Office of Clinical Pharmacology Integrated Review	
NDA Numbers:	NDAs 208798 and 208799
Associated INDs:	NDA 208798: IND 108838 NDA 208799: IND 72240
Link to EDR:	NDA208798: \\CDSESUB1\evsprod\NDA208798\208798.enx NDA208799: \\CDSESUB1\evsprod\NDA208799\208799.enx
Submissions Date:	NDA208798: 03/28/2016 NDA208799: 03/29/2016
Submission Type:	Standard 505(b)(2)
Proposed Brand Name:	NDA208798: ArmonAir RespiClick NDA208799: AirDuo RespiClick
Generic Name:	NDA208798: Fluticasone Propionate NDA208799: Fluticasone Propionate and Salmeterol Xinafoate
Applicant:	Teva
Route of Administration:	Oral inhalation
Dosage Form and strength:	NDA 208798: powder, for inhalation (55 mcg, 113 mcg, or 232 mcg) NDA 208799: powder, for inhalation (55/14 mcg, 113/14 mcg and 232/14 mcg)
Proposed Dosing Regimen:	NDA 208798: One inhalation of fluticasone propionate inhalation powder 55 mcg, 113 mcg, or 232 mcg twice daily. NDA 208799: One inhalation of fluticasone propionate/ salmeterol xinafoate inhalation powder 55/14 mcg, 113/14 mcg and 232/14 mcg twice daily.
Proposed Indication(s):	NDA208798 ▪ For the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older ▪ Not for the relief of acute bronchospasm NDA208799 ▪ For treatment of asthma in patients aged 12 years and older ▪ Not for the relief of acute bronchospasm
OCP Review Team:	Lei He PhD., Anshu Marathe PhD. (Team Leader)

1. Executive Summary

Teva has submitted NDA 208798 (fluticasone propionate (Fp) inhalation powder) and NDA 208799 (fluticasone propionate/salmeterol xinafoate (FS) inhalation powder), under 505(b)2 pathway seeking the marketing approval for Fp multidose dry powder inhaler (MDPI) and FS MDPI using FLOVENT DISKUS (fluticasone propionate inhalation powder, GSK) and ADVAIR DISKUS (fluticasone propionate and salmeterol xinafoate inhalation powder, GSK) as reference product, respectively. Both products are proposed "*for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Not indicated for the relief of acute bronchospasm*". The sponsor supports both NDA submissions with 6 clinical pharmacology studies.

Comparison of the proposed products, Fp MDPI and FS MDPI, with their corresponding reference products are shown in Tables 1 and 2. The proposed dosage strengths are 55, 113, and 232 mcg for Fp MDPI and 55/14, 113/14, and 232/14 mcg for FS MDPI. The proposed dosing regimens are 55, 113, and 232 mcg twice daily (BID) for Fp MDPI and 55/14, 113/14, and 232/14 mcg BID for FS MDPI. Note that the corresponding nominal dosage, 50, 100, and 250 mcg for Fp MDPI, and 50/12.5, 100/12.5, and 200/12.5 mcg for FS MDPI will be used throughout this review.

Also note that the trade name SPIROMAX® was used at the time of the Phase I and II studies (b) (4)

Table 1. Comparison of the proposed Fp MDPI and FLOVENT DISKUS

	NDA 208798	**NDA 020833 (Reference)**
Drug Product	Fp inhalation powder	FLOVENT DISKUS (Fp inhalation powder, GSK)
Device	Teva's device	FLOVENT DISKUS inhaler
Route of administration	Oral inhalation	Oral inhalation
Strength	50, 100, 200 mcg	50, 100, and 250 mcg
Dosing Regimen	Patients aged ≥12 years: 50, 100, 200 mcg BID	Dosing is based on prior asthma therapy. Patients aged ≥12 years: • Recommended starting dosage: 100-1000 mcg BID • Highest recommended dosage: 500-1000 mcg BID Patients aged 4-11 years: • Recommended starting dosage: 50 mcg BID • Highest recommended dosage: 100 mcg BID
Indications	• Maintenance treatment of asthma as prophylactic therapy in patients ≧12 years • (b) (4) • Not for relief of acute bronchospasm	• Maintenance treatment of asthma as prophylactic therapy in patients ≧4 years • Asthma patients requiring oral corticosteroid • Not for relief of acute bronchospasm

Table 2. Comparison of the proposed FS MDPI and ADVAIR DISKUS

	NDA 208799	**NDA 021077 (Reference)**
Drug Product	FS inhalation powder	ADVAIR DISKUS (FS inhalation powder, GSK)
Device	Teva's MDPI	ADVAIR DISKUS inhaler
Route of administration	Oral inhalation	Oral inhalation
Strength	50/12.5, 100/12.5, and 200/12.5 mcg	100/50, 250/50, and 500/50 mcg
Dosing Regimen	Asthma patients aged ≥12 years: 50/12.5, 100/12.5, and 200/12.5 mcg BID	Asthma patients aged ≥12 years: 100/50, 250/50, and 500/50 mcg. Starting dosage is based on asthma severity. Asthma patients aged 4-11 years: 100/50 mcg BID Maintenance treatment of COPD: 250/50 mcg BID
Indication	• Treatment of asthma ≥12 years • Not for the relief of acute bronchospasm	• Treatment of asthma ≥4 years • Maintenance treatment of airflow obstruction and reducing exacerbations in COPD • Not for the relief of acute bronchospasm

The following are the major findings of the current review:

Teva has developed Fp MDPI and FS MDPI, to deliver lower doses of Fp in the Fp MDPI, Fp and salmeterol xinafoate (Sx) in the FS MDPI than their corresponding reference products, FLOVENT DISKUS and ADVAIR DISKUS, while achieve similar or lower systemic exposure and similar efficacy.

1) Following the administration of the proposed products, Fp MDPI and FS MDPI, the systemic exposures of Fp and Sx were similar or lower compared to their corresponding reference products in asthma patients (Study FSS-AS-10042).

   Fp MDPI

   - Following the single dose administration of Fp MDPI (200 mcg×1 inhalation, the proposed highest dose) and FLOVENT DISKUS (250 mcg×2 inhalation (500 mcg total dose), note that the highest recommended dose is up to 1000 mcg depending on prior therapy), the systemic exposure (Cmax, AUC0-t, and AUC0-∞) of Fp were ~20-30% lower with Fp MDPI compared to FLOVENT DISKUS.

   FS MDPI

   - For Fp, following the single dose administration of FS MDPI (200/12.5 mcg×1 inhalation, the proposed highest dose), and ADVAIR DISKUS (500/50 mcg×1 inhalation, the highest recommended dose), the systemic exposure (Cmax, AUC0-t, and AUC0-∞) of Fp were similar between FS MDPI and ADVAIR DISKUS.

   - For Sx, following the single dose administration of FS MDPI (200/12.5 mcg×1 inhalation, the proposed highest dose) and ADVAIR DISKUS (500/50 mcg×1 inhalation, the highest

recommended dose), the systemic exposure (Cmax, AUC0-t, and AUC0-∞) to Sx was ~20% - 50% lower with FS MDPI compared with ADVAIR DISKUS, respectively.

2) Although the accumulation of Fp and Sx is expected to occur following BID administration of Fp MDPI and FS MDPI given the half-lives of Fp (T1/2 ~11 hours) and Sx (T1/2 ~12 hours), the systemic exposures of Fp and Sx are still expected to be lower or similar to their reference products. Therefore, some relevant information for Fp and Sx, including pharmacokinetics (PK), drug interaction, PK in special populations, systemic safety and others, could rely on the approved US labeling for FLOVENT DISKUS and ADVAIR DISKUS.

3) The dosing regimens of Fp MDPI (12.5, 25, 50, 100, 200 and 400 mcg) and FS MDPI (100/6.25, 100/12.5, 100/25, and 100/50 mcg) have been explored in three Phase II dose-ranging trials (Study FpS-AS-201, FpS-AS-202 and FSS-AS-201) in asthma patients. In one dose-ranging study for Fp MDPI (12.5, 25, 50, 100 mcg), an indication of dose response was observed based on trough FEV1 from baseline over 12-week treatment period. In the other dose-ranging study for Fp MDPI (50, 100, 200 and 400 mcg), 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 to the stopping criteria issue. In addition, the dose-ranging trial for FS MDP demonstrated a dose-related increase in baseline-adjusted FEV1 AUC0-12. Thus, the dosing regimens, 50, 100, and 200 mcg BID for Fp MDPI and 50/12.5, 100/12.5, and 200/12.5 mcg BID for FS MDPI, were selected for confirmation in two Phase III efficacy studies in asthma patients.

4) In both Phase III studies, in terms of the primary efficacy endpoints (Trough FEV1 and FEV1 AUC0-12h at Week 12), all the proposed doses for Fp MDPI (50, 100, and 200 mcg BID) and FS MDPI (50/12.5, 100/12.5, and 200/12.5 mcg BID) showed a clinically meaningful improvement (>0.100 L) compared to placebo. With the same dose of Fp in Fp MDPI and FS MDPI, FS MDPI showed additional clinical benefit compared to Fp MDPI. The primary efficacy endpoints for Fp MDPI showed a dose dependent increase numerically, however, the observed difference between doses appears not clinically meaningful. For FS MDPI, no apparent dose-dependent trend in the primary efficacy endpoints was observed. Please refer to the Clinical Review by Dr. Miya Paterniti and the Statistical Review by Dr. Yu Wang regarding the final risk/benefit assessment for the proposed doses for Fp MDPI and FS MDPI based on the efficacy and safety analysis of Phase III studies.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 208798 and NDA 208799 and finds the applications acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Fp is a synthetic trifluorinated corticosteroid with anti-inflammatory activity and Sx is a long-acting β2 agonist (LABA).

Teva has developed Fp MDPI and FS MDPI, using FLOVENT DISKUS (fluticasone propionate inhalation powder, GSK) and ADVAIR DISKUS (fluticasone propionate and salmeterol xinafoate inhalation powder, GSK) as reference product, respectively. Both Fp MDPI and FS MDPI are proposed "*for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. It is not indicated for the relief of acute bronchospasm."* The proposed dosing regimens are 50, 100, and 200 mcg BID for Fp MDPI and 50/12.5, 100/12.5, and 200/12.5 mcg BID for FS MDPI.

The Sponsor supports these two NDA submissions with 6 clinical pharmacology studies, including 3 PK studies and 3 dose-ranging studies.

Rationale for Dosing Regimen Selection

Teva has developed Fp MDPI and FS MDPI, to deliver lower doses of Fp in the Fp MDPI, and Fp and Sx in the FS MDPI than their corresponding reference products, FLOVENT DISKUS and ADVAIR DISKUS, while achieve similar or lower systemic exposure and similar efficacy.

The dosing regimens of Fp MDPI and FS MDPI have been explored in three Phase II dose-ranging trials and one Phase I PK study (FSS-AS-10042) in asthma patients before proceeding to two Phase III efficacy studies in asthma patients.

Fp MDPI dose-ranging studies

Two dose ranging studies were conducted and 50, 100, 200 mcg BID were selected as the dosing regimens for Fp MDPI and Fp in the combination product FS MDPI.

- In Study FpS-AS-201, all treatment groups (Fp MDPI 12.5, 25, 50, and 100 mcg, and FLOVENT DISKUS 100 mcg) showed an increase in trough FEV1 from baseline over 12-week treatment period with an indication of a dose response. In the comparison with placebo, clinically significant (>0.100 L) change in trough FEV1 was observed for Fp MDPI 25, 50, and 100 mcg and FLOVENT DISKUS 100 mcg, but not for Fp MDPI 12.5 mcg group. In addition, compared with FLOVENT DISKUS 100 mcg, Fp MDPI 50 mcg produced similar change in trough FEV1 but much lower systemic exposure.
- In Study FpS-AS-202, which include all 3 proposed doses (50, 100, and 200 mcg), no Fp dose was significantly different than Flovent Diskus 250 mcg. 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 to the stopping criteria issue. For more detailed information, refer to the Type B End-Of-Phase 2 meeting minutes (dated March 17, 2014 in DARRTS), the Clinical Review by Dr. Miya Paterniti, and the Statistical Review by Dr. Yu Wang.

FS MDPI dose-ranging study

- One dose-ranging trial for FS MDPI, Study FSS-AS-201, was conducted in patients with asthma. Following a single dose of FS MDPI at 100/6.25, 100/12.5, 100/25, and 100/50 mcg, the baseline-adjusted FEV1 AUC0-12 demonstrated a dose-related increase. The increase in FEV1 AUC0-12 following FS MDPI 100/12.5 was comparable to ADVAIR DISKUS 100/50 mcg and therefore was selected for further testing in Phase III studies.

PK Study FSS-AS-10042

Following the single dose administration of Fp MDPI (200 mcg×1 inhalation, the proposed highest dose), FS MDPI (200/12.5 mcg×1 inhalation, the proposed highest dose), FLOVENT DISKUS (250 mcg×2 inhalation, note that the highest recommended dose is even up to 1000 mcg depending on the prior asthma

therapy), and ADVAIR DISKUS (500/50 mcg×1 inhalation, the highest recommend dose), the systemic exposures of Fp in Fp MDPI, Fp and Sx in FS MDPI are similar or lower compared with the corresponding reference products.

Please refer to the Clinical Review by Dr. Miya Paterniti and the Statistical Review by Dr. Yu Wang regarding the final risk/benefit assessment for the proposed doses for Fp MDPI and FS MDPI based on the efficacy and safety analyses of Phase III studies.

Pharmacokinetics

NDAs 208798 (Fp inhalation powder) and 208799 (FS inhalation powder) were submitted under 505(b)2 pathway referencing FLOVENT DISKUS and ADVAIR DISKUS, respectively. The intent of PK assessment in these two NDAs was to compare the systemic exposures of Fp and Sx after the administration of Fp MDPI and FS MDPI to their corresponding reference products.

Fp

- Following the single dose administration of of Fp MDPI (200 mcg×1 inhalation), FS MDPI (200/12.5 mcg×1 inhalation), FLOVENT DISKUS (250 mcg×2 inhalation) and ADVAIR DISKUS (500/50 mcg×1 inhalation), the systemic exposure (Cmax, AUC0-t, and AUC0-∞) to Fp were ~20-30% lower with Fp MDPI than FLOVENT DISKUS, but were similar between FS MDPI and ADVAIR DISKUS
- Following oral inhalation of Fp MDPI, FS MDPI, or their reference products, FLOVENT DISKUS and ADVAIR DISKUS, Tmax of Fp is approximately 1 to 2 hours. The elimination half-life of Fp is approximately 11 hours. Over a dose range of Fp MDPI 12.5 to 400 mcg, the increases in Fp AUC0-t are approximately dose proportional while those for Cmax are slightly less than dose proportional. For Fp MDPI 50, 100, and 200 mcg doses, both AUC0-t and Cmax for Fp increase approximately dose-proportionally.
- The systemic exposure of Fp is similar between Fp MDPI and FS MDPI, suggesting the presence of Sx in FS MDPI does not affect Fp PK.

Sx

- Following the single dose administration of FS MDPI (200/12.5 mcg×1 inhalation) and ADVAIR DISKUS (500/50 mcg×1 inhalation), the Cmax and AUC of Sx was ~20% and 50% lower with FS MDPI compared with ADVAIR DISKUS, respectively.
- Following oral inhalation of FS MDPI or the reference product, ADVAIR DISKUS, the Tmax of Sx is approximately 0.07 to 2 hours. The elimination half-life of Sx is approximately 12 hours.
- Over a dose range of FS MDPI 100/6.25 to 100/50 mcg, the increases in Sx AUC0-t and Cmax were slightly greater than dose proportional. For FS MDPI 100/6.25, 100/12.5, and 100/25 mcg doses, both AUC0-t and Cmax for Sx increased in an approximately dose proportional manner.

2. Question Based Review

Teva submitted NDAs 208798 (Fp inhalation powder) and 208799 (FS inhalation powder) under 505(b)2 pathway referencing FLOVENT DISKUS and ADVAIR DISKUS, respectively. The intent of PK assessment in these two NDAs was to compare the systemic exposure of Fp and Sx after the administration of Fp MDPI and FS MDPI to their corresponding reference products. Only relevant information based on studies submitted in these two NDAs will be reviewed in this document.

Note that the proposed dosing regimens are 55, 113, and 232 mcg BID for Fp MDPI, and 55/14, 113/14, and 232/14 mcg BID for FS MDPI. The corresponding nominal dosage, 50, 100, and 250 mcg for Fp MDPI, and 50/12.5, 100/12.5, and 200/12.5 mcg for FS MDPI will be used throughout this review.

Also note that the trade name SPIROMAX® was used at the time of the Phase I and II studies (b) (4)

2.1 Regulatory History

FLOVENT DISKUS (50mcg, 100 mcg, and 200 mcg fluticasone propionate inhalation powder, GSK) was approved under NDA 020833 for "*the maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients 4 years of age and older; it is also indicated for patients requiring oral corticosteroid therapy for asthma*; *not indicated for the relief of acute bronchospasm.*"

ADVAIR DISKUS (100/50 mcg, 250/50 mcg, and 500/50 mcg fluticasone propionate and salmeterol xinafoate inhalation powder, GSK) was approved under NDA 021077 for the "*treatment of asthma in patients aged 4 years and older; maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD); not indicated for the relief of acute bronchospasm.*"

Teva submitted NDA 208798 (Fp inhalation powder) and NDA 208799 (FS inhalation powder), under 505(b)2 pathway on March 28, 2016 and March 29, 2016, respectively, seeking the marketing approval for Fp MDPIand FS MDPI using FLOVENT DISKUS and ADVAIR DISKUS as reference product, respectively. Both products are proposed "*for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Not indicated for the relief of acute bronchospasm".* The sponsor supports both NDA submissions with 6 clinical pharmacology studies.

2.2 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

The clinical pharmacology studies submitted under NDA 208798 and NDA208799 are summarized in Table 3, including three PK studies and three dose-ranging studies.

Table 3. Summary of clinical pharmacology studies

	Study ID	Objectives	Population	Study Design	Treatment and Device
PK study	FpS-AS-101	Pilot PK, safety	HVs (n=18)	R, OL, 3-period crossover, SD	Fp MDPI: 400mcg×2 Inh. FLOVENT DISKUS: 250 mcg×4Inh. FLOVENT HFA: 220mcg×4 Inh.
	FpS-AS-102	Pilot PK, safety	Japanese HVs (n=15) and Caucasian HVs (n=15)	R, OL, 3-period crossover, SD	Fp MDPI: 100mcg×4 Inh. Fp MDPI: 200mcg×4 Inh. FLOVENT DISKUS: 100mcg×4 Inh.
	FSS-AS-10042	PK, tolerability	Asthma patients ≥12 yr (n=43)	R, OL, 4-period crossover, SD	Fp MDPI: 200mcg×1 Inh. FS MDPI: 200/12.5 mcg×1 Inh. FLOVENT DISKUS: 250 mcg×2 Inh. ADVAIR DISKUS: 500/50mcg×1 Inh.
Dose-ranging study	FpS-AS-201	Dose-ranging, PK, efficacy, safety	Asthma patients ≥12 yr (n=622)	R, DB, OL, PC, parallel group, MD, 12-week treatment	Fp MDPI: 12.5mcg×1 Inh. BID Fp MDPI: 25mcg×1 Inh. BID Fp MDPI: 50mcg×1 Inh. BID Fp MDPI: 100mcg×1 Inh. BID FLOVENT DISKUS: 100 mcg×1 Inh. BID
	FpS-AS-202	Dose-ranging, PK, efficacy, safety	Asthma patients ≥12 yr (n=640)	R, DB, OL, PC, parallel group, MD, 12-week treatment	Fp MDPI: 50mcg×1 Inh. BID Fp MDPI: 100mcg×1 Inh. BID Fp MDPI: 200mcg×1 Inh. BID Fp MDPI: 400mcg×1 Inh. BID FLOVENT DISKUS: 250 mcg×1 Inh. BID
	FSS-AS-201	Dose-ranging, PK, efficacy, safety	Asthma patients ≥13 yr (n=72)	R, MC, DB, OL, PC, SD, 6-period crossover	Fp MDPI: 100 mcg×1 Inh. FS MDPI: 100/6.25 mcg×1 Inh. FS MDPI: 100/12.5 mcg×1 Inh. FS MDPI: 100/25 mcg×1 Inh. FS MDPI: 100/50 mcg×1 Inh. ADVAIR DISKUS: 100/50 mcg×1 Inh.

*HVs: healthy volunteers; R: randomized; OL: open label; DB: double blind; SD: single dose; MD: multiple dose; BID: twice daily; PC: positive control; Fp: Fluticasone propionate; FS: Fluticasone propionate/ Salmeterol xinafoate; MDPI: multidose dry powder inhaler; Inh.: inhalation.

**Note that the proposed commercial blends [redacted] kg scale) and commercial device (NB7/3 device variant) were used in PK study FSS-AS-10042 and all Phase III studies, but not other studies.

2.3 General Attributes of the Drug

2.3.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

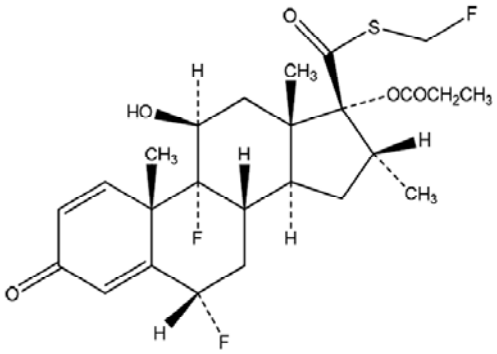
Drug Substance

Fp and Sx are both small molecule drugs. Their structures are shown in Figure 1.

Fp is a fine white powder. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol. Its molecular formula is $C_{25}H_{31}F_3O_5S$ and the molecular weight is 500.6.

Sx is a white to off-white fine powder. It is freely soluble in methanol; slightly soluble in ethanol and sparingly soluble in water. Its molecular formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ and the molecular weight is 603.75.

Fluticasone Propionate



Salmeterol Xinafoate

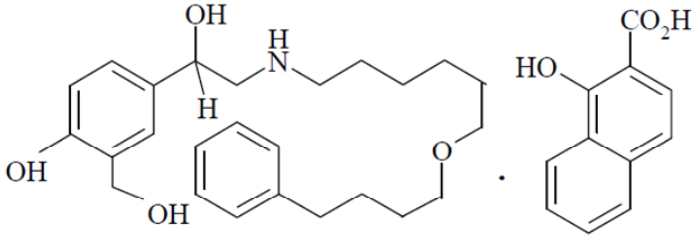


Figure 1. Molecular structure of fluticasone propionate and salmeterol xinafoate
(Source: Module 3.2.S and 3.2.P, EDRs of NDAs 208798 and 208799)

Drug Product

Both proposed Fp MDPI and FS MDPI products have three strengths. The metered, delivered, and norminal doses across products are summarized in the table as below.

Table 4. Summary of metered, delivered, and nominal doses across products and devices administered twice daily to adolescents and adults

Product	Metered Doses Per Inhalation (mcg)	Delivered Doses Per Inhalation (mcg)	Nominal Doses Per Inhalation (mcg)	Total Daily Doses (mcg)
Fp MDPI[a]	55, 113, 232	51, 103, 210	50, 100, 200	110 to 464
FLOVENT DISKUS[b]	50, 100, 250	46, 94, 229	-	200 to 2000
FLOVENT HFA[c]	50, 125, 250	44, 110, 220	-	176 to 1760
FS MDPI[a]	55/14, 113/14, 232/14	49/12.75, 100/12.75, 202/12.75	50/12.5, 100/12.5, 200/12.5	110/28 to 464/28
ADVAIR DISKUS[a]	100/50, 250/50, 500/50	93/45, 233/45, 465/45	-	200/100 to 1000/100

(Source: Table 1, Clinical Overview of NDA208799)

Fp MDPI product is an inhalation driven, reservoir type, multidose dry powder inhaler containing a blend of fluticasone propionate as the active pharmaceutical ingredient and lactose monohydrate as the excipient (Table 5). Each actuation represents one therapeutic dose of the product. The Fp MDPI device is white except for the mouthpiece cover which has a translucent green color. Each inhaler consists of an assembly of the following main components: (b) (4) .

Table 5. Composition of each inhaler of Fp MDPI products

Ingredient	55 mcg		113 mcg		232 mcg		Function	Reference to Standards
	Amount (mg)	% w/w	Amount (mg)	% w/w	Amount (mg)	% w/w		
Fluticasone propionate, (b) (4)	(b) (4)						Active ingredient	USP
Lactose monohydrate							(b) (4)	USP-NF
Target fill weight per inhaler[a]								

[a] A justification of the fill weight per inhaler is provided in Section 3.2.P.2.2 Drug Product.
(Source: Module 3.2.P, EDR of NDA 208798)

FS MDPI is an inhalation driven, reservoir type, multidose dry powder inhaler containing a blend of Fp and Sx as the active pharmaceutical ingredients, and lactose monohydrate as the excipient (Table 6). Each actuation represents one therapeutic dose of the product. The FS MDPI device is white except for the mouthpiece cover which has a translucent yellow color. Each inhaler consists of an assembly of the following main components: Upper Case Assembly, Bellows and Yoke Assembly, Filter, and Lower Case Assembly.

Table 6. Composition of Each Inhaler of FS MDPI Products

Ingredient	55/14 mcg		113/14 mcg		232/14 mcg		Function	Reference to Standards
	Amount	% w/w	Amount (mg)	% w/w	Amount (mg)	% w/w		
Fluticasone propionate, (b) (4)	(b) (4)						Active ingredient	USP
Salmeterol xinafoate, micronized[a]							Active ingredient	USP
Lactose monohydrate							(b) (4)	USP-NF
Target fill weight per inhaler[b]								

(Source: Module 3.2.P, EDR of NDA 208799)

2.3.2 What are the proposed mechanism of action and therapeutic indications?

Fp is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. Sx is a long-acting β2 agonist (LABA).

Both Fp MDPI and FS MDPI are proposed "*for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. It is not indicated for the relief of acute bronchospasm.*"

2.3.3 What are the proposed dosages and routes of administration?

Fp MDPI is supplied in multiple dosage strengths of Fp (50, 100, and 200 mcg) and is proposed to be administered BID through oral inhalation to deliver doses of 51, 103, and 210 mcg.

FS MDPI is supplied in multiple dosage strengths of Fp with a fixed dosage of Sx (50/12.5, 100/12.5, and 200/12.5 mcg) and is proposed to be administered BID through oral inhalation to deliver doses of 49/12.75, 100/12.75, and 202/12.75 mcg.

2.3.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The drugs which are approved for long term treatment of asthma in the US can be classified into the following classes:

1. *ICS:* fluticasone furoate (Arnuity), budesonide(Pulmicort), fluticasone propionate (Flovent), mometasone (Asmanex), beclomethasone (Qvar), ciclesonide(Alvesco)

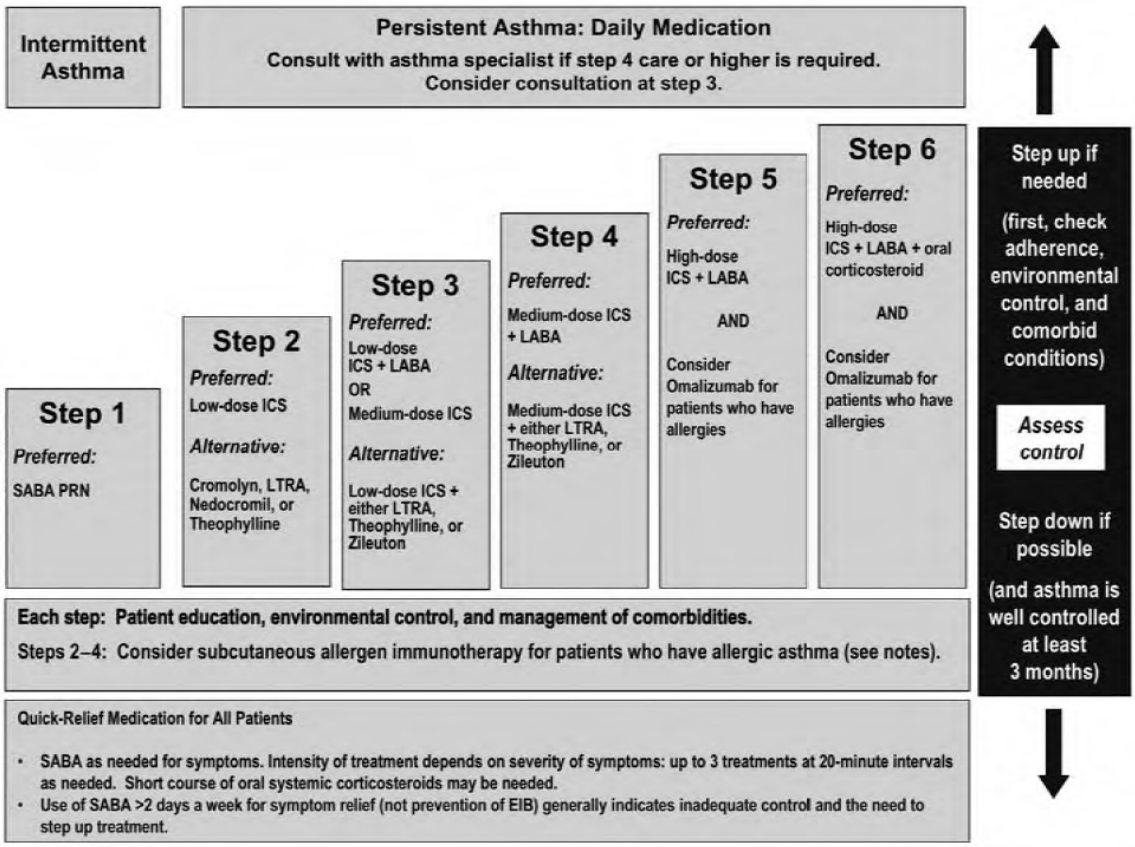
2. *LABA:* salmeterol (Serevent), formoterol (Foradil, Perforomist)

3. *ICS/LABA Combinations:*
   - fluticasone propionate+ salmeterol (Advair)
   - budesonide+ formoterol (Symbicort)
   - mometasone+formoterol (Dulera)
   - fluticasone furoate+vilanterol (Breo)

4. *Other medications*

- Leukotriene modifiers
  - LTRA: montelukast (Singulair), zafirlukast (Accolate)
  - 5-lipoxygenase inhibitor: zileuton (Zyflo)
- Immunomodulators: omalizumab (Xolair)
- Mast cell stabilizers: cromolyn sodium and nedocromil
- Systemic corticosteroid
- Methylxanthines: theophylline

Guidelines for the diagnosis and management of asthma were summarized in the diagram below:



(Source – Table 11, Guidelines for the diagnosis and management of asthma, summary report 2007)

2.4 General Clinical Pharmacology

2.4.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Teva has developed Fp MDPI and FS MDPI, to deliver lower doses of Fp in the Fp MDPI, and Fp and Sx in the FS MDPI than their corresponding reference products, FLOVENT DISKUS and ADVAIR DISKUS, while achieve similar or lower systemic exposure and similar efficacy.

The clinical pharmacology studies in the Fp MDPI and FS MDPI development programs include two pilot PK studies, one pivotal PK study, and three dose-ranging studies to establish the appropriate doses for each component before proceeding to Phase III studies. The dosing regimens, Fp MDPI 50, 100, and 200 mcg BID and FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg BID were selected for further evaluation in Phase III program.

PK study for Fp MDPI and FS MDPI

- Study FSS-AS-10042 is multicenter, open-label, randomized, 4-period crossover, single-dose study to determine the PK and tolerability of high strength Fp MDPI and FS MDPI compared to high strength FLOVENT DISKUS and ADVAIR DISKUS in asthma patients. The evaluated treatments include:
    - Fp MDPI 200 mcg, 1 inhalation
    - FS MDPI 200/12.5 mcg, 1 inhalation
    - FLOVENT DISKUS 250 mcg, 2 inhalations
    - ADVAIR DISKUS 500/50 mcg, 1 inhalation

Fp MDPI Dose-Ranging Studies

Two dose ranging studies were conducted and 50, 100, 200 mcg BID were selected as the dosing regimens for Fp MDPI and Fp in the combination product FS MDPI.

- Study FpS-AS-201 is a Phase II, randomized, double-blind, placebo- and open-label active-controlled, parallel-group, multicenter, 12-week dose-ranging study in asthma patients. The evaluated treatments include:
    - Fp MDPI 12.5 mcg, 1 inhalation, BID
    - Fp MDPI 25 mcg, 1 inhalation, BID
    - Fp MDPI 50 mcg, 1 inhalation, BID
    - Fp MDPI 100 mcg, 1 inhalation, BID
    - FLOVENT DISKUS 100 mcg, 1 inhalation, BID

- Study FpS-AS-202 is a Phase II, randomized, double-blind, placebo- and open-label active-controlled, parallel-group, multicenter, 12-week dose-ranging study in asthma patients. The evaluated treatments include:
    - Fp MDPI 50 mcg, 1 inhalation, BID
    - Fp MDPI 100 mcg, 1 inhalation, BID
    - Fp MDPI 200 mcg, 1 inhalation, BID
    - Fp MDPI 400 mcg, 1 inhalation, BID
    - FLOVENT DISKUS 250 mcg, 1 inhalation, BID

FS MDPI Dose-Ranging Study

One dose ranging study was conducted and 12.5 mcg was selected as the dose for Sx component in the combination product FS MDPI.

- Study FSS-AS-201 is a multicenter, randomized, double-blind and open-label active-controlled, single-dose, 6-period crossover, dose-ranging study in asthma patients. The evaluated treatments include:
    - FS MDPI 100/6.25 mcg , 1 inhalation
    - FS MDPI 100/12.5 mcg, 1 inhalation
    - FS MDPI 100/25 mcg, 1 inhalation
    - FS MDPI 100/50 mcg, 1 inhalation
    - Fp MDPI 100 mcg, 1 inhalation
    - ADVAIR DISKUS 100/50 mcg, 1 inhalation

The clinical pharmacology and biopharmaceutics studies supporting these two NDAs and their design features are listed under Section 2.1.

2.4.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Trough FEV1 was selected as the primary endpoint in Phase II dose ranging studies for Fp MDPI (Studies Fp-AS-201 and Fp-AS-202). Baseline-adjusted FEV1 $AUC_{0\text{-}12h}$ was selected as the primary endpoint in Phase II dose ranging study for FS MDPI (Study FS-AS-201). Both trough FEV1 and baseline-adjusted FEV1 $AUC_{0\text{-}12h}$ were selected as the primary endpoints for the Phase 3 studies, claiming lung function improvement. Both clinical endpoints have also been used in the development programs of other ICS/LABA for asthma.

2.4.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure response relationships?

In all relevant studies, only fluticasone and salmeterol concentrations in plasma were measured. No metabolites were quantified because the metabolites of fluticasone and salmeterol are not active and are not associated with efficacy or safety.

2.5 Dose/Exposure-Response

2.5.1 What are the characteristics of the exposure-response relationship for effectiveness?

For inhaled Fp and Sx, the systemic exposure is not directly related to clinical response (FEV1).

2.5.2 Have the dosing of Fp MDPI and FS MDPI been adequately explored?

The dosing regimens of Fp MDPI and FS MDPI have been explored in three Phase II dose-ranging trials and one Phase I PK study FSS-AS-10042 in asthma patients. The dosing regimens, 50, 100, and 200 mcg BID for Fp MDPI and 50/12.5, 100/12.5, and 200/12.5 mcg BID for FS MDPI, were further tested in Phase III studies in asthma patients.

Fp MDPI dose-ranging studies

Two dose-ranging trials for Fp MDPI, Studies FpS-AS-201 and FpS-AS-202, have been conducted in asthma patients.

In Study FpS-AS-201, all treatment groups (Fp MDPI 12.5, 25, 50, and 100 mcg, and FLOVENT DISKUS 100 mcg) showed an increase in LS mean FEV1 from baseline over the 12-week treatment period with an indication of a dose response. In the comparison of placebo versus each Fp MDPI dose, the change from baseline in trough FEV1 over the 12-week treatment period was clinically significant (>0.100 L) for Fp MDPI 25, 50, and 100 mcg and FLOVENT DISKUS 100 mcg groups, but not for Fp MDPI 12.5 mcg group. In addition, compared with FLOVENT DISKUS 100 mcg, Fp MDPI 50 mcg produced similar change in trough FEV1 but much lower systemic exposure (Tables 7 and 8).

In Study FpS-AS-202, which include all 3 proposed doses (50, 100, and 200 mcg), no Fp dose was significantly different than Flovent Diskus 250 mcg. Only the Fp 200 mcg dose appears significantly different from placebo and is the proposed high-dose for Fp. 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 to the stopping criteria issue. However, the systemic exposure of Fp appears comparable to that in Study FpS-AS-201 (Tables 9 and 10). For detailed information, refer to the Type B End-Of-Phase 2 meeting minutes (dated March 17, 2014 in DARRTS), the Clinical Review by Dr. Miya Paterniti, and the Statistical Review by Dr. Yu Wang.

Table 7. Change in FEV1 (L) from baseline over the 12-week treatment period (Study FpS-AS-201, FAS)

FEV_1		Fp MDPI				Placebo (N=102)	FLOVENT DISKUS (N=102)
		12.5 mcg (N=102)	25 mcg (N=101)	50 mcg (N=102)	100 mcg (N=102)		
At baseline	Mean (SD)	2.237 (0.6880)	2.228 (0.6098)	2.225 (0.6391)	2.264 (0.6645)	2.227 (0.5957)	2.191 (0.6708)
	Median (min, max)	2.120 (0.830, 4.230)	2.150 (0.970, 3.810)	2.240 (0.950, 3.980)	2.265 (0.790, 4.280)	2.110 (1.130, 4.010)	2.085 (0.780, 3.900)
At Week 12	Mean (SD)	2.412 (0.7016)	2.531 (0.7207)	2.480 (0.6663)	2.553 (0.7109)	2.490 (0.7275)	2.472 (0.5891)
	Median (min, max)	2.345 (0.890, 4.490)	2.415 (1.370, 4.190)	2.500 (0.990, 4.270)	2.500 (1.290, 4.220)	2.385 (0.970, 4.160)	2.365 (1.210, 4.160)
Change from baseline to Week 12[a]	LS mean	0.189	0.268	0.263	0.295	0.145	0.234
	SE[b]	0.0389	0.0380	0.0367	0.0388	0.0412	0.0367
	95% CI	(0.112, 0.266)	(0.194, 0.343)	(0.190, 0.335)	(0.219, 0.371)	(0.064, 0.226)	(0.162, 0.306)
Difference from Placebo	p-value	0.4395	0.0286	0.0339	0.0084	-	-
	LS mean	0.044	0.123	0.117	0.150	-	-
	95% CI	(-0.068, 0.155)	(0.013, 0.233)	(0.009, 0.226)	(0.039, 0.261)	-	-
Difference from FLOVENT DISKUS	p-value	0.4204	0.4515	0.5542	0.2382	0.1255	-
	LS mean	-0.042	0.039	0.030	0.062	-0.083	-
	95% CI	(-0.146, 0.061)	(-0.063, 0.141)	(-0.070, 0.130)	(-0.041, 0.165)	(-0.190, 0.023)	-

Source: Summary 15.2.2.1 and Listing 16.2.6.01

(Source: Study FpS-AS-201 report, Table 15)

Table 8. Fluticasone propionate pharmacokinetics descriptive analysis (Study FpS-AS-201)

Parameter	Fp MDPI				FLOVENT DISKUS 100 mcg (N=21)
	12.5 mcg (N=16)	25 mcg (N=22)	50 mcg (N=19)	100 mcg (N=17)	
Mean (SD) AUC_{0-t} (pg•h/mL)	21.6 (27.09)	42.0 (23.21)	63.2 (22.64)	153.8 (91.42)	103.4 (45.65)
Mean (SD) C_{max} (pg/mL)	5.4 (4.23)	10.0 (5.35)	12.9 (5.13)	33.6 (15.49)	23.4 (10.73)
Median (min, max) t_{max} (h)	1.1 (0.2, 4.0)	1.0 (0.1, 12.0)	1.0 (0.3, 12.0)	0.8 (0.2, 4.0)	1.0 (0.3, 12.0)

Source: FpS-AS-201 clinical study report, Table 27

(Source: Summary of clinical pharmacology of NDA208799, Table 21)

Table 9. Change in FEV1 (L) from baseline over the 12-week treatment period (Study FpS-AS-202, FAS)

FEV_1		Fp MDPI				Placebo (N=105)	FLOVENT DISKUS (N=103)
		50 mcg (N=107)	100 mcg (N=106)	200 mcg (N=102)	400 mcg (N=107)		
At baseline	Mean (SD)	2.078 (0.6336)	2.069 (0.5806)	2.008 (0.5695)	2.015 (0.6294)	2.005 (0.5478)	1.987 (0.5426)
	Median (min, max)	1.940 (1.040, 4.640)	2.010 (0.900, 3.680)	2.020 (0.960, 3.690)	1.950 (0.930, 3.900)	1.900 (0.930, 3.550)	1.905 (0.990, 3.720)
At Week 12	Mean (SD)	2.140 (0.6214)	2.190 (0.6660)	2.204 (0.5959)	2.108 (0.6140)	2.094 (0.6640)	2.215 (0.6724)
	Median (min, max)	2.030 (1.060, 4.730)	2.060 (1.010, 4.110)	2.180 (0.900, 3.730)	1.990 (0.970, 3.970)	1.950 (1.060, 3.490)	2.170 (1.110, 4.120)
Change from baseline to Week 12[a]	LS mean	0.060	0.100	0.148	0.101	0.049	0.145
	SE[b]	0.0327	0.0322	0.0338	0.0332	0.0366	0.0334
	95% CI	(-0.004, 0.125)	(0.037, 0.163)	(0.081, 0.214)	(0.035, 0.166)	(-0.023, 0.121)	(0.079, 0.210)
Difference from Placebo	p-value	0.8155	0.2950	0.0473	0.2922	-	-
	LS mean	0.011	0.051	0.099	0.052	-	-
	95% CI	(-0.085, 0.107)	(-0.045, 0.147)	(0.001, 0.196)	(-0.045, 0.148)	-	-
Difference from FLOVENT DISKUS	p-value	0.0869	0.3565	0.8526	0.3999	0.0716	-
	LS mean	-0.080	-0.043	0.009	-0.040	-0.090	-
	95% CI	(-0.172, 0.012)	(-0.135, 0.049)	(-0.085, 0.102)	(-0.133, 0.053)	(-0.187, 0.008)	-

Source: Summary 15.2.2.1, Summary 15.2.4.1, Listing 16.2.1.01 and Listing 16.2.6.01

(Source: Study FpS-AS-202 report, Table 15)

Table 10. Fluticasone propionate pharmacokinetics descriptive statistics (Study FpS-AS-202)

Parameter Statistic	Fp MDPI				FLOVENT DISKUS 250 mcg (N=16)
	50 mcg (N=18)	100 mcg (N=18)	200 mcg (N=18)	400 mcg (N=20)	
Mean (SD) AUC_{0-t} (pg•h/mL)	117.6 (145.79)	126.8 (33.73)	292.0 (162.28)	462.8 (262.45)	162.3 (74.79)
Mean (SD) C_{max} (pg/mL)	19.1 (15.53)	26.5 (6.18)	55.2 (29.12)	83.0 (44.32)	32.5 (13.92)
Median (min, max) t_{max} (h)	1.0 (0.2, 2.0)	0.9 (0.2, 8.0)	1.1 (0.3, 12.0)	0.8 (0.1, 12.0)	1.1 (0.5, 12.0)

Source: FpS-AS-202 clinical study report, Table 27

(Source: Summary of clinical pharmacology of NDA208799, Table 24)

FS MDPI dose-ranging study

One dose-ranging trial for FS MDPI, Study FSS-AS-201, was conducted in patients with asthma. Following a single dose of FS MDPI at 100/6.25, 100/12.5, 100/25, and 100/50 mcg, the baseline-adjusted FEV1 AUC0-12 demonstrated a dose-related increase. The increase in FEV1 AUC0-12 following FS MDPI 100/12.5 was comparable to ADVAIR DISKUS 100/50 mcg and therefore was selected for further testing in Phase III studies. In addition, the standardized LS mean of the baseline-adjusted FEV1 AUC0-

12 was significantly greater for all 4 FS MDPI groups and ADVAIR DISKUS compared to Fp MDPI 100 mcg (Tables 11 and 12).

Table 11. Comparison of standardized baseline-adjusted FEV1 AUC0-12 (mL) by treatment (Study FSS-AS-201, FAS)

Statistic	Fp MDPI	FS MDPI				ADVAIR DISKUS (n=66)
	100 mcg (n=67)	100/6.25 mcg (n=68)	100/12.5 mcg (n=69)	100/25 mcg (n=67)	100/50 mcg (n=68)	
Standardized baseline-adjusted FEV_1 AUC_{0-12} (mL)						
LS Mean	52.13	203.84	248.98	279.69	303.43	245.56
SE of LS Mean	38.071	38.072	38.025	38.121	38.062	38.148
p-value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
LS Mean (diff. from FP MDPI 100 mcg)		151.71	196.85	227.56	251.30	193.42
95% CI (diff. from FP MDPI 100 mcg)		(115.9, 187.5)	(161.2, 232.5)	(191.6, 263.5)	(215.6, 287.1)	(157.4, 229.5)
p-value for the linear trend test	<0.0001	-	-	-	-	-
p-value	<0.0001	0.0229	0.8503	0.0624	0.0017	-
LS Mean (diff. from ADVAIR DISKUS)	-193.42	-41.72	3.42	34.14	57.88	
95% CI (diff. from ADVAIR DISKUS)	(-229.5, -157.4)	(-77.6, -5.8)	(-32.3, 39.1)	(-1.8, 70.1)	(22.0, 93.7)	

(Source: Study FSS-AS-201report, Table 11)

Table 12. Pharmacokinetics of salmeterol after administration of FS MDPI or ADVAIR DISKUS (Study FSS-AS-201)

Parameter	FS MDPI				ADVAIR DISKUS 100/50 mcg (N=62)
	100/6.25 mcg (N=62)	100/12.5 mcg (N=65)	100/25 mcg (N=61)	100/50 mcg (N=61)	
Mean (SD) AUC_{0-t} (pg•h/mL)	32.8 (21.0)	69.9 (35.4)	133.5 (63.1)	309.3 (143.4)	173.5 (106.6)
Mean (SD) C_{max} (pg/mL)	16.0 (8.9)	35.8 (20.3)	67.5 (34.7)	154.5 (80.3)	42.3 (19.3)
Median (min, max) t_{max} (h)	0.1 (0.1, 12.1)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 1.5)	0.5 (0.1, 2.0)

Source: FSS-AS-201 clinical study report, Table 18

(Source: Summary of clinical pharmacology of NDA208799, Table 10)

PK study for Fp MDPI and FS MDPI

Study FSS-AS-10042 is multicenter, open-label, randomized, 4-period crossover, single-dose study to determine the PK and tolerability of high strength Fp MDPI and FS MDPI compared to high strength FLOVENT DISKUS and ADVAIR DISKUS in asthma patients.

For Fp, following the single dose administration of of Fp MDPI (200 mcg×1 inhalation), FS MDPI (200/12.5 mcg×1 inhalation), FLOVENT DISKUS (250 mcg×2 inhalation) and ADVAIR DISKUS (500/50 mcg×1 inhalation), the systemic exposure (Cmax, AUC0-t, and AUC0-∞) to Fp were ~20-30% lower with Fp MDPI than FLOVENT DISKUS, but were similar between FS MDPI and ADVAIR DISKUS (Tables 13 and 14).

For Sx, following the single dose administration of FS MDPI (200/12.5 mcg×1 inhalation) and ADVAIR DISKUS (500/50 mcg×1 inhalation), the Cmax and AUC of Sx was ~20% and 50% lower with FS MDPI compared with ADVAIR DISKUS, respectively (Table 15).

Table 13. Pharmacokinetic comparison for fluticasone propionate by treatment

Parameter	Treatment	n	Geometric LS mean	GMR	90% CI
C_{max} (pg/mL)	Fp MDPI	37	66.41	0.848	0.77-0.93
	FLOVENT	37	78.28		
AUC_{0-t} (pg•h/mL)	Fp MDPI	37	593.25	0.797	0.72-0.88
	FLOVENT	37	744.04		
$AUC_{0-\infty}$ (pg•h/mL)	Fp MDPI	30	616.45	0.758	0.69-0.83
	FLOVENT	30	812.91		

Source: FSS-AS-10042 clinical study report, Table 13

*Treatments: Fp MDPI 200 mcg x1; FLOVENT DISKUS 250 mcg x2

Table 14. Pharmacokinetic comparison for fluticasone propionate by treatment

Parameter	Treatment	n	Geometric LS mean	GMR	90% CI
C_{max} (pg/mL)	Fp MDPI	37	66.48	1.085	0.99-1.19
	FS MDPI	37	61.24		
	FS MDPI	36	61.92	1.005	0.92-1.10
	ADVAIR	36	61.62		
AUC_{0-t} (pg•h/mL)	Fp MDPI	36	593.20	1.089	0.98-1.21
	FS MDPI	36	544.77		
	FS MDPI	36	545.48	0.962	0.87-1.07
	ADVAIR	36	566.96		
$AUC_{0-\infty}$ (pg•h/mL)	Fp MDPI	25	623.60	1.068	0.96-1.19
	FS MDPI	25	583.68		
	FS MDPI	28	586.85	0.949	0.86-1.04
	ADVAIR	28	618.51		

Source: FSS-AS-10042 clinical study report, Table 14 and Table 16

*Treatments: Fp MDPI 200 mcg x1; FS MDPI 200/12.5 mcg x1; ADVAIR DISKUS 500/50 mcg x1

Table 15. Pharmacokinetic comparison for salmeterol by treatment

Parameter	Treatment	n	Geometric LS mean	GMR	90% CI
C_{max} (pg/mL)	FS MDPI	35	56.50	0.811	0.70-0.94
	ADVAIR	35	69.71		
AUC_{0-t} (pg•h/mL)	FS MDPI	35	119.65	0.496	0.46-0.54
	ADVAIR	35	241.22		
$AUC_{0-\infty}$ (pg•h/mL)	FS MDPI	34	134.37	0.511	0.47-0.55
	ADVAIR	34	262.69		

Source: FSS-AS-10042 clinical study report, Table 18

*Treatments: FS MDPI 200/12.5 mcg x1; ADVAIR DISKUS 500/50 mcg x1

Phase III studies for Fp MDPI and FS MDPI

Studies FSS-AS-301 and FSS-AS-30017 were Phase 3, 12-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled studies in adolescents and adults (12 years of age and older) with persistent asthma. The populations of these 2 studies were slightly different with regard to required pre-study asthma medication, implying a more severe population in Study FS-AS-30017. For FSS-AS-301, after a run-in period, patients were randomly assigned to Fp MDPI (50 or 100 mcg BID), FS MDPI (50/12.5 or 100/12.5 mcg BID), or placebo MDPI for the 12-week treatment period. For FSS-AS-30017, after a run-in period, patients were randomly assigned to Fp MDPI (100 or 200 mcg BID), FS MDPI (100/12.5 or 200/12.5 mcg BID), or placebo MDPI for the 12-week treatment period.

The primary efficacy endpoints for both studies, including change from baseline in trough FEV1 at Week 12 and standardized baseline-adjusted FEV1 AUC0-12h at Week 12 are shown in Tables 16 and 17 and Figures 2 and 3.

In both Phase III studies, in terms of the primary efficacy endpoints (Trough FEV1 and FEV1 AUC0-12h at Week 12), all the proposed doses for Fp MDPI (50, 100, and 200 mcg BID) and FS MDPI (50/12.5, 100/12.5, and 200/12.5 mcg BID) showed a clinically meaningful improvement (>0.100 L) compared to placebo. With the same dose of Fp in Fp MDPI and FS MDPI, FS MDPI showed additional clinical benefit compared to Fp MDPI. The primary efficacy endpoints for Fp MDPI showed a dose dependent increase numerically, however, the observed difference between doses appears not clinically meaningful. For FS MDPI, no apparent dose-dependent trend in primary efficacy endpoints was observed. Please refer to the Clinical Review by Dr. Miya Paterniti and the Statistical Review by Dr. Yu Wang regarding the final risk/benefit assessment for the proposed doses for Fp MDPI and FS MDPI based on the efficacy and safety analyses of Phase III studies.

Table 16. Analysis of change from baseline in trough FEV1 (L) [LS mean (95% CI)] at week 12 (FAS)

	Study FSS-AS-301					**Study FSS-AS-30017**				
	Placebo (n=129)	Fp MDPI 50 mcg BID (n=128)	Fp MDPI 100 mcg BID (n=129)	FS MDPI 50/12.5 mcg BID (n=128)	FS MDPI 100/12.5 mcg BID (n=128)	Placebo (n=143)	Fp MDPI 100 mcg BID (n=145)	Fp MDPI 200 mcg BID (n=146)	FS MDPI 100/12.5 mcg BID (n=141)	FS MDPI 200/12.5 mcg BID (n=145)
Change from baseline at week 12	0.053 (-0.015, 0.122)	0.172 (0.104, 0.240)	0.204 (0.137, 0.271)	0.319 (0.250, 0.388)	0.315 (0.246, 0.385)	-0.004 (-0.0065, 0.057)	0.119 (0.058, 0.180)	0.179 (0.119, 0.240)	0.271 (0.210, 0.332)	0.272 (0.212, 0.333)
Diff. from placebo	NA	0.119 (0.025, 0.212)	0.151 (0.057, 0.244)	0.266 (0.172, 0.360)	0.262 (0.168, 0.356)	NA	0.123 (0.038, 0.208)	0.183 (0.098, 0.268)	0.274 (0.189, 0.360)	0.276 (0.191. 0.361)

(Source: Adapted from Table 10, Summary of clinical efficacy)

Table 17. Analysis of standardized baseline-adjusted FEV1 AUEC0-12h (L) [LS mean (95% CI)] at week 12 by treatment group (FAS - serial spirometry subset)

	Study FSS-AS-301					Study FSS-AS-30017				
	Placebo (n=60)	Fp MDPI 50 mcg BID (n=63)	Fp MDPI 100 mcg BID (n=72)	FS MDPI 50/12.5 mcg BID (n=56)	FS MDPI 100/12.5 mcg BID (n=61)	Placebo (n=61)	Fp MDPI 100 mcg BID (n=64)	Fp MDPI 200 mcg BID (n=61)	FS MDPI 100/12.5 mcg BID (n=58)	FS MDPI 200/12.5 mcg BID (n=68)
Change from baseline at week 12	0.074 (-0.022, 0.170)	0.268 (0.178, 0.358)	0.254 (0.69, 0.339)	0.399 (0.305, 0.493)	0.408 (0.317, 0.500)	0.121 0.028, 0.214)	0.260 (0.169, 0.351)	0.267 (0.175, 0.359)	0.442 (0.345, 0.540)	0.446 (0.355, 0.538)
Diff. from placebo	NA	0.195 (0.078, 0.312)	0.180 (0.067, 0.294)	0.325 (0.203, 0.447)	0.335 (0.216, 0.453)	NA	0.139 (0.032, 0.246)	0.146 (0.038, 0.255)	0.322 (0.212, 0.432)	0.326 (0.221. 0.431)

(Source: Adapted from Table 12, Summary of clinical efficacy)

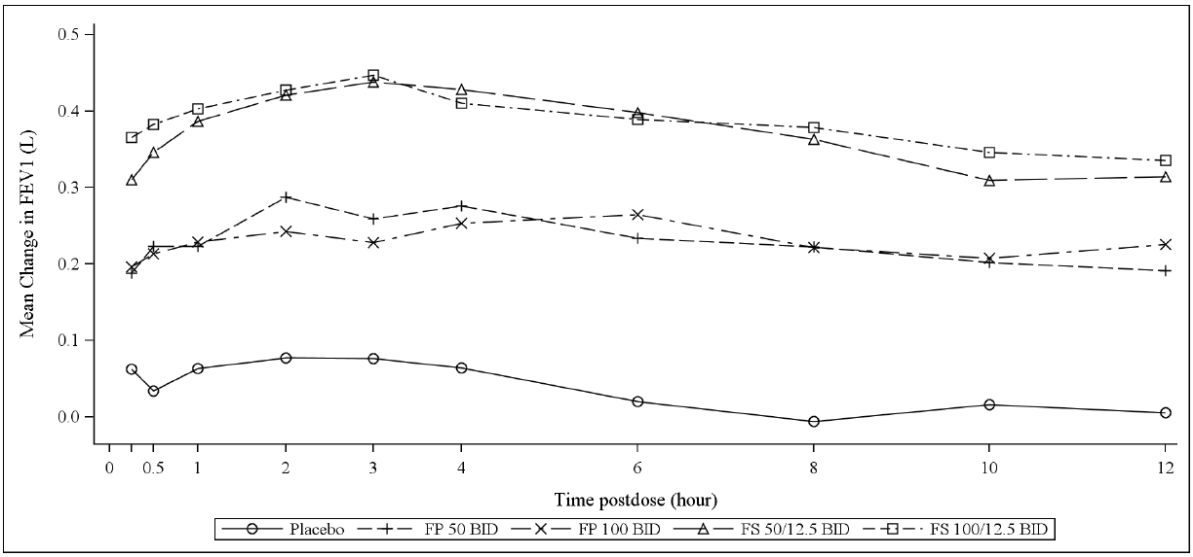


Figure 2. Mean change from baseline in FEV1 (L) at week 12 by timepoint and treatment group (FAS - serial spirometry subset; Study FSS-AS-301)

(Source: Summary of clinical efficacy, Figure 5)

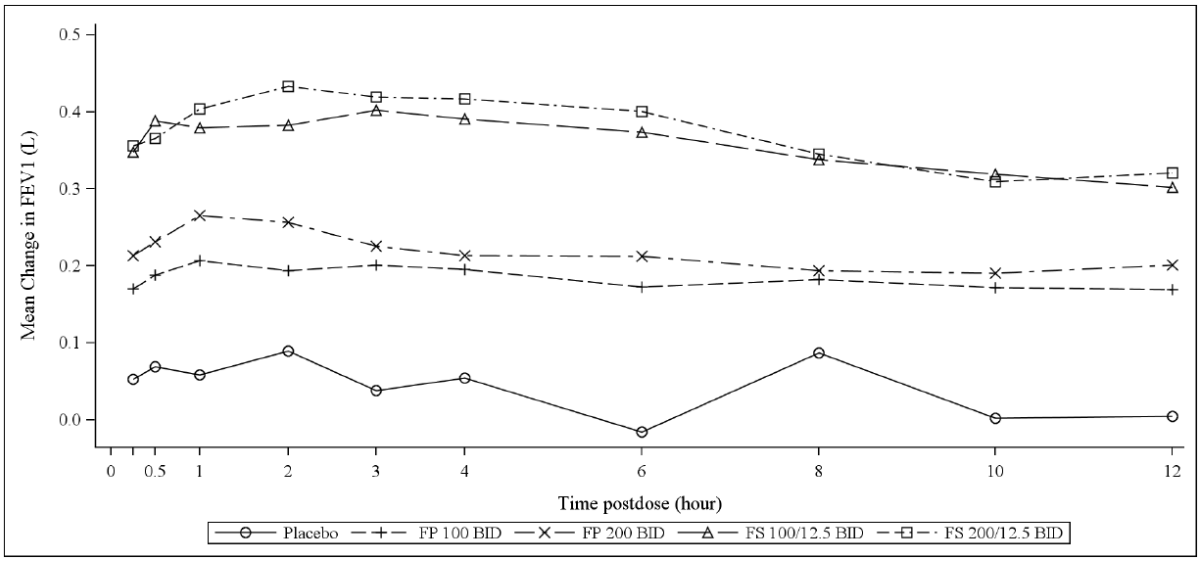


Figure 3. Mean change from baseline in FEV1 (L) at week 12 by timepoint and treatment group (FAS - serial spirometry subset; Study FSS-AS-30017)
(Source: Summary of clinical efficacy, Figure6)

2.6 What are the PK characteristics of the drug?

2.6.1 What are the PK parameters of Fp and Sx in asthma patients after the administration of Fp MDPI and FS MDPI?

In Study FSS-AS-10042, after single dose administration of Fp MDPI (200 mcg x 1 inhalation), FS MDPI (200/12.5 mcg x 1 inhalation), FLOVENT DISKUS (250 mcg x 2 inhalations), and ADVAIR DISKUS (500/50 mcg x 1 inhalation), Tmax of Fp is approximately 1 to 2 hours and the elimination half-life of Fp is approximately 11 hours. For Sx, the Tmax is approximately 0.07 to 2 hours, and the elimination half-life is approximately 12 hours.

2.6.2 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality for Fp and Sx was assessed using a power model in an exploratory manner in Studies FpS-AS-201 and FpS-AS-202 (Tables 18 and 19).

Fp
Over a dose range of Fp MDPI 12.5 to 400 mcg, the increases in Fp AUC0-t were approximately dose proportional while those for Cmax were slightly less than dose proportional. For Fp MDPI 50, 100, and 200 mcg doses, both Cmax and AUC0-t for Fp increased approximately dose proportionally.

Sx
Over a dose range of FS MDPI 100/6.25 to 100/50 mcg, the increases in Sx AUC0-t and Cmax were slightly greater than dose proportional. For the FS MDPI 100/6.25, 100/12.5, and 100/25 mcg doses, both Cmax and AUC0-t for Sx increased approximately dose proportionally.

Table 18. Fluticasone propionate dose proportionality for Fp MDPI (Studies FpS-AS-201 and FpS-AS-202)

Doses	Parameter	Estimated Slope for ln(Dose)	Standard Error	90% CI	
				Lower	Upper
12.5, 25, 50, 100, 200, and 400 mcg	AUC_{0-t}	0.9212	0.0610	0.820	1.022
	C_{max}	0.8191	0.0503	0.736	0.902
50, 100, and 200 mcg	AUC_{0-t}	0.9360	0.1223	0.733	1.139
	C_{max}	0.9451	0.1040	0.772	1.118

(Source: Summary of clinical pharmacology of NDA208798, Table 22)

Table 19. Salmeterol dose proportionality for FS MDPI (Study FSS-AS-201)

Doses	Parameter	Estimated Slope for ln(Dose)	Standard Error	90% CI	
				Lower	Upper
6.25, 12.5, 25, and 50 mcg	AUC_{0-t}	1.1058	0.0454	1.030	1.182
	C_{max}	1.0855	0.0424	1.015	1.156
6.25, 12.5, and 25 mcg	AUC_{0-t}	1.0716	0.0789	0.940	1.203
	C_{max}	1.0610	0.0680	0.947	1.175

(Source: Summary of clinical pharmacology of NDA208799, Table 29)

2.7 Intrinsic Factors

2.7.1 Race/Ethnicity

Study Fp-AS-102 is a single-center, open-label, randomized, 3-period crossover, single-dose pilot study in healthy Japanese (n=15) and Caucasian subjects (n=15) aged 20 to 45 years. Following the administration of Fp MDPI 100 mcg x 4 inhalations, Fp MDPI 200 mcg x 4 inhalations, and FLOVENT DISKUS 100 mcg x 4 inhalations, there is no statistically significant difference for AUC0-t and Cmax between the Japanese and Caucasian ethnic populations for all 3 treatments. Note that the product used in this study is not the proposed to-be-marketed drug product.

Table 20. Fluticasone propionate PK comparison [mean (± SD)] in Japanese and Caucasian subjects following oral inhalation of single doses of Fp MDPI and FLUTIDE DISKUS (N=15/group)

	Fp Spiromax 100 mcg × 4 (Treatment A)		Fp Spiromax 200 mcg × 4 (Treatment B)		Flutide Diskus 100 mcg × 4 (Treatment C)	
Parameter	Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian
C_{max} (pg/mL)	170.2 ± 46.2	182.7 ± 78.6	306.3 ± 77.7	294.5 ± 101.9	84.8 ± 24.0	92.2 ± 23.8
t_{max} (hr)[a]	1.00 [0.33-3.00]	1.00 [0.17-2.00]	1.00 [0.50-3.00]	0.75 [0.17-2.00]	1.25 [0.50-3.00]	0.75 [0.33-4.00]
AUC_{0-t} (pg·hr/mL)	1275 ± 284	1145 ± 319	2101 ± 445	1836 ± 498	681 ± 178	603 ± 159
$AUC_{0-\infty}$ (pg·hr/mL)	1465 ± 334[b]	1284 ± 368[c]	2466 ± 609[e]	2140 ± 563[g]	754 ± 17[h]	666 ± 199[i]
$t_{1/2}$ (hr)[k]	12.8 ± 3.9 [12.1]	9.8 ± 1.5 [9.6][d]	10.9 ± 2.1 [10.5][f]	10.4 ± 1.9 [10.1]	10.1 ± 1.8 [9.8]	9.4 ± 1.8 [9.1][j]
λ_z (hr^{-1})	0.0573 ± 0.0125	0.0723 ± 0.0101[d]	0.0662 ± 0.0130[f]	0.0683 ± 0.0112	0.0709 ± 0.0123	0.0761 ± 0.0145[j]
Extrapolation (%)	19.1 ± 5.4	12.3 ± 3.8[d]	16.1 ± 4.0[f]	13.5 ± 4.6	15.2 ± 3.8	12.0 ± 5.2[j]

(Source: Study FpS-AS-102 PK report, Table 1)

2.8 Extrinsic Factors

2.8.1 What are the drug-drug interactions?

In Study FSS-AS-10042, a post hoc comparison of Cmax, AUC0-t, and AUC0-∞ for Fp in Fp MDPI (200 mcg) versus FS MDPI (200/12.5 mcg) indicated that the systemic exposure of Fp is similar with Fp MDPI and FS MDPI, suggesting the presence of Sx in FS MDPI does not affect Fp PK (Table 21). No studies have been performed with FS MDPI to investigate the effect of Fp on Sx PK when given in combination.

Table 21. Fluticasone propionate PK comparisons following Fp MDPI and FS MDPI

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (A/B)	90% CI of Ratio (A/B)	Root MSE	Intra-patient CV
C_{max} (pg/mL)	A	37	66.48	1.085	0.99 – 1.19	0.236	0.239
	B	37	61.24				
AUC_{0-t} (hr*pg/mL)	A	36	593.20	1.089	0.98 – 1.21	0.268	0.273
	B	36	544.77				
$AUC_{0-\infty}$ (hr*pg/mL)	A	25	623.60	1.068	0.96 – 1.19	0.225	0.228
	B	25	583.68				

Source: Adhoc Summary 1
Treatment A: Fp MDPI 200 mcg; Treatment B: FS MDPI 200/12.5 mcg
(Source: Study FSS-AS-10042 report, Table 16)

2.9 General Biopharmaceutics

2.9.1 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

For both Fp MDPI and FS MDPI, the proposed commercial blends (b) (4) kg scale) and commercial device (NB7/3 device variant) were used in PK study FSS-AS-10042 and all Phase III studies.

2.10 Analytical Section

2.10.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Early studies in the Fp MDPI and FS MDPI clinical development programs employed bioanalytical methods for the determination of Fp or Sx alone, while the later study, FSS-AS-10042, employed a bioanalytical method for the simultaneous determination of Fp and Sx. The summary of bioanalytical methods used in Fp MDPI and FS MDPI clinical development programs are shown in Table 22.

As the proposed commercial products were used in PK study FSS-AS-10042 and all Phase III studies, only the method validation report P1197 is summarized below (Table 23).

Table 22. Summary of bioanalytical methods employed in Fp MDPI and FS MDPI clinical development programs

Analyte	Study	Bioanalytical Report	Method Validation Report
Fluticasone Propionate	FPS-AS-101	Report RPT02853, by (b) (4)	Report RPT02770 (Method Validation of an LC-MS/MS Assay for the Determination of Fluticasone Propionate in K3EDTA Human Plasma), by (b) (4)
	FPS-AS-102	Report RPT02855, by (b) (4)	
	FPS-AS-201	Report RTP03149, by (b) (4)	
	FPS-AS-202	Report RTP03234, by (b) (4)	
Salmeterol	FSS-AS-201	Report RTP03142, by (b) (4)	Report RPT02917 (Method Validation of an LC-MS/MS Assay for the Determination of Salmeterol in Human Plasma), by (b) (4)
Fluticasone Propionate and Salmeterol	FSS-AS-10042	Report DP-2015-152, by (b) (4)	Report P1197 (Method Validation for Quantitation of Fluticasone Propionate and Salmeterol in Human Plasma via UPLC® with MS/MS Detection), by (b) (4)

Table 23. Summary of method validation for quantitation of fluticasone propionate and salmeterol in human plasma via UPLC® with MS/MS detection (method validation report P1197)

PPD Project Code	AHCH2		
PPD Method ID	P1197		
Analytes	Fluticasone Propionate and Salmeterol		
Matrix	Human Plasma		
Anticoagulant	Potassium Oxalate/Sodium Fluoride		
Method Description	A 0.5-mL sample aliquot is fortified with 0.05 mL of fluticasone propionate-d_5 and salmeterol-d_3 internal standard working solution. Analytes are isolated through liquid-liquid extraction. The extract is evaporated under a nitrogen stream at 45 °C, and the remaining residue is reconstituted with 0.12 mL of reconstitution solution. The final extract is analyzed via UPLC® with MS/MS detection using positive ion electrospray.		
Sample Volume (µL)	0.5-mL		
Sample Storage Temperature	-20 °C or colder		
Fluticasone Propionate			
Internal Standard (IS)	Fluticasone Propionate-d_5		
Regression, Weighting	Linear, 1/concentration^2		
Average Recovery of Drug (%)	95.2%		
Average Recovery of IS (%)	92.2%		
Standard Curve Concentrations	0.500 to 200 pg/mL		
QC Concentrations	0.500, 1.20, 3.00, 10.0, 35.0, and 150 pg/mL		
QC Intra-assay Statistics (%)	Conc. (pg/mL)	Precision	Accuracy
	0.500	4.25 to 12.2%	-6.19 to 5.43%
	1.20	1.84 to 7.26%	-4.70 to 0.0206%
	3.00	1.88 to 2.85%	-1.84 to 0.800%
	10.0	1.27 to 2.12%	-0.603 to 0.141%
	35.0	1.56 to 2.27%	-0.0831 to 2.63%
	150	1.19 to 2.37%	0.761 to 2.27%
QC Inter-assay Statistics (%)	Conc. (pg/mL)	Precision	Accuracy
	0.500	9.39%	0.918%
	1.20	4.62%	-1.95%
	3.00	2.53%	-0.205%
	10.0	1.74%	-0.182%
	35.0	2.21%	1.31%
	150	2.00%	1.55%
Thawed Matrix Stability (hrs)	24.25 hours at room temperature		
Solution Stability (days)	Fluticasone Propionate 384 days at -20 °C in methanol Fluticasone Propionate-d_5 27 days at -20 °C in human plasma Fluticasone Propionate-d_5 382 days at -20 °C in methanol		

Solution Stress Stability (hours)	Fluticasone Propionate 15 hours at room temperature in methanol Fluticasone Propionate-d_5 19 hours at room temperature in methanol Fluticasone Propionate-d_5 7 hours at room temperature in human plasma
Extract Stability (hrs)	115.5 hours at 2 to 8 °C
Freeze-thaw Stability (cycles)	Five cycles thawed at room temperature
Frozen Matrix Storage Stability (days)	31 days at -20 °C and -70 °C
Whole Blood Stability	Two hours at room temperature and on ice
Dilutional Linearity	10.0 pg/mL diluted two-fold 500 pg/mL diluted five-fold
Selectivity	No significant interfering peaks noted in blank plasma samples
Hemolysis	No effect from hemolysis on the quantitation of fluticasone propionate
Lipemia	No effect from lipemia on the quantitation of fluticasone propionate

Salmeterol			
Internal Standard (IS)	Salmeterol-d_3		
Regression, Weighting	Linear, 1/concentration		
Average Recovery of Drug (%)	71.0%		
Average Recovery of IS (%)	76.1%		
Standard Curve Concentrations	0.500 to 200 pg/mL		
QC Concentrations	1.20, 3.00, 10.0, 35.0, and 150 pg/mL		
QC Intra-assay Statistics (%)	Conc. (pg/mL)	Precision	Accuracy
	0.500	2.27 to 4.27%	-4.88 to 8.11%
	1.20	2.74 to 3.11%	-1.85 to -0.926%
	3.00	1.64 to 2.24%	-1.50 to -0.370%
	10.0	1.34 to 2.75%	-0.809 to 0.415%
	35.0	1.54 to 2.75%	-0.537 to 1.50%
	150	1.36 to 2.42%	0.873 to 2.54%
QC Inter-assay Statistics (%)	Conc. (pg/mL)	Precision	Accuracy
	0.500	6.53%	0.505%
	1.20	2.75%	-1.45%
	3.00	1.87%	-1.01%
	10.0	2.10%	-0.286%
	35.0	2.17%	0.340%
	150	2.05%	1.32%
Thawed Matrix Stability (hrs)	24.25 hours at room temperature		
Solution Stability (days)	Salmeterol 468 days at -20 °C in methanol Salmeterol-d_3 27 days at -20 °C in human plasma Salmeterol-d_3 1236 days at -20 °C in methanol		
Solution Stress Stability (hours)	Salmeterol 7 hours at room temperature in methanol Salmeterol-d_3 7 hours at room temperature in methanol Salmeterol-d_3 7 hours at room temperature in human plasma		
Extract Stability (hrs)	101.25 hours at 2 to 8 °C		

Freeze-thaw Stability (cycles)	Five cycles thawed at room temperature
Frozen Matrix Storage Stability (days)	31 days at -20 °C and -70 °C
Whole Blood Stability	Two hours at room temperature and on ice
Dilutional Linearity	10.0 pg/mL diluted two-fold 500 pg/mL diluted five-fold
Selectivity	No significant interfering peaks noted in blank plasma samples
Hemolysis	No effect from hemolysis on the quantitation of salmeterol
Lipemia	No effect from lipemia on the quantitation of salmeterol

Note: 1. Analtye stability in frozen matrix was updated to 82 days and 249 days at -20 °C and -70 °C for fluticasone propionate and salmeterol in addendum 1 and addendum 2, respectively.
(Source: Method validation summary of R1197 report)

2.10.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in the PK samples. No metabolites were quantified because the metabolites of Fp and Sx are not active and associated with efficacy or safety.

2.10.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations of Fp and Sx were measured in plasma PK samples.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. Labeling statements to be removed are shown in ~~red strikethrough~~ font and suggested labeling to be included is shown in underline blue font.

NDAs 208798 (fluticasone propionate inhalation powder)

5 WARNINGS AND PRECAUTIONS

5.11 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FP TRADENAME is not recommended because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FP TRADENAME is not recommended because increased systemic corticosteroid adverse effects may occur.

Ritonavir: A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations *[see Clinical Pharmacology (12.3)]*. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

Formal pharmacokinetic studies using FP TRADENAME have not been conducted in patients with hepatic impairment. Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using FP TRADENAME have not been conducted in patients with renal impairment.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption

Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate was negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung was systemically absorbed.

Following FP TRADENAME administration (b) (4) occurring at approximately 1 hour after inhalation.

The mean peak concentration following a 232 mcg single oral inhalation of FP TRADENAME to patients 12 years and older with persistent asthma was 73 ng/mL. (b) (4)

Distribution

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Elimination

Terminal half-life estimate of fluticasone propionate following oral inhalation administration of FP TRADENAME was approximately 11.2 hours

Metabolism

The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite has less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion

Less than 5% of a radiolabeled oral dose of fluticasone propionate was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

~~*Age*: No pharmacokinetic studies have been performed with FP TRADENAME in children or geriatric patients. A subgroup analysis was conducted to compare patients aged 12-17 (n=16) and ≥18 (n=23) years following administration of 232 mcg FP TRADENAME.~~ (b) (4) ~~.~~

~~*Sex*: A subgroup analysis was conducted to compare male (n=22) and female (n=17) patients following administration of 232 mcg FP TRADENAME.~~ (b) (4)

(b) (4)

Renal Impairment: The effect of renal impairment of the pharmacokinetics of FP TRADENAME has not been evaluated.

Hepatic Impairment: Formal pharmacokinetic studies using FP TRADENAME have not been conducted in patients with hepatic impairment. However, since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma.

Drug Interaction Studies: In vitro and in vivo drug interaction studies have not been conducted with FP TRADENAME. Known clinically significant drug interactions are outlined in *Drug Interactions* (7).

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (Cmax) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{0-\tau}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{0-\tau}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: In a placebo-controlled crossover trial in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Following orally inhaled fluticasone propionate alone, $AUC_{2\text{-last}}$ averaged 1.559 ng•h/mL (range: 0.555 to 2.906 ng•h/mL) and $AUC_{2-\infty}$ averaged 2.269 ng•h/mL (range: 0.836 to 3.707 ng•h/mL). Fluticasone propionate $AUC_{2\text{-last}}$ and $AUC_{2-\infty}$ increased to 2.781 ng•h/mL (range: 2.489 to 8.486 ng•h/mL) and 4.317 ng•h/mL (range: 3.256 to 9.408 ng•h/mL), respectively, after coadministration of ketoconazole with orally inhaled fluticasone propionate. This increase in plasma fluticasone propionate concentration resulted in a decrease (45%) in serum cortisol AUC.

Erythromycin: In a multiple-dose drug interaction trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

NDA208799 (fluticasone propionate/salmeterol xinafoate inhalation powder)

5 WARNINGS AND PRECAUTIONS

5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FS TRADENAME is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.11 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10.2)]*. Therefore, FS TRADENAME, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of FS TRADENAME, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

7 DRUG INTERACTIONS

FS TRADENAME has been used concomitantly with other drugs, including short-acting beta$_2$-agonists, and intranasal corticosteroids, commonly used in patients with asthma without adverse drug reactions *[see Clinical Pharmacology (12.2)]*. No formal drug interaction trials have been performed with FS TRADENAME.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of FS TRADENAME, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FS TRADENAME is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: *Fluticasone Propionate:* A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations *[see Clinical Pharmacology (12.3)]*. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole: *Fluticasone Propionate:* Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC) but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction trial in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and Cmax increased 1.4-fold). Three (3) subjects were withdrawn due to beta$_2$-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration *[see Clinical Pharmacology (12.3)]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

FS TRADENAME should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of FS TRADENAME, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of FS TRADENAME, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non-Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of FS TRADENAME, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of FS TRADENAME with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

Formal pharmacokinetic studies using FS TRADENAME have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using FS TRADENAME have not been conducted in patients with renal impairment.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption

Fluticasone Propionate:

FS TRADENAME acts locally in the lung; therefore, plasma levels may not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate was negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung was systemically absorbed.

After administration of 232/14 mcg FS TRADENAME to patients aged 12 years and older with persistent asthma in a clinical trial, the mean C_{max} value of fluticasone propionate was 66 pg/mL with a median t_{max} value of approximately 1 hour.

(b) (4)

Salmeterol:

After administration of 232/14 mcg FS TRADENAME to patients aged 12 years and older with persistent asthma, the mean C_{max} values of salmeterol was 60 pg/mL. The median t_{max} was 5 minutes.

Distribution

Fluticasone Propionate:

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Salmeterol:

Volume of distribution data are not available for salmeterol.

The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Elimination

Fluticasone Propionate:

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Terminal half-life estimates of fluticasone propionate following oral inhalation administration of FS TRADENAME were approximately 10.8 hours.

Metabolism

The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite has less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion

Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Salmeterol:

Terminal half-life estimates for salmeterol for FS TRADENAME were approximately 12.6 hours.

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (greater than 99%) and has a long elimination half-life of 11 days.

Metabolism

Salmeterol base is extensively metabolized by hydroxylation.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α hydroxysalmeterol in vitro.

Excretion

In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days.

Special Populations

A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 subjects with asthma aged 4 to 77 years who received treatment with a combination dry powder inhaler of fluticasone propionate and salmeterol, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol, fluticasone propionate inhalation powder, HFA-propelled fluticasone propionate inhalation aerosol, or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone

propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution.

~~*Age:* No pharmacokinetic studies have been performed with FS TRADENAME in children or geriatric patients. A subgroup analysis was conducted to compare patients aged 12-17 (n=15) and ≥18 (n=23) years following administration of 232/14 mcg FS TRADENAME.~~ (b) (4) ~~.~~

~~*Sex:* A subgroup analysis was conducted to compare male (n=21) and female (n=16) patients following administration of 232/14 mcg FS TRADENAME.~~ (b) (4) ~~.~~

(b) (4)

Renal Impairment: The effect of renal impairment of the pharmacokinetics of FS TRADENAME has not been evaluated.

Hepatic Impairment: Formal pharmacokinetic studies using FS TRADENAME have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma.

~~*Drug Interaction Studies:*~~ (b) (4)

~~No studies have been performed with FS TRADENAME to investigate the effect of fluticasone propionate on salmeterol pharmacokinetics when given in combination~~ (b) (4)

Other Fluticasone Propionate and Salmeterol Inhalation Powder Products:

Drug Interactions: The population pharmacokinetic analysis from 9 controlled clinical trials in 350 subjects with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with $beta_2$-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (Cmax) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{0-\tau}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate Cmax and $AUC_{0-\tau}$ increased to 318 pg/mL (range: 110 to

648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Fluticasone Propionate: In a placebo-controlled crossover trial in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction trial in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: Fluticasone Propionate: In a multiple-dose drug interaction trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose trial in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol Cmax at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], $P = 0.12$), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], $P<0.04$), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], $P = 0.34$), and no change in plasma potassium.

4. Appendix

4.1. Individual Study Review

Study FpS-AS-101

Title: 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

Study Phase: Phase I, pilot study

Objectives

- Primary objective: to assess the PK profiles of single doses of fluticasone propionate administered as 2 inhalations from Fp MDPI 400 mcg and 4 inhalations from FLOVENT DISKUS 250 mcg and 4 inhalations from FLOVENT HFA MDI 220 mcg

- Secondary objective: to assess the safety profiles

Study Population: healthy subjects aged 18 to 45 years

Study Design
This was a single-center, open-label, randomized, 3-period crossover, single-dose, pilot study in healthy subjects aged 18 to 45 years. Eligible subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA) containing the following 3 treatment arms:

- Treatment A: Fp MDPI 400 mcg, 2 inhalations (800 mcg total dose)
- Treatment B: FLOVENT DISKUS 250 mcg, 4 inhalations (1000 mcg total dose)
- Treatment C: FLOVENT HFA MDI 220 mcg, 4 inhalations (880 mcg total dose)

Each treatment period was followed by a 5 to 8 day washout period except for the last treatment period.

PK Assessment
Plasma PK samples were obtained predose and at 0.03 (2 minutes), 0.08 (5 minutes), 0.17 (10 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 0.75 (45 minutes), and at 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0, and 24.0 hours postdose at each of the 3 treatment periods.

Results
A total of 18 healthy subjects were randomized and included in data analysis.

PK Results
The mean plasma concentration-versus-time profiles and PK parameters of fluticasone propionate following all 3 inhalers (Fp MDPI 800 mcg total dose [400 mcg x 2 inhalations], FLOVENT DISKUS 1000 mcg total dose [250 mcg x 4 inhalations] and FLOVENT HFA MDI 880 mcg total dose [220 mcg x 4 inhalations]) are presented in Figure 4.1.1 and Table 4.1.1.

Results showed that after oral inhalation of the Fp MDPI 800 mcg total dose, the AUC0-t and Cmax of Fp were higher compared with the FLOVENT DISKUS 1000 mcg total dose, and the FLOVENT HFA MDI 880 mcg total dose.

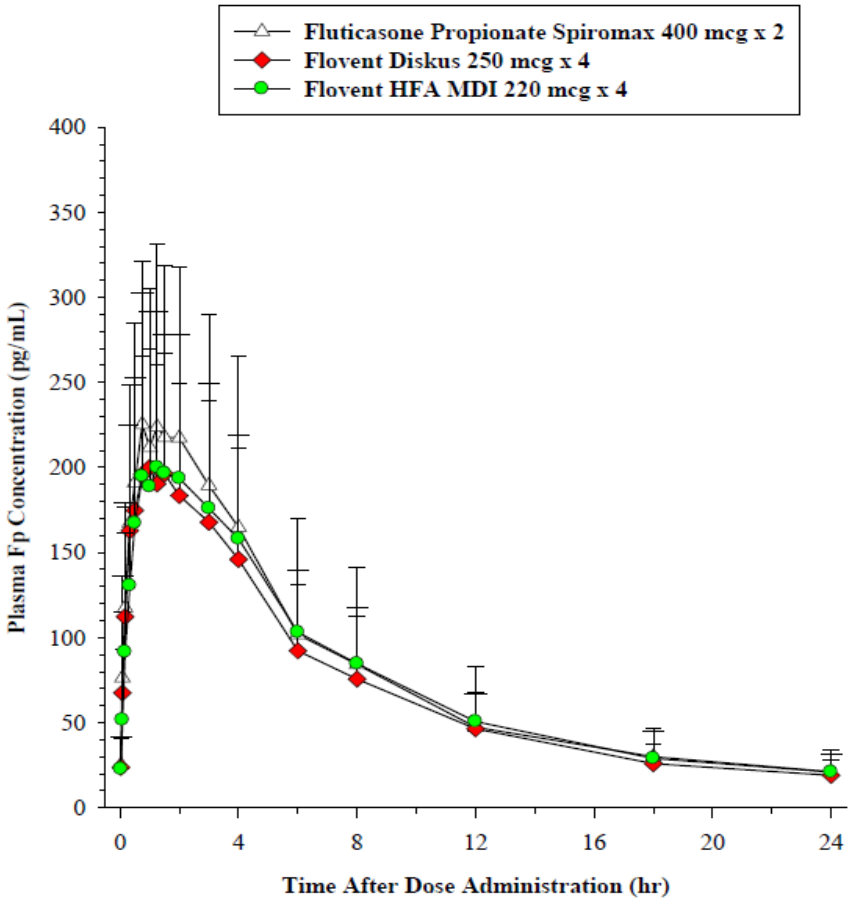


Figure 4.1.1. Mean (±SD) fluticasone propionate plasma concentration over 24 hours following inhalation of single doses of fluticasone propionate from each of the 3 study Inhalers (PK Analysis Set, N=18)

(Source: Study FpS-AS-101 PK report, Figure 2)

Table 4.1.1. Summary of the fluticasone propionate plasma PK parameters by treatment

Parameter	Fp Spiromax 400 mcg × 2 (Treatment A)	Flovent Diskus 250 mcg × 4 (Treatment B)	Flovent HFA MDI 220 mcg × 4 (Treatment C)
C_{max} (pg/mL)	250.7 ± 75.9	224.1 ± 79.9	214.2 ± 133.5
t_{max} (hr) [a]	1.00 [0.09-2.00]	1.00 [0.33-2.01]	1.01 [0.52-6.00]
AUC_{0-t} (pg·hr/mL)	1871 ± 632	1684 ± 693	1799 ± 1136
$AUC_{0-\infty}$ (pg·hr/mL)	2056 ± 774 [b]	1934 ± 829 [c]	2330 ± 1204 [d]
$t_{1/2}$ (hr) [e]	10.1 ± 2.4 [9.6]	9.2 ± 1.0 [9.1]	9.6 ± 2.0 [9.2] [f]
λ_z (hr^{-1})	0.0722 ± 0.0169	0.0759 ± 0.0077	0.0752 ± 0.0149 [f]
Extrapolation (%)	13.7 ± 5.1 [b]	12.9 ± 3.1	13.8 ± 4.7 [f]

(Source: Study FpS-AS-101 PK report, Table 1)

Conclusion

- Following the administration of Fp MDPI 400 mcg x 2 inhalations, the systemic exposure, Cmax and AUC of Fp is higher compared with the FLOVENT DISKUS 250 mcg x 4 inhalations.

Study FpS-AS-102

Title: An Open-Label, Randomized, Three-Period Crossover, Single-Dose Study to Compare the Pharmacokinetic, Safety and Tolerability Profiles Following Four Inhalations of Fluticasone Propionate SPIROMAX® 100 and 200 mcg and Four Inhalations of FLUTIDE® DISKUS® 100 mcg Administered in Healthy Japanese and Caucasian Subjects

Study Phase: Phase I, pilot study

Objectives

- Primary objective: to assess the PK profiles of single doses of fluticasone propionate administered as 4 inhalations from Fp MDPI 100 and 200 mcg (400 mcg and 800 mcg total doses, respectively) and 4 inhalations from FLUTIDE DISKUS 100 mcg (400 mcg total dose)

- Secondary objective: to assess the safety profiles

Study Population: healthy Japanese and Caucasian subjects aged 20 to 45 years

Study Design

This was a single-center, open-label, randomized, 3-period crossover, single-dose pilot study in healthy Japanese and Caucasian subjects aged 20 to 45 years. Eligible subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA) containing the following 3 treatment arms:

- Treatment A: Fp MDPI 100 mcg, 4 inhalations
- Treatment B: Fp MDPI 200 mcg, 4 inhalations
- Treatment C: FLUTIDE DISKUS 100 mcg, 4 inhalations

Each treatment period was followed by a 5- to 8-day washout period except for the last treatment period.

PK Assessment

Plasma PK samples were obtained predose and at 0.03 (2 minutes), 0.08 (5 minutes), 0.17 (10 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 0.75 (45 minutes), 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0, and 24.0 hours postdose at each of the 3 treatment periods.

Results

30 subjects (15 Caucasian and 15 Japanese) were randomly assigned to 6 treatment sequences comprising 3 crossed-over, single-dose, open-label treatments. All 30 subjects received all 3 study treatments and were included in data analyses (Table 4.1.2).

Table 4.1.2. Demographics overall and by ethnicity

Demographic variables	Japanese (N=15)	Caucasian (N=15)	Total (N=30)
Age, years			
Mean	31.3	31.3	31.3
SD	7.65	6.82	7.12
SE of mean	1.98	1.76	1.30
Median	29.0	32.0	30.5
Min, max	22.0, 45.0	22.0, 41.0	22.0, 45.0
Ethnicity, n (%)			
Japanese	15 (100)	0	15 (50)
Caucasian	0	15 (100)	15 (50)
Sex, n (%)			
Men	10 (67)	10 (67)	20 (67)
Women	5 (33)	5 (33)	10 (33)
Race, n (%)			
White	0	15 (100)	15 (50)
Black	0	0	0
Asian	15 (100)	0	15 (50)
American Indian or Alaskan Native	0	0	0
Pacific Islander	0	0	0
Other	0	0	0
Weight, kg			
Mean	64.4	73.8	69.1
SD	7.69	12.05	11.03
SE of mean	1.98	3.11	2.01
Median	67.3	74.9	69.5
Min, max	50.9, 75.7	49.9, 93.3	49.9, 93.3
Height, cm			
Mean	167.8	168.4	168.1
SD	7.53	7.31	7.29
SE of mean	1.94	1.89	1.33
Median	167.7	165.8	167.0
Min, max	154.1, 180.9	157.7, 178.5	154.1, 180.9
BMI, kg/m^2			
Mean	22.8	25.9	24.4
SD	2.09	3.22	3.10
SE of mean	0.54	0.83	0.57
Median	22.4	26.6	24.4
Min, max	20.1, 27.0	20.1, 30.4	20.1, 30.4

Source: Summary 15.1.3.1, Listing 16.2.4.01.

(Source: Study FpS-AS-102 report, Table 8)

PK Results

The mean plasma concentration-versus-time profiles and PK parameters of Fp following all 3 treatments (Fp MDPI 400 mcg total dose [100 mcg x 4 inhalations], Fp MDPI 800 mcg total dose [200 mcg x 4 inhalations], FLOVENT DISKUS 400 mcg total dose [100 mcg x 4 inhalations] are presented in Figures 4.1.2, 4.1.3 and Table 4.1.3.

Results indicated that in both ethnic populations, the systemic exposure of Fp is highest after oral inhalation of Fp MDPI 800 mcg total dose. Even with the same total daily dose of 400 mcg, the Cmax and AUC of Fp is higher after Fp MDPI 100 mcg x 4 inhalations compared to FLUTIDE DISKUS 100 mcg x 4 inhalations.

Statistical comparisons also showed that after oral inhalation of the Fp MDPI 400 mcg total dose, Fp MDPI 800 mcg total dose, and FLUTIDE DISKUS 400 mcg total dose, there is no statistically significant difference for AUC0-t and Cmax between the Japanese and Caucasian ethnic populations for all 3 treatments.

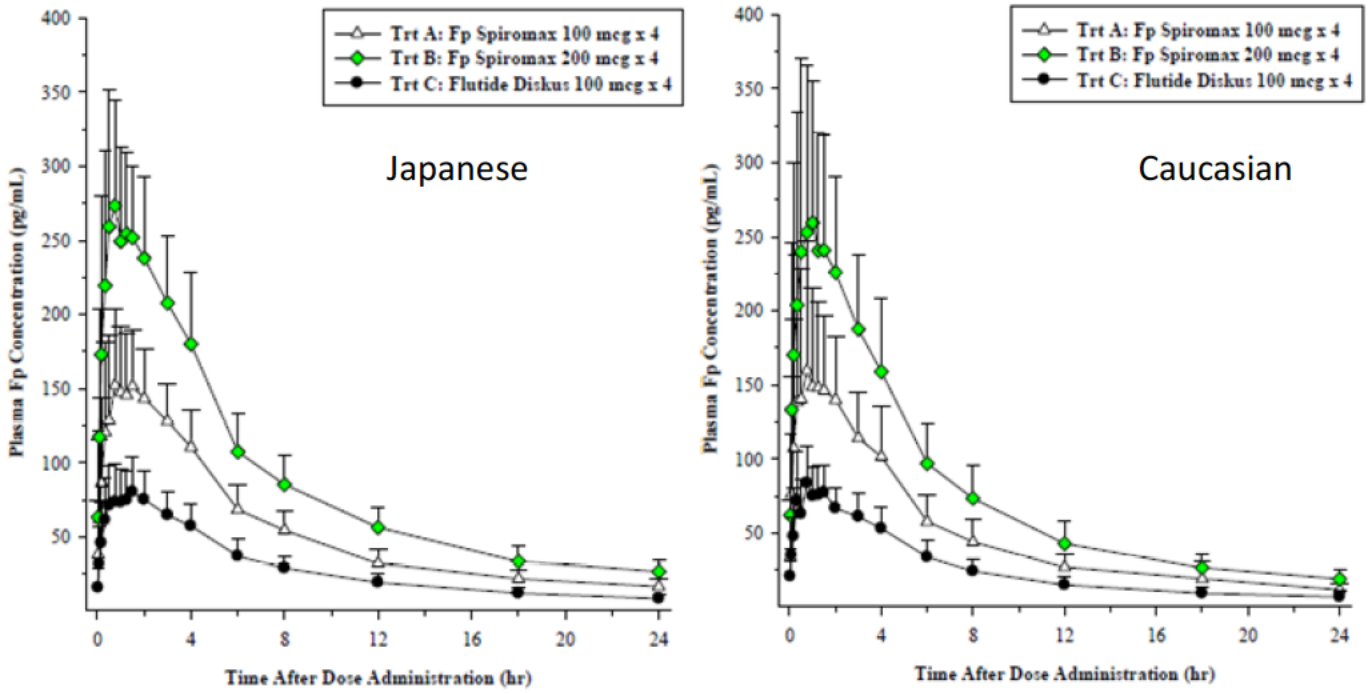


Figure 4.1.2. Mean (+ SD) plasma concentration-versus-time profiles of Fp in Japanese and Caucasian subjects following oral inhalation administration of a single dose of Fp MDPI 100 mcg × 4, Fp MDPI 200 mcg × 4, and FLUTIDE DISKUS 100 mcg × 4 (PK Analysis Set; N=15/Group)
(Source: Adapted from Figures 1 and 2, Study FpS-AS-102 PK report)

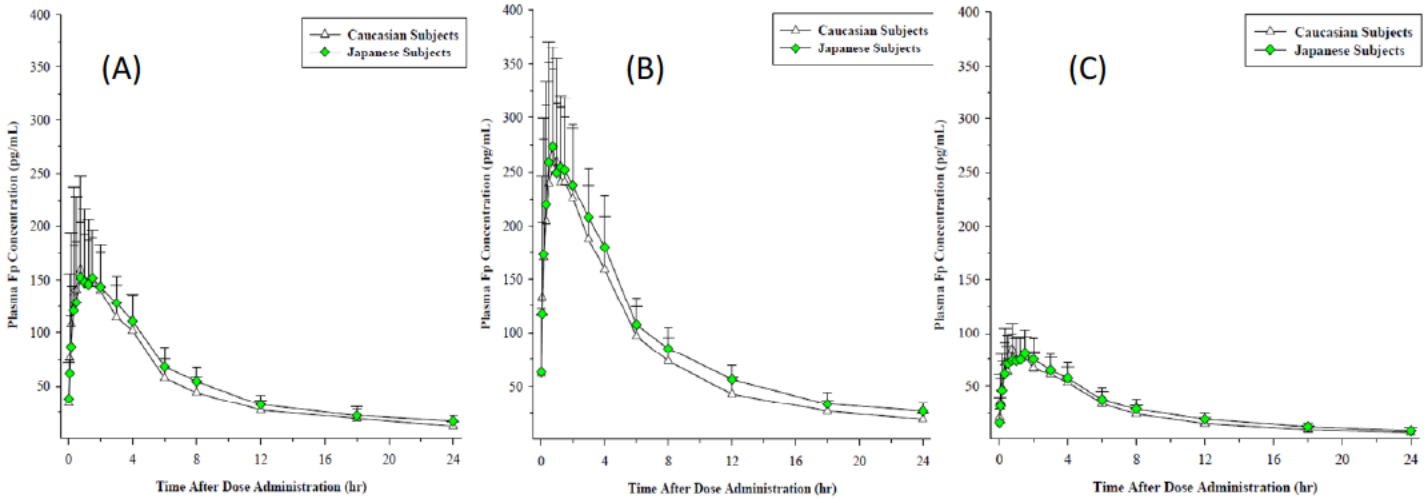


Figure 4.1.3. Ethic group comparison of Fp PK profiles in Japanese and Caucasian subjects following oral inhalation administration of a single dose of (A) Fp MDPI 100 mcg × 4, (B) Fp MDPI 200 mcg × 4, and (C) FLUTIDE DISKUS 100 mcg × 4 (PK Analysis Set; N=15/Group)
(Source: Adapted from Figures 3 and 5, Study FpS-AS-102 PK report)

Table 4.1.3. Mean (± SD) PK parameters of Fp in Japanese and Caucasian subjects following oral inhalation administration of single doses of Fp MDPI (100 mcg × 4 and 200 mcg × 4) and FLUTIDE DISKUS (100 mcg × 4) – PK Analysis Set (N=15/Group)

	Fp Spiromax 100 mcg × 4 (Treatment A)		Fp Spiromax 200 mcg × 4 (Treatment B)		Flutide Diskus 100 mcg × 4 (Treatment C)	
Parameter	**Japanese**	**Caucasian**	**Japanese**	**Caucasian**	**Japanese**	**Caucasian**
C_{max} (pg/mL)	170.2 ± 46.2	182.7 ± 78.6	306.3 ± 77.7	294.5 ± 101.9	84.8 ± 24.0	92.2 ± 23.8
t_{max} (hr)[a]	1.00 [0.33-3.00]	1.00 [0.17-2.00]	1.00 [0.50-3.00]	0.75 [0.17-2.00]	1.25 [0.50-3.00]	0.75 [0.33-4.00]
AUC_{0-t} (pg·hr/mL)	1275 ± 284	1145 ± 319	2101 ± 445	1836 ± 498	681 ± 178	603 ± 159
$AUC_{0-\infty}$ (pg·hr/mL)	1465 ± 334[b]	1284 ± 368[c]	2466 ± 609[e]	2140 ± 563[g]	754 ± 17[h]	666 ± 199[i]
$t_{1/2}$ (hr)[k]	12.8 ± 3.9 [12.1]	9.8 ± 1.5 [9.6][d]	10.9 ± 2.1 [10.5][f]	10.4 ± 1.9 [10.1]	10.1 ± 1.8 [9.8]	9.4 ± 1.8 [9.1][j]
λ_z (hr^{-1})	0.0573 ± 0.0125	0.0723 ± 0.0101[d]	0.0662 ± 0.0130[f]	0.0683 ± 0.0112	0.0709 ± 0.0123	0.0761 ± 0.0145[j]
Extrapolation (%)	19.1 ± 5.4	12.3 ± 3.8[d]	16.1 ± 4.0[f]	13.5 ± 4.6	15.2 ± 3.8	12.0 ± 5.2[j]

(Source: Study FpS-AS-102 PK report, Table 1)

Conclusions

- Following the administration of tested products (Fp MDPI 400 mcg, Fp MDPI 800 mcg, and FLUTIDE DISKUS 400 mcg total doses), there appears no marked difference in systemic exposure (Cmax and AUC) of Fp between Japanese and Caucasian subjects.
- Overall, inhaled single doses of fluticasone propionate ranging from 400 to 800 mcg total doses were generally well tolerated.

Study FSS-AS-10042

Title: 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

Study Phase: Phase I, PK study

Objectives

- Primary objective: to determine the PK profiles of fluticasone propionate and/or salmeterol from a single dose of Fp MDPI 200 mcg and FS MDPI 200/12.5 mcg as compared to FLOVENT DISKUS 500 mcg or ADVAIR DISKUS 500/50 mcg in patients with persistent asthma aged ≥12 years
- Secondary objectives: to assess safety and tolerability

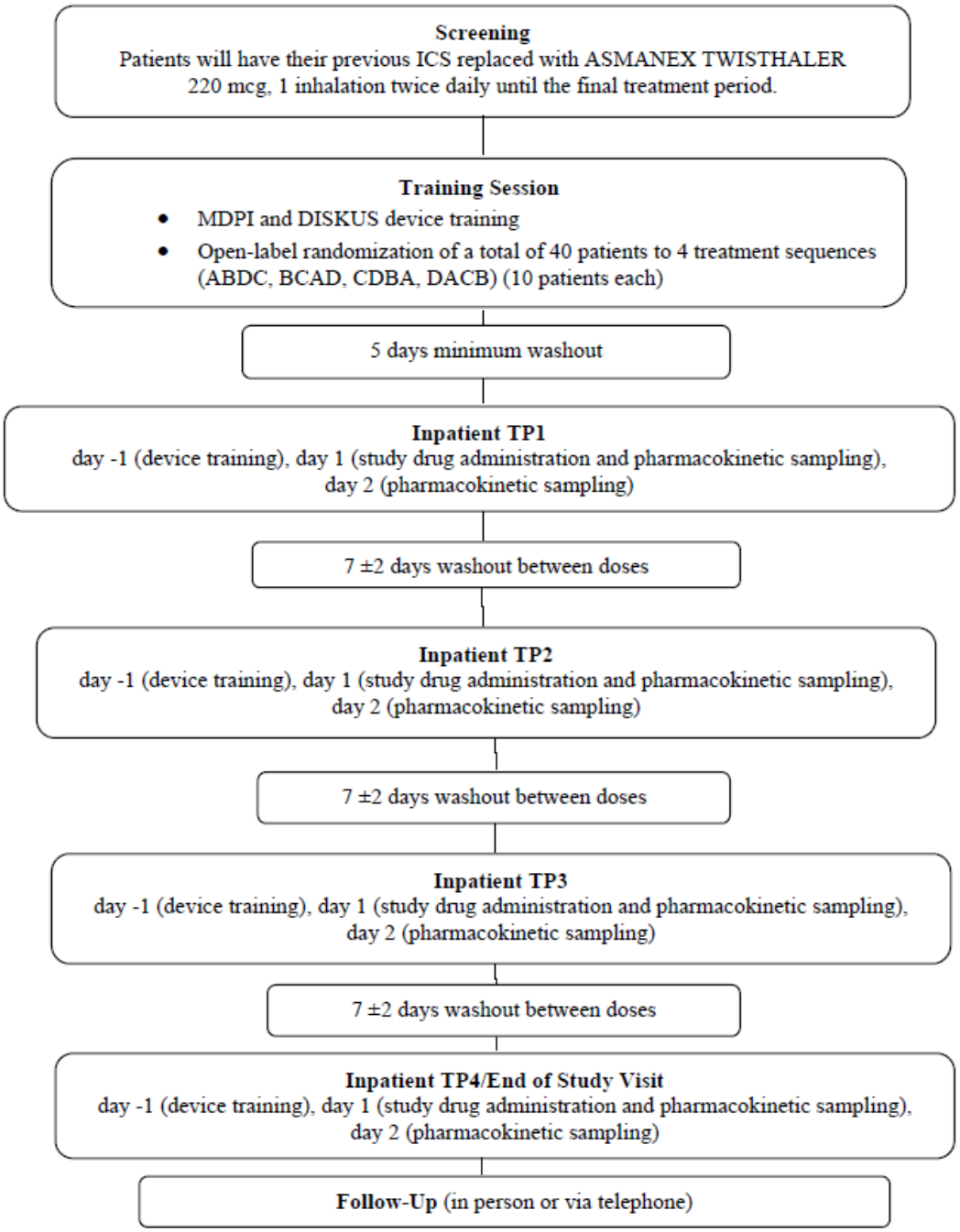
Study Population: patients with persistent asthma aged ≥12 years

Study Design
This was a multicenter, open-label, randomized, 4-period crossover, single-dose study in patients with persistent asthma aged 12 years and older. The training session (TS) was performed only after the investigator had determined that the patient met all of the inclusion criteria and none of the exclusion

criteria. Eligible patients were randomized to 1 of 4 treatment sequences (ABDC, BCAD, CDBA, or DACB) containing the following treatments:

- Treatment A: Fp MDPI 200 mcg, 1 inhalation
- Treatment B: FS MDPI 200/12.5 mcg, 1 inhalation
- Treatment C: FLOVENT DISKUS 250 mcg, 2 inhalations
- Treatment D: ADVAIR DISKUS 500/50 mcg, 1 inhalation

The study consisted of screening visit, 4 treatment periods (TPs), and follow-up visit. In each TP, device training was performed on day -1. Study drug was administered between 0700 and 0900 (±30 minutes) on day 1. PK assessments (plasma fluticasone propionate and/or salmeterol levels) were conducted up to 36 hours after dosing. After the final blood sample, patients underwent training and tolerability assessment to 2 inhalations with the active treatment that was to be administered during next TP and were released for a 7 (±2) days washout period before next TP. End of study visit procedures (except for vital signs) were performed after the last dose of study drug at TP4. Efficacy was not assessed during this study. The study schema is presented in Figure 4.1.4.



ICS=inhaled corticosteroid, TP1-4=treatment period 1, 2, 3 and 4, Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler
Treatment A: Fp MDPI 200 mcg, 1 inhalation; **Treatment B**: FS MDPI 200/12.5 mcg, 1 inhalation; **Treatment C**: fluticasone propionate (FLOVENT® DISKUS®, GlaxoSmithKline) 250 mcg, 2 inhalations; **Treatment D**: fluticasone propionate/salmeterol (ADVAIR® DISKUS®, GlaxoSmithKline) 500/50 mcg, 1 inhalation

Figure 4.1.4. Overall study schema
(Source: Study FSS-AS-10042 report, Figure 1)

PK Assessment

Plasma PK samples were obtained for determining the plasma concentrations of fluticasone propionate and salmeterol (as applicable)within approximately 30 minutes before dosing and at 0.08 (5 minutes), 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 16, 24, 30, and 36 hours after dosing during TP1 to TP4.

Results

Of 45 asthma patients screened, 43 patients were enrolled and 40 patients received at least 1 dose of study drug and were evaluated for safety in the study; 3 patients withdrew before taking any study drug. Pharmacokinetic was assessed in 40 patients who were dosed. The demographic information was shown in Table 4.1.4.

Table 4.1.4. Demographic information

Demographic variables	Total (N=43)
Age, years	
n	43
Mean	29.6
SD	17.12
Median	21.0
Min, max	12.0, 72.0
Age group, years, n (%)	
n	43
12-17	17 (40)
18+	26 (60)
Sex, n (%)	
n	43
Men	24 (56)
Women	19 (44)
Race, n (%)	
n	43
White	31 (72)
Black	11 (26)
Other	1 (2)
Ethnicity, n (%)	
n	43
Not Hispanic or Latino	33 (77)
Hispanic or Latino	10 (23)
Weight, kg	
n	43
Mean	76.3
SD	14.22
Median	74.4
Min, max	53.1, 111.7
Height, cm	
n	43
Mean	170.2
SD	11.19
Median	170.8
Min, max	149.0, 191.0
BMI, kg/m^2	
n	43
Mean	26.3
SD	4.10
Median	26.3
Min, max	18.3, 33.5

Source: Summary 15.1.2.1, Listing 16.2.3.1.
ITT=intent-to-treat population, BMI=body mass index, min=minimum, max=maximum, SD=standard deviation.
(Source: Study FSS-AS-10042 report, Table 7)

PK Results

Fp

The PK profiles of Fp in adult and adolescent patients with asthma after oral inhalation administration of Fp MDPI 200 mcg x 1 inhalation (Treatment A), FS MDPI 200/12.5 mcg x 1 inhalation (Treatment B),

FLOVENT DISKUS 250 mcg x 2 inhalations (Treatment C), and ADVAIR DISKUS 500/50 mcg x 1 inhalation (Treatment D) are presented in Figure 4.1.5. The PK analysis and comparison between treatments are shown in Tabels 4.1.5-4.1.8.

Results indicate following the administration of study products, the systemic exposure to Fp represented by geometric mean estimates of Cmax, AUC0-t, and AUC0-∞ were lower (~20%) in Fp MDPI compared with FLOVENT DISKUS , but were similar with FS MDPI and ADVAIR DISKUS. A post hoc comparison of Cmax, AUC0-t, and AUC0-∞ for Fp in Fp MDPI (200 mcg) versus FS MDPI (200/12.5 mcg) indicated that the systemic exposure of Fp is similar with Fp MDPI and FS MDPI, suggesting the presence of Sx in FS MDPI does not affect Fp PK.

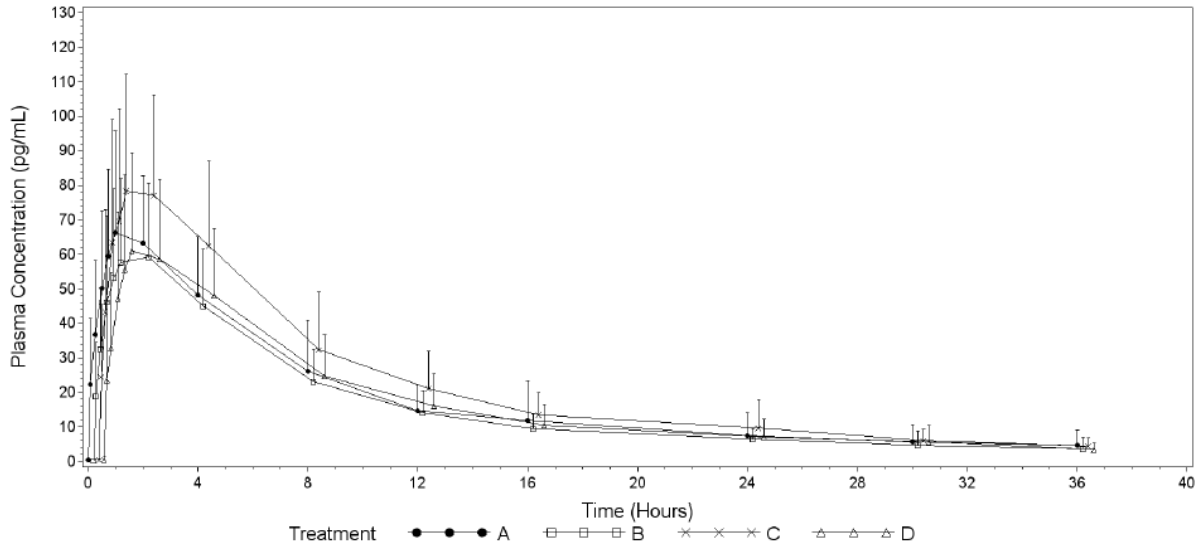


Figure 4.1.5. Linear mean (+SD) plasma concentration versus time profiles (0-36 hr) for fluticasone propionate by treatment
Treatment A: Fp MDPI 200 mcg; Treatment B: FS MDPI 200/12.5 mcg; Treatment C: FLOVENT DISKUS 250 mcg × 2; Treatment D: ADVAIR DISKUS 500/50 mcg
(Source: Adapted from Figure 3 of Study FSS-AS-10042 report)

Table 4.1.5. Summary of plasma PK parameters for fluticasone propionate by treatment

Parameter	Units	Statistic	Treatment A Fp MDPI 200 mcg (N=39)	Treatment C FLOVENT DISKUS 250 mcg × 2 (N=37)	Treatment B FS MDPI 200/12.5 mcg (N=37)	Treatment D ADVAIR DISKUS 500/50 mcg (N=37)
C_{max}	pg/mL	n	39	37	37	37
		Arith Mean	72.97	85.51	65.83	67.10
		Geo Mean	67.46	78.12	61.55	61.26
		Min, max	21.14, 158.50	21.05, 159.93	21.92, 139.10	11.22, 137.71
		CV (%)	38.9	38.9	36.9	39.9
AUC_{0-t}	hr*pg/mL	n	38	37	36	37
		Arith Mean	654.6	810.1	582.5	626.4
		Geo Mean	597.2	739.0	544.7	559.9
		Min, max	120.9, 1813.5	147.5, 1750.4	162.3, 870.9	53.2, 1099.7
		CV (%)	43.9	40.8	32.1	40.6
$AUC_{0-\infty}$	hr*pg/mL	n	32	33	30	33
		Arith Mean	709.1	875.5	626.4	687.0
		Geo Mean	642.5	796.4	585.6	608.1
		Min, max	128.5, 2157.6	155.0, 1868.6	170.7, 944.0	61.0, 1186.2
		CV (%)	48.8	41.0	32.2	42.6
$\%AUC_{extrap}$	%	n	32	33	30	33
		Arith Mean	7.8	7.8	6.9	8.5
		Geo Mean	7.4	7.3	6.7	7.8
		Min, max	3.2, 15.9	3.2, 15.1	4.3, 10.9	3.3, 14.9
		CV (%)	36.8	36.3	27.0	39.9
t_{max}	hr	n	39	37	37	37
		Median	1.00	1.00	1.98	1.00
		Min, max	0.50, 4.00	0.50, 4.02	0.08, 4.02	0.25, 4.05
		CV (%)	58.7	67.6	66.4	70.4
$t_{½}$	hr	n	32	33	30	33
		Arith Mean	11.28	10.96	10.80	11.34
		Geo Mean	11.19	10.86	10.71	11.09
		Min, max	8.28, 14.25	7.45, 14.44	7.64, 13.93	6.84, 16.78
		CV (%)	12.6	13.8	13.3	21.7

Source: Summary 15.2.3.1 and Listing 16.2.6.3.
N= total number of patients in each group, n=number of patients with applicable measurement.
(Source: Study FSS-AS-10042 report, Table 12)

Table 4.1.6. Fluticasone propionate PK comparisons for Cmax, AUC0-t and AUC0-∞ following administration of Treatment A (Fp MDPI 200 mcg) vs Treatment C (FLOVENT DISKUS 250 mcg×2, 500 mcg total dose)

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (A/C)	90% CI of Ratio (A/C)
C_{max} (pg/mL)	A vs C	37	66.41	0.848	0.77 – 0.93
			78.28		
AUC_{0-t} (hr*pg/mL)	A vs C	37	593.25	0.797	0.72 – 0.88
			744.04		
$AUC_{0-\infty}$ (hr*pg/mL)	A vsC	30	616.45	0.758	0.69 – 0.83
			812.91		

Source: Summary 15.2.5.1.
Treatment A: Fp MDPI 200 mcg; Treatment C: FLOVENT DISKUS 250 mcg × 2
(Source: Study FSS-AS-10042 report, Table 13)

Table 4.1.7. Fluticasone propionate PK comparisons for Cmax, AUC0-t and AUC0-∞ following administration of Treatment B (FS MDPI 200/12.5 mcg) vs Treatment D (ADVAIR DISKUS 500/50 mcg)

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (B/D)	90% CI of Ratio (B/D)
C_{max} (pg/mL)	B vs D	36	61.92	1.005	0.92 – 1.10
			61.62		
AUC_{0-t} (hr*pg/mL)	B vs D	36	545.48	0.962	0.87 – 1.07
			566.96		
$AUC_{0-\infty}$ (hr*pg/mL)	B vs D	28	586.85	0.949	0.86 – 1.04
			618.51		

Source: Summary 15.2.5.1.
Treatment B: FS MDPI 200/12.5 mcg; Treatment D: ADVAIR DISKUS 500/50 mcg
(Source: Study FSS-AS-10042 report, Table 14)

Table 4.1.8. Fluticasone propionate PK comparisons for Cmax, AUC0-t and AUC0-∞ following Treatment A (Fp MDPI 200 mcg) and Treatment B (FS MDPI 200/12.5 mcg)

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (A/B)	90% CI of Ratio (A/B)	Root MSE	Intra-patient CV
C_{max} (pg/mL)	A	37	66.48	1.085	0.99 – 1.19	0.236	0.239
	B	37	61.24				
AUC_{0-t} (hr*pg/mL)	A	36	593.20	1.089	0.98 – 1.21	0.268	0.273
	B	36	544.77				
$AUC_{0-\infty}$ (hr*pg/mL)	A	25	623.60	1.068	0.96 – 1.19	0.225	0.228
	B	25	583.68				

Source: Adhoc Summary 1
Treatment A: Fp MDPI 200 mcg; Treatment B: FS MDPI 200/12.5 mcg
(Source: Study FSS-AS-10042 report, Table 16)

The PK parameters of Fp following the administration of different products by age are shown in the Tables 4.1.9. Results indicate that following the administration of Fp MDPI 200 mg and FS MDPI 200/12.5 mcg, Cmax of Fp appears slightly lower, but AUC of Fp appears higher in subjects aged 12-17 years compared with subjects aged ≥18 years. The same was also observed following the administration of reference products, FLOVENT DISKUS 250mcg×2 and AFVAIR DISKUS 500/50mcg.

Table 4.1.9. PK parameters of fluticasone propionate by age

PK (Mean±SD)	FLOVENT DISKUS 250 mcg×2		Fp MDPI 200 mcg		AFVAIR DISKUS 500/50 mcg		FS MDPI 200/12.5 mcg	
	12-17 yrs (N=14)	18+ yrs (N=23)	12-17 yrs (N=16)	18+ yrs (N=23)	12-17 yrs (N=14)	18+ yrs (N=23)	12-17 yrs (N=15)	18+ yrs (N=22)
Cmax (pg/mL)	81.31±40.09	88.07±29.15	68.52±26.86	76.18±29.67	66.45±23.17	67.50±29.29	56.71±17.39	72.05±26.71
AUC0-t (h*pg/mL)	829±392	798±296	676±247	641±316	698±264	583±243	619±193	559±185
AUCinf (h*pg/mL)	938±427	835±312	781±245	660±400	756±307	647±284	627±284	626±191
Tmax (h) Median(min, max)	1.51 (0.50, 4.02)	1.00 (0.50, 4.00)	1.50 (0.75, 4.00)	1.00 (0.50, 4.00)	1.53 (0.50, 4.00)	1.00 (0.25, 4.00)	2.00 (0.75, 4.02)	1.00 (0.08, 4.00)
T1/2 (h) Median(min, max)	10.4 (7.5, 14.4)	10.9 (8.3, 13.5)	11.5 (8.6, 13.6)	11.4 (8.3, 14.3)	10.4 (7.3, 11.8)	11.1 (6.8, 16.8)	10.2 (8.5, 11.7)	10.9 (7.6, 13.9)

(Source: Adapted from Summary 15.2.11.1, Study FSS-AS-10042 report)

The PK parameters of Fp following the administration of different products by sex are shown in the Tables 4.1.10. Results indicate that following the administration of Fp MDPI 200 mg and FS MDPI 200/12.5 mcg, Cmax of Fp appears lower, but AUC of Fp appears higher in males compared with females.

Table 4.1.10. PK parameters of fluticasone propionate by sex

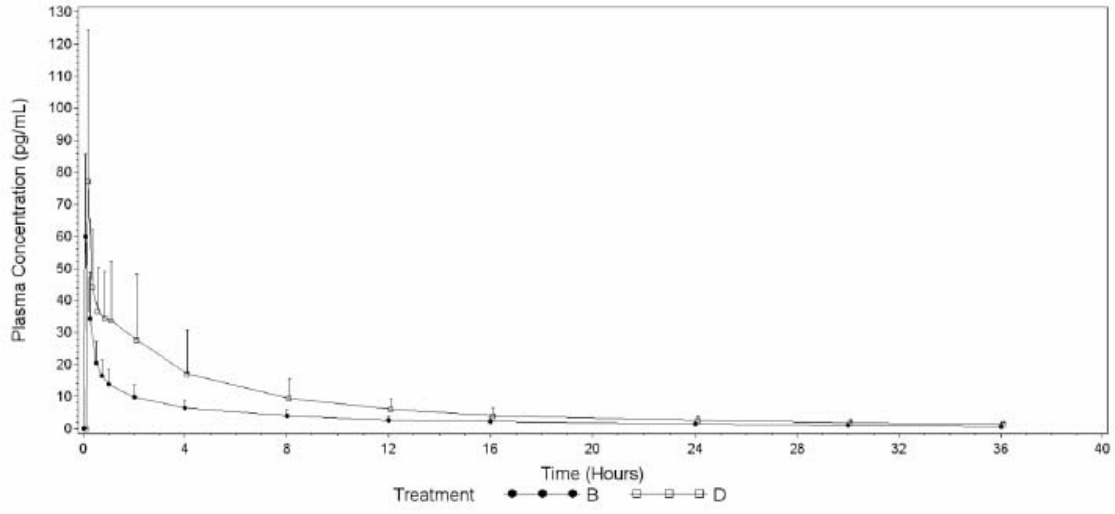
PK (Mean±SD)	FLOVENT DISKUS 250 mcg×2		Fp MDPI 200 mcg		AFVAIR DISKUS 500 mcg/50 mcg		FS MDPI 200/12.5 mcg	
	Male (N=21)	Female (N=16)	Male (N=22)	Female (N=17)	Male (N=21)	Female (N=16)	Male (N=21)	Female (N=16)
Cmax (pg/mL)	72.76±35.43	102.2±21.59	66.49±29.79	81.36±24.96	59.15±25.41	77.53±25.66	58.69±22.85	75.20±23.65
AUC0-t (h*pg/mL)	776±395	855±227	680±350	619±175	631±299	620±188	602±193	558±183
AUCinf (h*pg/mL)	823±427	946±235	742±427	654±130	701±350	670±217	631±219	621±189
Tmax (h) Mean(min, max)	2.00 (0.50, 4.02)	1.00 (0.50, 2.02)	2.00 (0.50, 4.00)	1.00 (0.50, 2.00)	2.00 (0.25, 4.05)	1.00 (0.50, 4.03)	2.00 (0.50, 4.00)	1.00 (0.08, 4.02)
T1/2 (h) Mean(min, max)	10.4 (7.5, 14.4)	11.2 (8.3, 13.5)	11.3 (8.3, 13.6)	11.9 (8.8, 14.3)	10.4 (6.8, 15.0)	11.2 (8.5, 16.8)	10.2 (7.6, 11.9)	11.0 (9.3, 13.9)

(Source: Adapted from Summary 15.2.9.1, Study FSS-AS-10042 report)

Sx

The PK profiles of Sx in adult and adolescent patients with asthma after oral inhalation administration of FS MDPI 200/12.5 mcg (Treatment B) and ADVAIR DISKUS 500/50 mcg (Treatment D) are presented in Figure 4.1.6. The PK analysis and comparison between treatments are shown in Tabels 4.1.11 and 4.1.12.

Results indicate following the administration of FS MDPI, Cmax of Sx was approximately 20% lower, and AUC0-t and AUC0-∞ of Sx were approximately 50% lower compared to the corresponding estimates of Sx following the administration of ADVAIR DISKUS.



Source: Summary 15.2.1.2 and Listing 16.2.6.2.
Treatment B: FS MDPI 200/12.5 mcg; Treatment D: ADVAIR DISKUS 500/50 mcg

Figure 4.1.6. Linear mean (+SD) plasma concentration versus time profiles (0-36 hr) for salmeterol by treatment

(Source: Adapted from Figure 4 of Study FSS-AS-10042 report)

Table 4.1.11. Summary of plasma pharmacokinetic parameters for salmeterol by treatment

			Treatment B	Treatment D
Parameter	**Units**	**Statistic**	**FS MDPI 200/12.5 mcg**	**ADVAIR DISKUS 500/50 mcg**
			(N=39)	**(N=37)**
C_{max}	pg/mL	n	38	35
		Arith Mean	60.06	81.08
		Geo Mean	54.32	68.50
		Min, max	16.49, 123.43	20.03, 197.36
		CV (%)	42.7	56.6
AUC_{0-t}	hr*pg/mL	n	37	35
		Arith Mean	125.3	271.3
		Geo Mean	118.1	241.1
		Min, max	47.9,265.3	95.3,763.8
		CV (%)	36.0	55.3
$AUC_{0-\infty}$	hr*pg/mL	n	36	35
		Arith Mean	141.2	297.1
		Geo Mean	133.3	264.7
		Min, max	57.3, 298.9	104.2, 837.4
		CV (%)	35.8	54.3
$\%AUC_{extrap}$	%	n	36	35
		Arith Mean	11.0	8.8
		Geo Mean	10.7	8.2
		Min, max	6.2, 17.8	2.5, 14.3
		CV (%)	24.3	36.2
t_{max}	hr	n	38	35
		Median	0.08	0.08
		Min, max	0.08, 0.75	0.07, 2.00
		CV (%)	105.4	166.6
$t_{½}$	hr	n	36	35
		Arith Mean	12.63	12.14
		Geo Mean	12.53	11.93
		Min, max	10.76, 16.02	8.12, 16.94
		CV (%)	12.5	18.9

Source: Summary 15.2.3.2 and Listing 16.2.6.4.
N= total number of patients in each group, n=number of patients with applicable measurement.
Treatment B: FS MDPI 200/12.5 mcg; Treatment D: ADVAIR DISKUS 500/50 mcg
(Source: Study FSS-AS-10042 report, Table 17)

Table 4.1.12. Salmeterol treatment comparisons for Cmax, AUC0-t and AUC0-∞

Parameter	**Treatment**	**n**	**Geometric LS Means**	**Ratio of Geometric LS Means (B/D)**	**90% CI of Ratio (B/D)**
C_{max} (pg/mL)	B	35	56.50	0.811	0.70 – 0.94
	D	35	69.71		
AUC_{0-t} (hr*pg/mL)	B	35	119.65	0.496	0.46 – 0.54
	D	35	241.22		
$AUC_{0-\infty}$ (hr*pg/mL)	B	34	134.37	0.511	0.47 – 0.55
	D	34	262.69		

Source: Summary 15.2.5.2.
Treatment B: FS MDPI 200/12.5 mcg; Treatment D: ADVAIR DISKUS 500/50 mcg
(Source: Study FSS-AS-10042 report, Table 18)

The PK parameters of Sx following the administration of different products by age are shown in the Table 4.1.13. Results indicate that following the administration of FS MDPI 200/12.5 mg, Sx Cmax appears higher, but AUC appears similar in subjects aged 12-17 years compared with subjects aged ≥18 years.

Table 4.1.13. PK parameters of salmeterol by age

PK (Mean±SD)	AFVAIR DISKUS 500 mcg/50 mcg		FS MDPI 200/12.5 mcg	
	12-17 yrs (N=14)	18+ yrs (N=23)	12-17 yrs (N=15)	18+ yrs (N=22)
Cmax (pg/mL)	94.03±57.75	72.45±34.92	67.86±22.44	54.98±26.85
AUC0-t (h*pg/mL)	257±95	281±180	125±33	126±52
AUCinf (h*pg/mL)	278±98	310±194	140±36	142±58
Tmax (h) Median(min, max)	0.08 (0.08, 2.00)	0.08 (0.07, 2.00)	0.08 (0.08, 0.13)	0.08 (0.08, 0.75)
T1/2 (h) Median(min, max)	11.2 (8.4, 14.8)	12.2 (8.1, 16.9)	11.7 (10.8, 13.9)	13.1 (10.8, 16.0)

(Source: Adapted from Summary 15.2.11.2, Study FSS-AS-10042 report)

The PK parameters of Sx following the administration of different products by sex are shown in the Table 4.1.14. Results indicate that following the administration of FS MDPI 200/12.5 mg, Sx Cmax and AUCs appears lower in males compared with females.

Table 4.1.14. PK parameters of salmeterol by sex

PK (Mean±SD)	AFVAIR DISKUS 500 mcg/50 mcg		FS MDPI 200/12.5 mcg	
	Male (N=19)	Female (N=16)	Male (N=22)	Female (N=16)
Cmax (pg/mL)	84.58±54.51	76.92±34.32	56.41±23.69	65.08±28.20
AUC0-t (h*pg/mL)	234±148	315±145	108±34	149±49
AUCinf (h*pg/mL)	255±151	348±163	122±38	165±55
Tmax (h) Median(min, max)	0.08 (0.07, 2.00)	0.08 (0.08, 2.00)	0.08 (0.08, 0.13)	0.08 (0.08, 0.75)
T1/2 (h) Median(min, max)	12.2 (8.1, 14.8)	11.8 (8.7, 16.9)	12.9 (10.8, 16.0)	12.0 (10.8, 16.0)

(Source: Adapted from Summary 15.2.9.2, Study FSS-AS-10042 report)

Conclusions

- Fp
  - Fp MDPI (200 mcg) vs. FLOVENT DISKUS (250 mcg×2)
    The systemic exposure to Fp (Cmax, AUC0-t, and AUC0-∞) is ~20% lower with Fp MDPI (200 mcg) compared to FLOVENT DISKUS (250 mcg×2).
  - FS MDPI (200/12.5 mcg) vs ADVAIR DISKUS (500/50 mcg)
    The systemic exposure of Fp (Cmax, AUC0-t, and AUC0-∞) is similar with FS MDPI and ADVAIR DISKUS.
- Sx
  - FS MDPI (200/12.5 mcg) vs ADVAIR DISKUS (500/50 mcg)
    Following the administration of FS MDPI, the systemic exposure to Sx is lower (Cmax was ~20% lower; AUC0-t and AUC0-∞ were ~ 50% lower) compared to ADVAIR DISKUS.
- Overall, single doses of Fp MDPI 200 mcg and FS MDPI 200/12.5 mcg were safe and well tolerated when compared to FLOVENT DISKUS 250 mcg × 2 and ADVAIR DISKUS 500/50 mcg.

Study FpS-AS-201

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 Phase: Phase II, dose-ranging study

Objectives

- Primary objective: to evaluate the dose response, efficacy, and safety of 4 different doses of fluticasone propionate (12.5, 25, 50, and 100 mcg) delivered as Fp SPIROMAX Inhalation Powder (hereafter called Fp MDPI) when administered twice daily in subjects 12 years of age and older with persistent asthma who are uncontrolled on nonsteroidal therapy

Study Population: subjects aged 12 years and older with asthma who were uncontrolled on nonsteroidal therapy

Study Design

This was a randomized, double-blind, placebo- and open-label active-controlled, parallel-group, multicenter, dose-ranging study in male and female subjects aged 12 years and older with asthma who were uncontrolled on nonsteroidal therapy. Upon successful completion of the run-in period, subjects who continued to meet eligibility criteria were randomized to 1 of 6 treatment groups:

- Fp MDPI 12.5 mcg BID
- Fp MDPI 25 mcg BID
- Fp MDPI 50 mcg BID
- Fp MDPI 100 mcg BID
- Placebo MDPI BID
- FLOVENT DISKUS 100 mcg BID

The treatment period of the study was 84 days±2 days (12 weeks) in duration. During the treatment period, subjects received the double-blind or open-label treatment to which they were randomized. The overall study schema is presented in Figure 4.1.7.

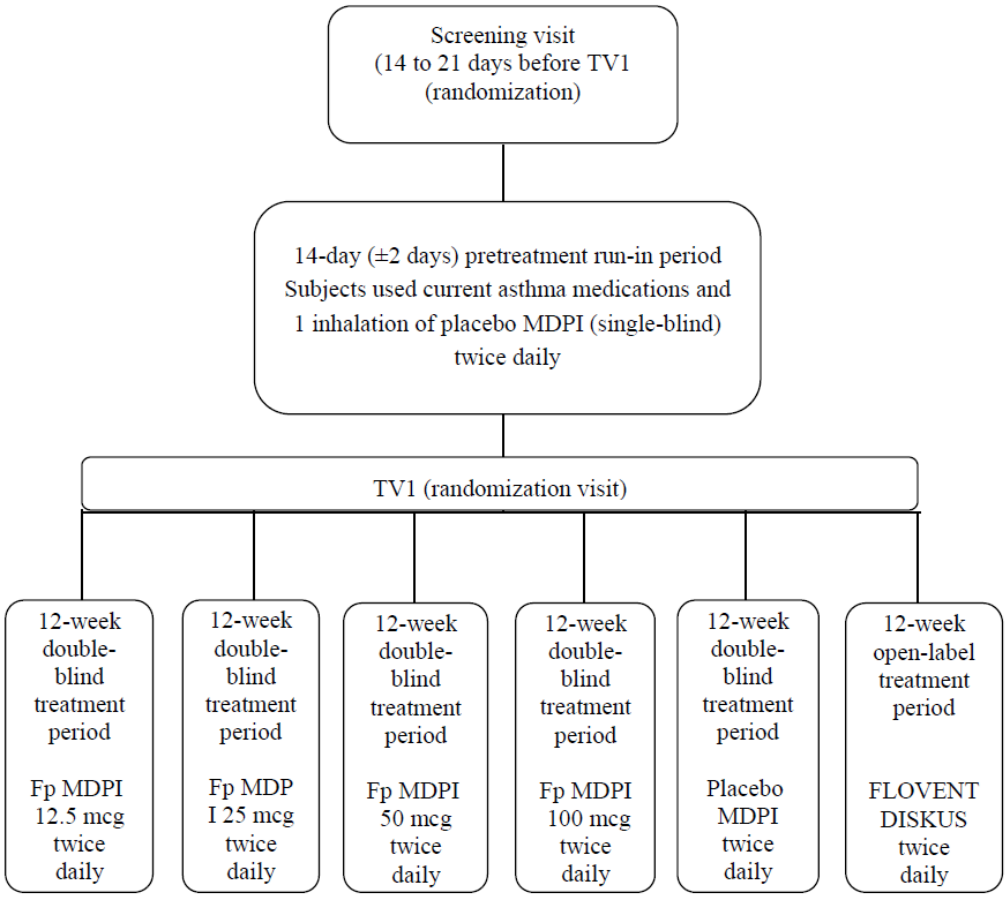


Figure 4.1.7. Overall study schema
(Source: Study FpS-AS-201 report, Figure 1)

Efficacy Assessment
The primary efficacy endpoint was the change from baseline in trough (AM predose and prerescue bronchodilator) FEV1 over the 12-week treatment period.

PK Assessment
Blood samples (~9 mL) for Fp PK assessment were obtained from a preselected subset of subjects (PK cohort) predose (within ~10 min before the AM dose administration) and at 0.08 (5 min), 0.17 (10 min), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1, 1.25, 1.5, 2, 4, 8, and 12 hr after the first dose of study medication at TV1.

Results

Efficacy Results
In all treatment groups, there was an increase in LS mean FEV1 from baseline over the 12-week treatment period with an indication of a dose response in the Fp MDPI groups: the LS mean changes are 0.170 L, 0.229 L, 0.243 L, and 0.267 L with Fp MDPI 12.5, 25, 50, and 100 mcg, respectively. In the comparison of placebo versus each Fp MDPI dose, the change from baseline in trough FEV1 over the 12-week treatment period was statistically significantly different (greater) for the 100 mcg group (LS mean difference 0.149 L, p = 0.0005), the 50 mcg group (0.126 L, p = 0.0027), and the 25 mcg group (0.111 L, p = 0.0086), but not for the lowest dose of 12.5 mcg (0.052 L, p = 0.2227) (Table 4.1.15).

Table 4.1.15. Change in FEV1 (L) from baseline over the 12-week treatment period (FAS)

FEV_1		Fp MDPI				Placebo (N=102)
		12.5 mcg (N=102)	25 mcg (N=101)	50 mcg (N=102)	100 mcg (N=102)	
At baseline	Mean (SD)	2.234 (0.6953)	2.239 (0.6173)	2.223 (0.6452)	2.252 (0.6550)	2.222 (0.6054)
	Median (min, max)	2.115 (0.830, 4.230)	2.270 (0.970, 3.810)	2.205 (0.950, 3.980)	2.265 (0.790, 4.280)	2.100 (1.130, 4.010)
Over the 12-week period	Mean (SD)	2.387 (0.6948)	2.450 (0.6560)	2.466 (0.6426)	2.526 (0.7251)	2.329 (0.6436)
	Median (min, max)	2.337 (0.870, 4.250)	2.404 (1.050, 4.014)	2.465 (1.042, 3.914)	2.501 (1.086, 4.430)	2.208 (1.234, 4.354)
Change from baseline over 12-week treatment period	LS mean	0.170	0.229	0.243	0.267	0.118
	SE[a]	0.0300	0.0295	0.0288	0.0300	0.0302
	95% CI	(0.111, 0.229)	(0.171, 0.287)	(0.187, 0.300)	(0.208, 0.326)	(0.058, 0.177)
Difference from placebo	p-value	0.2227	0.0086	0.0027	0.0005	-
	LS mean	0.052	0.111	0.126	0.149	-
	95% CI	(-0.032, 0.136)	(0.028, 0.194)	(0.044, 0.208)	(0.066, 0.233)	-

Source: Summary 15.2.1.1, Summary 15.2.4.1, Ad hoc Table 1.4, Listing 16.2.1.01 and Listing 16.2.6.01
(Source: Study FpS-AS-201 report, Table 13)

PK results

The PK analysis set included a total of 90 subjects from the pharmacokinetic cohort. Fp AUC0-t and Cmax increased with increasing dose of Fp MDPI and comparisons of AUC0-t and Cmax between doses of Fp MDPI indicated approximately dose proportional increases in both parameters across the doses levels tested (Fp MDPI 12.5, 25, 50, and 100 mcg) (Table 4.1.16).

Table 4.1.16. Fluticasone propionate pharmacokinetics descriptive statistics (PK Analysis Set)

Pharmacokinetic parameters	Statistic	Fp MDPI				Flovent Diskus (N=21)
		12.5 mcg (N=16)	25 mcg (N=22)	50 mcg (N=19)	100 mcg (N=17)	
AUC_{0-t} (pg•hr/mL)	Mean (SD)	21.6 (27.09)	42.0 (23.21)	63.2 (22.64)	153.8 (91.42)	103.4 (45.65)
	Median	10.2	37.4	64.2	130.2	121.3
	Min, max	1.7, 106.4	3.1, 103.2	11.7, 105.1	39.4, 359.7	46.9, 179.3
C_{max} (pg/mL)	Mean (SD)	5.4 (4.23)	10.0 (5.35)	12.9 (5.13)	33.6 (15.49)	23.4 (10.73)
	Median	3.7	8.9	12.8	31.9	22.8
	Min, max	2.6, 18.5	3.2, 28.8	4.6, 26.7	10.5, 69.2	11.4, 48.3
t_{max} (hr)	Mean (SD)	1.2 (0.97)	1.4 (2.43)	1.7 (2.55)	1.1 (0.95)	1.7 (2.61)
	Median	1.1	1.0	1.0	0.8	1.0
	Min, max	0.2, 4.0	0.1, 12.0	0.3, 12.0	0.2, 4.0	0.3, 12.0

Source: Summary 15.3.27, Listing 16.2.8.14
(Source: Study FpS-AS-201 report, Table 27)

Conclusions

- An increase in LS mean FEV1 from baseline over the 12-week treatment period was observed indicating a dose response in the Fp MDPI groups (12.5, 25, 50 and 100 mcg). In the comparison of placebo versus each Fp MDPI dose, 25 mcg is the lowest dose with statistically significant difference in the change from baseline in trough FEV1 over the 12-week.
- Fp AUC0-t and Cmax increased with dose of Fp MDPI (12.5, 25, 50, and 100 mcg) approximately dose proportionally.

Study FpS-AS-202

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 Phase: Phase II, dose-ranging study

Objective

- Primary objective: to evaluate the dose response, efficacy, and safety of 4 different doses of fluticasone propionate (50, 100, 200, and 400 mcg) delivered as Fp SPIROMAX Inhalation Powder (hereafter called Fp MDPI) when administered twice daily in subjects 12 years of age and older with severe persistent asthma who are uncontrolled on high dose ICS therapy.

Study Population: subjects 12 years of age and older with severe persistent asthma who are uncontrolled on high dose ICS therapy

Study Design
This was a randomized, double-blind, placebo- and open-label active-controlled, parallel-group, multicenter, dose-ranging study. Upon successful completion of the run-in period, subjects who continued to meet eligibility criteria were randomized to 1 of 6 treatment groups:

- Fp MDPI 50 mcg BID
- Fp MDPI 100 mcg BID
- Fp MDPI 200 mcg BID
- Fp MDPI 400 mcg BID
- Placebo MDPI BID
- FLOVENT DISKUS 250 mcg BID

The treatment period of the study was 84 days±2 days (12 weeks) in duration. During the treatment period, subjects received the double-blind or open-label treatment to which they were randomized. The overall study schema is presented in Figure 4.1.8.

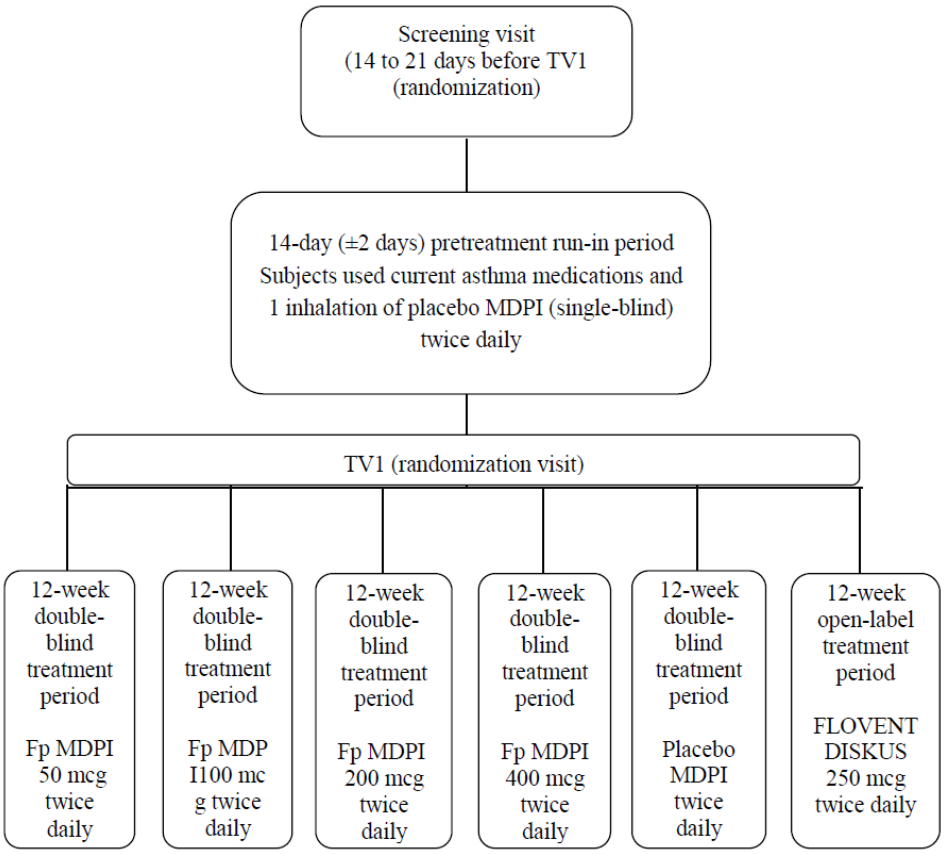


Figure 4.1.8. Overall study schema
(Source: Study FpS-AS-202 report, Figure 1)

Efficacy Assessment
The primary efficacy endpoint was the change from baseline in trough (AM predose and prerescue bronchodilator) FEV1 over the 12-week treatment period.

PK Assessment
Blood samples (~9 mL) for Fp PK assessment were obtained from a preselected subset of subjects (PK cohort) predose (within ~10 min before the AM dose administration) and at 0.08 (5 min), 0.17 (10 min), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1, 1.25, 1.5, 2, 4, 8, and 12 hr after the first dose of study medication at TV1.

Results

Efficacy Results
The increase in FEV1 from baseline after 12 weeks of therapy was approximately statistically significantly greater with Fp MDPI 200 mcg compared with placebo (LS mean difference from placebo of 0.099 L, p = 0.0473). There was no statistically significant difference between any of the other Fp MDPI doses (50, 100, and 400 mcg) compared with placebo. The LS mean change from baseline to week 12 with FLOVENT DISKUS was not statistically significantly different from Fp MDPI (any dose) or placebo (Table 4.1.17). For more detailed information, refer to the Type B End-Of-Phase 2 meeting minutes (dated March 17, 2014 in DARRTS), the Clinical Review by Dr. Miya Paterniti, and the Statistical Review by Dr. Yu Wang.

Table 4.1.17. Change in FEV1 (L) from baseline over the 12-week treatment period (FAS)

FEV_1		Fp MDPI				Placebo (N=105)	FLOVENT DISKUS (N=103)
		50 mcg (N=107)	100 mcg (N=106)	200 mcg (N=102)	400 mcg (N=107)		
At baseline	Mean (SD)	2.078 (0.6336)	2.069 (0.5806)	2.008 (0.5695)	2.015 (0.6294)	2.005 (0.5478)	1.987 (0.5426)
	Median (min, max)	1.940 (1.040, 4.640)	2.010 (0.900, 3.680)	2.020 (0.960, 3.690)	1.950 (0.930, 3.900)	1.900 (0.930, 3.550)	1.905 (0.990, 3.720)
At Week 12	Mean (SD)	2.140 (0.6214)	2.190 (0.6660)	2.204 (0.5959)	2.108 (0.6140)	2.094 (0.6640)	2.215 (0.6724)
	Median (min, max)	2.030 (1.060, 4.730)	2.060 (1.010, 4.110)	2.180 (0.900, 3.730)	1.990 (0.970, 3.970)	1.950 (1.060, 3.490)	2.170 (1.110, 4.120)
Change from baseline to Week 12[a]	LS mean	0.060	0.100	0.148	0.101	0.049	0.145
	SE[b]	0.0327	0.0322	0.0338	0.0332	0.0366	0.0334
	95% CI	(-0.004, 0.125)	(0.037, 0.163)	(0.081, 0.214)	(0.035, 0.166)	(-0.023, 0.121)	(0.079, 0.210)
Difference from Placebo	p-value	0.8155	0.2950	0.0473	0.2922	-	-
	LS mean	0.011	0.051	0.099	0.052	-	-
	95% CI	(-0.085, 0.107)	(-0.045, 0.147)	(0.001, 0.196)	(-0.045, 0.148)	-	-
Difference from FLOVENT DISKUS	p-value	0.0869	0.3565	0.8526	0.3999	0.0716	-
	LS mean	-0.080	-0.043	0.009	-0.040	-0.090	-
	95% CI	(-0.172, 0.012)	(-0.135, 0.049)	(-0.085, 0.102)	(-0.133, 0.053)	(-0.187, 0.008)	-

(Source: Study FpS-AS-202 report, Table 15)

PK Results

The PK analysis set included a total of 105 subjects from the pharmacokinetic cohort.

Fluticasone propionate AUC_{0-t} and C_{max} increased with increasing dose of Fp MDPI (Table 4.1.18) and comparisons of AUC_{0-t} and C_{max} between doses of Fp MDPI indicated approximately dose-proportional increases in both parameters across the dose levels tested (Fp MDPI 50, 100, 200, and 400 mcg).

Table 4.1.18. Fluticasone propionate pharmacokinetics descriptive statistics (PK Analysis Set)

Pharmacokinetic parameters	Statistic	Fp MDPI				FLOVENT DISKUS (N=16)
		50 mcg (N=18)	100 mcg (N=18)	200 mcg (N=18)	400 mcg (N=20)	
AUC_{0-t} (pg•hr/mL)	Mean (SD)	117.6 (145.79)	126.8 (33.73)	292.0 (162.28)	462.8 (262.45)	162.3 (74.79)
	Median	75.8	129.3	273.6	418.4	146.2
	Min, max	14.1, 533.8	80.5, 173.2	40.0, 690.7	0.0, 1042.4	84.6, 362.8
C_{max} (pg/mL)	Mean (SD)	19.1 (15.53)	26.5 (6.18)	55.2 (29.12)	83.0 (44.32)	32.5 (13.92)
	Median	14.0	26.4	53.4	74.9	29.3
	Min, max	2.7, 61.7	12.9, 39.1	15.4, 115.2	0.0, 153.5	16.4, 66.2
t_{max} (hr)	Mean (SD)	1.0 (0.54)	1.2 (1.85)	2.2 (3.58)	1.4 (2.60)	1.8 (2.75)
	Median	1.0	0.9	1.1	0.8	1.1
	Min, max	0.2, 2.0	0.2, 8.0	0.3, 12.0	0.1, 12.0	0.5, 12.0

Source: Summary 15.3.27, Listing 16.2.8.15
(Source: Study FpS-AS-202 report, Table 27)

Conclusions
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 to the stopping criteria issue. For more detailed information, refer to the Type B End-Of-Phase 2 meeting minutes (dated March 17, 2014 in DARRTS), the Clinical Review by Dr. Miya Paterniti, and the Statistical Review by Dr. Yu Wang.

Study FSS-AS-201

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 Phase: Phase II, dose-ranging study

Objectives
- Primary objective: to evaluate the dose response, efficacy and safety of 4 different doses of Sx (6.25 mcg, 12.5 mcg, 25 mcg, and 50 mcg) each combined with a fixed dose of Fp (100 mcg) delivered as FS MDPI when administered as a single dose in patients 12 years of age and older with persistent asthma

Study Population: patients 12 years of age and older with persistent asthma

Study Design
This was a multicenter, randomized, double-blind and open-label active-controlled, single-dose, 6-period crossover, dose-ranging study. Subjects who met randomization criteria were randomized to 1 of 6 treatment sequences containing the 6 treatments arms described in Table 4.1.19.

At each of the 6 treatment period visits, subjects self-administered a single dose of a double-blinded or open-labeled treatment to which they were randomized. Subjects withheld the AM dose of Fp MDPI and avoided use of rescue albuterol 6 hours before the treatment visits.

Subjects received their PM dose of Fp MDPI before leaving the investigational site during the end of their treatment visit. At the end of each treatment period, subjects continued to use 2 inhalations of Fp MDPI 50 mcg (100 mcg total dose) twice daily. Treatment periods 1 through 5 were followed by a washout period of 5 to 7 days.

Table 4.1.19. 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

(Source: Study FSS-AS-201, Table 2)

Efficacy Assessment

The primary efficacy endpoint for this study was the baseline-adjusted area under the curve for FEV_1 over 12 hours postdose (FEV_1 AUC_{0-12}).

PK Assessment

Blood samples (~9 mL) for Sx PK assessment were obtained at predose, and 0.08 (5 min), 0.17 (10 min), 0.25 (15 min), 0.5 (30 min), 1, 1.5, 2, 3, 4, 8, 12 hr after the AM dose.

Results

Efficacy Results

The baseline-adjusted FEV1 AUC0-12 demonstrated a dose-related increase in baseline-adjusted FEV1 AUC0-12 in subjects treated with FS MDPI at doses ranging from 100/6.25 to 100/50 mcg. The increase following ADVAIR DISKUS was comparable to that seen after FS MDPI 100/12.5. Statistical analysis indicated the standardized LS mean of the baseline-adjusted FEV1 AUC0-12 was significantly greater for all 4 FS MDPI groups and for ADVAIR DISKUS compared to Fp MDPI 100 mcg (all $p < 0.0001$). (Table 4.1.20 and Figure 4.1.9)

Table 4.1.20. Comparison of standardized baseline-adjusted FEV1 AUC0-12 (mL) by treatment (FAS)

Statistic	Fp MDPI	FS MDPI				ADVAIR DISKUS (n=66)
	100 mcg (n=67)	100/6.25 mcg (n=68)	100/12.5 mcg (n=69)	100/25 mcg (n=67)	100/50 mcg (n=68)	
Standardized baseline-adjusted FEV_1 AUC_{0-12} (mL)						
LS Mean	52.13	203.84	248.98	279.69	303.43	245.56
SE of LS Mean	38.071	38.072	38.025	38.121	38.062	38.148
p-value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
LS Mean (diff. from FP MDPI 100 mcg)		151.71	196.85	227.56	251.30	193.42
95% CI (diff. from FP MDPI 100 mcg)		(115.9, 187.5)	(161.2, 232.5)	(191.6, 263.5)	(215.6, 287.1)	(157.4, 229.5)
p-value for the linear trend test	<0.0001	-	-	-	-	-
p-value	<0.0001	0.0229	0.8503	0.0624	0.0017	-
LS Mean (diff. from ADVAIR DISKUS)	-193.42	-41.72	3.42	34.14	57.88	
95% CI (diff. from ADVAIR DISKUS)	(-229.5, -157.4)	(-77.6, -5.8)	(-32.3, 39.1)	(-1.8, 70.1)	(22.0, 93.7)	

Source: Summary 15.2.11 and Listing 16.2.6.01

(Source: Study FSS-AS-201, Table 11)

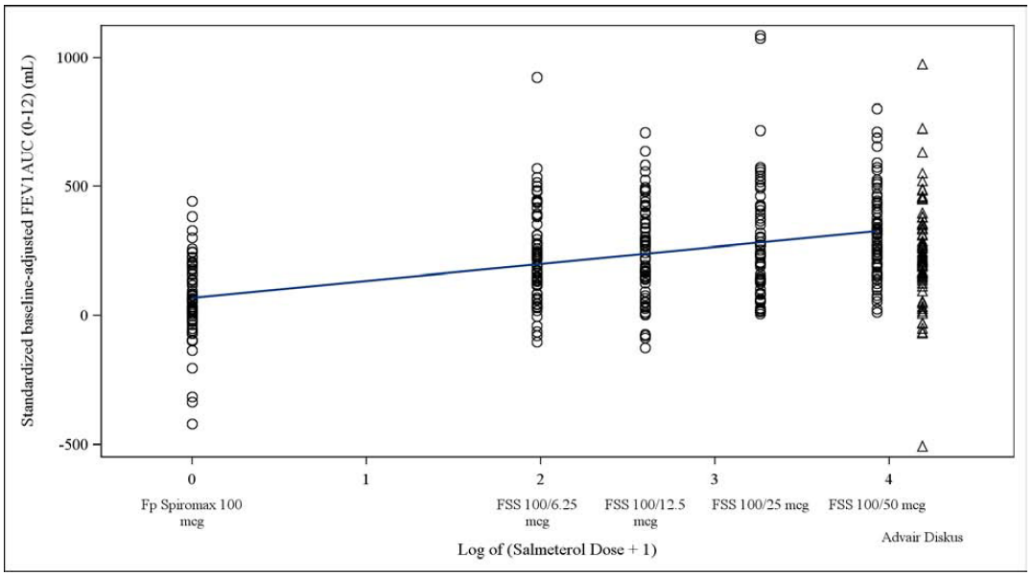
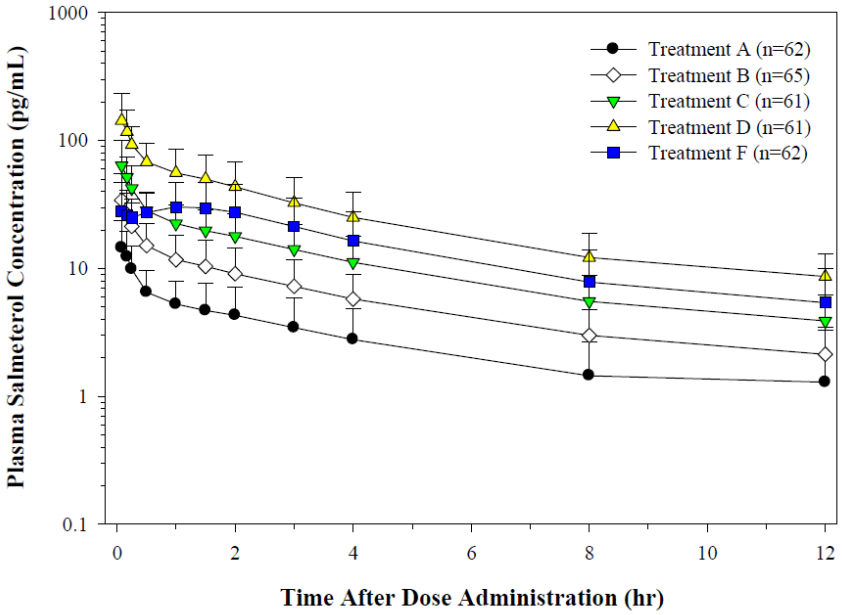


Figure 4.1.9. Scatter Plot of Baseline-adjusted FEV1 AUC(0-12) by Treatment Group (Full Analysis Set)

(Source: Study FSS-AS-201, Figure 2)

PK Results

Both AUC0-t and Cmax of Sx increased with increasing FS MDPI doses. Across all FS MDPI groups, tmax occurred earlier (median = 0.1 hr) compared to ADVAIR DISKUS (median = 0.5 hr). The systemic exposure (Cmax and AUCt) to Sx is lower after the administration of FS MDPI 100/12.5 mcg compared with ADVAIR DISCUS 100/50 mcg (Figure 4.1.10 and Table 4.1.21).



Treatment A: FS Spiromax 100/6.25 mcg

Treatment B: FS Spiromax 100/12.5 mcg

Treatment C: FS Spiromax 100/25 mcg

Treatment D: FS Spiromax 100/50 mcg

Treatment F: Advair Diskus 100/50 mcg

Figure 4.1.10. Mean plasma concentration-time profiles of salmeterol after treatment with FS MDPI and ADVAIR DISKUS
(Source: Study FSS-AS-201, Figure 5)

Table 4.1.21. Pharmacokinetics of salmeterol after administration of FS MDPI or ADVAIR DISKUS

Statistic	FS MDPI				ADVAIR DISKUS
	100/6.25 mcg (n=62)	100/12.5 mcg (n=65)	100/25 mcg (n=61)	100/50 mcg (n=61)	100/50 mcg (n=62)
AUC_{0-t} (pg*hr/mL)					
Mean±SD	32.8±21.0	69.9±35.4	133.5±63.1	309.3±143.4	173.5±106.6
Median	27.1	60.7	117.8	284.6	131.5
Min, Max	0.2, 140.6	0.0, 184.4	8.5, 348.5	95.3, 794.1	62.4, 516.2
C_{max} (pg/mL)					
Mean±SD	16.0±8.9	35.8±20.3	67.5±34.7	154.5±80.3	42.3±19.3
Median	15.1	30.7	60.5	136.4	36.9
Min, Max	1.1, 44.7	0.0, 93.4	5.9, 174.6	40.8, 439.5	12.4, 91.6
t_{max} (h)					
Mean±SD	0.4±1.5	0.2±0.4	0.2±0.3	0.2±0.3	0.8±0.7
Median	0.1	0.1	0.1	0.1	0.5
Min, Max	0.1, 12.1	0.1, 2.0	0.1, 2.0	0.1, 1.5	0.1, 2.0

(Source: Study FSS-AS-201, Table 18)

Conclusions

- The study demonstrated a dose-related improvement in pulmonary function with the 100 /12.5 mcg dose of FS MDPI providing similar benefits to ADVAIR DISKUS 100/50 mcg.
- The systemic exposure of Sx is lower after the administration of FS MDPI 100/12.5 mcg compared with ADVAIR DISKUS 100/50 mcg

4.2 Appendix – New Drug Application Filing Memo

Application Information			
NDA/BLA Number	208798	**SDN**	1
Applicant	Teva	**Submission Date**	03/28/2016
Generic Name	Fluticasone Propionate	**Brand Name**	ArmonAir RespiClick
Drug Class	Synthetic corticosteroid		
Indication	▪ For the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older ▪ Not for the relief of acute bronchospasm		
Dosage Regimen	One inhalation of fluticasone propionate inhalation powder 55 mcg, 113 mcg, or 232 mcg twice daily. Start dosage is based on asthma severity.		
Dosage Form	Powder, for inhalation	**Route of Administration**	Oral inhalation
OCP Division	DCP2	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Lei He, PhD	Anshu Marathe, PhD
Pharmacometrics		
Genomics		
Review Classification	☑ Standard ☐ Priority ☐ Expedited	
Filing Date	5/28/2016	**74-Day Letter Date** 6/11/2016
Review Due Date	12/24/2016	**PDUFA Goal Date** 1/28/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?
☑ Yes
✗ No
If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?
✗ Yes
☑ No
If yes list comment(s)

Is there a need for clinical trial(s) inspection?
✗ Yes
☑ No
If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ✗ No	Clinical Pharmacology Summary	☑ Yes ✗ No
Bioanalytical and Analytical Methods	☑ Yes ✗ No	Labeling	☑ Yes ✗ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		

☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☑ Other			Bioanalytical reports: 1) Report RPT02770 (Method Validation of an LC-MS/MS Assay for the Determination of Fluticasone Propionate in K3EDTA Human Plasma, by (b) (4) 2) Report P1197 (Method Validation for Quantitation of Fluticasone Propionate and Salmeterol in Human Plasma via UPLC® with MS/MS Detection, by (b) (4) 3) Report RPT02853 (Sample Analysis Report for FPS-AS-101, by (b) (4) 4) Report RPT02855 (Sample Analysis Report for FPS-AS-102, by (b) (4) 5) Report DP-2015-152 (Sample Analysis Report for FSS-AS-10042, by (b) (4) 6) Report RTP03149 (Sample Analysis Report for FPS-AS-201, by (b) (4) 7) Report RTP03234 (Sample Analysis Report for FPS-AS-202, by (b) (4)
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		1) Study FpS-AS-101 2) Study FpS-AS-102 3) Study FSS-AS-10042
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose		1) Study FpS-AS-201 2) Study FpS-AS-202 3) Study FSS-AS-201
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			

☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**	7	**In Vivo**	6
Total Number of Studies to be Reviewed				

Application Information

NDA/BLA Number	208799	**SDN**	1
Applicant	Teva	**Submission Date**	03/29/2016
Generic Name	Fluticasone Propionate and Salmeterol Xinafoate	**Brand Name**	AirDuo RespiClick
Drug Class	Synthetic corticosteroid/Long-acting β2 agonist		
Indication	▪ For treatment of asthma in patients aged 12 years and older ▪ Not for the relief of acute bronchospasm		
Dosage Regimen	One inhalation of fluticasone propionate/salmeterol xinafoate inhalation powder 55/14 mcg, 113/14 mcg and 232/14 mcg twice daily. Start dosage is based on asthma severity.		
Dosage Form	Powder, for inhalation	**Route of Administration**	Oral inhalation
OCP Division	DCP2	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Lei He, PhD	Anshu Marathe, PhD
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	5/28/2016	**74-Day Letter Date**	6/11/2016
Review Due Date	12/24/2016	**PDUFA Goal Date**	1/28/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

✗ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

✗ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

✗ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ✗ No	Clinical Pharmacology Summary	☑ Yes ✗ No
Bioanalytical and Analytical Methods	☑ Yes ✗ No	Labeling	☑ Yes ✗ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**

In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☑ Other			Bioanalytical reports: 1) Report RPT02770 (Method Validation of an LC-MS/MS Assay for the Determination of Fluticasone Propionate in K3EDTA Human Plasma, by (b) (4) 2) Report P1197 (Method Validation for Quantitation of Fluticasone Propionate and Salmeterol in Human Plasma via UPLC® with MS/MS Detection, by (b) (4) 3) Report RPT02917 (Method Validation of an LC-MS/MS Assay for the Determination of Salmeterol in Human Plasma, by (b) (4) 4) Report RPT02853 (Sample Analysis Report for FPS-AS-101, by (b) (4) 5) Report RPT02855 (Sample Analysis Report for FPS-AS-102, by (b) (4) 6) Report DP-2015-152 (Sample Analysis Report for FSS-AS-10042, by (b) (4) 7) Report RTP03149 (Sample Analysis Report for FPS-AS-201, by (b) (4) 8) Report RTP03234 (Sample Analysis Report for FPS-AS-202, by (b) (4)
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		4) Study FpS-AS-101 5) Study FpS-AS-102 6) Study FSS-AS-10042
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose		4) Study FpS-AS-201 5) Study FpS-AS-202 6) Study FSS-AS-201
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			

☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**	8	**In Vivo**	6
Total Number of Studies to be Reviewed				

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

/s/

LEI HE
10/28/2016

ANSHU MARATHE
10/28/2016