 0.229) <.001	-1.26	-1.11
		50 vs. Placebo	0.119(0.025, 0.212) 0.013	0.136 (0.057, 0.215) <.001	-1.13	-0.76

Source: Reviewer and Applicant Study 301CSR Table 18.

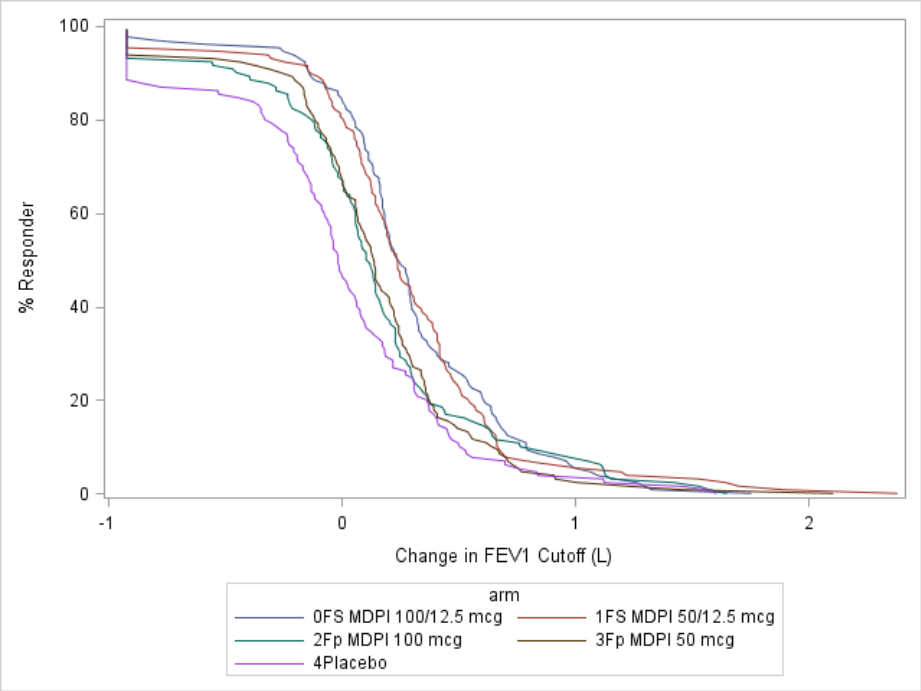
Note: *The tipping point is not reachable by a negative shift on the FS100/12.5 group due to high completion rate missing and missing pattern in the group (see details in Appendix). The result shown here was reached by positively shifting the Placebo arm missing data imputation in Trough FEV_1 measures.

3.2.7.3.3.2.2 Study 301 – Cumulative Responder Plot Analysis Results for Trough FEV_1

Figure 5 provides continuous responder curves (i.e., empirical distribution functions) on change from baseline in trough FEV_1 for Studies 301. These presentations are developed as described in Section 3.4.2. As shown in Figure 5, there is an initial drop from 100% to approximately 98% or below on the y-axis, corresponding to the proportions of patients who dropped out in each arm since patients with missing change from baseline data were classified as unsuccessfully treated for all thresholds. Generally, across the treatment arms, lack of improvement in FEV_1 from baseline was more frequent in the placebo or Fp monotherapy groups compared to the FS combination groups. Also evident from the figure is that there is clear separation between the treatment groups of placebo, Fp and FS.

For each pair of comparison, a corresponding rank sum statistic based on the Mann-Whitney-Wilcoxon test is calculated on the modified data. Results from the Mann-Whitney-Wilcoxon tests, are consistent with the m-BOCF ANCOVA results and provide reassurance that the overall conclusions that both FS and Fp are more effective than placebo in terms of trough FEV_1 are reliable despite missing data.

Figure 5. Empirical Distribution Function for Change from Baseline in Trough FEV_1 (Study 301, ITT)



Source: Reviewer

Table 28. Summary of Wilcoxon Rank Sum test on comparisons of interest based on modified data – Study 301 (ITT Population, Change from baseline trough FEV_1)

Comparison	Wilcoxon Two-Sample Test Two-sided p-value
FS MDPI 100/12.5 mcg BID versus Placebo MDPI	<0.0001
FS MDPI 50/12.5 mcg BID Placebo MDPI	<0.0001
Fp MDPI 100 mcg BID Placebo MDPI	0.0127
Fp MDPI 50 mcg BID Placebo MDPI	0.004

Source: Reviewer

3.2.7.4 Confirmative Study - Study 30017

3.2.7.4.1 Study 30017 - Demographics, Baseline Characteristics, and Disposition

Study 30017 compared the efficacy and safety of FS MDPI 100/12.5, FS MDPI 200/12.5, Fp MDPI 100, Fp MDPI 200 mcg BID and placebo administered for 12 weeks in adolescent and adult patients with persistent asthma symptomatic despite mid-dose or high-dose ICS therapy.

A total of 728 subjects were included in the ITT population. The demographics (Table 29) showed that the percentage of female subjects (60%) in the ITT population were higher than that of males (40%). The mean age was 44.7 years. There were 45 (6%) adolescent subjects. This trial was conducted in the United States, Canada, South Africa and five European countries. The number of subjects randomized across countries ranged from 3 (<1%) in Canada to 427 (59%) in the US. The majority of subjects were white (81%).

The overall mean FEV_1 reversibility was 29.5% at screening. The overall mean baseline FEV_1 was 2.1 L. The overall percent predicted FEV_1 was 65.2% at screening. Prior to the study, a slightly higher proportion of subjects were on ICS/LABA combination therapy (55%) as compared to 45% of subjects on ICS monotherapy.

Table 29. Study 30017: demographic and baseline characteristics (ITT Population)

		Fluticasone propionate MDPI		Fluticasone/Salmeterol MDPI		Placebo MDPI 0 mcg	Total
	Category	100 mcg BID	200 mcg BID	100/12.5 mcg BID	200/12.5 mcg BID		
N		146	146	145	146	145	728
Sex	F	94 (64%)	88 (60%)	79 (54%)	87 (60%)	91 (63%)	439 (60%)
	M	52 (36%)	58 (40%)	66 (46%)	59 (40%)	54 (37%)	289 (40%)
Age (Years)	Mean (SD)	45.7 (15.64)	44.4 (16.36)	44.3 (14.88)	44.7 (16.93)	44.5 (16.05)	44.7 (15.95)
	Median (Min, Max)	47.0 (12, 84)	46.0 (12, 81)	46.0 (12, 74)	45.5 (12, 76)	47.0 (13, 76)	46.5 (12, 84)
Age Group	12-17 Years	9 (6%)	10 (7%)	8 (6%)	12 (8%)	6 (4%)	45 (6%)
	18-64 Years	124 (85%)	119 (82%)	125 (86%)	115 (79%)	125 (86%)	608 (84%)
	65+ Years	13 (9%)	17 (12%)	12 (8%)	19 (13%)	14 (10%)	75 (10%)
Country	United States	87 (60%)	81 (55%)	88 (61%)	89 (61%)	82 (57%)	427 (59%)
	Poland	23 (16%)	23 (16%)	20 (14%)	25 (17%)	30 (21%)	121 (17%)

	Category	Fluticasone propionate MDPI		Fluticasone/Salmeterol MDPI		Placebo MDPI 0 mcg	Total
		100 mcg BID	200 mcg BID	100/12.5 mcg BID	200/12.5 mcg BID		
N		146	146	145	146	145	728
	Hungary	19 (13%)	20 (14%)	14 (10%)	12 (8%)	14 (10%)	79 (11%)
	Russia	8 (5%)	11 (8%)	10 (7%)	8 (5%)	7 (5%)	44 (6%)
	Ukraine	4 (3%)	6 (4%)	8 (6%)	9 (6%)	9 (6%)	36 (5%)
	South Africa	3 (2%)	4 (3%)	3 (2%)	1 (<1%)	2 (1%)	13 (2%)
	Czech Republic	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	5 (<1%)
	Canada	1 (<1%)	0	1 (<1%)	1 (<1%)	0	3 (<1%)
Race	White	111 (76%)	116 (79%)	112 (77%)	125 (86%)	124 (86%)	588 (81%)
	Black or African	31 (21%)	23 (16%)	28 (19%)	20 (14%)	18 (12%)	120 (16%)
	Asian	4 (3%)	3 (2%)	5 (3%)	1 (<1%)	1 (<1%)	14 (2%)
	Other	0	2 (1%)	0	0	2 (1%)	4 (<1%)
	American Indian	0	2 (1%)	0	0	0	2 (<1%)
Qualifying airway reversibility (%)	N	146	146	145	146	145	728
	Mean (SD)	28.8 (12.81)	31.5 (16.40)	30.0 (17.04)	29.0 (14.06)	28.3 (14.06)	29.5 (14.96)
	Median (Min, Max)	25.5 (8.0, 75.0)	28.0 (15.0, 132.0)	25.0 (14.0, 121.0)	25.0 (9.0, 77.0)	25.0 (2.0, 88.0)	25.0 (2.0, 132.0)
Baseline FEV_1 (L)	N	145	146	142	145	144	722
	Mean (SD)	2.1 (0.60)	2.1 (0.57)	2.2 (0.64)	2.1 (0.65)	2.1 (0.68)	2.1 (0.63)
	Median (Min, Max)	2.0 (0.9, 4.1)	2.0 (0.9, 3.6)	2.1 (1.1, 4.0)	1.9 (0.8, 3.7)	2.0 (0.8, 3.9)	2.0 (0.8, 4.1)
Percent Predicted FEV_1 (%)	N	145	146	142	145	144	722
	Mean (SD)	66.1 (10.75)	64.0 (10.07)	65.5 (10.85)	64.7 (11.23)	65.5 (10.75)	65.2 (10.73)
	Median (Min, Max)	66.5 (40.5, 85.0)	64.8 (40.5, 85.5)	67.0 (41.0, 85.0)	66.0 (40.0, 85.5)	66.0 (41.5, 84.5)	66.0 (40.0, 85.5)
Pre-screening Asthma Therapy	ICS	58 (40%)	63 (43%)	67 (46%)	73 (50%)	68 (47%)	329 (45%)
	ICS/LABA	88 (60%)	83 (57%)	78 (54%)	73 (50%)	77 (53%)	399 (55%)

Source: Reviewer.

3.2.7.4.2 Study 30017 - Analysis Populations and Disposition

A total of 728 subjects were randomized to treatment and were in the ITT population (Table 30). In the ITT population, 650 (89%) subjects completed and 78 (11%) withdrew early. The most common primary reasons (numerically) for withdrawal were disease progression (3%) and withdrawal by subject (3%), while the percentages of other reasons were all less than or equal to 1%. The placebo group had a considerably higher dropout rate (26%) compared with all the other arms. Within the placebo group, disease progression (12%), withdrawal by subject (5%) and lack of efficacy (5%) were the top contributors to dropout.

A serial spirometry subset (312) of the randomized subjects performed post-dose serial spirometry and the data was used for the SBA FEV_1 $AUEC_{0\text{-}12h}$ assessment at Week 12. The ITT-SSS population (100%) and FAS-SSS set (100%) included all the randomized SSS subjects.

The overall early withdrawal rate was 11% within the SSS. The pattern of common primary reasons for withdrawals within the SSS was similar to that of the overall population.

Table 30. Study 30017 patient populations and disposition by reason

Analysis Group, n (%)	Placebo	Fp MDPI (BID)		FS MDPI (BID)		Total
		100 mcg	200 mcg	100/12.5 mcg	200/12.5 mcg	
Full Study Set						
Randomized	145	146	146	145	146	728
ITT	145 (100%)	146 (100%)	146 (100%)	145 (100%)	146 (100%)	728 (100%)
Full Analysis Set	143 (99%)	145 (99%)	146 (100%)	141 (97%)	145 (99%)	720 (99%)
Completed Study	107 (74%)	136 (93%)	135 (92%)	136 (94%)	136 (93%)	650 (89%)
Non-Completers	38 (26%)	10 (7%)	11 (8%)	9 (6%)	10 (7%)	78 (11%)
Disease Progression	18 (12%)	0	3 (2%)	1 (<1%)	2 (1%)	24 (3%)
Withdrawal by Subject	7 (5%)	4 (3%)	3 (2%)	3 (2%)	2 (1%)	19 (3%)
Lack of Efficacy	7 (5%)	1 (<1%)	1 (<1%)	0	0	9 (1%)
Adverse Event	2 (1%)	2 (1%)	0	2 (1%)	2 (1%)	8 (1%)
Other	2 (1%)	1 (<1%)	0	2 (1%)	1 (<1%)	6 (<1%)
Protocol Violation	1 (<1%)	2 (1%)	2 (1%)	0	1 (<1%)	6 (<1%)
Lost to Follow-Up	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)
Non-compliance	0	0	1 (<1%)	0	0	1 (<1%)
Pregnancy	0	0	0	0	1 (<1%)	1 (<1%)
Serial Spirometry Subset (SSS)						
SSS-Randomized	61 (100%)	64 (100%)	61 (100%)	58 (100%)	68 (100%)	312 (100%)
SSS-ITT	61 (100%)	64 (100%)	61 (100%)	58 (100%)	68 (100%)	312 (100%)
SSS-Full Analysis Set	61 (100%)	64 (100%)	61 (100%)	58 (100%)	68 (100%)	312 (100%)
SSS-Completer Set	41 (67%)	58 (91%)	56 (92%)	57 (98%)	65 (96%)	277 (89%)
SSS-Non-Completers	20 (33%)	6 (9%)	5 (8%)	1 (2%)	3 (4%)	35 (11%)
Disease Progression	8 (13%)	0	2 (3%)	1 (2%)	1 (1%)	12 (4%)
Withdrawal by Subject	5 (8%)	2 (3%)	1 (2%)	0	1 (1%)	9 (3%)
Lack of Efficacy	5 (8%)	1 (2%)	0	0	0	6 (2%)
Adverse Event	2 (3%)	2 (3%)	0	0	0	4 (1%)
Lost to Follow-Up	0	0	1 (2%)	0	0	1 (<1%)
Non-compliance	0	0	1 (2%)	0	0	1 (<1%)
Pregnancy	0	0	0	0	1 (1%)	1 (<1%)

Analysis Group, n (%)	Placebo	Fp MDPI (BID)		FS MDPI (BID)		Total
		100 mcg	200 mcg	100/12.5 mcg	200/12.5 mcg	
Protocol Violation	0	1 (2%)	0	0	0	1 (<1%)

Source: Reviewer

3.2.7.4.3 Study 30017 - Primary Efficacy Results

3.2.7.4.3.1 Study 30017 - Planned Analyses Results

A summary of the SBA FEV_1 $AUEC_{0\text{-}12h}$ results at Week 12 is provided in Table 32. The least square mean of SBA FEV_1 $AUEC_{0\text{-}12h}$ values ranged from 0.260 L in the Fp MDPI 100 mcg BID group to 0.446 L in the FS MDPI 200/12.5 mcg BID group. Statistically significant differences were first observed in favor of the combination drugs relative to the single ingredient counterparts: FS 200/12.5 treatment relative to Fp 200 and FS 100/12.5 treatment relative to Fp 100. Following the pre-planned fixed-sequence multiple testing procedure, statistically significant differences were observed in favor of the combination drugs relative to placebo: FS 200/12.5 treatment relative to placebo and FS 100/12.5 treatment relative to placebo.

Table 31. Primary Analysis of Standardized Baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ (L) at Week 12 by Treatment Group (Full Analysis Set – Serial Spirometry Subset)

	Placebo MDPI	Fp MDPI		FS MDPI	
		100 mcg BID	200 mcg BID	100/12.5 mcg BID	200/12.5 mcg BID
N	N=61	N=64	N=61	N=58	N=68
LS Mean Change from Baseline (L) (SE)(95% CI)	0.121 (0.047) (0.028, 0.214)	0.260 (0.046) (0.169, 0.351)	0.267 (0.047) (0.175, 0.359)	0.442 (0.050) (0.345, 0.540)	0.446 (0.046) (0.355, 0.538)
Difference vs. Placebo, 95% CI, p-value		0.139 (0.032, 0.246) 0.011	0.146 (0.038, 0.255) 0.008	0.322 (0.212, 0.432) <.001	0.326 (0.221, 0.431) <.001
Difference vs. Fp MDPI 100 mcg BID, 95% CI, p-value			0.007 (-.099, 0.114) 0.895	0.182 (0.074, 0.291) 0.001	0.187 (0.082, 0.291) <.001
Difference vs. Fp MDPI 200 mcg BID, 95% CI, p-value				0.175 (0.066, 0.284) 0.002	0.179 (0.074, 0.285 <.001

Source: Reviewer

A summary of the mean change from baseline in trough FEV_1 (m-BOCF) is provided in Table 32. The mean change from baseline trough FEV_1 values ranged from 0.119 L in the Fp 100 mcg

BID group to 0.272 L in the FS 200/12.5 mcg BID group. Statistically significant differences were observed in favor of both FS MDPI and Fp MDPI each at two doses relative to placebo.

Table 32. Primary Analysis of Change from Baseline Trough FEV_1 at Week 12 by Treatment Group (Full Analysis Set)

	Placebo MDPI	Fp MDPI		FS MDPI	
		100 mcg BID	200 mcg BID	100/12.5 mcg BID	200/12.5 mcg BID
N	N=143	N=144	N=145	N=140	N=145
LS Mean Change from Baseline (L) (SE)(95% CI)	-.004 (0.031) (-.065, 0.057)	0.119 (0.031) (0.058, 0.180)	0.179 (0.031) (0.119, 0.240)	0.271 (0.031) (0.210, 0.332)	0.272 (0.031) (0.212, 0.333)
Difference vs. Placebo, CI, p-value		0.123 (0.038, 0.208) 0.005	0.183 (0.098, 0.268) <.001	0.274 (0.189, 0.360) <.001	0.276 (0.191, 0.361) <.001
Difference vs. Fp MDPI 100 mcg BID, CI, p-value			0.060 (-.024, 0.145) 0.163	0.152 (0.066, 0.237) <.001	0.153 (0.068, 0.238) <.001
Difference vs. Fp MDPI 200 mcg BID, CI, p-value				0.092 (0.006, 0.177) 0.036	0.093 (0.009, 0.178) 0.031

Source: Reviewer

Statistical significance was achieved for the hierarchy of pre-planned treatment comparisons with respect to the primary endpoints (Table 33). Therefore, this study provided evidence of efficacy for Fp 100 and 200 mcg BID, and for FS 100/12.5 mcg and 200/12.5 mcg, as well as evidence of the contribution of the LABA component to the efficacy of the two combination products.

Table 33. Study 30017: Results for Co-Primary Efficacy Endpoints According to Applicant's Multiple Testing Procedures

Endpoint	Drug	Dose Comparison	
		Study 30017	Results
SBA FEV_1 $AUEC_{0-12h}$	FS vs. Fp	200/12.5 vs. 200	0.179 (0.074, 0.285) <.001
		100/12.5 vs. 100	0.182 (0.074, 0.291) 0.001
	FS vs. Placebo	200/12.5 vs. Placebo	0.326 (0.221, 0.431) <.001
		100/12.5 vs. Placebo	0.322 (0.212, 0.432) <.001
Δ Trough FEV_1	FS vs. Placebo	200/12.5 vs. Placebo	0.276 (0.191, 0.361) <.001
		100/12.5 vs. Placebo	0.274 (0.189, 0.360) <.001
	Fp vs. Placebo	200 vs. Placebo	0.183 (0.098, 0.268) <.001
		100 vs. Placebo	0.123 (0.038, 0.208) 0.005

Source: Reviewer

3.2.7.4.3.2 Study 30017 - Sensitivity Analyses Results

3.2.7.4.3.2.1 Study 30017 - Tipping Point Analysis

Table 34 presents tipping point analysis results for Study 30017. In terms of change from baseline trough FEV_1, for the comparison of FS 200/12.5 over placebo, the estimated treatment effect at Week 12 was 0.276 L from the m-BOCF ANCOVA model, and the estimated treatment effect over the 12-week treatment period from the MMRM analysis based on observed data was 0.244 L, while the tipping point from the reviewer's analysis is -2.77 L. Therefore, an assumption that missing outcomes on the experimental treatment arm tended to be roughly ten-fold worse than the magnitude of the overall effect size was needed to tip the statistically significant result to not statistically significant (while assuming missing-at-random missing data on the placebo arm).

Again, most of the reviewer's tipping points are slightly smaller than the applicant reported ones, but the conclusions from the two sets of analyses are the same. For most of the comparisons, an assumed shift in the missing data assumptions on the experimental treatment arm of roughly 2-(-0.34 vs. 0.123 in Fp 100 vs. placebo) to 10-fold (-2.77 vs. 0.276 in FS 200/12.5 vs. placebo) times the size of the treatment effect would be needed to tip the positive decision on treatment efficacy. Such assumptions are considered very unlikely to be plausible. In addition, the range of tipping points from -0.34 L to -2.77 L includes values that are not possible. With these considerations, the tipping point sensitivity analysis results confirmed the validity of the positive primary analysis results, which were based on missing data handling methods that may have potentially violated the true unknown missingness mechnism.

Table 34. Study 30017: Tipping Point Analysis Results (Unit: L)

Endpoint	Drug	Planned Comparison	Primary Analysis Results	Estimated Effect from MMRM Over 12 weeks treatment period	Tipping Point	
					Applicant's	Reviewer's
Δ Trough FEV_1	FS vs. Placebo	200/12.5 vs. Placebo	0.276 (0.191, 0.361) <.001	0.244 (0.176, 0.312) <.001	-3.63	-2.77
		100/12.5 vs. Placebo	0.274 (0.189, 0.360) <.001	0.226 (0.158, 0.295) <.001	-3.66	-1.78
	Fp vs. Placebo	200 vs. Placebo	0.183 (0.098, 0.268) <.001	0.140 (0.072, 0.208) <.001	-1.52	-1.03
		100 vs. Placebo	0.123 (0.038, 0.208) 0.005	0.091 (0.023, 0.159) 0.009	-0.39	-0.34

Source: Reviewer and Applicant's Study 30017 CSR Table 18.

3.2.7.4.3.2.2 Study 30017 - Cumulative Responder Plot

Figure 6 provides continuous responder curves (i.e., empirical distribution functions) on change from baseline in trough FEV_1 for Study 30017. These presentations are developed as described in Section 3.4.2. As shown in Figure 6, there is an initial drop from 100% to approximately 74% for the placebo arm, corresponding to the 26% of patients who dropped out on placebo since patients with missing change from baseline data were classified as unsuccessfully treated for all

thresholds. Generally, across the treatment arms, lack of improvement in FEV_1 from baseline was more frequent in the placebo or Fp monotherapy groups compared to the FS combination groups. Also evident from the figure is that there is clear separation between the treatment groups of placebo, Fp and FS.

For each pair of comparison, a corresponding rank sum statistic based on the Mann-Whitney-Wilcoxon test is calculated on the modified data (Table 35). Results from the Mann-Whitney-Wilcoxon tests, are consistent with the m-BOCF ANCOVA results and provide reassurance that the overall conclusions that both FS and Fp are more effective than placebo in terms of trough FEV_1 are reliable despite the missing data.

Figure 6. Empirical Distribution Function for Change from Baseline in Trough FEV_1 (Study 30017, ITT)

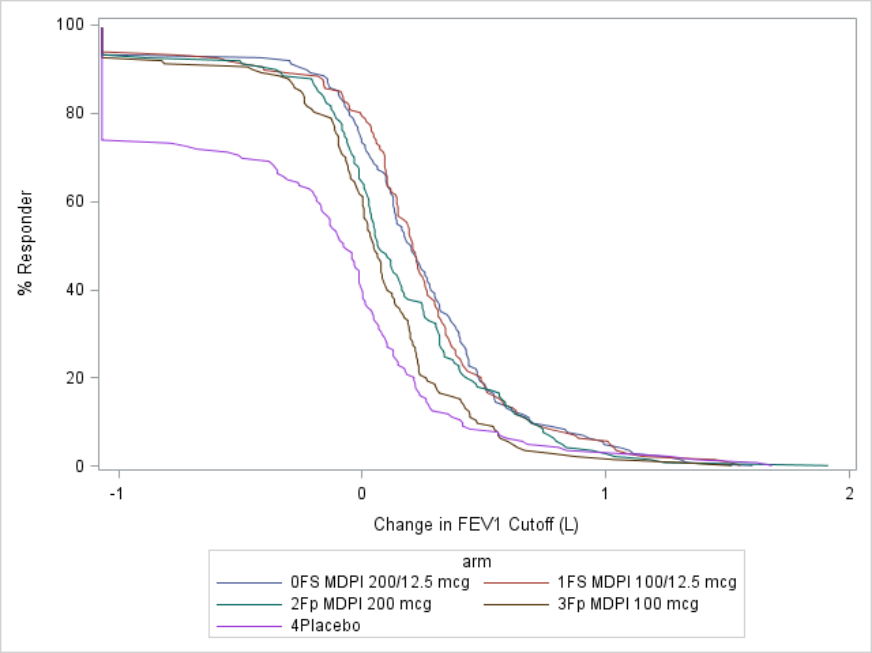


Table 35. Summary of Wilcoxon Rank Sum test on comparisons of interest based on modified data – Study 30017 (ITT Population, Change from baseline trough FEV_1)

Comparison	Wilcoxon Two-Sample Test Two-sided p-value
FS MDPI 200/12.5 mcg BID versus Placebo MDPI	<0.0001
FS MDPI 100/12.5 mcg BID Placebo MDPI	<0.0001
Fp MDPI 200 mcg BID Placebo MDPI	<0.0001
Fp MDPI 100 mcg BID Placebo MDPI	0.002

Source: Reviewer

3.3 Evaluation of Safety

The reader is referred to the Medical Review by Dr. Miya Paterniti for an evaluation of the safety of both FS MDPI and Fp MDPI in asthmatic patients.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This section provides subgroup analysis results by gender (Male and Female), age group (12-17, 18-64, and 65 +), race group (Black, Other, and White), and geographical region (US and non-US). The applicant reasoned that no study was powered to detect differences in efficacy between subgroups, and therefore summarized results in patient subgroups by pooling lung function data from the two phase 3 studies. The applicant didn't conduct any formal interaction tests. In the applicant's summaries, the common dose strengths were pooled together across studies. The applicant's conclusion upon these summaries is that improvement in lung function was consistently observed across all subgroups with reasonable sample sizes (ie, >10) in terms of 1) FS MDPI treatment over Fp MDPI treatment, 2) FS MDPI as compared with placebo, and 3) Fp MDPI as compared with placebo.

I first conducted subgroup analyses by pooling the phase 3 datasets together to check if there was any overall strong signal of treatment effect inconsistency among subgroups. Integrated results are presented in Table 36. There was no signal for a potential interaction between treatment effect and any subgroup. Considering the two phase 3 trials were conducted on patients whose entry asthma severity and control were at different steps of disease development, and the only common treatment arms in the two studies were the placebo arm and the FS 100/12.5 vs. Fp 100 pair, I also conducted and present subgroup analysis on an individual trial base. As this is a dual program supporting approvals for both Fp MDPI and FS MDPI, and there are co-primary endpoints to measure treatment effect on lung function, within each study, I will present the results by following the phase 3 primary endpoint testing hierarchy.

4.1.1 Statistical Method for Subgroup Analyses

For the pooled subgroup analysis on each primary endpoints, SBA $AUC_{0\text{-}12h}$ or Δ trough FEV_1, an interaction analysis was performed first with an ANCOVA model by adding to the primary analysis model covariates (including treatment, baseline FEV_1 value, age, center, sex, baseline asthma therapy) study ID, subgroup variable, study ID by treatment interaction, subgroup variable by treatment interaction. The significance of the interaction between treatment and subgroup was tested.

Within each individual study, for subgroup analyses on each primary endpoint, SBA $AUC_{0\text{-}12h}$ or Δ trough FEV_1, the model was adapted from the pre-specified primary efficacy analysis model. An interaction analysis was performed with an ANCOVA model by including treatment, baseline FEV_1 value, age, center, sex, baseline asthma therapy, the subgroup variable and a subgroup-by-treatment interaction as covariates. When a covariate in the model was the subgroup variable, it was replaced with the categorical version of itself when needed. A by-subgroup ANCOVA model was conducted to estimate the treatment effects within each subgroup. Within each study, for comparisons of FS vs. Fp, FS vs. placebo and Fp vs. placebo at each possible dose, treatment effects will be presented with least square mean estimate and confidence interval of the differences for each subgroup level using a forest plot.

4.1.2 Subgroup Analyses Results

My examination confirmed the applicant's conclusion of consistency of treatment effects across subgroup levels. Integrated analysis results are shown in Table 36. There were no statistically significant interactions in the integrated analyses of the two phase 3 studies, and when a nominally significant interaction was observed within a study, it was not observed in the other study. Lack of a significant treatment-by-subgroup interaction should not be interpreted as evidence that no interaction exists. However, estimated effects were largely similar across the subgroups evaluated. Definitive conclusions cannot be drawn due to limitations such as small sample size in some of the subgroups.

Details on interaction tests and results for the individual studies 301 and 30017 are summarized in Tables 37 and 38, respectively, for each of the co-primary efficacy endpoints as response variable, and for each subgroup variable. As there were multiple interaction tests conducted for multiple subgroup variables, these p-values are nominal and should be interpreted in the context of the multiple comparisons. While there were some signals for potential interactions, there were small sample sizes in certain subgroup levels, and an overall consistency of treatment effects was observed in the forest plots (shown in the Appendix in Figures 8-22).

Table 36. Pooled Phase 3 Studies (301 and 30017), Interaction Test Results for Subgroup Analysis

Subgroup Variable	Covariates in the Model				Subgroup*Treatment Interaction p-value	
	1	2	3	4		
	Original Primary Analysis Model Covariates	Subgroup Variable or Replacement	Add StudyID as a Stratification Factor	Interaction Terms	SBA $AUEC_{0-12h}$	Δ trough FEV_1
Sex	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Keep **Sex** unchanged	StudyID	Study ID*Treatment **Sex*Treatment**	0.3486	0.2791
Age Group	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Replace **Age** with **Age Group**	StudyID	Study ID*Treatment **Age Group*Treatment**	0.6516	0.2951
Region	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Replace **Center** with **Region**	StudyID	Study ID*Treatment **Region*Treatment**	0.0651	0.4830
Race Group	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Add **Race Group**	StudyID	Study ID*Treatment **Race Group*Treatment**	0.1442	0.9134

Source: Reviewer

Table 37. Study 301, Interaction Test Results for Subgroup Analysis

Subgroup Variable	Covariates in the Model			Subgroup*Treatment Interaction p-value	
	1	2	3		
	Original Primary Analysis Model Covariates	Subgroup Variable or Replacement	Interaction Term Due to Subgroup	Baseline adjusted AUC_{0-12h}	Δ trough FEV_1
Sex	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Keep **Sex** unchanged	Sex*Treatment	0.0672	0.1879
Age Group	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Replace **Age** with **Age Group**	Age Group*Treatment	0.1958	0.1145
Region	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Replace **Center** with **Region**	Region*Treatment	0.5689	0.7651
Race Group	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Add **Race Group**	Race Group*Treatment	0.5338	0.9533

Source: Reviewer

Table 38. Study 30017, Interaction Test Results for Subgroup Analysis

Subgroup Variable	Covariates in the Model			Subgroup*Treatment Interaction p-value	
	1	2	3		
	Original Primary Analysis Model Covariates	Subgroup Variable or Replacement	Interaction Term due to Subgroup	Baseline adjusted AUC_{0-12h}	Δ trough FEV_1
Sex	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Keep **Sex** unchanged	Sex*Treatment	0.6865	0.1128
Age Group	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Replace **Age** with **Age Group**	Age Group*Treatment	0.6482	0.3432
Region	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Replace **Center** with **Region**	Region*Treatment	**0.0015**	0.6414
Race Group	Treatment, Baseline FEV_1, Age, Center, Previous Asthma Therapy, Sex	Add **Race Group**	Race Group*Treatment	0.1169	0.8600

Source: Reviewer

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This section summarizes the statistical issues identified during the review of the data supporting the FS and Fp MDPI development program.

5.1.1 The Potential Impact of Missing Data

Methods for handling missing data in the primary analyses and sensitivity analyses were discussed in Section 3.2.4.2, and this reviewer's sensitivity analysis results were presented in Section 3.2.7. While the dropout rates in the phase 3 studies ranged from 2% to 23% depending on treatment arms, in the phase 2 studies, partially due to pre-specified discontinuation criteria for lack of efficacy, the dropout rates were greater, ranging from 12% to 45%. With the applicant's study data collection in which patients who discontinued treatment were not followed, and with the applicant's proposed missing data handling and primary analysis methods (assuming missing-at-random missing data or other strong and unverifiable assumptions), there is concern that the primary analysis does not reliably evaluate the intention-to-treat (ITT) estimand, i.e., the difference in outcome improvement for all randomized participants regardless of adherence. Therefore, we assessed the potential impact of missing data on the reliability of efficacy results through a series of tipping point analyses conducted for each statistically significant comparison with respect to trough FEV_1. In general, for each comparison, the analysis treated missing data in the control arm as MAR and allowed missing data in the experimental arm to be missing-not-at-random by systematically varying the degree of shift to the MAR imputed values. Assumed shifts were increased until reaching a tipping point at which the result of the comparison of interest changed from statistically significant to not statistically significant. Across the three trials with positive results, in all comparisons, the tipping points ranged from 2-fold to 10-fold the sizes of the observed treatment effects, assumptions which were generally considered implausible. In summary, the tipping point analyses support the primary analysis conclusions made by each of the three studies.

The cumulative responder plot approach was also applied to check the potential impact of missing data. Due to the substantially uneven dropout rates among the treatment arms with the placebo arms having the highest rate in each study, the CRP approach favored the active arms in each comparison. So while these test results are consistent with the primary analyses or even show greater evidence than the primary analysis in favor of the active arms, this approach was heavily influenced by the dropout rates and can only be used as supportive.

5.1.2 Reporting of Estimated Treatment Effect

Primary analyses of the primary endpoints in the phase 3 trials were all based on single imputation methods, LOCF in the case of SBA FEV_1 $AUEC_{0\text{-}12h}$ and m-BOCF in the case of change from baseline trough $FEV1_1$. While the validity of binary conclusions about evidence of efficacy made by the primary imputation methods were confirmed with tipping point sensitivity analyses, whether or not the LOCF or BOCF based efficacy analyses provide estimated effects that are sufficiently reliable for labeling is a separate issue that will need to be discussed further by the review team.

5.1.3 Totality of Evidence

While this review mainly evaluated the efficacy results by study, evaluation of the totality of evidence supporting the two applications (drugs) at each of the three proposed doses is our ultimate goal. There are several pieces of information, which may not be of equal importance, that we rely on collectively to draw our final conclusion:

1) As the proposed indication is quite broad for each drug, it is notable that the overall program showed efficacy across multiple asthma severity/control populations; this may provide stronger evidence than looking at a single population and then extrapolating to other populations;

2) The program failed to show evidence of efficacy for Fp MDPI in patients with persistent asthma who are symptomatic despite treatment with high-dose ICS (Study 202);

3) The clinical program did not provide replication of evidence of efficacy of each drug at each dose. The reason was partially due to design (lack of full replication), and partially due to the failed trial in high-dose ICS patients (Study 202). However, because three doses of both the proposed monotherapy and combination products were evaluated, with largely consistent findings of efficacy, direct evidence of efficacy for each dose is also supported by results for the other two doses;

4) The statistical evidence of treatment effects based on comparisons of Fp and FS to placebo in the Studies 201, 301, and 30017 was generally very strong (highly statistically significant p-values, often <0.001). Furthermore, sensitivity analyses demonstrated that the results were convincing despite the missing data.

5) Both FS and Fp are approved drugs in the US (administered using a different device) for which there have been previous findings of safety and effectiveness. It is by this thought that for the combination of an approved drug with a new device applied through the 505(b) (2) pathway, full replication of results may not be needed when the treatment effects demonstrated are consistent with previous trials of referenced drugs and doses, the evidence from each single study is persuasive, and there is supportive evidence from multiple doses in other studies.

Based on the above considerations, we consider the totality of evidence provided by the clinical program to support the effectiveness of the two drugs at each of the three proposed doses for the treatment of persistent asthma patients. However, it is notable that the only study conducted in patients uncontrolled on high-dose ICS did not show evidence of efficacy for Fp. At a minimum, these results should be included in labeling to inform prescribers and patients.

5.2 Collective Evidence

Across the four studies, the primary endpoint SBA FEV_1 $AUC_{0\text{-}12h}$ was used to assess the contribution of the bronchodilator effect of Sx to the efficacy of the FS combination therapy (based on a comparison to the Fp monotherapy), or to evaluate the treatment effect of the FS

combination therapy over placebo; the primary endpoint change from baseline in trough FEV_1 was used to assess the treatment effect of Fp monotherapy over placebo.

We summarize conclusions about the proposed products in the following sections.

5.2.1 Fp MDPI

5.2.1.1 Fp MDPI 200 mcg BID

In terms of change from baseline trough FEV_1, for Fp 200, the efficacy over placebo was demonstrated in Study 30017 only, with an estimated mean difference from placebo at the end of 12-week treatment period of 0.276 L (95% CI: 0.191, 0.361; p <.001). Study 202 failed to demonstrate efficacy of Fp 200 in persistent asthma patients who were symptomatic despite being on high-dose of ICS therapy.

5.2.1.2 Fp MDPI 100 mcg BID

In terms of change from baseline trough FEV_1, for Fp 100: in Study 201, the mean difference from placebo ***over*** the 12-week treatment period was 0.136 L (95% CI: 0.056, 0.216; p < 0.001); in Studies 301 and 30017, mean difference from placebo ***at*** the end of the 12-week treatment period was 0.151 L (95% CI: 0.057, 0.244; p = 0.002) and 0.123 L (95% CI: 0.038, 0.208; p = 0.005), respectively. Study 202 failed to demonstrate efficacy of Fp 100 in persistent asthma patients who were symptomatic despite being on high-dose of ICS therapy.

5.2.1.3 Fp MDPI 50 mcg BID

In terms of change from baseline trough FEV_1, for Fp 50: in Study 201, the mean difference from placebo ***over*** the 12-week treatment period was 0.107 L (95% CI: 0.027, 0.187; p = 0.009); in Study 301, mean difference from placebo ***at*** the end of the 12-week treatment period was 0.119 L (95% CI: 0.025, 0.212; p = 0.013). Study 202 failed to demonstrate efficacy of Fp 50 in in persistent asthma patients who were symptomatic despite being on high-dose of ICS therapy.

5.2.2 FS MDPI

5.2.2.1 FS MDPI 200/12.5 mcg BID

The efficacy of FS 50/12.5 mcg was demonstrated in a single study, Study 301: 1) with statistically significant greater improvement compared with placebo for primary endpoints of standardized baseline-adjusted (SBA) FEV_1 $AUEC_{0\text{-}12h}$ and trough FEV_1 at Week 12 with estimated effect sizes of 0.325 L (95% CI: 0.203, 0.447; p <.001) and 0.266 L (95% CI: 0.172, 0.360; p <.001), respectively; 2) with statistically significant greater improvement compared with Fp 50 for SBA FEV_1 $AUEC_{0\text{-}12h}$ with estimated effect size of 0.131 L (95% CI 0.011, 0.250; p = 0.032) , as the efficacy of monotherapy Fp 50 was established earlier.

5.2.2.2 FS 100/12.5 MDPI mcg BID

The efficacy of FS 100/12.5 mcg was demonstrated in both Study 301 and Study 30017, where statistically significant greater treatment differences in SBA FEV_1 $AUEC_{0-12h}$ were observed between FS 100/12.5 and placebo of 0.335 L (Study 301) and 0.322 (Study 30017); and in changes from baseline in trough FEV_1 of 0.262 L (Study 301) and 0.274 (Study 30017). As efficacy of Fp 100 was established earlier, the contribution of Sx to the efficacy of FS 100/12.5 mcg was demonstrated by statistically significant treatment differences of 0.179 L (Study 301) and 0.182 (Study 30017) between FS 100/12.5 and Fp 100 in SBA FEV_1 $AUEC_{0-12h}$.

5.2.2.3 FS 50/12.5 MDPI mcg BID

The efficacy of FS 50/12.5 mcg was demonstrated in Study 301: 1) with statistically significant greater improvement compared with placebo for primary endpoints of SBA FEV_1 $AUEC_{0-12h}$ and trough FEV_1 at Week 12 with estimated effect sizes of 0.325 L (95% CI: 0.203, 0.447; p <.001) and 0.266 L (95% CI: 0.172, 0.360; p <.001), respectively; 2) with statistically significant greater improvement compared with Fp for SBA FEV_1 $AUEC_{0-12h}$ with estimated effect size of 0.131L (95% CI 0.011, 0.250; p = 0.032) , as the efficacy of monotherapy Fp was established earlier. Of note, there was no replicate evidence for the efficacy of Fp 50/12.5.

5.3 Conclusions and Recommendations

Consistent with the intended indications, the four studies collectively spanned a broad disease severity/control spectrum of persistent asthma. Three of the studies showed strong evidence of treatment effects over placebo for the two drugs at the three proposed doses. However, Study 202 failed to demonstrate evidence of efficacy for mid- to high-dose of Fp MDPI in patients with persistent asthma who are symptomatic despite being on treatment with high-dose ICS. With considerations discussed in Section 5.1.3, we draw the following conclusions upon review of the Fp/FS MDPI dual program data:

The totality of evidence provided by the clinical program supports the effectiveness of Fp and FS at each of the three proposed doses for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. At a minimum, results from Study 202, which did not show evidence of efficacy for Fp in patients uncontrolled on high-dose ICS, should be included in labeling.

5.4 Labeling Recommendations (as applicable)

We have the following general comments:

- Primary analyses of the primary endpoints in the phase 3 trials were all based on single imputation methods, LOCF in the case of SBA FEV_1 $AUEC_{0-12h}$ and m-BOCF in the case of change from baseline trough $FEV1_1$. While the validity of binary conclusions about evidence of efficacy made by the primary imputation methods were confirmed with tipping point sensitivity analyses, whether or not the LOCF or BOCF based efficacy analyses provide estimated effects that are sufficiently reliable for labeling is a separate issue that will need to be discussed further by the review team.

- Because the only study conducted in patients uncontrolled on high-dose ICS did not show evidence of efficacy for Fp, these results should be included in labeling to inform prescribers and patients.

More specific recommendations on labeling may be made later in the review cycle.

6 Works Cited

Fanta, C. H. (2009, March 5). Asthma. *The New England Journal of Medicine*, pp. 1002-1014.

Taylor, D. R. (2008). A new perspective on concepts of asthma severity and control. *European Respiratory Journal*, pp. 545-554.

7 Appendix

7.1 Phase 2 Dose-ranging Studies

7.1.1 Log-dose Linearity Test

Table 39. Study 201 – Log-dose Linearity Test Contrast Coefficients

Study Drug	Daily Fp Dose (mcg)	Log (Dose +1)	Linear Coefficients	p value for linear contrast
Placebo (0)	0	0	-0.831	
Fp MDPI 12.5 mcg BID	25	3.258	-0.040	
Fp MDPI 25 mcg BID	50	3.932	0.124	0.0004
Fp MDPI 50 mcg BID	100	4.615	0.290	
Fp MDPI 100 mcg BID	200	5.303	0.457	

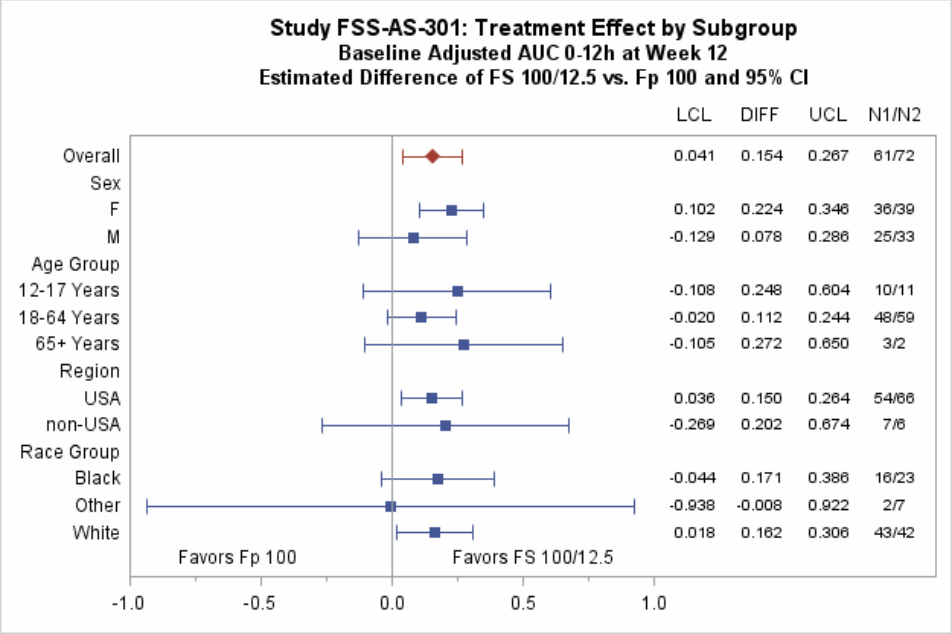
Table 40. Study 202 – Log-dose Linearity Test Contrast Coefficients

Study Drug	Daily Fp Dose (mcg)	Log (Dose +1)	Linear Coefficients	p value for linear contrast
Placebo (0)	0	0	-0.855	
Fp MDPI 50 mcg BID	100	4.615	0.018	
Fp MDPI 100 mcg BID	200	5.303	0.148	0.0866
Fp MDPI 200 mcg BID	400	5.994	0.279	
Fp MDPI 400 mcg BID	800	6.686	0.410	

7.2 By Study Subgroup Analysis Results

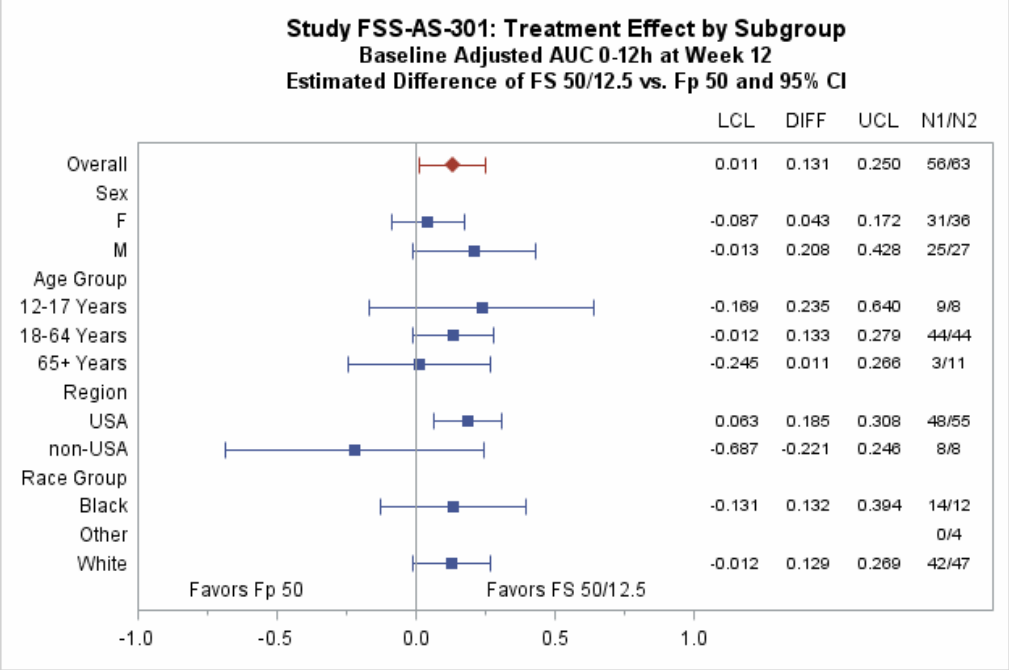
7.2.1 Study 301 Results

Figure 7. Study 301: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 100/12.5 vs. Fp 100)



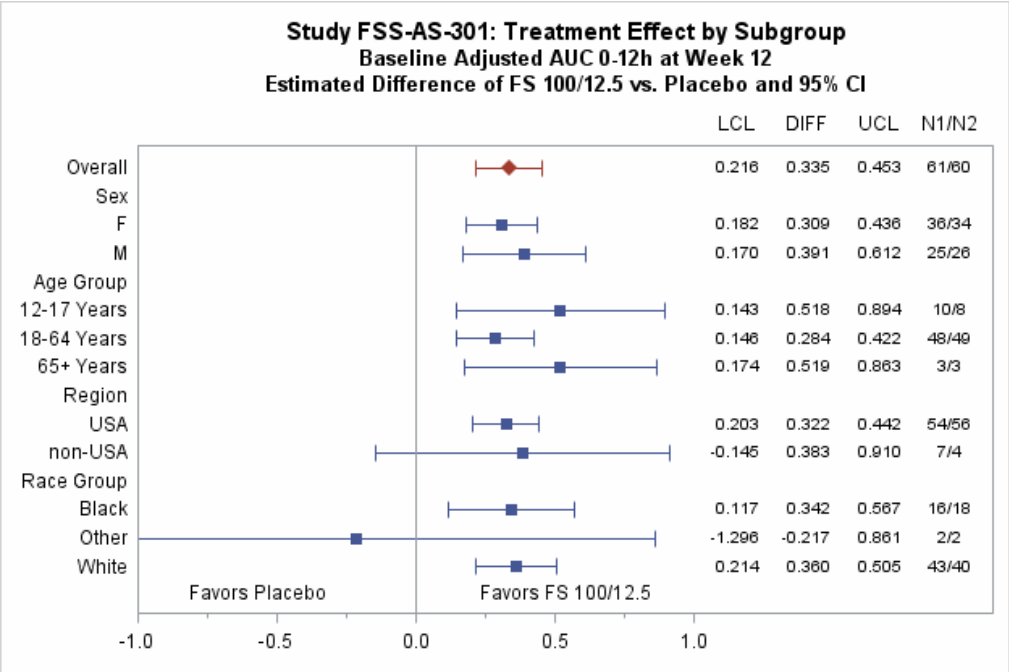
Source: Reviewer

Figure 8. Study 301: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 50/12.5 vs. Fp 50)



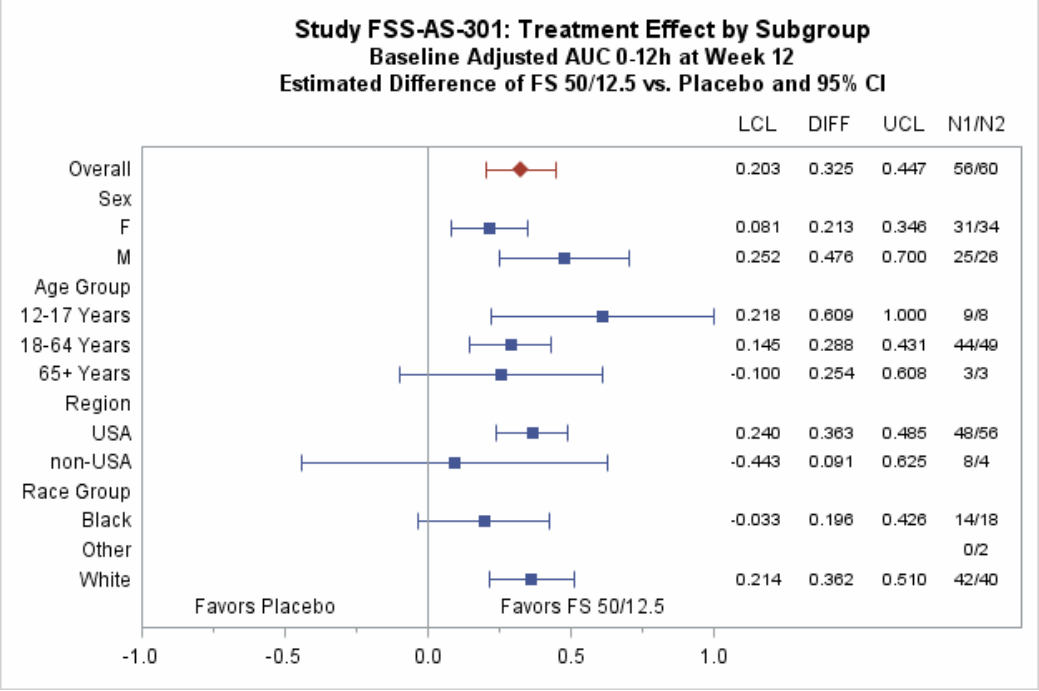
Source: Reviewer

Figure 9. Study 301: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 100/12.5 vs. Placebo)



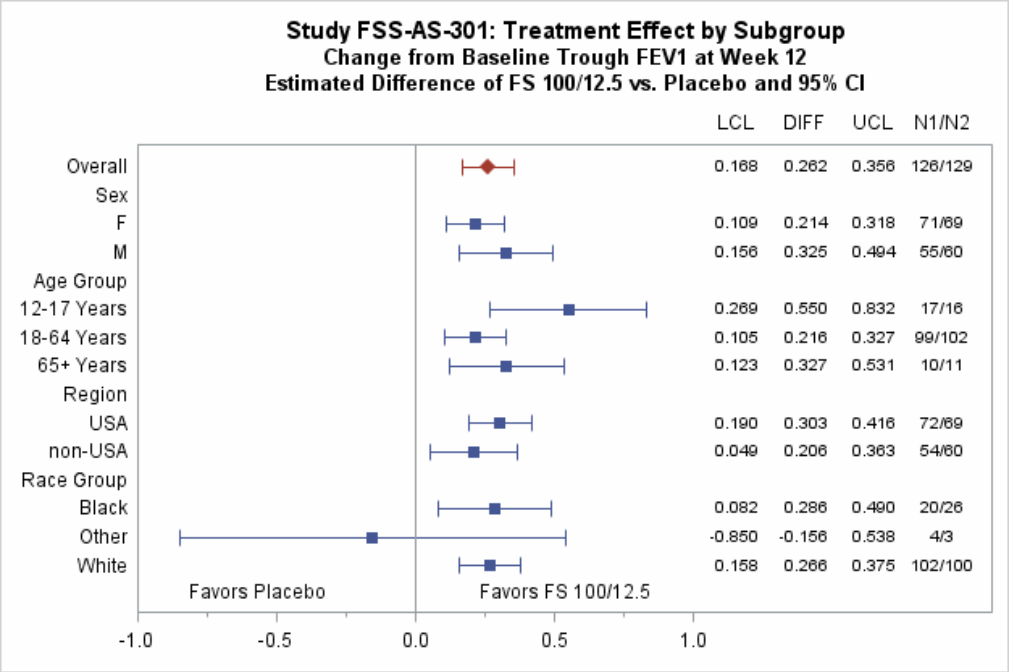
Source: Reviewer

Figure 10. Study 301: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 50/12.5 vs. Placebo)



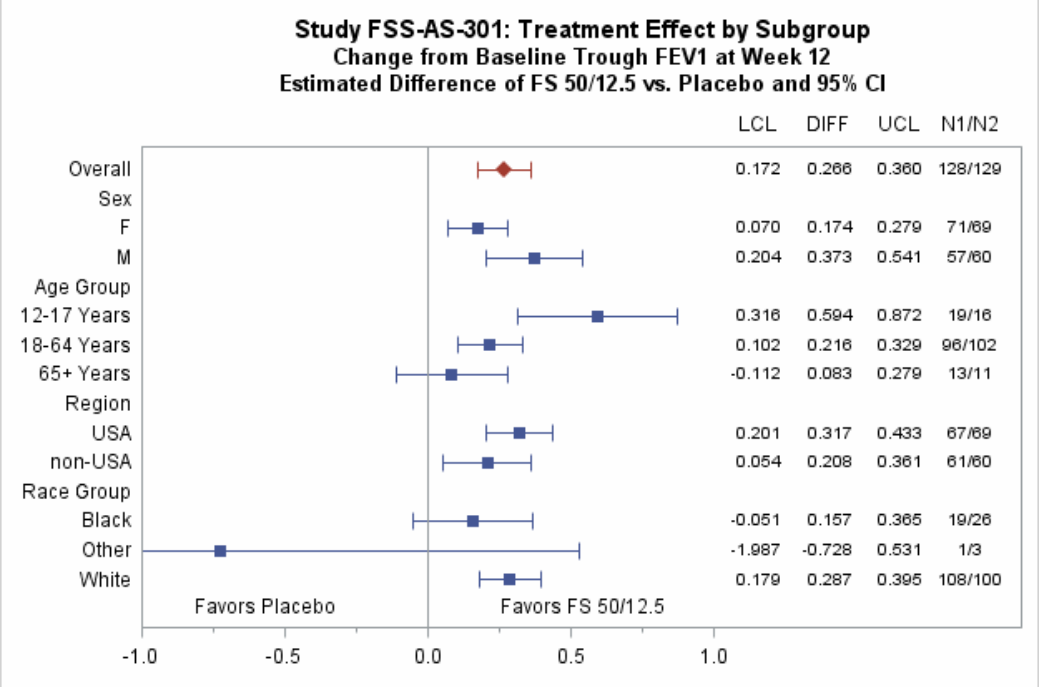
Source: Reviewer

Figure 11. Study 301: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (FS 100/12.5 vs. Placebo)



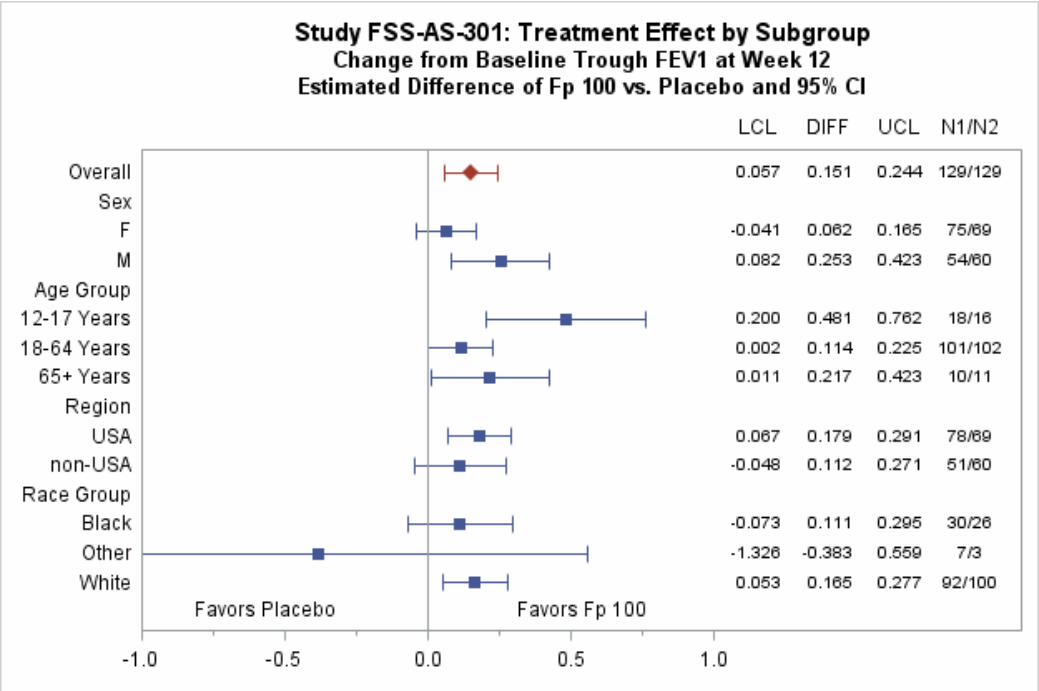
Source: Reviewer

Figure 12. Study 301: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (FS 50/12.5 vs. Placebo)



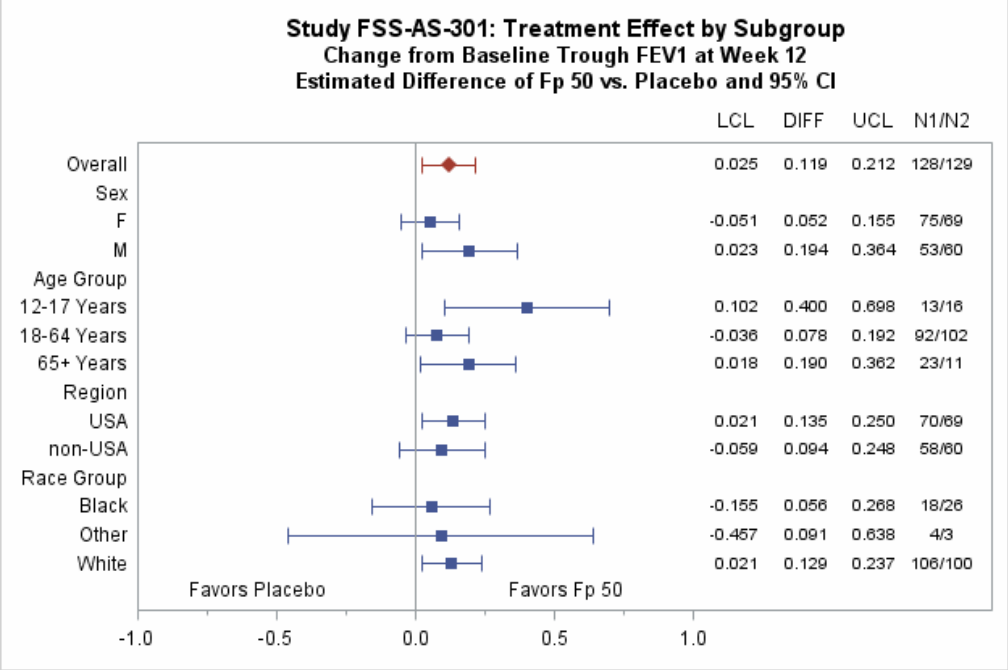
Source: Reviewer

Figure 13. Study 301: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (Fp 100 vs. Placebo)



Source: Reviewer

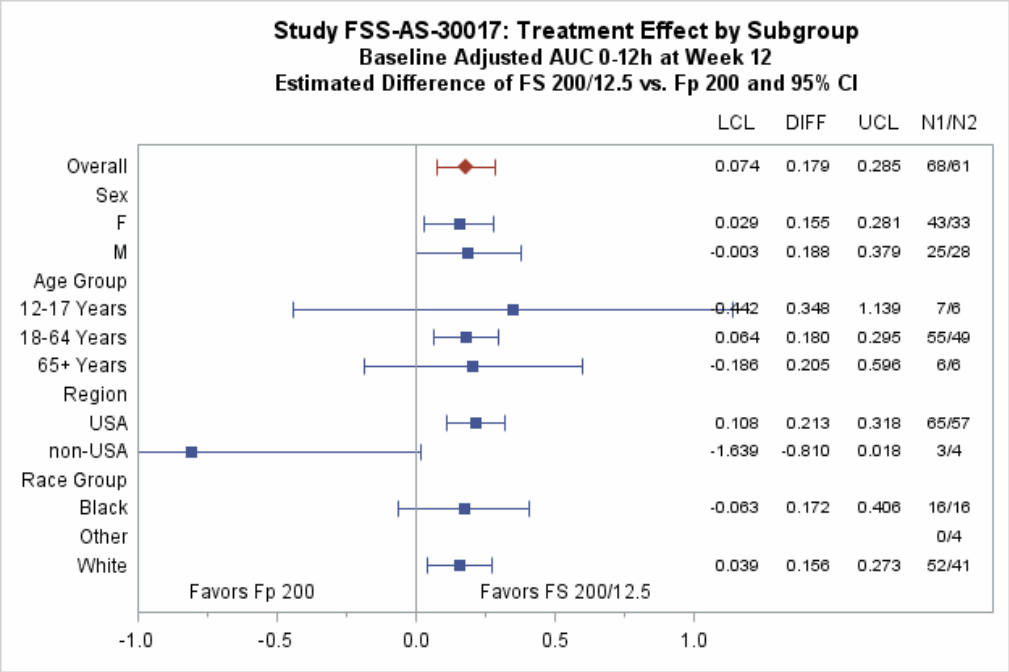
Figure 14. Study 301: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (Fp 50 vs. Placebo)



Source: Reviewer

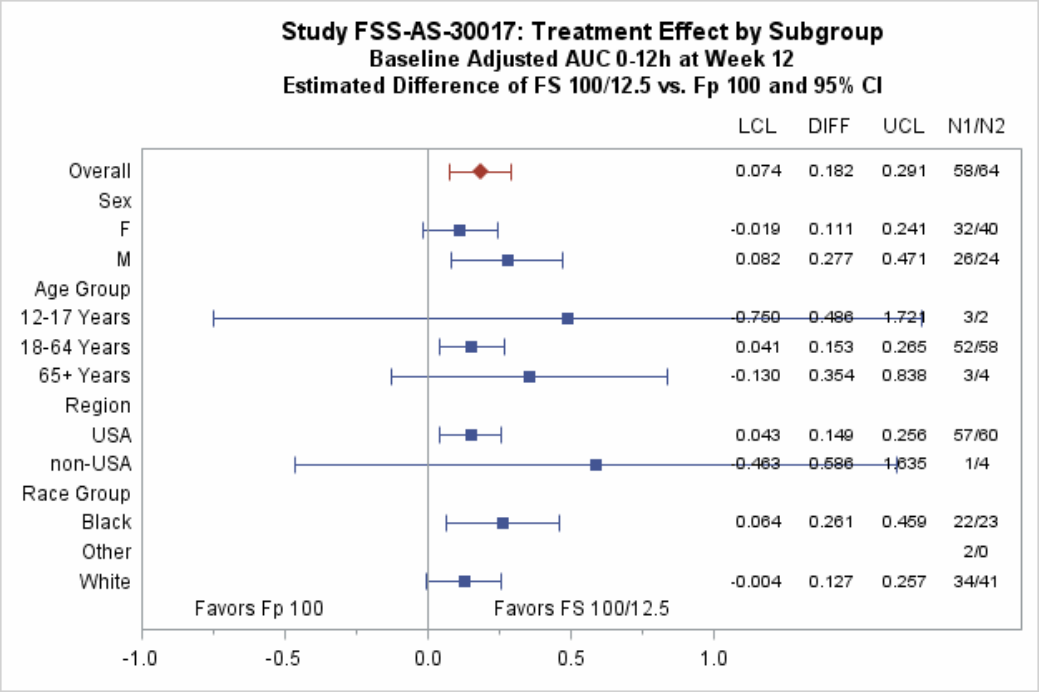
7.2.2 Study 30017 Results

Figure 15 Study 30017: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 200/12.5 vs. Fp 200)



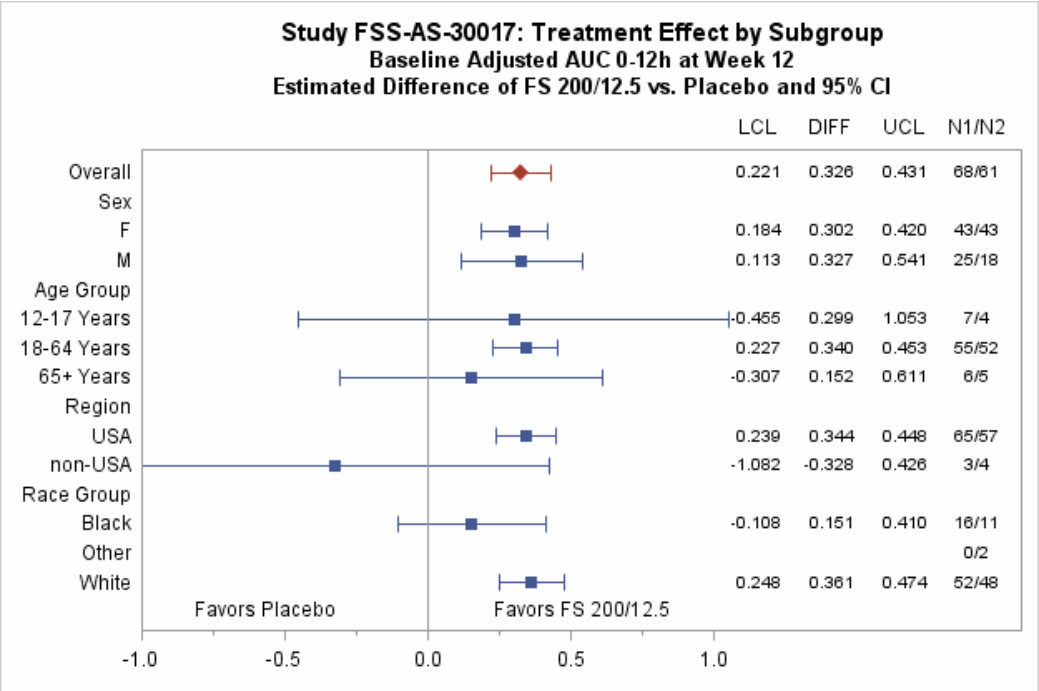
Source: Reviewer

Figure 16. Study 30017: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 100/12.5 vs. Fp 100)



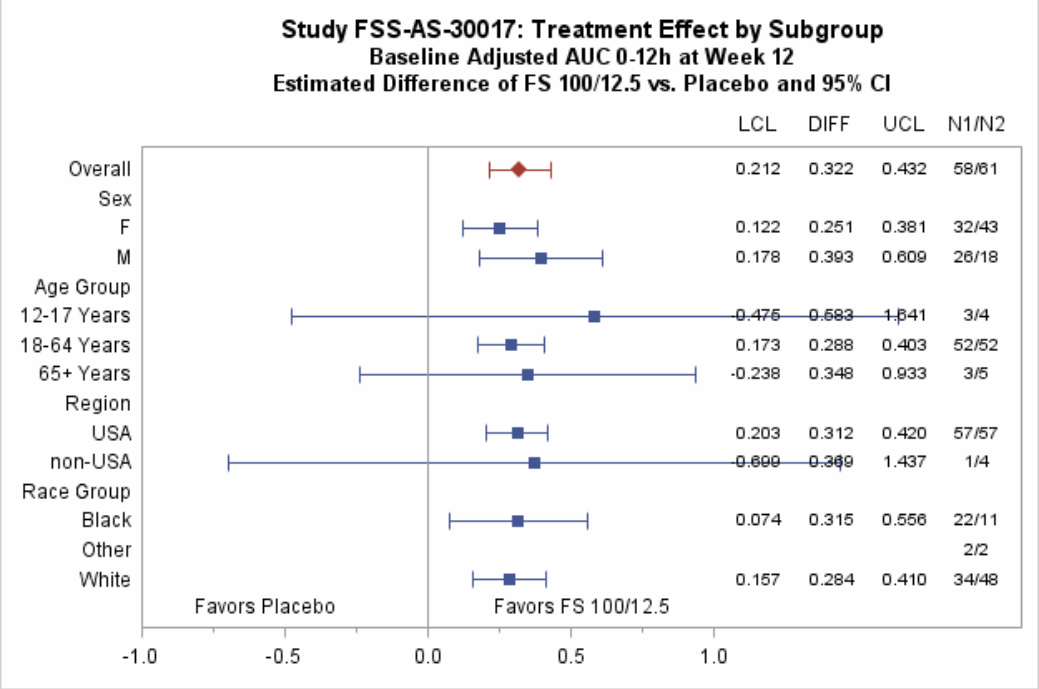
Source: Reviewer

Figure 17. Study 30017: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 200/12.5 vs. Placebo)



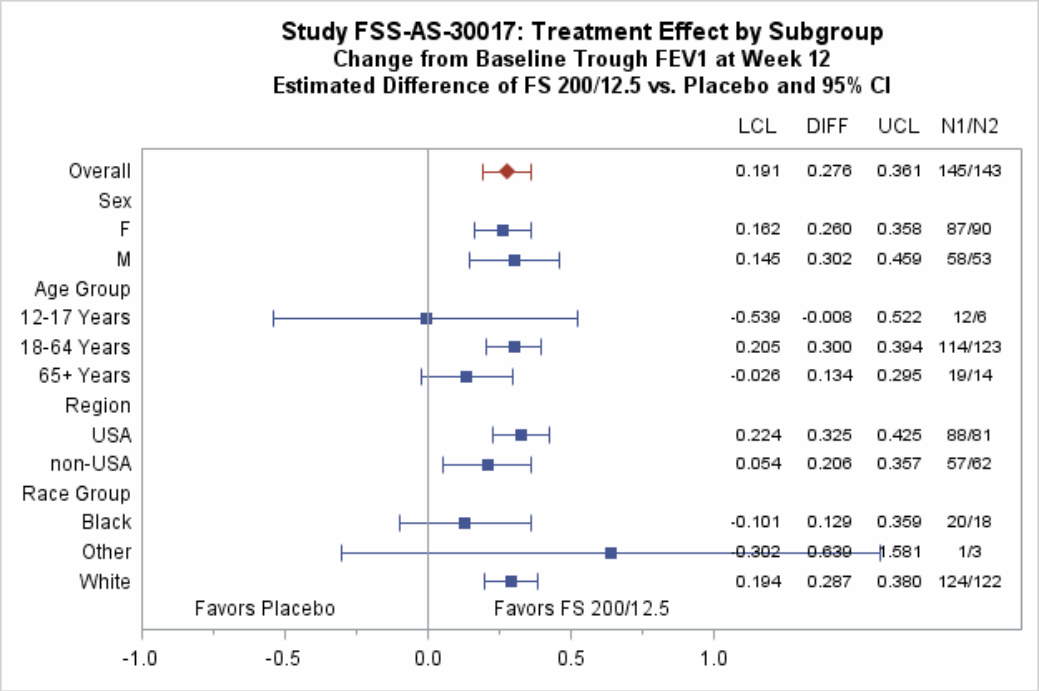
Source: Reviewer

Figure 18. Study 30017: Treatment Effect by Subgroup – Baseline Adjusted AUC_{0-12h} at Week 12 (FS 100/12.5 vs. Placebo)



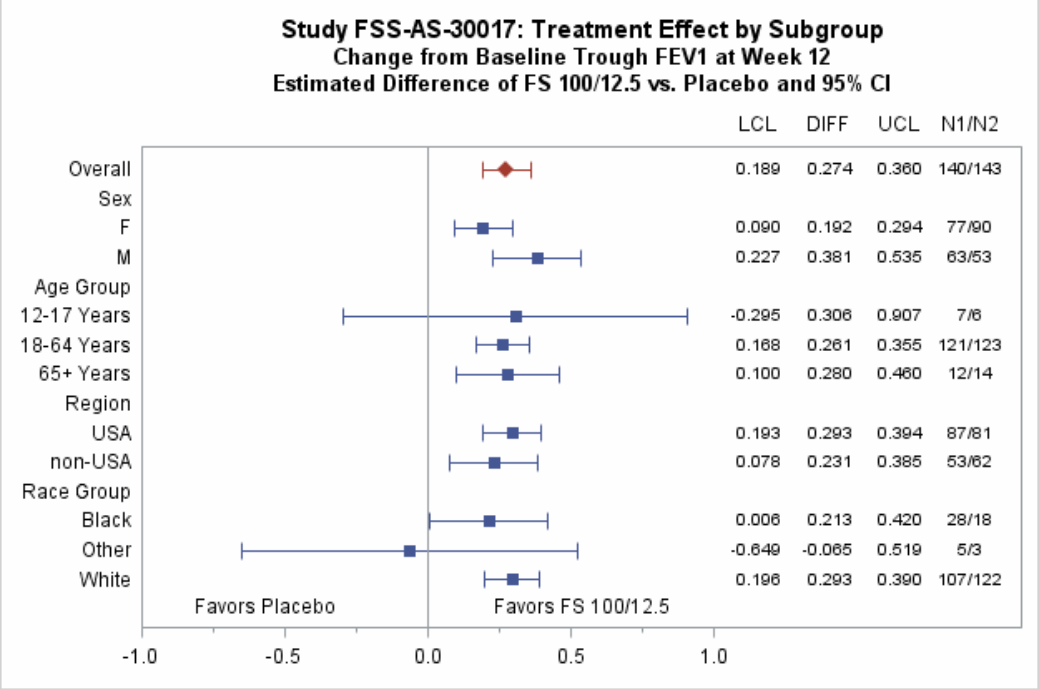
Source: Reviewer

Figure 19. Study 30017: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (FS 200/12.5 vs. Placebo)



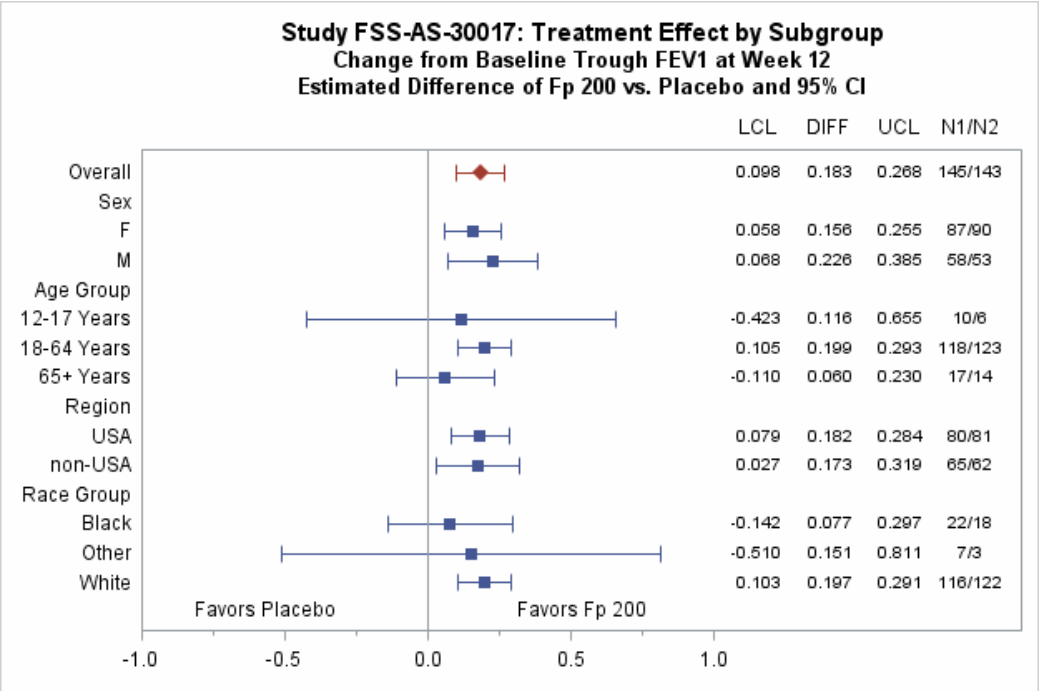
Source: Reviewer

Figure 20. Study 30017: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (FS 100/12.5 vs. Placebo)



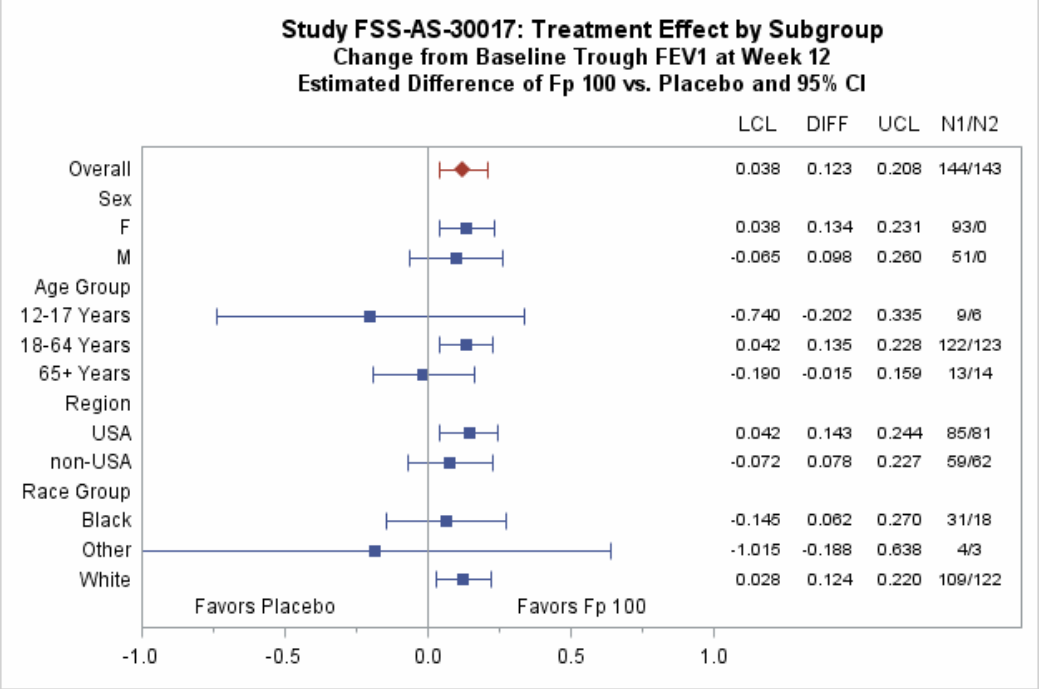
Source: Reviewer

Figure 21. Study 30017: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (Fp 200 vs. Placebo)



Source: Reviewer

Figure 22. Study 30017: Treatment Effect by Subgroup – Change from Baseline Trough FEV_1 at Week 12 (Fp 100 vs. Placebo)



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/s/

YU WANG
12/09/2016

GREGORY P LEVIN
12/09/2016

STATISTICAL FILING REVIEW FOR A NEW NDA/BLA

NDA/BLA Number:	208798
NDA/BLA Type:	Standard
Stamp Date:	March 28, 2016
Applicant:	Teva
Drug Name:	Fluticasone Propionate Multidose Dry Powder Inhaler
Indication:	Maintenance Treatment of Asthma as Prophylactic Therapy in Patients Aged 12 Years and Older
Statistical Team:	Yu (Jade) Wang (Reviewer), Gregory Levin (Team Lead)
Clinical Team:	Miya Paterniti (Reviewer), Banu Karimi-Shah (Team Lead)
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Project Manager:	Laura Musse

Introduction:

Fluticasone Propionate (Fp) Multidose Dry Powder Inhaler (MDPI) is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Fp MDPI is supplied in three doses of Fp: 55, 113 and 232 mcg. In parallel, Teva has also developed a combination product of fluticasone propionate/salmeterol MDPI (FS MDPI) at the doses of 55/12.5, 113/12.5 and 232/12.5 mcg (submitted under NDA 209799). The two clinical programs include a total of 9 studies (Table 1). Among them, there are 3 phase II dose ranging studies, one long term phase III safety study and two phase III efficacy and safety studies. For the efficacy review of Fp MDPI, the statistical review will focus on studies FpS-AS-201 (Fp201), FpS-AS-202 (Fp202), FSS-AS-301 (301) and FSS-AS-30017 (30017). These studies are all randomized, multi-center, parallel, double-blind placebo-controlled trials (the two phase II active controlled trials are double-blind for placebo and study drug and open label for active controls). These studies are selected to confirm the claimed efficacy of the study drug at each dose with replication. Table 2 gives a summary of the dose coverage of each study with the number of randomized subjects under each arm.

Table 1. Studies in the Fp MDPI and FS MDPI Clinical Program

Phase	**Type**	**Studies**	**Study Selected for Fp (NDA 209798) Review**
I	PK, safety, and tolerability	FpS-AS-101	
		FpS-AS-102	
		FSS-AS-10042	
II	Dose ranging	FpS-AS-201 (Fp201)	✓
		FpS-AS-202 (Fp202)	✓

Phase	Type	Studies	Study Selected for Fp (NDA 209798) Review
		FSS-AS-201 (FS201)	
III	Long term safety	FSS-AS-305	
	Efficacy and safety	FSS-AS-301 (301)	✓
		FSS-AS-30017 (30017)	✓

Table 2. Dose Strengths Covered by Each Selected Study and Number of Randomized Patients

Study	Placebo MDPI BID	Fp MDPI (mcg) BID						Flovent Diskus (mcg) BID	
		12.5	25	50	100	200	400	100	250
Fp201	104	103	104	104	103			104	
Fp202	106			107	107	106	107		107
301	100			129	130				
30017	145				146	146			

Filing Checklist:

On **initial** overview of the NDA/BLA application for refuse-to-file (RTF):

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _YES__
Potential Review Issues:

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.	✓			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			Adequacy of sensitivity analyses carried out by applicant will be a review issue.

Additional Discussion:

NA.

Comments for Applicant:

NA.

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/s/

YU WANG
06/03/2016

GREGORY P LEVIN
06/03/2016