CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208798 and 208799
Priority or Standard	Standard
Submit and Received Date	March 28 (208798) and March 29 (208799), 2016
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Division / Office	DPARP/ODEII/OND/CDER/FDA
Reviewer Name(s)	Miya Okada Paterniti, M.D.
Through CDTL	Banu Karimi-Shah, M.D.
Review Completion Date	October 25, 2016
Established Name	Fluticasone Propionate (Fp;208798) and Fluticasone Propionate/Salmeterol Xinafoate (FS; 208799)
(Proposed) Trade Name	ArmonAir (208798) and AirDuo (208799)
Therapeutic Class	Synthetic corticosteroid (Fp) and a synthetic corticosteroid/long-acting beta-agonist combination product (FS)
Applicant	Teva
Formulation(s)	Fp- 55 mcg, 113 mcg, and 232 mcg (208798); FS- 55/14 mcg, 113/14 mcg, 232/14 mcg (208799)
Dosing Regimen	One inhalation twice daily
Indication(s)	Treatment of asthma in patients aged 12 years and older
Intended Population(s)	Patients 12 years and older with asthma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on my review of the risk-benefit assessment, my recommendation is **Approval** pending revisions to the label.

1.2 Risk Benefit Assessment

In order to frame the discussion regarding risk-benefit assessment, a brief summary of the efficacy and safety of fluticasone propionate (Fp) and fluticasone propionate/salmeterol xinafoate (FS) administered via Teva's novel multidose dry powder inhaler (MDPI) is provided below.

Introduction

Teva submitted two NDAs, one for Fp MDPI and one for FS MDPI, for the treatment of asthma in patients 12 years of age and older.

Fp MDPI, is a fixed-dose inhaled corticosteroid (ICS) delivered in Teva's novel multidose dry powder inhaler (MDPI). Fp MDPI is supplied in multiple dosage strengths (50, 100, and 200 mcg). The 50, 100 and 200 mcg doses represent the nominal doses and will be used for the reminder of the review. The metered doses per inhalation, which will be included in the label, are 55, 113, and 232 mcg. Fp MDPI is administered as 1 inhalation twice daily.

The other proposed drug product, FS MDPI, is a fixed-dose combination inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) delivered in Teva's novel multidose dry powder inhaler (MDPI). The combination device contains fluticasone propionate as the ICS and salmeterol as the LABA. FS MDPI is supplied in multiple dosage strengths of fluticasone propionate (50, 100, and 200 mcg) with a fixed dose of salmeterol (12.5 mcg). The 50/12.5, 100/12.5 and 200/12.5 mcg doses represent the nominal doses and will be used for the reminder of the review. The metered doses per inhalation, which will be included in the label, are 55/14, 113/14, and 232/14 mcg. FS MDPI is administered as 1 inhalation twice daily.

Fp MDPI and FS MDPI have modified formulations and a novel device from that of the listed drugs (Flovent and Advair Diskus, GlaxoSmithKline) (b) (4) . Therefore, Teva conducted a full development program, including dose-ranging studies, to support the efficacy and safety of the Fp and FS products. The program consisted of 6 key studies: two 12-week Fp dose-ranging studies, a single dose salmeterol dose-ranging study, two 12-week efficacy and safety studies which included the usual factorial design to support the efficacy and safety the FS combination product, and a 26-week long-term safety study. Although the products are under two different NDAs (208798 and 208799), due to the nature of the development programs, and that

registration is sought for the dual combination product as well as one of the monocomponents, the data supporting the efficacy and safety of both Fp and FS can be found across all six studies. Therefore, the data for these two NDAs will be covered by this single review.

Summary of Clinical Findings

Summary of Efficacy

Fp MDPI (will be referred to as Fp) is proposed for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. FS MDPI (will be referred to as FS) is proposed for the treatment of asthma in patients 12 years of age and older. The program consisted of 6 key studies: two 12-week Fp dose-ranging studies (201 and 202), a single dose salmeterol dose-ranging study (FSS-201) , two 12-week efficacy and safety studies (301 and 30017) which included the usual factorial design to support the efficacy and safety the FS combination product, and a 26-week long-term safety study (305). Study 305 will be discussed in the Summary of Safety.

The Fp dose-ranging studies (201 and 202) were 12-week, randomized, double-blind, placebo and active-controlled studies that included the low (50 mcg), mid (100 mcg), and high (200 mcg) Fp doses and ranged from 12.5 to 400 mcg. The low (50 mcg) and mid (100 mcg) Fp doses were included in both Studies 201 and 202, while the high dose (200 mcg) was included only in Study 202. The comparator for Study 201 was Flovent Diskus 100 mcg (the marketed mid-dose) and the comparator for Study 202 was Flovent Diskus 250 mcg (the marketed high-dose). The salmeterol dose-ranging study (FSS-201) was a single-dose, double-blind (with the exception of the open-label active-control arm), placebo-controlled, dose-ranging study of salmeterol (0 to 50 mcg) compared to Advair 100 mcg/50 mcg.

For Study 201, which included the proposed low (50 mcg) and mid (100 mcg) doses of Fp, no Fp dose was significantly different than Flovent Diskus 100 mcg (the marketed mid-dose). All doses, with the exception of the lowest (12.5 mcg) were significantly different than placebo. The point estimate for the primary endpoint of FEV1 change from baseline to Week 12 for Flovent Diskus 100 mcg (234 mL; 95% CI (162 mL, 306 mL)) was between the Fp 12.5 mcg (189 mL; 95% CI (112 mL, 266 mL)) and Fp 25 mcg (268 mL; 95% CI (194 ML, 343 mL)). The proposed mid-dose for Fp (100 mcg) trended toward a larger improvement in FEV1 at Week 12 (295 mL; 95% CI (219 mL, 371 mL)) compared to marketed mid-dose for Flovent Diskus (100 mcg). Notably, the 25 mcg dose is proposed for the pediatric studies in 4-11 year olds. These results support the proposed Fp low (50 mcg) and mid (100 mcg) doses.

For Study 202, which included all 3 proposed doses (50, 100, and 200 mcg) no Fp dose was significantly different than Flovent Diskus 250 mcg (the marketed high-dose). Only the Fp 200 mcg dose was significantly different from placebo and is the proposed high-dose for Fp. The point estimate for the primary efficacy endpoint of FEV1 change from baseline to Week 12 for Flovent Diskus 250 mcg (145 mL; 95% CI (79 mL, 210 mL)), was between the Fp 100 mcg (100

mL; 95% CI (37 mL, 163 mL)) and Fp 200 mcg (148 mL; 95% CI (81 mL, 214 mL)). These results support the proposed Fp high dose at 200 mcg.

The exploration for salmeterol dose response was evaluated in study FSS-201. Study FSS-201 was a single-dose, cross-over study with 4 doses of salmeterol (6.25, 12.5, 25, and 50 mcg) combined with a fixed dose of fluticasone propionate (100 mcg) delivered as fluticasone propionate/salmeterol inhalation powder (FS). The comparators were Flovent Diskus 100 mcg (considered the 0 mcg salmeterol dose), and Advair 100 mcg/50 mcg. The maximum dose of 50 mcg is the dose of salmeterol that is currently marketed in Advair Diskus. The baseline-adjusted FEV1 AUC 0-12 hours demonstrated a dose-related increase in baseline adjusted FEV1 AUC 0-12. The primary endpoint for FS 100/50 mcg was significantly higher than Advair 100/50 mcg by 58 mL (95% CI (22 ml, 94 mL)). Advair 100/50 mcg was most closely comparable to FS 100/12.5 mcg (249 mL), with the smallest difference (3 mL; 95% CI (-32 mL, 39 mL)). The 12.5 mcg dose is the proposed fixed dose of salmeterol.

Studies 301 and 30017 were 12-week, randomized, double-blind, placebo-controlled studies of 3 doses of ICS (fluticasone propionate: 50, 100, and 200 mcg) with and without a fixed dose of LABA (salmeterol: 12.5 mcg) compared to placebo in 1375 patients (Study 301: n= 647, about 130 per treatment arm; Study 30017: n=728, about 145 per treatment arm) with persistent asthma. Study 301 included the low (50 mcg) and mid (100 mcg) doses of Fp and Study 30017 included the mid (100 mcg) and high (200 mcg) doses of Fp.

The patients enrolled in studies 301 and 30017 were predominantly female (58%), Caucasian (80%), and never smokers (86%), with a mean age of 43 years (range 12-86). Subjects had a mean FEV1 of 2.1L (66% predicted) and an FEV1/FVC ratio of 67%. About half of the patients were on ICS (57%) and the other half were on ICS/LABA (43%) therapy. The ICS strength was not reported.

For Study 301, out of the 647 subjects that were randomized, 93% (n=602) completed the study. The placebo group had the largest number of discontinued subjects (13%, n=17), predominantly for adverse events (which included asthma). All treatment arms (Fp 50 mcg twice daily (BID), Fp 100 mcg BID, FS 50/12.5 mcg BID, and FS 100/12.5 mcg BID) showed a significant improvement in the change from baseline in trough FEV1 at Week 12 compared to placebo. The treatment differences were 119 mL (95% CI (25 mL, 212 ml)), 151 mL (95% CI (57 mL, 244 mL)), 266 mL (95 % CI (172 mL, 360 mL)) and 262 mL (95% CI (168 mL, 356 mL)), respectively. FS 50/12.5 mcg showed a significant improvement compared to Fp 50 mcg (treatment difference 147 mL (95% CI (53 mL, 242 mL)) and Fp 100 mcg (treatment difference 115 mL (95% CI (21 mL, 210 mL)). FS 100/12.5 mcg also showed a significant improvement compared to Fp 100 mcg (treatment difference 111 mL (95% CI (17 mL, 206 mL)). Study 301 demonstrated the efficacy of two doses of Fp (50 and 100 mcg) over placebo; it also demonstrated the efficacy of the low and mid-dose combination of FS (50/12.5 mcg and 100 mcg/12.5 mcg) over placebo and over the individual Fp monocomponents at the same and higher ICS strengths.

For Study 30017, out of the 728 subjects that were randomized, 89% (n=650) completed the study. The placebo group had the largest number of discontinued subjects (26%, n=38), mainly for disease progression (12%, n=18). All treatment arms (Fp 100 mcg BID, Fp 200 mcg BID, FS 100/12.5 mcg BID, and FS 200/12.5 mcg BID) showed a significant improvement in the change from baseline in trough FEV1 at Week 12 compared to placebo. The treatment difference was 123 mL (95% CI (38 mL, 208 mL)), 183 mL (95% CI (98 mL, 268 mL)), 274 mL (95 % CI 189 mL, 360 m)) and 276 mL (95% CI 191 mL, 361 mL)), respectively. FS 100/12.5 mcg showed a significant improvement compared to Fp 100 mcg (treatment difference 152 mL (95% CI (66 mL, 237 mL)) and Fp 200 mcg (treatment difference 92 mL (95% CI (6 mL, 177 ml)). FS 200/12.5 mcg also showed a significant improvement compared to Fp 200 mcg (treatment difference 93 mL (95% CI (9 mL, 178 ml)). Study 30017 demonstrated the efficacy of the mid and high doses of Fp (100 mcg and 200 mcg) over placebo; it also demonstrated the efficacy of the mid- and high-dose combination of FS (100/12.5 mcg and 200/12.5 mcg) over placebo and the Fp monocomponents of similar and higher ICS strengths.

For both Studies 301 and 300017, there were no statistical comparisons within the Fp doses and FS doses. The point estimates did show a dose-response for the Fp doses, but not between the FS doses. The co-primary endpoint in the serial spirometry subset of patients (n=312 for each study) of the standardized baseline-adjusted FEV1 AUC 0-12h at Week 12 was generally similar to the results for the change from baseline in trough FEV1. The main difference was that the Fp 50 and 100 mcg doses did not show a dose response for their improvement over placebo.

The sensitivity analyses (cumulative proportion of responder analysis graph, tipping point, and multiple imputations under an assumption of missing not at random for those patients who withdrew due to worsening asthma) supported the primary and co-primary endpoint conclusions.

A subgroup analysis was performed by the sponsor by sex, age group (12 to 17, 18 to 64, and ≥ 65 years), race (white, black, and other), and by geographic region (USA and non-USA) based on the pooled FAS population. Overall, the subgroup analyses were consistent with the primary analysis, although no study was powered to detect difference in subgroups.

The key secondary endpoint was the time to 15% and 12% improvement from baseline in FEV1 post dose at baseline in the serial spirometry subset. For Study 301, 70% (n=39) and 57% (n=35) of the subjects in the FS 50/12.5 mcg and FS 100/12.5 mcg improved their FEV1 by 15% from baseline on Day 1, respectively. Of those subjects, the median time to an FEV1 improvement of 15% was 1.3 hours and 4.3 hours, respectively. Slightly more subjects achieved a 12% improvement in FEV1 on day 1 and the median time was slightly shorter than for 15%. A dose response was observed for both 15% and 12% time to improvement for the FS treatment arms (not evaluated for the Fp treatment arms). For Study 30017, 62% (n=36) and 81% (n=55) of the subjects on FS 100/12.5 mcg and FS 200/12.5 mcg improved their FEV1 by 15% from baseline on Day 1, respectively. Of those subjects, the median time to an FEV1 improvement of 15% was 0.9 hours and 0.8 hours, respectively. Slightly more subjects achieved a 12% improvement in FEV1 on day 1 and the median time was slightly shorter than for 15%. A dose response was not

observed for either a 15% or 12% time to improvement in post-dose FEV1 on day 1 from baseline.

Other secondary endpoints included peak expiratory flow (PEF), asthma symptom score, albuterol use, time to withdrawal for worsening asthma, and asthma quality of life questionnaire (AQLQ). Overall the secondary endpoints were supportive of the primary endpoint. The FS combination was not consistently superior to Fp, with the exception of the peak expiratory flow rate endpoint. A dose response was generally present with the exception of albuterol use in Fp 100 mcg compared to 200 mcg and AQLQ scores in the FS 100/12.5 mcg compared to FS 200/12.5 mcg.

Overall, efficacy for Fp 50 mcg, 100 mcg, and 200 mcg one inhalation BID and for FS 50/12.5 mcg, 100/12.5 mcg, and 200/12.5 mcg one inhalation BID for the treatment of asthma in patients aged 12 years and older has been demonstrated. Fp 50 mcg was supported by Studies 201, 202, and 301, Fp 100 mcg was supported by Studies 201, 202, 301, and 30017, Fp 200 mcg was supported by Studies 202 and 30017, FS 50/12.5 mcg was supported by Study 301, FS 100/12.5 mcg was supported by both Studies 301 and 30017, and FS 200/12.5 mcg was supported by Study 30017.

Studies 201, 202 and FS-201 supported the dose selection of both fluticasone propionate and salmeterol. Studies 301 and 30017 demonstrated the difference in the primary endpoint of change from baseline in trough FEV1 at Week 12 for all treatment arms compared to placebo, with a dose-response between doses of Fp and a statistically significant improvement in the combination of the ICS/LABA (FS) compared to the ICS (Fp) of the same or higher dose. The co-primary efficacy endpoint of standardized baseline-adjusted FEV1 AUC 0-12h at Week 12 in the serial spirometry subset of patients showed similar results. Efficacy is further supported by the key secondary endpoint of time to 15% and 12% improvement from baseline in FEV1 and the other secondary endpoints of PEF, asthma symptom score, albuterol use, time to withdrawal for worsening asthma, and AQLQ.

Summary of Safety

The safety profile for inhaled fluticasone propionate and salmeterol in this patient population is well-known, as they have been marketed for the treatment of asthma as Flovent Diskus (50 mcg, 100 mcg, and 250 mcg) 2-4 inhalations twice daily and in combination as Advair Diskus (100/50 mcg, 250/50 mcg, and 500/50 mcg) one inhalation twice daily at higher doses than Fp and FS since 1994 (Flovent Diskus) and 2000 (Advair Diskus). Moreover, ICSs have been used for treatment of asthma since 1987 and other ICS/LABAs have also been marketed since Advair was approved.

The safety evaluation for Fp and FS relies on the pooled results of the four 12-week studies (201, 202, 301, and 30017). The 26-week long-term extension study (305) provides supportive safety data. The mean exposure range for the four 12-week studies was 68-84 days, with the lowest

exposure in the placebo group (most early discontinuations in the placebo group were due to asthma adverse events and disease progression).

Dose response for safety was evaluated for Fp with doses from 12.5 to 400 mcg. The salmeterol dose response to safety was evaluated separately in Study FSS-201 (single doses ranging from 0 to 50 mcg). No dose response for any adverse event was noted, with the exception of oral candidiasis, which is a known dose-dependent safety concern for ICS.

One death was reported due to fulminant liver failure, in Study 30017. The event occurred in a 44 year old black female after receiving FS 100/12.5 mcg (one inhalation twice daily) for 37 days and starting a new herbal supplement (moringa oleifera) on Day 22. This is a potential case of Hy's law; however it is confounded by the use of an herbal supplement. Her liver function tests continued to be elevated and she died on day 72.

The overall occurrence of serious adverse events (SAEs) was equally distributed across treatment groups (0% – 2%). The only SAE that occurred in more than one patient was asthma exacerbation. Asthma exacerbation was reported in 4 (1%) patients in the placebo arm and 1 (1%) patient in the FS 200/12.5 mcg treatment arm.

Discontinuations due to AEs were balanced across treatment groups. Bronchitis, upper respiratory infection, asthma, cough, and dysphonia occurred in more than one patient. More patients discontinued due to asthma in the placebo group (n=5 (1%)) compared to the treatment groups (n=2 (<1%)).

The sponsor analyzed adverse events that were considered specific primary safety concerns for Fp and FS based on the known safety profile of these drugs in combination. The categories chosen for analyses were based on the warning and precautions in available prescribing information and included oral candidiasis, paradoxical bronchospasm and upper airway symptoms, immediate hypersensitivity reactions, immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density, effect on growth, hypokalemia and hyperglycemia, potential cardiovascular effects, potential central nervous system effects, glaucoma and cataracts, and eosinophilic conditions and Churg-Strauss syndrome. Bone mineral density measurements, and formal hypothalamic–pituitary–adrenal (HPA) axis and growth studies were not included in this clinical development program as the systemic exposure for these proposed products are lower or similar to the marketed products. Urinary cortisol was collected in Studies 202 and 305 and was consistent with the known effects of ICS on the HPA axis. EKGs were measured at baseline and Week 12 for the 4 pivotal studies (201, 202, 301, and 30017). For those studies which included FS treatment arms, the EKG results were consistent with the know safety profile of inhaled LABAs. Overall, the incidence of adverse events reported in these categories were consistent with the know safety profile of the marketed forms of inhaled fluticasone propionate and fluticasone propionate/salmeterol combination.

The incidence of adverse events was reported similarly across treatment groups. Nasopharyngitis, headache, upper respiratory infection, cough, oral candidiasis, and back pain

were the most frequent adverse events, occurring in 3% or more subjects in any treatment group. The incidence of oral candidiasis was dose-dependent. As with other ICSs, to reduce the risk of oral candidiasis patients are advised to rinse their mouth with water without swallowing after inhalation for ICS medications.

Although clinical labs were not collected for the Studies 301 and 30017, one death occurred in Study 30017 due to fulminant liver failure. In study 201 and 202, liver function tests were measured at screening and at Week 12. One subject on Fp 100 mcg had normal baseline liver function tests and elevated liver function tests at Week 12 (AST $\geq$ 10x ULN, ALT $\geq$ 5 x ULN, bilirubin within normal limits). In combination with death due to fulminant liver failure confounded by herbal supplement use, this report of highly elevated AST and ALT will need to be considered when finalizing the prescribing information.

Subgroup analyses for four 12-week studies included gender, age, race, and geographic location (US vs. non-US). Overall, there was no apparent difference in the safety profile by these subgroups.

A total of 9 subjects become pregnant during this clinical development program. Prior to the introduction of the updated PLLR format, the reference listed drug for both Fp and FS were considered pregnancy category C. The pregnancy adverse events and outcomes for the Fp and FS clinical studies are consistent with the know safety profile of fluticasone propionate and salmeterol.

The long-term (26-week), open-label safety study (Study 305) was consistent with the safety results of four 12-week studies.

Overall, the safety database is adequate to assess the safety of fluticasone propionate and fluticasone propionate/salmeterol in the novel MDPI device. The safety profile for Fp and FS are consistent with the know safety profile for the products alone and in combination. The potential Hy's law case and the case of elevated liver enzymes and will need to be considered further when finalizing the prescribing information. The safety findings should be factored into the risk-benefit assessment of Fp and FS for the treatment of asthma.

Risk-Benefit Assessment

The Fp and FS clinical development program has demonstrated robust efficacy for Fp 50 mcg, 100 mcg, and 200 mcg and for FS 50/12.5 mcg, 100/12.5 mcg, and 200/12.5 mcg one inhalation twice daily in a novel multidose dry powder inhaler for the treatment of asthma in patients 12 years of age and older. The safety profile is similar to the currently marketed inhaled fluticasone propionate and fluticasone propionate/salmeterol combination products. The risk-benefit supports the approval of these lower doses of inhaled fluticasone propionate and salmeterol in a novel dry powder inhalation device for the treatment of asthma.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements or commitments are recommended at the time of this review.

2 Introduction and Regulatory Background

2.1 Product Information

Fluticasone Propionate (Fp) Multidose Dry Powder Inhaler (MDPI)
The proposed drug product, Fp MDPI, is a fixed-dose inhaled corticosteroid (ICS) delivered in Teva's novel multidose dry powder inhaler (MDPI). Fp MDPI is supplied in multiple dosage strengths (50, 100, and 200 mcg). The 50, 100 and 200 mcg doses represent the nominal doses and will be used for the reminder of the review. The metered doses per inhalation, which will be included in the label, are 55, 113, and 232 mcg. Fp MDPI is administered as 1 inhalation twice daily.

Fluticasone Propionate/Salmeterol (FS) Multidose Dry Powder Inhaler (MDPI)
The proposed drug product, FS MDPI, is a fixed-dose combination inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) delivered in Teva's novel multidose dry powder inhaler (MDPI). The combination device contains fluticasone propionate as the ICS and salmeterol as the LABA. FS MDPI is supplied in multiple dosage strengths of fluticasone propionate (50, 100, and 200 mcg) with a fixed dose of salmeterol (12.5 mcg). The 50/12.5, 100/12.5 and 200/12.5 mcg doses represent the nominal doses and will be used for the reminder of the review. The metered doses per inhalation, which will be included in the label, are 55/14, 113/14, and 232/14 mcg. FS MDPI is administered as 1 inhalation twice daily.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Available Therapies for the Treatment of Asthma

Class	Generic Name	Brand Name	Approval Year
Inhaled Corticosteroids (ICS)	Fluticasone furoate DPI	Arnuity Ellipta	2014
	Beclomethasone dipropionate HFA	QVAR	2000
	Budesonide DPI/respules	Pulmicort	2006
	Fluticasone propionate HFA/Diskus	Flovent	1994
	Mometasone DPI/HFA	Asmanex	1987
	Ciclesonide HFA	Alvesco	2006
Combination inhaled corticosteroid/long-	Fluticasone furoate/vilanterol DPI	Breo Ellipta	2013
	Mometasone/formoterol HFA	Dulera	2010
	Budesonide/formoterol fumarate	Symbicort	2006

acting bronchodilator (ICS/LABA)	Fluticasone propionate/salmeterol xinafoate Diskus/HFA	Advair	2000
Immunomodulators	Omalizumab	Xolair (anti-IgE)	2003
	Mepolizumab	Nucala (anti-IL5)	2015
	Reslizumab	Cinqair (anti-IL5)	2016
Long-acting muscarinic antagonist	Tiotropium Bromide	Spiriva Respimat	2015*
Leukotriene modifiers	Montelukast	Singulair	1998
	Zafirlukast	Accolate	1996
	Zileuton	Zyflo	1996
Xanthines	Theophylline	Multiple	-
DPI = dry powder inhaler, HFA = hydrofluoroalkane *Approved for treatment of chronic obstructive lung disease in 2004			

2.3 Availability of Proposed Active Ingredient in the United States

Fp MDPI contains the same active ingredient as Flovent Diskus (GlaxoSmithKline) which is marketed at 50, 100, and 250 mcg doses. Flovent Diskus is dosed at 2-4 inhalations twice daily for patients 12 years of age and older. Fluticasone propionate is also available as Flovent HFA (GlaxoSmithKline), marketed at 44, 110, and 220 mcg, dosed at 2 inhalations twice daily for patients 12 years of age and older. Both Flovent Diskus and Flovent HFA are approved for the maintenance treatment of asthma as prophylactic therapy. Flovent Diskus and HFA are approved for adults and children down to 4 years of age. Children ages 4 to < 12 years are recommended to use 1-2 inhalations twice daily for Flovent Diskus and 2 inhalations twice daily for Flovent HFA.

Fluticasone propionate is also available for the treatment of seasonal and perennial allergic and non-allergic rhinitis, as FLONASE (fluticasone propionate nasal spray, GlaxoSmithKline), marketed at 50 mcg/spray, dosed at 2 sprays/ nostril once daily (200 mcg total daily dose), down to 4 years of age.

FS MDPI contains the same active ingredient as Advair Diskus (GlaxoSmithKline) which is marketed at 100/50, 250/50, and 500/50 mcg doses. The combination of fluticasone propionate and salmeterol is also available as Advair HFA (GlaxoSmithKline). Advair HFA is marketed as 45/21, 115/21, and 230/21mcg. Advair Diskus and HFA are dosed as 1 inhalation twice daily for the treatment of asthma. Advair Diskus is approved down to age 4 and Advair HFA is approved down to age 12.

The dosing of the available inhaled products (Flovent Diskus, Flovent HFA, Advair Diskus, and Advair HFA) compared to the proposed product is summarized in Table 2.

Table 2. Summary of Metered, Delivered, and Nominal Doses Across Products and Devices for patients ≥ 12 years of age

Product	Metered Doses Per Inhalation (mcg)	Delivered Dose Per Inhalation (mcg)	Nominal Doses Per Inhalation (mcg)	Inhalations Twice daily	Total Daily Doses (mcg)
Fp MDPI	55,113, 232	51, 103, 210	50, 100, 200	1	110 to 464
Flovent Diskus	50, 100, 250	46, 94, 229		2-4	200 to 2000
Flovent HFA	50, 125, 250	44, 110, 220		2-4	176 to 1760
FS MDPI	55/14, 113/14, 232/14	49/12.75, 100/12.75, 200/12.75	50/12.5 100/12.5 200/12.5	1	110/28 to 464/28
Advair Diskus	110/50, 250/50, 500/50	93/45, 233/45, 465/45		1	200/100 to 1000/100

Metered dose: the amount of drug measured by the device for delivery. The metered dose is the labeled dose.
Delivered dose: the amount of drug discharged from the mouthpiece
Source: Modified from Clinical Overview, Table 1, pg. 12

2.4 Important Safety Issues with Consideration to Related Drugs

In patients with asthma, LABA monotherapy has been associated with serious asthma related adverse events, including an increased risk of hospitalization, intubation, and death. LABA-containing drug products carry a Boxed Warning for these events. Due to the safety concern with LABA monotherapy, the risk of serious asthma-related events with LABAs when used in conjunction with an ICS was studied in a 26-week, randomized, double-blind study in 11,679 patients with persistent asthma (≥ 12 year of age) who were randomized 1:1 to either Flovent Diskus or Advair Diskus therapy. The risk of serious asthma-related deaths (death, endotracheal intubation, or hospitalization) was similar between groups (HR 1.03, 95% CI (0.62 to 1.66)). There were no asthma-related deaths; 2 patients in the fluticasone-only group underwent asthma related intubation. The risk of a severe asthma exacerbation was 21% lower in the fluticasone–salmeterol group than in the fluticasone-only group (hazard ratio, 0.79; 95% CI, 0.70 to 0.89), with at least one severe asthma exacerbation occurring in 480 of 5834 patients (8%) in the fluticasone–salmeterol group, as compared with 597 of 5845 patients (10%) in the fluticasone-only group (P<0.001).(1)

With respect to other safety issues, additional risks highlighted in current ICS/LABA product labeling include:

- Localized infections
- Immunosuppression
- Hypercorticism and adrenal suppression

- Paradoxical bronchospasm and upper airway symptoms
- Immediate hypersensitivity reactions
- Cardiovascular and central nervous system effects
- Reduction in bone mineral density
- Effect on growth
- Glaucoma and cataracts
- Eosinophilic conditions and Churg-Strauss syndrome
- Hypokalemia and hyperglycemia

These will be discussed in detail for this application in Section 7.3.5 Specific Primary Safety Concerns

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Prior to submission of this NDA, this product has been the subject of multiple regulatory interactions (as IND 108838 for Fp MDPI and IND 72240 for FS MDPI). Key regulatory milestones and meetings are summarized below in Table 3.

Table 3. Regulatory History

Interaction	FS MDPI date	Fp MDPI date	Highlights of Discussion
PIND	Dec 2005& Dec 2009	July 2010	Teva noted their product is Q1 and Q2 the same as Advair; however, the Office of Generic Drugs noted that FS cannot be approved via a 505(j) regulatory route as the device differs from Advair Diskus. A full clinical program is required to support each of the proposed dosage strengths and the contribution of each component of the combination.
IND opened	Oct 2012	Oct 2011	-
EOP2	Jan 2014		• Include a mid-dose treatment arm to Study 301 to demonstrate incremental benefit of the higher doses over the lower doses. • Include 6-month safety study • Include spacer study as the MDPI has the appearance of an metered dose inhaler (MDI)
Pre-NDA	Nov 2015		-

The protocols for the Fp and FS 12-week studies (301 and 30017) were submitted in June 2014 and we noted the primary endpoint was continuous (change from baseline in FEV1 over the 12-

week treatment period). We asked for a landmark endpoint (change from baseline at 12 weeks) to ensure that there was not a decrease in the treatment response over time.

After reviewing the final statistical analysis plan, submitted September 2015, we recommended that the ITT population (all randomized subjects) be used for the primary analysis. Teva used the full analysis set (all subjects randomized subjects who received at least 1 dose of study drug AND had at least 1 post baseline trough FEV1 assessment) for the primary endpoint as the results were already unblinded. The primary endpoint analysis was also conducted in the ITT population for supportive efficacy.

Teva marketed ProAir RespiClick, approved in March 2015, which uses a similar device to the proposed Fp and FS MDPIs. ProAir RespiClick is a short-acting beta-agonist (albuterol sulfate) inhalation powder approved for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. The RespiClick spacer study was performed with the ProAir RespiClick and notes that a spacer cannot be used with the RespiClick device. This study was conducted because the RespiClick device is similar in appearance to a metered dose inhaler (MDI) which is frequently used with a spacer. The Fp and FS MPDI will also include in the label that a spacer cannot be used based on the results of the ProAir RespiClick spacer study.

2.6 Other Relevant Background Information

There is no further relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. A high level DSI audit of the sponsor has been completed. While the final review is pending, preliminary reports indicate that there are no inspection issues which require action.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in theses NDAs were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under INDs 108838 and 72240 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of these NDA applications. Details of the financial disclosure are outlined below:

Covered Clinical Studies: FpS-AS-101, FpS-AS-102, 201, 202, FSS-AS-10042, FSS-201, 301, 30017, and 305.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of primary investigators identified: 158		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 3		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Fp is a corticosteroid with the chemical name 6α,9-difluoro-17 [[fluoromethyl)sulphanyl] carbonyl]-11β-hydroxy-16α- methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate. Fp is dispersed in a lactose monohydrate excipient and contained within a reservoir. A metered dose is delivered to a dose cup (b) (4) activated when the mouthpiece cover is opened. The dose is delivered to the subject through a cyclonic separator which is activated by subject inhalation. The cyclonic action of the device delivers fine particles of drug to the large and small airways of the lungs while the (b) (4) Each MDPI device provides approximately 60 dry powder doses.

The salmeterol in FS MDPI is salmeterol xinafoate ([Sx]; (b) (4)

Both Teva's RespiClick device and the MDPI device for the Fp and FS MDPI product included in this submission use a cyclone design that facilitates efficient de-agglomeration and aerosolization of the drug particles from the lactose carrier, (b) (4) .

A high level sponsor inspection noted that a black stripe was printed on packages of one batch of FS MDPI 50/12.5 mcg. This dose was used in the Study 301. The clinical investigator opened the pouch and placed the drug into a carton so the patient could not have been unblinded. The clinical investigator may have noted a different treatment arm, however there were 5 total treatment arms in Study 301, therefore the risk of unblinding was very low. An information request was sent to Teva to inquire how many patients received this batch number. A total of 129 subjects enrolled to FS 50/12.5 mcg in Study 301 were treated with this batch number. The number of subjects treated at one site was between 1 and 5 with one outlying site which treated 8 subjects. The sponsor noted that there was no indication that anyone who was directly involved in the dispensation of the investigational product to the patients was aware of any differences in the packaging across the 5 treatment arms. No questions or complaints regarding packaging differences were made by any Investigative Site personnel during the conduct of the trial.

Reviewer comment: Based on this explanation we are not concerned about unblinding.

The drug products used in the phase 1 PK studies and the phase 2 dose-ranging studies were not the to-be-marketed product, NB7/3. The NB7/3 was used for the PK study FSS-AS-10042 and in Studies 301 and 30017. Based on the CMC reviewer, the drug product differences are not a concern. There may be some variability with the 200 mg (high) dose, but this is not likely to be

large. (b) (4)
.

Teva also explored in vitro formulation interactions with delivery under test/lab conditions comparing Fp and FS. There were no interactions noted.

For Fp MDPI the 50, 100 and 200 mcg doses represent the nominal doses and will be used for the reminder of the review. The metered doses per inhalation, which will be included in the label, are 55, 113, and 232 mcg. The delivered doses per inhalation (discharged from the mouthpiece) are 51, 103, and 210 mcgs.

For FS MDPI the 50/12.5, 100/12.5 and 200/12.5 mcg doses represent the nominal doses and will be used for the reminder of the review. The metered doses per inhalation, which will be included in the label, are 55/14, 113/14, and 232/14 mcg. The delivered doses per inhalation (discharged from the mouthpiece) are 49/12.75, 100/12.75, and 202/12.75 mcgs.

For NDA 208798 for Fp, the CMC review team included Art Shaw (drug product), and Craig Bertha (Application Technical Lead). The CMC review team for NDA 208799 for FS included Xiaobin Shen (drug product) and Julia Pinto (Application Technical Lead). Ben Stevens (drug substance), Brian Rogers (process) and Christina Capacci-Daniel (facilities) reviewed both NDAs.

While the final review is pending, preliminary reports indicate that there are no inspection issues which require action.

4.2 Clinical Microbiology

Dr. Yong Hu from the product quality microbiology review is pending.

4.3 Preclinical Pharmacology/Toxicology

While the final review is pending, preliminary reports indicate that there are no the nonclinical program is adequate to support the approval of Fp and FS for asthma. For further details, refer to Dr. Brett Jones's nonclinical review.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology finds the application acceptable support the approval of Fp and FS for the treatment of asthma. For further details, refer to Dr. Lei He's and Anshu Marathe's clinical pharmacology review.

4.4.1 Mechanism of Action

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a selective long-acting beta-agonist (LABA). In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adreno receptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyperresponsiveness.

4.4.3 Pharmacokinetics

A total of 3 PK studies were conducted (Fps-AS-101, FpS-AS-102, and FSS-AS-10042, as summarized below:

Study identifier	Study title	Enrollment (age range)	Primary analysis
FpS-AS-101	An open-label, randomized, three-period crossover, single-dose pilot study to compare the pharmacokinetic and safety profiles following two inhalations of fluticasone propionate Spiromax 400 mcg versus four inhalations of FLOVENT DISKUS 250 mcg and four inhalations of FLOVENT HFA MDI 220 mcg administered in healthy volunteers	18 healthy subjects (18-45 years of age)	Pharmacokinetic profile of fluticasone propionate as determined by AUC_{0-t} and C_{max}
FpS-AS-102	An open-label, randomized, three-period crossover, single-dose pilot study to compare the pharmacokinetic and safety and tolerability profiles following four inhalations of fluticasone propionate Spiromax 100 mcg and 200 mcg and four inhalations of FLUTIDE DISKUS 100 mcg administered in healthy Japanese and Caucasian subjects	30 healthy subjects (20-45 years of age)	Pharmacokinetic profile of fluticasone propionate as determined by AUC_{0-t} and C_{max}
FSS-AS-10042	An open-label, crossover study to determine the pharmacokinetic profile and tolerability of single doses of high strength fluticasone propionate multidose dry powder inhaler and fluticasone propionate/salmeterol multidose dry powder inhaler compared to high strength FLOVENT® DISKUS® and ADVAIR® DISKUS® in patients with persistent asthma 12 years of age and older	43 subjects (12 years and older)	Pharmacokinetic profile of fluticasone propionate and/or salmeterol as determined by AUC_{0-t} and C_{max}

For Study 10042, Following the single dose administration of the proposed highest dosage of Fp MDPI (200 mcg×1 inhalation) and FS MDPI (200/12.5 mcg×1 inhalation), the systemic exposure of Fp and/or Sx is similar or lower compared with the corresponding reference products

following the approved dosage of Flovent Diskus (250 mcg×2 inhalation, the highest dosage is even up to 1000 mcg depending on the prior asthma therapy) and Advair Diskus (500/50 mcg×1 inhalation, the highest dosage).

There was no obvious difference for male, female, and age (12 to 17 years, 18+ years) subgroups when compared to the overall study population.

C_{max}, $AUC_{0-t,}$ and $AUC_{0-\infty}$ for fluticasone propionate were similar following oral inhalation administration via Fp and FS indicating a lack of interaction between fluticasone propionate and salmeterol.

The systemic exposures from the Fp MDPI increased with increasing dose of Fp MDPI, and comparisons of AUC_{0-t} and C_{max} indicated approximately dose-proportional increases in both parameters across the dose levels tested (Fp MDPI 50, 100, 200, and 400 mcg). The t_{max} was similar across treatments (median t_{max} ranged from 0.8 to 1.1 hours). There was a suggestion of a dose response with Fp MDPI in analyses of the primary efficacy variable of $FEV_{1.}$

A post-hoc analysis also showed that the systemic exposure of Fp is similar to in Fp and FS, suggesting that the presence of salmeterol in FS does not affect the Fp PK.

The PK of salmeterol was studied in Study FSS-201, the dose-ranging study for salmeterol (see Section 5.3.3 for a detailed protocol review). The mean plasma concentrations of salmeterol were highest at 5 minutes postdose for each FS dose level (0, 6.25, 12.5, 25, and 50 mcg). Thereafter, the mean plasma concentrations of salmeterol declined, but were still quantifiable through 12 hours postdose. Both AUC_{0-t} and C_{max} of salmeterol increased with increasing FS doses. Across all FS groups, t_{max} occurred earlier (median = 0.1 hr) compared to Advair Diskus (median = 0.5 hr). Highest mean plasma concentrations of salmeterol were attained later for Advair Diskus, but the levels subsequently declined in parallel with those for the FS doses. Only FS 100/50 mcg attained mean plasma concentrations of salmeterol that were greater than those obtained for Advair Diskus throughout the 12-hour sampling period. FS 100/12.5 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in Advair Diskus.

The Clinical Pharmacology Team recommends approval. Refer to the clinical pharmacology review by Dr. Lei He for further details (including Study a discussion of Study 101 and 102).

5 Sources of Clinical Data

The remainder of the review will refer to Fp MDPI as Fp and FS MDPI as FS.

5.1 Tables of Studies/Clinical Trials

Table 4. Sources of clinical data

Study	Design	Study Duration	Treatment Arms[1] (mcg)	N[2]	Population	Primary Endpoint
Dose-ranging Studies						
FpS-AS-201 *[USA, Ukraine, Hungary, Israel, Bulgaria, Poland, Croatia, Spain, Serbia]* *Jan 2012 – Jul 2013*	R, DB, PC and OL	12 weeks	Fp 12.5 Fp 25 Fp 50 Fp 100 Flovent Diskus 100[3] Placebo	103 104 104 103 104 104	≥ 12 year olds persistent asthma uncontrolled on non-steroidal therapy	Change from baseline in trough FEV1 **OVER** 12-week treatment
FpS-AS-202 *[USA, Canada, Ukraine, Hungary, Germany, Israel, Romania, Bulgaria, Poland, Spain, Greece, New Zealand, Croatia, Serbia]* *Apr 2012 – Oct 2013*	R, DB, PC and OL	12 weeks	Fp 50 Fp 100 Fp 200 Fp 400 Flovent Diskus 250[3] Placebo	107 107 106 107 107 106	≥ 12 year olds persistent asthma uncontrolled on high-dose ICS or ICS/LABA	Change from baseline in trough FEV1 **OVER** 12-week treatment
FSS-AS-201 *[USA]* *Jan 2013 – Jun 2013*	R, DB, OL, SD, CO	Singe-Dose	Fp 100/0 FS 100/6.25 FS 100/12.5 FS 100/25 FS 100/50 Advair Diskus 100/50	67 68 69 67 68 66	≥ 12 year olds persistent asthma uncontrolled on high-dose ICS or ICS/LABA	Baseline-adjusted FEV1 AUC0-12 hours
Fp and FS Efficacy and Safety Studies						
FSS-AS-301 *[US, Canada, Poland, Russia, South Africa, Ukraine, Hungary]* *Jul 2014 – Sept 2015*	R, DB, PC	12 weeks	FS 50/12.5 FS 100/12.5 Fp 50 Fp 100 Placebo	129 129 129 130 130	≥ 12 years old with asthma uncontrolled on low or mid-dose ICS or ICS/LABA therapy	1: (1) Change in trough FEV1 **AT** 12 weeks (2) FEV1 AUC (0-12) in subset at week 12 (n=312)

Table 4. Sources of clinical data

Study	Design	Study Duration	Treatment Arms[1] (mcg)	N[2]	Population	Primary Endpoint
FSS-AS-30017 *[USA, Canada, Czech Republic, Poland, Russia, South Africa, Ukraine, Hungary]* *Oct 2014 – Sept 2015*	R, DB, PC	12 weeks	FS 100/12.5 FS 200/12.5 Fp 100 Fp 200 Placebo	145 146 146 146 145	≥ 12 years old with asthma uncontrolled on mid or high-dose ICS or ICS/LABA therapy	1: (1) Change in trough FEV1 **AT** 12 weeks (2) FEV1 AUC (0-12) in subset at week 12 (n=312)
Long-Term Safety Trial						
FSS-AS-305 *[USA]* *Jul 2014 – Jul 2015*	R, OL, active-control	26 weeks	FS 100/12.5 FS 200/12.5 Fp 100 Fp 200 Flovent HFA 110 Flovent HFA 220 Advair Diskus 250/50 Advair Diskus 500/50	120 133 127 126 42 41 41 44	≥ 12 years old with asthma uncontrolled on mid-dose or high-dose ICS or ICS/LABA	Change from baseline in trough FEV1 over the 26-week treatment period

R=randomized, DB=double-blind, PC=placebo-controlled, OL=open label, CO = crossover, Fp=fluticasone propionate, FS=fluticasone propionate/salmeterol xinafoate, MDPI = multi-dose dry powder inhaler (RespiClick), FEV1=forced expiratory volume over 1 second, AUC=area under the curve, HFA= hydrofluoroalkane metered-dose inhaler, ICS=inhaled corticosteroid, LABA=long-active beta-agonist.
[1] One inhalation twice daily, [2]Number randomized, [3]Open-label
Source: ISE, Table 7, p 41-44, ISS, Table 11, pg. 75, Table of clinical studies; Study FSS 201, 301, 30017 and 305 CSRs pg. 1

5.2 Review Strategy

The program to support Fp and FS for the treatment of asthma in patients 12 years and older consisted of 6 key studies: two 12-week Fp dose-ranging studies, a single dose salmeterol dose-ranging study, two 12-week efficacy and safety studies which included the usual factorial design to support the efficacy and safety the FS combination product, and a 26-week long-term safety study. Although the products are under two different NDAs (208798 and 208799), due to the nature of the development programs, and that registration is sought for the dual combination product as well as one of the monocomponents, the data supporting the efficacy and safety of both Fp and FS can be found across all six studies. Therefore, the data for these two NDAs will be covered by this single review.

The protocols for the 5 controlled studies (201, 202, FSS-201, 301, and 30017) are summarized and reviewed in Section 5. The efficacy results for the two 12-week dose-ranging Fp studies (201 and 202) and the single-dose dose-ranging FS study (FSS-201) are provided in Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations. The safety results for

the two 12-week dose-ranging Fp studies (201 and 202) are included in the safety pool and are discussed in Section 7 Review of Safety. The safety results for the single-dose dose-ranging FS study (FSS-201) are reviewed in Section 7.2.2 Explorations for Dose Response. The efficacy results for the two 12-week Fp and FS efficacy and safety studies (301 and 30017) are discussed in Section 6 Review of Efficacy and the safety results are discussed in Section 7 Review of Safety.

Lastly, the 26-week open-label safety study protocol and results are discussed in Section 7.7.2 Long-term safety, with a brief discussion of efficacy in Section 6.1.10 Additional Efficacy Issues/Analyses.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study FpS-AS-201 (201)

Administrative Information

- **Study title:** A 12-Week Dose-Ranging Study to Evaluate the Efficacy and Safety of Fp SPIROMAX® (Fluticasone Propionate Inhalation Powder) Administered Twice Daily Compared With Placebo in Adolescent and Adult Subjects With Persistent Asthma Uncontrolled on Nonsteroidal Therapy
- **Study dates:** January 12, 2012 – July 10, 2013
- **Study sites:** USA, Ukraine, Hungary, Israel, Bulgaria, Poland, Croatia, Spain, Serbia
- **Study report date:** July 28, 2014

Reviewer comment: The trade name SPIROMAX ® was used at the time of the phase 1 and 2 studies; (b) (4)

Objectives/Rationale

Primary Objectives

Evaluate the dose response, efficacy, and safety of 4 different doses of Fp delivered via the RespiClick device when administered twice daily in subjects 12 years of age and older with persistent asthma that are uncontrolled on nonsteroidal therapy.

Study Design and Conduct

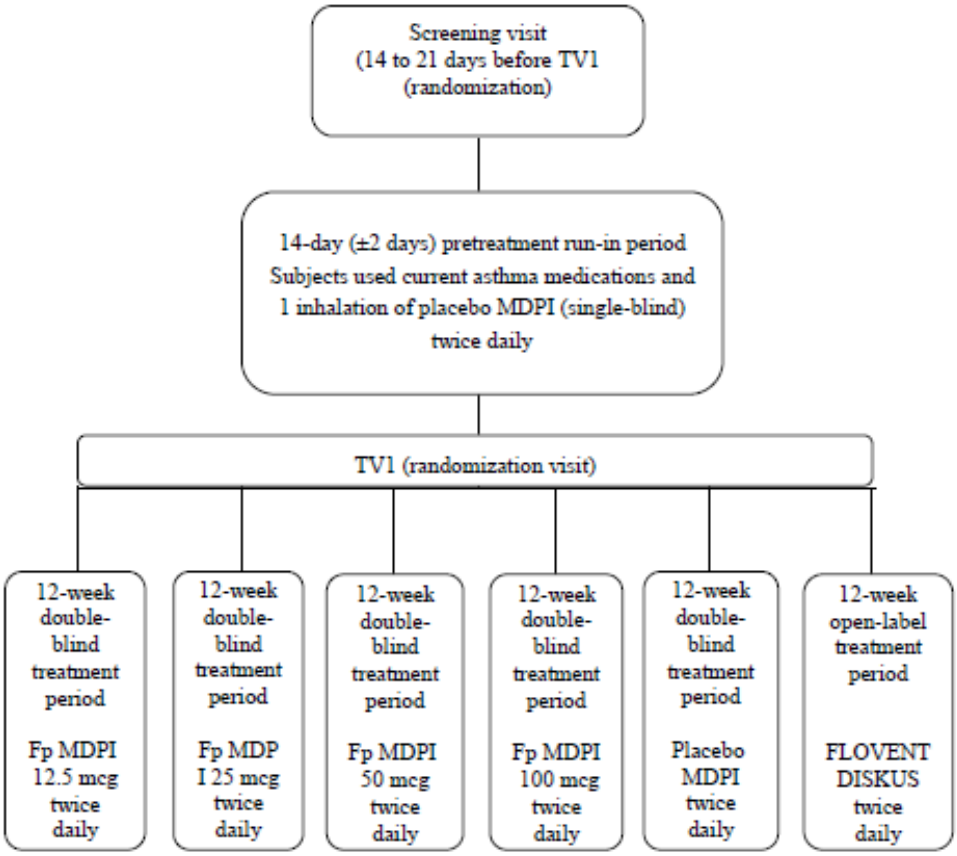
Overview

Study 201 was a 12-week, randomized, double-blind, placebo- and open-label, active-controlled, parallel-group, multicenter, dose-ranging study in subjects aged 12 years and older with asthma who were uncontrolled on nonsteroidal therapy. After a 14-day run-in period on their current

asthma medications, subjects were randomized to the one of 4 different doses (12.5, 25, 50, or 100 mcg) of Fp, placebo, or the active control (Flovent Diskus 100 mcg) and treated with one inhalation twice daily for 12 weeks. Fp and placebo were given in a blinded fashion. Flovent Diskus was open-label as its appearance is different than the MDPIs. A follow-up visit occurred after 1 week (week 13).

The study design for Study 201 is depicted in Figure 1.

Figure 1. Study 201: Study Design



Source: Study 201 CSR, Fig 1, pg. 26

The schedules of assessments are shown in Figure 2.

Figure 2. Study 201: Schedule of Assessments

Procedures	Screening visit[a]	Treatment period						Follow-up (investigational site visit or phone contact)
		Randomization visit					End of therapy	
Visit/contact	SV	TV1	TV2	TV3	TV4	TV5	TV6/TdV[b]	
Week of study	−3 to −2	0	1	2	4	8	12	13
Treatment day	−21 to −14[c]	1	7 (±2)	14 (±2)	28 (±2)	56 (±2)	84 (±2)	7 (±2) after TV6 or TdV
Informed consent/assent[d]	X							
Demography	X							
Medical history	X							
Asthma history	X							
Medication history	X							
Inclusion/exclusion criteria	X	X						
Vital signs	X	X	X	X	X	X	X	
12-lead ECG	X						X	
Physical examination	X						X	
Oropharyngeal examination	X	X	X	X	X	X	X	
Serum pregnancy test (if applicable)	X						X	
Urine pregnancy test (if applicable)		X	X	X	X	X		
Clinical laboratory tests (chemistry, hematology, urinalysis)	X[e]						X[c]	
Serial blood sampling (pharmacokinetic cohort only)		X[f]						
Administer asthma control test		X			X	X	X	
Reversibility testing	X[a]							
PFT	X[a]	X	X	X	X	X	X	
Calculate FEV_1/PEF stability limits		X						
PEF/diary device – dispense and train	X							
PEF/diary data transmission and review		X	X	X	X	X	X	
Review of stopping criteria for worsening asthma[g]			X	X	X	X		
Register subject in IWRS/IVRS	X							
Treatment device training (proper use and storage)	X	X	X	X	X	X		
Dispense placebo MDPI	X							
Collect placebo MDPI		X						
Dispense rescue medication[h]	X	X		X	X	X		
Collect rescue medication[h]		X		X	X	X	X	
Randomization criteria review		X						
Register randomization/treatment assignment via IVRS/IWRS		X						X
Dispense study drug[i]		X			X	X		

Register visit and/or study drug dispensed in IWRS/IVRS		X	X	X	X	X	X	
Review study drug storage conditions with subject		X	X	X	X	X		
Witness self-administration of study drug		X	X	X	X	X		
Collect study drug					X	X	X	
Adverse event monitoring	X[j]	----------	----------	----------	----------	----------	----------	X
Dispense subject medication worksheet	X	X	X	X	X	X		
Concomitant medication review	X	----------	----------	----------	----------	----------	----------	X
Schedule visit	X	X	X	X	X	X	X	
Discontinue subject via IVRS/IWRS							X	
Collect PEF/diary device							X	
Discuss asthma treatment options with subject							X	

Source: Study 201 CSR, Table 1, pgs. 27-29

Population

Key Inclusion Criteria

1. ≥ 12 years of age
2. Asthma diagnosis as defined by the National Institutes of Health
3. FEV1 40-85% predicted
4. 15% reversibility of FEV1 within 30 minutes following 2-4 inhalations of albuterol
5. Permitted asthma therapies: short-acting beta-agonist (SABA) or non-corticosteroid maintenance therapy (including leukotriene modifiers, theophylline, and chromones). If on low-dose ICS (100 mcg Fp twice daily or equivalent) had to undergo 2 week washout.
6. If female, was not currently pregnant, breastfeeding, or attempting to become pregnant, had a negative serum pregnancy test, and was of non-childbearing potential or if childbearing potential, then had to be willing to commit to using acceptable methods of birth control.

Key Exclusion Criteria

1. History of life-threatening asthma (i.e. requiring intubation and/or associated with hypercapnia, respiratory arrest, or hypoxic seizure).
2. Upper or lower respiratory, sinus, or middle ear infection (bacterial or viral) within 2 week of screening or prior to the randomization visit.
3. Asthma exacerbation requiring oral corticosteroids within 3 months or hospitalization within 6 months
    a. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular non-corticosteroid maintenance therapy.

4. Glaucoma, cataracts, ocular herpes simplex, or malignancy other than basal cell carcinoma.
5. Historical or current evidence of a clinically significant disease (including cystic fibrosis, and chronic obstructive pulmonary disease), defined as any disease that in the opinion of the investigator would have put the safety of the subject at risk through participation, or which could have affected the efficacy or safety analysis if the disease/condition exacerbation during the study.
6. Current malignancy (excluding basal cell carcinoma). If the subject had a history of malignancy, this was acceptable if the subject had been in remission for 1 year.
7. Current or treated tuberculosis
8. Uncontrolled hypertension (systolic BP ≥ 160 or diastolic BP > 100)
9. Stroke within 3 months
10. Immunologic compromise, HIV, Hepatitis B or C
11. Current oral candidiasis
12. History of an adverse reaction to any β_2-agonist, sympathomimetic drug, or intranasal, inhaled, or systemic corticosteroid, or to any of the constituents of the dry powder inhalers (i.e. lactose).
13. Severe allergy to milk protein
14. Use of systemic, oral or depot corticosteroids within 12 weeks
    a. Topic steroids (≤1% hydrocortisone cream), intranasal steroids, and ocular steroids at a stable dose x 4 weeks was permitted
15. Immunosuppressive medications within 4 weeks
16. Allergy immunotherapy not stable for at least 90 days
17. Use of potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) within 4 weeks prior to the SV. Mild and moderate CYP3A4 inhibitors were permitted.
18. History of alcohol or drug abuse within 2 years
19. Current smoker, smoking history of ≥10 pack years, or use of tobacco products (cigarettes, cigars, chewing tobacco, or pipe tobacco) within 1 year.

Randomization Criteria

1. Predose percent predicted FEV1 of 40% to 85% of their predicted normal and FEV1 reversibility of ≥15% if not demonstrated at the SV
2. Any combination of the asthma symptom scores (≥1 day-time plus night-time) or albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period (immediately preceding TV1).
3. No changes in asthma medications, excluding albuterol.
4. No occurrence of an upper or lower respiratory illness (allowed to rescreen 2 weeks after resolution of the infection).
5. No asthma exacerbations
    a. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular non-corticosteroid maintenance therapy.

6. No visual evidence of oral candidiasis

Asthma Symptom Scores

Daily asthma symptom scores, were recorded in the AM and PM before peak expiratory flow (PEF), study drug or rescue medication. The score was assessed for cough, wheeze, shortness of breath, and chest tightness as follows:

Daytime (Determined in the evening)
0 = No symptoms during the day
1 = Symptoms for 1 short period during the day
2 = Symptoms for 2 or more short periods during the day
3 = Symptoms for most of the day which did not affect my normal daily activities
4 = Symptoms for most of the day which did affect my normal daily activities
5 = Symptoms so severe that I could not go to work or perform normal daily activities

Nighttime (Determined in the morning)
0 = No symptoms during the night
1 = Symptoms causing me to wake once (or wake early)
2 = Symptoms causing me to wake twice or more (including waking early)
3 = Symptoms causing me to be awake for most of the night
4 = Symptoms so severe that I did not sleep at all.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate.

Concomitant medications

ICS, LABS, oral corticosteroids and other medications were prohibited or restricted during this study as outline in Table 5.

Table 5. Study 201: Prohibited and Restricted Concomitant Medications

Type of medication	Limitation
Low-dose ICS (100 mcg fluticasone propionate twice daily or equivalent)	Low-dose ICS must be washed out for a minimum of 2 weeks before the start of the SV.
ICS/LABA combinations and all other ICSs	Prohibited for 6 weeks prior to SV
CYP3A4 inhibitors (ritonavir, ketoconazole, etc.) – Strong only, moderate, and mild are allowed.	Prohibited 4 weeks prior to SV
β-Adrenergic Receptor Blocking Agents	Prohibited 4 weeks prior to SV
Systemic, topical, oral or depot corticosteroids (See exceptions[a])	Prohibited 12 weeks prior to SV
Immunosuppressive therapy (See exception[b])	Prohibited 4 weeks prior to SV
Anti-IgE therapy (omalizumab)	Prohibited 12 weeks prior to SV
LABA	Prohibited 2 weeks prior to SV
Oral β_2-agonists	Prohibited from the point of screening throughout the study duration
All antihistamines (nasal, oral, and ocular) 1. For subjects on a stable dose prior to or starting at the SV 2. For subjects on prn antihistamine use	 1. Discontinue use for 24 hours prior to any study visit and resume use after completion of each study visit 2. Discontinue use for 24 hours prior to any study visit AND use is limited to no more than 7 days total during the treatment period.
Leukotriene modifiers, theophylline and cromones 1. If therapies are the subject's regular nonsteroidal asthma therapy 2. If SABA alone is the subject's regular nonsteroidal asthma therapy	 1. Continue noncorticosteroid noncorticosteroid maintenance therapy through Run-in period and discontinue at TV1 2. Prohibited for 2 weeks prior to SV
Any other investigational drug	Prohibited for 30 days prior to SV

[a] Topical corticosteroid (≤1% hydrocortisone cream) for dermatological diseases was permitted, intranasal corticosteroids and ocular corticosteroids were permitted as long as subjects were on a stable daily dose for a minimum of 4 weeks prior to the SV and remained on this stable daily dose throughout the study period
[b] Immunotherapy for the treatment of allergy at a stable maintenance dose for at least 90 days prior to the SV and which remained at a stable dose without escalation throughout the study was permitted
CYP3A4=cytochrome P450 isoenzyme pathway 3A4; ICS=inhaled corticosteroids; LABA=long-acting β_2-agonists; prn=as-needed; SABA=short acting β_2-agonists; SV=screening visit; TV1=treatment visit 1

Source: CSR, Table 3, pg. 44

Treatment groups

Run-in:

- Continued current asthma medications (i.e. non-corticosteroid maintenance medication and SABAs as needed for relief of asthma symptoms). SABAs were replaced with albuterol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation).
- One inhalation of placebo MDPI (single-blind)

Treatment:

- Albuterol HFA MDI as needed for relief of asthma symptoms
- Subjects were randomized to 1 of 6 treatment groups as described in Table 6.

Table 6. Study 201: Treatment Groups

Treatment group	Device	Total daily dose (mcg)
A	Fp MDPI 12.5 mcg twice daily	25 mcg
B	Fp MDPI 25 mcg twice daily	50 mcg
C	Fp MDPI 50 mcg twice daily	100 mcg
D	Fp MDPI 100 mcg twice daily	200 mcg
E	Placebo MDPI twice daily	0 mcg
F	FLOVENT DISKUS 100 mcg twice daily	200 mcg

Fp MDPI=fluticasone propionate multidose dry powder inhaler

Source: CSR, Table 2, pg. 40

Flovent Diskus consists of a dry powder formulation of Fp in a lactose excipient and is marketed by GlaxoSmithKline, Research Triangle Park, North Carolina, and is approved for use for the maintenance treatment of asthma as prophylactic therapy in patients 4 years and older.

Placebo MDPI was provided in devices identical in appearance to Fp MDPI. Each placebo device contained lactose monohydrate without the active ingredient.

Blinding

The run-in period was single blinded (subject blinded). The treatment period was double-blind with respect to Fp and placebo. Flovent Diskus was administered in an open-label manner. The MDPI devices (placebo or Fp) were white and colorless opaque plastid dry powder inhalers. Flovent Diskus is an orange plastic, metered, disc-shaped device containing fluticasone propionate.

Compliance

Compliance was assessed by review of the dose counter at each study visit. Noncompliance was defined at administering study drug on <80% of the days. If noncompliance was demonstrated at ≥2 visits the subject could have been withdrawn from the study.

Reviewer comment: This is acceptable given that if patients were noncompliant with the study drug it would decrease the treatment effect.

Efficacy Endpoints

Primary Endpoint

- Change from baseline in trough (AM pre-dose and pre-albuterol) FEV1 over the 12-week treatment period.

Reviewer comment: This differs from the Studies 301 and 30017 which looked at a landmark endpoint of FEV1 at Week 12 and not a continuous endpoint over 12-weeks. Notably, the landmark endpoint is included under other efficacy endpoints. Additionally, the AUC 0-12 hour co-primary endpoint at Week 12 that is included in Studies 301 and 30017 is not include here.

Secondary Endpoints

All secondary endpoints were assessed over the 12-week treatment period.

- Change from baseline in weekly average of daily trough AM PEF (pre-dose and pre-albuterol) over 12 weeks
- Change from baseline in weekly average of daily PM PEF over 12 weeks
- Change from baseline in percentage of rescue-free 24-hour periods (treatment period)
- Time to withdrawal due to meeting stopping criteria for worsening asthma (treatment period)

Other Efficacy Endpoints

All other efficacy endpoints are change from baseline in…

- trough FEV1 at weeks 1, 2, 4, 8, and, 12
- trough FEV1 at week 12
- daily trough AM PEF over the first 14 days
- daily trough AM PEF over each week until week 12
- weekly average of daily trough AM PEF over each 4 week period (weeks 1-4, 5-8, 9-12).
- weekly average of daily trough AM PEF at week 12
- Asthma control test (ACT) every 4 weeks and over weeks 1-12
- total daily use of albuterol (number of inhalations) over the first 14 days
- weekly average of total daily use of albuterol over week 1-12
- weekly average of total daily use of albuterol at week 12
- percentage of symptom-free days during the treatment period.

Efficacy Endpoint Parameters

Primary Efficacy Parameter
Trough FEV1 was measured via spirometry which was conducted based on American Thoracic Society and ERS criteria. All FEV1 data were submitted to a central reading center for evaluation. Spirometry was conducted at screening, Week 0, 1 (baseline), 2, 4, 8, and 12. Albuterol was held for 6 hours prior to spirometry.

Secondary Efficacy Parameters

PEF
Peak expiratory flow (PEF) was determined in the AM and PM as the highest value of 3 measurements, before administration of study or rescue medications, using a handheld electronic peak flow meter. Baseline trough PEF was defined as the average of recorded (nonmissing) trough over the 7 days directly preceding Week 0.

Rescue Medication Use
Number of inhalations of albuterol used each day and each night was self-recorded in the subject's diary. Baseline was defined as the percentage of rescue-free days over the 7 days directly preceding Week 0.

Stopping Criteria for Worsening Asthma

1. FEV1 below the stability limit value
    a. Stability limit = best pre-albuterol FEV1 at Week 0 x 80%
2. PEF below the stability limit for > 3 days (out of 7 days)
    a. Stability limit = mean AM PEF available from 7 days preceding Week 0 x 80%
3. >2 days of ≥ 12 inhalations of albuterol
4. Asthma exacerbation
    a. Run-in or prescreening: defined as worsening asthma requiring any treatment other than rescue albuterol/salbutamol and/or the subject's regular noncorticosteroid maintenance therapy, including the use of systemic corticosteroids and/or ER visit or hospitalization, a change in the subject's regular non-corticosteroid maintenance therapy, or the addition of another asthma medication.
    b. Treatment period: defined as worsening asthma requiring any treatment other than study drug or rescue albuterol/salbutamol including the use of systemic corticosteroids and/or ER visit or hospitalization, or the addition of other asthma medications.

Asthma exacerbations were not recorded as adverse events unless they met the criteria of an SAE. Subjects with asthma exacerbations meeting the serious adverse events definition,

requiring oral or injectable corticosteroid use or any change in their asthma therapy were to be discontinued from the study due to meeting stopping criteria.

Reviewer comment: The 80% stability limit is based on the NHLBI asthma guidelines of asthma control (FEV1 or peak flow 60-80% predicted/personal best is considered not well-controlled, SABA use > 2 days a week).

Other Efficacy Parameters

Asthma Control Test
The ACT is a 5-item subject-completed tool that assesses day and night symptoms, use of rescue medications, and impact of asthma on daily functioning. Each item is scored on a 5-point scale, summed, and scores range from 5-25. The ACT was captured at baseline, weeks 4, 8, and 12. Baseline was defined as the value of the ACT score at Week 0.

Reviewer comment: The MCID for ACT has not been established. The sponsor notes scores ≤ 19 indicate poorly controlled asthma.(2)

Symptom-free days
Baseline was defined as the percentage of symptom free-days over the 7 days directly preceding Week 0. A 24 hour symptom free period as defined as an ACT score of 0 for both daytime and nighttime entries.

Safety Parameters

Safety parameters consisted of clinical labs (Screening and Week 12), vital signs (pulse and blood pressure – all treatment visits), ECGs (blinded reader at central center; screening and Week 12), physical exam (including body weight and height; screening and Week 12), oropharyngeal exams (all treatment visits), and concomitant medication use.

The list of clinical labs is given in Table 7

Table 7. Study 201: Clinical labs

Serum chemistry	Hematology	Urinalysis
Calcium	Hemoglobin	Protein
Sodium	Hematocrit	Glucose
Potassium	RBC count	Ketones
Chloride	—MCV	pH
Creatinine	—MCH	Specific gravity
Glucose	—MCHC	RBCs
BUN	Platelet count	Bilirubin
Uric acid	WBC count and differential count and percentage	Nitrite
ALT	—polymorphonuclear leukocytes (neutrophils)	Leukocytes
AST	—lymphocytes	Urine pregnancy test (TV1-TV5)
GGT	—eosinophils	
Alkaline phosphatase	—monocytes	
Total protein	—basophils	
Albumin		
Total bilirubin		
Direct bilirubin		
Serum pregnancy (SV,TV6/TdV)		
Bicarbonate		
LDH		
Phosphorus		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyl transpeptidase; LDH= lactate dehydrogenase; MCH= mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; min=minimum; max=maximum; N=number of subjects; RBC=red blood cell; SV=screening visit, TdV= early discontinuation visit; TV6=treatment visit 6; WBC=white blood cell

Source: CSR, Table 4, pg. 56

PK substudy

Approximately 20% of subjects participated in PK assessments at Week 0 over 12 hours to assess AUC 0-t, Cmax, and Tmax. For subjects randomized to placebo, samples from pre-dose and 45 minutes post-dose were analyzed.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Site 10136 (Ryan Klein, MD) was excluded from the efficacy and PK analyses due to GCP concerns. Data from this site was still included in the safety analyses.

Statistical Plan

Primary endpoint: The primary analysis was performed using a mixed model repeated measures (MMRM) analysis with effects due to baseline trough FEV1, sex, age, visit, treatment, and visit-by-treatment interaction. Missing data was not implicitly imputed, however all nonmissing data were used in the analysis to test the linear in log-dose time-averaged trend and to estimate the time-averaged difference between treatment groups over 12 weeks. PFT data was excluded from the analysis if it was collected after prohibited medication or more than 1 week since the last dose of study drug.

A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 0.05 level. Specifically, the 2-sided linear in log-dose time-averaged trend test was first performed at the 0.05 level of significance. Only if this trend test demonstrated overall efficacy of Fp (a significantly positive trend), was the highest Fp dose (100 mcg twice daily) to be compared with placebo with a 2-sided test at the 0.05 level of significance. If the highest Fp dose was found to be effective (resulting in a significantly greater time averaged FEV_1 mean than placebo), the next highest Fp dose (50 mcg twice daily) was compared with placebo with a 2-sided test at the 0.05 level of significance. The testing was to proceed through the lower Fp doses until an Fp dose was not found to be effective or all the Fp doses had been tested.

Secondary endpoints:
Testing of secondary efficacy variables at the 4 dosage levels was carried out in a sequential manner.

Analyses Population

Intent-to-Treat (ITT) Population
All randomized subjects with treatment assigned based upon the treatment randomized regardless of which treatment they actually received. The ITT was used for supportive efficacy (FAS was the primary efficacy analysis set). All efficacy analyses were performed using the ITT population and for all study population summaries, with the exception of the disposition table.

Full Analysis Set (FAS)
All subjects in the ITT population who received at least 1 dose of study drug AND had at least 1 post-baseline trough FEV1 assessment. The FAS was the primary efficacy analysis set.

Per-Protocol (PP) Population
The PP population included all data from randomized subjects prior to experiencing major protocol violations.

Pharmacokinetic (PK) Analysis Set
A subset of the PP population that was enrolled in the PK substudy.

Safety Population
All randomized subjects who received at least 1 dose of study drug. Treatment was assigned as given, regardless of randomization group.

Protocol Amendments

A total of 4 amendments were made to the protocol. The protocol amendments that occurred after patients were enrolled are listed below.

Amendment 3 (February 10, 2012)
Inclusion and exclusion criteria were amended. A total of 385 subjects were randomized under this version of the protocol

Amendment 4 (October 12, 2012)
Subjects were allowed to retest or rescreen if they failed spirometry or reversibility testing at screening, the dose of bronchodilator for reversibility was increased and the definitions for the statistical population was changed. These changes were made after 400 subjects were randomized. A total of 220 subjects were randomized to the study under this version of the protocol.

Reviewer comment: The amendments were considered minor.

Protocol Deviations

A list of protocol violations and deviations are listed in Table 8.

Table 8. Study 201: Protocol Violations ≥ 2% in any treatment arm (ITT)

	Fp 12.5 mcg N=103	Fp 25 mcg N=104	Fp 50 mcg N=104	Fp 100 mcg N=103	Placebo N=104	Flovent Diskus N=104	Total N=622
Subjects with at least 1 violation and/or deviation	50 (49)	51 (49)	39 (38)	52 (50)	58 (56)	42 (40)	292 (47)
Violations	20 (19)	20 (19)	11 (11)	20 (19)	26 (25)	17 (16)	114 (18)
Stopping criteria	9 (9)	12 (12)	7 (7)	12 (12)	13 (13)	9 (9)	62 (10)
Prohibited med	6 (6)	4 (4)	1 (<1)	4 (4)	4 (4)	4 (4)	23 (4)
Inclusion criteria	3 (3)	3 (3)	1 (<1)	2 (2)	4 (4)	1 (<1)	14 (2)
Other	3 (3)	2 (2)	0	2 (2)	4 (4)	3 (3)	14 (2)
Deviations	40 (39)	38 (37)	32 (31)	41 (40)	43 (41)	33 (32)	227 (36)
Prohibited med	22 (21)	20 (19)	15 (14)	27 (26)	29 (28)	21 (20)	134 (22)
Restricted med	14 (14)	14 (13)	14 (13)	9 (9)	11 (11)	7 (7)	69 (11)
Inclusion criteria	4 (4)	5 (5)	5 (5)	7 (7)	6 (6)	5 (5)	32 (5)
Incorrect med timing	4 (4)	3 (3)	1 (<1)	2 (2)	1 (<1)	4 (4)	15 (2)

Source: CSR, Table 12, pg. 92

A total of 292 (47%) of subjects had 1 or more protocol violations and/or deviations. This was generally similar across treatment groups with the lowest (38%) in the Fp 50 mcg group and the highest in the placebo group (56%). A total of 114 (18%) were considered major violations. The most frequently occurring major violation was related to stopping criteria for worsening asthma in all groups. See Secondary Efficacy Parameters for further details.
The most frequently reported protocol deviation were prohibited medications (134 subjects (22%)). A total of 38 (6%) subjects discontinued due to protocol violations.

5.3.2 Study FpS-AS-202 (202)

Administrative Information

- **Study title:** A 12-Week Dose-Ranging Study to Evaluate the Efficacy and Safety of Fp SPIROMAX® (Fluticasone Propionate Inhalation Powder) Administered Twice Daily Compared with Placebo in Adolescent and Adult Subjects with Severe Persistent Asthma Uncontrolled on High Dose Inhaled Corticosteroid Therapy
- **Study dates:** April 30, 2012 to October 9, 2013
- **Study sites:** USA, Canada, Ukraine, Hungary, Germany, Israel, Romania, Bulgaria, Poland, Spain, Greece, New Zealand, Croatia, Serbia
- **Study report date:** September 30, 2014

Reviewer comment: The trade name SPIROMAX ® was used at the time of the phase 1 and 2 studies; (b) (4)

Objectives/Rationale

Primary Objectives

Evaluate the dose response, efficacy, and safety of 4 different doses of Fp delivered via the RespiClick device when administered twice daily in subjects 12 years of age and older with persistent asthma that are uncontrolled on high dose ICS or ICS/LABA therapy.

Study Design and Conduct

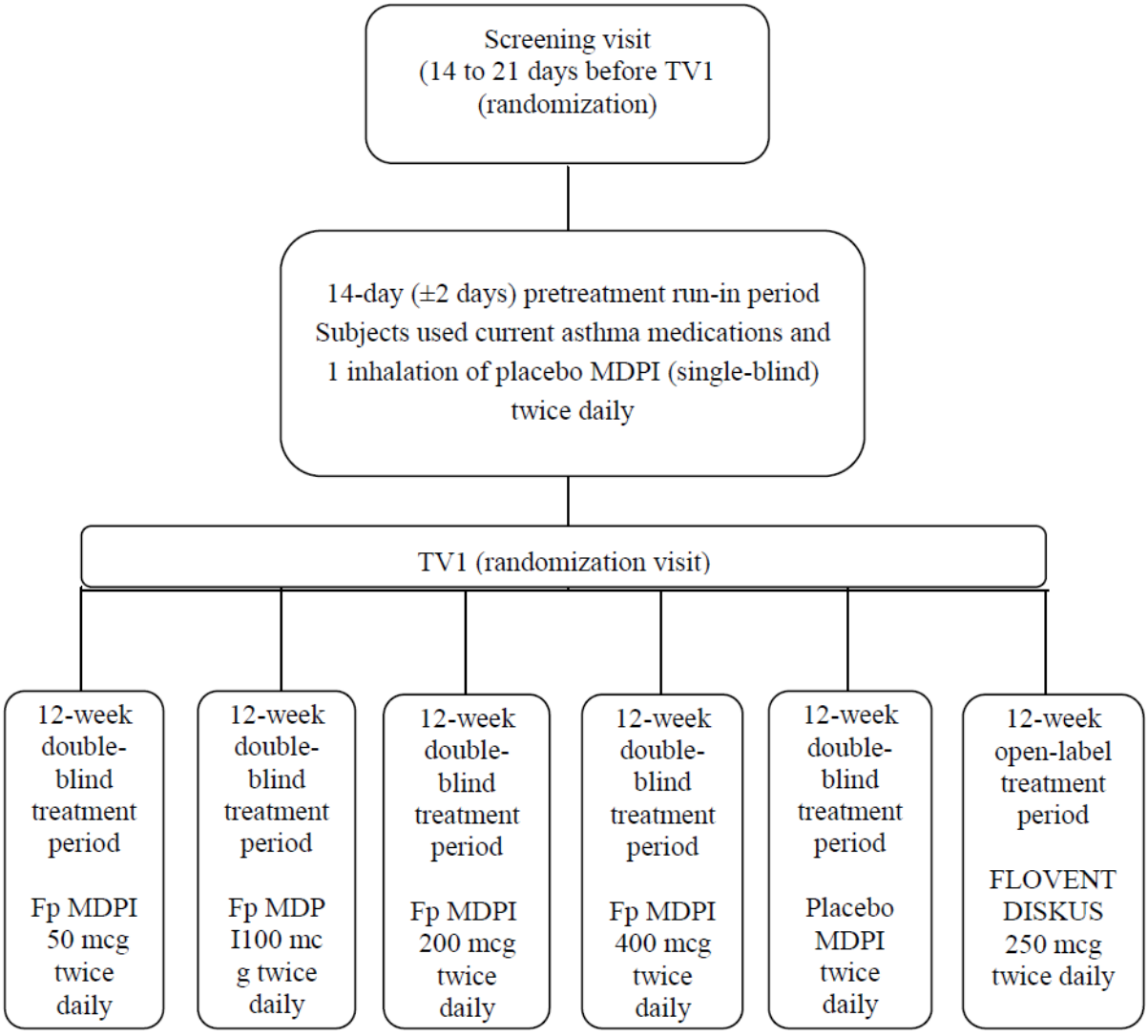
Overview

Study 202 was a 12-week, randomized, double-blind, placebo- and open-label, active-controlled, parallel-group, multicenter, dose-ranging study in subjects aged 12 years and older with asthma who were uncontrolled on high dose ICS or ICS/LABA therapy. After a 14-day run-in period on their current asthma medications (SABA and ICS at fixed doses), subjects were randomized to one of 4 different doses (50, 100, 200 and 400 mcg) of Fp, placebo, or the active control (Flovent Diskus 250 mcg) and treated with one inhalation twice daily for 12 weeks. The MDPI and

placebo were given in a blinded fashion, but the Flovent Diskus was open-label as its appearance is different than the MDPIs. A follow-up visit occurred after 1 week (week 13).

The study design for Study 202 is depicted in Figure 3.

Figure 3. Study 202: Study Design



Source: Study 202 CSR, Fig 1, pg. 32

The schedules of assessments are shown in Figure 4

Figure 4. Study 202: Schedule of Assessments

Procedures	Screening Visit	Treatment Period									Follow-up (Investigational site visit or Phone Contact)
		Random-ization Visit								End of Therapy	
Visit/Contact	SV[a]	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9/TdV[b]	Follow-up
Week of Study	−3 to −2	0	1	2	3	4	6	8	10	12	13
Treatment Day	−21 to −14[c] (±2)	1	7 (±2)	14 (±2)	21 (±2)	28 (±2)	42 (±2)	56 (±2)	70 (±2)	84 (±2)	7 (±2) after TV9 or TdV
Informed Consent/Assent[d]	X										
Demography	X										
Medical history	X										
Asthma history	X										
Medication history	X										
Inclusion/exclusion criteria	X	X									
Vital signs	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X									X	
Physical examination	X									X	
Oropharyngeal examination	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test (if applicable)	X									X	
Urine pregnancy test (if applicable)		X	X	X	X	X	X	X	X		
Clinical laboratory tests (chemistry, hematology, urinalysis)	X[e]									X[e]	
Dispense 24-hour urine cortisol collection materials	X[f]								X[f]		
24-hour urine cortisol collection		X[g]								X[g]	

Register randomization/treatment assignment via IWRS/IVRS		X									
Dispense study drug[k]		X				X		X			
Register visit and/or study drug dispensed in IWRS/IVRS		X	X	X		X		X		X	
Review study drug storage conditions with subject	X	X	X	X	X	X	X	X	X		
Witness self-administration of study drug		X	X	X	X	X	X	X	X		
Collect study drug						X		X		X	
Adverse event monitoring[l]	X----------										----------X
Dispense subject medication worksheet	X	X	X	X	X	X	X	X	X		
Concomitant medication review	X----------										----------X
Schedule visit	X	X	X	X	X	X	X	X	X	X	
Discontinue subject via IWRS/IVRS										X	
Collect PEF/diary device										X	
Discuss asthma treatment options with subject.										X	

Serial blood sampling (pharmacokinetic cohort only)		X[h]								
Administer asthma control test		X				X		X		X	
Reversibility testing	X[a]										
PFT	X	X	X	X	X	X	X	X	X	X	
Calculate FEV_1/PEF Stability limits		X									
PEF/diary device- dispense and train	X										
PEF/diary data transmission and review		X	X	X	X	X	X	X	X	X	
Review of stopping criteria for worsening asthma[j]			X	X	X	X	X	X	X	X	
Register subject in IWRS/IVRS	X										
Treatment device training (proper use and storage)	X	X	X	X	X	X	X	X	X		
Dispense placebo MDPI	X										
Collect placebo MDPI		X									
Dispense rescue medication[j]	X	X		X		X		X			
Collect rescue medication[j]		X		X		X		X		X	
Randomization criteria review		X									

Source: Study 202 CSR, Table 1, pgs. 27-29

Reviewer comment: Compared to Study 201, Study 202 had more 3 more study visit interspersed over the study period (e.g. week 3, week 6, and week 10).

Population

Key Inclusion Criteria

1. ≥ 12 years of age
2. Asthma diagnosis as defined by the National Institutes of Health
3. FEV1 40-85% predicted
4. 12% reversibility of FEV1 within 30 minutes following 2-4 inhalations of albuterol
5. Permitted asthma therapies: SABA and ICS maintenance therapy for a minimum of 8 weeks, with a stable high-dose (either has as ICS monotherapy or ICS/LABA combination) for ≥ 4 weeks. See Table 9 for details.

   a. Subjects on a mid-dose ICS combined with LABA could have the LABA discontinued and ICS could be increased to a qualifying high-dose.

6. If female, was not currently pregnant, breastfeeding, or attempting to become pregnant, had a negative serum pregnancy test, and was of non-childbearing potential or if childbearing potential, then had to be willing to commit to using acceptable methods of birth control.

Table 9. Study 202: List of allowed baseline ICS therapy

Asthma Therapy	Daily Dose (mcg/day)
Fluticasone propionate HFA MDI	≥880 mcg
Fluticasone propionate DPI	≥1000 mcg
Beclomethasone dipropionate DPI	≥2000 mcg
Beclomethasone dipropionate HFA (QVAR)	≥640 mcg
Beclomethasone dipropionate HFA (Clenil Modulite)	≥2000 mcg
Budesonide DPI	≥1600 mcg
Budesonide MDI	≥1600 mcg
Flunisolide	≥2000 mcg
Triamcinolone acetonide	≥2000 mcg
Mometasone furoate DPI	≥880 mcg
Ciclesonide HFA MDI	≥640 mcg

Source: CSR, pg. 39

Reviewer comment: Study 201 which enrolled patients on non-steroidal asthma therapy also had a higher reversibility threshold of 15% to compensate.

Key Exclusion Criteria

1. History of life-threatening asthma (i.e. requiring intubation and/or associated with hypercapnia, respiratory arrest, or hypoxic seizure).
2. Upper or lower respiratory, sinus, or middle ear infection (bacterial or viral) within 2 weeks of screening or prior to the randomization visit.
3. Asthma exacerbation requiring oral corticosteroids within 3 months or hospitalization within 6 months
   a. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular non-corticosteroid maintenance therapy.
4. Glaucoma, cataracts, ocular herpes simplex, or malignancy other than basal cell carcinoma.

5. Historical or current evidence of a clinically significant disease (including cystic fibrosis, and chronic obstructive pulmonary disease), defined as any disease that in the opinion of the investigator would have put the safety of the subject at risk through participation, or which could have affected the efficacy or safety analysis if the disease/condition exacerbation during the study.
6. Current malignancy (excluding basal cell carcinoma). If the subject had a history of malignancy, this was acceptable if the subject had been in remission for 1 year.
7. Current or treated tuberculosis
8. Uncontrolled hypertension (sBP ≥ 160 or dBP > 100)
9. Stroke within 3 months
10. Immunologic compromise, HIV, Hepatitis B or C
11. Current oral candidiasis
12. History of an adverse reaction to any β_2-agonist, sympathomimetic drug, or intranasal, inhaled, or systemic corticosteroid, or to any of the constituents of the dry powder inhalers (i.e. lactose).
13. Severe allergy to milk protein
14. Use of systemic, oral or depot corticosteroids within 12 weeks
    b. Topic steroids (≤1% hydrocortisone cream), intranasal steroids, and ocular steroids at a stable dose x 4 weeks was permitted
15. Immunosuppressive medications within 4 weeks
16. Allergy immunotherapy not stable for at least 90 days
17. Use of potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) within 4 weeks prior to the SV. Mild and moderate CYP3A4 inhibitors were permitted.
18. History of alcohol or drug abuse within 2 years
19. Current smoker, smoking history of ≥10 pack years, or use of tobacco products (cigarettes, cigars, chewing tobacco, or pipe tobacco) within 1 year.

Reviewer comment: For Study 201, patients were excluded for oral steroid use within 3 months and hospitalization within 6 months.

Randomization Criteria

1. Pre-dose percent predicted FEV1 of 40% to 85% of their predicted normal and FEV1 reversibility of ≥15% if not demonstrated at the SV
2. Any combination of the asthma symptom scores (≥1 day-time plus night-time) or albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period (immediately preceding TV1).
3. No changes in asthma medications, excluding albuterol.
4. No occurrence of an upper or lower respiratory illness (allowed to rescreen 2 weeks after resolution of the infection).
5. No asthma exacerbations

   a. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular ICS maintenance therapy.
6. No visual evidence of oral candidiasis

Asthma Symptom Scores

Daily asthma symptom scores, were recorded in the AM and PM before PEF, study drug or rescue medication. The score was assessed for cough, wheeze, shortness of breath, and chest tightness as follows:

Daytime (Determined in the evening)
0 = No symptoms during the day
1 = Symptoms for 1 short period during the day
2 = Symptoms for 2 or more short periods during the day
3 = Symptoms for most of the day which did not affect my normal daily activities
4 = Symptoms for most of the day which did affect my normal daily activities
5 = Symptoms so severe that I could not go to work or perform normal daily activities

Nighttime (Determined in the morning)
0 = No symptoms during the night
1 = Symptoms causing me to wake once (or wake early)
2 = Symptoms causing me to wake twice or more (including waking early)
3 = Symptoms causing me to be awake for most of the night
4 = Symptoms so severe that I did not sleep at all.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate.

Concomitant medications

LABAs, antihistamines, and leukotriene modifiers as well as other medications were prohibited or restricted during this study as outline in Table 10.

Table 10. Study 202: Prohibited and Restricted Concomitant Medications

Type of medication	Limitation
CYP3A4 inhibitors (ritonavir, ketoconazole, etc.) Strong and Moderate	Prohibited 4 weeks prior to SV and throughout study
β-Adrenergic Receptor Blocking Agents	Prohibited 4 weeks prior to SV and throughout study
Anti-IgE therapy (omalizumab)	Prohibited 12 weeks prior to SV and throughout study
Inhaled LABA [a]	Prohibited 1 week prior to SV and throughout study
Oral β_2-agonists	Discontinued at SV and prohibited throughout study
All antihistamines (nasal, oral and ocular)	Discontinued use for 24 hours prior to any study visit and resumed use after completion of each study visit
Leukotriene modifiers	Prohibited 2 weeks prior to SV and throughout study
Theophyllines	Prohibited 2 weeks prior to SV and throughout study
Cromones	Prohibited 4 weeks prior to SV and throughout study
Anticholinergics	Prohibited 4 weeks prior to SV and throughout study
Systemic, topical, oral, or depot corticosteroids (See exceptions in Section 9.4.8)	Prohibited 4 weeks prior to SV and throughout study
Immunosupressive therapy (see exception in Section 9.4.8)	Prohibited 4 weeks prior to SV and throughout study
Any other investigational drug	30 days

Source: CSR, Table 3, pg. 50

Treatment groups

Run-in:

- Continued current asthma medications (i.e. ICS and SABAs). SABAs were replaced with albuterol HFA MDI (90 mcg/actuation).
- One inhalation of placebo MDPI (single-blind)

Treatment:

- Albuterol HFA MDI as needed for relief of asthma symptoms
- Subjects were randomized to 1 of 6 treatment groups as described in Table 11.

Table 11. Study 202: Treatment Groups

Treatment group	Device	Total daily dose (mcg)
A	Fp MDPI 50 mcg twice daily	100 mcg
B	Fp MDPI 100 mcg twice daily	200 mcg
C	Fp MDPI 200 mcg twice daily	400 mcg
D	Fp MDPI 400 mcg twice daily	800 mcg
E	Placebo MDPI twice daily	0 mcg
F	FLOVENT DISKUS 250 mcg twice daily	500 mcg

Source: CSR, Table 2, pg. 46

Flovent Diskus also consists of a dry powder formulation of Fp in a lactose excipient and is marketed by GlaxoSmithKline, Research Triangle Park, North Carolina, and is approved for use for the maintenance treatment of asthma as prophylactic therapy in patients 4 years and older.

Placebo MDPI was provided in devices identical in appearance to Fp MDPI. Each placebo device contained lactose monohydrate without the active ingredient

Blinding

The run-in period was single blinded (subject blinded). The treatment period was double-blind with respect to Fp and placebo. Flovent Diskus was administered in an open-label manner. The MDPI devices (placebo or Fp) were white and colorless opaque plastid dry powder inhalers. Flovent Diskus is an orange plastic, metered, disc-shaped device containing fluticasone propionate.

Compliance

Compliance was assessed by review of the dose counter at each study visit. Noncompliance was defined at administering study drug on <80% of the days. If noncompliance was demonstrated at ≥2 visits the subject could have been withdrawn from the study.

Reviewer comment: This is acceptable given that if patients were noncompliant with the study drug it would decrease the treatment effect.

Efficacy Endpoints

Primary Endpoint

- Change from baseline in trough (AM pre-dose and pre-albuterol) FEV1 over the 12-week treatment period.

Reviewer comment: This differs from Studies 301 and 30017 which looked at a landmark endpoint of FEV1 at Week 12 and not a continuous endpoint over 12-weeks. Notably, the landmark endpoint is included under other efficacy endpoints.

Secondary Endpoints

All secondary endpoints were assessed over the 12-week treatment period.

- Change from baseline in weekly average of daily trough AM PEF (pre-dose and pre-albuterol) over 12 weeks
- Change from baseline in weekly average of daily PM PEF over 12 weeks
- Change from baseline in percentage of rescue-free 24-hour periods (treatment period)
- Time to withdrawal due to meeting stopping criteria for worsening asthma (treatment period)

Other Efficacy Endpoints

All other efficacy endpoints are change from baseline in…

- trough FEV1 at weeks 1, 2, 4, 8, and, 12
- trough FEV1 at week 12
- daily trough AM PEF over the first 14 days
- daily trough AM PEF over each week until week 12
- weekly average of daily trough AM PEF over each 4 week period (weeks 1-4, 5-8, 9-12).
- weekly average of daily trough AM PEF at week 12
- Asthma control test (ACT) every 4 weeks and over weeks 1-12
- total daily use of albuterol (number of inhalations) over the first 14 days
- weekly average of total daily use of albuterol over week 1-12
- weekly average of total daily use of albuterol at week 12
- percentage of symptom-free days during the treatment period.

Efficacy Endpoint Parameters

Primary Efficacy Parameter

Trough FEV1 was measured via spirometry which was conducted based on American Thoracic Society and ERS criteria. All FEV1 data were submitted to a central reading center for evaluation. Spirometry was conducted at screening, Week 0, 1 (baseline), 2, 3, 4, 6, 8, 10, and 12. Albuterol was held for 6 hours prior to spirometry.

Secondary Efficacy Parameters

PEF
Peak expiratory flow (PEF) was determined in the AM and PM as the highest value of 3 measurements, before administration of study or rescue medications, using a handheld electronic peak flow meter. Baseline trough PEF was defined as the average of recorded (nonmissing) trough over the 7 days directly preceding Week 0.

Rescue Medication Use
Number of inhalations of albuterol used each day and each night was self-recorded in the subject's diary. Baseline was defined as the percentage of rescue-free days over the 7 days directly preceding Week 0.

Stopping Criteria for Worsening Asthma

1. FEV1 below the stability limit value
    a. Stability limit = best pre-albuterol FEV1 at Week 0 x 80%
2. PEF below the stability limit for > 3 days (out of 7 days)
    a. Stability limit = mean AM PEF available from 7 days preceding Week 0 x 80%
3. >2 days of ≥ 12 inhalations of albuterol
4. Asthma exacerbation
    a. Defined as worsening asthma requiring any treatment other than study drug or rescue albuterol including the use of systemic steroids and/or ER visit or hospitalization.

Asthma exacerbations were not recorded as adverse events unless they met the criteria of an SAE. Subjects with asthma exacerbations meeting the serious adverse events definition, requiring oral or injectable corticosteroid use or any change in their asthma therapy were to be discontinued from the study due to meeting stopping criteria.

Reviewer comment: Study 201 did not include nighttime asthma symptoms as stopping criteria for worsening asthma. The 80% stability limit is based on the NHLBI asthma guidelines of asthma control (FEV1 or peak flow 60-80% predicted/personal best is considered not well-controlled, SABA use > 2 days a week). (3)

Other Efficacy Parameters

Asthma Control Test
The ACT is a 5-item subject-completed tool that assesses day and night symptoms, use of rescue medications, and impact of asthma on daily functioning. Each item is scored on a 5-point scale, summed, and scores range from 5-25. The ACT was captured at baseline, weeks 4, 8, and 12. Baseline was defined as the value of the ACT score at Week 0.

Reviewer comment: The MCID for ACT has not been established. The sponsor notes scores ≤ 19 indicate poorly controlled asthma.(2)

Symptom-free days
Baseline was defined as the percentage of symptom free-days over the 7 days directly preceding Week 0. A 24 hour symptom free period as defined as an ACT score of 0 for both daytime and nighttime entries.

Safety Parameters

Safety parameters consisted of clinical labs (Same labs as Study 201, see Table 7; Screening, and Week 12), vital signs (pulse and blood pressure – all treatment visits), ECGs (blinded reader at central center; screening and Week 12), physical exam (including body weight and height; screening and Week 12), oropharyngeal exams (all treatment visits), and concomitant medication use.

PK substudy
Approximately 20% of subjects participated in PK assessments at Week 0 over 12 hours to assess AUC 0-t, Cmax, and Tmax. For subjects randomized to placebo, samples from pre-dose and 45 minutes post-dose were analyzed. Subjects on fluticasone propionate at baseline could be switched to an equivalent dose of mometasone furoate if they were selected for the PK substudy.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Statistical Plan

Primary endpoint: The primary analysis was performed using a mixed model repeated measures (MMRM) analysis with effects due to baseline trough FEV1, sex, age, visit, treatment, and visit-by-treatment interaction. Missing data was not implicitly imputed, however all nonmissing data were used in the analysis to test the linear in log-dose time-averaged trend and to estimate the time-averaged difference between treatment groups over 12 weeks. PFT data was excluded from the analysis if it was collected after prohibited medication or more than 1 week since the last dose of study drug.

A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 0.05 level. Specifically, the 2-sided linear in log-dose time-averaged trend test was first performed at the 0.05 level of significance. Only if this trend test demonstrated overall efficacy of Fp (a significantly positive trend), was the highest Fp dose (100 mcg twice daily) to be compared with placebo with a 2-sided test at the 0.05 level of significance. If the highest Fp dose was found to be effective (resulting in a significantly greater time averaged FEV_1 mean than placebo), the next highest Fp dose (50 mcg twice daily) was compared with placebo with a 2-sided test at the 0.05 level of significance. The testing was to proceed through the lower Fp MDPI doses until an Fp dose was not found to be effective or all the Fp doses had been tested.

Secondary endpoints:
Testing of secondary efficacy variables at the 4 dosage levels was carried out in a sequential manner.

Analyses Population

Intent-to-Treat (ITT) Population
All randomized subjects with treatment assigned based upon the treatment randomized regardless of which treatment they actually received. The ITT was used for supportive efficacy (FAS was the primary efficacy analysis set). All efficacy analyses were performed using the ITT population and for all study population summaries, with the exception of the disposition table.

Full Analysis Set (FAS)
All subjects in the ITT population who received at least 1 dose of study drug AND had at least 1 postbaseline trough FEV1 assessment. The FAS was the primary efficacy analysis set.

Per-Protocol (PP) Population
The PP population included all data from randomized subjects prior to experiencing major protocol violations.

Pharmacokinetic (PK) Analysis Set
A subset of the PP population that was enrolled in the PK substudy.

Safety Population
All randomized subjects who received at least 1 dose of study drug. Treatment was assigned as given, regardless of randomization group.

Urinary Cortisol (UC) Population
The UC population consisted of subjects whose urine samples did not have confounding factors (listed below) that would affect the interpretation of the results.

- urine volumes <600ml (females) or <800 (males)
- 24-hour creatinine excretion below the lower limit of the threshold range (the threshold range was defined as the mean ±2.5 standard deviation (SD), and the normal range was the mean ±2.0 SD)
- collection time intervals outside 24 ±2 hours
- end date of baseline is greater than the date of the first dose of the study
- start date of the end of treatment urine collection is more than 1 day after the final dose of study drug
- used any corticosteroid in violation of the protocol
- missing baseline and/or end of treatment urine cortisol assessment

Protocol Amendments

A total of 6 amendments were made to the protocol. The protocol amendments that occurred after patients were enrolled are listed below.

Amendment 4 (April 30, 2012)
Inclusion and exclusion criteria were amended. A total of 23 subjects were randomized under this version of the protocol

Amendment 5 (July 30, 2012)
This amendment modified inclusion criteria to clarify the study population. A total of 84 subjects were randomized to the study under this version of the protocol.

Amendment 6 (December 20, 2012)
This amendment modified inclusion criteria to allow retesting and rescreening. A total of 530 subjects were randomized to the study under this version of the protocol.

Reviewer comment: The amendments were considered minor.

Protocol Deviations

A list of protocol violations and deviations are listed in Table 12.

Table 12. Study 202: Protocol violations ≥ 2% in any treatment arm (ITT)

	Fp 50 mcg N=107	Fp 100 mcg N=107	Fp 200 mcg N=106	Fp 400 mcg N=107	Placebo N=106	Flovent Diskus N=107	Total N=640
Subjects with at least 1 violation and/or deviation	45 (42)	46 (43)	57 (54)	40 (37)	50 (47)	54 (50)	292 (46)
Violations	25 (23)	31 (29)	36 (34)	30 (28)	35 (33)	45 (42)	202 (32)
Stopping criteria	14 (13)	24 (22)	21 (20)	20 (19)	15 (14)	26 (24)	120 (19)
Other	8 (7)	10 (9)	11 (10)	8 (7)	13 (12)	10 (9)	60 (9)
Inclusion criteria	2 (2)	3 (3)	7 (7)	2 (2)	5 (5)	8 (7)	27 (4)
Prohibited med	4 (4)	2 (2)	4 (4)	4 (4)	6 (6)	6 (6)	26 (4)
Primary endpoint criteria	3 (3)	1 (<1)	1 (<1)	5 (5)	3 (3)	6 (6)	19 (3)
Deviations	25 (23)	23 (21)	27 (25)	12 (11)	27 (25)	15 (14)	129 (20)
Inclusion criteria	12 (11)	10 (9)	10 (9)	7 (7)	9 (8)	9 (8)	57 (9)
Prohibited med	6 (6)	6 (6)	9 (8)	1 (<1)	6 (6)	3(3)	31 (5)
Medication taken within 6 hours of spirometry	6 (6)	2 (2)	5 (5)	2 (2)	7 (7)	2 (2)	24 (4)
Other	1 (<1)	2 (2)	3 (3)	1 (<1)	5 (5)	3 (3)	15 (2)

Source: CSR, Table 12, pg. 99

A total of 292 (46%) of subjects had 1 or more protocol violations and/or deviations. This was generally similar across treatment groups with the lowest (37%) in the Fp 400 mcg group and the

highest in the Fp MDPI 200 mcg group (54%). A total of 202 (32%) were considered major violations. The most frequently occurring major violation was related to stopping criteria (120 subjects (19%)) in all groups. The most frequently reported protocol deviation were inclusion criteria (57 subjects (9%)). A total of 45 (7%) subjects discontinued due to protocol violations.

The majority of protocol violations were due to stopping criteria for worsening asthma. See Secondary Efficacy Parameters for further details.

5.3.3 Study FSS-AS-201(FSS-201)

Administrative Information

- **Study title:** A Six-Period, Crossover, Dose-Ranging Study to Evaluate the Efficacy and Safety of Four Doses of FS SPIROMAX® (Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder) Administered as Single Doses Compared with Single Doses of Fluticasone Propionate SPIROMAX and Open-Label ADVAIR® DISKUS® in Adult and Adolescent Subjects with Persistent Asthma
- **Study dates:** January 22, 2013 to June 2, 2013
- **Study sites:** USA
- **Study report date:** May 7, 2015

Reviewer comment: The trade name SPIROMAX ® was used at the time of the phase 1 and 2 studies; (b) (4)

Objectives/Rationale

Primary Objectives

Evaluate the dose response, efficacy, and safety of 4 different doses of salmeterol xinafoate (6.25 mcg, 12.5 mcg, 25 mcg, and 50 mcg) each combined with a fixed dose of fluticasone propionate (100 mcg) delivered as fluticasone propionate/salmeterol inhalation powder (FS) when administered as a single dose in patients 12 years of age and older with persistent asthma.

Study Design and Conduct

Overview

Study FSS-201 was a 6-period crossover, single-dose, dose-ranging study with 4 doses of FS (fluticasone propionate/salmeterol xinafoate) compared to Fp and Advair Diskus in subjects 12 years and older with persistent asthma. Subjects had a screening/run-in period of 14 days, followed by 5 weeks of weekly crossover treatments, and a follow-up period conducted 7 days after the end of study procedures. Baseline ICS treatment (Fp 50 mcg 2 puffs twice daily) was administered throughout the study.

The schedules of assessments are shown in Figure 5.

Figure 5. Study FSS-201: Schedule of Assessments

Visit	SV	TV1-TV5[a]	TV6	EOS[b]	TdV	Follow-up Telephone Contact
Period	Screening Visit/Run-in Period	Treatment Periods 1-5	Treatment Period 6	End of Study	Early Withdrawal	
Treatment Day	−14 (±2)	1 and 5-7 days after each treatment visit	5–7 days after TV5	Immediately after TV6	Unscheduled	7 (±2) days post EOS or TdV
Written informed consent/assent/HIPAA authorization	X					
Review Inclusion/Exclusion criteria	X					
Demography	X					
Medical history including 30 day prior medication history	X					
Menses data collection	X			X	X	
Study qualifying spirometry	X					
Demonstration of reversibility	X					
Physical examination	X			X[c]	X	
Oropharyngeal examination	X	X	X		X	
12-lead ECG (supine)	X	X	X		X[d]	
Vital signs (seated)	X	X	X		X	
Height	X					
Weight	X					
Serum pregnancy test (if applicable)	X			X	X	
Urine pregnancy test (if applicable)		X	X			
Clinical laboratory evaluations[e]	X	X	X	X	X	
Study drug training	X	X	X			
Peak flow meter and daily diary training	X	X				
Dispense peak flow meter and daily diary	X	X[f]				
Dispense rescue medication	X	X[g]				
Dispense study drug	X	X				
Study drug administration		X	X			
Spirometry (12-hour serial FEV_1)[h]		X	X			

Visit	SV	TV1-TV5[a]	TV6	EOS[b]	TdV	Follow-up Telephone Contact
Period	Screening Visit/Run-in Period	Treatment Periods 1-5	Treatment Period 6	End of Study	Early Withdrawal	
Treatment Day	−14 (±2)	1 and 5-7 days after each treatment visit	5–7 days after TV5	Immediately after TV6	Unscheduled	7 (±2) days post EOS or TdV
Spirometry (single)					X[i]	
Pharmacokinetic blood sample collection[j]		X	X			
Register visit/ randomization/treatment assignment via IVRS/IWRS	X	X	X	X	X	
Concomitant medication monitoring	X	X	X		X	X
Adverse event monitoring	X	X	X	X	X	X
Collect rescue medication			X		X	
Collect daily diary		X	X		X	
Collect PEF meter			X		X	
Collect study drug		X	X		X	
Schedule next visit/contact	X	X		X		
Discuss asthma discharge therapy				X	X	

Source: Study FSS-201 CSR, Table 1, pgs. 31-32

Population

Key Inclusion Criteria

1. ≥ 12 years of age
2. Asthma diagnosis as defined by the National Institutes of Health
3. FEV1 40-85% predicted
4. 15% reversibility of FEV1 within 30 minutes following 2-4 inhalations of albuterol
5. Permitted asthma therapies: SABA and ICS maintenance therapy for a minimum of 8 weeks, with a stable high-dose (either has as ICS monotherapy or ICS/LABA combination) for ≥ 4 weeks. See Table 13 for details.
    a. Subjects on a mid-dose ICS combined with LABA could have the LABA discontinued and ICS could be increased to a qualifying high-dose.
6. If female, was not currently pregnant, breastfeeding, or attempting to become pregnant, had a negative serum pregnancy test, and was of non-childbearing potential or if childbearing potential, then had to be willing to commit to using acceptable methods of birth control.

7. Subjects are required to be on a stable dose of SABA and an ICS for a minimum of 8 weeks. LABAs must be discontinued 2 weeks prior to screening.

Table 13. Study FSS-201: List of allowed baseline ICS therapy

Asthma Therapy	Maximum Daily Dose (mcg/day)
Fluticasone propionate HFA MDI	≤ 500 mcg
Fluticasone propionate DPI	≤ 500 mcg
Beclomethasone dipropionate HFA (QVAR)	≤ 320 mcg
Budesonide DPI	≤ 720 mcg
Flunisolide	≤ 2000 mcg
Mometasone furoate DPI	≤ 440 mcg
Ciclesonide HFA MDI	≤ 320 mcg

Source: CSR, pg. 34

Reviewer comment: This study has the same reversibility threshold as Study 201. Notably, Study 202 had a lower reversibility threshold of 12%.

Key Exclusion Criteria

1. History of life-threatening asthma (i.e. requiring intubation and/or associated with hypercapnia, respiratory arrest, or hypoxic seizure).
2. Upper or lower respiratory, sinus, or middle ear infection (bacterial or viral) within 2 week of screening or prior to the randomization visit.
3. Asthma exacerbation requiring oral corticosteroids within 3 months or hospitalization within 6 months
    c. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular non-corticosteroid maintenance therapy.
4. Glaucoma, cataracts, or ocular herpes simplex
5. Historical or current evidence of a clinically significant disease (including cystic fibrosis, and chronic obstructive pulmonary disease), defined as any disease that in the opinion of the investigator would have put the safety of the subject at risk through participation, or which could have affected the efficacy or safety analysis if the disease/condition exacerbation during the study.
6. Current malignancy (excluding basal cell carcinoma). If the subject had a history of malignancy, this was acceptable if the subject had been in remission for 1 year.

7. Current or treated tuberculosis
8. Uncontrolled hypertension (systolic BP ≥ 160 or diastolic BP > 100)
9. Stroke within 3 months
10. Immunologic compromise, HIV, Hepatitis B or C
11. Current oral candidiasis
12. History of an adverse reaction to any β_2-agonist, sympathomimetic drug, or intranasal, inhaled, or systemic corticosteroid, or to any of the constituents of the dry powder inhalers (i.e. lactose).
13. Severe allergy to milk protein
14. Use of systemic, oral or depot corticosteroids within 12 weeks
    d. Topic steroids (≤1% hydrocortisone cream), intranasal steroids, and ocular steroids at a stable dose x 4 weeks was permitted
15. Immunosuppressive medications within 4 weeks
16. Allergy immunotherapy not stable for at least 90 days
17. History of alcohol or drug abuse within 2 years
18. Current smoker, smoking history of ≥10 pack years, or use of tobacco products (cigarettes, cigars, chewing tobacco, or pipe tobacco) within 1 year.

Reviewer comment: For Study 201, patients were excluded for oral steroid use within 3 months and hospitalization within 6 months.

Randomization Criteria

1. Pre-dose percent predicted FEV1 of 40% to 85% of their predicted normal
2. No changes in asthma medication
3. No asthma exacerbation defined as worsening of asthma requiring any treatment other than rescue albuterol.
4. Asthma symptom scores <2 for the previous 24 hours.
5. No changes in asthma medications, excluding albuterol.
6. No occurrence of an upper or lower respiratory illness (allowed to rescreen 2 weeks after resolution of the infection).
7. Compliance with the daily diary.
8. No visual evidence of oral candidiasis

Asthma Symptom Scores

Daily asthma symptom scores, were recorded in the AM and PM before PEF, study drug or rescue medication. The score was assessed for cough, wheeze, shortness of breath, and chest tightness as follows:

Daytime (Determined in the evening)
0 = No symptoms during the day
1 = Symptoms for 1 short period during the day
2 = Symptoms for 2 or more short periods during the day
3 = Symptoms for most of the day which did not affect my normal daily activities
4 = Symptoms for most of the day which did affect my normal daily activities

5 = Symptoms so severe that I could not go to work or perform normal daily activities

Nighttime (Determined in the morning)
0 = No symptoms during the night
1 = Symptoms causing me to wake once (or wake early)
2 = Symptoms causing me to wake twice or more (including waking early)
3 = Symptoms causing me to be awake for most of the night
4 = Symptoms so severe that I did not sleep at all.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate.

Concomitant medications

The following medications were prohibited or restricted during this study, as outlined in Table 14.

Table 14. Study FSS-201: Prohibited and Restricted Concomitant Medications

Medication	Time Discontinued Prior To Screening Visit
Oral steroids/ Systemic steroids	6 weeks
Investigational drugs	4 weeks (30 days)
β-adrenergic antagonists (β-blockers) and nonselective β-receptor antagonists (eg, β-blocking antihypertensives).	4 weeks (30 days)
Tricyclic antidepressants	4 weeks (30 days)
CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, macrolide antibiotics, etc.)	4 weeks (30 days)
Immunosuppressive therapy (See exceptions in Section 9.4.7)	4 weeks (30 days)
Orally inhaled anticholinergics (eg, Spiriva, Atrovent HFA)	1 week (7 days)
Leukotriene modifiers	2 weeks (14 days)
Theophylline and cromones	2 weeks (14 days)
LABA	2 weeks (14 days)
All antihistamines (nasal, oral, and ocular) Subjects on a stable dose prior to or starting at the SV Subject on as needed antihistamine use	Discontinued use for 24 hours prior to the study visit and resumed use after completion of each study visit Discontinued use for 24 hours prior to any study visit
MAO inhibitors	1 week (7 days)
Oral β_2-adrenergic agonists or products known to have β_2-agonist activity	3 days (72 hours)
Non-K+ sparing diuretics	1 day (24 hours)

CYP3A4=cytochrome P450 isoenzyme 3A4; HFA=hydrofluoroalkane; LABA=long-acting β_2-adrenergic agonist; MAO=monoamine oxidase; SV=screening visit

Tobacco products were prohibited for 1 year prior and throughout the study.

SABAs (replaced with Albuterol HFA MDI) were allowed during the run-in and treatment phases of the study, but were restricted 6 hours prior to spirometry at the screening visit.

ICS was replaced with Fp 50 mcg and took 2 inhalations twice daily

Topical (low dose), intranasal (stable daily dose x 4 weeks), and ocular steroids (stable daily dose x 4 weeks), were allowed. Other nasal sprays (nasalcrom and saline) were also permitted.

Immunotherapy was permitted if at a stable dose for at least 90 days.

At the single-dose treatment visit, subjects withheld the morning dose of Fp (because they were receiving Fp 100 mcg in the combination device given at the treatment visit) and avoided use of albuterol 6 hours prior to the visit.

Treatment groups

Run-in (14 days):

- ICS was replaced with Fp MDPI 50 mcg 2 inhalations twice daily and SABAs were replaced with albuterol HFA MDI (90 mcg/actuation).

Treatment:

- Subjects were randomized to 1 of 6 single-dose treatment groups as described in Table 15.

Table 15. Study FSS-201: Treatment Groups

Treatment Group	Devices	Total Dose (mcg)	Blinding
A	FS MDPI 100/6.25 mcg	100/6.25 mcg	Double-blind
B	FS MDPI 100/12.5 mcg	100/12.5 mcg	Double-blind
C	FS MDPI 100/25 mcg	100/25 mcg	Double-blind
D	FS MDPI 100/50 mcg	100/50 mcg	Double-blind
E	Fp MDPI 100 mcg	100 mcg	Double-blind
F	ADVAIR DISKUS 100/50 mcg	100/50 mcg	Open-label

Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler

Source: CSR, Table 2, pg. 39

Advair Diskus is marketed by GlaxoSmithKline, Research Triangle Park, North Carolina.

Washout (5-7 days)

- Same medication regiment as the run-in period

Blinding
The FS doses were double-blinded. The Advair Diskus was open-label.

Compliance
Compliance was assessed by review of the subject diary between the screening visit and the randomization visit. Noncompliance was defined at administering study drug on <60% of the days. If noncompliance was demonstrated at ≥2 visits the subject could have been withdrawn from the study.

Reviewer comment: This is acceptable given that if patients were noncompliant with the study drug it would decrease the treatment effect.

Efficacy Endpoints

Primary Endpoint

- Baseline-adjusted area under the curve for FEV_1 over 12 hours post dose (FEV_1 AUC_{0-12}).

Secondary Endpoint

- Change from baseline in FEV1 at 12 hours

Other Efficacy Endpoints

- baseline-adjusted maximum FEV1 within 12 hours post dose
- proportion of subjects who achieved at least a 200 mL increase in FEV1 within 12 hours post dose
- duration of effect: how long subjects experienced an increase of at least 12% above baseline FEV 1 and how long subjects experienced an increase of at least 15% above baseline FEV1
- proportion of subjects who experience at least 12% or 15% increase in FEV1 at 12 hours from baseline

PK Parameters (AUC 0-t, Cmax, and Tmax) were also assessed for adult patients (≥ 18 years of age).

Efficacy Endpoint Parameters

Trough FEV1 was measured via spirometry which was conducted based on American Thoracic Society and ERS criteria. Albuterol was held for 6 hours prior to spirometry.

Safety Parameters

Safety parameters consisted of clinical labs (hematology and chemistry), urine samples, pregnancy tests, potassium and glucose prior to and 15 minutes after study drug administration, vital signs (pulse and blood pressure), ECGs (blinded reader at central center; prior to and 5-10 min post dose), physical exam (including body weight), oropharyngeal exams, and concomitant medication use. Subjects ≥ 18 years of age fasted prior to treatment.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Statistical Plan

Primary endpoint: The primary analysis was defined as the area under the curve for baseline-adjusted FEV1 measurements from the pre dose to 12 hours post dose time points based on actual time of measurement and was standardized by dividing the actual time of the last FEV1 measurement.

Baseline-adjusted FEV1 was calculated as post dose FEV1 after subtracting period specific baseline FEV1. The period-specific baseline FEV1 was measured at pre dose within 5 minutes of AM dose administration at each treatment visit. If that value was missing, then FEV1 measured at 30 minutes predose was used as the period-specific baseline. The primary analysis was performed using an ANCOVA model with fixed effects of sequence, period and treatment, a random effect of subject within sequence, and a covariate of period specific baseline FEV1. A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 2-sided 0.05 level.

Secondary endpoints:

The secondary endpoint was analyzed in an ANCOVA model with fixed effects of sequence, period and treatment, a random effect of subject within sequence, and a covariate of period-specific baseline FEV1.

Analyses Population

Intent-to-Treat (ITT) Population

All randomized subjects. Treatment was assigned based on randomization.

Full Analysis Set (FAS)

All subjects in the ITT population who received at least 1 dose of study drug AND had at least 1 evaluable standardized baseline-adjusted FEV1 AUC 0-12. The FAS was the primary efficacy analysis set for the efficacy analyses.

Per-Protocol (PP) Population
The PP population included all data from randomized subjects prior to experiencing major protocol violations. Protocol violations were determined prior to unblinding. Since the use of incorrect study drug was considered a protocol violation, for treatment assignment in the PP population, "as randomized" was the same as "as treated". The PP population served as the supportive population for efficacy analyses.

Pharmacokinetic (PK) Analysis Set
The PK analysis set included all patients ≥ 18 years of age in the FAS with sufficient data to calculate the PK parameters, prior to experience a protocol violation. Treatment was assigned as actually received. Subjects who violated inclusion/exclusion criteria were excluded from the PK analysis.

Safety Population
All randomized subjects who received at least 1 dose of study drug. Treatment was assigned as actually received, regardless of randomization group.

Protocol Amendments

There was one amendment made to the protocol on December 17, 2012 before any subjects were screened. The protocol amendments that occurred after patients were enrolled are listed below.

Protocol Deviations

A total of 8 (11%) of subjects had ≥1 protocol violations, including 4 (6%) for excluded medications, 3 (4%) for primary objective variables, and 2 (3%) for noncompliance.

The primary objective variable reasons included 1 subject that missed the 2nd treatment visit due to a family emergency, one subject was given the wrong treatment kit at study visit 6, and one spirometry at treatment visit 2 was outside of the 1 hour from baseline window.

5.3.4 Study FSS-AS-301 (301)

Administrative Information for Study 301

- **Study title:** A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult

Patients with Persistent Asthma Symptomatic Despite Low-dose or Mid-dose Inhaled Corticosteroid Therapy

- **Study dates:** July 23, 2014 to September 21, 2015
- **Study sites:** US, Canada, Poland, Russia, South Africa, Ukraine, Hungary
- **Study report date:** February 15, 2016

Objectives/Rationale

Primary Objectives

To evaluate the efficacy of Fp and FS when administered over 12 weeks in patients 12 years of age and older with persistent asthma.

Secondary Objectives

- To evaluate the efficacy of Fp and FS based on patient-reported outcomes and secondary efficacy measures in patients with persistent asthma treated over 12 weeks
- To evaluate the safety and tolerability of Fp and FS in patients with persistent asthma treated over 12 weeks

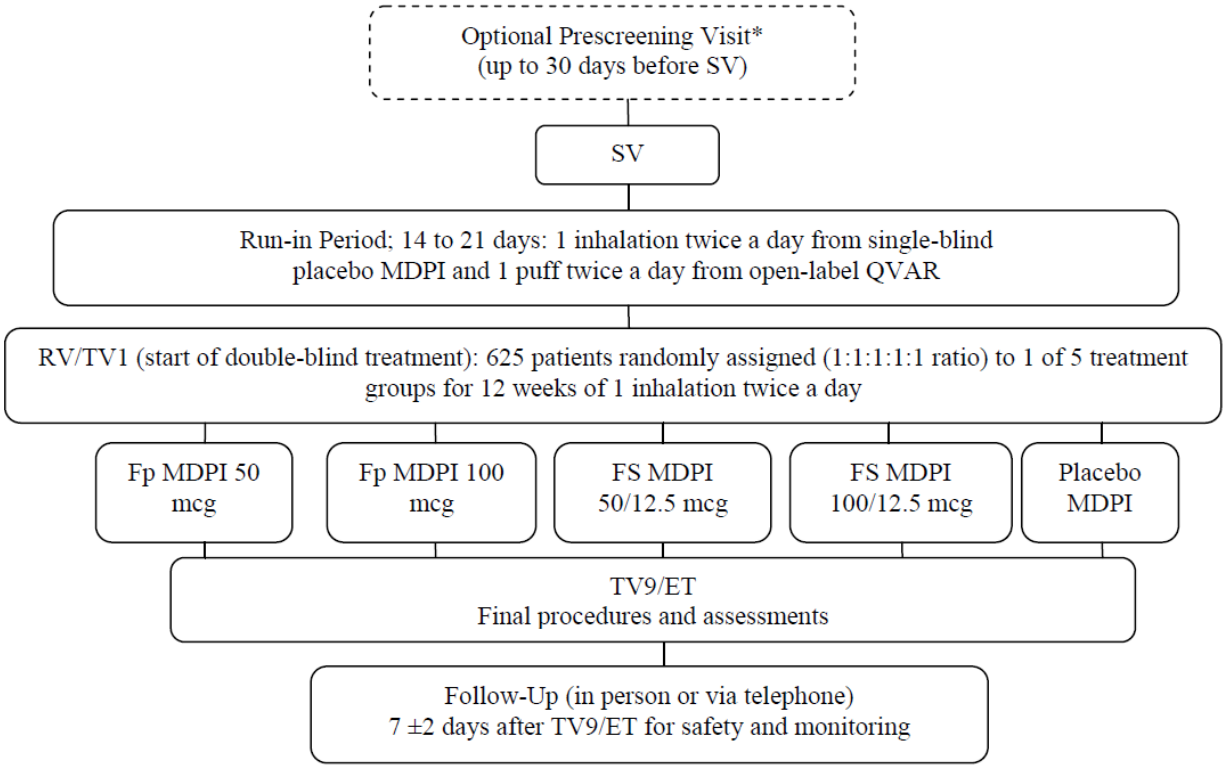
Study Design and Conduct

Overview
Study 301 was a 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, study in subjects aged 12 years and older with persistent asthma, previously treated with low-dose or mid-dose ICS or ICS/LABA therapy. After a 14 to 21-day run-in period, subjects were randomized to one of 4 different treatment arms (Fp 50 mcg, Fp 100 mcg, FS 50/12.5 mcg, or FS 100/12.5 mcg one inhalation twice daily) or placebo for 12 weeks. A follow-up visit occurred after 1 week (Week 13).

During the run-in period, subjects discontinued their current asthma medications and were provided with an albuterol HFA MDI for symptomatic relief, and open-label QVAR (40 mcg HFA MDI 1 inhalation twice daily) and a single-blinded placebo MDPI device (1 inhalation twice a day)

The study design for Study 301 is depicted in Figure 6.

Figure 6. Study 301: Study Design



* Required for patients whose prestudy asthma therapy included a LABA in addition to an ICS.
ET = early termination; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; QVAR = beclomethasone dipropionate hydrofluoroalkane metered-dose inhaler; RV = randomization visit; SV = screening visit; TV1 = treatment visit 1; TV9 = treatment visit 9

Source: CSR, Fig 1, pg. 27

The schedules of assessments are shown in Figure 7.

Figure 7. Study 301: Schedule of Assessments

Procedures and assessments[a]	Pretreatment run-in		Double-blind treatment period (visit/week)[b]									Follow-up
	SV[c,d]	RV/TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	ET	Follow-Up[e]
	Screening 14-21 days before RV	Baseline after 14-21 days of run-in	W1 Day 8 ±2	W2 Day 15 ±2	W3 Day 22 ±2	W4 Day 29 ±2	W6 Day 43 ±2	W8 Day 57 ±2	W10 Day 71 ±2	W12 Day 85 ±3	Early termi-nation	W13 7 ±2 days after TV9/ET
Informed consent/assent	X[f]											
Assign patient identification number	X[f]											
Medical and psychiatric history	X											
Asthma and asthma therapy history	X											
Prior medication history	X											
Demography	X											
Inclusion and exclusion criteria	X											
Full physical examination, including height and weight	X									X	X	
Electrocardiography	X									X	X	
Review randomization criteria		X										
Oropharyngeal exam	X	X	X	X	X	X	X	X	X	X	X	
Vital signs measurement (BP and pulse)	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test (if applicable)	X	X	X	X	X	X	X	X	X	X	X	
Dispense empty Teva MDPI trainer	X											
Training in use of Teva MDPI	X	X	X	X	X	X	X	X	X			
Dispense run-in period drug kit (placebo and QVAR [or equivalent], with training)	X											
AQLQ(S)/PAQLQ(S) administered[g]		X								X	X	
ACT administered		X				X		X		X	X	
Training in use of PEF and diary	X	X	X	X	X	X	X	X	X			
Dispense daily diary	X	X	X	X	X	X	X	X	X			
Dispense PEF meter	X											
Collect run-in period drug kit		X										
Dispense rescue medication (as needed)	X	X	X	X	X	X	X	X	X			
Predose spirometry with reversibility testing[h]	X											
Calculate FEV_1 and PEF stability limits to determine alert criteria		X										
Measure PEF[i]	X	X	X	X	X	X	X	X	X	X	X	
Predose spirometry		X[j]	X	X	X	X	X	X	X	X	X	
Review alert criteria for worsening asthma or asthma exacerbation[k]	X	X	X	X	X	X	X	X	X	X	X	X
Randomization to double-blind drug via IRT		X										
Dispense double-blind study drug[l]		X				X		X				
Supervised administration of study drug at investigational center	X[m]	X	X	X	X	X	X	X	X	X	X	
Postdose spirometry (12-hour serial)[n]		X								X	X	
Assess study compliance		X	X	X	X	X	X	X	X	X	X	
Collect patient diary		X	X	X	X	X	X	X	X	X	X	
Collect double-blind study drug						X		X		X	X	
Adverse event inquiry and recording	X[o]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X[o]	X	X	X	X	X	X	X	X	X	X	X
Collect rescue medication										X	X	
End patient participation via IRT											X	X
Discuss further treatment options										X	X	

Source: CSR, Table 1, pgs. 28-29

Population

Key Inclusion Criteria

1. ≥ 12 years of age
2. Asthma diagnosis as defined by the National Institutes of Health ≥ 3 months
3. No asthma exacerbations or changes in asthma medication for at least 30 days
4. FEV1 40-85% predicted
5. 15% reversibility AND ≥ 200 mL increase from baseline in FEV1 (in patients ≥ 18 years of age) within 30 minutes following 2-4 inhalations of albuterol
6. Current asthma therapy: SABA for ≥ 8 weeks, low-dose or mid-dose ICS either as ICS or ICS/LABA combination for ≥ 1 month. If on ICS/LABA must have prescreening visit to change to ICS monotherapy and stable for 1 month. Qualifying ICS/LABA doses are listed in Table 16.
7. If female, was not currently pregnant, breastfeeding, or attempting to become pregnant, had a negative serum pregnancy test, and was of non-childbearing potential or if childbearing potential, then had to be willing to commit to using acceptable methods of birth control.

Table 16. Study 301: Qualifying ICS doses

Qualifying ICS (as ICS or ICS/LABA)	Dosage range (mcg/day) inclusive
Fluticasone HFA	88-500
Fluticasone DPI	50-500
Budesonide HFA (80 or 160 mcg/dose)	80-480
Budesonide HFA (100 or 200 mcg/dose)	100-400
Budesonide DPI	90-720
Beclomethasone dipropionate HFA small particle (eg, QVAR 40 or 80 mcg/dose)	40-240
Beclomethasone dipropionate HFA large particle (eg, Beclate or Clenil Modulate, 50 or 100 mcg/dose)	50-400
Mometasone DPI (110 or 220 mcg/dose)	110-440
Mometasone pMDI (100 or 200 mcg/dose)	200-400
Ciclesonide HFA	80-240
Flunisolide pMDI	320-480
Fluticasone/salmeterol HFA	90-500
Fluticasone/salmeterol DPI	100-500
Budesonide/formoterol MDI	80-480
Budesonide/formoterol DPI	100-400

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; HFA = hydrofluoroalkane; DPI = dry powder inhaler; MDI = metered-dose inhaler; pMDI = pressurized metered-dose inhaler

Key Exclusion Criteria

1. History of life-threatening asthma (i.e. requiring intubation and/or associated with hypercapnia, respiratory arrest, or hypoxic seizure).
2. Upper or lower respiratory, sinus, or middle ear infection (bacterial or viral) within 2 week of screening or prior to the randomization visit.
3. Asthma exacerbation requiring oral corticosteroids within 1 month or hospitalization within 2 months
    a. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular non-corticosteroid maintenance therapy.
4. Glaucoma, cataracts, ocular herpes simplex, or malignancy other than basal cell carcinoma.
5. Historical or current evidence of a clinically significant disease (cardiovascular, hepatic, renal, hematologic, neuropsychological, endocrine, gastrointestinal, and pulmonary (including cystic fibrosis and bronchiectasis)), defined as any disease that in the opinion of the investigator would have put the safety of the subject at risk through participation, or which could have affected the efficacy or safety analysis if the disease/condition exacerbation during the study.
6. Current malignancy (excluding basal cell carcinoma). If the subject had a history of malignancy, this was acceptable if the subject had been in remission for 1 year.
7. Current or treated tuberculosis
8. Uncontrolled hypertension (systolic BP $\geq$ 160 or diastolic BP > 100)
9. Stroke within 3 months
10. Immunologic compromise, HIV, Hepatitis B or C
11. Ocular disturbances, including glaucoma, cataract or herpes simplex infection
12. Untreated oral candidiasis, not agreeing to treatment
13. Known hypersensitivity to any corticosteroids, salmeterol, or any of the excipients in the study drug or rescue medication formulation (i.e. lactose)
14. Use of systemic, oral or depot corticosteroids within 30 days
    a. Topic steroids ($\leq$1% hydrocortisone cream), intranasal steroids, and ocular steroids at a stable dose x 4 weeks was permitted
15. Immunosuppressive medications within 4 weeks
16. Allergy immunotherapy not stable for at least 30 days (and started $\geq$ 90 days).
17. Use of potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) within 30 days prior to the SV.
18. History of alcohol or drug abuse within 2 years
19. Current smoker, smoking history of $\geq$10 pack years, or use of tobacco products (cigarettes, cigars, chewing tobacco, or pipe tobacco) within 1 year.
20. The patient had previously participated as a randomized patient in a study of Fp or FS.

Reviewer comment: There are a few minor differences in the exclusion criteria compared to the phase 2 studies, as follows:

- *The asthma exacerbation exclusion is slightly more conservative compared to the phase 2 studies (3 months for an exacerbation and 6 months for a hospitalization vs. 1 month and 2 months, respectively).*
- *The allergy immunotherapy exclusion is also slightly more conservative than the phase 2 studies (stable for 30 days vs 90 days).*
- *Subjects are allowed in this study with oral candidiasis as long as they agree to treatment (subjects with evidence of oral candidiasis, regardless of whether they were treated or not, were excluded from the phase 2 studies).*
- *Prior systemic steroid use was less conservative than the phase 2 studies. Systemic steroids were not allowed within 30 days, compared to 12 weeks for the phase 2 studies.*

Randomization Criteria

1. Pre dose percent predicted FEV1 of 40% to 85% of their predicted normal
2. Any combination of the asthma symptom scores (≥1 day-time plus night-time) or albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period (immediately preceding TV1).
3. No changes in asthma medications, excluding albuterol.
4. No occurrence of an upper or lower respiratory illness (allowed to rescreen 2 weeks after resolution of the infection).
5. No asthma exacerbations
    a. Asthma exacerbation was defined as any worsening of asthma requiring any treatment other than rescue albuterol or the subject's regular non-corticosteroid maintenance therapy. This included requiring the use of systemic corticosteroids and/or ED visit or hospitalization. Urgent care/ED visits where the treatment was limited to a single dose of nebulized albuterol/salbutamol did not meet the criteria of an asthma exacerbation.
6. No visual evidence of oral candidiasis.
7. Complied with daily diary (≥4 days out of 7)
8. Daytime or nighttime asthma symptom score of ≥1 or albuterol rescue use on ≥1 occasion on at least 4 of the 7 days immediately preceding the randomization visit.

Reviewer comment: These randomization criteria select for asthma patients that are not well controlled to very poorly controlled, per NHLBI guidelines(3), despite low dose ICS (1 puff twice daily from an open-label QVAR 40 mcg HFA MDI). The trial design and inclusion/exclusion criteria are appropriate.

Concomitant medications

The following medications were prohibited during the study, as outlined in Table 17.

Table 17. Study 301: Prohibited Medications During Study

Type of medication	Washout period before the screening visit (unless otherwise specified)
Anti-immunoglobulin E therapy (omalizumab)	90 days
Any other investigational drug	30 days
Aspirin[a]	1 day
Beta-adrenergic receptor blocking agents	30 days
Bisphosphonates oral or iv (eg, alendronate, ibandronate)	30 days
Corticosteroids (oral, iv, intra-articular, intramuscular)[b]	30 days
Cromones	14 days
Decongestants (eg, pseudoephedrine, phenylpropanolamine, phenylephrine)	Discontinue 24 hours before SV, RV, and TV1-TV9 and resume use after the visit
Immunologically active biologic medications (eg, anti-tumor necrosis factor alpha, abatacept)	90 days
Immunosuppressive therapy (eg, methotrexate, gold, azathioprine)	30 days
Immunotherapy[c]	Initiation within 90 days or change in dose within 30 days
Inhaled anticholinergic medication (eg, tiotropium bromide)	7 days
Inhaled corticosteroids other than study drug	Permitted at SV, but discontinue upon entering run-in
Inhaled LABA	7 days
Intranasal aerosol corticosteroids (QNASL® [Teva], ZYTONNA® [Sunovion])[d]	Discontinue at SV
Leukotriene modifiers	7 days
Monoamine oxidase inhibitors	14 days
Oral β2-agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (eg, loratadine, diphenhydramine, cetirizine)	Discontinue 24 hours before SV, RV, and TV1-TV9 and resume use after completion of the visit

Strong CYP3A4 inhibitors (eg, azole antifungals, ritonavir, clarithromycin)	30 days
Theophyllines	14 days
Topical dermatologic corticosteroids (intermediate to high potency eg, CUTIVATE® (PharmaDerm), ELOCON® (Schering Corporation)[e]	14 days
Marijuana (medical, legal, and illegal)	30 days before the SV and throughout the study
Electronic cigarettes	Discontinue 24 hours before the SV and discontinue upon entering run-in
Tricyclic antidepressants	14 days

[a] Chronic stable doses of aspirin (no more than 325 mg/day) for cardiovascular prophylaxis are allowed.
[b] Chronic stable doses of ocular steroids of at least 7 days duration, with doses expected to remain stable throughout the study, are allowed.
[c] Immunotherapy for the treatment of allergies by any route is permitted as long as therapy was initiated 90 days or more before the SV and the patient has been on a stable dose for 30 days or more before the SV. The patient must remain on this stable regimen throughout the study.
[d] Chronic stable doses of aqueous intranasal corticosteroids of at least 7 days' duration before the SV and stable throughout the study duration for the treatment of allergic rhinitis are allowed throughout the study.
[e] Chronic and as-needed doses of low potency topical corticosteroids (eg, 1% hydrocortisone cream, desonide, flucinolone cream 0.01%) covering <20% of body surface area are allowed; no occlusive dressings are allowed.
SV=screening visit; RV=randomization visit; iv=intravenous; TV1-9=treatment visits 1-9; LABA=long-acting β_2 agonist; CYP=cytochrome P450.

Source: Study 301 protocol, Table 4, pages 70-71

Other medications were permitted, but with restrictions, as detailed below:

- Corticosteroids
    - Chronic and as-needed low potency topical steroids, not to exceed 20% of the body surface area or with occlusive dressings.
    - Intranasal steroids (aerosol formulations are prohibited; chronic stable dose for ≥ 7 days).
    - Ocular steroids (chronic stable dose for ≥ 30 days).
- Antihistamines for the treatment of allergic rhinitis (with a 24 hour washout period prior to any visit).

- Aspirin ≤ 325 mg/day for cardiovascular prophylaxis (chronic stable dose).

Treatment groups

Run-in:

- SABAs were replaced with albuterol HFA MDI (90 mcg/actuation).
- ICS or ICS/LABA was discontinued and replaced with 1 puff twice daily from an open-label QVAR 40 mcg HFA MDI (or equivalent).
- One inhalation twice daily of placebo MDPI (single-blind)

Treatment:

- Albuterol HFA MDI as needed for relief of asthma symptoms
- Subjects were randomized to 1 of 5 treatment groups as described in Table 18.

Table 18. Study 301: Treatment Groups

Treatment arm	Active devices	Total daily dose	Blinding
A	Fp MDPI 50 mcg	100 mcg	Double-blind
B	Fp MDPI 100 mcg	200 mcg	Double-blind
C	FS MDPI 50/12.5 mcg	100/25 mcg	Double-blind
D	FS MDPI 100/12.5 mcg	200/25 mcg	Double-blind
E	Placebo MDPI	0 mcg	Double-blind

Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler

Source: CSR, Table 1, pg. 25

Placebo MDPI was provided in devices identical in appearance to Fp. Each placebo device contained lactose monohydrate without the active ingredient

Efficacy Endpoints

Primary Endpoint

- change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 at week 12 (TV9)
- standardized baseline-adjusted area under the effect curve for FEV1 from time 0 to 12 hours postdose (FEV1 AUEC0-12h) at week 12 (TV9), analyzed for the subset of approximately 300 patients who performed postdose serial spirometry

Key secondary Endpoint

- time (median and mean) to 15% and 12% improvement from baseline in FEV1 postdose at TV1 in the serial spirometry subset

Secondary Endpoints

- change from baseline in the weekly average of the daily trough AM PEF over the 12-week treatment period
- change from baseline in the weekly average of the total daily asthma symptom score (the total daily asthma symptom score is the average of the daytime and nighttime scores) over weeks 1 to 12
- change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12
- time to patient withdrawal for worsening asthma during the 12-week treatment period
- change from baseline in the AQLQ(S) (patients ≥18 years of age only) score at week 12 or at endpoint

Other Efficacy Endpoints

- change from baseline in the weekly average of the daily trough PM PEF over the 12-week treatment period
- time to meeting alert criteria for worsening asthma during the 12-week treatment period
- change from baseline in total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over the first 14 days on study drug and change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) at weeks 4, 8, and 12 or at endpoint (i.e., the last post baseline observation)
- change from baseline in percentage of rescue-free 24-hour periods (defined as 24-hour periods with no rescue medication usage) during the 12-week treatment period
- change from baseline in percentage of symptom-free 24-hour periods (defined as 24-hour periods with asthma symptom scores of 0) during the 12-week treatment period
- change from baseline in percentage of asthma-control 24-hour period (defined as 24-hour periods with asthma symptom scores of 0 and no rescue medication usage) during the 12-week treatment period
- proportion of patients meeting alert criteria for worsening asthma during the 12-week treatment period
- proportion of patients withdrawn for worsening asthma during the 12-week treatment period
- change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 at weeks 1, 2, 3, 4, 6, 8, 10, and 12 or at endpoint

- change from baseline in trough (AM predose and pre-rescue bronchodilator) FEF25-75 over weeks 1 to 12 and at weeks 1, 2, 3, 4, 6, 8, 10, and 12 or at endpoint
- change from baseline in trough (AM predose and pre-rescue bronchodilator) FVC over weeks 1 to 12 and at weeks 1, 2, 3, 4, 6, 8, 10, and 12 or at endpoint
- proportion of patients who achieve at least a 15%, 12%, or 200-mL increase in FEV1 within 12 hours postdose at TV1 and TV9 or at endpoint
- time (median and mean) to 15% and 12% improvement from baseline in FEV1 postdose at TV9
- duration of effect: how long patients experience an increase of at least 15% above baseline FEV1 at TV1 and TV9
- proportion of patients achieving a clinically significant change from baseline (minimum important difference [MID] ≥0.5) in the AQLQ(S) (patients ≥18 years of age only) or PAQLQ(S) (patients 12 to 17 years of age only) score at week 12 or at endpoint
- change from baseline in ACT score at weeks 4, 8, and 12, and over weeks 1 to 12 or at endpoint
- proportion of patients with ACT score ≤19 at weeks 4, 8, and 12, and over weeks 1 to 12 or at endpoint

Reviewer comment: All efficacy endpoints are identical to the Study 301.

Efficacy Endpoint Parameters

Primary Efficacy Parameter
Trough FEV1 and FEV1 AUC 0-12 hours was measured via spirometry which was conducted based on American Thoracic Society and ERS criteria. All FEV1 data were submitted to a central reading center for evaluation. Spirometry was conducted at screening, Week 0, 1 (baseline), 2, 4, 8, and 12. Albuterol was held for 6 hours prior to spirometry. The baseline spirometry for both the predose FEV1 and the FEV1 AUC 0-12 hours was defined as the average of the 30 minute and 10 minute predose measurements obtained at the randomization visit.

Post-dose serial spirometry was assessed in a subset of subjects (n=300), at 15, and 30 minutes, then 1, 2, 3, 4, 6, 8, 10, and 12 hours. Serial spirometry was stopped if a patient required albuterol treatment for worsening asthma symptoms.

Secondary Efficacy Parameters

PEF
Peak expiratory flow (PEF) was determined in the AM and PM as the highest value of 3 measurements, before administration of study or rescue medications, using a handheld electronic peak flow meter. Baseline trough PEF was defined as the average of recorded (nonmissing) trough over the 7 days before randomization.

Asthma Symptom Scores

Daily asthma symptom scores, were recorded in the AM and PM before PEF, study drug or rescue medication. The total daily asthma symptom score is the average of the daytime and nighttime scores. The range for the total daily symptom score is 0 to 4.5, 4.5 being the worst. Baseline was the average of the 7 days before randomization. The score was assessed for cough, wheeze, shortness of breath, and chest tightness as follows:

Daytime (Determined in the evening)
0 = No symptoms during the day
1 = Symptoms for 1 short period during the day
2 = Symptoms for 2 or more short periods during the day
3 = Symptoms for most of the day which did not affect my normal daily activities
4 = Symptoms for most of the day which did affect my normal daily activities
5 = Symptoms so severe that I could not go to work or perform normal daily activities

Nighttime (Determined in the morning)
0 = No symptoms during the night
1 = Symptoms causing me to wake once (or wake early)
2 = Symptoms causing me to wake twice or more (including waking early)
3 = Symptoms causing me to be awake for most of the night
4 = Symptoms so severe that I did not sleep at all.

Rescue Medication Use

Number of inhalations of albuterol used each morning and each night was self-recorded in the subject's diary. Baseline was defined as the percentage of rescue-free days over the 7 days prior to randomization.

Stopping Criteria for Worsening Asthma

Patients who experienced a clinical asthma exacerbation were withdrawn if the investigator determined that withdrawal was necessary to help control the patient's asthma. An exacerbation was defined as worsening asthma requiring any significant treatment other than study drug or rescue medication (SABA). Significant treatment included the use of systemic corticosteroids and/or urgent care/ED visit or hospitalization. Urgent care/ED visits where the treatment was limited to a single dose of nebulized albuterol/salbutamol did not meet the criteria of significant treatment.

Alert Criteria for Worsening Asthma

If any of the alert criteria were met, the investigator determined whether the patient's overall clinical picture was consistent with worsening asthma and if the patient should be withdrawn from the study.

1. FEV1 below the stability limit value
    a. Stability limit = best pre-albuterol FEV1 at Week 0 x 80%
2. PEF below the stability limit for ≥4 days (out of 7 days)

   a. Stability limit = mean AM PEF available from 7 days preceding Week 0 x 80%
3. >3 days of ≥ 12 inhalations of albuterol
4. ≥ 2 days with nighttime symptom scores >2

Asthma exacerbations were not recorded as adverse events unless they met the criteria of an SAE. Subjects with asthma exacerbations meeting the serious adverse events definition, requiring oral or injectable corticosteroid use or any change in their asthma therapy were to be discontinued from the study due to meeting stopping criteria.

Reviewer comment: The 80% stability limit is based on the NHLBI asthma guidelines of asthma control (FEV1 or peak flow 60-80% predicted/personal best is considered not well-controlled).

AQLQ

The AQLQ(S) (September 2010 version; patients aged ≥18 years) was self-administered by the patients at the investigational center at the randomization visit and at Week 12. The questionnaire is a tool to measure the impact of asthma on a patient's quality of life (physical, emotional, social, and occupational). The AQLQ(S) was administered only to patients 18 years and older. The adult questionnaire contains 32 items with a 2-week recall period and applies a 7-point Likert scale (7=not impaired at all – 1=severely impaired) to questions in the 4 domains of activity limitations, symptoms, emotional function, and environmental stimuli. Total scores were based on available data; handling of missing data is described in statistical analysis plan. Scores range from 1 to 7, with higher scores indicating better quality of life. Baseline was the last assessment recorded before randomization.

Time to 15% and 12% Improvement in Postdose Serial Spirometry

Time to 15% improvement was defined as the time elapsed from the time of first dose to the first time when 15% improvement from baseline in FEV1 was achieved at the randomization visit. If an exact 15% increase was not achieved at a measured time point, then the time was estimated by linear interpolation between the time point with the first increase greater than 15% and the time point immediately before. Patients who did not achieve the 15% improvement were censored at the time of last serial spirometry assessment at randomization visit. Analogous definitions were applied to the 12% improvement.

Percentage of Rescue-Free 24-Hour Periods

A minimum of 60% of full days during the 12-week treatment period (or relative to the number of days that the patient participated in the study) could not be missing in order for a patient to be included in this analysis.

Percentage of Symptom-Free 24-hour periods

A minimum of 60% of full days during the 12-week treatment period (or relative to the number of days that the patient participated in the study) could not be missing in order for a patient to be included in this analysis.

Percentage of Asthma-Control 24-Hour Period
Asthma-control 24-hour periods were defined as 24-hour periods with asthma symptom score of 0 and no rescue medication use. A minimum of 60% of full days during the 12-week treatment period (or relative to the number of days that the patient participated in the study) could not be missing in order for a patient to be included in this analysis.

Proportion of Patients Who Achieve ≥ 15%, 12% or 200 mL Increase in Postdose Serial Spirometry
Based on FEV1 at Week 12 (or endpoint) compared to randomization visit (baseline) in 300 subjects (subset) who performed postdose serial spirometry.

Proportion of Patients Achieving a Clinically Significant Change from Baseline in the AQLS(S) or PAQLS(S)
The proportion of patients achieving a clinically significant change from baseline (MID≥0.5) in the AQLQ(S) (patients ≥18 years of age only) or PAQLQ(S) (patients 12 to 17 years of age only) score at week 12 or at endpoint was assessed. Patients used the PAQLQ(S)\ throughout the study even if they turned 18 years of age before TV9/ET. The pediatric version differs from the adult version in the recall period (1 week rather than 2) and the number of questions and domains; it has 23 questions in 3 domains for activity limitations, symptoms, and emotional function. The baseline value was the last assessment before randomization.

Asthma Control Test
The ACT is a simple, patient-completed questionnaire used for the assessment of overall asthma control. The 5 items included in the ACT assess daytime and nighttime asthma symptoms, use of rescue medication, and impact of asthma on daily functioning. Each item in the ACT is scored on a 5-point scale, with summation of all items providing scores ranging from 5 to 25. The scores span the continuum of poor control of asthma (score of 5) to complete control of asthma (score of 25), with a cutoff score of 19 indicating patients with poorly controlled asthma. If any of the questions were not completed, then the total score was set to missing. The baseline value was the last assessment recorded before randomization.

Safety Parameters

Safety parameters consisted of urine pregnancy tests (every visit), vital signs (pulse and blood pressure – all treatment visits), ECGs (blinded reader at central center; screening and Week 12), physical exam (including body weight and height; screening and Week 12), oropharyngeal exams (all treatment visits), and concomitant medication use.

Withdrawal Due to an Adverse Event
If a patient was withdrawn from the study for multiple reasons that included adverse events, the termination page of the CRF indicated that the withdrawal was related to an adverse event. An exception to this requirement was the occurrence of an adverse event that in the opinion of the investigator was not severe enough to warrant discontinuation, but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason

for discontinuation was need to take a prohibited medication, not the adverse event. Patients could also be withdrawn for asthma exacerbation, but this was not recorded as an adverse event unless it met the criteria of a serious adverse event.

Asthma Exacerbations

Asthma exacerbations were not considered adverse events unless they met the definition of a serious adverse event (with the exception of one event that was severe (required systemic steroids for ≥ 3 days), but did not meet SAE criteria, based on an older version of the protocol).

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Statistical Plan

Primary endpoint analysis

A fixed-sequence multiple testing procedure was used to control the overall Type I error rate at the 0.05 level (2-sided) for the primary endpoints analysis as shown in Table 19.

Table 19. Study 301: Multiple Testing Procedures for Primary Endpoints

Sequence	Primary Endpoint	Hypothesis Testing
1	**[1]** Standardized baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12	FS MDPI 200/12.5 mcg BID versus Fp MDPI 200 mcg BID
		↓
2	**[1]** Standardized baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12	FS MDPI 100/12.5 mcg BID versus Fp MDPI 100 mcg BID
		↓
3	**[1]** Standardized baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12	FS MDPI 200/12.5 mcg BID versus placebo
		↓
4	**[1]** Standardized baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12	FS MDPI 100/12.5 mcg BID versus placebo
		↓
5	**[2]** Change from baseline in trough FEV_1 at week 12	FS MDPI 200/12.5 mcg BID versus placebo
		↓
6	**[2]** Change from baseline in trough FEV_1 at week 12	FS MDPI 100/12.5 mcg BID versus placebo
		↓
7	**[2]** Change from baseline in trough FEV_1 at week 12	Fp MDPI 200 mcg BID versus placebo
		↓
8	**[2]** Change from baseline in trough FEV_1 at week 12	Fp MDPI 100 mcg BID versus placebo

FEV_1AUEC_{0-12h} = area under the effect curve for forced expiratory volume in 1 second from zero to 12 hours postdose; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler, BID = twice daily; Fp MDPI = fluticasone propionate multidose dry powder inhaler

Source: CSR, Figure 2, pg. 61

Reviewer comment: Based on the order of hierarchy the primary goal was for the study to show benefit of the combination (ICS/LABA) over the monoproduct (ICS), followed by the efficacy of the combination product over placebo. It is also notable here that the standardized baseline-adjusted FEV1 AUC 0-12 was listed first in the hierarchy despite the first primary endpoint for the study was change from baseline in trough FEV1.

Change from Baseline in Trough FEV1 at Week 12

The baseline FEV1 was the average of the 2 predose FEV1 measurements (30 and 10 minutes) at the randomization visit. If one time point was missing, the other was used. If both were missing, baseline was treated as missing. Missing data was accounted for by the modified baseline observation carried forward (BOCF) method. A sensitivity analysis using an ANCOVA model with effects due to baseline trough AM FEV_1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment. Contrasts for pairwise treatment comparisons of interest were constructed. The estimated treatment difference for each contrast of interest was presented together with the 2-sided 95% CI for the difference and the p-value.

Supportive Primary Analyses
These analyses were conducted for the ITT population. No multiplicity adjustment was made for supportive analyses of the primary endpoints.

- Standardized baseline-adjusted FEV1 AUEC0-12wk was calculated using the trapezoidal rule. The modified BOCF method was used to address missing data from serial spirometry patients who did not perform serial spirometry at Week 12. If baseline FEV1 was missing, area under the effect curve values were set to missing. The endpoint was analyzed using an ANCOVA model with effects due to baseline trough FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment. Contrasts for pairwise treatment comparisons were constructed.

- Change from baseline in trough FEV1 over the 12-week treatment period was analyzed using a MMRM with effects due to baseline FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), visit, treatment, and visit-by-treatment interaction. Missing data were not implicitly imputed in the MMRM analysis, but all nonmissing data for a patient were used within the analysis to estimate the time-averaged difference between treatment groups over 12 weeks.

- Change from baseline in trough FEV1 after the 12-week treatment period using MMRM was analyzed as described for change over the 12-week period. The change from baseline in trough FEV1 after the 12-week treatment period was also analyzed using an ANCOVA model with effects due to baseline FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data using last observation carried forward (LOCF).

Sensitivity analysis
A **cumulative proportion of responders analysis graph** was provided for the change from baseline in trough FEV1 at Week 12. The graph presents the proportion of responders (y-axis) over the entire range of possible cutoff points (x-axis).

A **tipping point** analysis was also performed for the comparisons that were determined to be significant in the main analyses. The tipping point analyses tested the robustness of study results in light of missing data. This analysis was performed for all comparisons of the active drugs to placebo, as well as for comparisons of FS to Fp. The initial shift value was 0 (representing

missing at random) and treatment comparisons were made. The shift was then increased and the process repeated until the treatment effect was no longer significant at the 5% level. The shift point at which the effect was no longer significant is the tipping point. For comparisons of FS with Fp, a decrease in the value of the efficacy variable was applied to each imputed value only for patients in the FS treatment group. If the tipping point analysis indicates that the tipping point consists of unreasonable values, then the robustness of the study results is supported.

Similar to the tipping point analysis, another sensitivity analysis was performed that utilizes **multiple imputations under an assumption of missing not at random (MNAR) for those patients who withdrew due to worsening asthma**. The initial shift value was 0 (representing missing at random) and it was then increased by increments of 0.10 L.

Standardized Baseline-Adjusted FEV1 AUEC 0-12 hours At Week 12
A subset of approximately 300 patients performed serial spirometry. Data from these assessments were analyzed using the trapezoidal rule based on actual time of measurement. It was standardized by dividing it by the number of hours between the start time of dose administration and the end time of the last nonmissing FEV1 measurement. The baseline FEV1 was the average of the 2 predose FEV1 measurements (30 and 10 minutes predose) at the RV. If 1 of these was missing, the nonmissing value was used; if both were missing, baseline was treated as missing. Baseline-adjusted FEV1 was calculated as postdose FEV1 after subtracting the baseline FEV1 value. If a patient was missing postdose spirometry measurements intermittently, then those missing values were ignored and the trapezoidal rule simply spanned the missing time point(s). An ANCOVA model with fixed effects of treatment, sex, (pooled) center, previous therapy (ICS or ICS/LABA), and with covariates of age and baseline FEV1. For those serial spirometry patients who did not perform serial spirometry at week 12, missing data were imputed via LOCF for the main analysis. A sensitivity analysis used a modified BOCF method, where the postdose value of FEV1 at TV1 was used. Contrasts for pairwise treatment comparisons of interest were constructed.

Secondary endpoints:

Secondary endpoints were analyzed using the FAS population. Testing of secondary endpoints occurred when all comparisons of the primary endpoints were significant at 0.05.
At the point where the p-value is greater than 0.05, no further comparisons is interpreted inferentially. The hierarchy (if all primary efficacy endpoints were significant) is listed in Table 20.

Table 20. Study 301: Multiple Testing Procedures for Secondary Endpoints for Fp

Secondary Endpoint	Hypothesis Testing	
	Fp MDPI 100 mcg BID versus placebo	Fp MDPI 50 mcg BID versus 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) at endpoint	→	

Secondary Endpoint	Hypothesis Testing				
	FS MDPI 100/12.5 mcg BID versus placebo	FS MDPI 50/12.5 mcg BID versus placebo	FS MDPI 100/12.5 mcg BID versus Fp MDPI 100 mcg BID	FS MDPI 50/12.5 mcg BID versus Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID versus Fp MDPI 100 mcg BID
[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	→	→	→	→	

FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; BID = twice daily; PEF = peak expiratory flow; AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities

Treatment comparisons will begin with the change from baseline in weekly average of daily trough morning PEF (first secondary endpoint) with the Fp 100 mcg versus placebo, or FS 100/12.5 mcg versus placebo. If the resulting p-value is less than 0.05, then the next comparison(s) of interest will be made according to the direction of the arrows. To the right, this will be the same endpoint to compare Fp 50 mcg versus placebo, or FS 50/12.5 mcg versus placebo. This process will continue testing sequentially through the next study drug/strength for each variable and at a given strength through the order presented in Table 4 and Table 5, until either all comparisons of interest are made, or until the point at which the resulting p-value for a comparison is greater than 0.05. At the point where the p-value is greater than 0.05, no further comparisons of either that strength or that measure can be made. This procedure allows for control of the Type I error for comparisons at a particular study drug/strength over the 5 secondary endpoints, as well as comparisons over study drugs/strengths within a particular endpoint. However, it does not control the overall Type I error.

Analyses Population

Intent-to-Treat (ITT) Population
All randomized subjects with treatment assigned based upon the treatment randomized regardless of which treatment they actually received. The ITT was used for supportive efficacy.

Full Analysis Set (FAS)
All subjects in the ITT population who received at least 1 dose of study drug AND had at least 1 post baseline trough FEV1 assessment. The FAS was the primary efficacy analysis set. Pulmonary function test data could be excluded from the FAS for visits in which patients took (within 7 days of the visit) any of a limited subset of prohibited asthma medications that could significantly confound interpretation. These medications were oral or systemic corticosteroids; LABAs or long-acting muscarinic antagonists, leukotriene receptor antagonists/5-leukotriene oxidase inhibitors (e.g., zileuton [ZYFLO® (Cornerstone Therapeutics)]); and oral B-agonists. A blinded statistical data review (SDR) meeting was conducted before database lock in order to determine and document the PFT data excluded from the FAS.

Per-Protocol (PP) Population
The PP population included all data from randomized subjects prior to experiencing major protocol violations and who had greater than 80% compliance to the study drug over the entire treatment period.

Safety Population
All randomized subjects who received at least 1 dose of study drug. Treatment was assigned as given, regardless of randomization group.

Protocol Amendments

A total of 3 amendments were made to the protocol. All 3 amendments occurred after subject enrollment began.

Amendment 1 (November 17, 2014) – 115 subjects enrolled

- Under the Division's advice, the primary endpoint was changed from change from baseline in trough FEV1 OVER the 12 week treatment period to standardized baseline-adjusted FEV1 AUEC 0-12 weeks.

- Clarification was provided about when a severe asthma exacerbation (defined in the original protocol as one that required systemic corticosteroid use for ≥3 days or hospitalization) would be considered a serious adverse event.

Amendment 2 (February 19, 2015) – 309 subjects enrolled

- The inclusion criteria were modified to allow patients on mid-dose ICS therapy to participate in the study (in addition to those on low-dose ICS therapy already included in the study).

Amendment 3 (July 14, 2015) – 647 subjects enrolled

- Based on discussions with the US FDA, the primary endpoint was changed from standardized change from baseline-adjusted trough (AM predose and pre-rescue bronchodilator) FEV_1 $AUEC_{0\text{-}12wk}$ at week 12 (TV9) to change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV_1 at week 12 (TV9).

- As recommended by the US FDA, the CPRA graph was added to examine all possible response levels of interest

Reviewer comment: The Division recommended a landmark endpoint (at Week 12) as products associated with initial large differences between treatment and placebo, but small (if any) difference from placebo at the end of the double blind treatment period are clinically undesirable so that the landmark analysis is preferred to an analysis of the average over time.

Protocol Deviations

A total of 102 (16%) of subjects had 1 or more protocol violations. Major protocol violations were reported for 14 (2%) patients, and the proportions did not differ greatly among the groups. The most common of these was use of excluded concomitant medication or treatment. Minor protocol violations were reported for 88 (14%) patients, which included greater numbers in the FS 50/12.5 mcg (26 (20%) patients) and Fp 100 mcg (22 (17%) patients) groups than in the other groups. The most common of these overall was noncompliance to study drug (35%, n=5).

5.3.5 Study FSS-AS-30017 (30017)

Study 301 and Study 30017 were similarly designed. This protocol review will focus on the differences between the Studies and will refer back to the protocol review for Study 301 when applicable.

Administrative Information

- **Study title:** A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients with Persistent Asthma Symptomatic Despite Inhaled Corticosteroid Therapy
- **Study dates:** October 1, 2014 to September 26, 2015
- **Study sites:** USA, Canada, Czech Republic, Poland, Russia, South Africa, Ukraine, Hungary
- **Study report date:** February 16, 2016

Objectives/Rationale

See Objectives/Rationale for Study 301.

Study Design and Conduct

Overview

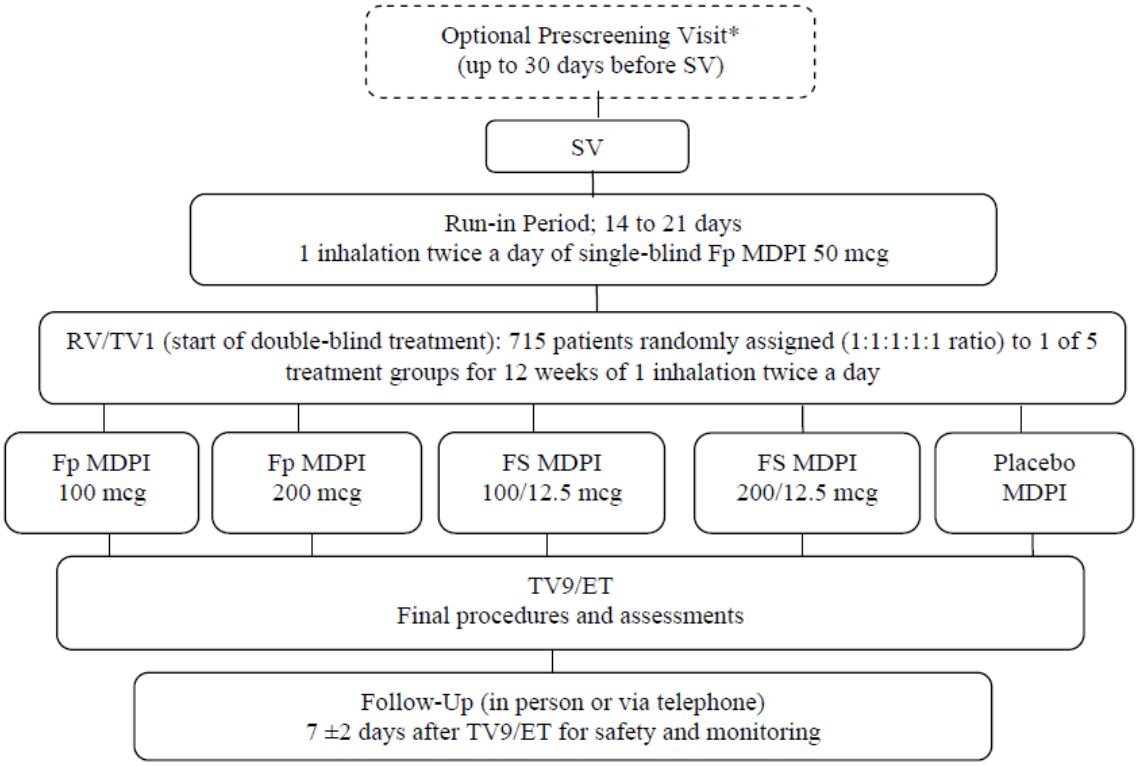
Study 30017 was a 12-week, randomized, double-blind, placebo -controlled, parallel-group, multicenter, study in subjects aged 12 years and older with persistent asthma, previously treated with ICS or ICS/LABA therapy. After a 14 to 21-day run-in period, subjects were randomized to one of 4 different treatment arms (Fp 100 mcg, Fp 200 mcg, FS 100/12.5 mcg, or FS 200/12.5 mcg one inhalation twice daily) or placebo for 12 weeks. A follow-up visit occurred after 1 week (week 13).

During the run-in period, subjects discontinued their current asthma medications and were provided with an albuterol HFA MDI for symptomatic relief, and single-blinded Fp 50 mcg device (1 inhalation twice a day).

Reviewer comment: Study 301 treated patients with open-label QVAR (40 mcg HFA MDI 1 inhalation twice daily) and a placebo MDPI instead of Fp 50 mcg. The dose of both ICS's are considered low-dose, therefore no effect on baseline characteristics is anticipated.

The study design for Study 30017 is depicted in Figure 8.

Figure 8. Study 30017: Study Design



* Required for patients whose prestudy asthma therapy included a LABA in addition to an ICS.
ET = early termination; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; RV = randomization visit; SV = screening visit; TV1 = treatment visit 1; TV9 = =treatment visit 9

Source: CSR, Fig 1, pg. 26

The schedules of assessments are shown in Figure 9.

Figure 9. Study 30017: Schedule of Assessments

Procedures and assessments[a]	Pretreatment run-in		Double-blind treatment period (visit/week)[b]									Follow-Up
	SV[c,d]	RV/TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	ET	Follow-Up[e]
	Screening 14-21 days before RV	Baseline after 14-21 days of run-in	W1 Day 8 ±2	W2 Day 15 ±2	W3 Day 22 ±2	W4 Day 29 ±2	W6 Day 43 ±2	W8 Day 57 ±2	W10 Day 71 ±2	W12 Day 85 ±3	Early termi-nation	W13, 7 ±2 days after TV9/ET
Informed consent/assent	X[f]											
Assign patient identification number	X[f]											
Medical and psychiatric history	X											
Asthma and asthma therapy history	X											
Prior medication history	X											
Demography	X											
Inclusion and exclusion criteria	X											
Full physical examination, including height and weight	X									X	X	
Electrocardiography	X									X	X	
Review randomization criteria		X										
Oropharyngeal exam	X	X	X	X	X	X	X	X	X	X	X	
Vital signs measurement (BP and pulse)	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test (if applicable)	X	X	X	X	X	X	X	X	X	X	X	
Dispense empty Teva MDPI trainer	X											
Training in use of Teva MDPI	X	X	X	X	X	X	X	X	X			
Dispense single-blind run-in drug (Fp MDPI 50 mcg, with training)	X											
AQLQ(S)/PAQLQ(S) administered[g]		X								X	X	
ACT administered		X				X		X		X	X	
Training in use of PEF and diary	X	X	X	X	X	X	X	X	X			
Dispense daily diary	X	X	X	X	X	X	X	X	X			
Dispense PEF meter	X											
Collect single-blind run-in drug		X										
Dispense rescue medication (as needed)	X	X	X	X	X	X	X	X	X			
Predose spirometry with reversibility testing[h]	X											
Calculate FEV_1 and PEF stability limits to determine alert criteria		X										
Measure PEF[i]	X											
Predose spirometry		X[j]	X	X	X	X	X	X	X	X	X	
Review alert criteria for worsening asthma or asthma exacerbation[k]	X	X	X	X	X	X	X	X	X	X	X	X
Randomization to double-blind drug via IRT		X										
Dispense double-blind study drug[l]		X				X		X				
Supervised administration of study drug at investigational center	X[m]	X	X	X	X	X	X	X	X	X	X	
Postdose spirometry (12-hour serial)[n]		X								X	X	
Assess study compliance		X	X	X	X	X	X	X	X	X	X	
Collect patient diary		X	X	X	X	X	X	X	X	X	X	
Collect double-blind study drug						X		X		X	X	
Adverse event inquiry and recording	X[o]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X[o]	X	X	X	X	X	X	X	X	X	X	X
Collect rescue medication										X	X	
End patient participation via IRT											X	X
Discuss further treatment options										X	X	

Source: CSR, Table 1, pgs. 28-29

Population

Key Inclusion Criteria

1. ≥ 12 years of age with a diagnosis of persistent asthma for ≥ 3 months
2. No asthma exacerbations or changes in asthma medication for at least 30 days
3. FEV1 40-85% predicted

4. 15% reversibility AND ≥ 200 mL increase from baseline in FEV1 (in patients ≥ 18 years of age) within 30 minutes following 2-4 inhalations of albuterol
5. Current asthma therapy: SABA for ≥ 8 weeks, ICS either as ICS or ICS/LABA combination for ≥ 1 month. If on ICS/LABA must have prescreening visit to change to ICS monotherapy and stable for 1 month. Qualifying ICS/LABA doses are listed in Table 21.
6. If female, was not currently pregnant, breastfeeding, or attempting to become pregnant, had a negative serum pregnancy test, and was of non-childbearing potential or if childbearing potential, then had to be willing to commit to using acceptable methods of birth control.

Reviewer comment: For Study 301, the current asthma therapy is low or mid-dose ICS. Study 30017 does not specify the dose of ICS, however the qualifying ICS dose ranges as listed in Table 21 are mid and high-dose.

Table 21. Study 30017: Qualifying ICS/LABA

Qualifying ICS (as ICS or ICS/LABA)	Dosage range (mcg/day)
Fluticasone HFA	>200
Fluticasone DPI	>200
Budesonide HFA (80 or 160 mcg/dose)	>160
Budesonide HFA (100 or 200 mcg/dose)	>200
Budesonide DPI	>200
Beclomethasone dipropionate HFA small particle (eg, QVAR 40 or 80 mcg/dose)	>160
Beclomethasone dipropionate HFA large particle (eg, Beclate or Clenil Modulate, 50 or 100 mcg/dose)	>300
Mometasone DPI (110 or 220 mcg/dose)	>220
Mometasone pMDI (100 or 200 mcg/dose)	>200
Ciclesonide HFA	>160
Flunisolide pMDI	>320
Fluticasone/salmeterol HFA	>200
Fluticasone/salmeterol DPI	>200
Budesonide/formoterol MDI	>160
Budesonide/formoterol DPI	>200

ICS=inhaled corticosteroid; LABA=long-acting beta agonist; HFA=hydrofluoroalkane; DPI=dry powder inhaler; MDI=metered-dose inhaler; pMDI=pressurized metered-dose inhaler.

Source: CSR, Table 3, pg. 30 - 31

Key Exclusion Criteria

See Key Exclusion Criteria for Study 301.

Randomization Criteria

See Randomization Criteria for Study 301.

Concomitant medications

See Concomitant medications for Study 301.

Treatment groups

Run-in:

- SABAs were replaced with albuterol HFA MDI (90 mcg/actuation).
- ICS or ICS/LABA was discontinued and replaced with 1 puff twice daily Fp MDPI 50 mcg.

Treatment:

- Albuterol HFA MDI as needed for relief of asthma symptoms
- Subjects were randomized to 1 of 5 treatment groups as described in Table 22.

Table 22. Study 30017: Treatment Groups

Treatment arm	Active device	Total daily dose (mcg)	Blinding
A	Fp MDPI 100 mcg	200	Double-blind
B	Fp MDPI 200 mcg	400	Double-blind
C	FS MDPI 100/12.5 mcg	200/25	Double-blind
D	FS MDPI 200/12.5 mcg	400/25	Double-blind
E	Placebo MDPI	0	Double-blind

Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler

Source: CSR, Table 1, pg. 25

Placebo MDPI was provided in devices identical in appearance to Fp. Each placebo device contained lactose monohydrate without the active ingredient.

Reviewer comment: Study 301 treated patients with open-label QVAR (40 mcg HFA MDI 1 inhalation twice daily) and a placebo MDPI instead of a Fp during the run-in period.

Endpoints

See Efficacy Endpoints, Efficacy Endpoint Parameters, and Safety Parameters for Study 301.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Statistical Plan

See Statistical Plan for Study 301. The statistical analysis plan sections were identical, with the exception of the doses. The hierarchy for the primary endpoint was also similar to Study 301, with the low and mid doses substituted for the mid and low dose, respectively.

Protocol Amendments

A total of 4 amendments were made to the protocol. All 4 amendments occurred after subject enrollment began.

Amendment 1 (December 2, 2014) – 147 subjects enrolled

- Clarification was provided about when a severe asthma exacerbation (defined in the original protocol as one that required systemic corticosteroid use for ≥3 days or hospitalization) would be considered a serious adverse event.

Amendment 2 (December 10, 2014) – 147 subjects enrolled

- Administrative changes only

Amendment 3 (February 19, 2015) – 543 subjects enrolled

- Inclusion criteria amended to allow patients to enroll despite having changes in their ICS treatment over 1 month prior to screening.

Amendment 4 (April 9, 2015) – 602 subjects enrolled

- Based on discussions with the US FDA, the primary endpoint was changed from change from baseline in trough FEV1 OVER 12 weeks to AT Week 12. The primary endpoint for serial spirometry was specified as standardized change from baseline-adjusted trough (AM predose and pre-rescue bronchodilator) FEV_1 $AUEC_{0\text{-}12wk}$ at week 12.

- As recommended by the US FDA, the CPRA graph was added to examine all possible response levels of interest

Reviewer comment: The Division recommended a landmark endpoint (at Week 12) as products associated with initial large differences between treatment and placebo, but small (if any) difference from placebo at the end of the double blind treatment period are clinically undesirable so that the landmark analysis is preferred to an analysis of the average over time.

Protocol Deviations

A total of 142 (20%) of subjects had 1 or more protocol violations. Major protocol violations were reported for 24 (3%) patients, and the proportions was higher for the placebo group (9 (6%)) compared to the active treatment group (1-4%). The most common of these was noncompliance to study drug (12 (2%)) and use of excluded concomitant medications (11 (2%)). Minor protocol violations were reported for 126 (17%) patients.

6 Review of Efficacy

Efficacy Summary

Fp MDPI (will be referred to as Fp) is proposed for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. FS MDPI (will be referred to as FS) is proposed for the treatment of asthma in patients 12 years of age and older. The program consisted of 6 key studies: two 12-week Fp dose-ranging studies (201 and 202), a single dose salmeterol dose-ranging study (FSS-201) , two 12-week efficacy and safety studies (301 and 30017) which included the usual factorial design to support the efficacy and safety the FS combination product, and a 26-week long-term safety study (305). Study 305 will be discussed in the Summary of Safety.

The Fp dose-ranging studies (201 and 202) were 12-week, randomized, double-blind, placebo and active-controlled studies that included the low (50 mcg), mid (100 mcg), and high (200 mcg) Fp doses and ranged from 12.5 to 400 mcg. The low (50 mcg) and mid (100 mcg) Fp doses were included in both Studies 201 and 202, while the high dose (200 mcg) was included only in Study 202. The comparator for Study 201 was Flovent Diskus 100 mcg (the marketed mid-dose) and the comparator for Study 202 was Flovent Diskus 250 mcg (the marketed high-dose). The salmeterol dose-ranging study (FSS-201) was a single-dose, double-blind (with the exception of the open-label active-control arm), placebo-controlled, dose-ranging study of salmeterol (0 to 50 mcg) compared to Advair 100 mcg/50 mcg.

For Study 201, which included the proposed low (50 mcg) and mid (100 mcg) doses of Fp, no Fp dose was significantly different than Flovent Diskus 100 mcg (the marketed mid-dose). All doses, with the exception of the lowest (12.5 mcg) were significantly different than placebo. The point estimate for the primary endpoint of FEV1 change from baseline to Week 12 for Flovent Diskus 100 mcg (234 mL; 95% CI (162 mL, 306 mL)) was between the Fp 12.5 mcg (189 mL; 95% CI (112 mL, 266 mL)) and Fp 25 mcg (268 mL; 95% CI (194 ML, 343 mL)). The proposed mid-dose for Fp (100 mcg) trended toward a larger improvement in FEV1 at Week 12 (295 mL;

95% CI (219 mL, 371 mL)) compared to marketed mid-dose for Flovent Diskus (100 mcg). Notably, the 25 mcg dose is proposed for the pediatric studies in 4-11 year olds. These results support the proposed Fp low (50 mcg) and mid (100 mcg) doses.

For Study 202, which included all 3 proposed doses (50, 100, and 200 mcg) no Fp dose was significantly different than Flovent Diskus 250 mcg (the marketed high-dose). Only the Fp 200 mcg dose was significantly different from placebo and is the proposed high-dose for Fp. The point estimate for the primary efficacy endpoint of FEV1 change from baseline to Week 12 for Flovent Diskus 250 mcg (145 mL; 95% CI (79 mL, 210 mL)), was between the Fp 100 mcg (100 mL; 95% CI (37 mL, 163 mL)) and Fp 200 mcg (148 mL; 95% CI (81 mL, 214 mL)). These results support the proposed Fp high dose at 200 mcg.

The exploration for salmeterol dose response was evaluated in study FSS-201. Study FSS-201 was a single-dose, cross-over study with 4 doses of salmeterol (6.25, 12.5, 25, and 50 mcg) combined with a fixed dose of fluticasone propionate (100 mcg) delivered as fluticasone propionate/salmeterol inhalation powder (FS). The comparators were Flovent Diskus 100 mcg (considered the 0 mcg salmeterol dose), and Advair 100/50 mcg. The maximum dose of 50 mcg is the dose of salmeterol that is currently marketed in Advair Diskus. The baseline-adjusted FEV1 AUC 0-12 hours demonstrated a dose-related increase in baseline adjusted FEV1 AUC 0-12. The primary endpoint for FS 100/50 mcg was significantly higher than Advair 100/50 mcg by 58 mL (95% CI (22 ml, 94 mL)). Advair was most closely comparable to FS 100/12.5 mcg (249 mL), with the smallest difference (3 mL; 95% CI (-32 mL, 39 mL)). The 12.5 mcg dose is the proposed fixed dose of salmeterol.

Studies 301 and 30017 were 12-week, randomized, double-blind, placebo-controlled studies of 3 doses of ICS (fluticasone propionate: 50, 100, and 200 mcg) with and without a fixed dose of LABA (salmeterol: 12.5 mcg) compared to placebo in 1375 patients (Study 301: n= 647, about 130 per treatment arm; Study 30017: n=728, about 145 per treatment arm) with persistent asthma. Study 301 included the low (50 mcg) and mid (100 mcg) doses of Fp and Study 30017 included the mid (100 mcg) and high (200 mcg) doses of Fp.

The patients enrolled in studies 301 and 30017 were predominantly female (58%), Caucasian (80%), and never smokers (86%), with a mean age of 43 years (range 12-86). Subjects had a mean FEV1 of 2.1L (66% predicted) and an FEV1/FVC ratio of 67%. About half of the patients were on ICS (57%) and the other half were on ICS/LABA (43%) therapy. The ICS strength was not reported.

For Study 301, out of the 647 subjects that were randomized, 93% (n=602) completed the study. The placebo group had the largest number of discontinued subjects (13%, n=17), predominantly for adverse events (which included asthma). All treatment arms (Fp 50 mcg twice daily (BID), Fp 100 mcg BID, FS 50/12.5 mcg BID, and FS 100/12.5 mcg BID) showed a significant improvement in the change from baseline in trough FEV1 at Week 12 compared to placebo. The treatment differences were 119 mL (95% CI (25 mL, 212 ml)), 151 mL (95% CI (57 mL, 244 mL)), 266 mL (95 % CI (172 mL, 360 mL)) and 262 mL (95% CI (168 mL, 356 mL)),

respectively. FS 50/12.5 mcg showed a significant improvement compared to Fp 50 mcg (treatment difference 147 mL (95% CI (53 mL, 242 mL)) and Fp 100 mcg (treatment difference 115 mL (95% CI (21 mL, 210 mL)). FS 100/12.5 mcg also showed a significant improvement compared to Fp 100 mcg (treatment difference 111 mL (95% CI (17 mL, 206 mL)). Study 301 demonstrated the efficacy of two doses of Fp (50 and 100 mcg) over placebo; it also demonstrated the efficacy of the low and mid-dose combination of FS (50/12.5 mcg and 100 mcg/12.5 mcg) over placebo and over the individual Fp monocomponents at the same and higher ICS strengths.

For Study 30017, out of the 728 subjects that were randomized, 89% (n=650) completed the study. The placebo group had the largest number of discontinued subjects (26%, n=38), mainly for disease progression (12%, n=18). All treatment arms (Fp 100 mcg BID, Fp 200 mcg BID, FS 100/12.5 mcg BID, and FS 200/12.5 mcg BID) showed a significant improvement in the change from baseline in trough FEV1 at Week 12 compared to placebo. The treatment difference was 123 mL (95% CI (38 mL, 208 mL)), 183 mL (95% CI (98 mL, 268 mL)), 274 mL (95 % CI 189 mL, 360 m)) and 276 mL (95% CI 191 mL, 361 mL)), respectively. FS 100/12.5 mcg showed a significant improvement compared to Fp 100 mcg (treatment difference 152 mL (95% CI (66 mL, 237 mL)) and Fp 200 mcg (treatment difference 92 mL (95% CI (6 mL, 177 ml)). FS 200/12.5 mcg also showed a significant improvement compared to Fp 200 mcg (treatment difference 93 mL (95% CI (9 mL, 178 ml)). Study 30017 demonstrated the efficacy of the mid and high doses of Fp (100 mcg and 200 mcg) over placebo; it also demonstrated the efficacy of the mid- and high-dose combination of FS (100/12.5 mcg and 200/12.5 mcg) over placebo and the Fp monocomponents of similar and higher ICS strengths.

For both Studies 301 and 300017, there were no statistical comparisons within the Fp doses and FS doses. The point estimates did show a dose-response for the Fp doses, but not between the FS doses. The co-primary endpoint in the serial spirometry subset of patients (n=312 for each study) of the standardized baseline-adjusted FEV1 AUC 0-12h at Week 12 was generally similar to the results for the change from baseline in trough FEV1. The main difference was that the Fp 50 and 100 mcg doses did not show a dose response for their improvement over placebo.

The sensitivity analyses (cumulative proportion of responder analysis graph, tipping point, and multiple imputations under an assumption of missing not at random for those patients who withdrew due to worsening asthma) supported the primary and co-primary endpoint conclusions.

A subgroup analysis was performed by the sponsor by sex, age group (12 to 17, 18 to 64, and ≥ 65 years), race (white, black, and other), and by geographic region (USA and non-USA) based on the pooled FAS population. Overall, the subgroup analyses were consistent with the primary analysis, although no study was powered to detect difference in subgroups.

The key secondary endpoint was the time to 15% and 12% improvement from baseline in FEV1 post dose at baseline in the serial spirometry subset. For Study 301, 70% (n=39) and 57% (n=35) of the subjects in the FS 50/12.5 mcg and FS 100/12.5 mcg improved their FEV1 by 15% from baseline on Day 1, respectively. Of those subjects, the median time to an FEV1 improvement of

15% was 1.3 hours and 4.3 hours, respectively. Slightly more subjects achieved a 12% improvement in FEV1 on day 1 and the median time was slightly shorter than for 15%. A dose response was observed for both 15% and 12% time to improvement for the FS treatment arms (not evaluated for the Fp treatment arms). For Study 30017, 62% (n=36) and 81% (n=55) of the subjects on FS 100/12.5 mcg and FS 200/12.5 mcg improved their FEV1 by 15% from baseline on Day 1, respectively. Of those subjects, the median time to an FEV1 improvement of 15% was 0.9 hours and 0.8 hours, respectively. Slightly more subjects achieved a 12% improvement in FEV1 on day 1 and the median time was slightly shorter than for 15%. A dose response was not observed for either a 15% or 12% time to improvement in post-dose FEV1 on day 1 from baseline.

Other secondary endpoints included peak expiratory flow (PEF), asthma symptom score, albuterol use, time to withdrawal for worsening asthma, and asthma quality of life questionnaire (AQLQ). Overall the secondary endpoints were supportive of the primary endpoint. The FS combination was not consistently superior to Fp, with the exception of the peak expiratory flow rate endpoint. A dose response was generally present with the exception of albuterol use in Fp 100 mcg compared to 200 mcg and AQLQ scores in the FS 100/12.5 mcg compared to FS 200/12.5 mcg.

Overall, efficacy for Fp 50 mcg, 100 mcg, and 200 mcg one inhalation BID and for FS 50/12.5 mcg, 100/12.5 mcg, and 200/12.5 mcg one inhalation BID for the treatment of asthma in patients aged 12 years and older has been demonstrated. Fp 50 mcg was supported by Studies 201, 202, and 301, Fp 100 mcg was supported by Studies 201, 202, 301, and 30017, Fp 200 mcg was supported by Studies 202 and 30017, FS 50/12.5 mcg was supported by Study 301, FS 100/12.5 mcg was supported by both Studies 301 and 30017, and FS 200/12.5 mcg was supported by Study 30017.

Studies 201, 202 and FS-201 supported the dose selection of both fluticasone propionate and salmeterol. Studies 301 and 30017 demonstrated the difference in the primary endpoint of change from baseline in trough FEV1 at Week 12 for all treatment arms compared to placebo, with a dose-response between doses of Fp and a statistically significant improvement in the combination of the ICS/LABA (FS) compared to the ICS (Fp) of the same or higher dose. The co-primary efficacy endpoint of standardized baseline-adjusted FEV1 AUC 0-12h at Week 12 in the serial spirometry subset of patients showed similar results. Efficacy is further supported by the key secondary endpoint of time to 15% and 12% improvement from baseline in FEV1 and the other secondary endpoints of PEF, asthma symptom score, albuterol use, time to withdrawal for worsening asthma, and AQLQ.

6.1 Indication

Fp

- Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older
- Not indicated for the relief of acute bronchospasm

Reviewer comment: [redacted] (b) (4)

FS

- The treatment of asthma in patients aged 12 years and older.
- Not indicated for the relief of acute bronchospasm

6.1.1 Methods

The program to support Fp and FS for the treatment of asthma in patients 12 years and older consisted of 6 key studies: two 12-week Fp dose-ranging studies (201 and 202), a single dose salmeterol dose-ranging study (FSS-201), two 12-week efficacy and safety studies which included the usual factorial design to support the efficacy and safety the FS combination product (301 and 30017), and a 26-week long-term safety study (305). Replicate efficacy for Fp at the low dose (50 mcg) is based on Studies 201, 202, and 301, at the mid dose (100 mcg) is based on Studies 201, 202, 301, and 30017, and at the high dose (200 mcg) is based on Studies 202, and 30017. The efficacy of FS for the low dose (50 mcg/12.5 mcg) is based on Study 301, at the mid dose (100/12.5 mcg) is based on Studies 301, and 30017, and at the high dose (200/12.5 mcg) is based on Study 30017.

The efficacy results for the two 12-week dose-ranging Fp studies (201 and 202) and the single-dose dose-ranging FS study (FSS-201) are provided in Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations. The efficacy results for the two 12-week Fp and FS efficacy and safety studies (301 and 30017) are discussed in Section 6 Review of Efficacy and the safety results are discussed in Section 7 Review of Safety.

Lastly, the 26-week open-label safety results are discussed in Section 7.7.2 Long-term safety, with a brief discussion of efficacy in Section 6.1.10 Additional Efficacy Issues/Analyses

Efficacy results are based on the sponsor's submission, unless otherwise indicated. The Agency's statistical review of the efficacy is mentioned where applicable. For further details, see the complete statistical review of the efficacy by Dr. Yu Wang.

6.1.2 Demographics

The demographics for the combined study population are displayed in Table 23.

Table 23. Baseline demographics (Studies 301 and 30017 ITT Population)								
	Placebo N=275	Fp MDPI (mcg; BID) N=551			FS MDPI (mcg; BID) N=549			Total N=1375
		50	100	200	50/12.5	100/12.5	200/12.5	
N	275	129	276	146	129	274	146	1375
Sex, n (%)								
Male	114 (41)	54 (42)	106 (38)	58 (40)	58 (45)	123 (45)	59 (40)	572 (42)
Race, n (%)								
White	225 (82)	107 (83)	204 (74)	116 (79)	109 (84)	217 (79)	125 (86)	1103 (80)
Black	44 (16)	198 (14)	61 (22)	23 (16)	19 (15)	48 (18)	20 (14)	233 (17)
Asian	3 (1)	1 (<1)	4 (1)	2 (1)	1 (<1)	4 (<1)	0	15 (1)
Other	3 (1)	3 (2)	7 (3)	5 (3)	0	5 (2)	1 (<1)	24 (2)
Age in Years								
Mean (SD)	43 (17)	43 (18)	43 (17)	44 (16)	41 (19)	43 (16)	45 (17)	43 (17)
Median	45	43	45	46	41	45	45	45
Min-Max	12-78	12-79	12-84	12-81	12-86	12-74	12-76	12-86
Age in class, n (%)								
12-17	23 (8)	13 (10)	27 (10)	10 (7)	19 (15)	27 (10)	12 (8)	131 (10)
18-64	227 (83)	93 (72)	226 (82)	119 (82)	97 (75)	225 (82)	115 (79)	1102 (80)
≥ 65 years	25 (9)	23 (18)	23 (8)	17 (12)	13 (10)	22 (8)	19 (13)	142 (10)
Weight (kg)								
Mean (SD)	82 (21)	79 (21)	82 (23)	85 (23)	80 (20)	83 (22)	84 (23)	82 (22)
Height in cm								
Mean (SD)	169 (10)	168 (9)	168 (11)	169 (10)	169 (9)	169 (9)	168 (10)	168 (10)
Body mass index (kg/m2)								
Mean (SD)	29 (7)	28 (7)	29 (7)	30 (7)	28 (7)	29 (7)	29 (7)	29 (7)
Smoking history, n (%)								
Never smoked	240 (87)	115 (89)	233 (84)	125 (86)	116 (90)	228 (83)	126 (86)	1183 (86)
Ex-smoker	35 (13)	14 (11)	43 (16)	21 (14)	13 (10)	46 (17)	20 (14)	192 (14)
Number of pack years	4 (3)	2 (2)	4 (3)	5 (2)	3 (3)	4 (3)	3 (3)	4 (3)

Source: Modified from ISE, Table 9, pg. 66

Baseline demographics were balanced across treatment groups. The mean age for Studies 301 and 30017 was 43 years, with a range of 12-86 years. Most patients were female (58%), Caucasian (80%), and never smokers (86%).

Baseline asthma characteristics

Baseline asthma disease characteristics are summarized in Table 24.

Table 24. Baseline disease characteristics (Studies 301 and 30017 combined ITT Population)

	Placebo N=275	Fp MDPI (mcg; BID) N=551			FS MDPI (mcg; BID) N=549			Total N=1375
		50 N=129	100 N=276	200 N=146	50/12.5 N=129	100/12.5 N=274	200/12.5 N=146	
N	273	129	274	146	128	268	145	1363
FEV1 (L), Mean (SD)	2.2 (0.6)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)	2.3 (0.7)	2.2 (0.6)	2.1 (0.7)	2.1 (0.6)
Min, Max	0.8, 3.9	0.8, 4.1	0.9, 4.1	0.9, 3.6	1.0, 3.9	1.1, 4.0	0.8, 3.7	0.8, 4.1
FVC (L), Mean (SD)	3.2 (0.9)	3.2 (1.0)	3.2 (0.9)	3.2 (0.9)	3.4 (0.9)	3.3 (0.9)	3.2 (1.0)	3.2 (0.9)
FEF 25-75 (L/s), Mean (SD)	1.4 (0.7)	1.4 (0.6)	1.5 (0.7)	1.3 (0.7)	1.7 (0.8)	1.4 (0.7)	1.3 (0.7)	1.4 (0.7)
FEV1/FVC (%), Mean (SD)	67 (10)	67 (9)	68 (11)	66 (11)	69 (12)	67 (10)	65 (10)	67 (10)
Min, Max	38, 90	45, 95	38, 100	39, 99	40, 96	42, 95	40, 93	38, 100
% predicted FEV1, Mean (SD)	66 (11)	67 (10)	67 (10)	64 (10)	70 (11)	66 (11)	65 (11)	66 (11)
Min, Max	41, 85	45, 84	41, 86	41, 86	41, 85	41, 92	40, 86	40, 92
Previous asthma therapy, n (%)								
ICS	170 (62)	89 (69)	141 (51)	63 (43)	90 (70)	164 (60)	73 (50)	790 (57)
ICS/LABA	105 (38)	40 (31)	135 (49)	83 (57)	39 (30)	110 (40)	73 (50)	585 (43)

Source: Modified from ISE, Table 10, pg. 69-70

Baseline demographics were generally balanced within and across studies. The ratio of ICS to ICS/LABA use shifted towards ICS/LABA use with increasing Fp treatment arms, which is reflective of the different inclusion criteria for Study 301 (50 and 100 mcg doses) and Study 30017 (100 and 200 mcg doses). Subjects in Study 301 could be on low to mid dose ICS and Subjects in Study 30017 could be on mid to high dose ICS. Subjects on high dose ICS baseline therapy are more likely to be on ICS/LABA based on the NAEPP guidelines.(3)

When looking at the individual studies, the baseline FEV1 and percent predicted FEV1 was 2.2L and 67%, respectively, for Study 301 for all subjects compared to 2.1L and 65%, respectively, for Study 30017. Reversibility results were not provided. Given the slightly lower FEV1 and % predicted FEV1, Study 30017 had a slightly more severe population, which is consistent with the inclusion criteria for baseline asthma therapy.

Reviewer comment: In Study 301, the FS 100/12.5 mcg treatment arm had a maximum % predicted FEV1 over the inclusion criteria of 85%. This did not appear to affect the mean which was within the range of the other treatment arms.

Concomitant therapies

Baseline therapies

Nearly all patients had previous metered dose inhaler experience. For Studies 301 and 30017, prior dry powder inhaler use was reported in 80% and 86%, respectively. For Study 301, the most common prior asthma therapy was salbutamol (85%) and fluticasone propionate (38%). The ICS strengths were not provided. The types asthma therapy at baseline was similar in Study 30017. Medications for conditions other than asthma were reported for ≥ 5% of patients overall. These included cetirizine, ibuprofen, loratadine, acetaminophen, lisinopril, and vitamins. The treatment groups were comparable in their use of prior medications.

On-treatment concomitant therapies

For Study 301, 69% of subjects received at least 1 concomitant medication during the study. The most common was antihistamines (25%), non-steroidal anti-inflammatory drugs (NSAIDs; 18%), agents acting on the renin-angiotensin system (i.e. lisinopril, losartan; 16%), and analgesics (15%). Notably 6% of subjects received antibiotic therapy. In Study 30017, 79% of subjects received at least 1 concomitant medication. The distribution was similar to Study 301. There was no notable difference between treatment groups and placebo for either study.

Concomitant Diseases

For Study 301, all subjects had at least 1 prior medical condition. The most common was allergic rhinitis (40%), followed by season allergy (29%), hypertension (23%), postmenopausal (19%), perennial rhinitis (19%), headache (12%), and gastroesophageal reflux disease (GERD; 11%). Study 30017 had similar findings.

Reviewer comment: Baseline disorders are consistent with what would be expected with an asthma population.

6.1.3 Subject Disposition

Study sites

Study 301 was conducted in 104 centers (calculated by this reviewer, but 129 centers are listed in the CSR) in the USA, Canada, Poland, Russia, South Africa, Ukraine, Hungary. About 60% of sites were located in the US. A total of 356 (56%) of subjects were enrolled in United States (US) sites (calculated by this reviewer).

Study 30017 was conducted in 118 centers (calculated by this reviewer, although 147 centers are listed in the CSR) in the USA, Canada, Czech Republic, Poland, Russia, South Africa, Ukraine, and Hungary. A total of 424 (59%) of subjects were enrolled in US sites (calculated by this reviewer).

Patients

Patient disposition for Study 301 is summarized in Table 25 and Study 30017 is summarized in Table 26.

Table 25. Baseline disposition (Study 301 Randomized)

	Study 301 (mcg)					
	Placebo N=130	Fp 50 BID N=129	Fp 100 BID N=130	FS 50/12.5 BID N=129	FS 100/12.5 BID N=129	Total N=647
Randomized/Intent-to-treat (ITT)	130 (100)	129 (100)	130 (100)	129 (100)	129 (100)	647 (100)
Not treated	1 (<1)	0	1 (<1)	1 (<1)	3 (2)	6 (<1)
Full Analysis Set (FAS)	129 (>99)	128 (>99)	129 (>99)	128 (>99)	126 (98)	640 (99)
Safety Population	129 (>99)	129 (100)	129 (>99)	128 (>99)	126 (98)	641 (>99)
Per-Protocol Population (PP)	128 (98)	125 (97)	125 (96)	127 (98)	126 (98)	631 (98)
Serial Spirometry Subset	60 (100)	63 (100)	72 (100)	56 (100)	61 (100)	312 (100)
FAS/ITT	60 (100)	63 (100)	72 (100)	56 (100)	61 (100)	312 (100)
PP	59 (98)	61 (97)	70 (97)	56 (100)	61 (100)	307 (98)
Completed Study	113 (87)	121 (94)	121 (93)	121 (94)	126 (98)	602 (93)
Discontinued Study	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 patient	2 (2)	3 (2)	2 (2)	2 (2)	0	9 (1)
Noncompliance to study medication	0	0	1 (<1)	0	0	1 (<1)
Protocol violation	1 (<1)	1 (<1)	1 (<1)	0	0	3 (<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)
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)

Source: Study 301 CSR, Table 6, pgs. 85-86

For Study 301, the majority of subjects included in the randomized and ITT populations were also included in the full analysis set (which was used for the primary endpoint analysis), with the exception of 7 (1%) subjects. About half of these excluded subjects were in the FS 100/12.5 mcg treatment arm (n=3), with the remainder being generally equally distributed among treatment arms. The number of subjects that discontinued the study was similar across treatment arms (2-7%) and higher in the placebo group (n=17, 13%). The majority of subjects discontinued due to an adverse event, including asthma.

Reviewer comment: The higher rate of discontinuation in the placebo group is expected, in that adverse events included asthma.

Table 26. Baseline disposition: Study 30017 (Randomized)

	Study 30017 (mcg)					
	Placebo N=145	Fp 100 BID N=146	Fp 200 BID N=146	FS 100/12.5 BID N=145	FS 200/12.5 BID N=146	Total N=728
Randomized/Intent-to-treat (ITT)	145 (100)	146 (100)	146 (100)	145 (100)	146 (100)	728 (100)
Not treated	1 (<1)	1 (<1)	0	2 (1)	1 (<1)	5 (<1)
Full Analysis Set (FAS)	143 (99)	145 (>99)	146 (100)	141 (97)	145 (>99)	720 (99)
Safety Population	144 (>99)	145 (>99)	146 (100)	143 (99)	145 (>99)	723 (>99)
Per-Protocol Population (PP)	140 (97)	142 (97)	144 (99)	143 (99)	144 (99)	713 (98)
Serial Spirometry Subset	61 (100)	64 (100)	61 (100)	58 (100)	68 (100)	312 (100)
FAS/ITT	61 (100)	64 (100)	61 (100)	58 (100)	68 (100)	312 (100)
PP	57 (93)	63 (98)	59 (97)	58 (100)	68 (100)	305 (98)
Completed Study	107 (74)	136 (93)	135 (92)	134 (94)	136 (93)	650 (89)
Discontinued Study	38 (26)	10 (7)	11 (8)	9 (6)	10 (7)	78 (11)
Death	0	0	0	1 (<1)	0	0
Adverse event	2 (1)	2 (1)	0	1 (<1)	2 (1)	8 (1)
Withdrawal by patient	7 (5)	4 (3)	3 (2)	3 (2)	2 (1)	19 (3)
Noncompliance to study medication	0	0	1 (<1)	0	0	1 (<1)
Protocol violation	1 (<1)	2 (1)	2 (1)	0	1 (<1)	6 (<1)
Disease progression	18 (12)	0	3 (2)	1 (<1)	2 (1)	24 (3)
Pregnancy	0	0	0	0	1 (<1)	1 (<1)
Lost to follow-up	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	4 (<1)
Lack of efficacy	7 (5)	1 (<1)	1 (<1)	0	0	9 (1)
Other	2 (1)	0	0	2 (1)	1 (<1)	6 (<1)

Source: Study 30017 CSR, Table 6, pgs. 82-83

For Study 30017, the majority of subjects included in the randomized and ITT populations were also included in the full analysis set (which was used for the primary endpoint analysis), with the exception of 8 (1%) subjects. Half of these excluded subjects were in the FS 100/12.5 mcg treatment arm (n=4), with the remainder being generally equally distributed among treatment arms. The number of subjects that discontinued the study was similar across treatment arms (6-8%) and higher in the placebo group (n=38, 26%). The majority of subjects discontinued in the placebo arm due to disease progression (n=18, 12%).

Reviewer comment: The higher rate of discontinuation in the placebo group is expected, in that adverse events included asthma. The higher rate of discontinuation in this placebo group (26%) compared to Study 301 (17%) suggests that this patient population had more severe asthma (which is consistent with the enrollment criteria of mid to high dose ICS compared to Study 301 which was low to mid dose ICS).

Compliance

Noncompliance (see definition in protocol review in Section 5.3.4 FSS-AS-301 and in Section 5.3.5 FSS-AS-30017) was included as a protocol violation (see Section 5.3.4 FSS-AS-301 and Section 5.3.5 FSS-AS-30017 for a full list of protocol violations). For Study 301, 36 (5%) of subjects were reported as noncompliant to study medication. For Study 30017, 52 (7%) of subjects were reported to be noncompliant with study medication. One patient from each study was discontinued for noncompliance.

Reviewer comment: Noncompliance with study medication would decrease the treatment effect; therefore the 7% of subjects from Study 30017 who were noncompliant is not necessarily concerning.

6.1.4 Analysis of Primary Endpoint

Primary Efficacy Results

The co-primary endpoints for the Studies 301 and 30017 are as follows:

- change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 at week 12

- standardized baseline-adjusted area under the effect curve for FEV1 from time 0 to 12 hours postdose (FEV1 AUC0-12h) at week 12, analyzed for the subset of approximately 300 patients who performed postdose serial spirometry

As detailed in the protocol review (Section 5) for Studies 301 and 30017, Statistical Analysis Plan, the primary endpoint analysis were conducted using a fixed-sequence multiple testing procedure was used to control the overall Type I error at the 2-sided 0.05 level. The full analysis set was initially set as the primary endpoint analysis set, however our Division prefers the ITT analysis set. The results were unblinded prior to the new primary analysis population change; therefore the tables below are for the full analysis set, with differences stated for the ITT population. There were 7 and 8 subjects excluded in the FAS population, compared to the ITT population, in Study 301 and 30017, respectively.

Table 27. Primary Endpoint for Studies 301 and 30017: Change from Baseline in Trough FEV1 (mL) at Week 12 (FAS Population)

	Study 301 (mcg)					Study 30017 (mcg)				
LS mean	Placebo N=129	Fp 50 BID N=128	Fp 100 BID N=129	FS 50/12.5 BID N=128	FS 100/12.5 BID N=126	Placebo N=143	Fp 100 BID N=145	Fp 200 BID N=146	FS 100/12.5 BID N=141	FS 200/12.5 BID N=145
n	129	128	129	128	126	143	144	145	140	145
Baseline	2,188	2,134	2,166	2,302	2,162	2,132	2,069	2,075	2,154	2,083
Change from baseline at Week 12	53	172	204	319	315	0	119	179	271	272
95% CI	-15,122	104,240	137,271	250,388	246,385	-65,57	58,180	119,240	210,332	212,333
Diff to **Placebo**	-	119	151	266	262	-	123	183	274	276
95% CI	-	25,212	57,244	172,360	168,356	-	38,208	98,268	189,360	191,361
Diff to **50 mcg BID**	-	-	-	147	-	-	-	-	-	-
95% CI	-	-	-	53,242	-	-	-	-	-	-
Diff to **100 mcg BID**	-	-	-	115	111	-	-	-	152	-
95% CI	-	-	-	21,210	17,206	-	-	-	66,237	-
Diff to **200 mcg BID**	-	-	-			-	-	-	92	93
95% CI	-	-	-			-	-	-	6,177	9,178

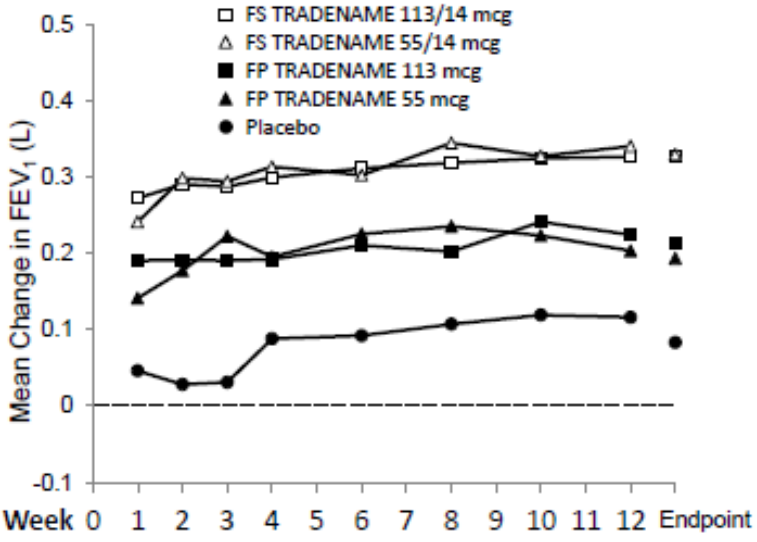
Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate; BID = twice daily; LS=least squares; Diff=difference; CI=confidence interval
Source: ISE, Table 13, pg. 78-79, Study 301 CSR, Table Summary 15.2.5.1.1, pg. 351, Study 30017 CSR, Table Summary 15.2.5.1.1, pg. 376

In both studies, all treatment arms showed a significant improvement in the change from baseline in trough FEV1 compared to placebo (Study 301 treatment difference: 119 mL (95% CI: 25, 212), 151 mL (95% CI: 57, 244), 266 mL (95% CI: 172, 360 mL), 262 mL (95% CI: 168 mL, 356 mL) respectively; Study 30017 treatment difference: 123 mL (95% CI: 38 mL, 208 mL), 183 mL (95 % CI: 98 mL, 268 mL), 274 mL (95% CI: 189 mL, 360 mL), 276 mL (95% CI: 191 mL, 361 mL), respectively). In Study 301, FS 50/12.5 mcg showed a significant improvement compared to Fp 50 mcg (147 mL difference (95% CI (53 mL, 242 mL)) and Fp 100 mcg (115 mL difference (95% CI (21 mL, 210 mL)). FS 100/12.5 mcg also showed a significant improvement compared to Fp 100 mcg (111 mL difference (95% CI (17 mL, 206 mL)). In Study 30017, FS 100/12.5 mcg showed a significant improvement compared to Fp 100 mcg (152 mL difference (95% CI (66 mL, 237 mL)) and Fp 200 mcg (92 mL difference (95% CI (6 mL, 177 mL)). FS 200/12.5 mcg also showed a significant improvement compared to Fp 200 mcg (93 mL difference (95% CI (9 mL, 178 mL). In both studies, there were no statistical comparisons within the Fp doses and FS doses. The point estimates did show a dose-response for the Fp doses, but not between FS doses.

Reviewer comment: The Agency's statistical analysis confirmed these results. See Dr. Yu Wang's statistical review for further details.

The mean change from baseline in trough FEV1 at each visit by treatment group was also analyzed by the sponsor [redacted] (b) (4) as shown in Figure 10 for Study 301 and Figure 11 for Study 30017. Of note, these analyses were ad hoc.

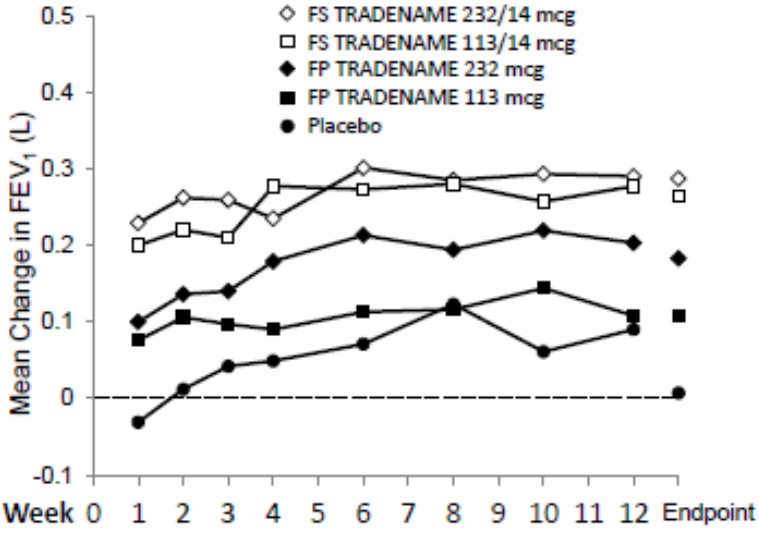
Figure 10. Study 301: Mean (+/-SE) Change From Baseline in Trough FEV1 Weekly and at Endpoint by Treatment Group (FAS)



	N		N		N	N
FS TRADENAME 113/14 mcg	126		126		126	126
FS TRADENAME 55/14 mcg	128		123		123	128
FP TRADENAME 113 mcg	129		125		120	129
FP TRADENAME 55 mcg	128		123		122	128
Placebo	129		124		115	129

Source: ISE, Figure 1, pg. 82 and Fp and FS prescribing information, Figure 2

Figure 11. Study 30017: Mean (+/- SE) Change From Baseline in Trough FEV1 Weekly by Treatment Group (FAS)



	N		N		N	N
FS TRADENAME 232/14 mcg	145		142		136	145
FS TRADENAME 113/14 mcg	140		137		136	140
FP TRADENAME 232 mcg	146		142		136	145
FP TRADENAME 113 mcg	145		138		135	144
Placebo	143		121		107	143

Source: ISE, Figure 1, pg. 83 and Fp and FS prescribing information, Figure 5

Notably, the results at Week 12 in Figure 10 and Figure 11 are not the same as the primary endpoint results at Week 12. This is due to the different methods of handling missing data for the Week 12 analysis (last observation carried forward (LOCF)) and the primary analysis at endpoint analysis (baseline observation carried forward (BOCF)). The different results at Week 12 and at Endpoint are most apparent for the placebo group, due to the higher number of discontinuations. The affect in the placebo group is most apparent in Study 30017.

The co-primary endpoint of the standardized baseline-adjusted FEV1 AUC 0-12h at Week 12 was analyzed in the serial spirometry subset of patients. The results are summarized in Table 28.

Table 28. Primary Endpoints for Studies 301 and 30017: Standardized Baseline-Adjusted FEV1 AUC 0-12h (mL) at Week 12 (Serial Spirometry Subset, FAS and ITT Population)

	Study 301 (mcg)					Study 30017 (mcg)				
	Placebo N=60	Fp 50 BID N=63	Fp 100 BID N=72	FS 50/12.5 BID N=56	FS 100/12.5 BID N=61	Placebo N=61	Fp 100 BID N=64	Fp 200 BID N=61	FS 100/12.5 BID N=58	FS 200/12.5 BID N=68
LS Mean	74	268	254	399	408	121	260	267	442	446
95% CI	-22,170	178,358	169,339	305,493	317,500	28,214	169,351	175,359	345,540	355,538
Diff to **Placebo** of LS Mean	-	195	180	325	335	-	139	146	322	326
95% CI	-	78,312	67,294	203,447	216,453	-	32,246	38,255	212,432	221,431
Diff to **50 mcg BID** of LS Mean	-	-	-	131	-	-	-	-	-	-
95% CI	-	-	-	11,250	-	-	-	-	-	-
Diff to **100 mcg BID** of LS Mean	-	-	-	145	154	-	-	-	182	-
95% CI	-	-	-	28,261	41,267	-	-	-	74,291	-
Diff to **200 mcg BID** of LS Mean	-	-	-			-	-	-	175	179
95% CI	-	-	-			-	-	-	66,284	74,285

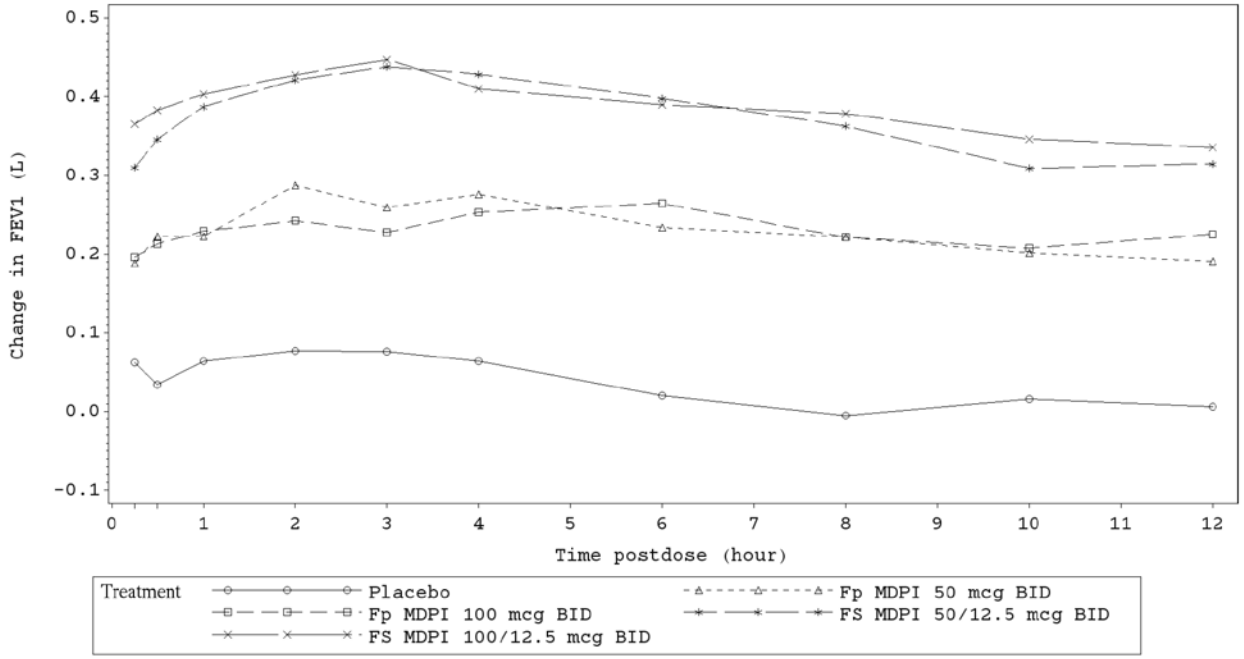
Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate; BID = twice daily; LS=least squares; Diff=difference; CI=confidence interval
Source: ISE, Table 15, pg. 87-88

The results for the co-primary endpoint of the standardized baseline-adjusted FEV1 AUC 0-12h at Week 12 in the serial spirometry subset of patients was generally similar to the co-primary endpoint of change from baseline in trough FEV1. The main difference is that in Study 301, the Fp 50 and 100 mcg doses did not show a dose response for their improvement over placebo.

Reviewer comment: The Agency's statistical analysis confirmed these results. See Dr. Yu Wang's statistical review for further details.

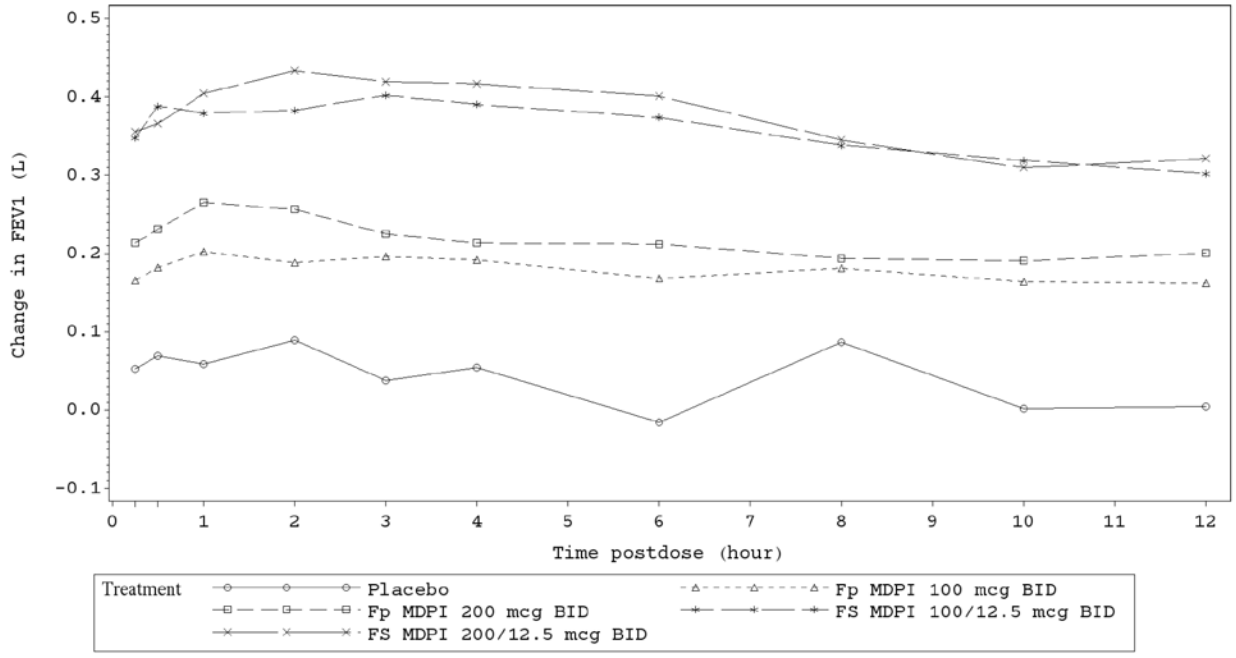
The mean change from baseline in FEV1 at Week 12 in the serial spirometry subset by time point and treatment group is also displayed in Figure 12 for Study 301 and Figure 13 for Study 30017.

Figure 12. Study 301: Mean Change from Baseline in FEV1 (L) at Week 12 by Time Point and Treatment Group (FAS; Serial Spirometry Subset)



Source: Study 301 CSR, Figure 6, pg. 114

Figure 13. Study 30017: Mean Change from Baseline in FEV1 (L) at Week 12 by Time Point and Treatment Group (FAS; Serial Spirometry)



Source: Study 30017 CSR, Figure 6, pg. 113

Sensitivity Analysis

Overall the sensitivity analyses were consistent with the primary analyses.

A sensitivity analysis using the ITT population (which was preferred by the Division as the primary endpoint analysis population) was consistent with the FAS population analysis for the primary endpoint of change from baseline in trough FEV1. The FAS and ITT population were identical for the spirometry subset for the evaluation of the co-primary endpoint of the standardized baseline-adjusted FEV1 AUC 0-12h at Week 12.

The sponsor conducted a cumulative proportion of responders analysis graph as an additional sensitivity analysis. The differentiation between the treatment arms that was seen in the primary analysis was also seen in this analysis.

A tipping point analysis was also performed for the change from baseline in trough FEV1 over the 12-week treatment period to assess the effects of missing data. The tipping points were unreasonable from a clinical perspective for all cases.

Similar to the tipping point analysis, another sensitivity analysis was performed that utilizes multiple imputations under an assumption of missing not at random (MNAR) for those patients who withdrew due to worsening asthma. The initial shift value was 0 (representing missing at random) and it was then increased by increments of 0.10 L. There were few patients in the active groups (0.7%) whose missing data was due to disease progression or lack of efficacy, and there were more such patients in the placebo group (4.6%). When imputed values for these patients were shifted, the p-value of this multiple-imputation became even smaller than the observed p-value. Regardless of how large a negative adjustment was made, in all cases the active group response was always significantly better than that in the placebo group. This was also the case with the comparisons of FS to Fp because of the small numbers of patients involved. This sensitivity analysis also supports the primary endpoint conclusions.

Further discussion of efficacy can be found in Dr. Yu Wang's statistical review.

6.1.5 Analysis of Secondary Endpoints(s)

Key Secondary Endpoint

The sponsor analyzed the time (median and mean) to 15% and 12% improvement from baseline in FEV1 post dose at baseline in the serial spirometry subset as the key secondary endpoint, as summarized in Table 29.

Table 29. Key Secondary Endpoint for Studies 301 and 30017; Serial Spirometry Subset - FAS)

	Study 301 (mcg)					Study 30017 (mcg)				
	Placebo N=60	Fp 50 BID N=63	Fp 100 BID N=72	FS 50/12.5 BID N=56	FS 100/12.5 BID N=61	Placebo N=61	Fp 100 BID N=64	Fp 200 BID N=61	FS 100/12.5 BID N=58	FS 200/12 .5 BID N=68
Time (median and mean) to 15% improvement from baseline in FEV1 post dose at baseline										
Number of patients with events, n (%)	19 (32)	21 (33)	28 (39)	39 (70)	35 (57)	22 (36)	15 (23)	27 (44)	36 (62)	55 (81)
Median (hours) (95% CI)	NE	NE	NE	1.3 (0.60, 2.75)	4.3 (1.07, NE)	NE	NE	NE (3.84, NE)	0.9 (0.48, 11.96)	0.8 (0.31, 1.77)
Log-rank test p-value	-									
Comparison to placebo		0.65	0.41	<0.01	<0.01		0.13	0.41	<0.01	<0.01
Comparison to Fp 50 mcg BID	-	-	-	<0.01	NA	-	-	-	-	-
Comparison to Fp 100 mcg BID	-	-	-	<0.01	0.01	-	-	-	<0.01	-
Comparison to Fp 200 mcg BID	-	-	-	-	-	-	-	-	<0.01	<0.01
Time (median and mean) to 12% improvement from baseline in FEV1 post dose at baseline										
Number of events, n (%)	24 (40)	29 (46)	32 (44)	47 (84)	43 (70)	24 (39)	28 (44)	34 (56)	42 (72)	58 (85)
Median (hours) (95% CI)	NE	NE	NE	0.5 (0.30, 1.55)	1.0 (0.46, 3.72)	NE	NE	6.9 (2.69, NE)	0.4 (0.29, 1.68)	0.4 (0.25, 0.81)
Log-rank test p-value	-									
Comparison to placebo		0.36	0.46	<0.01	<0.01		0.77	0.11	<0.01	<0.01
Comparison to Fp 50 mcg BID	-	-	-	<0.01	NA	-	-	-	-	-
Comparison to Fp 100 mcg BID	-	-	-	<0.01	<0.01	-	-	-	<0.01	-
Comparison to Fp 200 mcg BID	-	-	-	-	-	-	-	-	<0.01	<0.01

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate; BID = twice daily
Source: ISE, Table 27, pgs. 141-142, Table 28, pgs. 143-144, Summary 12.1 pg. 782

For Study 301, 70% (n=39) and 57% (n=35) of the subjects in the FS 50/12.5 mcg and FS 100/12.5 mcg, respectively, improved their FEV1 by 15% from baseline on Day 1. Of those subjects, the median time to an FEV1 improvement of 15% was 1.3 hours and 4.3 hours, respectively. Slightly more subjects achieved a 12% improvement in FEV1 on day 1 (84% (n=47) and 70% (n=43) for FS 50/12.5 mcg and FS 100/12.5 mcg, respectively). Of those subjects, the median time was slightly shorter than for 15% (30 minutes and 1 hour, respectively). A dose response was observed for both 15% and 12% improvement for FS 50/12.5 mcg compared to FS 100/12.5 mcg, although Fp on its own, is not considered a bronchodilator.

For Study 30017, 62% (n=36) and 81 % (n=55) of the subjects on FS 100/12.5 mcg and FS 200/12.5 mcg, respectively, improved their FEV1 by 15% from baseline on Day 1. Of those subjects, the median time to an FEV1 improvement of 15% was 0.9 hours and 0.8 hours (, respectively. Slightly more subjects achieved a 12% improvement in FEV1 on day 1 (72% (n=42) and 85% (n=58) for FS 100/12.5 mcg and FS 200/12.5 mcg, respectively). Of those subjects, the median time was slightly shorter than for 15% (0.4 hours for both FS 100/12.5 mcg and FS 200/12.5 mcg). A dose response was not observed for FS 100/12.5 mcg compared to FS 200/12.5 mcg for either a 15% or 12% improvement in post-dose FEV1 on day 1 from baseline.

For both studies, the subjects who achieved a 15% or 12% improvement in FEV1 on day 1 from baseline for the FS treatment arms were significantly different than placebo and the Fp treatment arms.

In Study 301, for the 142 (46%) total subjects (including 19 placebo subjects) who reached 15% improvement in post-dose FEV1 at baseline, 37 (12%) did so within 15 minutes. More subjects in the FS treatment arms achieved a 15% improvement (18-20%) within 15 minutes compared to the Fp treatment arms (10%), although no clear dose dependent increase was demonstrated. Out of the remaining 105 subjects, 18 (6%) reached 15% improvement after 5 hours. The results were similar results for a 12% improvement.

Study 30017 was similar, except that the difference between the FS and Fp treatment arms were more pronounced (21-34% of subjects on FS reached 15% improvement within 15 minutes compared to 3-5% for subjects on Fp).

Other Secondary Endpoints

The results for the secondary endpoints are summarized for both studies, in Table 30. All primary endpoint comparisons as specified in the fixed-sequence multiple testing procedure were statistically significant, therefore inferential testing was extended to the secondary efficacy endpoints.

Table 30. Secondary Endpoints for Studies 301 and 30017 (FAS)

	Study 301 (mcg)					Study 30017 (mcg)				
	Placebo N=129	Fp 50 BID N=128	Fp 100 BID N=129	FS 50/12.5 BID N=128	FS 100/12.5 BID N=126	Placebo N=143	Fp 100 BID N=145	Fp 200 BID N=146	FS 100/12.5 BID N=141	FS 200/12.5 BID N=145
Change from baseline in weekly average of the daily trough morning PEF (mL/min) over 12 weeks										
n	128	128	129	128	125	142	145	146	141	145
Baseline	358	363	359	360	352	351	339	345	357	343
Change from baseline (LS mean (SE), 95% CI)	4 (3) (-3, 10)	11 (3) (5, 17)	15 (3) (8, 21)	25 (3) (19, 31)	24 (3) (18, 31)	-11 (3) (-16,-6)	6 (2) (1,10)	7 (2) (3,12)	19 (2) (14,23)	20 (3) (16,25)
Comparison to placebo (95% CI)	-	7 (-2,16)	11 (2,19)	21 (13,30)	21 (12,29)	-	17 (10,23)	18 (12,25)	30 (23,36)	31 (25,38)
Comparison to Fp 50 mcg BID (95%	-	-	-	14 (6,23)	-	-	-	-	-	-

CI)										
Comparison to Fp 100 mcg BID (95% CI)	-	-	-	11 (2,19)	10 (1,18)	-	-	-	13 (6,20)	-
Comparison to Fp 200 mcg BID (95% CI)	-	-	-	-	-	-	-	-	11 (5,18)	13 (6,19)
Change from baseline in the weekly average of the total daily asthma symptom score (range 0-4.5) over week 1-12										
n	128	128	129	128	125	142	145	146	141	145
Baseline	0.80	0.83	0.78	0.78	0.78	0.88	0.80	0.90	0.95	0.94
Change from baseline (LS mean (SE), 95% CI)	-0.14 (0.04) (-0.20, -0.07)	-0.28 (0.03) (-0.34, -0.22)	-0.30 (0.03) (-0.36, -0.24)	-0.33 (0.03) (-0.39, -0.27)	-0.36 (0.03) (-0.43, -0.30)	-0.09 (0.03) (-0.15, -0.02)	-0.28 (0.03) (-0.35, -0.22)	-0.24 (0.03) (-0.31, -0.18)	-0.36 (0.03) (-0.43, -0.30)	-0.39 (0.03) (-0.46, -0.33)
Comparison to placebo (95% CI)	-	-0.14 (-0.23, -0.06)	-0.17 (-0.25, -0.08)	-0.19 (-0.28, -0.11)	-0.23 (-0.32, -0.14)	-	-0.20 (-0.29, -0.10)	-0.16 (-0.25, -0.06)	-0.28 (-0.37, -0.18)	-0.30 (-0.40, -0.21)
Comparison to Fp 50 mcg BID (95% CI)	-	-	-	-0.05 (-0.14, 0.04)	-	-	-	-	-	-
Comparison to Fp 100 mcg BID (95% CI)	-	-	-	0.03 (-0.11, 0.06)	-0.06 (-0.15, 0.02)	-	-	-	-0.08 (-0.17, 0.01)	-
Comparison to Fp 200 mcg BID (95% CI)	-	-	-	-	-	-	-	-	-0.12 (-0.21, -0.03)	-0.15 (-0.24, -0.06)
Change from baseline in weekly average of the total daily use of albuterol										
n	129	128	129	128	126	143	145	146	141	145
Baseline (number of inhalations)	1.4	1.3	1.2	1.2	1.1	1.7	1.6	1.8	2.0	1.9
Change from baseline (LS mean (SE), 95% CI)	-0	-0.47 (0.09) (-0.65, -0.29)	-0.47 (0.09) (-0.65, -0.29)	-0.71 (0.09) (-0.89, -0.52)	-0.68 (0.09) (-0.86, -0.49)	0.17 (0.11) (-0.05, 0.39)	-0.44 (0.11) (-0.65, -0.23	-0.53 (0.11) (-0.74, -0.32)	-0.82 (0.11) (-1.03, -0.61)	-0.90 (0.11) (-1.11, -0.69)
Comparison to placebo (95% CI)	-	-0.46 (-0.72, -0.21)	-0.46 (-0.72, -0.21)	-0.70 (-0.96, -0.45)	-0.68 (-0.93, -0.42)	-	-0.61 (-0.91, -0.31)	-0.70 (-1.0, -0.40)	-0.99 (-1.29, -0.69)	-1.07 (-1.37, -0.77)
Comparison to Fp 50 mcg BID (95% CI)	-	-	-	-0.24 (-0.50, 0.01)	-	-	-	-	-	-
Comparison to Fp 100 mcg BID (95% CI)	-	-	-	-0.24 (-0.49, 0.01)	-0.21 (-0.47, 0.04)	-	-	-	-0.38 (-0.68 -0.08)	-
Comparison to Fp 200 mcg BID (95% CI)	-	-	-	-	-	-	-	-	-0.29 (-0.58, 0.01)	-0.36 (-0.66, -0.07)
Time to patient withdrawal for worsening asthma (days) during the 12-week treatment period										
n	129	128	129	128	126	143	145	146	141	145
Number of patients with events (%)	4 (3)	1 (<1)	1 (<1)	1 (<1)	0	20 (14)	1 (<1)	3 (2)	1 (<1)	4 (3)
Kaplan-Meier estimate of probability of remaining in study at week 12 (95% CI)	0.97 (0.92, 0.99)	0.99 (0.94, 1.0)	0.99 (0.94, 1.0)	0.99 (0.94 1.0)	1.0 (-,-)	0.85 (0.78, 0.90)	0.99 (0.95, 1.00)	0.98 (0.94, 0.99)	0.99 (0.95, 1.00)	0.97 (0.93, 0.99)

Comparison to placebo (p-value, Hazard Ratio)	-	0.170 0.24	0.168 0.24	0.172 0.24	0.044 0	-	<0.000 0.04	0.000 0.13	0.000 0.04	0.000 0.17
Comparison to Fp 50 mcg BID (p-value, Hazard Ratio)	-	-	-	0.993 1.01	-	-	-	-	-	-
Comparison to Fp 100 mcg BID (p-value, Hazard Ratio)	-	-	-	1.000 1.00	0.313 0.00	-	-	-	0.996 1.00	
Comparison to Fp 200 mcg BID (p-value, Hazard Ratio)	-	-	-	-	-	-	-	-	0.325 0.34	0.720 1.33
AQLQ(S)										
n	97	108	103	102	109	101	126	125	130	124
Baseline	4.9	5.2	5.0	5.1	5.0	4.9	5.0	4.9	4.9	5.0
Change from baseline (LS mean (SE), 95% CI)	0.34 (0.08) (0.18, 0.49)	0.59 (0.07) (0.44, 0.73)	0.64 (0.07) (0.49, 0.78)	0.57 (0.08) (0.42, 0.71)	0.81 (0.07) (0.67, 0.95)	0.20 (0.08) (0.05, 0.35)	0.33 (0.07) (0.20, 0.47)	0.42 (0.07) (0.28, 0.55)	0.59 (0.07) (0.45, 0.72)	0.54 (0.07) (0.40, 0.67)
Comparison to placebo (95% CI)	-	0.25 (0.05, 0.46)	0.30 (0.09, 0.51)	0.23 (0.02, 0.44)	0.47 (0.27, 0.68)	-	0.13 (-0.07, 0.33)	0.22 (0.02, 0.42)	0.38 (0.18, 0.58)	0.33 (0.13, 0.53)
Comparison to Fp 50 mcg BID (95% CI)	-	-	-	-0.02 (-0.22, 0.18)	-	-	-	-	-	-
Comparison to Fp 100 mcg BID (95% CI)	-	-	-	-0.07 (-0.28, 0.13)	0.17 (-0.03, 0.37)	-	-	-	0.25 (0.07, 0.44)	-
Comparison to Fp 200 mcg BID (95% CI)	-	-	-	-	-	-	-	-	0.17 (-0.02, 0.35)	0.12 (-0.07, 0.31)

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate; BID = twice daily, PEF=peak expiratory flow, AQLQ=asthma quality of life questionnaire, - = not evaluated
Source: ISE, Table 19, pg. 100, Table 20, pg. 101, Table 21, pgs. 104-105, Summary Table 8.1, pg. 539 (used to find error in table from pg. 112), Table 22, pg. 112, Table 23, pg. 118, Table 24, pg. 125-126, Table 25, pg. 132-33.

Overall the secondary endpoints were supportive of the primary endpoint. Notably, the sponsors hierarchy approach for the analyses of the secondary endpoints controlled the Type I error for comparisons at a particular study drug/strength, as well as the comparisons over study drug/strengths within in a particular endpoint, however it did not control for the overall Type I error. See the statistical analysis plan in the protocol review for Study 301 in Section 5.3.4. Additionally, the hierarchy rules did not appear to be implemented correctly in that the comparison for the first endpoint in the hierarchy (PEF) did not meet the criteria of $p<0.05$ for the comparison of Fp 50 mcg vs. placebo for Study 301 and the 4th endpoint in the hierarchy (time to withdrawal for worsening asthma) did not meet the criteria of $p<0.05$ for the Fp 100 mcg vs. placebo comparison. See Dr. Yu Wang's statistical review for further details.

Study 30017 may have enrolled subjects with more severe asthma as the baseline comparisons were slightly worse for Study 30017 compared to Study 301 for the asthma symptom score and

albuterol use. The FS combination was not consistently superior to Fp, with the exception of the peak expiratory flow rate endpoint. A dose response was generally present with the exception of albuterol use in Fp 100 mcg compared to 200 mcg and AQLQ scores in the FS 100/12.5 mcg compared to FS 200/12.5 mcg.

Peak Expiratory Flow (PEF)

The endpoint of daily trough morning PEF was analyzed as the change from baseline in the weekly average over the 12 week treatment period. At baseline the treatment arms between and across studies were comparable. The Fp 50 mcg treatment arm was not statistically different than placebo, therefore inferential testing for this comparison was not performed for the other secondary efficacy endpoints. Statistical significance was achieved for the treatment difference of all other doses.

For the combination arms, statistically significant differences were observed for FS 50/12.5 mcg compared to Fp 50 mcg and Fp 100 mcg, FS 100/12.5 compared to Fp 100 mcg and Fp 200 mcg, and FS 200/12.5 compared to Fp 200 mcg. No statistical comparisons were made between the Fp doses and between the FS doses; however, the point estimate increased slightly for the Fp 50 mcg (7 mL/min) compared to the Fp 100 mcg (11 ml/min) treatment arms. The 95% CI for the treatment difference (comparison to placebo) were overlapping between the Fp and FS doses for both studies. There were no obvious differences in the point estimates for the Fp 100 mcg (17 ml/min) compared to 200 mcg (18 ml/min) doses or the FS 50/12.5 mcg (21 ml/min) compared to 100/12.5 mcg (21 ml/min) or FS 100/12.5 mcg (30 ml/min) compared to 200/12.5 mcg (31 ml/min).

Asthma Symptom Scores

The endpoint of total daily asthma symptom score was analyzed as the change from baseline in the weekly average over weeks 1 to 12. The total daily symptom score is an average of the daytime (0-5) and nighttime (0.4) scores, with the higher score indicating worse symptoms. At baseline, Study 30017 had slightly higher symptom scores (0.80-0.95) compared to Study 301 (0.78-0.83). Within studies the treatment arms were comparable at baseline, with the exception of Fp 100 mcg treatment arm in Study 30017 that was notably lower (0.80) than the other treatment arms (i.e. 0.95 for FS 100/12.5 mcg). All treatment arms showed a significant treatment difference compared to placebo.

For the combination arms, a statistical difference was shown for the FS 200/12.5 mcg arm compared to Fp 200 mcg and for the FS 100/12.5 mcg compared to Fp 200 mcg. No differences were noted FS 100/12.5 mcg compared to Fp 100 mcg or FS 50/12.5 compared to Fp 50 mcg or Fp 100 mcg.

No statistical comparisons were made between the Fp doses and between the FS doses; however, the point estimate increased slightly for the Fp 50 mcg (-0.14) compared to the Fp 100 mcg (-

0.17) treatment arms, the FS 50/12.5 mcg (-0.19) compared to the FS 100/12.5 mcg (-0.23), and for FS 100/12.5 mcg (-0.28) compared to FS 200/12.5 mcg (-0.30). The 95% CI for the treatment difference (comparison to placebo) were overlapping between the Fp and FS doses for both studies. The point estimate for the treatment effect was smaller for Fp 200 mcg (-0.16) compared to Fp 100 mcg (-0.20).

Daily Albuterol Use

The endpoint of total daily albuterol use was analyzed as the change from baseline in the weekly average of total daily inhalations of albuterol over the 12 week treatment period. At baseline, Study 30017 had slightly more albuterol use (1.6- 2.0) compared to Study 301 (1.1-1.4). Within studies the treatment arms were comparable at baseline. All treatment arms showed a significant treatment difference compared to placebo.

For the combination arms, a statistical difference was shown for the FS 200/12.5 mcg arm compared to Fp 200 mcg and for the FS 100/12.5 mcg compared to Fp 100 mcg (only in Study 30017). No differences were noted FS 100/12.5 mcg compared to Fp 200 mcg or FS 50/12.5 compared to Fp 50 mcg or Fp 100 mcg.

No statistical comparisons were made between the Fp doses and between the FS doses; however, the point estimate increased slightly in Study 30017 for the Fp 100 mcg (-0.61) compared to the Fp 200 mcg (-0.70) treatment arms, the FS 100/12.5 mcg (-0.99) compared to the FS 200/12.5 mcg (-1.07). The 95% CI for the treatment difference (comparison to placebo) were overlapping between the Fp and FS doses for both studies. There was no apparent dose response in Study 301.

Withdrawal for worsening asthma

This endpoint was analyzed as the number of patients withdrawn due to meeting stopping criteria for worsening asthma. Stopping criteria was defined as a having an exacerbation (worsening asthma requiring any significant treatment other than study drug or rescue medication (SABA)) that in the opinion of the investigator determined that withdrawal was necessary to help control the patient's asthma. Also if patient's met alert criteria (FEV1 below the 80% of baseline, PEF below 80% weekly baseline for $\geq$ 4/7 days, >3 days of $\geq$ 12 inhalations of albuterol $\geq$ 2 days with nighttime symptom scores >2) subjects were evaluated to see if the investigator determined that withdrawal was necessary to help control the patient's asthma.

In Study 301, there were too few patients withdrawn for worsening asthma to reach statistical significance, although more patients (n=4) withdrew in the placebo arm, compared to the treatment arms (n=0 in the FS 100/12.5 mcg arm and n=1 in the other treatment arms).

In Study 30017 significantly more patients withdrew in the placebo arm for worsening asthma (n=20 (14%)) compared to the treatment arms (Fp 100mcg (n=1, <1%), Fp 200 mcg (n=3, 2%), FS 100/12.5 mcg (n=1, <1%), FS 200/12.5 mcg (n=4, 3%)). The increased number of patient

withdrawals due to worsening asthma in the placebo group in Study 30017 (n=20, 14%) compared to Study 301 (n=4 (3%)) may indicate that patients had more severe asthma.

Comparisons of the FS to Fp within each study were not significantly different.

No statistical comparisons were made between the Fp doses and between the FS doses. There was no apparent dose response in Study 30017. There were too few events to make meaningful comparisons between doses in Study 301.

Asthma Quality of Life Questionnaire (AQLQ)

This endpoint was analyzed as the change from baseline in AQLQ score at Week 12. The AQLQ(S) was administered only to patients 18 years and older. This 32 item questionnaire included questions related to activity limitations, symptoms, emotional function, and environmental stimuli. Scores range from 1 to 7, with higher scores indicating better quality of life.

At baseline the studies and treatment arms were comparable. All treatment arms showed a significant treatment difference compared to placebo.

For the combination arms, a statistical difference was shown for the FS 100/12.5 mcg arm compared to Fp 100 mcg in Study 30017, but not Study 301. No differences were noted for FS 50/12.5 compared to Fp 50 mcg or Fp 100 mcg, FS 100/12.5 mcg compared to Fp 200 mcg, or FS 200/12.5 mcg compared to 200 mcg.

No statistical comparisons were made between the Fp doses and between the FS doses; however, for Study 301 the point estimate for the treatment difference increased slightly for the Fp 50 mcg (0.25) compared to the Fp 100 mcg (0.30) treatment arms, the FS 500/12.5 mcg (0.23) compared to the FS 100/12.5 mcg (0.47). For Study 30017, the point estimate for the treatment difference also increased slightly for the Fp 100 mcg (0.13) compared to the Fp 200 mcg (0.22) treatment arms. The FS treatment arms in Study 30017 did not show a dose response. The 95% CI for the treatment difference (comparison to placebo) were overlapping between the Fp and FS doses for both studies. In other asthma programs, AQLQ score was analyzed as a responder rate. The sponsor did not include this analysis.

6.1.6 Other Endpoints

The sponsor had multiple other endpoints (see Study 301 and 30017 Other Efficacy Endpoints in Section 5) which were also supportive of the primary analysis.

(b) (4) the sponsor did an ad hoc analysis in the serial spirometry subset of the mean change from baseline in FEV1 at Day 1 at 15 minutes (which was the first evaluated time point), as summarized in Table 31 for both studies.

Table 31. Change from Baseline in Trough FEV1 (mL) at baseline 15-minutes post treatment (301 and 30017; FAS)

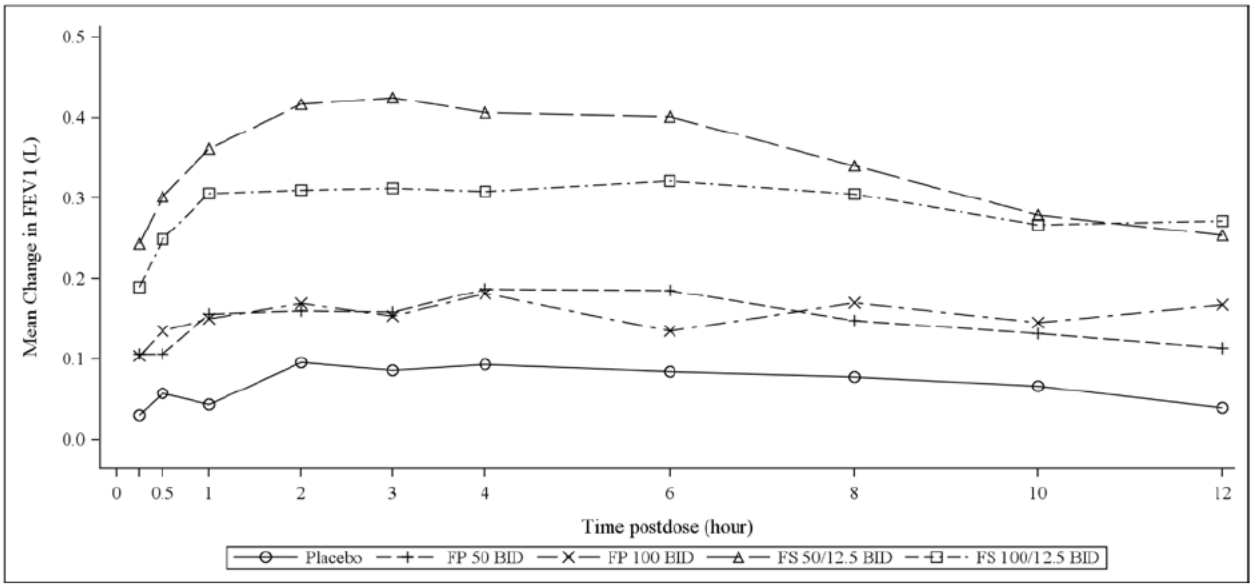
	Study 301 (mcg)					Study 30017 (mcg)				
	Placebo N=129	Fp 50 BID N=128	Fp 100 BID N=129	FS 50/12.5 BID N=128	FS 100/12.5 BID N=126	Placebo N=143	Fp 100 BID N=145	Fp 200 BID N=146	FS 100/12.5 BID N=141	FS 200/12.5 BID N=145
N	60	61	71	56	61	61	62	61	58	68
Mean (SE)	36 (34)	120 (32)	113 (31)	254 (33)	200 (32)	86 (29)	58 (29)	87 (28)	245 (30)	273 (28)
Comparison to placebo Mean (95% CI)		83 (2, 165)	76 (-3, 155)	216 (132, 301)	164 (82, 246)	-	-28 (-92, 37)	1 (-64, 66)	160 (93, 226)	187 (124, 251)
Comparison to Fp 50 mcg BID Mean (95% CI)	-	-	-	133 (50, 216)	NA	-	-	-	-	-
Comparison to Fp 100 mcg BID Mean (95% CI)	-	-	-	140 (59, 221)	88 (9, 166)	-	-	-	187 (122, 253)	-
Comparison to Fp 200 mcg BID Mean (95% CI)	-	-	-	-	-	-	-	-	159 (93, 224)	186 (123, 250)

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate; BID = twice daily, PEF=peak expiratory flow, AQLQ=asthma quality of life questionnaire, - = not evaluated
Source: ISE, Ad hoc Table 1, pg. 795 - 796

The FS treatment arms did improve at 15 minutes (on Day 1) significantly more than placebo (treatment difference 216 mL, 160-164 mL, and 187 mL, respectively). Conversely the Fp treatment arms did not significantly improve at 15 minutes compared to placebo, with the exception of Fp 50 mcg. However, the confidence interval for the Fp 50 mcg difference compared to placebo was nearly 0 (2 mL). Efficacy at 15 minutes for the ICS alone is questionable.

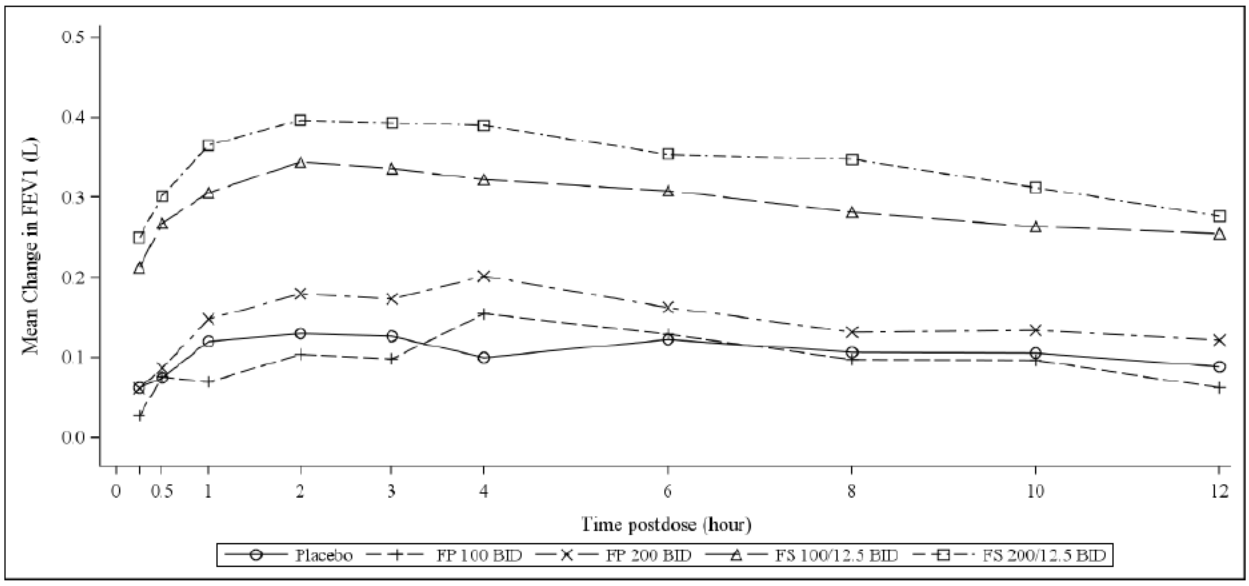
The change from baseline in FEV1 (L) at Day 1 by time point is also displayed graphically for Study 301 (Figure 14) and Study 30017 (Figure 15).

Figure 14. Study 301: Mean Change from Baseline in FEV1 (L) at Day 1 by Time point and Treatment Group (FAS; Serial Spirometry Subset)



Source: Study 301 CSR, Figure 7, pg. 115

Figure 15. Study 30017: Mean Change from Baseline in FEV1 (L) at Day 1 by Time Point and Treatment Group (FAS; Serial Spirometry Subset)



Source: Study 30017 CSR, Figure 7, pg. 114

(b) (4)

6.1.7 Subpopulations

A subgroup analysis was performed by the sponsor by sex, age group (12 to 17, 18 to 64, and ≥ 65 years), race (white, black, and other), and by geographic region (USA and non-USA) based on the pooled FAS population. The majorities of the 1375 total subjects enrolled in the Fp and FS 12-week studies were female (58%), 18 to 64 years of age (80%), and white (80%). Overall, the subgroup analyses were consistent with the primary analysis, although no study was powered to detect difference in subgroups.

Notably, in Study 301 the adolescent age group (12-17 years) showed a greater treatment effect for the FEV1 change from baseline at Week 12 for the Fp and FS treatment arms in Study 301 compared to the older age groups; however, the comparisons for the FS and Fp groups were not significant in the 12-17 year age group, but were significant the 18-64 year age group. The number of adolescents in the Study 30017 was too small to show similar results.

For race, although the black subgroup showed similar trends to the white subgroup and overall group, the comparisons were not significant due to the small number of subjects (17% overall) compared to the white subgroup.

Reviewer comment: The Agency's statistical reviewer generally agreed with the sponsor's subgroup analysis conclusions. For further details regarding the statistical analysis, see Dr. Yu Wang's statistical review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two PK studies (FpS-AS-101, FSS-AS-10042) were conducted to support the dosing recommendations. The sponsor also conducted two 12-week dose-ranging studies (Study 201 and Study 202) for Fp and one single-dose dose-ranging study for FS (FSS-201). These are discussed below. For additional detail regarding the PK studies, refer to Section 4.4 Clinical Pharmacology.

The Clinical Pharmacology reviewer concurs with the selection of dosing regimens, 50, 100, and 200 mcg BID for Fp, and 50/12.5, 100/12.5, and 200/12.5 mcg BID for FS, for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.

FpS-AS-101

In Study FpS-AS-101 over the range of inhaled, delivered Fp doses (800 to 1000 mcg total doses, administered as a single dose per treatment) that were evaluated in this study, the shapes of the plasma concentration-versus-time profiles for Fp were similar for the Fp 800 mcg total dose, the Flovent Diskus 1000 mcg total dose, and the Flovent HFA MDI 880 mcg total dose.

FSS-AS-10042

Following the single dose administration of the proposed highest dosage of Fp (200 mcg×1 inhalation) and FS (200/12.5 mcg×1 inhalation), the systemic exposure of Fp and/or Sx is similar or lower compared with the corresponding reference products following the approved dosage of Flovent Diskus (250 mcg×2 inhalation, the highest dosage is even up to 1000 mcg depending on the prior asthma therapy) and Advair Diskus (500/50 mcg×1 inhalation, the highest dosage).

There was no evidence of interaction between Fp and salmeterol; pharmacokinetic parameters of Fp were similar when administered via Fp and FS. There was no obvious difference for male, female, and age (12 to 17 years, ≥18 years) subgroups when compared to the overall study population.

Study 201

The protocol for this study is discussed in detail in Section 5.3 Study FpS-AS-201 (201). Demographics for Study 201 are listed in **Table 32**.

Table 32. Study 201: Baseline demographics (ITT Population)

	Placebo N=104	Fp 12.5 mcg N=103	Fp 25 mcg N=104	Fp 50 mcg N=103	Fp 100 mcg N=103	Flovent Diskus N=104	Total N=622
Sex, n (%)							
Male	49 (47)	46 (45)	41 (39)	44 (42)	43 (42)	41 (39)	264 (42)
Race, n (%)							
White	85 (82)	91 (88)	91 (88)	90 (87)	85 (83)	85 (82)	527 (85)
Black	17 (16)	10 (10)	11 (11)	12 (12)	14 (14)	17 (16)	81 (13)
Asian	0	1 (<1)	2 (2)	2 (2)	4 (4)	1 (<1)	10 (2)
Other	2 (2)	1 (<1)	0	0	0	1 (<1)	4 (<1)
Age in Years							
Mean (SD)	40 (15)	41 (17)	42 (16)	39 (16)	37 (15)	40 (15)	40 (16)
Median	38	42	45	41	35	38	40
Min-Max	12 - 77	12 - 74	12 – 78	12 – 72	12 – 73	12 – 81	12 - 81
Age in class, n (%)							
12-17	5 (5)	10 (10)	7 (7)	14 (13)	9 (9)	7 (7)	52 (8)
18-64	93 (89)	85 (83)	90 (87)	86 (83)	88 (85)	93 (89)	535 (86)
≥ 65 years	6 (6)	8 (8)	7 (7)	4 (4)	6 (6)	4 (4)	35 (6)
Weight (kg)							
Mean (SD)	81 (20)	82 (23)	80 (20)	79 (23)	85 (24)	82 (24)	82 (22)
Height in cm							
Mean (SD)	170 (9)	169 (11)	169 (9)	169 (10)	169 (11)	169 (9)	169 (10)
Body mass index (kg/m2)							
Mean (SD)	28 (7)	29 (7)	28 (6)	28 (7)	30 (8)	28 (7)	28 (7)

All treatments were based on one inhalation twice daily
Source: Modified from Study 201 CSR, Table 7, pg. 79

The population for Study 201 was similar to Studies 301 and 30017 in that it was predominantly female (58%), white (85%), with a mean age of 40 years.

A total of 622 subjects were randomized in Study 201, with 22% (n=139) who discontinued the study. More subjects (39% (n=41)) discontinued the study in the placebo group. The most common reason for discontinuation was meeting stopping criteria (n=54 (9%)). See protocol review in Section 5 for Study 201 for stopping criteria. The stopping criteria discontinued subjects with more severe or uncontrolled asthma which would drop subjects with decreased FEV1 thus, increasing FEV1 in placebo and decreasing the treatment effect.

The results for the primary endpoint are summarized in Table 33.

Table 33. Study 201: Change in FEV1 (mL) from Baseline to Week 12 (FAS)

	Placebo N=102	Fp 12.5 mcg BID N=102	Fp 25 mcg BID N=101	Fp 50 mcg BID N=102	Fp 100 mcg BID N=102	Flovent Diskus 100 mcg BID N=102
FEV1 at baseline, mean	2,227	2,237	2,228	2,225	2,264	2,191
Change in FEV1from baseline to Week 12 LS mean, 95% CI	145 (64, 226)	189 (112, 266)	268 (194, 343)	263 (190, 335)	295 (219, 371)	234 (162, 306)
Difference from Placebo LS mean, 95% CI	-	44 (-68, 155)	123 (13, 233)	117 (9, 226)	150 (39, 261)	-

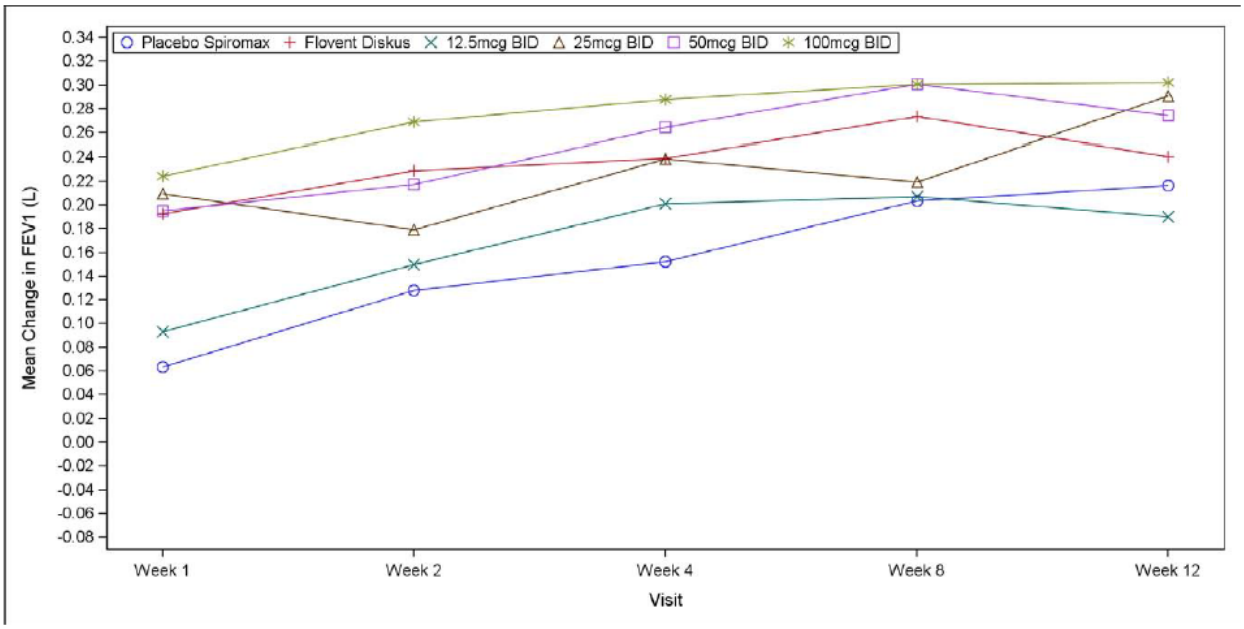
Source: Modified from Study 201 CSR, Table 15, pg. 98

All doses, with the exception of the lowest (12.5 mcg) were significantly different than placebo. The point estimate for the primary endpoint of FEV1 change from baseline to Week 12 for Flovent Diskus 100 mcg (234 mL; 95% CI (162 mL, 306 mL)) was between the Fp 12.5 mcg (189 mL; 95% CI (112 mL, 266 mL)) and Fp 25 mcg (268 mL; 95% CI (194 ML, 343 mL)). The proposed mid-dose for Fp (100 mcg) trended toward a larger improvement in FEV1 at Week 12 (295 mL; 95% CI (219 mL, 371 mL)) compared to marketed mid-dose for Flovent Diskus (100 mcg). Notably, the 25 mcg dose is proposed for the pediatric studies in 4-11 year olds. These results support the proposed Fp low (50 mcg) and mid (100 mcg) doses.

Reviewer comment: The Agency's statistical analysis did not exactly the sponsor's efficacy results for Study 201 as the programming details were not provided; however, the overall conclusions and trends were the same. See Dr. Yu Wang's statistical review for further details.

A similar pattern is seen when looking at the change from baseline in FEV1 (L) by week, as displayed in Figure 16.

Figure 16. Study 201: Change from Baseline to Each Visit in FEV1 (L) by Treatment Group (FAS)



Source: Study 201 CSR, Figure 3, pg. 105

The secondary endpoints (am peak expiratory flow, rescue free days, and time to withdrawal for worsening asthma) were consistent with the primary endpoint.

Study 202

The protocol for this study is discussed in detail in Section 5.3 Study FpS-AS-202 (202). The demographics for Study 202 are listed in **Table 34**.

Table 34. Study 202: Baseline demographics (ITT Population)

	Placebo N=106	Fp 50 mcg N=107	Fp 100 mcg N=107	Fp 200 mcg N=106	Fp 400 mcg N=107	Flovent Diskus N=107	Total N=640
Sex, n (%)							
Male	41 (39)	44 (41)	52 (49)	40 (38)	35 (33)	49 (46)	261 (41)
Race, n (%)							
White	96 (91)	96 (90)	94 (88)	93 (88)	91 (85)	95 (89)	565 (88)
Black	8 (8)	9 (8)	12 (11)	12 (11)	13 (12)	11 (10)	65 (10)
Asian	2 (2)	1 (<1)	1 (<1)	1 (<1)	2 (2)	0	7 (1)
Other	0	0	0	0	1 (<1)	0	1 (<1)
Age in Years							
Mean (SD)	50 (13)	48 (15)	49 (13)	48 (14)	51 (13)	49 (13)	49 (13)
Median	52	50	51	48	54	51	51
Min-Max	14 - 78	13 – 78	14 – 75	12 – 77	14 – 70	14 – 83	12 - 83
Age in class, n (%)							
12-17	1 (<1)	2 (2)	3 (3)	1 (<1)	1 (<1)	1 (<1)	9 (1)
18-64	94 (89)	94 (88)	99 (93)	90 (85)	90 (84)	96 (90)	563 (88)
≥ 65 years	11 (1)	11 (10)	5 (5)	15 (14)	16 (15)	10 (9)	68 (11)
Weight (kg)							
Mean (SD)	86 (25)	87 (24)	87 (23)	84 (22)	84 (21)	83 (17)	85 (22)
Height in cm							
Mean (SD)	168 (9)	169 (13)	169 (9)	168 (8)	167 (10)	168 (8)	168 (10)
Body mass index (kg/m2)							
Mean (SD)	31 (9)	31 (18)	30 (8)	30 (8)	30 (7)	30 (6)	30 (10)

All treatments were based on one inhalation twice daily
Source: Modified from Study 202 CSR, Table 7, pg. 81

The population for Study 202 was similar to Studies 301 and 30017 and was predominantly female (59%), white (88%), with a mean age of 49 years.

A total of 640 subjects were randomized in Study 202, with 28% (n=181) who discontinued the study. More subjects (45% (n=48)) discontinued the study in the placebo group. The most common reason for discontinuation was meeting stopping criteria (n=112 (18%)). See protocol review in Section 5 for Study 202 for stopping criteria. The stopping criteria discontinued subjects with more severe or uncontrolled asthma which would drop subjects with decreased FEV1 thus, increasing FEV1 in placebo and decreasing the treatment effect.

The results for the primary endpoint are summarized in Table 35.

Table 35. Study 202: Change in FEV1 (mL) from Baseline to Week 12 (FAS)						
	Placebo N=105	Fp 50 mcg BID N=107	Fp 100 mcg BID N=106	Fp 200 mcg BID N=102	Fp 400 mcg BID N=107	Flovent Diskus 250 mcg BID N=103
FEV1 at baseline, mean	2,005	2,078	2,069	2,008	2,015	1,987
Change in FEV1from baseline to Week 12 LS mean, 95% CI	49 (-23, 121)	60 (-4, 125)	100 (37, 163)	148 (81, 214)	101 (35, 166)	145 (79, 210)
Difference from Placebo LS mean, 95% CI	-	11 (-85, 107)	51 (-45, 147)	99 (1, 196)	52 (-45, 148)	-
Source: Modified from Study 202 CSR, Table 15, pg. 105						

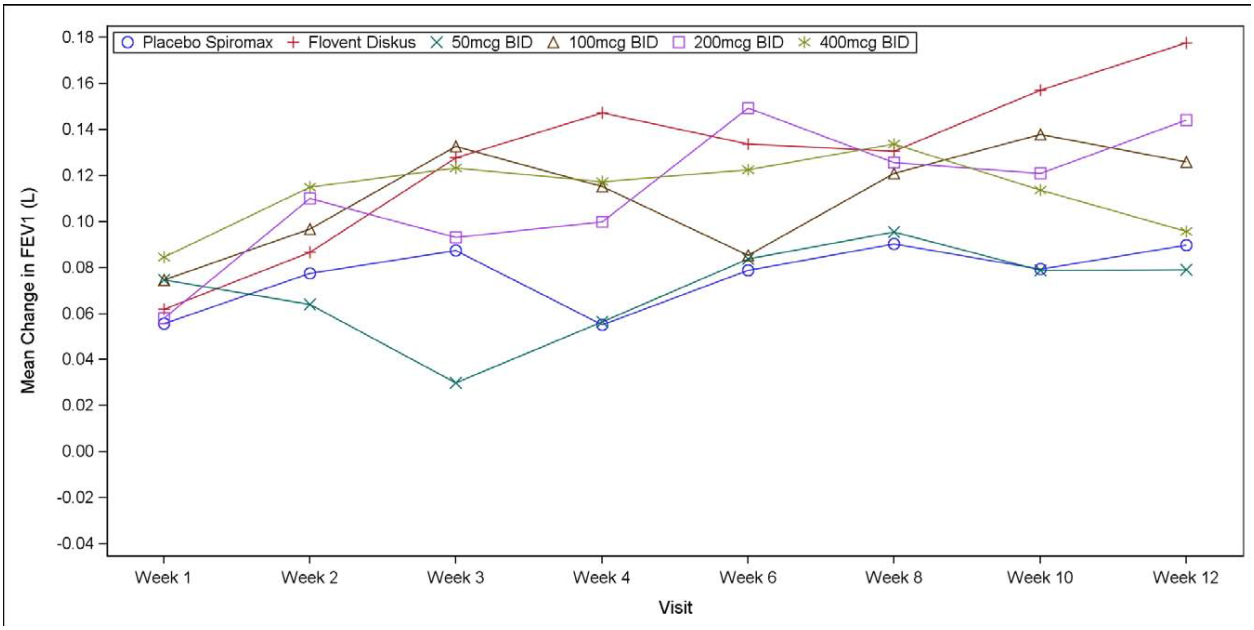
For Study 202, which included all 3 proposed doses (50, 100, and 200 mcg) no Fp dose was significantly different than Flovent Diskus 250 mcg (the marketed high-dose). Only the Fp 200 mcg dose was significantly different from placebo and is the proposed high-dose for Fp. The point estimate for the primary efficacy endpoint of FEV1 change from baseline to Week 12 for Flovent Diskus 250 mcg (145 mL; 95% CI (79 mL, 210 mL)), was between the Fp 100 mcg (100 mL; 95% CI (37 mL, 163 mL)) and Fp 200 mcg (148 mL; 95% CI (81 mL, 214 mL)). These results supported the proposed Fp high dose at 200 mcg.

Reviewer comment: The Agency's statistical analysis did not exactly the sponsor's efficacy results for Study 201 as the programming details were not provided; however, the overall conclusions and trends were the generally the same. See Dr. Yu Wang's statistical review for further details.

The lack of benefit over placebo for all treatment groups, except for Fp 200 mcg, which was barely significant with the 95% bound at 1 mL, is likely due nearly half of the subjects (45% (n=48)) in the placebo group discontinuing, and most (n=33 (31%)) due to stopping criteria which included a decrease in FEV1 below 80% of the best baseline value. The stopping criteria discontinued subjects with decreased FEV1 thus, increasing FEV1 in placebo and decreasing the treatment effect. These stopping criteria were not used for the Fp and FS 12-week efficacy and safety studies (301 and 30017).

A similar pattern is seen when look at the change from baseline in FEV1 (L) by week, as displayed in Figure 17.

Figure 17. Study 202: Change from Baseline to by Week in FEV1 (L) (FAS)



Reviewer comment: The changes from baseline FEV1 at week 12 were of larger magnitude in Study 201 compared to Study 202, likely due to the differences in study population and study design. Study 201 enrolled patients on non-ICS therapy and Study 202 enrolled patients on high-dose ICS or ICS/LABA and they were allowed to continue their asthma medication during the run-in period. The baseline for Study 202 reflects the subject's current ICS use. Study 202 supports the high dose (Fp 200 mcg) as this was significantly different than placebo. Study 201 supports the low and mid doses (Fp 50 and 100 mcg).

Study FSS-201

The exploration for salmeterol dose response was evaluated in study FSS-201. Study FSS-201 was a single-dose, cross-over study with 4 doses of salmeterol (6.25, 12.5, 25, and 50 mcg) combined with a fixed dose of fluticasone propionate (100 mcg) delivered as fluticasone propionate/salmeterol inhalation powder (FS). The comparators were Flovent Diskus 100 mcg (considered the 0 mcg salmeterol dose), and Advair 100 mcg/50 mcg. The maximum dose of 50 mcg is the dose of salmeterol that is currently marketed in Advair Diskus. The protocol for Study FSS-201 is detailed in Section 5.3.3 Study FSS-AS-201(FSS-201).

Reviewer comment: Salmeterol was not tested as a monoproduct due to the LABA safety concerns of serious asthma outcomes (hospitalizations, intubations, and death).

A total of 72 subjects were randomized, all of whom received at least 1 dose of study drug, with 65 (90%) completing the study. Of the 7 (10%) patients who withdrew from the study, 1 withdrew for an adverse event (asthma exacerbation). All 72 randomized subjects were included in the full analysis population, which was used for the primary efficacy analysis. The subject demographic was similar to the other phase 2 and 3 programs in the development program. The

primary efficacy variable was the standardized (ANCOVA with fixed effects of sequence, period, and treatment) baseline-adjusted FEV1 AUC 0-12 hours. The results for the primary efficacy variable are displayed in Table 36.

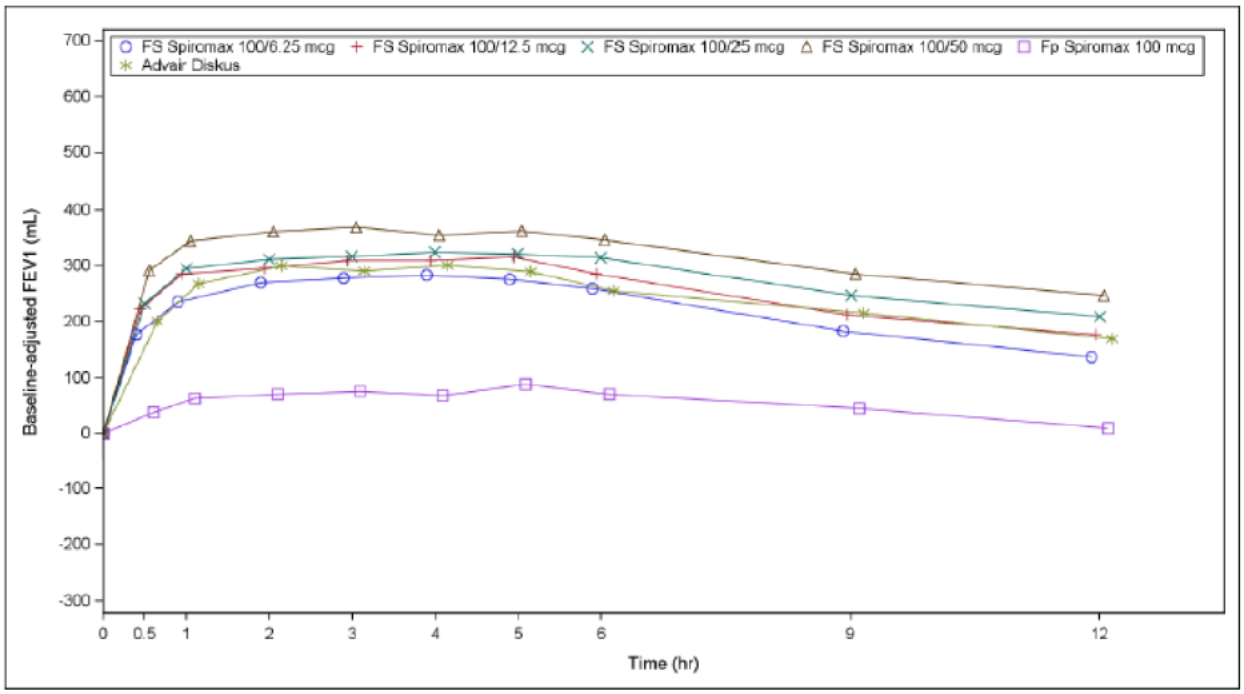
Table 36.Study FSS-201: Primary Endpoint Baseline-Adjusted FEV1 AUC 0-12 hours (mL) (FAS Population)

	Fp (mcg)	FS (mcg)				Advair
	100 N=67	100/6.25 N=68	100/12.5 N=69	100/25 N=67	100/50 N=68	100/50 N=66
Baseline FEV1	2308	2293	2313	2346	2282	2309
Standardized baseline-adjusted FEV1 AUC 0-12h						
LS mean[1,2]	52	204	249	280	303	245
LS mean diff from Fp 100 mcg		152	197	228	251	193
95% CI		116, 188	161, 233	192, 264	216, 287	157, 230
LS mean diff from Advair	-193	-42	3	34	58	
95% CI	-230, -157	-78, -6	-32, 39	-2, 70	22, 94	

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate; LS=least squares; Diff=difference; CI=confidence interval
[1] The SE for the LS mean was 38 for all groups.
[2] No CI was provided, but p<0.0001 for all salmeterol containing arms compared to no salmeterol
Source: Study FSS-201 CSR, Table 10 and 11, pg. 75

The baseline-adjusted FEV1 AUC 0-12 hours demonstrated a dose-related increase across treatment groups. All salmeterol containing (FS) treatment arms had a significantly higher standardized baseline-adjusted FEV1 AUC 0-12 hours compared to Fp alone. The primary endpoint for FS 100/50 mcg was significantly higher than Advair 100/50 mcg by 58 mL (95% CI (22 ml, 94 mL)). Advair was most closely comparable to FS 100/12.5 mcg (249 mL), with the smallest difference (3 mL; 95% CI (-32 mL, 39 mL)). The 12.5 mcg dose is the proposed fixed dose of salmeterol. These results are also shown in graphical format in Figure 18.

Figure 18. Study FSS-201: Mean Baseline Adjusted FEV1 0-12 hours by Treatment Group (FAS)



Secondary endpoints supported the primary analysis. See the protocol summary (Section 5.3.3 Study FSS-AS-201(FSS-201)) for a complete list of secondary endpoints.

To support the key secondary endpoints in Studies 301 and 30017, the time to onset when FEV1 is > 12% was evaluated, and is summarized in Table 37.

Table 37. Other Efficacy Endpoint for FSS-201: Time to onset when FEV1 > 12% increase from baseline (FAS Population)

	Fp (mcg)	FS (mcg)				Advair
	100 N=67	100/6.25 N=68	100/12.5 N=69	100/25 N=67	100/50 N=68	100/50 N=66
Time (hours) to onset when FEV1 is > 12% increase from baseline						
N	23	44	47	44	54	47
Mean	4.1	1.3	1.3	1.4	1.0	1.4
SD	2.9	1.2	1.3	1.5	0.9	1.3
Min-Max	0.4 – 12.0	0.4 – 5.0	0.4 – 6.0	0.4 – 6.0	0.4 – 4. 9	0.4 – 6.0
Duration (hours) of 12% response from baseline						
N	22	44	47	44	54	47
Mean	3.5	6.8	7.4	9.0	8.9	7.4
SD	3.3	4.6	4.2	3.7	3.9	4.2
Min-Max	0.5 – 11.5	0.5 – 11.6	1.0 – 11.6	0.9 – 11.6	0.5 – 11.6	1.0 – 11.6

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol xinafoate;
Source: Study FSS-201 CSR, Table 17, pg. 83

The time to onset when FEV1 > 12% increased from baseline ranged from 1 to 1.4 hours, with the shortest duration occurring in highest salmeterol dose group (FS 100/50 mcg).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Section 6.1.10 for discussion.

6.1.10 Additional Efficacy Issues/Analyses

The open-label, active-controlled, 26-week safety study (Study 305) did incorporate a primary efficacy variable of the change from baseline in trough FEV1 over the 26-week treatment period. The analysis was based on the full analysis set (see Table 48 for subject disposition). The results of this efficacy endpoint are summarized in Table 38.

Table 38. Study 305 Primary Endpoint Analysis (FAS) – Change from baseline in trough FEV1 (mL) over the 26-week treatment period

	Fp (mcg; BID)		Flovent HFA (mcg: BID)		FS (mcg; BID)		Advair Diskus (mcg; BID)	
	100 N=123	200 N=120	110 N=42	220 N=41	100/12.5 N=119	200/12.5 N=130	250/50 N=40	500/50 N=44
LS mean (SE)	62 (24)	77 (25)	53 (42)	90 (42)	116 (25)	100 (24)	117 (42)	41 (40)
95% CI	15, 110	28, 125	-29, 135	8, 171	67, 166	54, 146	34, 199	-37, 119
Fp vs. Flovent								
LS mean difference (SE)	9 (48)	-13 (48)						
95% CI	-84, 103	-107, 81						
FS vs. Advair								
LS mean difference (SE)					0 (49)	59 (46)		
95% CI					-95, 95	-32, 150		

Source: Study 305 CSR, Table 23, pg. 118

With the exception of Flovent HFA 110 mcg and Advair Diskus 500/50 the trough FEV1 over the 26-week treatment period showed a significant improvement from baseline. The point estimate for the improvement in FEV1 was similar across doses within each treatment group, but was larger in the FS compared to the Fp groups, consistent with the four 12-week placebo-controlled studies. There was no difference between Fp and Flovent HFA or between FS and Advair Diskus. (b) (4)

(b) (4)

7 Review of Safety

Safety Summary

The safety profile for inhaled fluticasone propionate and salmeterol in this patient population is well-known, as they have been marketed for the treatment of asthma as Flovent Diskus (50 mcg, 100 mcg, and 250 mcg) 2-4 inhalations twice daily and in combination as Advair Diskus (100/50 mcg, 250/50 mcg, and 500/50 mcg) one inhalation twice daily at higher doses than Fp and FS since 1994 (Flovent Diskus) and 2000 (Advair Diskus). Moreover, ICSs have been used for treatment of asthma since 1987 and other ICS/LABAs have also been marketed since Advair was approved.

The safety evaluation for Fp and FS relies on the pooled results of the four 12-week studies (201, 202, 301, and 30017). The 26-week long-term extension study (305) provides supportive safety data. The mean exposure range for the four 12-week studies was 68-84 days, with the lowest exposure in the placebo group (most early discontinuations in the placebo group were due to asthma adverse events and disease progression).

Dose response for safety was evaluated for Fp with doses from 12.5 to 400 mcg. The salmeterol dose response to safety was evaluated separately in Study FSS-201 (single doses ranging from 0 to 50 mcg). No dose response for any adverse event was noted, with the exception of oral candidiasis, which is a known dose-dependent safety concern for ICS.

One death was reported due to fulminant liver failure, in Study 30017. The event occurred in a 44 year old black female after receiving FS 100/12.5 mcg (one inhalation twice daily) for 37 days and starting a new herbal supplement (moringa oleifera) on Day 22. This is a potential case of Hy's law, however it is confounded by the use of an herbal supplement. Her liver function tests continued to be elevated and she died on day 72.

The overall occurrence of serious adverse events (SAEs) was equally distributed across treatment groups (0% – 2%). The only SAE that occurred in more than one patient was asthma exacerbation. Asthma exacerbation was reported in 4 (1%) patients in the placebo arm and 1 (1%) patient in the FS 200/12.5 mcg treatment arm.

Discontinuations due to AEs were balanced across treatment groups. Bronchitis, upper respiratory infection, asthma, cough, and dysphonia occurred in more than one patient. More patients discontinued due to asthma in the placebo group (n=5 (1%)) compared to the treatment groups (n=2 (<1%)).

The sponsor analyzed adverse events that were considered specific primary safety concerns for Fp and FS based on the known safety profile of these drugs in combination. The categories chosen for analyses were based on the warning and precautions in available prescribing information and included oral candidiasis, paradoxical bronchospasm and upper airway symptoms, immediate hypersensitivity reactions, immunosuppression, hypercorticism and

adrenal suppression, reduction in bone mineral density, effect on growth, hypokalemia and hyperglycemia, potential cardiovascular effects, potential central nervous system effects, glaucoma and cataracts, and eosinophilic conditions and Churg-Strauss syndrome. Bone mineral density measurements, and formal hypothalamic–pituitary–adrenal (HPA) axis and growth studies were not included in this clinical development program as the systemic exposure for these proposed products are lower or similar to the marketed products. Urinary cortisol was collected in Studies 202 and 305 and was consistent with the known effects of ICS on the HPA axis. EKGs were measured at baseline and Week 12 for the 4 pivotal studies (201, 202, 301, and 30017). For those studies which included FS treatment arms, the EKG results were consistent with the know safety profile of inhaled LABAs. Overall, the incidence of adverse events reported in these categories were consistent with the know safety profile of the marketed forms of inhaled fluticasone propionate and fluticasone propionate/salmeterol combination.

The incidence of adverse events was reported similarly across treatment groups. Nasopharyngitis, headache, upper respiratory infection, cough, oral candidiasis, and back pain were the most frequent adverse events, occurring in 3% or more subjects in any treatment group. The incidence of oral candidiasis was dose-dependent. As with other ICSs, to reduce the risk of oral candidiasis patients are advised to rinse their mouth with water without swallowing after inhalation for ICS medications.

Although clinical labs were not collected for the Studies 301 and 30017, one death occurred in Study 30017 due to fulminant liver failure. In study 201 and 202, liver function tests were measured at screening and at Week 12. One subject on Fp 100 mcg had normal baseline liver function tests and elevated liver function tests at Week 12 (AST $\geq$ 10x ULN, ALT $\geq$ 5 x ULN, bilirubin within normal limits). In combination with death due to fulminant liver failure confounded by herbal supplement use, this report of highly elevated AST and ALT will need to be considered when finalizing the prescribing information.

Subgroup analyses for four 12-week studies included gender, age, race, and geographic location (US vs. non-US). Overall, there was no apparent difference in the safety profile by these subgroups.

A total of 9 subjects become pregnant during this clinical development program. Prior to the introduction of the updated PLLR format, the reference listed drug for both Fp and FS were considered pregnancy category C. The pregnancy adverse events and outcomes for the Fp and FS clinical studies are consistent with the know safety profile of fluticasone propionate and salmeterol.

The long-term (26-week), open-label safety study (Study 305) was consistent with the safety results of four 12-week studies.

Overall, the safety database is adequate to assess the safety of fluticasone propionate and fluticasone propionate/salmeterol in the novel MDPI device. The safety profile for Fp and FS are consistent with the know safety profile for the products alone and in combination. The potential

Hy's law case and the case of elevated liver enzymes and will need to be considered further when finalizing the prescribing information. The safety findings should be factored into the risk-benefit assessment of Fp and FS for the treatment of asthma.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based primarily on the pooled results of the four 12-week studies (201, 202, 301, and 30017) studies. The safety results for the single-dose dose-ranging FS study (FSS-201) are reviewed in Section 7.2.2 Explorations for Dose Response. One 6-month, long-term, open-label safety study is presented separately, as supportive safety in Section 7.7.2 Long-term safety.

All analyses were based on the safety population, unless otherwise specified.

7.1.2 Categorization of Adverse Events

Studies 201 and 202 used MedDRA 15.0 and Studies 301, 30017, and 305 used MedDRA 17.0. There were no relevant changes between the versions.

AEs were recorded from the time the patient signed the informed consent until the end of study (including the follow-up period). AEs that occurred during a washout period were attributed to the last treatment given.

For Studies 301 and 30017, the severity of the AE was characterized as mild (no limitation of usual activities), moderate (some limitation of usual activities), or severe (inability to carry out usual activities). Slightly different severity definitions were used in Studies 201 and 202, as follows: mild (adverse event which was easily tolerated), moderate (adverse event sufficiently discomforting to interfere with daily activity), or severe (adverse event which prevented normal daily activities) adverse events. When the severity of an adverse event changed more than once a day, the maximum severity for the event was listed. If the severity changed over a number of days, these mini-events or changes were recorded separately (i.e., having distinct onset dates).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor established two safety groupings for the safety analyses of this clinical development program, as follows:

1. The 12-week Fp and FS efficacy and safety studies (301 and 30017)
2. The 12-week Fp dose-ranging studies (201 and 202) and the 12-week Fp and FS efficacy and safety studies (301 and 30017)

The Fp dose-ranging (201 and 202) and the Fp and FS efficacy and safety studies (301 and 30017) were pooled due to similar study design (12-week, randomized, placebo-controlled) and eligibility criteria. This review will focus on the larger safety grouping, which includes all 4 12-week placebo-controlled studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure for the four 12- week studies is summarized in **Table 39**.

Table 39. Overall exposure (days) (Studies 201, 202, 301, and 30017 Safety population)

	Placebo N=483	Fp (mcg; BID) N=1390						FS (mcg; BID) N=542			Flovent Diskus N=210	
	-	12.5	25	50	100	200	400	50/12.5	100/12.5	200/12.5	100	250
n	483	103	104	340	484	252	107	128	269	145	104	106
Mean	68	72	73	77	78	76	70	82	84	83	72	69
SD	28	26	25	20	19	21	27	12	10	11	25	28
Min	1	1	3	1	3	2	2	7	1	21	6	1
Max	95	92	100	104	93	98	90	91	97	97	89	90
Source: Modified from ISS, Table 16, p 88												

The mean exposure range for the four 12-week studies was 68-84 days, with the lowest exposure in the placebo group (most early discontinuations in the placebo group were due to asthma adverse events and disease progression).

7.2.2 Explorations for Dose Response

Dose response for Fp and FS were evaluated throughout the safety review as the four 12-week studies incorporated 6 doses of the Fp and 3 doses of the Fp combined with a fixed dose of salmeterol.

The exploration for safety for a salmeterol dose response was evaluated in study FSS-201, which included a range of salmeterol doses from 0 to 50 (50 mcg is the currently approved fixed salmeterol dose given in combination with varying doses of ICS to treat asthma). The results of this evaluation are discussed here.

Study FSS-201 was a single-dose, cross-over study with 6 doses of salmeterol (0, 6.25, 12.5, 25, and 50 mcg) combined with a fixed dose of fluticasone propionate (100 mcg) delivered as fluticasone propionate/salmeterol inhalation powder (FS). The protocol for Study FSS-201 is detailed in Section 5.3.3 Study FSS-AS-201(FSS-201).

Reviewer comment: Salmeterol was not tested as a monoproduct due to the LABA safety concerns of serious asthma outcomes (hospitalizations, intubations, and death).

The safety population comprised of 72 randomized subjects all of whom received at least 1 dose of study drug. The safety population was used for all analyses of safety data. The subject demographic was similar to the four 12- week studies. A total of 7 (10%) of patients withdrew from the study, with 1 withdrawing for an adverse event (asthma exacerbation).

There were no deaths or serious adverse events. Adverse events were similar across treatment groups. No adverse event occurred more than once in any salmeterol treatment group.

ECGs (12-lead) were performed before and 5 and 10 minutes after treatment administration. Out of the 72 randomized subjects, 24 had abnormal baseline ECGs. At endpoint, 13 subjects with normal baseline readings had abnormal ECGs, while 7 subjects with abnormal baseline ECGs normalized at endpoint. None of the changes could be ascribed to any of the treatment arms, not were the individual subject findings considered clinically significant. A common finding was sinus bradycardia. There were clinically meaningful changes in heart rate or ECG parameters.

Clinical chemistry, hematology, urinalysis, and pregnancy tests were collected. Due to the known effects of beta-agonists, potassium and glucose were collected pre and 15-minutes post FS dosing. There were no clinically meaningful trends in mean changes from baseline, nor notable shifts for serum chemistry variables or urinalysis parameters. Minor shifts were noted in some hematology parameters.

Reviewer comments: The salmeterol dose-ranging study did not include doses higher than the approved salmeterol dose used in combination with fluticasone propionate (50 mcg) with a well-established safety profile. As expected, we did not see any concerning safety signals in this single-dose, dose-ranging salmeterol study.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required to further explore the safety profile of nintedanib

7.2.4 Routine Clinical Testing

The 12-week Fp dose-ranging studies (201 and 202) included routine clinical testing: clinical chemistry, hematology, urinalysis, pregnancy testing, 12 lead ECGs, physical exam including oropharyngeal examination, and vital signs. Given the known safety profile of fluticasone propionate and fluticasone propionate/salmeterol and the safety results from the 12-week Fp dose-ranging studies, the 12-week Fp and FS efficacy studies (301 and 30017) only included pregnancy tests. The routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

ICS
The four 12-week studies incorporated monitoring for toxicities associated with ICS use by evaluating AEs for localized infections (including those of the mouth and pharynx with Candida albicans), paradoxical bronchospasm and upper airway symptoms, immediate hypersensitivity reactions, evidence of immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density or associated consequences (i.e., vertebral fractures), effects on growth, and eosinophilic conditions including Churg-Strauss Syndrome. Details of the AE analysis can be found in Section 7.1.2 Categorization of Adverse Events and Section 7.3.4 Significant Adverse Events.

ICS use can result in suppression of endogenous corticosteroid production, especially at higher doses. Since the impact of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis is well documented, limited assessments of cortisol were performed in this clinical program. Urine cortisol (24-hour collection) was evaluated in the higher dose-ranging Fp Study (202) and the 6-month open-label safety study (305).

Growth effects were not specifically studied given the known effects of fluticasone propionate on growth.

LABA
FS was reviewed in the context of the recently completed LABA safety studies which showed that in 11,679 adolescent (≥ 12 years of age) and adults asthma patients with a history of a severe asthma exacerbation in the year before randomization, but not during the previous month, salmeterol in a fixed-dose combination with fluticasone propionate did not have a significantly higher risk of serious asthma-related events than those who received fluticasone alone.(1)

The salmeterol containing studies (FSS-201, 301 and 30017) incorporated monitoring for toxicities associated with LABA use including specific cardiac AEs, vital sign, and ECG parameters.

7.3 Major Safety Results

Safety Results

7.3.1 Deaths

One death was reported for fulminant liver failure in Study 30017 in a 44 year old black female after receiving FS 100/12.5 mcg BID for 37 days (5.3 weeks). On day 30, her liver function tests

were ALT 630 U/L (normal: 10 to 33 U/L), AST 988 U/L (normal: 10 to 36 U/L), and total bilirubin 85.5 mcm/L (normal: 1.7 to 18.8 mcm/L). Baseline liver function tests are unknown, although there is no mention in the narrative that this patient had a history of liver function abnormalities. She withdrew from the study on day 38. On day 51 her liver function tests were ALT 767 U/L, AST 2257 U/L, and total bilirubin 439.3 mcm/L. She died on day 72. The death certificate was not available.

She began taking Moringa oleifera, an herbal supplement on day 22. Moringa oleifera has long been used in alternative medicine. Although Moringa can be used for 'liver protection', one 14-day rat study with doses up to 1000 mg/kg lead to small, but statistically significant dose-dependent increases in liver enzymes. Another 3-week guinea pig study showed ballooning degeneration of the liver. Conversely, other rat studies show improvement in liver enzymes or protective effects against hepatotoxicity of various antitubercular drugs and acetaminophen. (4)

Reviewer comment: It is unlikely that FS caused the liver failure given the long history of use with fluticasone propionate/salmeterol xinafoate at higher doses and no reported issues with hepatic injury. Rather, the herbal supplement, morgana oleifera, that was started about 2 weeks before the elevated liver enzymes were noted, is a more likely culprit. This is a potential case of Hy's law, confounded by the use of an herbal supplement.

7.3.2 Nonfatal Serious Adverse Events

An overview of SAEs for the four 12-week studies is provided in **Table 40**.

Table 40. Serious Adverse Events (Studies 201, 202, 301, 30017; Safety population)

PT	Placebo N=483	Fp (mcg; BID) N=1390						FS (mcg; BID) N=542			Flovent Diskus N=210	
		12.5 N=103	25 N=104	50 N=340	100 N=484	200 N=252	400 N=107	50/12.5 N=128	100/12.5 N=269	200/12.5 N=542	100 N=104	250 N=106
Pts with ≥ 1 SAE	6 (1)	0	0	2 (1)	5 (1)	2 (1)	0	0	3 (1)	2 (1)	2 (2)	0
Anemia	0	0	0	0	1 (<1)*[a]	0	0	0	0	0	0	0
MI	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Pan-creatitis	0	0	0	0	0	0	0	0	1 (<1)*	0	0	0
Pyrexia	0	0	0	0	0	1 (<1)	0	0	0	0	0	0
Chole-cystitis	0	0	0	0	0	0	0	0	1 (<1)*	0	0	0
Chole-Lithiasis	0	0	0	0	0	0	0	0	1 (<1)*	0	0	0
Jaundice	0	0	0	0	0	0	0	0	1 (<1)*	0	0	0
Ana-phylactic shock	0	0	0	0	0	0	0	0	0	0	1 (1)	0
Pneu-	0	0	0	0	0	0	0	0	0	1 (1)[a]	0	0

Table 40. Serious Adverse Events (Studies 201, 202, 301, 30017; Safety population)												
monia												
Kidney infection	0	0	0	0	1 (<1)	0	0	0	0	0		0
Groin abscess	0	0	0	0	0	0	0	0	0	0	1 (1)	0
Hypo-volemia	1 (<1)	0	0	0	0	0	0	0	0	0	0	0
Breast cancer	0	0	0	0	0	0	0	0	1 (<1) [α]	0	0	0
Plasma cell myeloma	0	0	0	0	1 (<1) [α]	0	0	0	0	0	0	0
Prostate cancer	0	0	0	1 (<1)		0	0	0	0	0	0	0
Grand mal convulsion	0	0	0	0	1 (<1) [α]	0	0	0	0	0	0	0
Migraine	0	0	0	1 (<1)	0	0	0	0	0	0	0	0
Abortion spon-taneous	1 (<1) [α]	0	0	0	0	0	0	0	0	0	0	0
Uterine Hemor-Hage	0	0	0	0	1 (<1)* [α]	0	0	0	0	0	0	0
Asthma	4 (1) [γ]	0	0	0	0	0	0	0	0	1 (1) [α]	0	0
Hyper-tension	0	0	0	0	1 (<1)	0	0	0	0	0	0	0

PT = preferred term, Fp = fluticasone propionate, BID = twice daily, FS = fluticasone propionate/salmeterol, SAE = serious adverse event, Pts = patients, MI = myocardial infarction

* = indicates same patient, α = patient was discontinued due to the AE, ♣ = patient died due to AE, γ = 3 of these patients discontinued to the adverse event of asthma

Source: Modified from ISS, Table 39, pg. 164 – 165

The overall occurrence of SAEs was equally distributed across treatment groups (0% – 2%). The only SAE that occurred in more than one patient was asthma exacerbation. Asthma exacerbation (see Section 5 for definition of asthma exacerbation) was reported in 4 (1%) patients in the placebo arm and 1 (1%) patient in the 200/12.5 mcg FS treatment arm.

Reviewer comment: Overall, these SAEs do not raise any safety concerns given the known safety profile of fluticasone propionate and fluticasone propionate/salmeterol for the treatment of asthma.

7.3.3 Dropouts and/or Discontinuations

AE's leading to premature treatment discontinuation for all 3 studies are summarized in Table 41.

Table 41. AEs Leading to Discontinuation (Studies 201, 202, 301, 30017; Safety population)												
PT	**Placebo N=483**	**Fp (mcg; BID) N=1390**						**FS (mcg; BID) N=542**			**Flovent Diskus N=210**	
		12.5 N=103	25 N=104	50 N=340	100 N=484	200 N=252	400 N=107	50/12.5 N=128	100/12.5 N=269	200/12.5 N=542	100 N=104	250 N=106
Pts with ≥ 1 AE leading to d/c	11 (2)	0	0	2 (1)	6 (1)	1 (<1)	1 (1)	3 (2)	2 (1)	2 (1)	2 (2)	0
Anemia	0	0	0	0	1 (<1)*	0	0	0	0	0	0	0
Tachy-cardia	0	0	0	0	0	0	0	1 (1)	0	0	0	0
Lip swelling	1 (<1)	0	0	0	0	0	0	0	0	0	0	0
Jaundice	0	0	0	0	0	0	0	0	1 (<1)*	0	0	0
Bronchitis	1 (<1)	0	0	0	1 (<1)	0	0	0	0	1 (<1)*		0
Pneu-monia	0	0	0	0	0	0	0	0	0	1 (1)	0	0
URI	0	0	0	0	1 (<1)	0	0	1 (<1)	0	0	1 (<1)	0
Respir-atory Tract infection	0	0	0	0	0	0	0	0	0	0	1 (1)	0
Naso-pharyngitis	1 (<1)	0	0	0	0	0	0	0	0	0	0	0
Back pain	0	0	0	0	0	0	0	1 (1)	0	0	0	0
Muscle spasms	0	0	0	1 (<1)*	0	0	0	0	0	0	0	0
Breast cancer	0	0	0	0	0	0	0	0	1 (<1)	0	0	0
Plasma cell myeloma	0	0	0	0	1 (<1)	0	0	0	0	0	0	0
Grand mal convulsion	0	0	0	0	1 (<1)	0	0	0	0	0	0	0
Dizziness	0	0	0	1 (<1)	0	0	0	0	0	0	0	0
Abortion spon-taneous	1 (<1)	0	0	0	0	0	0	0	0	0	0	0
Anxiety	0	0	0	1 (<1)*	0	0	0	0	0	0	0	0
Uterine Hemor-Hage	0	0	0	0	1 (<1)*	0	0	0	0	0	0	0
Asthma	5 (1)	0	0	0	0	1 (<1)	0	0	0	1 (1)*	0	0
Cough	1 (<1)*	0	0	0	1 (<1)	0	0	0	0	0	0	0

Table 41. AEs Leading to Discontinuation (Studies 201, 202, 301, 30017; Safety population)												
Dysphonia	1 (<1)*	0	0	1 (<1)*	0	0	0	0	0	0	0	0
Rash	0	0	0	0	0	0	1 (<1)	0	0	0	0	0
Hyper-tension	1 (<1)	0	0	0	0	0	0	0	0	0	0	0

PT = preferred term, Fp = fluticasone propionate, BID = twice daily, FS = fluticasone propionate/salmeterol, SAE = serious adverse event, Pts = patients, MI = myocardial infarction, URI = upper respiratory tract infection
* = indicates same patient, ♣ = patient died due to AE
Source: Modified from ISS, Table 341, pg. 172-174

Discontinuations due to AEs were balanced across treatment groups. Bronchitis, URI, asthma, cough, and dysphonia occurred in more than one patient. More patients discontinued due to asthma in the placebo group (n=5 (1%)) compared to the treatment groups (n=2 (<1%))

7.3.4 Significant Adverse Events

Adverse events of special interest for ICS and LABA are discussed in Section 7.3.5. Serious adverse events are discussed in Section 7.3.2, and adverse events leading to discontinuation are discussed in Section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

The sponsor analyzed adverse events that were considered specific primary safety concerns for Fp and FS based on the known safety profile of fluticasone propionate and fluticasone propionate/salmeterol for the treatment of asthma. The categories chosen for analyses were based on the warning and precautions in the prescribing information. These analyses are discussed here.

Oral Candidiasis

The incidence of oral candidiasis, including oral fungal infection, oropharyngeal candidiasis, and oropharyngitis fungal, was higher in the FS treated patients (1.6% to 3.4%) compared with the placebo group (0.4%) or Flovent treatment groups (0.9% to 1.0%) but lower compared with the Fp treatment groups (0% to 7.5%). All instances of oral candidiasis were mild or moderate in severity. See **Table 44** for additional information.

Paradoxical Bronchospasm and Upper Airway Symptoms

The incidence of patients who had adverse events in the system organ class (SOC) of respiratory, thoracic, and mediastinal disorders was similar across treatment groups, was not dose-dependent, and ranged from 2% to 8% for Fp, 5% to 8% for FS, and 3% to 5% for Flovent, compared to 8% for placebo. The most frequently reported (>2% in any treatment group) adverse events in the SOC of respiratory, thoracic, and mediastinal disorders were cough and oropharyngeal pain. No

patients treated with FS or Fp had an adverse event of bronchospasm. One patient (0.4%) treated with placebo had an adverse event of mild bronchospasm.

Immediate Hypersensitivity Reactions

A total of 15 subjects had hypersensitivity reactions, as detailed in **Table 42**.

Table 42. Oral candidiasis related AEs (Studies 201, 202, 301, 30017; Safety population)

PT	Placebo N=483	Fp (mcg; BID) N=1390						FS (mcg; BID) N=542			Flovent Diskus N=210	
		12.5 N=103	25 N=104	50 N=340	100 N=484	200 N=252	400 N=107	50/12.5 N=128	100/12.5 N=269	200/12.5 N=542	100 N=104	250 N=106
Pts with ≥ 1 hyper-sensitivity AE	2	0	0	2	1	1	1	1	2	2	2	1
Hyper sensitivity	0	0	0	0	0	0	0	0	0	1[b]	0	0
Ana-phylactic shock	0	0	0	0	0	0	0	0	0	0	1[b]	0
Urti-caria	0	0	0	1[a]	0	0	0	1[a]	1[a]	0	1[b]	1[b]
Rash	2[b]	0	0	1[a/b]	1[a/b]	0	1[a/b]	0	0	1[a/b]	0	0
Hypo-ten-sion	0	0	0	0	0	1[a]	0	0	1[a]	0	0	0

PT = preferred term, Fp = fluticasone propionate, BID = twice daily, FS = fluticasone propionate/salmeterol, AE = adverse event, Pts = patients, a=mild, b=moderate, a/b= mild or moderate
Source: Modified from ISS, pg. 177

The SAE of anaphylactic shock was reported in the Flovent treatment arm. Overall, the hypersensitivity adverse events are consistent with the known safety profile of fluticasone propionate and fluticasone propionate/salmeterol for the treatment of asthma.

Immunosuppression

The types of AEs in the infections and infestations SOC reported in the safety pool (nasopharyngitis, URI, and oral candidiasis) were consistent with the known safety profile of ICS treatment of patients with asthma.

Hypercorticism and Adrenal Suppression

Exogenously administered ICSs can result in suppression of endogenous corticosteroid production, especially at higher doses. A relationship between plasma levels of Fp and inhibitory effects on stimulated cortisol production is reported in the fluticasone propionate and fluticasone

propionate/salmeterol prescribing information after 4 weeks of treatment with Fp inhalation aerosol.

Since the impact of Fp on the hypothalamic–pituitary–adrenal (HPA) axis is well documented, and the systemic exposure for Fp and FS is similar or lower than the approved products, limited assessments of cortisol were performed in the FS clinical program. Twenty four-hour urine cortisol level was evaluated in studies using the higher doses of FS or Fp. Urinary cortisol assessments were performed for Study 202 and 305 and will be discussed in Section 7.4.2 Laboratory Findings.

Reduction in Bone Mineral Density

Bone mineral density was not specifically measured in the four 12-week studies given the known effects on bone mineral density of fluticasone propionate. There were no adverse events or reported instances of decreased bone mineral density or associated consequences (i.e., vertebral fractures).

Effect on Growth

Growth was not specifically measured in the four 12-week studies as the effects of fluticasone propionate on growth as is well documented, and the systemic exposure for fluticasone propionate as Fp and FS is similar or lower than the approved products.

Hypokalemia and Hyperglycemia

Beta-receptors activate the Na/K pump; therefore beta-agonists (salmeterol) increase the Na/K pump leading to increased intracellular potassium and hypokalemia. Beta-agonists also affect glucose homeostasis by modulating insulin secretion, liver metabolism, and uptake of glucose into muscle. No adverse events of hypokalemia or hyperglycemia were reported for patients treated with FS.

Potential Cardiovascular Effects

Excessive beta-agonist stimulation can affect the cardiovascular system and salmeterol has been associated with a clinically significant cardiovascular effect in some patients as measured by EKG changes, pulse rate, blood pressure, and/or symptoms.

The incidence of patients who had adverse events in the SOC of cardiac disorders was not dose-dependent, and ranged from 0% to 2% for Fp and FS, and 0% for Flovent, compared to 1% for placebo. The most frequently reported adverse event was palpitations (3 patients treated with FS, 2 patients treated with Fp, and 0 patients treated with placebo). The incidence of patients who had adverse events in the SOC of vascular disorders was also not dose-dependent, and ranged from 1% to 2% for Fp, 1% for FS, and 0-3% for Flovent, compared to 1% for placebo.

Hypertension was more frequently reported among patients treated with Fp (13 patients (0.9%)) compared with FS (4 patients (0.7%)) or placebo (3 patients (0.6%)).

Potential Central Nervous System Effects

Excessive beta-agonist stimulation can affect the central nervous system. The incidence of patients who had adverse events in the SOC of nervous system disorders was not dose-dependent, and ranged from 5-8% for Fp, 3-7% for FS, 4-5% for Flovent, compared to 5% for placebo. The most frequently reported adverse event was headache (FS, n=24 (4.4%); Fp, n=67 (4.8%); placebo, n=21 (4.3%)) with no dose effect. One patient treated with Fp 100 mcg had a serious adverse event of severe grand mal convulsion. Dizziness and migraine occurred in more than one subject treated with FS (dizziness: FS, n=7 (1.3%); Fp, n=10 (0.7%); placebo, n=1 (0.2%): migraine: FS, n=2 (0.4%); Fp, n=3 (0.2%); placebo, n=0) with no dose effect.

Glaucoma and Cataracts

There were no instances of glaucoma or cataracts in the four 12-week studies.

Eosinophilic Conditions and Churg-Strauss Syndrome

There were no instances of eosinophilic conditions or Churg-Strauss syndrome in the four 12-week studies.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse events in 3 or more subjects in the four 12-week studies are listed in **Table 43**.

Table 43. Common Adverse Events ≥ 3% and More Common Than Placebo (Studies 201, 202, 301, 30017; Safety population)

PT	Placebo N=483	Fp (mcg; BID) N=1390						FS (mcg; BID) N=542			Flovent Diskus N=210	
		12.5 N=103	25 N=104	50 N=340	100 N=484	200 N=252	400 N=107	50/12.5 N=128	100/12.5 N=269	200/12.5 N=542	100 N=104	250 N=106
Pts with ≥ 1 AE	163 (34)	31 (30)	32 (31)	111 (33)	157 (32)	94 (37)	41 (38)	46 (36)	96 (36)	61 (42)	32 (31)	27 (26)
Naso-Pharyngitis	19 (4)	4 (4)	5 (5)	19 (6)	21 (4)	11 (4)	2 (2)	11 (9)	13 (5)	10 (7)	1 (1)	4 (4)
Headache	21 (4)	5 (5)	5 (5)	10 (3)	28 (6)	12 (5)	7 (7)	7 (6)	13 (5)	4 (3)	5 (5)	4 (4)
URI	17 (4)	7 (7)	2 (2)	15 (4)	22 (5)	9 (4)	2 (2)	6 (5)	8 (3)	6 (4)	4 (4)	3 (3)
Cough	11 (2)	0	0	3 (1)	7 (1)	7 (3)	1 (1)	3 (2)	10 (4)	1 (1)	0	1 (1)
Oral candidiasis[a]	2 (<1)	0	1 (1)	5 (2)	9 (2)	9 (4)	8 (8)	2 (2)	6 (2)	5 (3)	1 (1)	1 (1)
Back pain	6 (1)	0	1 (1)	4 (1)	8 (2)	3 (1)	3 (3)	4 (3)	2 (1)	0	0	0

PT = preferred term, Fp = fluticasone propionate, BID = twice daily, FS = fluticasone propionate/salmeterol, AE = adverse event, Pts = patients, URI = upper respiratory infection
a=includes oropharyngeal candidiasis, oral fungal infection, and oropharyngitis fungal (see Table 44)
Source: Modified from ISS, Table 30, pg. 132

The incidence of adverse events was reported similarly across treatment groups. Nasopharyngitis, headache, upper respiratory infection, cough, oral candidiasis, and back pain were the most frequent adverse events, occurring in at least 3% of subjects and more commonly than placebo in any treatment group. The incidence of oral candidiasis was dose-dependent.

Reviewer's comment: To reduce the risk of oral candidiasis patients are advised to rinse their mouth with water without swallowing after inhalation for ICS medications. Rinsing after treatment administration was also incorporated into the study protocols, therefore this rate represents that intervention. These common AEs are consistent with the known safety profile of fluticasone propionate and fluticasone propionate/salmeterol.

7.4.2 Laboratory Findings

Clinical labs were not collected for Studies 301 and 30017 unless indicated. For Study 201 and 202, clinical labs were collected at screening and at Week 12 (for the list of collected labs see Table 7). There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory variable. Shifts in clinical laboratory values from the normal range at baseline to outside the normal range occurred with similar frequency across the treatment groups.

Liver Enzymes

Although clinical labs were not routinely measured for Study 30017, there was one death reported due to fulminant liver failure with elevated liver enzymes as follows: ALT 20x ULN, AST 27x ULN, Bilirubin 5x ULN (see Section 7.3.1 Deaths for further details). This was considered a potential Hy's law case (ALT or AST > 3x ULN and Bilirubin > 2x ULN) for a patient treated for 5 weeks with FS 100/12.5 mcg, but was confounded due to herbal supplement use(Moringa oleifera) after starting the study. Given the known safety profile of fluticasone

propionate and fluticasone propionate/salmeterol at higher doses to treat asthma, this is unlikely to be due to FS.

In Studies 201 and 202, abnormal liver enzymes were observed. In Study 201, elevations in liver enzymes were reported for 1 patient in the Fp 12.5 mcg group (AST ≥3 - ≤ 5×ULN), 1 patient in the Fp 25 mcg group (bilirubin ≥2×ULN with normal AST and ALT), and 1 patient in the Flovent 100 mcg group (AST ≥3 - ≤ 5×ULN). In Study 202, elevations in liver enzymes were reported for 1 patient in the Fp 100 mcg group. At baseline the ALT and AST were within normal limits (52 and 60 U/L, respectively). At Week 12 the ALT increased to ≥5×ULN (387 U/L), the AST increased to ≥10×ULN (616 U/L). Bilirubin increased from 13 umol/L to 20 umol/L, but was still within normal limits. The increased liver function tests were not reported as adverse events and there were no adverse events noted with this increased in liver function tests and no follow-up labs were performed. Review of the graphic patient profile (patient 80519006) by this reviewer did not note any concomitant medications or other reasons for the increase in liver function tests. No cases of elevated liver function tests were reported in the placebo group for any study in the four 12-week studies.

Reviewer comment: The subject with increased ALT ≥ 5x and AST ≥10 x is concerning, however given the bilirubin was within normal limits, there were no adverse events reported with the increased liver function tests, and the safety experience for both fluticasone propionate and fluticasone propionate/salmeterol at higher doses is well-established, it is unlikely that this is a true safety concern for Fp or FS

Potential Hypokalemia and Hypoglycemia

See Section 7.3.5 Submission Specific Primary Safety Concerns

Potential Hypocorticism and Adrenal Suppression

Exogenously administered ICSs can result in suppression of endogenous corticosteroid production, especially at higher doses. A relationship between plasma levels of Fp and inhibitory effects on stimulated cortisol production is reported in the fluticasone propionate and fluticasone propionate/salmeterol prescribing information after 4 weeks of treatment with Fp inhalation aerosol.

Since the impact of Fp on the hypothalamic–pituitary–adrenal (HPA) axis is well documented, and the systemic exposure for Fp and FS is similar or lower than the approved products, limited assessments of cortisol were performed in the FS clinical program. Twenty four-hour urine cortisol level was evaluated in studies using the higher doses of FS or Fp. Urinary cortisol assessments were performed for Study 202 and 305 are discussed below.

For Study 202, 24-hour urinary cortisol was collected within 7 days of baseline and Week 12. Subjects who discontinued early did not have the 2nd urinary cortisol collection. Urine samples were excluded for low volume (< 600 mL females or < 800 mL males), low creatinine (below

lower limit of ± 2.5 SD of the normal), not being collected within 24 hours (± 2 hours), use of prohibited corticosteroids (within 4 weeks), and if either day 1 or week 12 collection was missing.

At baseline the mean values ranged from 64 to 74 mcg/24 hours. The change from baseline at Week 12 for Fp was 6, -2, -1, -12 mcg/24 hours for Fp 50, 100, 200, and 400 mcg, respectively. There was no dose response. The placebo group change at Week 12 was -1 mcg/24 hours and Flovent was -9 mcg/24 hours.

For Study 305, 24-hour urinary cortisol was collected at baseline, Week 14, and Week 26 (or early termination visit) in a subset of patients.

In the urine cortisol analysis subset, the median change from baseline in 24-hour urine-free cortisol ranged from –3.50 to 2.00 mcg/24 hours a week 14 and from –6.00 to –1.00 mcg/24 hours a week 26. To compare, the mean at baseline ranged from 19 to 30 mcg/24 hours.

Reviewer comment: The results of the urinary cortisol evaluation are consistent with the known effects of ICS on cortisol levels.

7.4.4 Electrocardiograms (ECGs)

ECGs were measured at baseline and Week 12 for all four 12-week studies.

In general, the ECG safety profile was consistent with the known safety profile of LABAs.

In Study 301, no patients on LABA therapy (FS) had any adverse events in the investigations SOC related to ECGs. A total of 3 subjects on FS had adverse events in the cardiac disorders SOC (palpitations, tachycardia, and ventricular extra systoles in the 50/12.5 mcg treatment arm), compared to 3 on placebo (n=2) and Fp with supraventricular extra systoles and atrial fibrillation. None of these were serious and one (tachycardia in FS 50/12.5 mcg) led to withdrawal.

In Study 30017, 5 subjects reported AEs in the cardiac disorders SOC, 4 on FS (palpitations in 2 patients and 1st degree AV block in 1 patient on FS 200/12.5 mcg, and tachycardia in 1 patient on FS 100/12.5 mcg), and 1 on Fp (angina pectoris on Fp 200 mcg).

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted with this application. The long-term safety study (Study 305) is reviewed in Section 7.7.2 Long-term safety.

7.4.6 Immunogenicity

Immunogenicity is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Adverse event rates did not show a dose-related effect, with the exception of oral candidiasis. The adverse events related to oral candidiasis are summarized in **Table 44**.

Table 44. Oral candidiasis related AEs (Studies 201, 202, 301, 30017; Safety population)

PT	Placebo N=483	Fp (mcg; BID) N=1390						FS (mcg; BID) N=542			Flovent Diskus N=210	
		12.5 N=103	25 N=104	50 N=340	100 N=484	200 N=252	400 N=107	50/12 5 N=128	100/12.5 N=269	200/12.5 N=542	100 N=104	250 N=106
Pts with ≥ 1 Oral candidiasis-related AE	2 (<1)	0	1 (1)	5 (2)	9 (2)	9 (4)	8 (8)[a]	2 (2)	6 (2)	5 (3)	1 (1)	1 (1)
Oral candidiasis	2 (<1)	0	1 (1)	5 (2)	9 (2)	9 (4)	4 (4)	2 (2)	6 (2)	3 (2)	1 (1)	1(1)
Oral fungal infection	0	0	0	0	0	0	3 (3)	0	0	0	0	0
Oro-Pharyngeal Candidiasis	0	0	0	0	0	0	1 (1)	0	0	2 (1)	0	0
Oropharyngitis fungal	0	0	0	0	0	0	1 (1)	0	0	0	0	0

PT = preferred term, Fp = fluticasone propionate, BID = twice daily, FS = fluticasone propionate/salmeterol, AE = adverse event, Pts = patients, URI = upper respiratory infection
a=one patient reported two AEs.
Source: Modified from ISS, Table Summary 9.3.2, pgs. 1262-1263

Oral candidiasis-related AEs were reported in a dose-related fashion, with the highest incidence in the Fp 400 mcg group. Oral candidiasis is a known safety concern for inhaled corticosteroids.

Reviewer's comment: To reduce the risk of oral candidiasis patients are advised to rinse their mouth with water without swallowing after inhalation for ICS medications. Rinsing after treatment administration was also incorporated into the study protocols, therefore this rate represents that intervention. These common AEs are consistent with the known safety profile of fluticasone propionate and fluticasone propionate/salmeterol.

7.5.2 Time Dependency for Adverse Events

Time dependency for Adverse Events was not evaluated in this clinical development program.

7.5.3 Drug-Demographic Interactions

Subgroup analyses for the four 12-weeks studies were performed for AEs for intrinsic factors (gender, age, and race) and extrinsic factors (geographic location (US vs. non-US)).

Several subgroup categories were small, and their safety results should therefore be considered with caution. In particular, these were adolescents (12-17 years of age: n=192 (7%)), subjects ≥

65 years of age (n=245 (9%)), and subjects who were black (n=379 (14%)). Overall, there was no apparent difference in the AE profile by sex, age, or race.

By region, the rates of AEs were higher in the US (range 31-48%) vs. non-US (14-41%), although the general patterns of AEs were similar.

7.5.4 Drug-Disease Interactions

Hepatic impairment

Fluticasone propionate and salmeterol are predominantly cleared by the liver. Current prescribing information advises to monitor patients with hepatic impairment for signs of increased drug exposure, as elevation of hepatic enzymes were reported in ≥ 1% of subjects in clinical trials. The elevations were transient and did not lead to discontinuation from trials. Formal PK studies using fluticasone propionate and fluticasone propionate/salmeterol were not conducted in patients with hepatic impairment. The sponsor also proposes to include the same language in the Fp and FS labels.

Renal Impairment

No formal PK studies were conducted in patients with renal impairment. No dosing or monitoring is being proposed, nor is included in the fluticasone propionate and fluticasone propionate/salmeterol prescribing information.

Other

As salmeterol is a sympathomimetic amine, FS should be used with caution in patients with convulsive disorder, thyrotoxicosis, or in those who are usually responsive to sympathomimetic amines. Beta-agonists (when dose intravenously) have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

7.5.5 Drug-Drug Interactions

The drug-drug interactions for fluticasone propionate and fluticasone propionate/salmeterol as well known and are listed below:

- Inhibitors of CP450 3A4
- Monoamine Oxidase Inhibitors and Tricyclic Antidepressants
- Beta-Adrenergic Receptor Blocking Agents
- Non-potassium sparing Diuretics

Further details regarding drug-drug interactions can be found in the clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

A total of 9 subjects became pregnant during this clinical development program, as outlined in **Table 45**.

Table 45. Pregnancies: (Studies 201, 202, 301, 300017, and 305: Safety population)

PT	Placebo N=483	Fp (mcg; BID) N=1390						FS (mcg; BID) N-542			Flovent Diskus/HFA N=210	
		12.5 N=103	25 N=104	50 N=340	100 N=611	200 N=378	400 N=107	50/12.5 N=128	100/12.5 N=389	200/12.5 N=675	100/110 N=146	250/220 N=147
Normal newborn	1											
Live Birth												1
Miscarriage						1						
Ectopic	1					1						
On-going												1[a]
Lost to follow-up			1									
Not available			1							1		

PT = preferred term, Fp = fluticasone propionate, BID = twice daily, FS = fluticasone propionate/salmeterol, AE = adverse event, Pts = patients, URI = upper respiratory infection
a=Flovent HFA 220 mcg treatment arm of Study 305
Source: Modified from ISS, pg. 238; Study 305 CSR, Table 9 pg. 69

Out of a total of 9 subjects become pregnant during this clinical development program, there was 1 normal newborn, 1 live birth, 1 miscarriage, 1 ectopic pregnancy, 3 lost to follow-up, and 1 on-going. Prior to the introduction of the updated PLLR format, fluticasone propionate and fluticasone propionate/salmeterol were considered pregnancy category C. The pregnancy adverse events and outcomes for the Fp and FS clinical studies are consistent with the know safety profile of fluticasone propionate and salmeterol.

For further details regarding human reproduction and pregnancy data, including lactation, see the pharmacology-toxicology review from Dr. Luqi Pei.

7.6.3 Pediatrics and Assessment of Effects on Growth

Efficacy and safety information for the adolescent population 12-17 years of age is presented throughout this review. For the population of 4-11 year olds, the sponsor submitted their pediatric study protocol (PSP) in April 2014, and it was agreed upon in October 2014. The first PSP amendment, submitted April 2015, was agreed upon in September 2015. The second PSP amendment was received during these NDA reviews (July 2016) and agreed upon in September

2016. The PSP includes a waiver for 0-3 years and a deferral for 4-11 years. Teva is conducting one PK study in 4-11 year olds (FSS-PK-10007) with an estimated completion date of quarter 3, 2016. Teva also proposed to conduct one 12-week, randomized, double-blind, placebo-controlled study in 4-11 year olds with an estimate initiation date of quarter 4, 2016 with a completion date of quarter 3, 2018.

The Pediatric Review Committee (PeRC) discussed these NDAs on October 19, 2016 and was in agreement with the waiver for children 0-3 years and of age and the deferral for patients 4-11 years.

Growth was not specifically measured in the four 12-week studies as the effects of fluticasone propionate on growth as is well documented, and the systemic exposure for fluticasone propionate as Fp and FS is similar or lower than the approved products.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One patient in Study 305 was randomized to 200/12.5 mcg (1 inhalation twice daily), but inadvertently took 2 inhalations twice daily for 2 weeks. The patient reported moderate insomnia during those 2 weeks.

7.7 Additional Submissions / Safety Issues

7.7.1 120-day Safety Update

All study reports were completed at the time of submission. No new information was submitted for the 120-day safety update.

7.7.2 Long-term safety

The long-term safety evaluation for Fp and FS relies on Study 305, a 6-month, open-label study of the mid-(100 mcg and 100/12.5 mcg) and high dose (200 mcg and 200/12.5 mcg) Fp and FS, respectively, with an active control group (Flovent HFA 110 and 220 mcg; Advair Diskus 250/50 mcg and 500/50 mcg), all administered at one inhalation twice daily. This section contains a brief review of the protocol and the results of the study.

The safety results for Study 305 showed similar demographics and disposition to the four 12-week studies. A range of 83-92% of subjects completed the 6-month study. The most common cause of discontinuation was withdrawal by subject. The mean duration of exposure ranged from 166 days (23.7 weeks) to 172 days (24.5 weeks) and was similar between treatment groups.

The incidence of SAEs was similar between the treatment groups within both the ICS and ICS/LABA cohorts. Asthma (exacerbation) was the most frequently reported serious adverse event (n=24 (4%) overall) with the highest incidence occurring in the FS 200/12.5 mcg group (n=8 (6%)). The adverse events leading to discontinuation were similar in frequency and type to

the four 12-week studies. The most common adverse event was upper respiratory infection occurring in 16 – 31% of subjects. Oral candidiasis was the only adverse event that appeared to be dose-related.

Overall, the safety results for Study 305 were consistent with the four 12-week studies and the known safety profile of inhaled fluticasone propionate and fluticasone propionate/salmeterol in subjects with asthma.

Study FSS-AS-305 (305)

Administrative Information

- **Study title:** A 26-Week Open-Label Study to Assess the Long-Term Safety of Fluticasone Propionate Multidose Dry Powder Inhaler and Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients 12 Years of Age and Older with Persistent Asthma
- **Study dates:** July 14, 2014 to July 20, 2015
- **Study sites:** USA
- **Study report date:** February 3, 2016

Objectives/Rationale

Primary Objectives

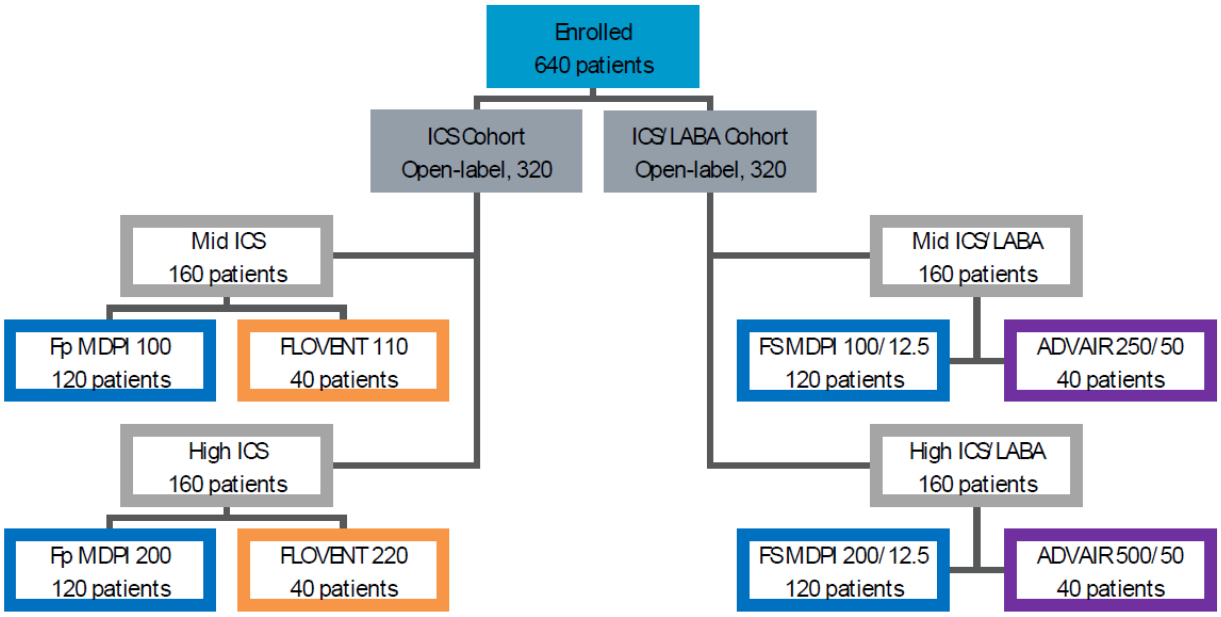
The primary objective of the study was to evaluate the long-term safety of Fp and FS at the mid and high dose over 26 weeks in patients 12 years of age and older with persistent asthma.

Study Design and Conduct
Overview

Study 305 was a 26-week, randomized, open-label, active-controlled study in patients with persistent asthma. After a 14-day run-in period, on their current asthma medications (SABAs were replaced with albuterol HFA), subjects were randomized to the one of 8 different treatment arms (Fp 100 mcg, Fp 200 mcg, FS 100/12.5 mcg, Advair Diskus 250/50 mcg, FS 200/12.5, and Advair Diskus 500/50 mcg one inhalation twice daily, Flovent HFA 110 mcg, Flovent HFA 220 mcg 2 puffs twice daily). Subjects requiring oral steroids, emergency room visits, or hospitalizations for asthma were allowed to remain in the study based on investigator judgment. A follow-up visit occurred after 1 week (week 13).

The study design for Study 305 is depicted in Figure 19.

Figure 19. Study 305: Study Design



ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; FLOVENT = FLOVENT HFA; ADVAIR = ADVAIR DISKUS
Note: Numbers after drug names denote treatment strength in mcg.

Source: CSR, Fig 1, pg. 26

The schedules of assessments are shown in Figure 20.

Figure 20. Study 305: Schedule of Assessments

Procedures and assessments[a]	Pretreatment		Treatment Period (visit/day or week)[b]								Follow-up Visit[c]
	SV[d,e]	RV/TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8		
	Screening 14 ±2 days before RV	Baseline after 14 ±2 days of run-in	W2 Day 15 ±2	W6 Day 43 ±2	W10 Day 71 ±2	W14 Day 99 ±2	W18 Day 127 ±2	W22 Day 155 ±2	W26 Day 183 ±2	Early termination	W27 7±2 days after TV8/ET
Informed consent/assent	X[f,g]										
Assign patient identification number	X[g]										
Inclusion and exclusion criteria	X	X									
Demography	X										
Medical, psychiatric, asthma, asthma therapy history	X	X									
Prior medication history	X										
Vital signs measurement (pulse and BP)	X	X	X	X	X	X	X	X	X	X	
Full physical examination, including height and weight	X	X							X	X	
Oropharyngeal examination[h]	X	X	X	X	X	X	X	X	X	X	
24-hour urine cortisol		X				X			X	X[i]	
Electrocardiography[j]	X								X	X	
Predose spirometry with reversibility testing[k]	X										
Trough spirometry[l]		X	X	X	X	X	X	X	X	X	
Clinical laboratory evaluations	X								X	X	
Urine pregnancy test (if applicable)		X	X	X	X	X	X	X			
Serum pregnancy test (if applicable)	X								X	X	
Training in use of PEF and daily diary	X	X	X	X	X	X	X	X			
Dispense patient diary	X	X	X	X	X	X	X	X			
Dispense PEF meter	X										
Dispense rescue medication (after SV, as needed)	X	X	X	X	X	X	X	X			
ACT questionnaire		X	X	X	X	X	X	X	X	X	
Adverse event inquiry and recording	X[m]	X	X	X	X	X	X	X	X	X	X
Change in medical history		X	X	X	X	X	X	X	X	X	X
Concomitant medication usage[n]	X	X	X	X	X	X	X	X	X	X	X
Review randomization criteria		X									
Calculate FEV_1 and PEF stability limits to determine alert criteria		X									
Review alert criteria for worsening asthma or asthma exacerbation[o]	X	X	X	X	X	X	X	X			X
Randomization to study drug via IRT		X									
Dispense study drug[p]		X	X	X	X	X	X	X			
Study drug training (Teva MDPI, DISKUS, or HFA)		X	X	X	X	X	X	X			
Supervised administration of study drug at investigational center		X	X	X	X	X	X	X			
Assess study compliance		X	X	X	X	X	X	X	X	X	
Collect patient diary		X	X	X	X	X	X	X	X	X	
Collect study drug		X	X	X	X	X	X	X	X	X	
Collect rescue medication									X	X	
End patient participation via IRT										X	X
Discuss further treatment options									X	X	

Source: CSR, Table 1, pgs. 28-29

Population

Key Inclusion Criteria

1. ≥ 12 years of age
2. Asthma diagnosis as defined by the National Institutes of Health ≥ 3 months
3. No asthma exacerbations or changes in asthma medication for at least 30 days
4. FEV1 ≥ 40% predicted
5. 12% reversibility AND ≥ 200 mL increase from baseline in FEV1 (in patients ≥ 18 years of age) within 30 minutes following 2-4 inhalations of albuterol
6. Current asthma therapy: SABA for ≥ 8 weeks, ICS either as ICS or ICS/LABA combination for ≥ 8 weeks. Low-dose ICS without LABA were not eligible for this study. Low-dose ICS/LABA could be entered into the mid-dose ICS treatment arm. Qualifying ICS/LABA doses are listed in **Table 46**.
7. If female, was not currently pregnant, breastfeeding, or attempting to become pregnant, had a negative serum pregnancy test, and was of non-childbearing potential or if childbearing potential, then had to be willing to commit to using acceptable methods of birth control.

The qualifying ICS and ICS/LABA doses are summarized in Table 46.

Table 46. Study 305: Qualifying ICS and ICS/LABA

Qualifying ICS/LABA	**Dosage range (mcg/day)**
Fluticasone/salmeterol HFA	180
Fluticasone/salmeterol DPI	200
Budesonide/formoterol HFA (80 mcg/dose)	160-240
Mometasone/formoterol pMDI (100 or 200 mcg/dose)	200
Fluticasone HFA	>180-460
Fluticasone DPI	>200-500
Budesonide HFA (80, 160, or 320 mcg/dose)	>240-480
Budesonide DPI	>180-720
Beclomethasone dipropionate HFA small particle (eg, QVAR® [a registered trademark of IVAX LLC, a member of the Teva Group], 40 or 80 mcg/dose)	>160-240
Ciclesonide	160-240
Mometasone pMDI (100 or 200 mcg/dose)	>200-400
Mometasone DPI (110 or 220 mcg/dose)	>220-440

Fluticasone HFA	>460
Fluticasone DPI	>500
Budesonide HFA (80, 160, or 320 mcg/dose)	>480
Budesonide DPI	>720
Beclomethasone dipropionate HFA small particle (eg, QVAR, 40 or 80 mcg/dose)	>240
Ciclesonide	>240
Mometasone pMDI (100 or 200 mcg/dose)	>400
Mometasone DPI (110 or 220 mcg/dose)	>440

Source: CSR, Tables 4, 5, 6, pg. 31

Reviewer comment: Compared to the Studies 301 and 30017 patients were required to be on ICS or ICS/LABA for longer (8 weeks vs 4 weeks), although the maintenance/stable dose is 4 weeks. The reversibility criterion is lower (12%) than the Studies 301 and 30017 (15%).

Key Exclusion Criteria

The exclusion criteria were the same as Studies 301 and 30017. For references, see Key Exclusion Criteria for Study 301.

Randomization Criteria

The randomization criteria were the same as Studies 301 and 30017, with the exception of the FEV1 criteria (< 40% predicted as listed in the inclusion criteria without the 85% limit). For reference, see Randomization Criteria for Study 301.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate.

Concomitant medications

The prohibited medications were the same as Studies 301 and 30017. For reference, see Table 17 for Study 301.

Treatment groups

Run-in:

- SABAs were replaced with Proair HFA MDI (90 mcg/actuation).
- ICS or ICS/LABA was continued

Treatment:

- Proair HFA MDI as needed for relief of asthma symptoms
- Subjects were randomized to 1 of 8 treatment groups as described in **Table 47**.

- Subjects on low-dose ICS/LABA were assigned to the mid-dose ICS treatment arm
- Subjects on mid-dose ICS/LABA could be assigned to either mid-dose ICS/LABA or high-dose ICS if the investigator determined the patient was controlled without their LABA before randomization. A 7-day LABA washout occurred before subjects were eligible to join the high-dose ICS treatment arm.

Table 47. Study 305: Treatment Groups

Strength	Treatment Arm	Active Devices	Total Daily Dose (mcg)	Blinding
Medium	A	Fp MDPI 100 mcg	200 mcg	Open-label
	B	FLOVENT HFA 110 mcg	440 mcg	Open-label
High	C	Fp MDPI 200 mcg	400 mcg	Open-label
	D	FLOVENT HFA 220 mcg	880 mcg	Open-label

Strength	Treatment Arm	Active Devices	Total Daily Dose (mcg)	Blinding
Medium	E	FS MDPI 100/12.5 mcg	200/25 mcg	Open-label
	F	ADVAIR DISKUS 250/50 mcg	500/100 mcg	Open-label
High	G	FS MDPI 200/12.5 mcg	400/25 mcg	Open-label
	H	ADVAIR DISKUS 500/50 mcg	1000/100 mcg	Open-label

FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler

Source: CSR, Table 1 and 2, pg. 25

Flovent HFA 110 mcg and Flovent HFA 220 mcg Inhalation Aerosols are marketed in the US by GlaxoSmithKline. Patients in treatment groups B and D were instructed to take 2 puffs twice daily, which provided a daily dose of 440 mcg Fp and 880 mcg Fp, respectively.

Advair Diskus 250/50 contains a dry powder formulation of Fp 250 mcg and salmeterol equivalent to 50 mcg of salmeterol base in a lactose excipient; Advair Diskus 500/50 contains 500 mcg of Fp and 50 mcg of salmeterol base. Patients in treatment groups F and H were instructed to take 1 inhalation twice daily, which provided a daily dose of FS of 500/100 mcg and 1000/100 mcg, respectively.

Safety Endpoints

The primary objective of this study was safety.

Primary Safety Measures and Variables

- Adverse events

- Safety parameters consisted of urine pregnancy tests (every visit), vital signs (pulse and blood pressure – all treatment visits), ECGs (blinded reader at central center; screening and Week 12), physical exam (including body weight and height; screening and Week 12), oropharyngeal exams (all treatment visits), change in medical history, 24-hour urine cortisol (screening, Week 14, and Week 26), and concomitant medication use.

Safety Efficacy Parameters

Withdrawal Due to an Adverse Event
If a patient was withdrawn from the study for multiple reasons that included adverse events, the termination page of the CRF indicated that the withdrawal was related to an adverse event. An exception to this requirement was the occurrence of an adverse event that in the opinion of the investigator was not severe enough to warrant discontinuation, but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation was need to take a prohibited medication, not the adverse event. Patients could also be withdrawn for asthma exacerbation, but this was not recorded as an adverse event unless it met the criteria of a serious adverse event.

Asthma Exacerbations
Asthma exacerbations were not considered adverse events unless they met the definition of a serious adverse event (with the exception of one event that was severe (required systemic steroids for ≥ 3 days), but did not meet SAE criteria, based on an older version of the protocol).

Primary Efficacy Endpoint

- Change from baseline in trough FEV1 over the 26-week treatment period

Other Efficacy Endpoints

- Change from baseline in FVC and FEF 25-75 over the 26-week treatment period
- Time to first asthma exacerbation
- Number of severe asthma exacerbations
- Medication used for worsening asthma (medication days)
- Amount of rescue medication used
- Number and percentage of symptom-free days
- Number and percentage of rescue medication-free days
- Number of withdrawals due to worsening asthma
- Change from baseline in asthma symptoms scores
- Change from baseline in ACT score
- Change from baseline in AM PEF
- Unscheduled office or unscheduled outpatient visits for any reason

- ED and urgent care facility usage for any reasons
- Hospitalization for any reason
- Intercurrent illness and subsequent antibiotic use.

Efficacy Endpoint Parameters

Primary Efficacy Parameter
Trough FEV1 and FEV1 AUC 0-12 hours was measured via spirometry which was conducted based on American Thoracic Society and ERS criteria. All FEV1 data were submitted to a central reading center for evaluation. Spirometry was conducted at screening, Week 0, 1 (baseline), 2, 4, 8, and 12. Albuterol was held for 6 hours prior to spirometry. The baseline spirometry for both the predose FEV1 and the FEV1 AUC 0-12 hours was defined as the average of the 30 minute and 10 minute predose measurements obtained at the randomization visit.

Post-dose serial spirometry was assessed in a subset of subjects (n=312), at 15, and 30 minutes, then 1, 2, 3, 4, 6, 8, 10, and 12 hours. Serial spirometry was stopped if a patient required albuterol treatment for worsening asthma symptoms.

Efficacy Endpoint Parameters

Efficacy endpoint parameters were similar to Studies 301 and 30017, with the follow exceptions.

Asthma Exacerbation
A severe asthma exacerbation was defined as an event requiring systemic corticosteroid use for ≥3 days or hospitalization or an ED visit because of asthma symptoms that required treatment with systemic corticosteroids.

Medications Used for Worsening Asthma
Worsening asthma was based on calculated stability values.

Ethics
An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Monitoring during the course of the study revealed inadequate GCP compliance, gross data quality issues, noncompliance with the protocol, and lack of investigator oversight at investigational center 12143 (Dr. Craig Thurm, MD). Participation in the study was terminated because the investigational center failed to resolve these issues. Because of these problems, data from this investigational center are considered unreliable. However, since this is a safety study, the data were included in the safety population. Because only 8 patients were treated at this investigational center (2 with Fp 100 mcg, 4 with Fp 200 mcg, and 2 with FS 200/12.5 mcg), making up 1.2% of the overall safety population, the problems at the investigational center are unlikely to have compromised the study objectives. The data were also included in the ITT population, which was used for summaries related to study conduct. Data from investigational

center 12143 were excluded from the FAS, which was used for summaries and analyses of efficacy data. Data from 5 patients at this investigational center were also excluded from the urine cortisol analysis subset of the safety population because of questionable start and end dates and times of collection.

Statistical Plan

The full analysis set (all randomized subjects who received at least 1 dose of study drug AND had at least 1 post-baseline trough FEV1 assessment) was used for the efficacy analyses.

Baseline was defined as the last assessment recorded before randomization, unless otherwise specified. For data collected daily in patient diaries, baseline was defined as the average of daily data recorded in the 7 days before randomization. For AM PEF, if 7 days of data were not available, available data from within the 7-day period were used, unless there was less than 4 days of data, in which case data from beyond the 7-day period were used.

Ad hoc analyses were performed for the incidence of all asthma exacerbations and for incidence of severe asthma exacerbations.

Efficacy Analysis

The primary endpoint was analyzed using a MMRM with effects due to baseline FEV1, sex, age, (pooled) investigational center, visit, treatment, and visit-by-treatment interaction. Missing data were not explicitly imputed in the MMRM analyses, but all nonmissing data for a patient were used within the analysis to estimate the time-averaged difference between treatment groups over 26 weeks.

While safety was the primary objective of the study, there was reasonable power for demonstrating non-inferiority of the study drug to the comparator drug within each cohort. The statistical analysis plan specified that non-inferiority would be demonstrated if the lower limit of the 95% CIs for the treatment difference was greater than –125 mL. This range has been used in recent non-inferiority studies in asthma and is well within what has been proposed as a minimally perceivable improvement for asthma therapeutics.(5)

Protocol Amendments

There was 1 amendment made on January 14, 2015 to the protocol when 674 subjects had been enrolled in the study.

The primary reason for the amendment was to change when an asthma exacerbation was to be considered a serious adverse event. An asthma exacerbation, regardless of severity, was to be recorded as an adverse event only if it met the criteria of a serious adverse event. Otherwise they were to be recorded only on the asthma exacerbation page of the CRF. Before the amendment was issued, the definition of a serious adverse event mandated that any severe asthma

exacerbation, defined as an event that required systemic corticosteroid use for ≥3 days or hospitalization or an ED visit because of asthma requiring treatment with systemic Corticosteroids, was required to be reported as a serious adverse event regardless of whether it met the standard criteria for serious adverse events. The amendment removed this requirement, thus instituting more standard criteria for the definition of a serious adverse event.

Safety

Demographics

Overall the demographic characteristics for Study 305 were similar to the four 12- week studies, with a mean range of 38-46 years, predominantly female (52-70%) and Caucasian (62-88%).

Disposition

The disposition of the subjects in Study 305 is listed in Table 48.

Table 48. Study 305 Subject Disposition (Randomized)

n (%)	Fp (mcg; BID)		Flovent HFA (mcg: BID)		FS (mcg; BID)		Advair Diskus (mcg; BID)	
	100 N=127	200 N=126	110 N=42	220 N=41	100/12.5 N=120	200/12.5 N=133	250/50 N=41	500/50 N=44
ITT population	127 (100)	126 (100)	42 (100)	41 (100)	120 (100)	133 (100)	41 (100)	44 (100)
Full analysis set	123 (97)	120 (95)	42 (100)	41 (100)	119 (>99)	130 (98)	40 (98)	44 (100)
Safety population	127 (100)	125 (>99)	42 (100)	41 (100)	120 (100)	133 (100)	41 (100)	44 (100)
Completed study	111 (87)	113 (90)	35 (83)	36 (88)	110 (92)	116 (87)	36 (88)	38 (86)
Discontinued from study	16 (13)	13 (10)	7 (17)	5 (12)	10 (8)	17 (13)	5 (12)	6 (14)
Adverse event	2 (2)	1 (<1)	1 (2)	1 (2)	3 (3)	0	2 (5)	1 (2)
Withdrawal by subject	9 (7)	6 (5)	3 (7)	2 (5)	4 (3)	9 (7)	2 (5)	2 (5)
Noncompliance	1 (<1)	0	2 (5)	0	0	0	0	1 (2)
Protocol Violation	0	0	0	0	0	1 (<1)	0	0
Disease Progression	0	0	0	0	0	2 (2)	0	0
Lost to follow-up	3 (2)	3 (2)	1 (2)	1 (2)	2 (2)	2 (2)	1 (2)	2 (5)
Lack of Efficacy	0	0	0	0	1 (<1)	1 (<1)	0	0
Other	1 (<1)	3 (2)	0	1 (2)	0	2 (2)	0	0

Source: Study 305 CSR, Summary 15.1.1.2, pg. 209

Exposure

The mean duration of exposure ranged from 166 days (23.7 weeks) to 172 (24.5 weeks). Exposure was similar between treatment groups (Table 49).

Table 49. Study 305 Exposure (Safety population)

Duration of Treatment (days)	Fp (mcg; BID)		Flovent HFA (mcg; BID)		FS (mcg; BID)		Advair Diskus (mcg; BID)	
	100	200	110	220	100/12.5	200/12.5	250/50	500/50

	N=127	N=126	N=42	N=41	N=120	N=133	N=41	N=44
Mean (SD)	169 (41)	170 (40)	166 (44)	171 (36)	172 (36)	168 (43)	170 (41)	170 (32)
Source: Study 305 CSR, Table 14, pg. 84								

Deaths

There were no deaths in this 6-month open-label safety study.

SAEs

The incidence of SAEs was similar between the treatment groups within both the ICS and ICS/LABA cohorts. Similar to the four 12-week studies, asthma (exacerbation) was the most frequently reported serious adverse event (n=24 (4%) overall): FS treatment groups (range: 3% to 6%), Fp treatment groups (range: 3% to 5%), Advair groups (range: 2% to 5%), and none of the patients in the Flovent treatment groups. Two patients each reported SAEs of biliary colic (1 patient treated with Fp 100 mcg and 1 patient treated with FS 200/12.5 mcg and pneumonia (1 patient treated with FS 200/12.5 mcg and 1 patient treated with Advair 500/50 mcg. All other serious adverse events occurred in 1 patient each.

AEs leading to discontinuation

A total of 11 patients withdrew due to adverse events, as listed in Table 50 (each letter represents one patient).

Table 50. Study 305 AEs leading to withdrawal (Safety population)								
PT	**Fp (mcg; BID)**		**Flovent HFA (mcg; BID)**		**FS (mcg; BID)**		**Advair Diskus (mcg; BID)**	
	100 N=127	200 N=126	110 N=42	220 N=41	100/12.5 N=120	200/12.5 N=133	250/50 N=41	500/50 N=44
	169 (41)	170 (40)	166 (44)	171 (36)	172 (36)	168 (43)	170 (41)	170 (32)
Asthma	A							K
Dysphonia	B							
URI			C					
Defect conduction intraventricular			D					
Sinus bradycardia			D					
Hypertension				E				
Dizziness					F			
Nausea					F			
Vomiting					F			
GERD					G			
Chest discomfort					H			
Feeling jittery					H			
Cough					H			
Pain in extremity							I	
Allergic rhinitis							J	

Each letter represents one patient. URI = upper respiratory infection, GERD = gastroesophageal reflux disease
Source: ISS, pg. 175

The type and frequency and adverse events leading to discontinuation are similar to the four 12-week studies.

Common AEs

The common adverse events occurring in more than 3% of subjects in either the Fp or FS treatment arms are listed in Table 51.

Table 51. Study 305 Common Adverse Events occurring ≥3% of patients in Fp or FS treatment arms (Safety population)

PT	Fp (mcg; BID)		Flovent HFA (mcg; BID)		FS (mcg; BID)		Advair Diskus (mcg; BID)	
	100 N=127	200 N=126	110 N=42	220 N=41	100/12.5 N=120	200/12.5 N=133	250/50 N=41	500/50 N=44
	169 (41)	170 (40)	166 (44)	171 (36)	172 (36)	168 (43)	170 (41)	170 (32)
Patients with at least 1 AE	85 (67)	83 (66)	29 (69)	29 (71)	92 (77)	86 (65)	29 (71)	30 (68)
URI*	24 (19)	20 (16)	13 (31)	8 (20)	24 (21)	25 (19)	11 (27)	7 (16)
Sinusitis	15 (12)	6 (5)	3 (7)	3 (7)	9 (8)	14 (11)	4 (10)	8 (18)
Nasopharyngitis	17 (13)	13 (10)	7 (17)	5 (12)	15 (13)	12 (9)	4 (10)	4 (9)
Oropharyngeal pain	13 (10)	6 (5)	5 (12)	1 (2)	7 (6)	9 (7)	0	4 (9)
Asthma	6 (5)	4 (3)	0	0	3 (3)	9 (7)	1 (2)	2 (5)
Cough	10 (8)	13 (10)	3 (7)	4 (10)	14 (12)	8 (6)	2 (5)	1 (2)
Bronchitis	5 (4)	5 (4)	3 (7)	1 (2)	4 (3)	7 (5)	1 (2)	1 (2)
Oral candidiasis	6 (5)	5 (4)	0	5 (12)	5 (4)	5 (4)	2 (5)	5 (11)
UTI	3 (2)	2 (2)	0	2 (5)	2 (2)	4 (3)	0	1 (2)
Acute sinusitis	1 (<1)	2 (2)	0	2 (5)	2 (2)	4 (3)	0	1 (2)
Headache	5 (4)	6 (5)	2 (5)	1 (2)	9 (8)	4 (10)	3 (2)	2 (5)
Influenza	10 (8)	8 (6)	2 (5)	5 (12)	7 (6)	3 (2)	2 (5)	1 (2)
Nausea	2 (2)	2 (2)	1 (2)	1 (2)	5 (4)	3 (2)	0	0
Vomiting	1 (<1)	1 (<1)	2 (5)	0	4 (3)	3 (2)	0	0
Pyrexia	3 (2)	3 (2)	1 (2)	0	3 (3)	3 (2)	0	3 (7)
Rhinitis allergic	1 (<1)	2 (2)	0	1 (2)	7 (6)	2 (2)	3 (7)	0
Nasal Congestion	2 (2)	3 (2)	0	2 (5)	3 (3)	0	0	2 (5)
Arthralgia	0	5 (4)	2 (5)	1 (2)	2 (2)	1 (<1)	1 (2)	0
Myalgia	4 (3)	0	0	0	0	1 (<1)	2 (5)	0

URI = upper respiratory infection, UTI = urinary tract infection
*Includes viral URI
Source: NDA 208799 ISS, Table 35, pg. 148-149; NDA 208798 ISS, Table 27, pg. 119; Study 305 CSR, Table 16, pg. 88

The incidence of adverse events was similar between groups, with FS 100/12.5 mcg having the most number of subjects reporting AEs (n=92 (77%)), and the lowest in FS 200/12.5 mcg treatment arm (n=86 (65%)). The most common adverse event was upper respiratory infection occurring in 16 – 31% of subjects. As in the four 12-week studies, oral candidiasis was the only adverse event that appeared to be dose-related. The common adverse events are generally similar to the four 12-week studies and are consistent with the expected safety profile of an ICS and an ICS/LABA for asthma.

7.7.3 Other indications

Another formulation of fluticasone propionate/salmeterol (Advair Diskus 250/50) is approved for the maintenance treatment and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). FS is not being proposed to treat COPD at this time.

8 Postmarketing Experience

Fp and FS have never been marketed, however fluticasone propionate and the combination of fluticasone propionate and salmeterol have been marketed in dry-power inhalers and metered dose inhalers as Flovent Diskus/HFA and Advair Diskus/HFA since 1994 and 2000 respectively.

The post-marketing experience included in the prescribing information for fluticasone propionate and fluticasone propionate/salmeterol products used for the treatment of asthma are as follows:

- Cardiac Disorders: Arrhythmias (including atrial fibrillation, extra systoles, supraventricular tachycardia), ventricular tachycardia.

- Endocrine Disorders: Cushing's syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

- Eye Disorders: Glaucoma.

- Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

- Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

- Infections and Infestations: Esophageal candidiasis.

- Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

- Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

- Nervous System Disorders: Paresthesia, restlessness.

- Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

- Reproductive System and Breast Disorders: Dysmenorrhea.

- Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

- Skin and Subcutaneous Tissue Disorders: Ecchymosis, photodermatitis.

- Vascular Disorders: Pallor.

The post-marketing experience included in the prescribing information for Flovent Diskus and Flovent HFA (and is also proposed to be included in the Fp label) is as follows:

- Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, and throat soreness.
- Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, and osteoporosis.
- Eye: Cataracts.
- Immune System Disorders: Immediate and delayed hypersensitivity reactions, including anaphylaxis, rash, angioedema, and bronchospasm, have been reported. Anaphylactic reactions in patients with severe milk protein allergy have been reported.
- Infections and Infestations: Esophageal candidiasis.
- Psychiatry: Agitation, aggression, anxiety, depression, and restlessness. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.
- Respiratory: Asthma exacerbation, bronchospasm, chest tightness, dyspnea, immediate bronchospasm, pneumonia, and wheeze.
- Skin: Contusions and ecchymosis

9 Appendices

9.1 Literature Review/References

1. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, Buaron KS, Pascoe SJ. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. *N Engl J Med* 2016; 374: 1822-1830.
2. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, Kosinski M, Pendergraft TB, Jhingran P. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549-556.
3. NAEPP. Expert Panel Report EPR 3 Guidelines for the Diagnosis and Management of Asthma, National Asthma Education and Prevention Program; 2007.
4. Stohs SJ, Hartman MJ. Review of the Safety and Efficacy of Moringa oleifera. *Phytother Res* 2015; 29: 796-804.
5. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.

9.2 Labeling Recommendations

Trade Name:

The trade name SPIROMAX ® was used when the 12-week Fp dose-ranging studies (201 and 202), the salmeterol dose-ranging study (FSS-201), and the some of the early PK studies (FpS-AS-101 and FpS-AS-102) were conducted. (b) (4) .

The proposed trade name for Fp MDPI, ArmonAir RespiClick, and for FS MDPI, AirDuo RespiClick, has been reviewed by the Office of Medication Error Prevention and Risk Management, under the Office of Surveillance and Epidemiology and was determined to be acceptable.

Suggested Revisions to Proposed Labeling

While the labeling has not been finalized at the time this review is being completed, we have proposed the following general recommendations as summarized in **Table 52**.

Table 52. Labeling recommendations

Label Section	**General Recommendations**
Section 1 Indications and Usage	• Fp: (b) (4) • Fp: Generalize indication from 'Maintenance treatment of asthma as prophylactic therapy' to 'Treatment of asthma'
Section 2 Dosage and Administration	• (b) (4) .
Section 6 Adverse Reactions	• Consider including inhaled corticosteroid growth studies
Section 14	• Add in two 12-week dose-ranging study results • (b) (4) • (b) (4)

9.3 Advisory Committee Meeting

This application is for a lower dosing regimen with the same route of administration for fluticasone propionate and the combination of fluticasone propionate/salmeterol, which is already approved for the treatment of asthma; therefore an Advisory Committee Meeting was not warranted.

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/s/

MIYA O PATERNITI
10/25/2016

BANU A KARIMI SHAH
10/26/2016